

Structure-activity Relationship Studies and Biological Evaluation of Selective Sphingosine  
Kinase Inhibitors

Emily Anne Morris

Thesis submitted to the faculty of the Virginia Polytechnic Institute and State University in  
partial fulfillment of the requirements for the degree of

Master of Science  
In  
Chemistry

Webster L. Santos, Chair  
David G.I. Kingston  
Paul R. Carlier

April 20<sup>th</sup>, 2015  
Blacksburg, VA

Keywords: sphingosine 1-phosphate, sphingosine kinase inhibitors, structure-activity  
relationships, guanidine inhibitors

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## ABSTRACT

Sphingosine 1-phosphate (S1P) has become a prevalent drug discovery target due to studies implicating it to several disease pathologies such as fibrosis, sickle cell disease, inflammation, diabetes, and cancer. S1P functions to induce cell proliferation and migration. S1P signaling occurs through intracellular targets or transport outside of the cell via ABC transporters, where it acts as a ligand to G-protein coupled receptors (S1P<sub>1-5</sub>). Sphingosine kinase (SphK) 1 and 2 phosphorylate sphingosine to S1P; these are the only enzymes known to mediate the phosphoryl transfer. Inhibiting either or both SphKs helps to modulate S1P, which may be useful as a therapeutic avenue for disease states where S1P signaling has gone awry.

Herein, we document our efforts in profiling the structure-activity relationships (SAR) of SphK2 through an iterative process of synthesis and biological testing. First, an SAR structured around the head and linker region of our lead molecule, **SLR080811**, was performed. **SLR080811** has a  $K_i$  of 1.3  $\mu$ M and is 5-fold selective for SphK2. The modifications performed on **SLR080811** yielded two promising inhibitors: **SLP120701** (SphK2 selective with a  $K_i$  of 1.2  $\mu$ M) and **SLP7111228** (>200 fold selective for SphK1 with a  $K_i$  of 48 nM). *In vitro* studies in U937 cells yielded a decrease in S1P levels with the introduction of inhibitors. Mouse studies provided insight into the pharmacokinetic effect of our SphK2-selective inhibitors, revealing an increase in S1P levels in the blood. When *in vivo* studies were performed with the SphK1 selective inhibitor, S1P levels in blood decreased. These molecules provide the chemical biology tools to determine the effect of modulating S1P levels *in vivo*.

We also focused our investigation on the tail region of the pharmacophore. From this study, **SLM6031434** and **SLM6041418** were discovered and both proved to be more potent and selective SphK2 inhibitors than **SLR080811**. **SLM6031434** has a  $K_i$  of 370 nM and is 23-fold selective for SphK2. **SLM6041418** has a  $K_i$  of 430 nM and is 24-fold selective for SphK2. Consistent with our previous observations, *in vitro* studies showed a decrease in S1P levels when inhibitor was introduced. Similarly, *in vivo* studies resulted in an increase of S1P levels in the blood. These compounds are positioned towards animal models of disease.

## Acknowledgements

First and foremost, I would like to thank my advisor, Dr. Santos, for his support and for giving me guidance throughout my project. He has always believed in me and pushed me to be a better chemist. He has also been very patient and understanding when I was struggling both in my research and other areas of my life. I am very happy that I joined his group because I have learned a lot and made some great friends along the way. He is always walking through the lab lending a helpful hand which was beneficial when I was really struggling. It also makes you feel like he cares about your progress and wants to see you succeed.

Next, I would like to thank my committee members, Dr. Kingston and Dr. Carlier. They push you both in class and in committee meetings, which helps to make you a stronger, more independent person. Their excitement and curiosity during my presentations has helped me appreciate the work that I do.

I would like to thank all of my group members over the years. Dr. Mithun Raje for helping me get on my feet my first year in the group. Dr. Neeraj Patwardhan for being a great friend and co-worker. He was always available to help me when I needed it, and for that I am grateful. My sphingosine group members, Beth Childress, Molly Congdon, Dr. Srinath Pashikanti, for always being available to talk and work out problems with our research and for the laughs and conversation in between. I would like to thank Beth for providing the jams in lab and tolerating my awful singing and dancing. I would like to thank Dr. Xi Guo for all the goofy conversations and accepting me into your life and family. I would like to thank Jess Wynn for being weird with me, no questions asked. I would also like to thank Dr. David Bryson, Dr. Brandon Thorpe, Dr. Jason Crumpton, Ken Knott, Dr. Wenyu Zhang, Joe Calderone, Amanda Nelson, Cheryl Peck,

Russell Snead, Hao Li, Ashley Peralta, Sean Rafferty, Chris Sibley, and Dr. Astha Verma for their help, support, and friendship.

Lastly, I would like to thank my family. They are the most loving and supportive people I know. My mom, Cindy Settle, is always there to cheer me up and made sure to check on me every couple of days to make sure I was surviving. My dad, Jimmy Morris, for calling me every night to see how my day was and dropping everything to visit if I was having a rough time. My grandparents and aunts for loving and supporting me along this journey. My college roommates, Bekah Lindner, Madeline Pillow, and Lacey Graybeal, for all their love and support over the past 8 years. I would like to thank my boyfriend, Eugene Camerino. Without him, I don't know if I would have made it through graduate school. He has been my rock, the calm to my crazy, and my best friend.

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## List of abbreviations

ABC= ATP-binding cassette

AC= Adenylate cyclase

Akt= Protein kinase B

cAMP= Cyclic Adenosine Monophosphate

CDC42= Cell division control protein 42 homolog

CTGF= Connective tissue growth factor

ER= endoplasmic reticulum

ERK= Extracellular signal-regulated kinase

GPCR= G-protein coupled receptor

IP<sub>3</sub>= Inositol 1, 4, 5-triphosphate

$K_i$ = Inhibition constant

$K_m$ = Michaelis constant

MEK= MAPK/ERK kinase

PI3K= Phosphatidylinositol 3-kinase

PKA= Protein kinase A

PKC= Protein kinase C

PLC= Phospholipase C

S1P= Sphingosine-1-phosphate

SphK= Sphingosine kinase

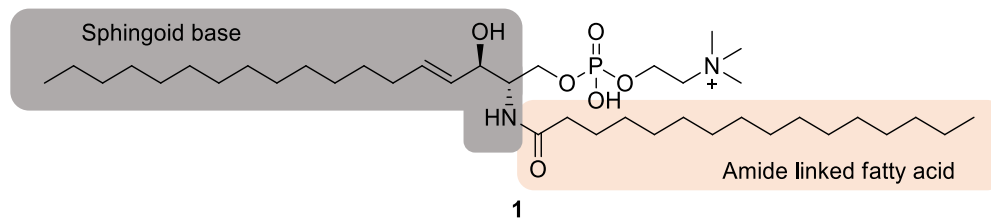
SPP= Sphingosine-1-phosphate phosphatase

TGF- $\beta$ = Transforming growth factor-beta

## Chapter 1. Sphingosine kinase 2 inhibitors as a fibrosis therapy

### 1.1 Sphingolipids

The basic structure of sphingolipids consists of a sphingoid base and an amide linked fatty acid (Fig. 1.1). Sphingosine 1-phosphate (S1P), ceramide, sphingosine (Sph), and sphingomyelin are all sphingolipids (Fig. 1.2). Sphingolipids have several roles in the cell such as cell survival, apoptosis, and migration.<sup>1</sup> Additionally, sphingolipids are responsible for controlling and maintaining the structure of the membrane by arranging vertically and laterally.<sup>1-3</sup>

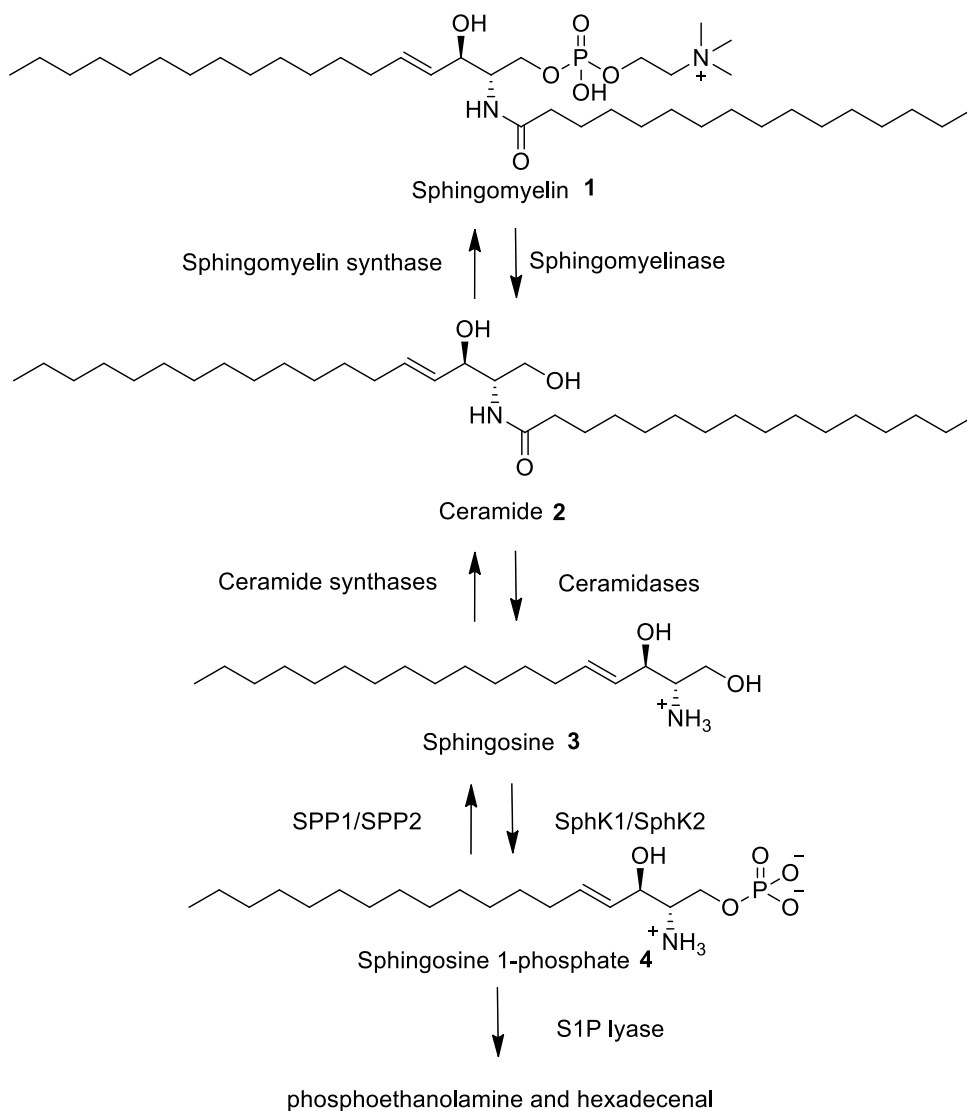


**Figure 1.1** Structure of Sphingolipids.

### 1.2 Ceramide/S1P Pathway

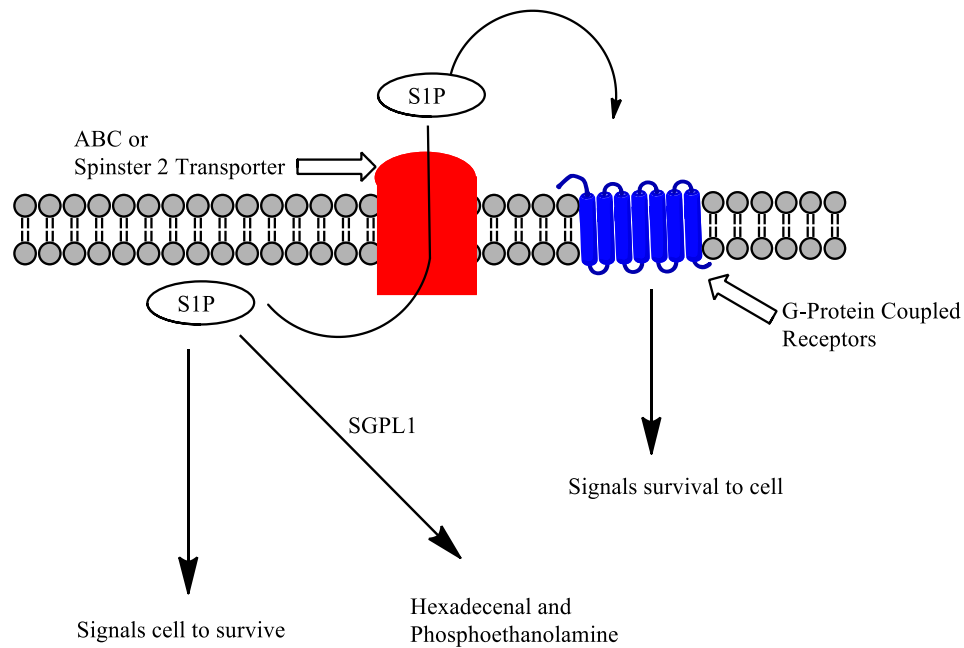
The ceramide/S1P pathway is shown in Figure 1.2.<sup>1</sup> The pathway starts with sphingomyelin (1), which can be dephosphorylated by sphingomyelinase to afford ceramide (2). Sphingomyelinase is activated by biological stresses, cytokines, and upon protein/receptor binding.<sup>4</sup> Once synthesized, ceramide (2) can then be phosphorylated by sphingomyelin synthase back to sphingomyelin (1) or ceramidase can cleave the fatty acid chain to generate Sph (3). Sph (3) can then be converted back to ceramide (2) by ceramide synthases or it can be phosphorylated to S1P (4) by sphingosine kinase 1 (SphK1) or sphingosine kinase 2 (SphK2). S1P (4) can subsequently be dephosphorylated back to Sph (3) by either S1P phosphatase-1 or S1P

phosphatase-2 or degraded by S1P lyase to afford phosphoethanolamine and hexadecenal.<sup>1</sup> Within the ceramide/S1P pathway, all transformations are reversible with the exception of the degradation of S1P (4) into phosphoethanolamine and hexadecenal.<sup>3</sup> The S1P produced can be used to signal inside of the cell or it can be transported outside of the cell for signaling.<sup>5</sup>



**Figure 1.2** Ceramide/S1P Pathway.

S1P is transported out of the cell by ATP-binding cassette (ABC) transporters or the spinster homolog 2 transporter, allowing it to bind to any one of its five known G-protein coupled receptors (GPCRs) found on the cell surface (Fig. 1.3).<sup>6-8</sup> Through the GPCRs, signals are transduced inside of the cell. Interestingly, ceramide (2) and Sph (3) both promote apoptosis or cell growth arrest.<sup>5, 9, 10</sup> S1P (4), on the other hand, stimulates cell proliferation, growth, and movement.<sup>2, 4, 5</sup> Depending on which side the equilibrium lies within the ceramide/S1P pathway, the cell can be signaled to undergo apoptosis or it can be signaled to proliferate, survive, and migrate.

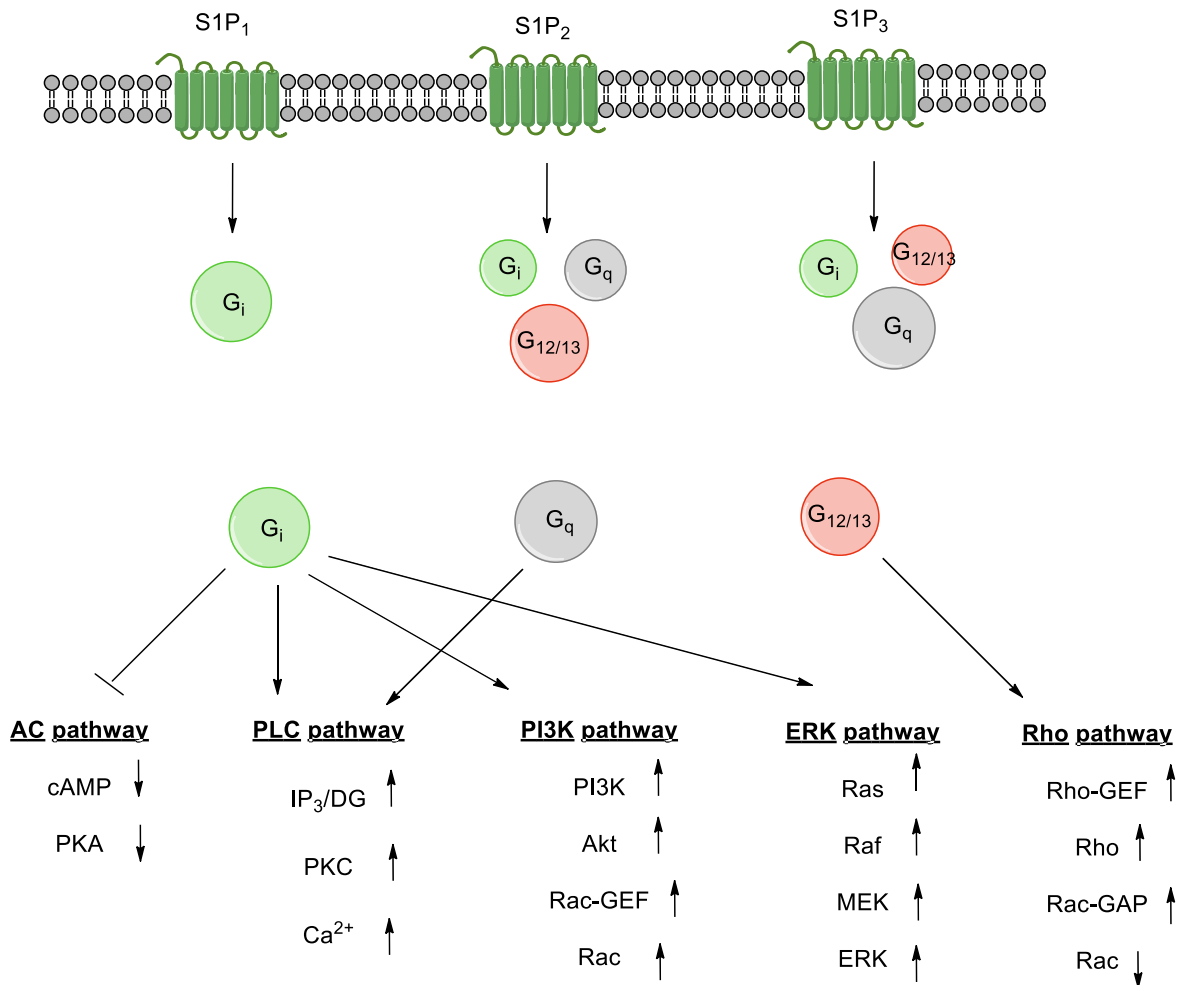


**Figure 1.3** Example of how S1P can be exported out of the cell to GPCRs.<sup>11</sup>

### 1.3 Inside-out Signaling

There are five known GPCRs for S1P: S1P<sub>1</sub>, S1P<sub>2</sub>, S1P<sub>3</sub>, S1P<sub>4</sub>, and S1P<sub>5</sub> (Fig. 1.4).<sup>5, 12, 13</sup> S1P<sub>1</sub>, S1P<sub>2</sub>, and S1P<sub>3</sub> are found in most tissues.<sup>3</sup> The two least common are located in separate

areas. Lymphoid tissues, white blood cells, and lungs are the primary sites for S1P<sub>4</sub>, and S1P<sub>5</sub> mainly resides in the central nervous system, brain, and skin.<sup>3,5</sup> The binding of S1P to a GPCR results in a conformational change that uncouples the G-proteins: G<sub>i</sub>, G<sub>q</sub>, and G<sub>12/13</sub>.<sup>3</sup> Once the G-protein is activated, S1P<sub>n</sub> α and βγ subunits signal different primary messenger pathways such as the adenylate cyclase (AC), phospholipase C (PLC), phosphatidylinositol 3-kinase (PI3K), extracellular signal-regulated kinase (ERK), and Rho pathways.<sup>3,14</sup> Those pathways communicate to secondary messengers within the pathway to produce the desired function from S1P.<sup>3</sup>



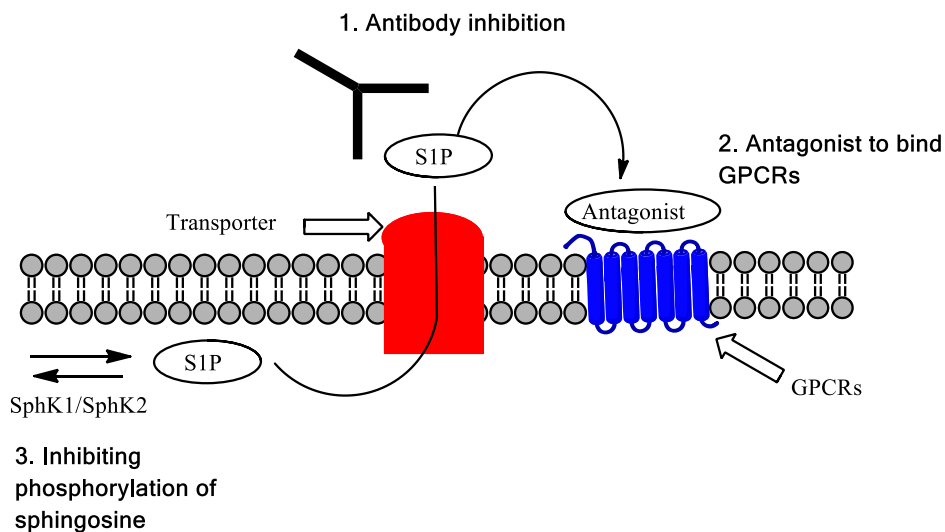
**Figure 1.4** Different pathways coupled to GPCRs S1P<sub>1-5</sub>.<sup>3</sup>

S1P<sub>1</sub> impedes the AC pathway and triggers the PLC, PI3K, and ERK pathways by interacting to only G<sub>i</sub>.<sup>3, 11, 13, 15</sup> The PLC and ERK pathways are responsible for cell proliferation.<sup>4, 16</sup> The PI3K pathway increases Rac expression and leads to migration and construction of adherens junctions.<sup>3</sup> S1P<sub>2</sub>, mainly associated with G<sub>12/13</sub>, signals through the Rho pathway to inhibit cell migration.<sup>3, 13, 15, 17</sup> S1P<sub>3</sub> mainly couples to G<sub>q</sub> and leads to cell-proliferation.<sup>3, 15</sup> When S1P<sub>4</sub> and S1P<sub>5</sub> are present, S1P<sub>4</sub> selectively stimulates PLC, ERK, and CDC42, while S1P<sub>5</sub> prefers G<sub>i</sub> and G<sub>12</sub>.<sup>3, 15</sup>

#### **1.4 Inhibition of S1P Signaling**

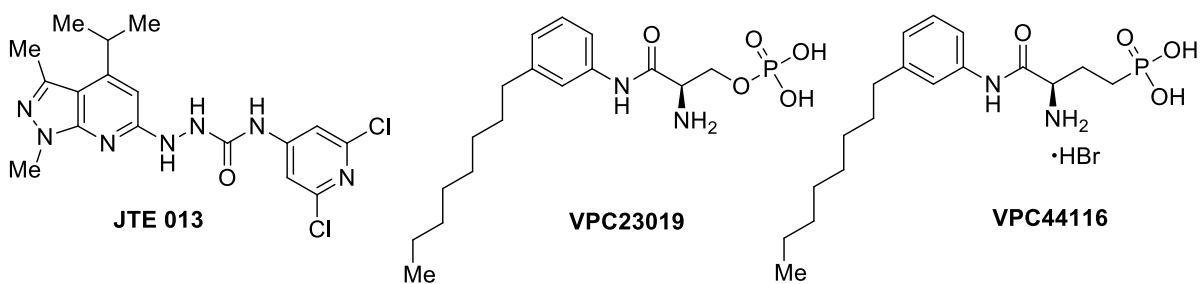
There are three strategies towards inhibition of S1P signaling (Fig. 1.5).<sup>5</sup> The first utilizes an antibody to remove/decrease circulating levels of S1P.<sup>18, 19</sup> Antibodies remove S1P by acting like a sponge and absorbing S1P. Over the past ten years, there have been two monoclonal antibodies (mAB) that have stood out, both published by Sabbadini and colleagues. First, there was the murine derived anti-S1P mAB (*Sphingomab*<sup>TM</sup>).<sup>18, 19</sup> Experiments performed on xenografts and allografts in nude mice demonstrated reduced tumor progression and neutralized S1P-induced proliferation.<sup>19</sup> Based on the success of the murine mAB, a humanized version was developed (*Sonepcizumab*<sup>TM</sup>).<sup>18</sup> ELISA assays showed that both the human and the murine mABs inhibit S1P around 89% at 2 μM and do not have other lipid targets, suggesting selectivity for S1P.<sup>18</sup> The humanized mAB is currently going through Phase I trials in cancer and age-related macular degeneration.<sup>11</sup>





**Figure 1.5** Three different locations to inhibit S1P signaling.<sup>5</sup>

Second, antagonists can be prepared to bind the GPCRs, block S1P binding, and prevent downstream signaling. To date, there have been few antagonists reported (Fig. 1.6). In 2001, **JTE 013** was described as a S1P<sub>2</sub> receptor antagonist.<sup>20</sup> The antagonist showed IC<sub>50</sub> values around 17 nM for human S1P<sub>2</sub>.<sup>20</sup> Further studies, however, suggest that the effects seen in animal models were due to off-target effects.<sup>21</sup> The next example is **VPC23019**, published by Davis et al. in 2005.<sup>22</sup> This antagonist proved to be selective for S1P<sub>1</sub> and S1P<sub>3</sub> with K<sub>i</sub> values of 25 and 300 nM.<sup>22</sup> Against thyroid and ovarian cancer cells, phosphorylation of S1P was inhibited with the addition of **VPC23019**.<sup>5</sup> In an SAR of **VPC23019** study, the phosphate moiety was exchanged for a phosphonate to generate **VPC44116**.<sup>23</sup> Receptor affinity remained constant with the modification; however, **VPC44116** caused capillary leakage.<sup>23</sup> Among many issues that may impede antagonist development is finding a pan-antagonist with potency that achieves the desired biological output. This issue can be exacerbated by downstream signaling pathways that could lead to undesirable side effects.



**Figure 1.6** S1P receptor antagonists.

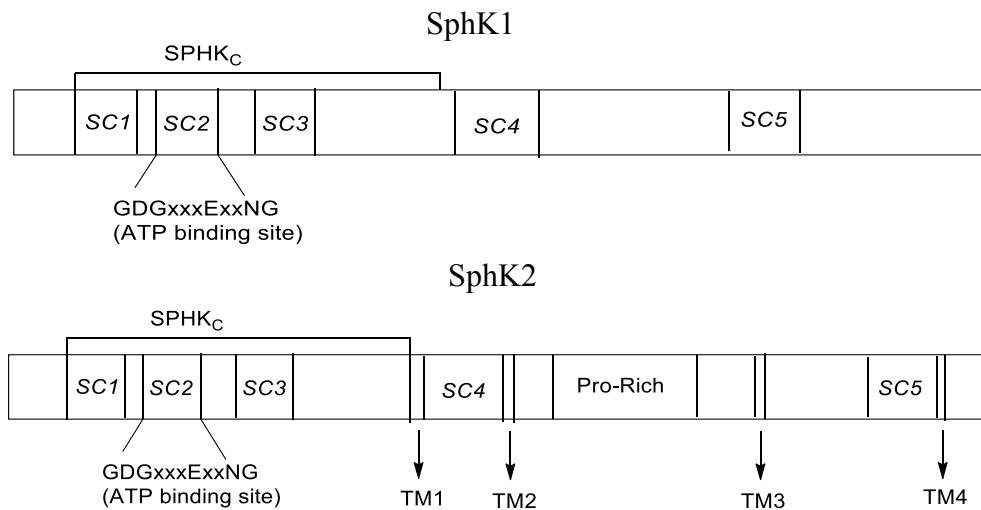
Inhibition of SphK1 and/or SphK2 within the cell is the third option. Inhibiting S1P production should theoretically decrease and subsequently shift the equilibrium towards sphingosine and ceramide, the two molecules that promote apoptosis. This strategy can potentially be useful with certain diseases where the main goal is to promote apoptosis.

### 1.5 SphK1 and SphK2 Biochemistry

Although SphK1 and SphK2 share some cellular functions, they have different characteristics that make them unique, such as cellular location and amino acid sequence composition (Fig. 1.7).<sup>5</sup> SphK1, until activated, is localized in the cytoplasm.<sup>3, 24</sup> After activation/stimuli, translocation to the plasma membrane to phosphorylate Sph occurs.<sup>3, 5</sup> SphK1 has been shown to stimulate cell survival and has been shown to be prominent in a range of tumors.<sup>1, 2, 24</sup> Due to a high concentration of SphK1 in erythrocytes, S1P concentration in blood is more pronounced than in tissues and cells.<sup>2, 3, 5</sup> In contrast, SphK2 is found in the nucleus, endoplasmic reticulum (ER), and mitochondria.<sup>11, 25</sup> SphK2 has been shown to be activated by EGF and phorbol ester.<sup>5, 24, 26</sup> It is associated with tumor growth in breast and colon cancer cells, giving evidence that it is anti-apoptotic.<sup>27</sup> Surprisingly, it has also been shown to be pro-

apoptotic.<sup>13, 27-30</sup> Studies show that proteasomal degradation causes an elimination of the BH3 domain, part of the Bcl2-protein family that triggers this pro-apoptotic effect.<sup>31</sup>

SphK1 and SphK2 also have distinct amino acid sequences (Fig. 1.7).<sup>15</sup> SphK1, comprised of 384 amino acids, has five conserved domains (SC) which include all ATP binding sequences.<sup>15</sup> Out of the five, three bind  $Mg^{2+}$ -ATP.<sup>3</sup> Another conserved domain is responsible for recognizing sphingosine.<sup>3</sup> SphK2, comprised of 618 amino acids, has the same 5 conserved domains in addition to 4 hydrophobic transmembrane (TM) regions and a proline rich domain, which binds the SH3 domain of signaling proteins such as Ras, CDC42, and PI3K.<sup>5, 15, 30</sup> Although SphK1 and SphK2 have different localization in the cell, in the end they perform at least one function: phosphorylation of sphingosine to produce S1P. Mouse genetic studies show that a single kinase knock-out is not fatal but a double knock-out is embryonically lethal due to the poor development of the vasculature.<sup>32</sup>

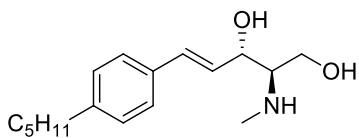


**Figure 1.7** Amino acid sequence and domain of SphK1 (top) and SphK2 (bottom).<sup>15</sup>

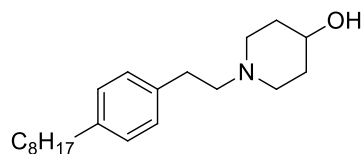
## 1.6 SphK inhibitors

The difference in amino acid sequence and localization theoretically allows it to be possible to synthesize selective inhibitors for SphK1 and SphK2. Significant progress has been made towards potent SphK1 inhibitors (Figure 1.8). Initial SphK inhibitors were designed to mimic sphingosine (**SK1-I**, **SG-12**, **(R)-FTY720-OMe**).<sup>33, 34</sup> This led to inhibitors with  $K_i$ 's in the 3-25  $\mu$ M range. Since then, inhibitors in the nanomolar range have emerged for SphK1 and low micromolar range for SphK2. Genzyme developed a SphK1 inhibitor, **Genzyme 51**, with an  $IC_{50}$  of 58 nM.<sup>35</sup> Administration of this compound in mice yielded a half-life of 7.6 hours and moderate bioavailability.<sup>35</sup> The most potent SphK1 inhibitor at the moment is **PF-543**, which has a reported  $K_i$  of 3.6 nM and 100-fold selectivity.<sup>36</sup> A recent study has showed promise for this inhibitor as a therapy for sickle cell disease.<sup>37</sup> Introduction of **PF-543** in *in vivo* and *in vitro* studies resulted in reduction of sickling of red blood cells and improvement in inflammation and hemolysis.<sup>37</sup> The elucidation of an x-ray crystal structure of SphK1 with **PF-543** shows binding in a bent, or “J-shape,” within the pocket (Fig. 1.9).<sup>38</sup> A hydrophobic pocket was observed with the terminal phenyl ring of **PF-543** docked inside.<sup>38</sup> Another interaction observed was Asp264 hydrogen bonding with the nitrogen and hydroxyl in the head group.<sup>38</sup> Knowing these interactions and having a crystal structure available can aid in developing more potent inhibitors of SphK1.

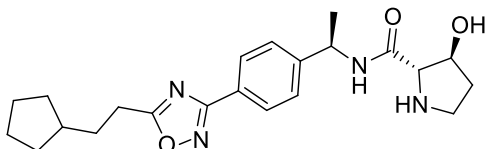
**SphK1 selective inhibitors**



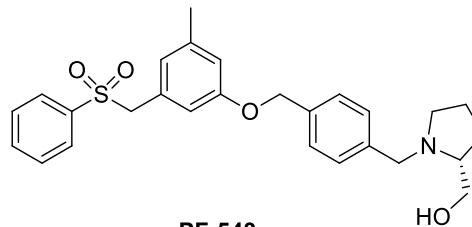
**SK1-I**  
 $K_i$  ( $\mu\text{M}$ ): SphK1 10  
SphK2 >100



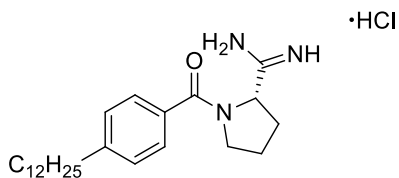
**RB-005**  
 $\text{IC}_{50}$  ( $\mu\text{M}$ ): SphK1 3.6  
SphK2 --



**Genzyme 51**  
 $\text{IC}_{50}$  ( $\mu\text{M}$ ): SphK1 0.058  
SphK2 --

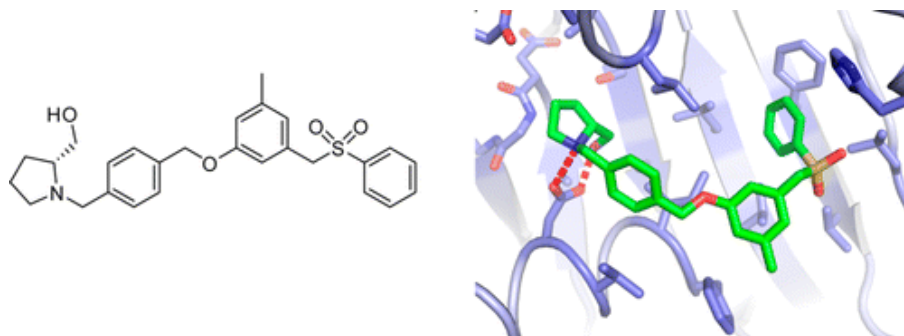


**PF-543**  
 $K_i$  ( $\mu\text{M}$ ): SphK1 0.0036  
SphK2 --



**VPC96091**  
 $K_i$  ( $\mu\text{M}$ ): SphK1 0.130  
SphK2 1.5

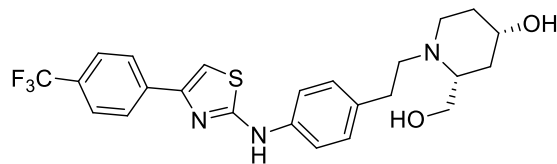
. **Figure 1.8** Inhibitors of SphK1: Structures and inhibitory activity.



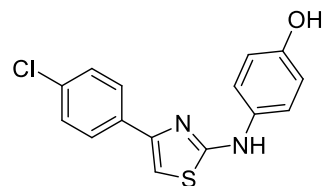
**Figure 1.9** Crystal structure of **PF-543** docked in SphK1 [Reprinted from Wang, J.; Knapp, S.; Pyne, N. J.; Pyne, S.; Elkins, J. M., Crystal Structure of Sphingosine Kinase 1 with PF-543. *ACS Med. Chem. Lett.* **2014**, 5, 1329-1333. Copyright 2014 ACS Med. Chem. Lett.].

There are potent nonselective inhibitors of SphK (Fig. 1.10). From the earlier generation, **SKI-II** is a nonselective, micromolar range inhibitor.<sup>39</sup> This inhibitor not only inhibits SphK, but also oestrogen receptor signaling.<sup>40</sup> In 2013, an x-ray co-crystal structure of SphK1 with **SKI-II** was published by Wang, et.al.<sup>41</sup> The crystal structure showed the inhibitor bound in the sphingosine binding pocket.<sup>41</sup> Also in 2013, a potent dual inhibitor was released by Amgen, **Amgen 82**, which exhibited  $IC_{50}$  values of 0.1  $\mu\text{M}$  for SphK2 and 0.02  $\mu\text{M}$  for SphK1.<sup>42</sup> Derivatives from the Amgen series were docked into the SphK1 x-ray crystal structure to evaluate the interactions. From the co-crystal structure, evidence showed similar interactions as the x-ray crystal structure of **PF-543** with SphK1. Hydrogen bonding and electrostatic interactions are observed between Asp178 and the compounds hydroxymethyl and nitrogen on the head group, respectively.<sup>42</sup> The hydroxymethyl group also forms hydrogen bonds with water molecules to form a small network with amino acid residues within the binding pocket.<sup>42</sup> The second hydroxyl group participates in hydrogen bonding interactions with Asp81.<sup>42</sup> This compound was tested in mice and showed a decrease in SIP.<sup>42</sup>

### Nonselective inhibitors



**Amgen 82**  
 $IC_{50}$  ( $\mu\text{M}$ ): SphK1 0.02  
SphK2 0.1



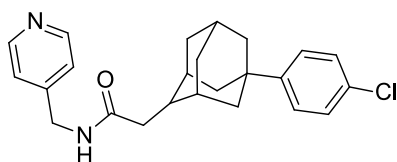
**SKI-II**  
 $K_i$  ( $\mu\text{M}$ ): SphK1  $16 \pm 1.3$   
SphK2  $7.9 \pm 0.6$

**Figure 1.10** Nonselective inhibitors of SphK: Structures and inhibitory activity.

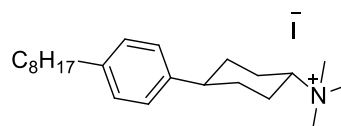
Currently there are no reported SphK2 inhibitors with sub-micromolar inhibition values, but several do display potential (Fig. 1.11). **ABC294640** ( $K_i \sim 10 \mu\text{M}$ ) was one of the first SphK2 selective inhibitors to be reported.<sup>43</sup> It has been tested against many diseases, such as “osteoarthritis, rheumatoid arthritis, Crohn’s disease, ulcerative colitis, and diabetic retinopathy.”<sup>14</sup> **ABC294640** has made it to phase I clinical trials where it is being evaluated as a treatment for solid tumors.<sup>14</sup> The next group of inhibitors to emerge (**K145** and **trans-12a**) show inhibition values ranging between 6-8  $\mu\text{M}$ .<sup>44, 45</sup> In 2012, **SLR080811** was published as a 1  $\mu\text{M}$  SphK2-selective inhibitor.<sup>29</sup> The synthesis of **SLR080811** was recently published by the Santos group.<sup>46</sup> **SLR080811** has a characteristic aliphatic chain, a 1,2,4-oxadiazole linker, and a guanidinium head group. An *in vitro* scintillation proximity assay using recombinant enzymes from Sf9 insect cells revealed a  $K_i$  value of 12  $\mu\text{M}$  for SphK1 and 1.3  $\mu\text{M}$  for SphK2. **SLR080811** has a 5-fold selectivity for SphK2. The selectivity is based on the  $K_i/K_m$  value of SphK2 divided by the  $K_i/K_m$  value of SphK1. Inhibition of SphK2 *in vitro* led to a decrease in S1P levels in U937 cells.<sup>29</sup> In mouse kidney fibroblasts, a decrease in S1P was found with SphK1-null and wild-type cells, but no change was seen in SphK-null cells, suggesting that **SLR080811** is targeting SphK2.<sup>29</sup>

Because this compound exhibited good selectivity for SphK2 and had impressive  $K_i$  values, it was tested *in vivo* in mice.

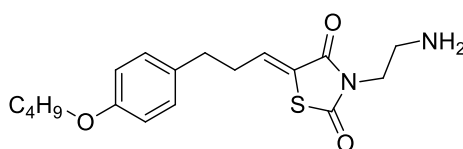
**SphK2 selective inhibitors**



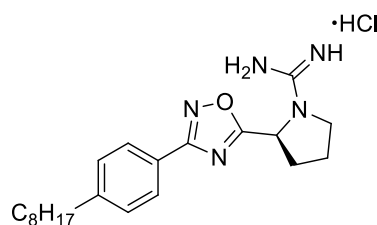
**ABC294640**  
 $K_i$  (  $\mu\text{M}$ ): SphK1 --  
 SphK2  $9.8 \pm 1.4$



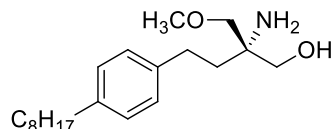
**trans-12a**  
 $K_i$  (  $\mu\text{M}$ ): SphK1  $60 \pm 6$   
 SphK2  $8 \pm 2$



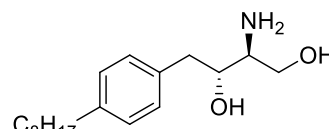
**K145**  
 $K_i$  (  $\mu\text{M}$ ): SphK1 --  
 SphK2  $6.4 \pm 0.7$



**SLR080811**  
 $K_i$  (  $\mu\text{M}$ ): SphK1 12  
 SphK2 1.3



**(R)-FTY720-OMe**  
 $K_i$  (  $\mu\text{M}$ ): SphK1 --  
 SphK2  $16.5 \pm 1$



**SG-12**  
 $\text{IC}_{50}$  (  $\mu\text{M}$ ): SphK1 --  
 SphK2 22

. **Figure 1.11** Inhibitors of SphK2: Structures and inhibitory activity.

When **SLR080811** was administered to SphK1-null mice, the blood S1P levels decreased, similar to *in vitro* studies, suggesting that **SLR080811** is targeting SphK2 *in vivo*.<sup>29</sup> In SphK2 null mice, administration of **SLR080811** has no effect on blood S1P levels as expected.<sup>29</sup> Surprisingly, it was found that in wild-type mice, upon administration of **SLR080811**, S1P concentrations increased.<sup>29</sup> Theoretically, S1P should have decreased following the addition of **SLR080811**,



because it has been shown to decrease SphK2 activity. The reason for this increase in S1P is currently unknown but it recapitulates the genetic knock-out mice studies. More research needs to be performed to learn about the intracellular effects of SphK2 inhibition.

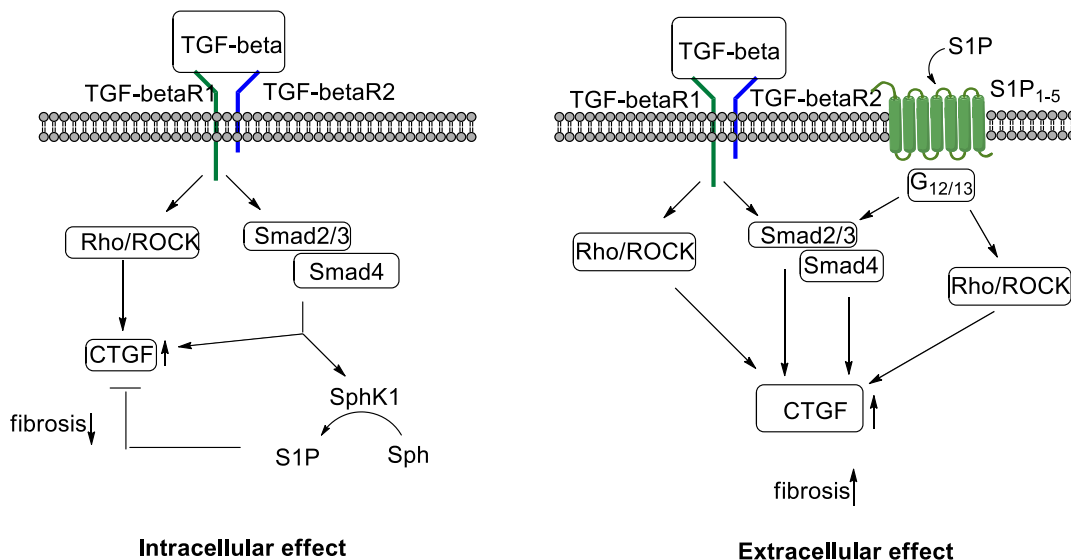
## 1.7 Fibrosis

Recent studies found that an increase in intracellular S1P could have therapeutic potential against fibrosis.<sup>47, 48</sup> Fibrosis is, by definition, excessive wound healing leading to an extra buildup of scar tissue.<sup>47, 48</sup> Fibrosis occurs after chronic injury to an organ.<sup>17, 47</sup> The typical response is to heal the wound; however, when the healing process becomes dysregulated, pro-fibrotic mediators can be released.<sup>48-50</sup> This causes the formation of myofibroblasts to produce extracellular matrix that, in surplus, causes fibrotic buildup.<sup>17, 47-50</sup> An excessive buildup of extra cells and scar tissue following surgery or organ injury can ultimately lead to destruction of the organ.<sup>48</sup> Finding an effective treatment for fibrosis is crucial, especially for industrialized nations. In 2008, Wynn published statistical data stating in industrialized nations, around 45% of all deaths are attributed to some sort of fibrotic disease.<sup>47, 50</sup> The main organs affected are the lungs, kidneys, liver, skin, and heart.<sup>17, 47-49</sup> S1P could be an important effector of fibrosis, because when the S1P<sub>1</sub> receptor is activated, S1P<sub>1</sub> promotes protection specifically for the endothelial barrier and vascular leakage.<sup>15, 17, 47-49</sup> The positive signaling unfortunately only occurs with the S1P<sub>1</sub> receptor but not with the S1P<sub>2</sub> or S1P<sub>3</sub> receptors.<sup>47, 49, 51</sup> S1P<sub>2/3</sub> may be viable targets for therapy if an antagonist were to bind to the receptors to block negative signaling.<sup>47</sup>

An increase in intracellular S1P has been shown to effect fibrosis.<sup>47</sup> These effects could be attributed to (i) the equilibrium not reverting back to ceramide from S1P by interfering with the ceramide/S1P pathway because ceramide showed evidence of being pro-fibrotic,<sup>47</sup> or (ii) an

increase in S1P is accompanied by a decrease in connective tissue growth factor (CTGF).<sup>47, 48</sup> An increase in CTGF has been shown to promote fibrosis.<sup>47</sup>

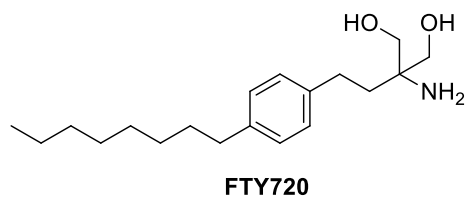
Another signaling agent that is pro-apoptotic is transforming growth factor-beta (TGF- $\beta$ ).<sup>17, 47, 48, 50</sup> TGF- $\beta$ , on one hand, activates SphK1 and increases intracellular S1P production via the SMAD pathway. On the other hand, TGF- $\beta$  activates S1P<sub>2/3</sub>, Rho/ROCK pathway, and SMAD pathway, increasing CTGF.<sup>47, 48</sup> However, when S1P is exported out of the cell, the only receptor that shows anti-fibrotic protective effects is S1P<sub>1</sub>, while S1P<sub>2</sub> and S1P<sub>3</sub> show pro-fibrotic effects.<sup>47, 49</sup> Therefore, an increase in extracellular S1P has been shown to have unfavorable pro-fibrotic effects (Fig. 1.12).<sup>47</sup>



**Figure 1.12** Demonstration of intracellular and extracellular effects of S1P.<sup>47</sup>

One drug that has been tested as a therapy for fibrosis is **FTY720** (Gilenya<sup>TM</sup>) (Fig. 1.13).<sup>5</sup> **FTY720** is a prodrug that is a substrate for SphK2. Phosphorylated **FTY720** binds to 4 of the S1P receptors, with the exception being S1P<sub>2</sub>. It is a receptor agonist but a functional antagonist as it

causes internalization of the receptor.<sup>5, 12, 24, 33, 47, 52</sup> It works as a therapeutic agent for fibrosis when it binds as an agonist to S1P<sub>3</sub>.<sup>5, 47</sup> More studies need to be conducted on SphK inhibitors to determine if they can control therapeutic effects for fibrosis from inside the cell by regulating amounts of S1P. So here a crossroad is met: an increase in intracellular S1P is therapeutic, but if the S1P transported out of the cell binds to receptors S1P<sub>2/3</sub>, then it is not therapeutic. The amount of S1P transported outside of the cell is unknown. Studies are currently underway in the Lynch group at the University of Virginia to understand whether SphK inhibition can have beneficial effects towards fibrosis.



**Figure 1.13** FTY720.

## 1.8 Thesis Overview

Chapter 1 introduced the sphingolipid family, their roles in cellular regulation, and ties to different diseases are described. A short review of various inhibitors and disease indications is included. Finally, fibrosis is evaluated in detail and how S1P plays a potential role in fibrosis therapy. In chapter 2, structure-activity relationship studies are revealed that lead to potent SphK2 inhibitors. Structure modifications include a variety of head and linker group modifications as well as late stage tail modifications on **SLR080811**. The synthetic work and biological evaluation of compounds are presented. *In vivo* studies with **SLP120701** reveal effects on S1P levels as well as pharmacokinetics. Chapter 3 discloses the tail region

modifications and structure-activity relationships based on **SLR080811**. Synthesis and biological data evaluation are also described. In Chapter 4, supplemental information for the characterization of chapters 2 and 3 are included. This information includes instrumentation, experimental procedures, and characterization. Spectra from NMR and LC-MS analysis are included.

## 1.9 References

1. Furuya, H.; Shimizu, Y.; Kawamori, T., Sphingolipids in cancer. *Cancer and Metastasis Rev.* **2011**, *30*, 567-576.
2. Kim, R. H.; Takabe, K.; Milstien, S.; Spiegel, S., Export and functions of sphingosine-1-phosphate. *Biochem. Biophys. Acta* **2009**, *1791*, 692-696.
3. Kihara, A.; Mitsutake, S.; Mizutani, Y.; Igarashi, Y., Metabolism and biological functions of two phosphorylated sphingolipids, sphingosine 1-phosphate and ceramide 1-phosphate. *Prog. Lipid. Res.* **2007**, *46*, 126-144.
4. Cuvillier, O.; Pirianov, G.; Kleuser, B.; Vanek, P. G.; Coso, O. A.; Gutkind, J. S.; Spiegel, S., Suppression of ceramide-mediated programmed cell death by sphingosine-1-phosphate. *Nature* **1996**, *381*, 800-803.
5. Takabe, K.; Paugh, S. W.; Milstien, S.; Spiegel, S., "Inside-Out" signaling of sphingosine-1-phosphate: Therapeutic targets. *Pharmacol. Rev.* **2008**, *60*, 181-195.
6. Sato, K.; Malchinkhuu, E.; Horiuchi, Y.; Mogi, C.; Tomura, H.; Tosaka, M.; Yoshimoto, Y.; Kuwabara, A.; Okajima, F., Critical role of ABCA1 transporter in sphingosine 1-phosphate release from astrocytes. *J. Neurochem.* **2007**, *103*, 2610-2619.

7. Takabe, K.; Kim, R. H.; Allegood, J. C.; Mitra, P.; Ramachandran, S.; Nagahashi, M.; Harikumar, K. B.; Hait, N. C.; Milstien, S.; Spiegel, S., Estradiol induces export of sphingosine 1-phosphate from breast cancer cells via ABCC1 and ABCG2. *J. Biol. Chem.* **2010**, *285*, 10477-10486.
8. Hisano, Y.; Kobayashi, N.; Yamaguchi, A.; Nishi, T., Mouse SPNS2 functions as a sphingosine-1-phosphate transporter in vascular endothelial cells. *Plos One* **2012**, *7*.
9. Cuvillier, O., Sphingosine in apoptosis signaling. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **2002**, *1585*, 153-162.
10. Pettus, B. J.; Chalfant, C. E.; Hannun, Y. A., Ceramide in apoptosis: an overview and current perspectives. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **2002**, *1585*, 114-125.
11. Pyne, N. J.; Pyne, S., Sphingosine 1-phosphate and cancer. *Nat. Rev. Cancer* **2010**, *10*, 489-503.
12. Pyne, S.; Pyne, N. J., Translational aspects of sphingosine 1-phosphate biology. *Trends Mol. Med.* **2011**, *17*, 463-472.
13. Rosen, H.; Gonzalez-Cabrera, P. J.; Sanna, M. G.; Brown, S., Sphingosine 1-phosphate receptor signaling. In *Annu. Rev. Biochem.*, Annual Reviews: Palo Alto, 2009; Vol. 78, pp 743-768.
14. Neubauer, H. A.; Pitson, S. M., Roles, regulation and inhibitors of sphingosine kinase 2. *FEBS J.* **2013**, *280*, 5317-5336.
15. Spiegel, S.; Milstien, S., Sphingosine 1-phosphate, a key cell signaling molecule. *J. Biol. Chem.* **2002**, *277*, 25851-25854.
16. Hannun, Y. A.; Obeid, L. M., Principles of bioactive lipid signalling: lessons from sphingolipids. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 139-150.

17. Takuwa, Y.; Ikeda, H.; Okamoto, Y.; Takuwa, N.; Yoshioka, K., Sphingosine-1-phosphate as a mediator involved in development of fibrotic diseases. *Biochem. Biophys. Acta* **2012**.
18. O'Brien, N.; Jones, S. T.; Williams, D. G.; Cunningham, H. B.; Moreno, K.; Visentin, B.; Gentile, A.; Vekich, J.; Shestowsky, W.; Hiraiwa, M.; Matteo, R.; Cavalli, A.; Grotjahn, D.; Grant, M.; Hansen, G.; Campbell, M.-A.; Sabbadini, R., Production and characterization of monoclonal anti-sphingosine-1-phosphate antibodies. *J. Lipid Res.* **2009**, *50*, 2245-2257.
19. Visentin, B.; Vekich, J. A.; Sibbald, B. J.; Cavalli, A. L.; Moreno, K. M.; Matteo, R. G.; Garland, W. A.; Lu, Y. L.; Yu, S. X.; Hall, H. S.; Kundra, V.; Mills, G. B.; Sabbadini, R. A., Validation of an anti-sphingosine-1-phosphate antibody as a potential therapeutic in reducing growth, invasion, and angiogenesis in multiple tumor lineages. *Cancer Cell* **2006**, *9*, 225-238.
20. Kawasaki, H.; Ozawa, K.; Yamamoto, K. Pyrazolopyridine compounds and use thereof as drugs. WO0198301, Dec 21, 2001.
21. Salomone, S.; Potts, E. M.; Tyndall, S.; Ip, P. C.; Chun, J.; Brinkmann, V.; Waeber, C., Analysis of sphingosine 1-phosphate receptors involved in constriction of isolated cerebral arteries with receptor null mice and pharmacological tools. *Br. J. Pharmacol.* **2008**, *153*, 140-147.
22. Davis, M. D.; Clemens, J. J.; Macdonald, T. L.; Lynch, K. R., Sphingosine 1-phosphate analogs as receptor antagonists. *J. Biol. Chem.* **2005**, *280*, 9833-9841.
23. Foss, F. W., Jr.; Snyder, A. H.; Davis, M. D.; Rouse, M.; Okusa, M. D.; Lynch, K. R.; Macdonald, T. L., Synthesis and biological evaluation of gamma-aminophosphonates as potent, subtype-selective sphingosine 1-phosphate receptor agonists and antagonists. *Bioorg. Med. Chem.* **2007**, *15*, 663-677.

24. Maceyka, M.; Harikumar, K. B.; Milstien, S.; Spiegel, S., Sphingosine-1-phosphate signaling and its role in disease. *Trends Cell Biol.* **2012**, *22*, 50-60.
25. Kennedy, A. J.; Mathews, T. P.; Kharel, Y.; Field, S. D.; Moyer, M. L.; East, J. E.; Houck, J. D.; Lynch, K. R.; Macdonald, T. L., Development of amidine-based sphingosine kinase 1 nanomolar inhibitors and reduction of sphingosine 1-phosphate in human leukemia cells. *J. Med. Chem.* **2011**, *54*, 3524-3548.
26. Hait, N. C.; Allegood, J.; Maceyka, M.; Strub, G. M.; Harikumar, K. B.; Singh, S. K.; Luo, C.; Marmorstein, R.; Kordula, T.; Milstien, S.; Spiegel, S., Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. *Science* **2009**, *325*, 1254-1257.
27. Xiao, M.; Liu, Y. G.; Zou, F., Sensitization of human colon cancer cells to sodium butyrate-induced apoptosis by modulation of sphingosine kinase 2 and protein kinase D. *Exp. Cell. Res.* **2012**, *318*, 43-52.
28. Edmonds, Y.; Milstien, S.; Spiegel, S., Development of small-molecule inhibitors of sphingosine-1-phosphate signaling. *Pharmacol. Ther.* **2011**, *132*, 352-360.
29. Kharel, Y.; Raje, M. R.; Gao, M.; Gellett, A. M.; Tomsig, J. L.; Lynch, K. R.; Santos, W. L., Sphingosine kinase type 2 inhibition elevates circulating sphingosine 1-phosphate. *Biochem. J.* **2012**, 149-157.
30. Venkataraman, K.; Thangada, S.; Michaud, J.; Oo, M. L.; Ai, Y.; Lee, Y.-M.; Wu, M.; Parikh, N. S.; Khan, F.; Proia, R. L.; Hla, T., Extracellular export of sphingosine kinase-1a contributes to the vascular S1P gradient. *Biochem. J.* **2006**, *397*, 461-471.
31. Liu, H.; Toman, R. E.; Goparaju, S. K.; Maceyka, M.; Nava, V. E.; Sankala, H.; Payne, S. G.; Bektas, M.; Ishii, I.; Chun, J.; Milstien, S.; Spiegel, S., Sphingosine kinase type 2 is a putative BH3-only protein that induces apoptosis. *J. Biol. Chem.* **2003**, *278*, 40330-40336.

32. Mizugishi, K.; Yamashita, T.; Olivera, A.; Miller, G. F.; Spiegel, S.; Proia, R. L., Essential role for sphingosine kinases in neural and vascular development. *Mol. Cell. Biol.* **2005**, *25*, 11113-11121.
33. Lim, K. G.; Sun, C.; Bittman, R.; Pyne, N. J.; Pyne, S., (R)-FTY720 methyl ether is a specific sphingosine kinase 2 inhibitor: Effect on sphingosine kinase 2 expression in HEK 293 cells and actin rearrangement and survival of MCF-7 breast cancer cells. *Cell Signal.* **2011**, *23*, 1590-1595.
34. Kim, J. W.; Kim, Y. W.; Inagaki, Y.; Hwang, Y. A.; Mitsutake, S.; Ryu, Y. W.; Lee, W. K.; Ha, H. J.; Park, C. S.; Igarashi, Y., Synthesis and evaluation of sphingoid analogs as inhibitors of sphingosine kinases. *Bioorg. Med. Chem.* **2005**, *13*, 3475-3485.
35. Xiang, Y.; Hirth, B.; Kane, J. L., Jr.; Liao, J.; Noson, K. D.; Yee, C.; Asmussen, G.; Fitzgerald, M.; Klaus, C.; Booker, M., Discovery of novel sphingosine kinase-1 inhibitors. Part 2. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4550-4554.
36. Schnute, M. E.; McReynolds, M. D.; Kasten, T.; Yates, M.; Jerome, G.; Rains, J. W.; Hall, T.; Chrencik, J.; Kraust, M.; Cronin, C. N.; Saabye, M.; Highkin, M. K.; Broadus, R.; Ogawa, S.; Cukyne, K.; Zawadzke, L. E.; Peterkin, V.; Iyanar, K.; Scholten, J. A.; Wendling, J.; Fujiwara, H.; Nemirovskiy, O.; Wittwer, A. J.; Nagiec, M. M., Modulation of cellular S1P levels with a novel, potent and specific inhibitor of sphingosine kinase-1. *Biochem. J.* **2012**, *444*, 79-88.
37. Zhang, Y.; Berka, V.; Song, A.; Sun, K.; Wang, W.; Zhang, W.; Ning, C.; Li, C.; Zhang, Q.; Bogdanov, M.; Alexander, D. C.; Milburn, M. V.; Ahmed, M. H.; Lin, H.; Idowu, M.; Zhang, J.; Kato, G. J.; Abdulmalik, O. Y.; Zhang, W.; Dowhan, W.; Kellems, R. E.; Zhang, P.; Jin,



- J.; Safo, M.; Tsai, A.-L.; Juneja, H. S.; Xia, Y., Elevated sphingosine-1-phosphate promotes sickling and sickle cell disease progression. *J. Clin. Invest.* **2014**, *124*, 2750-2761.
38. Wang, J.; Knapp, S.; Pyne, N. J.; Pyne, S.; Elkins, J. M., Crystal structure of sphingosine kinase 1 with PF-543. *ACS Med. Chem. Lett.* **2014**, *5*, 1329-1333.
39. French, K. J.; Schrecengost, R. S.; Lee, B. D.; Zhuang, Y.; Smith, S. N.; Eberly, J. L.; Yun, J. K.; Smith, C. D., Discovery and evaluation of inhibitors of human sphingosine kinase. *Cancer Res.* **2003**, *63*, 5962-5969.
40. Antoon, J. W.; Meacham, W. D.; Bratton, M. R.; Slaughter, E. M.; Rhodes, L. V.; Ashe, H. B.; Wiese, T. E.; Burow, M. E.; Beckman, B. S., Pharmacological inhibition of sphingosine kinase isoforms alters estrogen receptor signaling in human breast cancer. *J. Mol. Endocrinol.* **2011**, *46*, 205-216.
41. Wang, Z.; Min, X.; Xiao, S.-H.; Johnstone, S.; Romanow, W.; Meininger, D.; Xu, H.; Liu, J.; Dai, J.; An, S.; Thibault, S.; Walker, N., Molecular basis of sphingosine kinase 1 substrate recognition and catalysis. *Structure* **2013**, *21*, 798-809.
42. Gustin, D. J.; Li, Y.; Brown, M. L.; Min, X.; Schmitt, M. J.; Wanska, M.; Wang, X.; Connors, R.; Johnstone, S.; Cardozo, M.; Cheng, A. C.; Jeffries, S.; Franks, B.; Li, S.; Shen, S.; Wong, M.; Wesche, H.; Xu, G.; Carlson, T. J.; Plant, M.; Morgenstern, K.; Rex, K.; Schmitt, J.; Coxon, A.; Walker, N.; Kayser, F.; Wang, Z., Structure guided design of a series of sphingosine kinase (SphK) inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4608-4616.
43. French, K. J.; Zhuang, Y.; Maines, L. W.; Gao, P.; Wang, W.; Beljanski, V.; Upson, J. J.; Green, C. L.; Keller, S. N.; Smith, C. D., Pharmacology and antitumor activity of ABC294640, a selective inhibitor of sphingosine kinase-2. *J. Pharmacol. Exp. Ther.* **2010**, *333*, 129-139.

44. Liu, K.; Guo, T. L.; Hait, N. C.; Allegood, J.; Parikh, H. I.; Xu, W.; Kellogg, G. E.; Grant, S.; Spiegel, S.; Zhang, S., Biological characterization of 3-(2-amino-ethyl)-5-(3-(4-butoxyphenyl)-propylidene)-thiazolidine-2,4-dione (K145) as a selective sphingosine kinase-2 inhibitor and anticancer agent. *Plos One* **2013**, *8*.
45. Raje, M. R.; Knott, K.; Kharel, Y.; Bissel, P.; Lynch, K. R.; Santos, W. L., Design, synthesis and biological activity of sphingosine kinase 2 selective inhibitors. *Bioorg. Med. Chem.* **2012**, *20*, 183-194.
46. Patwardhan, N. N.; Morris, E. A.; Raje, M. R.; Gao, M.; Kharel, Y.; Tomsig, J. L.; Lynch, K. R.; Santos, W. L., Structure-activity relationship studies and in vivo activity of guanidine-based sphingosine kinase inhibitors: Discovery of SphK 1 and 2 selective inhibitors. *J. Med. Chem.* **2015**, *58*, 1879-1899.
47. Schwalm, S.; Pfeilschifter, J.; Huwiler, A., Sphingosine-1-phosphate: A Janus-faced mediator of fibrotic diseases. *Biochem. Biophys. Acta* **2012**, *1831*, 239-250.
48. Pyne, N. J.; Dubois, G.; Pyne, S., Role of sphingosine 1-phosphate and lysophosphatidic acid in fibrosis. *Biochem. Biophys. Acta* **2012**.
49. Shea, B.; Tager, A., Sphingolipid regulation of tissue fibrosis. *Open Rheumatol. J.* **2012**, *6*, 123-129.
50. Wynn, T. A., Cellular and molecular mechanisms of fibrosis. *J. Pathol.* **2008**, *214*, 199-210.
51. Mathews, T. P.; Kennedy, A. J.; Kharel, Y.; Kennedy, P. C.; Nicoara, O.; Sunkara, M.; Morris, A. J.; Wamhoff, B. R.; Lynch, K. R.; Macdonald, T. L., Discovery, biological evaluation, and structure-activity relationship of amidine based sphingosine kinase inhibitors. *J. Med. Chem.* **2010**, *53*, 2766-2778.

52. Lynch, K. R.; Macdonald, T. L., Sphingosine 1-phosphate chemical biology. *Biochem. Biophys. Acta* **2008**, *1781*, 508-512.

## **Chapter 2. Structure-Activity Relationship studies and *In Vivo* Activity of Guanidine-based Sphingosine Kinase Inhibitors: Discovery of SphK 1 and SphK 2 Selective Inhibitors**

### **2.1 Contributions**

The work in this chapter was done by several members in the Santos group. Synthesis of inhibitors was performed by the author, Dr. Neeraj Patwardhan, Dr. Mithun Raje, and Dr. Ming Gao. Biological analysis was done by Dr. Yugesh Kharel and Dr. Kevin Lynch of the Pharmacology department of the University of Virginia. The final manuscript was written by Dr. Neeraj Patwardhan and Dr. Webster Santos. The author contributed to the majority of the inhibitor synthesis, experimental write up, and revision of the manuscript. Reprinted (adapted) with permission from *Journal of Medicinal Chemistry* [Patwardhan, N. N.\*; Morris, E.A.\*; Raje, M.R.; Gao, M.; Kharel, Y.; Tomsig, J.L.; Lynch, K.R.; Santos, W.L., Structure-activity relationship studies and in vivo activity of guanidine-based sphingosine kinase inhibitors: Discovery of SphK 1 and 2 selective inhibitors. *J. Med. Chem.* **2015**, 58, 1879-1899. Copyright © 2015 American Chemical Society]

## 2.2 Abstract

Sphingosine 1-phosphate (S1P) is a pleiotropic signaling molecule that acts as a ligand for five G-protein coupled receptors (S1P<sub>1-5</sub>), whose downstream effects are implicated in a variety of important pathologies including sickle cell disease, cancer, inflammation, and fibrosis. The synthesis of S1P is catalyzed by sphingosine kinase (SphK) isoforms 1 and 2; hence, inhibitors of this phosphorylation step are pivotal in understanding the physiological functions of SphKs. To date, SphK1 and 2 inhibitors with the potency, selectivity, and *in vivo* stability necessary to determine the potential of these kinases as therapeutic targets are lacking. Herein, we report the design, synthesis, and structure-activity relationship studies of guanidine-based SphK inhibitors bearing an oxadiazole ring in the scaffold. Our studies demonstrate that **SLP120701**, a SphK2 selective inhibitor ( $K_i = 1 \mu\text{M}$ ), decreases S1P levels in histiocytic lymphoma (U937) cells. Surprisingly, homologation with a single methylene unit between the oxadiazole and heterocyclic ring afforded a SphK1 selective inhibitor in **SLP7111228** ( $K_i = 48 \text{ nM}$ ), which also decreased S1P levels in cultured U937 cells. *In vivo* application of both compounds, however, resulted in contrasting effect in circulating levels of S1P. Administration of **SLP7111228** depressed blood S1P levels while **SLP120701** increased levels of S1P. Taken together, these compounds provide an *in vivo* chemical toolkit to interrogate the effect of increasing or decreasing S1P levels, and whether such a maneuver can have implications in disease states.

## 2.3 Introduction

The lysophospholipid sphingosine 1-phosphate (S1P) is a pleiotropic signaling molecule that regulates growth, survival, and migration of many cell types. S1P acts as an extracellular mediator by binding to five G-protein coupled receptors (S1P<sub>1-5</sub>), leading to diverse physiological and pathophysiological processes.<sup>1</sup> Biosynthesis of S1P is realized only by phosphorylation of sphingosine, which is generated by the catabolism of more complex sphingolipids such as sphingomyelin and ceramide or taken up by cells from their environment. The enzyme responsible for this phosphoryl transfer exists as two isoforms encoded by unlinked genes: sphingosine kinase 1 (SphK1) and 2 (SphK2). SphKs have been implicated in a variety of disease states including sickle cell disease,<sup>2</sup> cancer,<sup>1,3</sup> atherosclerosis,<sup>4</sup> and asthma,<sup>5</sup> among others. SphK1's role in cancer is widely studied, where correlations between expression and severity of disease, drug resistance and/or reduced patient survival have been reported.<sup>3,6</sup> However, pharmacological intervention to lessen SphK1 activity and control the 'SphK rheostat'—i.e., changing the equilibrium of S1P/Sph ratio—failed to demonstrate statistically significant effects on cell viability, suggesting that S1P's role in oncology or other diseases is complex.<sup>7</sup> Interestingly, the S1P generated by each SphK isoenzyme has been reported to result in opposing biological effects, implying conflicting roles by these enzymes. For example, SphK1 overexpression increases cell survival and proliferation<sup>8</sup> whereas SphK2 overexpression induces cell cycle arrest and apoptosis.<sup>9,10</sup> The latter effect can be explained through the interaction of Bcl-X<sub>L</sub> with the BH<sub>3</sub> domain within SphK2.<sup>11</sup> In addition, there is also a difference in their subcellular localization: SphK1 is mostly in the cytoplasm and migrates to the plasma membrane upon phosphorylation<sup>12,13</sup> while SphK2 can localize in the nucleus to inhibit DNA synthesis and regulate HDAC1/2 activity.<sup>14,15</sup> Gene deletion studies in mice indicate that there is some functional redundancy between the two enzymes as Sphk1<sup>-/-</sup> and Sphk2<sup>-/-</sup> mice

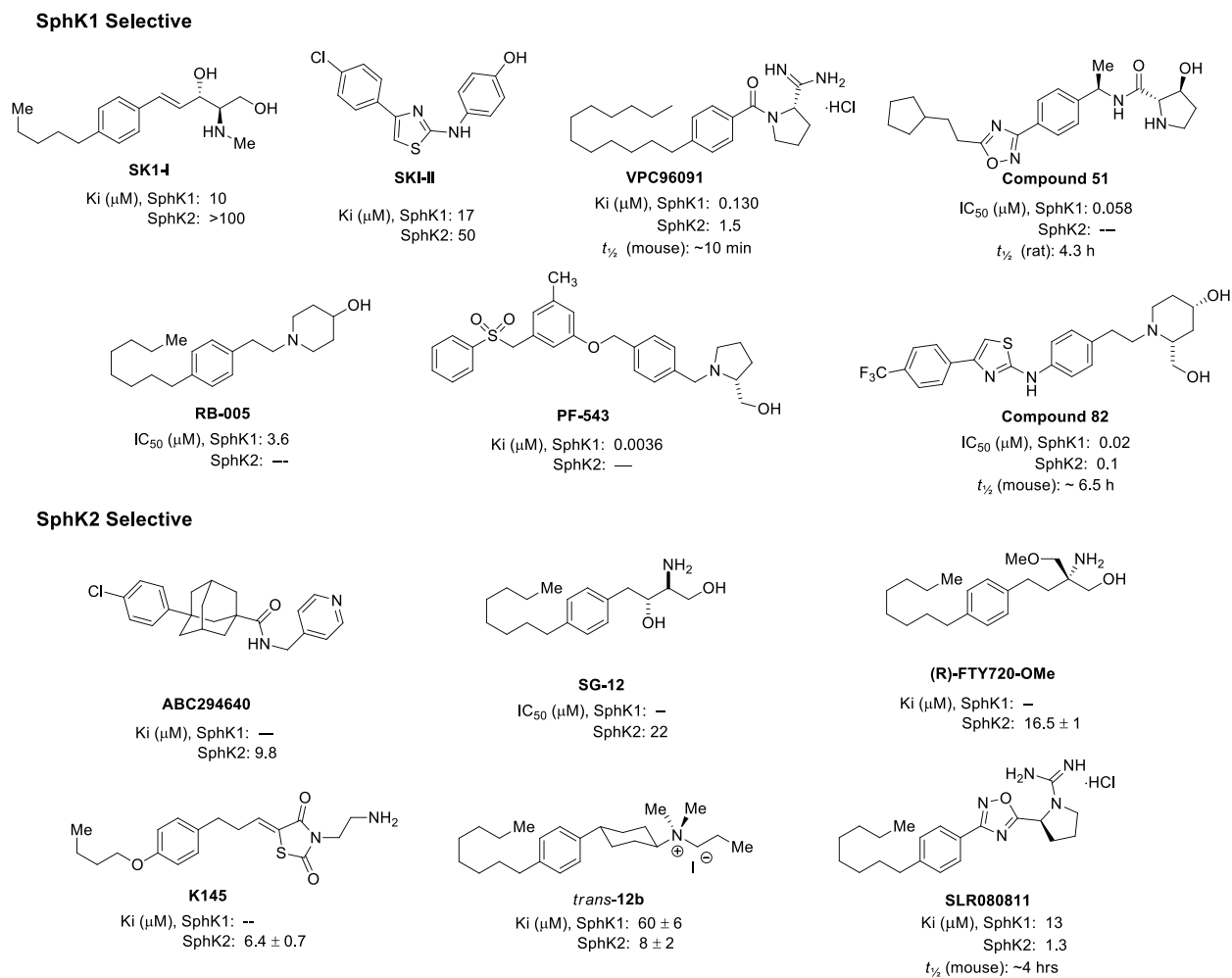
are viable, fertile, and phenotypically unremarkable.<sup>16,17</sup> However, germ line inactivation of all 4 SphK alleles is embryonically lethal (day E12.5-13.5) as a result of impaired neurological and vascular development.<sup>18</sup> The circulating level of S1P in SphK1-null mice is reduced by about 2-fold while, curiously, SphK2-null mice have more than double wild type S1P levels in blood and plasma.<sup>18-21</sup>

Because of the potential role of S1P in a variety of diseases, pharmacological inhibition of SphKs with small molecules has been a subject of interest both in academia and pharmaceutical industry. Figure 2.1 illustrates the structures of reported SphK inhibitors.<sup>22</sup> SphK1, for which selective inhibitors have been developed, has been the focus of most studies. Because early inhibitors used to interrogate the function of SphK1 had  $K_i$ 's in the mid micromolar range (e.g. **SKI-I**, **SKI-II**, **dimethylsphingosine**), some of the biological effects attributed to SphK1 activity may be due to off-target interactions. Indeed, these compounds are best described as molecules that include in their properties 'inhibition of SphK1' rather than the commonly used 'SphK1 inhibitors'. The discovery of selective, nanomolar inhibitors such as **PF-543**, **VPC96091**, and compound **51** will be useful chemical tools to better understand SphK1 function, although some of these have limited *in vivo* stability<sup>23, 24</sup> or their effect on S1P levels *in vivo* have not been documented.<sup>25</sup> The potent, dual SphK1/2 inhibitor, **82**, was recently described to decrease S1P concentration when administered in mice.<sup>7, 26</sup> In contrast to SphK1, there is a paucity of SphK2 selective inhibitors;<sup>27</sup> indeed with SphK2, we have found it challenging to duplicate the selectivity and potency readily achieved with SphK1 inhibitors. **ABC294640**<sup>28</sup> ( $K_i$  10  $\mu$ M) was the first compound with SphK2 inhibitor properties reported and it has been deployed in a variety of disease models where it has been reported to have remarkable efficacy. These models include ulcerative colitis,<sup>29</sup> Crohns disease,<sup>30</sup> ischemia/reperfusion injury,<sup>31</sup> osteoarthritis,<sup>32</sup> and colon cancer.<sup>33</sup>

However, **ABC294640** has at least one reported additional mode of action which is binding to the oestrogen receptor and acting as a partial agonist similar to tamoxifen.<sup>34</sup> Hence, attributing **ABC294640** effects to SphK2 is difficult. Other inhibitors such as **SG-12**,<sup>35</sup> **(R)-FTY720-OMe**,<sup>36</sup> **K145**,<sup>37</sup> and *trans*-**12b**<sup>38</sup> are reported as SphK2 inhibitors, albeit with moderate potency and selectivity. Hence, new scaffolds with the potency and selectivity are needed to investigate SphK1 and 2 functions *in vivo*.<sup>39</sup>

Recently, we reported a novel guanidine-based compound, **SLR080811**, as a selective SphK2 inhibitor.<sup>40</sup> It was the most potent and selective inhibitor of SphK2 at that time with *in vitro* activity on U937 cells and *in vivo* activity in mice. In continuation of our investigations in understanding SphKs, we herein describe the design, synthesis, and structure-activity relationship studies of guanidine-based SphK inhibitors. Our studies reveal SphK1 and SphK2 inhibitors based on the same scaffold, but with the distinction of a key methylene unit that induces a switch in isoform selectivity. These inhibitors are the most potent and selective inhibitors reported with *in vitro* and *in vivo* effects of altering cellular and blood S1P levels.





**Figure 2.1.** Structures, inhibitory activity, and half-lives of SphK inhibitors.

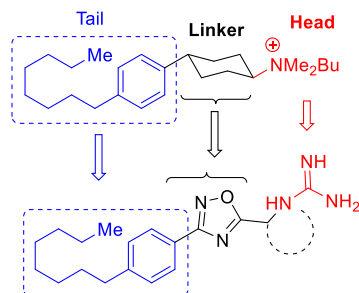
## 2.4 Results and Discussion

### 2.4.1 Design of inhibitors

Previous reports detailed our efforts to develop SphK2-selective inhibitors that led to the identification of quaternary ammonium salts that were fairly potent and moderately selective.<sup>38, 41</sup> Compound *trans*-**12b** was shown to be ~8-fold selective towards SphK2 with a  $K_i$  of 8  $\mu\text{M}$  (Figure 2.1). The inhibition data validated our hypothesis that a positive charge is essential for electrostatic

interaction, perhaps with the catalytic Asp residues present in the SphKs binding pocket, which has been shown to be important for recognition of Sph by the enzyme.<sup>42</sup> Furthermore, recent high resolution structure studies of SphK1 indicated involvement of the catalytic Asp81 residue in the activation of the primary hydroxyl of sphingosine.<sup>43</sup> We thus concluded that a polar, and preferably charged, species was most likely to exhibit the desired inhibition activity towards these enzymes.

To define the structure-activity relationships of SphK inhibitors, the structure of *trans*-**12b** was divided into three regions: the quaternary ammonium group as the head, the cyclohexyl ring as the linker, and the 4-octylphenyl group as the tail (Figure 2.2). In this chapter, we highlight the development of second generation SphK inhibitors with a focus on both the linker and head group region, which features an oxadiazole and a guanidine functional group, respectively. The guanidine group as the warhead is attractive because it is charged under physiological conditions and possesses the ability for electrostatic interaction with the active site Asp residue, an interaction akin to that of the quaternary amine group in *trans*-**12b**. We were further encouraged with this strategy because compounds with carboximidamide functionalities (amidines) are present in SphK1 inhibitors.<sup>24, 44</sup> Furthermore, we replaced the flexible cyclohexyl ring with a rigid heteroaromatic 1,2,4-oxadiazole linker to minimize the entropic cost of binding and introduce the potential for hydrogen bonding. The 4-octylphenyl tail was kept constant as previously defined by a prior chain length study.<sup>41</sup>

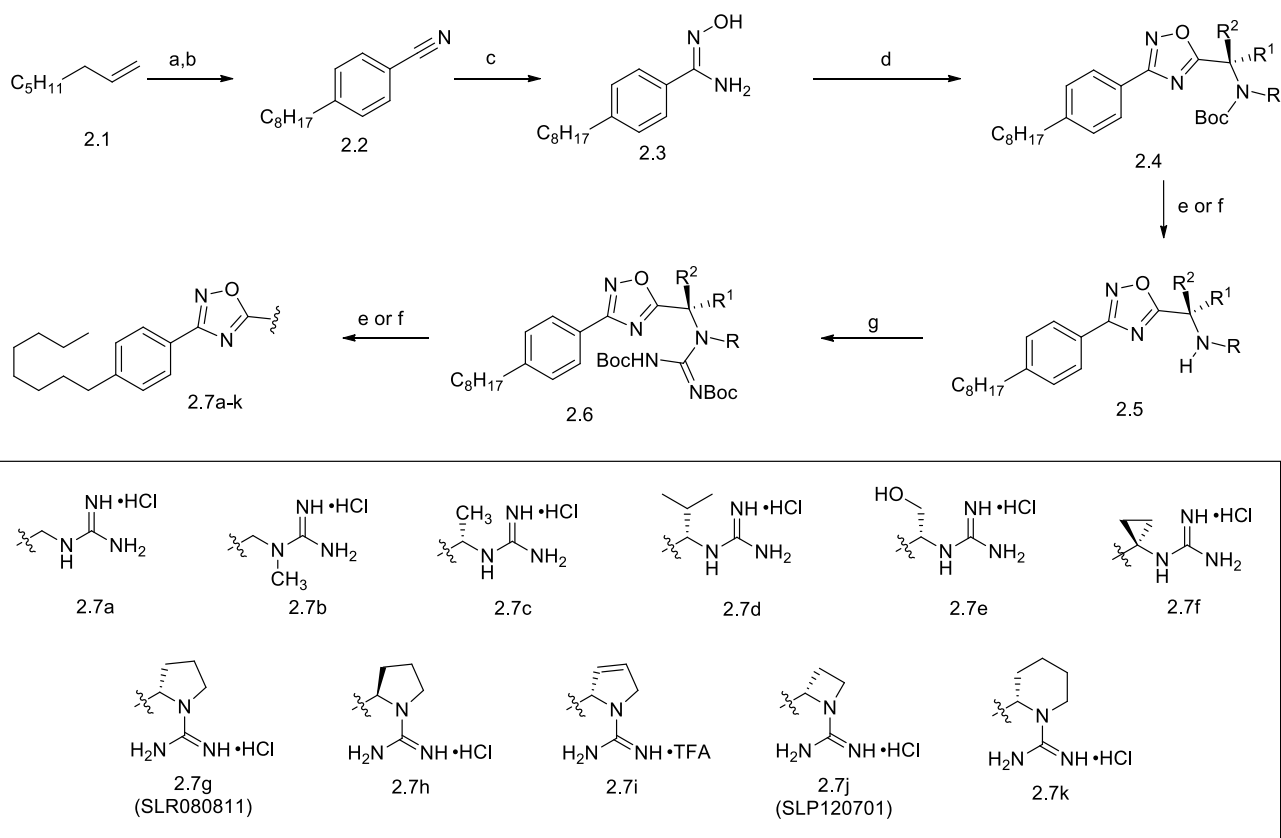


**Figure 2.2.** Scaffold modifications toward second generation SphK2 inhibitors.

### 2.4.2 Chemical Synthesis

The synthesis of guanidine derivatives is shown in Scheme 2.1. 4-Octyl benzonitrile **2.2** was synthesized via hydroboration of 1-octene (**2.1**) with 9-borabicyclo [3.3.1] nonane (9-BBN) followed by a Suzuki-Miyaura cross-coupling reaction of 4-iodobenzonitrile. Treatment of benzonitrile **2.2** with hydroxylamine hydrochloride and triethylamine in refluxing ethanol afforded the common intermediate amidoxime **2.3** in excellent yield. Subsequent coupling with the desired amino acid using HCTU followed by dehydration at 80 °C yielded 1,2,4-oxadiazole **2.4**. Removal of the Boc group was accomplished with trifluoroacetic acid or by bubbling HCl gas, which produced the desired amine **2.5** was then converted to bis-Boc protected guanidine **2.6** over a period of three days using with N, N'-di-Boc-1H-pyrazole-1-carboxamide and Hunig's base. Standard deprotection conditions afforded compounds **2.7a-k**.

**Scheme 2.1.** Synthesis of Analogues **2.7a-k**.

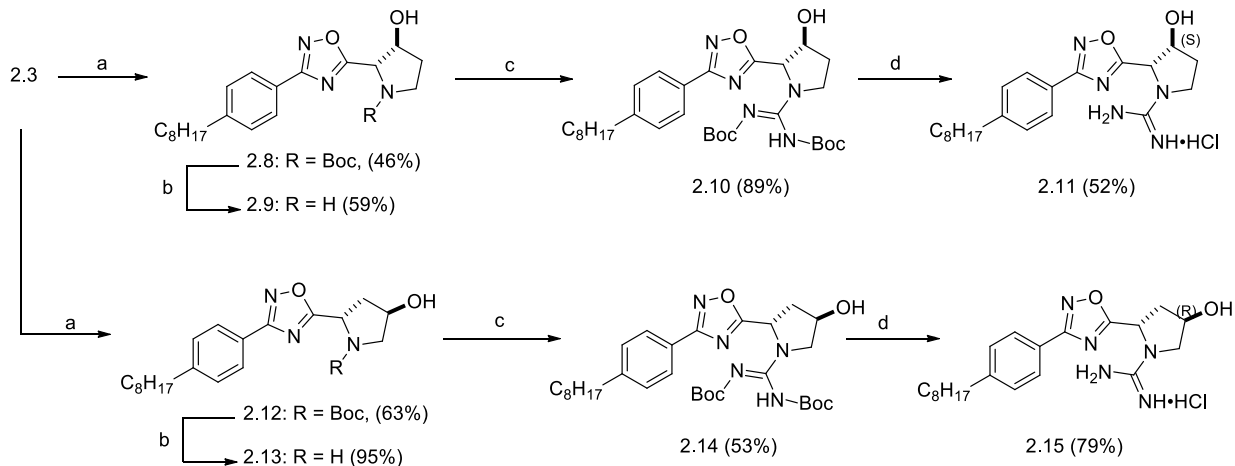


Reagents and conditions; (a) 9-BBN, THF, rt, 18h; (b) 4-iodobenzonitrile, Cs<sub>2</sub>CO<sub>3</sub>, Pd(dppf)Cl<sub>2</sub>, DMF, 80 °C, 18h, 62%; (c) HONH<sub>2</sub>•HCl, Et<sub>3</sub>N, EtOH, reflux, 2h, 92%; (d) Boc-protected amino acid, DIEA, HCTU•PF<sub>6</sub>, DMF, 80 °C, 18h, 20-82%; (e) HCl, MeOH, 5 min, 59-100%; (f) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-12h, 59-100%; (g) N,N'-di-Boc-1H-pyrazole-1-carboxamidine, DIEA, CH<sub>3</sub>CN, rt, 3-6 days, 18-81%.

To mimic the hydroxyl moieties in sphingosine, hydroxyl groups were installed on the pyrrolidine ring as presented in Scheme 2.2. Following the standard synthetic sequence of coupling-guanidylation-deprotection, (*S*)-3-hydroxy- and (*R*)-4-hydroxy derivatives **2.11** and **2.15**, respectively, were synthesized. Further, we reversed the stereochemistry of the hydroxyl

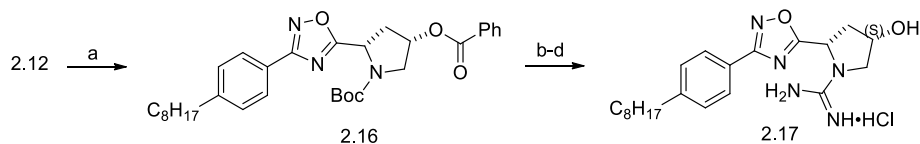
group on the 4-position of the pyrrolidine ring (Scheme 2.3). Inversion was accomplished under Mitsunobu conditions using benzoic acid as the nucleophile to provide compound **2.16**. Subsequent saponification afforded the corresponding alcohol, which was converted to product **2.17**. Inversion of the hydroxyl group on the 3-position was attempted but not successful (Scheme 2.4). First, a Mitsunobu reaction was performed on **2.8**, however only starting material was isolated. Next, inversion of the hydroxyl group in the 3-position was attempted on (2*S*, 3*S*)-2-benzyl 1-*tert*-butyl 3-hydroxypyrrolidine-1,2-dicarboxylate **2.20**. One inversion was accomplished with benzoic acid to afford **2.21** and the other was accomplished with DAST to generate **2.22**, which was followed by removal of the benzyl protecting group. Unfortunately, the Mitsunobu reactions attempted with smaller nucleophiles, such as acetic acid and water, provided no product. Once **2.21** and **2.22** were at hand, formation of the oxadiazole was attempted. Possibly, because of steric interactions with the hydroxyl group being on the same face as the carboxylic acid, cyclization of the oxadiazole ring did not occur; no desired product was isolated. To conclude the modifications of the head group, derivatives possessing the nitrogen in different positions of four (**2.26a**) or five (**2.26b**) membered ring heterocycles were synthesized as shown in Scheme 2.5.

**Scheme 2.2.** Synthesis of derivatives **2.11** and **2.15**.



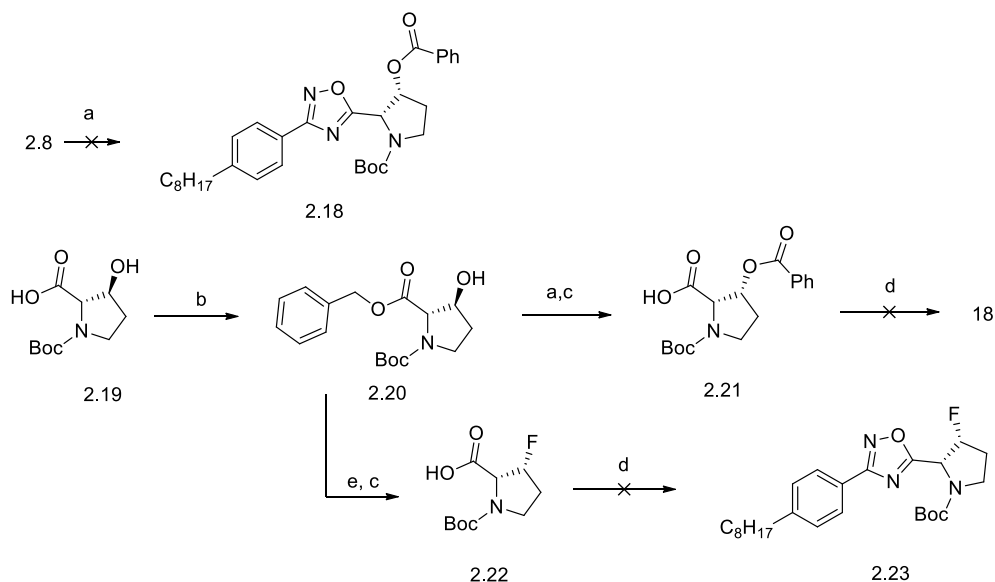
Reagents and conditions: (a) Boc-amino acid, DIEA, HCTU•PF<sub>6</sub>, DMF, 80 °C, 18h; (b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-12h; (c) N,N'-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, rt, 3 days; (d) HCl, MeOH.

**Scheme 2.3.** Synthesis of **2.17**.



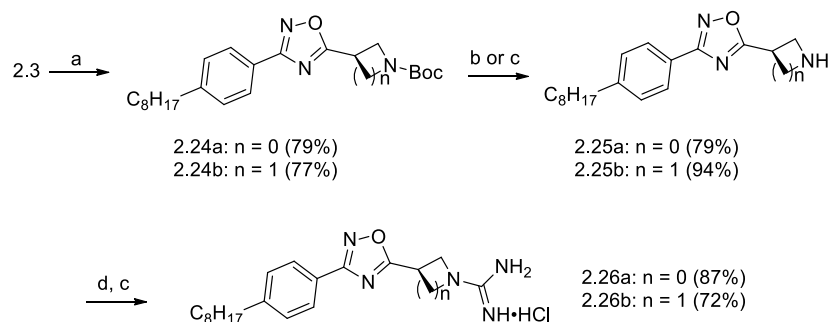
Reagents and conditions: (a) PPh<sub>3</sub>, DIAD, PhCOOH, THF, 0 °C, rt, 18h, 75%; (b) 2N NaOH, H<sub>2</sub>O: THF (1:1), rt, 18h, 95%; (c) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-12h, 45%; (d) N,N'-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, rt, 3 days, 79%; (e) HCl, MeOH, 22%.

**Scheme 2.4.** Inversion of the hydroxyl group on the 3-position.



Reagents and conditions: (a)  $\text{PPh}_3$ , DIAD,  $\text{PhCOOH}$ , THF, 0 °C, rt, 18h; (b)  $\text{Cs}_2\text{CO}_3$ , MeOH, 0 °C, 1h, then benzyl bromide, DMF, rt, 20h, 51%; (c)  $\text{H}_2$ , Pd/C, EtOH, rt, 18h, 38-66%; (d) Boc-amino acid, DIEA,  $\text{HCTU}\cdot\text{PF}_6$ , DMF, 80 °C, 18h; (e) DAST, dry DCM, -78 °C, rt, 5h, 69%.

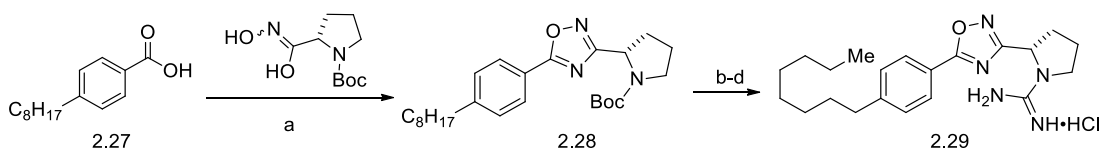
**Scheme 2.5.** Synthesis of **2.26a-b**.



Reagents and conditions: (a) Amino acid, DIEA,  $\text{HCTU}\cdot\text{PF}_6$ , DMF, 80 °C, 18h; (b) TFA,  $\text{CH}_2\text{Cl}_2$ , 3-12h; (c) HCl, MeOH; (d)  $N,N'$ -di-Boc-1H-pyrazole-1-carboxamide, DIEA,  $\text{CH}_3\text{CN}$ , rt, 3 days.

Next, constitutional isomers of the oxadiazole moiety were synthesized. As illustrated in Scheme 2.6, 1,2,4-oxadiazole **2.29**, wherein the position of the 4-octylphenyl and pyrrolidine rings are reversed, was generated by coupling of 4-octylbenzoic acid with the amidoxime of Boc-proline to afford compound **2.28**, which was subsequently deprotected and guanydilated to yield product **2.29**. The alternative structure, 1,3,4-oxadiazole **2.32**, was synthesized as depicted in Scheme 2.7. Key intermediate tetrazole **2.30** was produced by reacting benzonitrile **3** with  $\text{NaN}_3$  at reflux temperature.<sup>45</sup> Under DCC coupling conditions at elevated temperature, compound **2.31** was isolated and converted to guanidine **2.32** using standard procedures. It is worth noting that when Boc deprotection was tried with HCl gas, no desired product was isolated due to degradation. Slow addition of the TFA to deprotect the Boc group provided the desired product with no degradation observed. Finally, synthesis of a derivative **2.35** was attempted in which a methylene unit was installed between the phenyl and oxadiazole linker (Scheme 2.8). After accomplishing the Suzuki coupling to yield **2.33** and transformation of the nitrile to the amidoxime **2.34**, cyclization to form the 1,2,4-oxadiazole was attempted. Unfortunately, the desired product was not isolated and the derivative was no longer pursued.

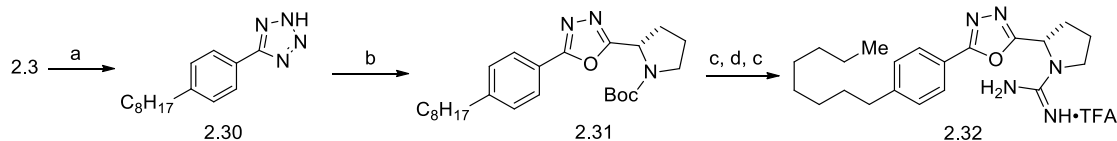
**Scheme 2.6.** Synthesis of reverse 1,2,4-oxadiazole **2.29**.



Reagents and conditions: (a) DIEA, HCTU•PF<sub>6</sub>, DMF, 80 °C, 18h, 19%; (b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-12h, 89%; (c) N,N'-di-Boc-1H-pyrazole-1-carboxamidine, DIEA, CH<sub>3</sub>CN, rt, 3 days, 19%; (d) HCl, MeOH, 28%.

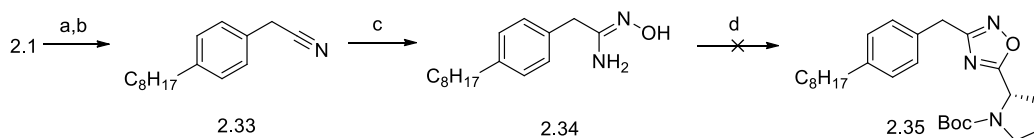


**Scheme 2.7.** Synthesis of 1,3,4-oxadiazole **2.32**.



Reagents and conditions: (a) NaN<sub>3</sub>, NH<sub>4</sub>Cl, DMF, reflux, 4h, quant; (b) Boc-Proline, DCC, toluene, 110 °C, 4h, 67%; (c) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-12h, quant; (d) N,N'-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, rt, 3 days.

**Scheme 2.8.** Attempted synthesis of **2.35**.

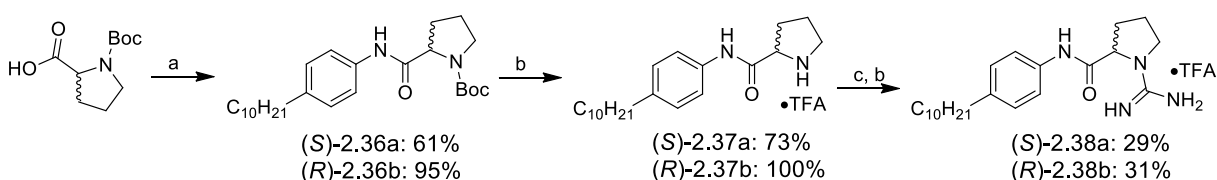


Reagents and conditions; (a) 9-BBN, THF, rt, 18h; (b) 2-(4-iodophenyl)acetonitrile, Cs<sub>2</sub>CO<sub>3</sub>, Pd(dppf)Cl<sub>2</sub>, DMF, 80 °C, 18h, 24%; (c) HONH<sub>2</sub>·HCl, Et<sub>3</sub>N, EtOH, reflux, 2h, 16%; (d) Boc-protected amino acid, DIEA, HCTU·PF<sub>6</sub>, DMF, 80 °C, 18h.

To determine whether the oxadiazole linker is required for our structure, we synthesized compounds **2.38-2.42**. First, we started with the synthesis of amide linkers. Activation of Boc-proline with ethylchloroformate followed by addition of 4-decylaniline afforded **2.36a-b** as single enantiomers (Scheme 2.9). Deprotection, guanidylation, and deprotection yielded guanidines **2.38a-b**. A homologated derivative was achieved by the reduction of benzonitrile **2.2**, which after subsequent reactions afforded compound **2.40** (Scheme 2.10). Further, a reversed amide analog was synthesized using amide coupling chemistry with 4-ocylbenzoic acid **2.27**, and following standard protocols yielded guanidine **2.42** (Scheme 2.11). Next, synthesis was

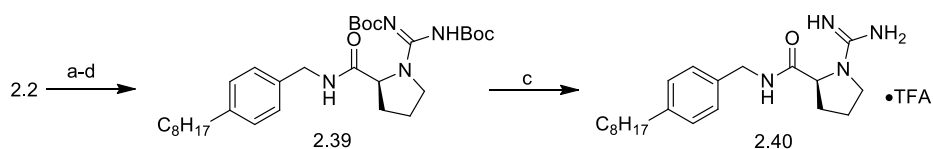
attempted to make a fused ring derivative, with phthalimide as the linker. As can be seen in Scheme 2.12, many attempts were tried to add on the octyl tail, to no avail. Table 2.1 details the conditions tried. Furthermore, we inserted carbon spacers between the oxadiazole and pyrrolidine rings. Employing Boc-homoproline and a further homologated derivative afforded compounds **2.48a-b** as shown in Scheme 2.13.

**Scheme 2.9.** Synthesis of amide analogs **2.38a-b**.



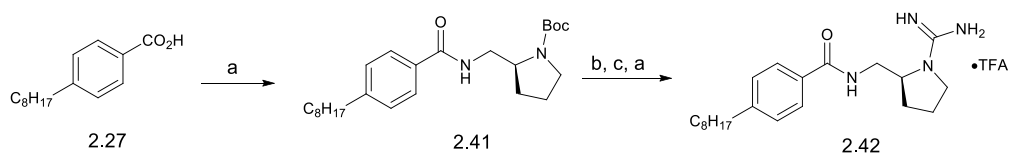
Reagents and conditions: (a) Ethylchloroformate, Et<sub>3</sub>N, 0 °C, 30 min, then 4-decylaniline, 0 °C; (b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-12h; (c) N,N'-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, rt, 3 days.

**Scheme 2.10.** Synthesis of amide analog **2.40**.



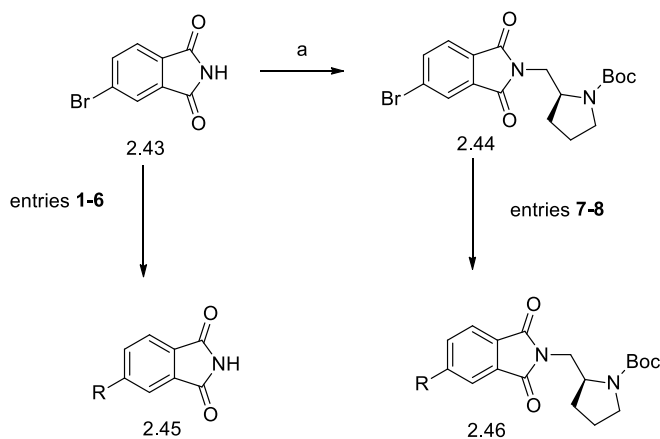
Reagents and conditions: (a) Lithium aluminum hydride, 0 °C to rt, 1h; (b) Ethylchloroformate, Et<sub>3</sub>N, Boc-*L*-Proline, 0 °C to reflux; (c) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-12h, quant.; (d) N,N'-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, rt, 3 days, 28% over 4 steps.

**Scheme 2.11.** Synthesis of amide analog **2.42**.



Reagents and conditions: (a) EDC, Et<sub>3</sub>N, NHS, CH<sub>2</sub>Cl<sub>2</sub>, rt then *tert*-butyl (*S*)-2-(aminomethyl)pyrrolidine-1-carboxylate, 85%; (b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-12h, quant; c) *N,N'*-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, rt, 3 days, 47%.

**Scheme 2.12.** Attempted synthesis of phthalimide derivative **2.46**.

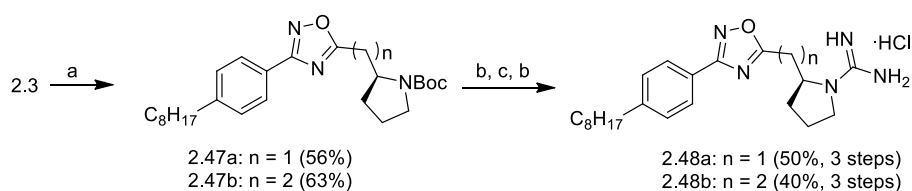


Reagents and conditions: (a) (*S*)-*tert*-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate, DIAD, PPh<sub>3</sub>, THF, 0 °C, rt, 12h, 22%.

**Table 2.1.** Conditions tested for formation of **2.45** and **2.46**.

Entry	Reaction <sup>a</sup>	Catalyst	Yield <sup>b</sup>	R
<b>1</b>	Sonogashira	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	<1%	C <sub>8</sub> H <sub>15</sub>
<b>2<sup>c</sup></b>	Sonogashira	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	<1%	C <sub>8</sub> H <sub>15</sub>
<b>3</b>	Suzuki	Pd(dppf)Cl <sub>2</sub>	10% crude	C <sub>8</sub> H <sub>17</sub>
<b>4</b>	Suzuki	Tetrakis	5%	C <sub>8</sub> H <sub>17</sub>
<b>5</b>	Sonogashira	Tetrakis	3%	C <sub>8</sub> H <sub>15</sub>
<b>6<sup>d</sup></b>	Suzuki	Pd(dppf)Cl <sub>2</sub>	<1%	C <sub>8</sub> H <sub>17</sub>
<b>7</b>	Sonogashira	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	NR	C <sub>8</sub> H <sub>15</sub>
<b>8</b>	Suzuki	Pd(dppf)Cl <sub>2</sub>	10% crude	C <sub>8</sub> H <sub>17</sub>

<sup>a</sup> Sonogashira conditions: Pd catalyst, Et<sub>3</sub>N, 1-octyne, CuI, DMF, 80 °C, 18h; Suzuki conditions: 1) 1-octene, THF, 9-BBN, rt, 18h; 2) 5-bromoisindoline-1,3-dione, Cs<sub>2</sub>CO<sub>3</sub>, Pd catalyst, DMF, 60 °C, 18h. <sup>b</sup> Isolated yield. <sup>c</sup> Replaced CuI with CuBr. <sup>d</sup> Only used DMF and heated to 100 °C.

**Scheme 2.13.** Synthesis of homologated compounds **2.48a-b**.

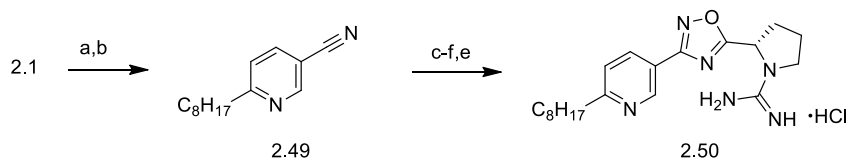
Reagents and conditions: (a) DIEA, HCTU·PF<sub>6</sub>, DMF, 80 °C, 18h; (b) HCl, MeOH; (c) N,N'-di-Boc-1H-pyrazole-1-carboxamidine, DIEA, CH<sub>3</sub>CN, rt, 3 days.

Next, a few derivatives of **SLR080811** were synthesized to probe hydrogen bond donors and acceptors in the vicinity of the phenyl ring. First, following general procedure, the phenyl ring was exchanged for a pyridine ring to provide compound **2.50** (Scheme 2.14). Next, we explored the amide bond being in the tail region rather than the linker region to evaluate its effects (Scheme 2.15). Synthesis began with amide coupling of the benzoic acid and the desired amine, assisted

by EDC and NHS, to give compounds **2.52a-d**. Next, general procedures were followed to afford compounds **2.55a-d**.

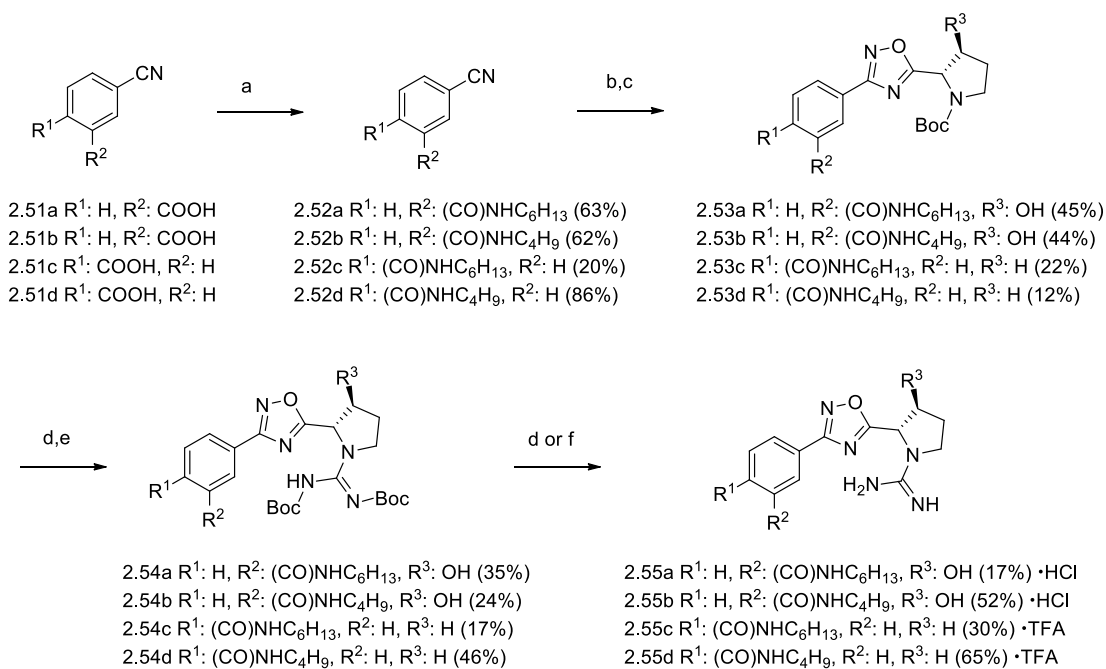
The final derivative of **SLR080811** resumes analysis of whether the octyl carbon tail is the best length. Synthesis of a nonyl carbon tail followed general procedures to afford compound **2.58** (Scheme 2.16).

**Scheme 2.14.** Synthesis of pyridine compound **2.50**.



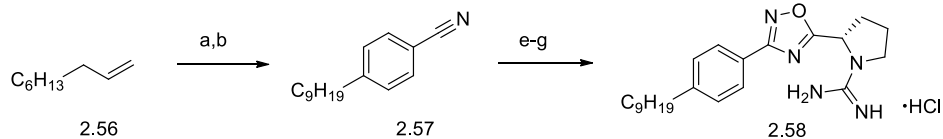
Reagents and conditions; (a) 9-BBN, THF, rt, 18h; (b) 6-iodonicotinonitrile,  $\text{Cs}_2\text{CO}_3$ ,  $\text{Pd}(\text{dppf})\text{Cl}_2$ , DMF, 80 °C, 18h, 56%; (c)  $\text{HONH}_2 \cdot \text{HCl}$ ,  $\text{Et}_3\text{N}$ , EtOH, reflux, 2h, 62%; (d) Boc-protected amino acid, DIEA,  $\text{HCTU} \cdot \text{PF}_6$ , DMF, 80 °C, 18h, 49%; (e) HCl, MeOH, 91%; (f)  $\text{N,N}'$ -di-Boc-1H-pyrazole-1-carboxamide, DIEA,  $\text{CH}_3\text{CN}$ , rt, 3 days, 58%.

**Scheme 2.15.** Synthesis of amide compounds **2.55a-d**.



Reagents and conditions; (a) amine, cyanobenzoic acid, NHS, EDC, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 18h; (b) HONH<sub>2</sub>·HCl, Et<sub>3</sub>N, EtOH, reflux, 2h; (c) Boc-protected amino acid, DIEA, HCTU·PF<sub>6</sub>, DMF, 80 °C, 18h; (d) HCl, MeOH; (e) N,N'-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, rt, 3 days; (f) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-12h.

**Scheme 2.16.** Synthesis of compound **2.58**.



Reagents and conditions; (a) 9-BBN, THF, rt, 18h; (b) 4-iodobenzonitrile, Cs<sub>2</sub>CO<sub>3</sub>, Pd(dppf)Cl<sub>2</sub>, DMF, 80 °C, 18h, 24%; (c) HONH<sub>2</sub>·HCl, Et<sub>3</sub>N, EtOH, reflux, 2h, 61%; (d) Boc-*L*-proline, DIEA, HCTU·PF<sub>6</sub>, DMF, 80 °C, 18h, 54%; (e) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 3-12h, quant.; (f) N,N'-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, rt, 3 days, 49%; (g) HCl, MeOH, 5 min, 63%.

## 2.5 Structure-Activity Relationships of Analogs and *in vivo* Activity

Analysis of reported SphK inhibitors suggests an optimal length, which is a positive charge 18-21 atoms from the omega carbon of the lipid tail. Hence, compounds bearing the guanidine head group with a 1,2,4-oxadiazole linked to a 4-octylphenyl chain were synthesized and screened for their inhibitory activity against recombinant Sphk1 and SphK2 at a concentration of 1  $\mu$ M. Most of these compounds contained a diversifying moiety on the alpha carbon or on the internal nitrogen because the coupling partners were derived from amino acids.

As shown in Table 2.2, glycine-derived guanidine **2.7a** and others bearing methyl (**2.7c**), isopropyl (**2.7d**), and hydroxymethyl (**2.7e**) on the alpha carbon demonstrated modest inhibition (less than 20% when present at 1  $\mu$ M). The analog methylated on the internal nitrogen (**2.7b**, derived from sarcosine) was inactive. Surprisingly, compound **2.7f**, a cyclopropyl-containing derivative, showed little activity although cyclopropyl amidines were previously found to be nanomolar inhibitors of SphK1.<sup>24, 44</sup> Compounds **2.7a-f** appear to be slightly SphK1 selective. However, when a pyrrolidine ring was introduced (**2.7g**, **SLR080811**), a sharp increase in inhibitory activity was observed along with a reversal in selectivity towards SphK2. The calculated  $K_i$  for **SLR080811** was 13  $\mu$ M and 1.3  $\mu$ M for SphK1 and 2, respectively, and it had a 10-fold selectivity towards SphK2 (Table 2.4). The inhibitory effect of **SLR080811** was highly dependent on the (*S*)-stereochemistry at alpha carbon center of the pyrrolidine ring as the (*R*)-enantiomer **2.7h** was markedly less potent as a SphK inhibitor.

In an effort to improve the activity of **SLR080811** further, a more conformationally restricted analog, **2.7i**, wherein a double bond was introduced on the aliphatic ring, was synthesized. However, this compound was significantly less potent (Table 2.2). Contraction of the pyrrolidine to a four-membered azetidine ring, **2.7j** (**SLP120701**), afforded a compound that was

equipotent with **SLR080811**. In contrast, ring expansion of the pyrrolidine to generate the piperidine analog, **2.7k**, resulted in a compound with severely diminished activity, presumably as a result of the change in dihedral angle that orients the guanidine group in a suboptimal position. We next explored the effect of hydroxyl groups on the pyrrolidine ring in an attempt to mimic the hydroxyl groups on Sph. Such a strategy has recently been used with SphK1 inhibitors.<sup>23, 26</sup> Compound **2.11**, which has a (3*S*)-hydroxyl group, was equipotent at both the SphK1 and SphK2 enzymes, albeit with less potency than the parent compound (Table 2.2). (4*R*)-**2.15** retained SphK2 selectivity, but was less potent than **SLP120701** while its stereoisomer (4*S*)-**2.17** was significantly less active (Tables 2.2-2.4). A compound with (3*R*)-hydroxyl group was not tested as our attempts to synthesize it failed.

To determine the optimal position of the guanidine group around the heterocyclic ring, we installed the nitrogen atom away from the alpha carbon to generate azetidine (**2.26a**) and pyrrolidine (**2.26b**). Both of these compounds were essentially inactive in our assay. We also investigated effect of heteroatoms of the oxadiazole ring as positional isomers of oxadiazoles are known to possess varying pharmacokinetic properties.<sup>46</sup> Hence, reversed 1,2,4-oxadiazole **2.29** and 1,3,4-oxadiazole **2.32** were synthesized. While (5-phenyl)-1,2,4-oxadiazole **2.29** had inhibitory activity indistinguishable from **SLP120701**, **2.32** did not inhibit SphK2 at 1  $\mu$ M (Tables 2.2-2.4). These studies suggest that the isolated nitrogen atom interacts with the target protein, possibly via hydrogen bonding.

In an effort to discover a surrogate for the oxadiazole ring, we installed an amide bond between the phenyl and pyrrolidine rings. Anilide **2.38a** and **2.38b** possessing opposite stereochemistry at the alpha carbon were both inactive towards SphK1 and 2. Since the amide bonds in these compounds are approximately one bond shorter than the corresponding oxadiazole

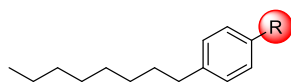


and can be ‘off register’ in the enzyme binding pocket, we synthesized the homologated benzylamide **2.40** and found that it possessed no significant inhibitory effect. To perform a thorough analysis, we also synthesized the reversed homologated analog **2.42** and found a similar activity. Hence, we conclude that an amide bond is not a sufficient replacement for the oxadiazole ring.

We next focused our attention on the spacing between the oxadiazole and pyrrolidine rings; compound **2.48a** (**SLP7111228**) and **2.48b** contain one or two methylene units, respectively. To our surprise, we observed a complete switch in isoform selectivity as **2.48a** showed 88% inhibition at SphK1 while exhibiting 20% inhibition at SphK2. The calculated  $K_i$  of **SLP111228** for SphK1 is 48 nM and >10  $\mu$ M for SphK2 (Table 2.4), affording > 200-fold selectivity. This compound is the most potent SphK1 selective compound reported to date. Further extension of the linker in **2.48b** resulted in substantial decrease in both SphK1 and SphK2 inhibitory activity.

Derivatives of **SLR080811** were evaluated next for their inhibitory activity (Table 2.3). Based on availability of human SphK2, a transition with our testing occurred and these 6 compounds were the first ones tested against human SphK2 rather than mouse SphK2. First, the pyridine compound **2.50** showed no SphK2 inhibition and slight SphK1 inhibition. This indicates that the nitrogen of the pyridine ring does not help inhibition by offering a hydrogen bond acceptor within the ring. Next, amide bonds located in the tail region were evaluated. Compounds **2.55a-d** yielded little to no inhibition against both SphKs, providing evidence against hydrogen bonding interactions adjacent to the phenyl ring. Finally, the nonyl tail version of **SLR080811** resulted in no inhibition of SphK1 and inhibition of hSphK2 to 23%.

**Table 2.2.** hSphK1 and mSphK2 inhibitory activity.<sup>a</sup>

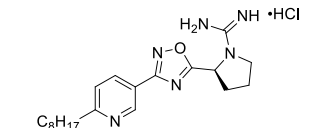
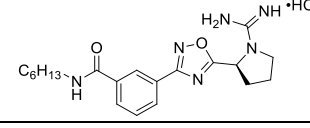
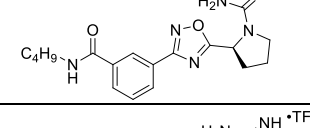
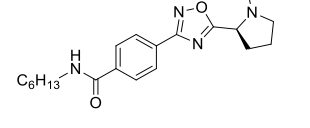
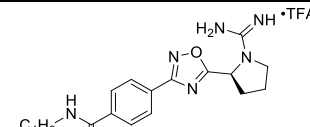
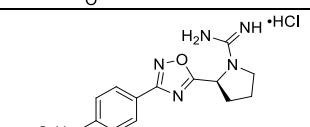


Compd	R	% hSphK1 activity	% mSphK2 activity	Compd	R	% hSphK1 activity	% mSphK2 activity
<b>2.7a</b>		75 ± 2	90 ± 2	<b>2.15</b>		98 ± 1	70 ± 1
<b>2.7b</b>		98 ± 3	90 ± 2	<b>2.17</b>		96 ± 1	90 ± 1
<b>2.7c</b>		78 ± 5	94 ± 6	<b>2.26a</b>		84 ± 3	96 ± 1
<b>2.7d</b>		70 ± 5	85 ± 1	<b>2.26b</b>		88 ± 4	95 ± 1
<b>2.7e</b>		94 ± 1	99 ± 2	<b>2.29</b>		91 ± 5	42 ± 4
<b>2.7f</b>		88 ± 3	98 ± 2	<b>2.32</b>		96 ± 2	91 ± 4
<b>2.7g</b>		88 ± 1	44 ± 4	<b>2.38a</b>		100 ± 3	83 ± 2
<b>2.7h</b>		93 ± 7	90 ± 2	<b>2.38b</b>		100 ± 1	100 ± 1

<b>2.7i</b>		94 ± 1	96 ± 4	<b>2.40</b>		95 ± 3	95 ± 1
<b>2.7j</b>		92 ± 2	56 ± 2	<b>2.42</b>		90 ± 3	75 ± 13
<b>2.7k</b>		98 ± 4	92 ± 1	<b>2.48a</b>		12 ± 3	80 ± 4
<b>2.11</b>		69 ± 2	65 ± 1	<b>2.48b</b>		77 ± 2	100 ± 3

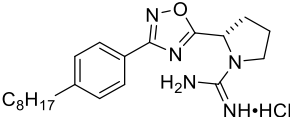
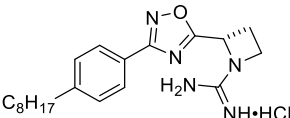
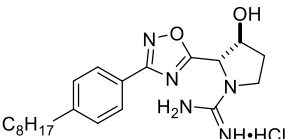
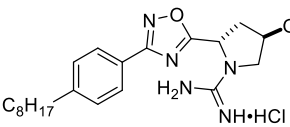
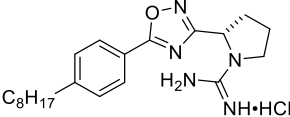
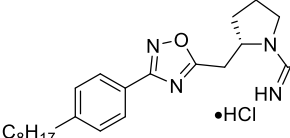
<sup>a</sup> SphK activity is represented as % of control (without inhibitor). SphK expression was forced in insect cells infected with recombinant baculovirus, and activity in a cleared lysate was measured using 5 μM (for SphK1) or 10 μM (for SphK2) sphingosine and 250 μM [<sup>32</sup>P]-ATP. Each compound was assayed at a concentration of 1 μM in triplicate, except for **2.48a** (assayed at 3 μM with SphK2). Control = activity without inhibitor.

**Table 2.3.** hSphK1 and hSphK2 inhibitory activity.<sup>a</sup>

Compd	Structure	% hSphK1 activity	% hSphK2 activity
<b>2.50</b>		77 ± 1	117 ± 5
<b>2.55a</b>		83 ± 2	96 ± 4
<b>2.55b</b>		77 ± 5	96 ± 5
<b>2.55c</b>		79 ± 1	103 ± 1
<b>2.55d</b>		83 ± 1	98 ± 1
<b>2.58</b>		93 ± 12	23 ± 9

<sup>a</sup> SphK activity is represented as % of control (without inhibitor). Human SphK expression was forced in insect cells infected with recombinant baculovirus, and activity in a cleared lysate was measured using 5 μM (for SphK1) or 10 μM (for SphK2) sphingosine and 250 μM [<sup>32</sup>P]-ATP. Each compound was assayed at a concentration of 1 μM in triplicate. Control = activity without inhibitor.

**Table 2.4.**  $K_i$  of selected inhibitors at SphK1 and SphK2.

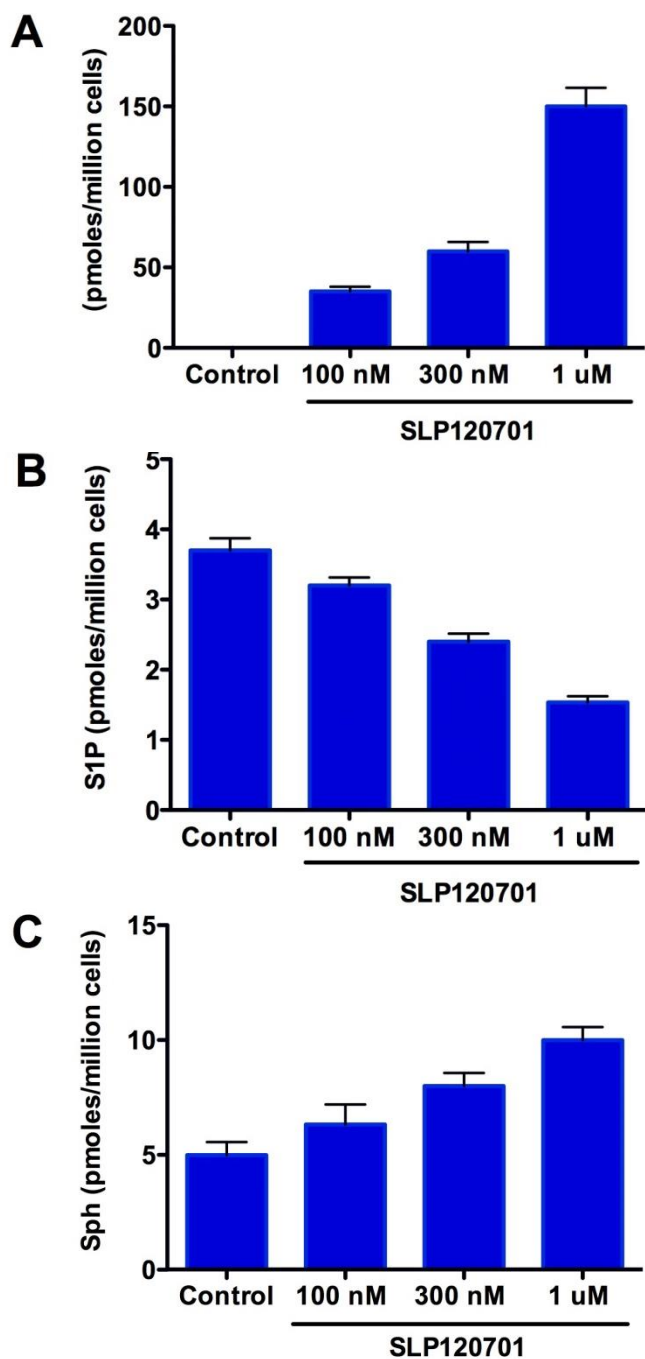
Entry	Compound	Structure	$K_i$ ( $\mu\text{M}$ )	
			SphK1	SphK2
1	<b>SLR080811 (2.7g)</b>		$13 \pm 1$	$1.3 \pm 0.4$
2	<b>SLP120701 (2.7j)</b>		$>10$	$1.2 \pm 0.2$
3	<b>SLM120401 (2.11)</b>		$>10$	$>10$
4	<b>BD22 (2.15)</b>		$>10$	$5.2 \pm 1$
5	<b>SLM6111202 (2.29)</b>		$>10$	$1.1 \pm 0.2$
6	<b>SLP7111228 (2.48a)</b>		$0.048 \pm 0.01$	$>10$

As azetidine derivative **SLP120701** had a similar binding constant ( $K_i = 1.2 \mu\text{M}$ ) but was more selective towards SphK2 than the pyrrolidine analog **SLR080811**, we performed biochemical characterization to determine its *in vitro* and *in vivo* properties (Table 2.4 and Fig. 2.3). First, U937 cells (a myeloid cell line isolated from a patient with histiocytic lymphoma), which express both SphK1 and SphK2, were incubated with **SLP120701**. After cell lysis and sample preparation, the inhibitor, sphingosine, and S1P were quantified using LC-MS-MS. As shown in Fig. 2.3, a dose-dependent accumulation of **SLP120701** was observed with a

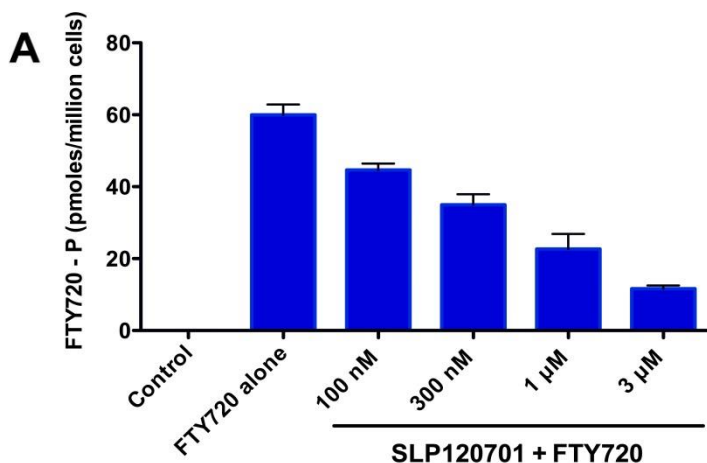
concomitant decrease of S1P and increase in Sph levels. These results suggest that SphKs were inhibited in whole cells and that **SLP120701** penetrates these cells effectively.

To determine whether **SLP120701** was inhibiting SphK2 in these cells, the cultures were treated with the SphK2 selective substrate, **FTY720**, and the resulting phosphorylated **FTY720** (**FTY720-P**) was monitored (Figure 2.4).<sup>47, 48</sup> Addition of **FTY720** to U937 cells resulted in accumulation of **FTY720-P**, which should be dampened in the presence of an inhibitor. As expected, increasing **SLP120701** from 0.1 to 3  $\mu$ M was accompanied by decreased amounts of **FTY720-P**, a trend that reached a minimum at 3  $\mu$ M. These *in vitro* studies indicate that the decrease in S1P and **FTY720-P** as a function of **SLP120701** concentration may be attributed to inhibition of SphK2.

To ascertain whether inhibition of SphK2 has an effect on the levels of sphingoid bases *in vivo*, we treated C57BL/6 mice with a single intraperitoneal dose of **SLP120701** (10 mg/kg) and monitored S1P, Sph, and inhibitor concentration in blood using LC-MS-MS. In contrast to our *in vitro* studies, S1P levels increased to approximately two-fold following injection of the SphK2 selective inhibitor (Fig. 2.5). This phenomenon is consistent with S1P levels observed in Sphk2<sup>-/-</sup> mice where the blood S1P level is 3-4 times higher than wild type control mice.<sup>18-21</sup> We also observed a modest increase in Sph levels (Fig. 2.5B). Further monitoring of compound disappearance from blood suggests a half-life of approximately 8 hours, which is significantly longer than **SLR080811**.<sup>40</sup>

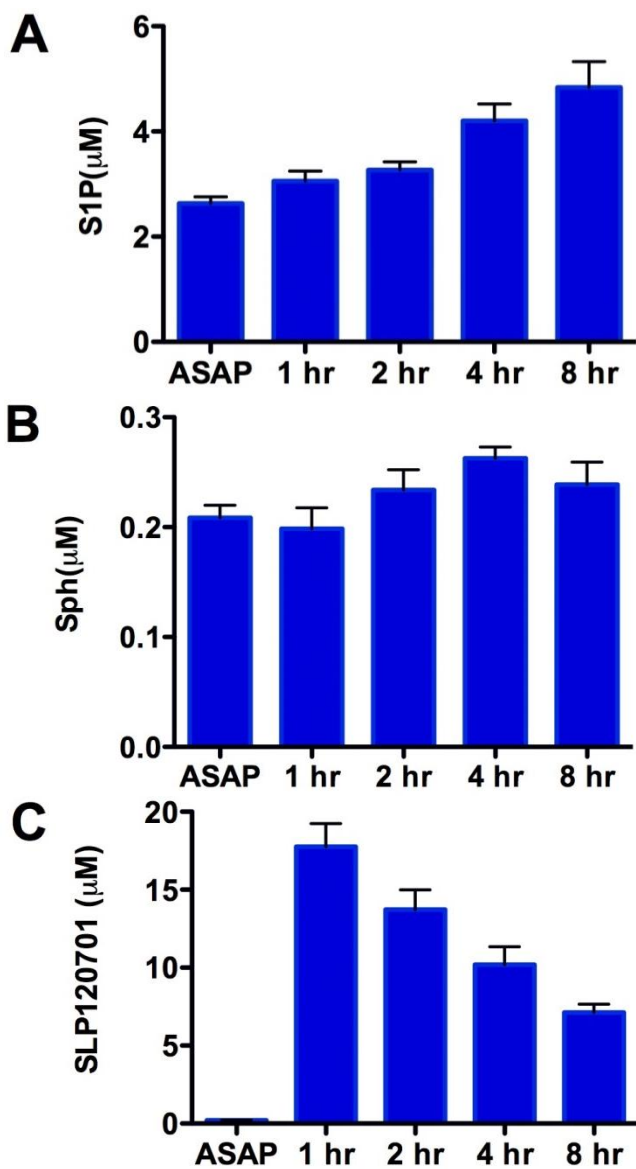


**Figure 2.3.** Effect of **SLP120701** on sphingolipids in U937 cells. After 2h of incubation, cells were harvested by centrifugation, lysed, and levels of (A) **SLP120701**, (B) S1P, and (C) sphingosine were measured using LC-MS-MS. Amounts associated with cells are expressed as the number of pmoles per  $10^6$  cells. Each value was determined in triplicate.



**Figure 2.4.** Inhibition of SphK2 by **SLP120701**. Cultured U937 cells were incubated with 1  $\mu$ M of FTY720 and increasing concentrations of **SLP120701**. After 2h of exposure, cells were harvested by centrifugation, lysed, and levels of **FTY720** and **FTY720-phosphate (FTY720-P)** were quantified using LC-MS-MS. Amounts associated with cells are expressed as the number of pmoles per  $10^6$  cells. Each value was measured in triplicate.



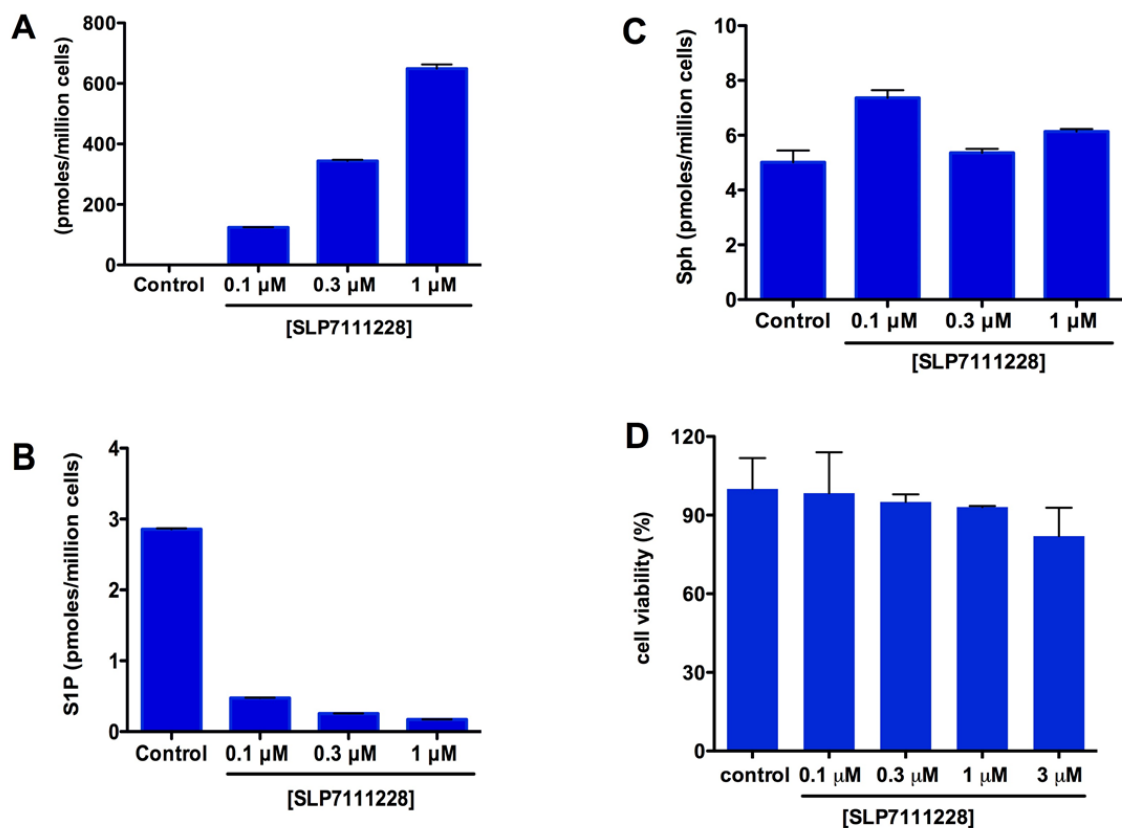


**Figure 2.5.** S1P, Sph, and SLP120701 levels in the blood of mice injected with SLP120701. Wild-type mice were injected (i.p.) with a single dose (10 mg/kg) and blood was drawn at indicated time points. Levels of S1P (a), sphingosine (b), and SLP120701 (c) from blood samples of WT mice were measured by LC-MS-MS. The standard deviations are values from a group of three to five mice.

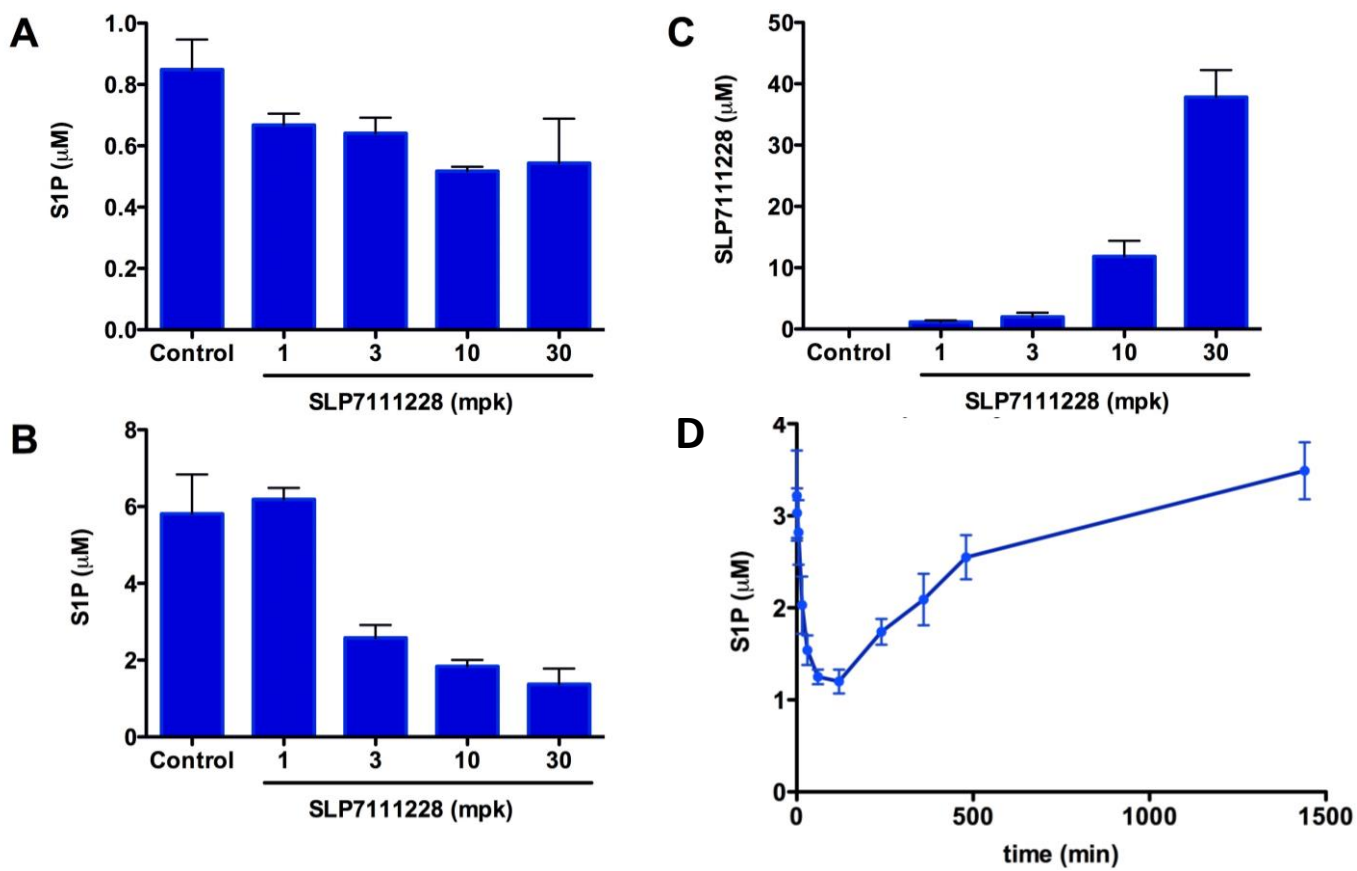
To compare the effects of SphK1 inhibition, we similarly subjected U937 cells with SphK1 selective inhibitor SLP7111228. As expected, a dose dependent accumulation of SLP7111228 in

these cells is observed (Fig. 2.6A). This property is accompanied by a marked decrease in S1P level in a dose dependent fashion (Fig. 2.6B). Interestingly, addition of 100 nM of this compound resulted in approximately 90% depression of cellular S1P, which is significantly larger compared to the decrease in S1P levels seen with SphK2 selective inhibitor **SLP120701** (Fig. 2.3B). When Sph levels were measured as a function of inhibitor concentration, no statistical change was observed (Fig. 2.6C), which is again in contrast with Sphk2 inhibition. We further determined the effect of **SLP120701** on the viability of U937 cells as recent reports suggested that SphK1-selective inhibitors such as **PF-543**<sup>23</sup> and compound A/B<sup>7</sup> had no effect on the viability of cancer cells (Fig. 2.6D). Our studies similarly demonstrate that inhibition of SphK1 via **SLP120701** up to 3  $\mu$ M over 24 hours has no cytotoxicity effects on cancer cell growth.

To determine the effect of **SLP7111228** *in vivo*, we injected increasing concentration of this compound in rats intraperitoneally. As shown in Fig. 2.7A, plasma S1P levels decreased slightly (up to 25% of control) as the inhibitor concentration increased. S1P levels in plasma are known to be significantly lower than in blood. In contrast, blood S1P levels show a marked dose-dependent depression, which reaches a minimum at about 80% when compared to vehicle (Fig. 2.7B). Finally, our studies suggest that **SLP7111228** has an *in vivo* half-life of over 4 hours and that its effect of lowering S1P level is sustained over a period of at least 6 hours (Fig. 2.7C-D).



**Figure 2.6.** Effect of **SLP7111228** on sphingolipids and viability of U937 cells. After 2h of incubation, cells were harvested by centrifugation, lysed, and levels of (A) **SLP7111228**, (B) S1P, and (C) sphingosine were measured using LC-MS-MS. Amounts associated with cells are expressed as the number of pmoles per  $10^6$  cells. Each value was determined in triplicate. (D) Cell viability. Increasing concentration of inhibitor was added to U937 cells and cell growth was measured after 24 hours. Each value was determined in duplicate.



**Figure 2.7.** Effect of **SLP7111228** upon IP administration in rats. Rats were injected with indicated dose and blood was drawn 2 hours post injection. Levels of S1P in (a) plasma, (b) blood, and (c) **SLP7111228** are shown at indicated inhibitor concentration. (d) Time-course experiment with 10 mg/kg **SLP7111228** showing blood S1P levels. Samples were analyzed by LC-MS-MS. The standard deviations are values from a group of three to five rats.

## 2.6 Conclusions

The second generation inhibitors reported herein feature a guanidine moiety as a warhead and an oxadiazole heterocycle as the linker. Structure-activity studies with this scaffold suggest that conformational restriction of the guanidine group is essential for potent kinase inhibitory activity. Further, decoration of the pyrrolidine ring with a hydroxyl group to mimic the hydroxyl

moiety in sphingosine does not increase potency of the compounds, although the compound bearing a (3*R*)-hydroxyl group may have beneficial effect. Our studies also demonstrate that amides are not a good replacement for oxadiazole rings or addition to the tail group in our scaffold and that the position of the isolated nitrogen of the oxadiazole ring is important. A surprising finding in these investigations is that the insertion of a single methylene unit as a spacer between the oxadiazole and pyrrolidine rings resulted in a SphK inhibitor with reversed selectivity, favoring SphK1.

Profiling of SphK1 (**SLP7111228**) and SphK2 (**SLP120701**) both *in vitro* and *in vivo* reveal interesting observations. First, both inhibitors have an effect of depressing S1P levels in U937 cells. Curiously, SphK1 inhibitors decrease S1P levels further compared to SphK2 inhibitors *in vitro*. Whether this an activity associated with the potency of these compounds is a possibility, but we note that these compounds are avidly taken up by these cells. Secondly, *in vivo* administration of these inhibitors in mice and rats resulted in opposite effects on blood S1P levels. That is, a decrease in blood S1P level is observed with SphK1 inhibitor while there is an increase with SphK2 inhibitors. While these observations are consistent with mouse gene ‘knock out’ studies, our results are notable in that: (1) **SLP120701** is the second SphK2 inhibitor profiled to result in increased circulating levels of S1P<sup>40</sup>— **ABC294640** (a low potency compound that has SphK2 inhibitor properties) had the opposite effect of decreased S1P levels.<sup>49</sup> Our results suggest that increased blood S1P levels are a property of SphK2 selective inhibitors. (2) **SLP120701** has an improved *in vivo* half-life as compared to the pyrrolidine analog, **SLR080811**. (3) **SLP7111228** is the most potent and selective (> 200 fold) SphK1 inhibitor reported to date with favorable *in vivo* stability. Interestingly, a single dose of 10 mg/kg in rats decreases blood S1P levels by about 80%. With these two chemical tools in hand, we have the capacity to increase or decrease blood

S1P levels and such studies will aid in determining the pathophysiological effects of such maneuvers in live animals.

## 2.7 References

1. Kunkel, G. T.; Maceyka, M.; Milstien, S.; Spiegel, S., Targeting the sphingosine-1-phosphate axis in cancer, inflammation and beyond. *Nat. Rev. Drug Discov.* **2013**, *12*, 688-702.
2. Zhang, Y.; Berka, V.; Song, A.; Sun, K.; Wang, W.; Zhang, W.; Ning, C.; Li, C.; Zhang, Q.; Bogdanov, M.; Alexander, D. C.; Milburn, M. V.; Ahmed, M. H.; Lin, H.; Idowu, M.; Zhang, J.; Kato, G. J.; Abdulmalik, O. Y.; Zhang, W.; Dowhan, W.; Kellems, R. E.; Zhang, P.; Jin, J.; Safo, M.; Tsai, A. L.; Juneja, H. S.; Xia, Y., Elevated sphingosine-1-phosphate promotes sickling and sickle cell disease progression. *J. Clin. Invest.* **2014**, *124*, 2750-61.
3. Pyne, N. J.; Tonelli, F.; Lim, K. G.; Long, J. S.; Edwards, J.; Pyne, S., Sphingosine 1-phosphate signalling in cancer. *Biochem. Soc. Trans.* **2012**, *40*, 94-100.
4. Daum, G.; Grabski, A.; Reidy, M. A., Sphingosine 1-phosphate: A regulator of arterial lesions. *Arterioscler. Thromb. Vac. Biol.* **2009**, *29*, 1439-43.
5. Price, M. M.; Oskeritzian, C. A.; Falanga, Y. T.; Harikumar, K. B.; Allegood, J. C.; Alvarez, S. E.; Conrad, D.; Ryan, J. J.; Milstien, S.; Spiegel, S., A specific sphingosine kinase 1 inhibitor attenuates airway hyperresponsiveness and inflammation in a mast cell-dependent murine model of allergic asthma. *J. Allergy Clin. Immunol* **2013**, *131*, 501-11.
6. Pyne, N. J.; Pyne, S., Sphingosine 1-phosphate and cancer. *Nature reviews. Cancer* **2010**, *10*, 489-503.
7. Rex, K.; Jeffries, S.; Brown, M. L.; Carlson, T.; Coxon, A.; Fajardo, F.; Frank, B.; Gustin, D.; Kamb, A.; Kassner, P. D.; Li, S.; Li, Y.; Morgenstern, K.; Plant, M.; Quon, K.; Ruefli-

- Brasse, A.; Schmidt, J.; Swearingen, E.; Walker, N.; Wang, Z.; Watson, J. E.; Wickramasinghe, D.; Wong, M.; Xu, G.; Wesche, H., Sphingosine kinase activity is not required for tumor cell viability. *PloS one* **2013**, *8*, e68328.
8. Olivera, A.; Kohama, T.; Edsall, L.; Nava, V.; Cuvillier, O.; Poulton, S.; Spiegel, S., Sphingosine kinase expression increases intracellular sphingosine-1-phosphate and promotes cell growth and survival. *J. Cell Biol.* **1999**, *147*, 545-557.
9. Maceyka, M.; Sankala, H.; Hait, N. C.; Le Stunff, H.; Liu, H.; Toman, R.; Collier, C.; Zhang, M.; Satin, L. S.; Merrill, A. H.; Milstien, S.; Spiegel, S., SphK1 and SphK2, sphingosine kinase isoenzymes with opposing functions in sphingolipid metabolism. *J. Biol. Chem.* **2005**, *280*, 37118-37129.
10. Okada, T.; Ding, G.; Sonoda, H.; Kajimoto, T.; Haga, Y.; Khosrowbeygi, A.; Gao, S.; Miwa, N.; Jahangeer, S.; Nakamura, S., Involvement of N-terminal-extended form of sphingosine kinase 2 in serum-dependent regulation of cell proliferation and apoptosis. *J. Biol. Chem.* **2005**, *280*, 36318-25.
11. Liu, H.; Toman, R. E.; Goparaju, S. K.; Maceyka, M.; Nava, V. E.; Sankala, H.; Payne, S. G.; Bektas, M.; Ishii, I.; Chun, J.; Milstien, S.; Spiegel, S., Sphingosine kinase type 2 is a putative BH3-only protein that induces apoptosis. *J. Biol. Chem.* **2003**, *278*, 40330-40336.
12. Jarman, K. E.; Moretti, P. A.; Zebol, J. R.; Pitson, S. M., Translocation of sphingosine kinase 1 to the plasma membrane is mediated by calcium- and integrin-binding protein 1. *J. Biol. Chem.* **2010**, *285*, 483-92.
13. Pitson, S. M.; Moretti, P. A.; Zebol, J. R.; Lynn, H. E.; Xia, P.; Vadas, M. A.; Wattenberg, B. W., Activation of sphingosine kinase 1 by ERK1/2-mediated phosphorylation. *The EMBO journal* **2003**, *22*, 5491-500.

14. Igarashi, N.; Okada, T.; Hayashi, S.; Fujita, T.; Jahangeer, S.; Nakamura, S., Sphingosine kinase 2 is a nuclear protein and inhibits DNA synthesis. *J. Biol. Chem.* **2003**, *278*, 46832-46839.
15. Hait, N. C.; Allegood, J.; Maceyka, M.; Strub, G. M.; Harikumar, K. B.; Singh, S. K.; Luo, C.; Marmorstein, R.; Kordula, T.; Milstien, S.; Spiegel, S., Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. *Science* **2009**, *325*, 1254-7.
16. Zemann, B.; Urtz, N.; Reuschel, R.; Mechtcheriakova, D.; Bornancin, F.; Badegruber, R.; Baumruker, T.; Billich, A., Normal neutrophil functions in sphingosine kinase type 1 and 2 knockout mice. *Immunol. Lett.* **2007**, *109*, 56-63.
17. Allende, M. L.; Sasaki, T.; Kawai, H.; Olivera, A.; Mi, Y.; van Echten-Deckert, G.; Hajdu, R.; Rosenbach, M.; Keohane, C. A.; Mandala, S.; Spiegel, S.; Proia, R. L., Mice deficient in sphingosine kinase 1 are rendered lymphopenic by FTY720. *J. Biol. Chem.* **2004**, *279*, 52487-92.
18. Mizugishi, K.; Yamashita, T.; Olivera, A.; Miller, G. F.; Spiegel, S.; Proia, R. L., Essential role for sphingosine kinases in neural and vascular development. *Mol. Cell. Biol.* **2005**, *25*, 11113-21.
19. Allende, M. L.; Sasaki, T.; Kawai, H.; Olivera, A.; Mi, Y. D.; van Echten-Deckert, G.; Hajdu, R.; Rosenbach, M.; Keohane, C. A.; Mandala, S.; Spiegel, S.; Proia, R. L., Mice deficient in sphingosine kinase 1 are rendered lymphopenic by FTY720. *J. Biol. Chem.* **2004**, *279*, 52487-52492.
20. Zemann, B.; Kinzel, B.; Muller, M.; Reuschel, R.; Mechtcheriakova, D.; Urtz, N.; Bornancin, F.; Baumruker, T.; Billich, A., Sphingosine kinase type 2 is essential for



- lymphopenia induced by the immunomodulatory drug FTY720. *Blood* **2006**, *107*, 1454-1458.
21. Olivera, A.; Mizugishi, K.; Tikhonova, A.; Ciaccia, L.; Odom, S.; Proia, R. L.; Rivera, J., The sphingosine kinase-sphingosine-1-phosphate axis is a determinant of mast cell function and anaphylaxis. *Immunity* **2007**, *26*, 287-97.
  22. Plano, D.; Amin, S.; Sharma, A. K., Importance of sphingosine kinase (SphK) as a target in developing cancer therapeutics and recent developments in the synthesis of novel SphK inhibitors. *J. Med. Chem.* **2014**, *57*, 5509-24.
  23. Schnute, M. E.; McReynolds, M. D.; Kasten, T.; Yates, M.; Jerome, G.; Rains, J. W.; Hall, T.; Chrencik, J.; Kraus, M.; Cronin, C. N.; Saabye, M.; Highkin, M. K.; Broadus, R.; Ogawa, S.; Cukyne, K.; Zawadzke, L. E.; Peterkin, V.; Iyanar, K.; Scholten, J. A.; Wendling, J.; Fujiwara, H.; Nemirovskiy, O.; Wittwer, A. J.; Nagiec, M. M., Modulation of cellular S1P levels with a novel, potent and specific inhibitor of sphingosine kinase-1. *Biochem. J.* **2012**, *444*, 79-88.
  24. Mathews, T. P.; Kennedy, A. J.; Kharel, Y.; Kennedy, P. C.; Nicoara, O.; Sunkara, M.; Morris, A. J.; Wamhoff, B. R.; Lynch, K. R.; Macdonald, T. L., Discovery, biological evaluation, and structure-activity relationship of amidine based sphingosine kinase inhibitors. *J. Med. Chem.* **2010**, *53*, 2766-2778.
  25. Xiang, Y. B.; Hirth, B.; Kane, J. L.; Liao, J. K.; Noson, K. D.; Yee, C.; Asmussen, G.; Fitzgerald, M.; Klaus, C.; Booker, M., Discovery of novel sphingosine kinase-1 inhibitors. Part 2. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4550-4554.
  26. Gustin, D. J.; Li, Y.; Brown, M. L.; Min, X.; Schmitt, M. J.; Wanska, M.; Wang, X.; Connors, R.; Johnstone, S.; Cardozo, M.; Cheng, A. C.; Jeffries, S.; Franks, B.; Li, S.; Shen,

- S.; Wong, M.; Wesche, H.; Xu, G.; Carlson, T. J.; Plant, M.; Morgenstern, K.; Rex, K.; Schmitt, J.; Coxon, A.; Walker, N.; Kayser, F.; Wang, Z., Structure guided design of a series of sphingosine kinase (SphK) inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4608-16.
27. Neubauer, H. A.; Pitson, S. M., Roles, regulation and inhibitors of sphingosine kinase 2. *FEBS Journal* **2013**, *280*, 5317-5336.
28. French, K. J.; Zhuang, Y.; Maines, L. W.; Gao, P.; Wang, W.; Beljanski, V.; Upson, J. J.; Green, C. L.; Keller, S. N.; Smith, C. D., Pharmacology and antitumor activity of ABC294640, a selective inhibitor of sphingosine kinase-2. *J. Pharmacol. Exp. Ther.* **2010**, *333*, 129-139.
29. Maines, L. W.; Fitzpatrick, L. R.; French, K. J.; Zhuang, Y.; Xia, Z.; Keller, S. N.; Upson, J. J.; Smith, C. D., Suppression of ulcerative colitis in mice by orally available inhibitors of sphingosine kinase. *Dig. Dis. Sci.* **2008**, *53*, 997-1012.
30. Maines, L. W.; Fitzpatrick, L. R.; Green, C. L.; Zhuang, Y.; Smith, C. D., Efficacy of a novel sphingosine kinase inhibitor in experimental Crohn's disease. *Inflammopharmacology* **2010**, *18*, 73-85.
31. Shi, Y.; Rehman, H.; Ramshesh, V. K.; Schwartz, J.; Liu, Q.; Krishnasamy, Y.; Zhang, X.; Lemasters, J. J.; Smith, C. D.; Zhong, Z., Sphingosine kinase-2 inhibition improves mitochondrial function and survival after hepatic ischemia-reperfusion. *J. Hepatol.* **2012**, *56*, 137-45.
32. Maines, L.; Fitzpatrick, L.; French, K.; Zhuang, Y.; Xia, Z.; Keller, S.; Upson, J.; Smith, C., Suppression of ulcerative colitis in mice by orally available inhibitors of sphingosine kinase. *Dig. Dis. Sci.* **2008**, *53*, 997-1012.

33. Chumanevich, A. A.; Poudyal, D.; Cui, X.; Davis, T.; Wood, P. A.; Smith, C. D.; Hofseth, L. J., Suppression of colitis-driven colon cancer in mice by a novel small molecule inhibitor of sphingosine kinase. *Carcinogenesis* **2010**, *31*, 1787-93.
34. Antoon, J. W.; White, M. D.; Meacham, W. D.; Slaughter, E. M.; Muir, S. E.; Elliott, S.; Rhodes, L. V.; Ashe, H. B.; Wiese, T. E.; Smith, C. D.; Burow, M. E.; Beckman, B. S., Antiestrogenic effects of the novel sphingosine kinase-2 inhibitor ABC294640. *Endocrinology* **2010**, *151*, 5124-35.
35. Hara-Yokoyama, M.; Terasawa, K.; Ichinose, S.; Watanabe, A.; Podyma-Inoue, K. A.; Akiyoshi, K.; Igarashi, Y.; Yanagishita, M., Sphingosine kinase 2 inhibitor SG-12 induces apoptosis via phosphorylation by sphingosine kinase 2. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2220-2224.
36. Lim, K. G.; Sun, C.; Bittman, R.; Pyne, N. J.; Pyne, S., (R)-FTY720 methyl ether is a specific sphingosine kinase 2 inhibitor: Effect on sphingosine kinase 2 expression in HEK 293 cells and actin rearrangement and survival of MCF-7 breast cancer cells. *Cell. Signal.* **2011**, *23*, 1590-1595.
37. Liu, K.; Guo, T. L.; Hait, N. C.; Allegood, J.; Parikh, H. I.; Xu, W.; Kellogg, G. E.; Grant, S.; Spiegel, S.; Zhang, S., Biological characterization of 3-(2-amino-ethyl)-5-[3-(4-butoxyphenyl)-propylidene]-thiazolidine-2,4-dione (K145) as a selective sphingosine kinase-2 inhibitor and anticancer agent. *PloS one* **2013**, *8*, e56471.
38. Raje, M. R.; Knott, K.; Kharel, Y.; Bissel, P.; Lynch, K. R.; Santos, W. L., Design, synthesis and biological activity of sphingosine kinase 2 selective inhibitors. *Bioorg. Med. Chem.* **2012**, *20*, 183-194.

39. Santos, W. L.; Lynch, K. R., Drugging sphingosine kinases. *ACS Chem. Biol.* **2014**, DOI: 10.1021/cb5008426.
40. Kharel, Y.; Raje, M.; Gao, M.; Gellett, A. M.; Tomsig, J. L.; Lynch, K. R.; Santos, W. L., Sphingosine kinase type 2 inhibition elevates circulating sphingosine 1-phosphate. *Biochem. J.* **2012**, *447*, 149-57.
41. Knott, K.; Kharel, Y.; Raje, M. R.; Lynch, K. R.; Santos, W. L., Effect of alkyl chain length on sphingosine kinase 2 selectivity. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6817-6820.
42. Yokota, S.; Taniguchi, Y.; Kihara, A.; Mitsutake, S.; Igarashi, Y., Asp177 in C4 domain of mouse sphingosine kinase 1a is important for the sphingosine recognition. *FEBS Lett.* **2004**, *578*, 106-110.
43. Wang, Z.; Min, X.; Xiao, S. H.; Johnstone, S.; Romanow, W.; Meininger, D.; Xu, H.; Liu, J.; Dai, J.; An, S.; Thibault, S.; Walker, N., Molecular basis of sphingosine kinase 1 substrate recognition and catalysis. *Structure* **2013**, *21*, 798-809.
44. Kennedy, A. J.; Mathews, T. P.; Kharel, Y.; Field, S. D.; Moyer, M. L.; East, J. E.; Houck, J. D.; Lynch, K. R.; Macdonald, T. L., Development of amidine-based sphingosine kinase 1 nanomolar inhibitors and reduction of sphingosine 1-phosphate in human leukemia cells. *J. Med. Chem.* **2011**, *54*, 3524-3548.
45. Kun, S.; Nagy, G. Z.; Toth, M.; Czece, L.; Van Nhien, A. N.; Docsa, T.; Gergely, P.; Charavgi, M. D.; Skourti, P. V.; Chrysina, E. D.; Patonay, T.; Somsak, L., Synthesis of variously coupled conjugates of D-glucose, 1,3,4-oxadiazole, and 1,2,3-triazole for inhibition of glycogen phosphorylase. *Carbohydr. Res.* **2011**, *346*, 1427-38.
46. Boström, J.; Hogner, A.; Llinàs, A.; Wellner, E.; Plowright, A. T., Oxadiazoles in medicinal chemistry. *J. Med. Chem.* **2011**, *55*, 1817-1830.

47. Billich, A.; Bornancin, F.; Devay, P.; Mechtcheriakova, D.; Urtz, N.; Baumruker, T., Phosphorylation of the immunomodulatory drug FTY720 by sphingosine kinases. *J. Biol. Chem.* **2003**, *278*, 47408-47415.
48. Paugh, S. W.; Payne, S. G.; Barbour, S. E.; Milstien, S.; Spiegel, S., The immunosuppressant FTY720 is phosphorylated by sphingosine kinase type 2. *FEBS Lett.* **2003**, *554*, 189-193.
49. Snider, A. J.; Ruiz, P.; Obeid, L. M.; Oates, J. C., Inhibition of sphingosine kinase-2 in a murine model of lupus nephritis. *PLoS One* **2013**, *8*, e53521.

## **Chapter 3. Structure-activity relationship studies on sphingosine kinase 2 inhibitor**

### **SLR080811**

#### **3.1 Contributions**

The work in this chapter was done in collaboration with the University of Virginia. The author was responsible for the synthesis of the inhibitors. Biological characterization was performed by Dr. Kevin Lynch and Dr. Yugesh Kharel at the University of Virginia.

#### **3.2 Foreword**

This chapter is a continuation of work performed in Chapter 2. This chapter focuses on an SAR of **SLR080811**, our lead compound introduced in Chapter 2. Modifications are performed on the tail region of the molecule, whereas earlier studies focused on different regions of the molecule.

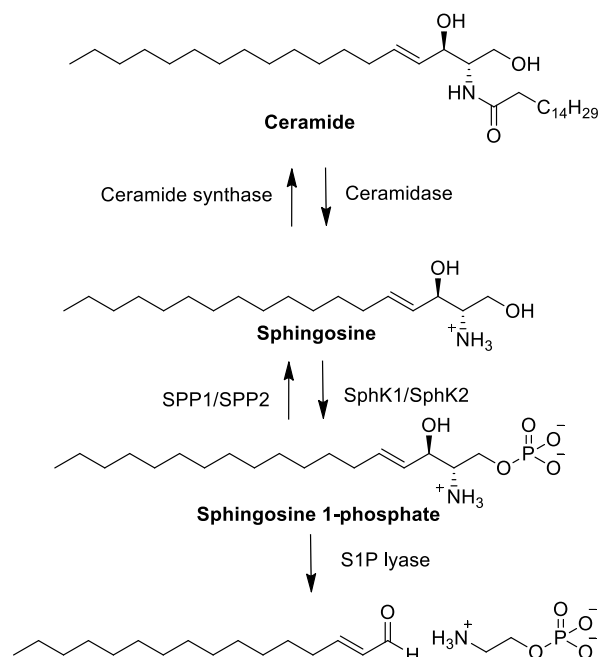
### 3.3 Abstract

Sphingosine 1-phosphate (S1P) has become a prevalent target due to evidence implicating it to several disease pathologies such as fibrosis, sickle cell, inflammation, diabetes, and cancer. S1P is known as a cell proliferation and migration signaling molecule. S1P provides the signals either through intracellular targets or by being transported outside of the cell where it can bind to G-protein coupled receptors. S1P is produced intracellularly when sphingosine kinase (SphK) 1 or 2 phosphorylates sphingosine. Inhibiting either or both SphKs helps to modulate S1P which may aid in developing therapies related to S1P signaling. Herein, we report the design, synthesis, and structure-activity relationship studies of SphK2 inhibitors. Our studies revealed a SphK2 selective inhibitor with a  $K_i$  of 370 nM, **SLM6031434** and selectivity of 23-fold over SphK1. *In vitro* studies in U937 cells decreased S1P levels while administration in mice resulted in an increase in S1P levels in blood.

### 3.4 Introduction

Sphingosine 1-phosphate (S1P), a member of the sphingolipid family, is a signaling molecule found in various cells and tissues that are responsible for actions such as cell migration and proliferation.<sup>1</sup> Because of these signaling functions, S1P has been tied to several diseases including fibrosis, sickle cell, cancer, diabetes.<sup>2-6</sup> S1P is part of a signaling pathway within the cell (Fig. 3.1).<sup>2</sup> Ceramide (Cer) can be converted to sphingosine (Sph) through amide bond cleavage facilitated by ceramidase. Sph can be converted to Cer or phosphorylated by sphingosine kinase 1 or 2 (SphK1 or 2) to generate S1P. S1P has three different routes to venture: back to Sph, degraded by S1P lyase, or interact with its targets to elicit signals.<sup>2</sup> All transformations except the degradation of S1P by S1P lyase are reversible.<sup>2</sup> S1P's targets are located both intracellularly and extracellularly. Intracellularly, S1P interacts with HDAC1/2 to affect transcription of c-Fos; extracellularly, S1P binds to G-protein coupled receptors, S1P<sub>1-5</sub>, to elicit a variety of cellular effects.<sup>1, 7, 8</sup> In contrast to S1P, Cer and Sph signal cell growth arrest and apoptosis.<sup>1, 9, 10</sup> Modulating the equilibrium towards Cer or S1P can be therapeutically beneficial for certain disease states.



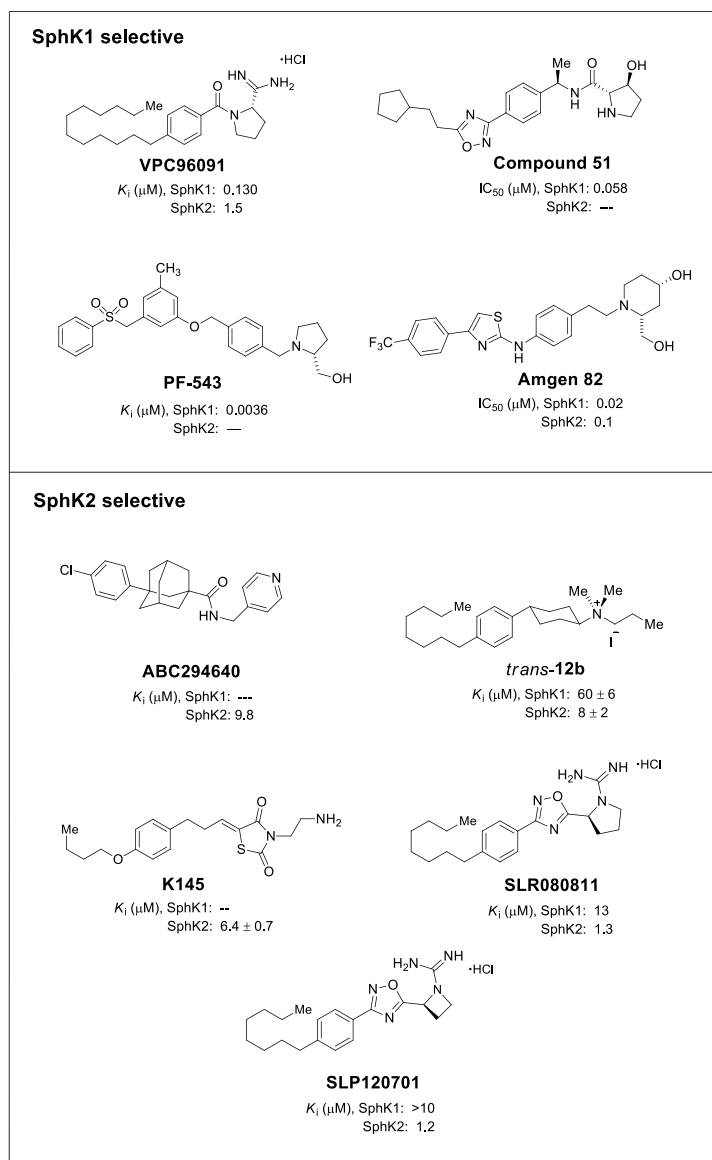


**Figure 3.1.** Equilibrium within the cell between Cer and S1P.

One way to influence the equilibrium is to target the enzymes responsible for the conversions. These efforts have been centered towards the enzymes that convert Sph to S1P, SphK1 and SphK2. While both phosphorylate S1P, both differ in location, cell effects, and size.<sup>1, 11</sup> SphK2 is larger by 234 amino acids due to an extra proline rich region and five additional transmembrane regions.<sup>12</sup> SphK2 is located in the nucleus, mitochondria, and endoplasmic reticulum whereas SphK1 is located in the cytoplasm.<sup>7, 12, 13</sup> The produced S1P may vary in function; S1P synthesized by SphK1, which has been well-studied, promotes cell growth and proliferation.<sup>14</sup> S1P produced by SphK2, which is not as well-studied, has been shown to promote cell growth while in other studies it was shown to promote cell death.<sup>15-17</sup>

Differences between the kinases allows for the synthesis of selective inhibitors (Fig. 3.2). There are more SphK1 inhibitors than SphK2 reported because SphK1 has been studied to a greater extent.<sup>11, 18-23</sup> SphK1 inhibitors are well below the micromolar range and improving in

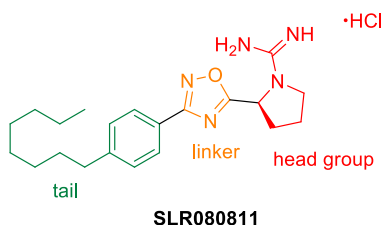
part due to the recent elucidation of SphK1's x-ray crystal structure.<sup>24, 25</sup> A few of the inhibitors, such as **PF-543** and an analog of **Amgen 82**, have been docked into SphK1, which has provided valuable information on key interactions within the binding pocket.<sup>18, 25</sup> Due to a lack of x-ray crystal structure and emerging investigations, SphK2 inhibitors are in the mid-low micromolar range, with plenty of room to improve. The Santos group recently published a SphK2 inhibitor with ~1  $\mu\text{M}$   $K_i$  and 10-fold selectivity for SphK2 over SphK1 (**SLR080811**, Fig. 3.2).<sup>16, 23</sup> This is currently the most potent published SphK2 inhibitor.



**Figure 3.2.** SphK selective inhibitors.

The pharmacophore for **SLR080811** can be broken down into three regions: a proline head group bearing a guanidine moiety, a 1,2,4-oxadiazole linker, and a para-octyl phenyl tail (Fig. 3.3). The synthesis of **SLR080811** and its derivatives was recently published in 2015.<sup>23</sup> A variety of natural and unnatural amino acids were tested as head groups, as previously discussed

in Chapter 2 (Table 2.2). Both *S*-proline and *S*-azetidine were demonstrated to be the most effective head groups for our scaffold. A surprising finding is that the azetidine derivative had a doubled half-life relative to the proline derivative. Further, various isomers of oxadiazole rings and amides were also evaluated as linker groups in the scaffold. The 1,2,4-oxadiazole ring and amides were also evaluated as linker groups in the scaffold. The 1,2,4-oxadiazole ring showed to be the most effective linker. This chapter discusses the SAR of the tail region of **SLR080811**, explores substituent effects on the benzene ring, and modification of the octyl tail.



**Figure 3.3.** **SLR080811** pharmacophore.

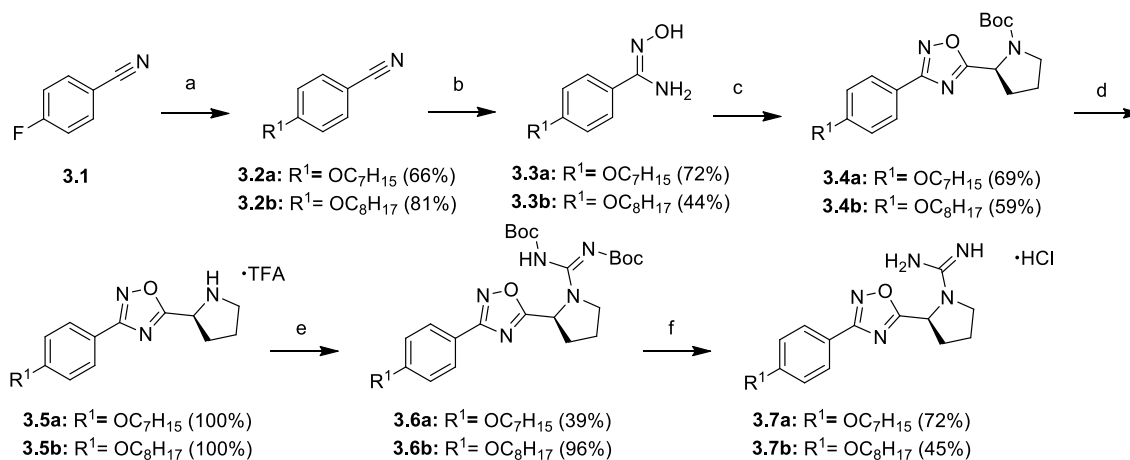
## 3.5. Results and discussion

### 3.5.1 Synthesis of inhibitors

The linker and head group portions of **SLR080811** have been investigated; hence, the tail region became the focus area of investigation. To rapidly synthesize a diverse library of tail groups, an ether linkage was introduced (Scheme 3.1). A nucleophilic aromatic substitution was performed on 4-fluorobenzonitrile **3.1** with an alcohol to afford compound **3.2**. Nitrile **3.2** was treated with hydroxylamine and triethylamine to convert the nitrile to amidoxime **3.3**. Compound **3.3** underwent cyclization when refluxed with HCTU•PF<sub>6</sub> and Boc-*L*-proline to form the 1,2,4-oxadiazole **3.4**. Following Boc removal with trifluoroacetic acid, amine salt **3.5** was then reacted with *N,N'*-di-Boc-1H-pyrazole-1-carboxamide and diisopropylethylamine to

yield the guanylated intermediate **3.6**. A subsequent deprotection of the Boc groups with HCl in methanol yielded final products **3.7a** and **3.7b**.

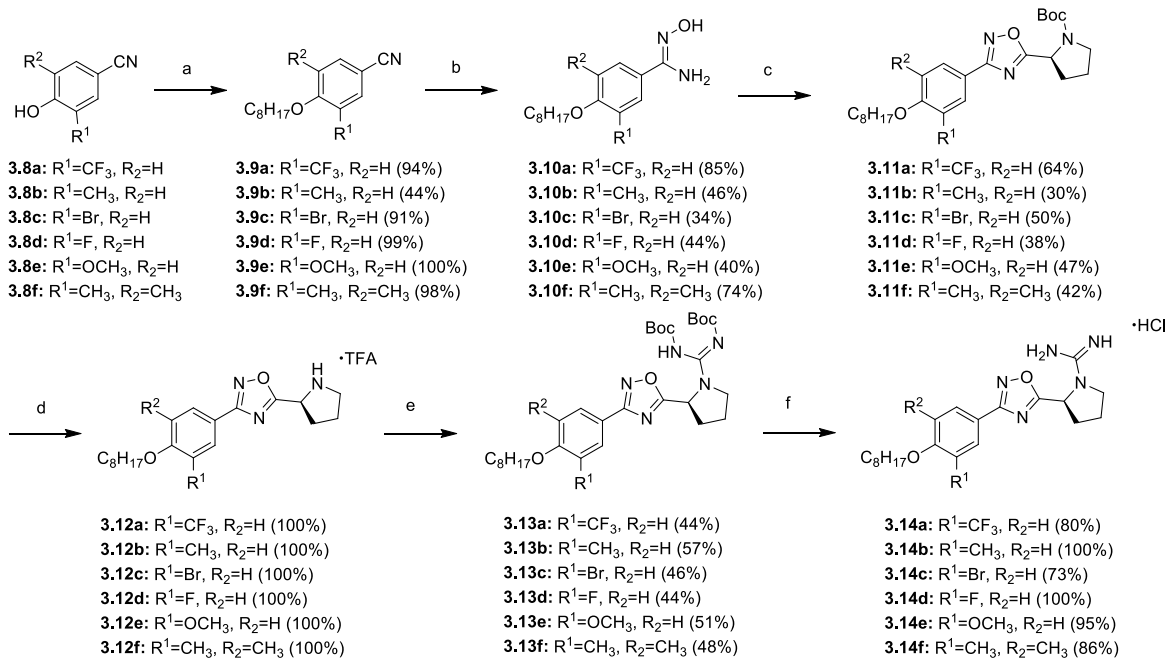
**Scheme 3.1.** Synthesis of analogues **3.7a-b**.



Reagents and conditions: a) R<sup>1</sup>-OH, KO<sup>t</sup>Bu, THF, reflux, 18 h; b) HO-NH<sub>2</sub>•HCl, Et<sub>3</sub>N, 95% EtOH, reflux, 2-3 h; c) Boc-*L*-Proline, HCTU•PF<sub>6</sub>, DIEA, DMF, 100 °C, 18 h; d) 1:1 TFA:CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; e) *N,N'*-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, microwave, 50 °C, 2 h; f) HCl, MeOH.

Compounds **3.14a-f** were synthesized to investigate the effect of substitutions on the internal ring (Scheme 3.2). A Williamson ether reaction was performed with 4-hydroxy-3-(trifluoromethyl) benzonitrile **3.8a-f**, potassium carbonate, and 1-bromooctane to provide **3.9a-f**. Compound **3.9a-f** was reacted with hydroxylamine and triethylamine to give amidoximes **3.10a-f**. Coupling with HCTU•PF<sub>6</sub> and Boc-*L*-proline gave the 1,2,4-oxadiazole intermediates **3.11a-f**. Deprotection of the Boc group with trifluoroacetic acid followed by guanylation with *N,N'*-di-Boc-1H-pyrazole-1-carboxamide afforded intermediates **3.13a-f**. A final deprotection of the Boc groups with HCl yielded final products **3.14a-f**.

**Scheme 3.2.** Synthesis of analogues **3.14a-f**.

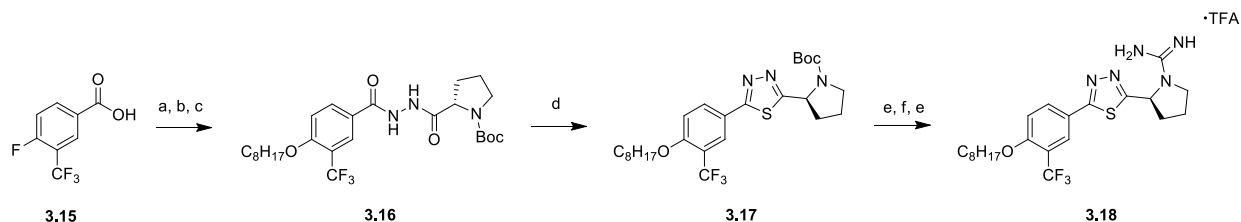


Reagents and conditions: a) 1-bromooctane, K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN, reflux, 18 h; b) HO-NH<sub>2</sub>·HCl, Et<sub>3</sub>N, 95% EtOH, reflux, 2-3 h; c) Boc-*L*-Proline, HCTU·PF<sub>6</sub>, DIEA, DMF, 100 °C, 18 h; d) 1:1 TFA:CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; e) *N,N'*-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, microwave, 50 °C, 2 h; f) HCl, MeOH.

Next, we investigated possible isosteres for the 1,2,4-oxadiazole ring (Scheme 3.3).<sup>23</sup> Inspired by an S1P receptor agonist containing a 1,3,4-thiadiazole moiety, a 1,3,4-thiadiazole linker was explored.<sup>26</sup> To achieve this, nucleophilic aromatic substitution was performed on 4-fluoro-3-trifluoromethyl benzoic acid **3.15** with 1-octanol. The resulting carboxylic acid moiety was converted to a hydrazide via an amide coupling protocol facilitated by hydrazine, HCTU·PF<sub>6</sub>, and DIEA. Amide coupling between hydrazide and Boc-*L*-proline gave compound **3.16**. Lawesson's reagent was reacted with **3.16** to yield 1,3,4-thiadiazole **3.17**. Boc deprotection using trifluoroacetic acid resulted in amine salt **3.18**, which was guanylated with N,

N'-di-Boc-1H-pyrazole-1-carboxamide. Deprotection of the Boc groups afforded the TFA salt **3.18**.

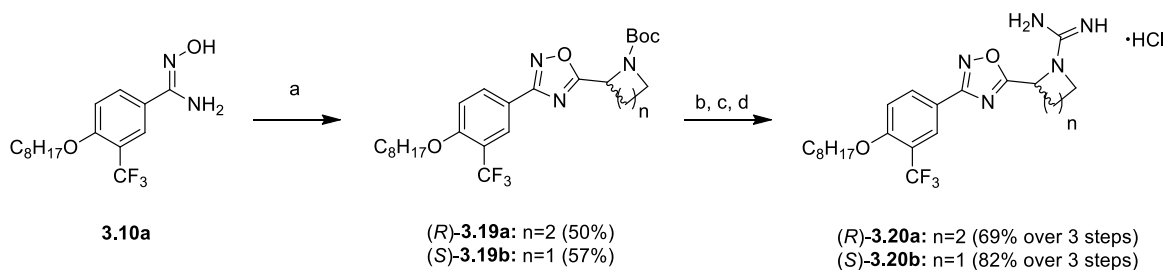
**Scheme 3.3.** Synthesis of analog **3.18**.



Reagents and conditions: a) 1-octanol, KOtBu, THF, reflux, overnight; b) hydrazine, HCTU, DIEA, 4:1 CH<sub>2</sub>Cl<sub>2</sub>:DMF, rt, 2 h; c) Boc-*L*-Proline, HCTU·PF<sub>6</sub>, DIEA, 2:1 CH<sub>2</sub>Cl<sub>2</sub>:DMF, rt, 2 h, 32% (over 3 steps); d) Lawesson's reagent, toluene, reflux, 2 h, 32%; e) TFA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 8 h, 100% conversion; f) N,N'-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, rt, 3 days, 51%.

Next, we probed the head group region (Scheme 3.4). Previous reports indicated that the proline head group to be an effective head group but when exchanged for an azetidine, the half-life increased *in vivo*.<sup>23</sup> We hypothesize that a similar manipulation will result in increased half-life. Further, to determine whether activity is dependent on the pyrrolidine stereochemistry, the *R*-proline derivative was also synthesized. Briefly, the 1,2,4-oxadiazole was formed by reacting **3.10a** with HCTU·PF<sub>6</sub>, DIEA, and either Boc-*L*-azetidine or Boc-*D*-proline to give compounds **3.19a** and **3.19b**. Deprotection of the Boc group with TFA followed by guanylation using N, N'-di-Boc-1H-pyrazole-1-carboxamide and a final deprotection with HCl gave the final amine salts **3.20a-b**.

**Scheme 3.4.** Synthesis of analogues **3.20a-b**.

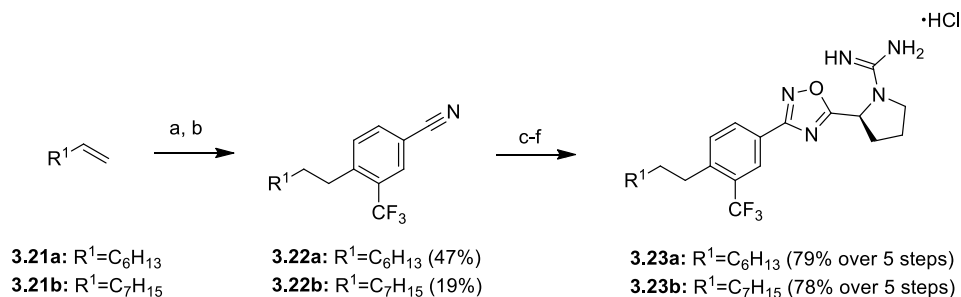


Reagents and conditions: a) Boc-*D*-proline or Boc-*L*-azetidine, HCTU•PF<sub>6</sub>, DIEA, DMF, 100 °C, overnight; b) 1:1 TFA:CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; c) *N,N'*-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, microwave, 50 °C, 2 h; d) HCl, MeOH.

Next, tail derivatives were prepared to explore the alkyl tail length dependency (whether an octyl or heptyl group is optimal) on activity. In this case, we exchanged the oxygen ether linkage to a carbon atom (Scheme 3.5). A hydroboration reaction was performed with 9-BBN and the respective alkenes **3.21a-b** overnight at room temperature. Subsequently, a Suzuki coupling reaction with the hydroborated product in the presence of PdCl<sub>2</sub> (dppf), cesium carbonate, and 4-iodo-3-(trifluoromethyl) benzonitrile yielded compounds **3.22a-b**. Next, the nitrile in intermediates **3.22a-b** was transformed to an amidoxime. Following that reaction, the intermediates underwent oxadiazole cyclization, Boc deprotection, guanylation, and a second Boc deprotection to afford the final HCl salts **3.23a-b**.



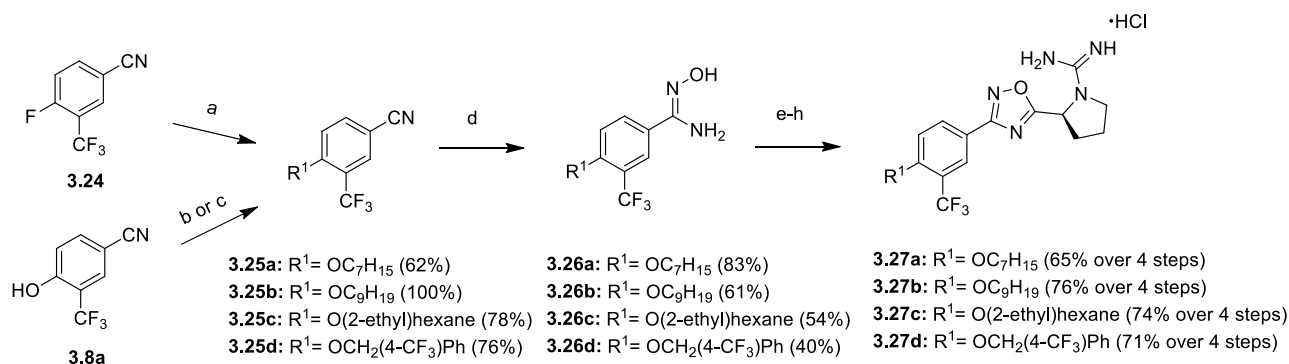
**Scheme 3.5.** Synthesis of analogues **3.23a-b**.



Reagents and conditions: a) 1) 9-BBN, THF, rt, overnight; b) PdCl<sub>2</sub>(dppf), Cs<sub>2</sub>CO<sub>3</sub>, DMF, reflux, 18 h; c) HO-NH<sub>2</sub>·HCl, Et<sub>3</sub>N, 95% EtOH, reflux, 2-3 h; d) Boc-*L*-Proline, HCTU·PF<sub>6</sub>, DIEA, DMF, 100 °C, overnight; e) 1:1 TFA:CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; f) HCl, MeOH; g) *N,N'*-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, microwave, 50 °C, 2 h.

The synthesis of additional ether-linked lipophilic groups is shown in Scheme 3.6. The goal was to evaluate the optimal ether tail length for inhibition and whether branching and benzyl tails improve interactions in the binding pocket. Thus, 1-bromoheptane or 1-bromo-2-ethylhexane was reacted with 4-hydroxy-3-(trifluoromethyl) benzonitrile **3.8a** and potassium carbonate to give compounds **3.25a** and **3.25c**. Nucleophilic aromatic substitution of 1-nonanol with 4-fluoro-3-(trifluoromethyl) benzonitrile **3.24** and potassium *tert*-butoxide yielded **3.25b**. To synthesize **3.25d**, 4-(trifluoromethyl) benzyl alcohol was reacted with **3.8a** under Mitsunobu reaction conditions. From there, intermediates **3.25a-d** were treated with hydroxylamine and triethylamine to yield amidoximes **3.25a-d**. Subsequently, intermediates **3.25a-d** underwent oxadiazole cyclization, Boc deprotection, guanylation, and a second Boc deprotection to afford HCl salts **3.27a-d**.

**Scheme 3.6.** Synthesis of analogues **3.27a-d**.

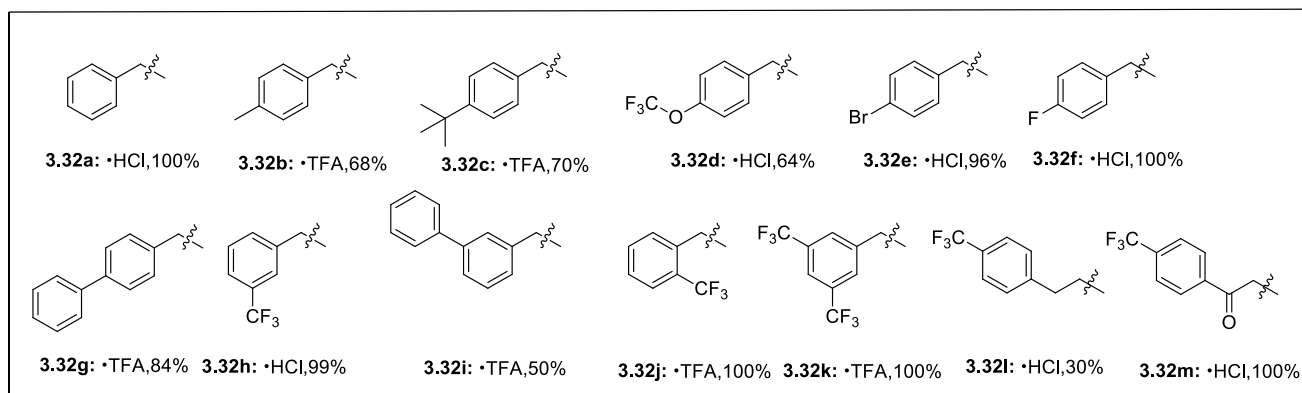
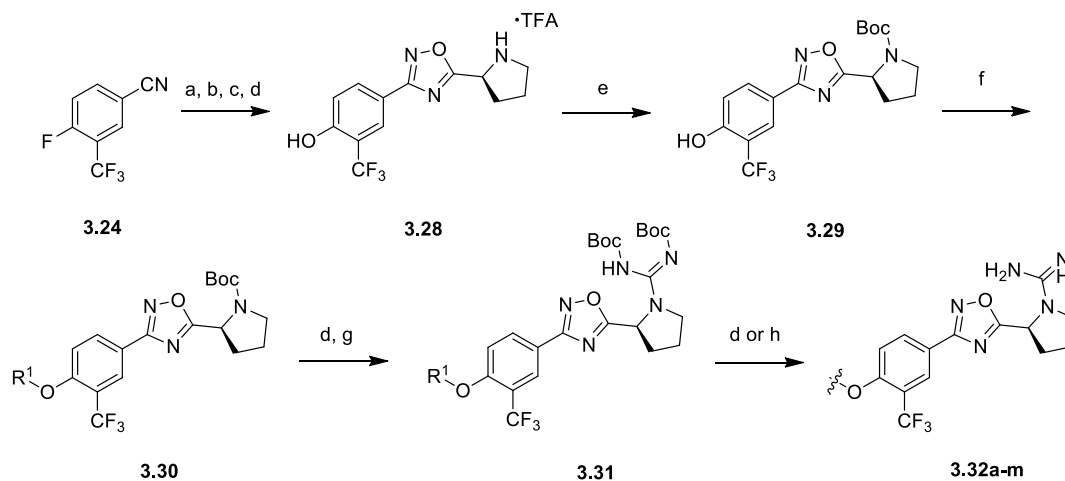


Reagents and conditions: a) 1-nonanol, KO<sup>t</sup>Bu, THF, reflux, 18 h; b) 4-(trifluoromethyl) benzyl alcohol, PPh<sub>3</sub>, 40% DIAD in toluene, THF, reflux, 3-4 h; c) 1-bromo-2-ethylhexane or 1-bromoheptane, K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN, reflux, 18 h; d) HO-NH<sub>2</sub>•HCl, Et<sub>3</sub>N, 95% EtOH, reflux, 2-3 h; e) Boc-*L*-Proline, HCTU•PF<sub>6</sub>, DIEA, DMF, 100 °C, 18 h; f) 1:1 TFA:CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h; g) *N,N'*-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, microwave, 50 °C, 2 h; h) HCl, MeOH.

From these modifications, the benzyl tail demonstrated the best inhibition. Thus, the benzyl tail was further probed to determine whether other substituents can improve inhibitory activity (Scheme 3.7). To facilitate a rapid synthesis of new analogs, key intermediate **3.29** was synthesized. To achieve this strategy, nucleophilic aromatic substitution with 4-fluoro-3-(trifluoromethyl) benzonitrile **3.24** and potassium *tert*-butoxide was performed. Following formation of the 1,2,4-oxadiazole ring, Boc deprotection was completed with TFA, which removed the Boc on the nitrogen and the *tert*-butyl group on the phenol oxygen, to give compound **3.28**. Reprotection of the pyrrolidine nitrogen using Boc-anhydride and triethylamine yielded key intermediate **3.29**. The benzyl tail groups were added utilizing a Williamson ether synthesis to afford **3.30**. Removal of Boc group yielded amine salts that were guanylated with

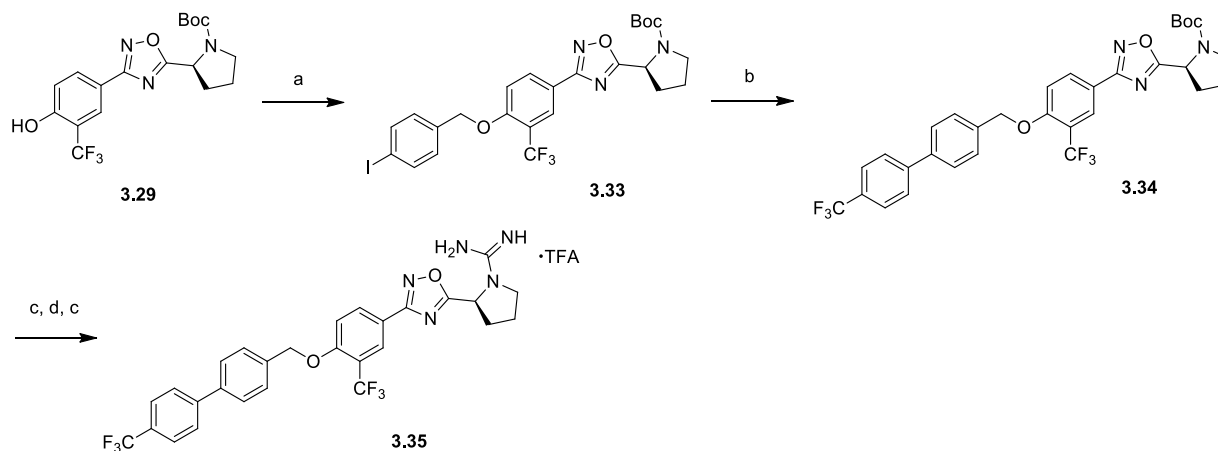
N, N'-di-Boc-1H-pyrazole-1-carboxamidinium providing intermediate **3.31**. Subsequently, a final deprotection, either with HCl or TFA, yielded products **3.32a-m**. It is noted that TFA deprotections became favorable over HCl because of synthetic issues. When the benzyl group contained an electron-donating rather than an electron-withdrawing group, side products were observed with HCl. This was also observed with TFA but only when excess amount was used. Therefore, the switch was made to TFA because the rate of addition can be controlled. Hence, slow addition of TFA was performed and the reaction was carefully monitored by TLC. For the more elaborate biphenyl group, a Suzuki coupling procedure was implemented (Scheme 3.8).

**Scheme 3.7.** Synthesis of analogues **3.32a-m**.



Reagents and conditions: a) KO<sup>t</sup>Bu, THF, reflux, 1-2 h, 77%; b) HO-NH<sub>2</sub>·HCl, Et<sub>3</sub>N, 95% EtOH, reflux, 2-3 h, 77%; c) Boc-*L*-Proline, HCTU·PF<sub>6</sub>, DIEA, DMF, 100 °C, 18 h, 29%; d) TFA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1-12 h, 64-100%; e) (Boc)<sub>2</sub>O, Et<sub>3</sub>N, 1,4-dioxane, rt, 3-4 h, 55%; f) R<sup>1</sup>-Br, K<sub>2</sub>CO<sub>3</sub>, acetone, reflux, 1-2 h, 25-88%; g) N,N'-di-Boc-1H-pyrazole-1-carboxamide, DIEA, CH<sub>3</sub>CN, microwave, 50 °C, 2 h, 31-73%; h) HCl, MeOH, 30-100%.

### Scheme 3.8. Synthesis of analogue 3.35.



Reagents and conditions: a) 4-iodobenzyl bromide,  $K_2CO_3$ , acetone, reflux, 1-2 h, 70%; b) (4-trifluoromethyl)phenyl boronic acid,  $Pd(dppf)Cl_2$ ,  $CS_2CO_3$ , reflux, 18 h, 46%; c) TFA,  $CH_2Cl_2$ , rt, 3-12 h, 87%; d) N,N'-di-Boc-1H-pyrazole-1-carboxamide, DIEA,  $CH_3CN$ , microwave, 50 °C, 2 h, 37%.

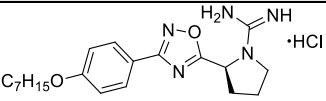
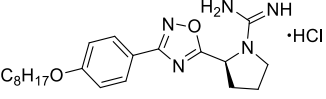
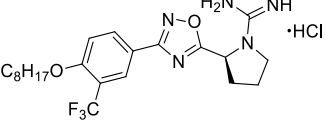
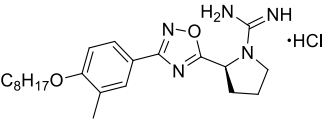
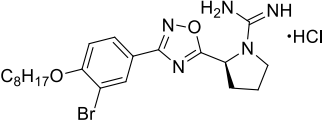
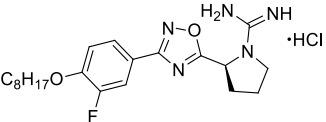
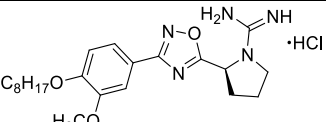
### 3.5.2 Biological evaluation

The inhibitory effects of the derivatives synthesized were measured using a previously reported assay.<sup>16, 23</sup> Three concentrations of inhibitor were tested in duplicate: 1  $\mu M$  against hSphK1 and 0.3  $\mu M$  and 1  $\mu M$  against hSphK2. Compounds were tested at 1  $\mu M$  for both enzymes, and as our focus is inhibition of SphK2, these compounds were also tested at a more stringent concentration of 0.3  $\mu M$  (Table 3.1). In general, little to no inhibition was observed with SphK1, with the exception of **3.27a**. This is a desirable result because it suggests that SphK2 appears to be the major target of the derivatives.

The first modifications, **3.7a-b**, showed little to no inhibition of hSphK1 or hSphK2 activity. This is comparable to inhibition values shown by **SLR080811** (91% hSphK2 activity), which is our lead compound. The data suggests that inhibition is not altered when the tail

changes from an octyl ether to an octyl chain although there is a “one-atom” spacer between the two. It is hypothesized that the oxygen of the ether is not in a position to facilitate favorable binding interactions in the enzyme binding site.

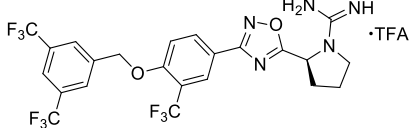
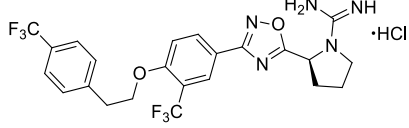
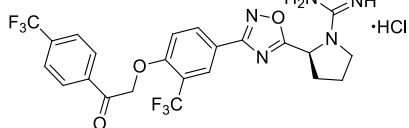
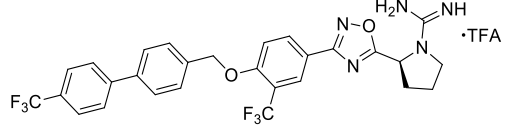
**Table 3.1.** SphK inhibitory activity<sup>a</sup>

<b>Cmpd</b>	<b>Structure</b>	<b>% SphK1 activity (1 μM)</b>	<b>% SphK2 activity (1 μM)</b>	<b>% SphK2 activity (0.3 μM)</b>
<b>3.7a</b>		99 ± 6	77 ± 6	98 ± 1
<b>3.7b</b>		89 ± 3	92 ± 2	97 ± 1
<b>3.14a</b>		94 ± 5	20 ± 2	49 ± 4
<b>3.14b</b>		102 ± 4	36 ± 3	47 ± 5
<b>3.14c</b>		98 ± 4	40 ± 4	55 ± 8
<b>3.14d</b>		92 ± 3	66 ± 5	85 ± 2
<b>3.14e</b>		97 ± 3	68 ± 10	81 ± 1

<b>3.14f</b>		$91 \pm 3$	$47 \pm 11$	$63 \pm 9$
<b>3.18</b>		$109 \pm 5$	$33 \pm 7$	$54 \pm 3$
<b>3.20a</b>		$107 \pm 2$	$94 \pm 10$	$94 \pm 8$
<b>3.20b</b>		$84 \pm 2$	$33 \pm 11$	$44 \pm 3$
<b>3.23a</b>		$94 \pm 5$	$22 \pm 2$	$44 \pm 1$
<b>3.23b</b>		$91 \pm 5$	$41 \pm 4$	$61 \pm 1$
<b>3.27a</b>		$65 \pm 4$	$42 \pm 8$	$86 \pm 15$
<b>3.27b</b>		$103 \pm 1$	$21 \pm 12$	$42 \pm 1$
<b>3.27c</b>		$95 \pm 3$	$86 \pm 1$	$105 \pm 4$
<b>3.27d</b>		$80 \pm 1$	$23 \pm 3$	$35 \pm 3$

<b>3.32a</b>		$90 \pm 6$	$58 \pm 2$	$83 \pm 10$
<b>3.32b</b>		$101 \pm 5$	$41 \pm 8$	$55 \pm 1$
<b>3.32c</b>		$96 \pm 1$	$35 \pm 6$	$45 \pm 9$
<b>3.32d</b>		$82 \pm 10$	$21 \pm 2$	$24 \pm 3$
<b>3.32e</b>		$89 \pm 11$	$33 \pm 1$	$45 \pm 2$
<b>3.32f</b>		$84 \pm 2$	$33 \pm 14$	$41 \pm 4$
<b>3.32g</b>		$88 \pm 6$	$19 \pm 7$	$26 \pm 6$
<b>3.32h</b>		$97 \pm 1$	$41 \pm 4$	$58 \pm 2$
<b>3.32i</b>		$86 \pm 1$	$41 \pm 3$	$77 \pm 4$
<b>3.32j</b>		$84 \pm 5$	$61 \pm 1$	$84 \pm 13$



<b>3.32k</b>		92 ± 5	52 ± 2	62 ± 4
<b>3.32l</b>		84 ± 7	36 ± 15	54 ± 5
<b>3.32m</b>		93 ± 7	60 ± 2	89 ± 3
<b>3.35</b>		100 ± 4	20 ± 2	39 ± 8

<sup>a</sup> SphK activity is represented as % of control (without inhibitor). Human SphK expression was forced in insect cells infected with recombinant baculovirus, and activity in a cleared lysate was measured using 5 μM (for SphK1) or 10 μM (for SphK2) sphingosine and 250 μM [<sup>32</sup>P]-ATP. Each compound was assayed in duplicate. Control = activity without inhibitor.

When probing the effects of substituents on the phenyl ring, **3.14a-f** showed selectivity for hSphK2 over hSphK1, with most displaying no inhibitory activity against hSphK1. Against hSphK2, **3.14a** with the trifluoromethyl moiety showed the best activity, inhibiting hSphK2 activity to 20% at 1 μM. Compound **3.14b**, the methyl analog, exhibited slightly decreased inhibition with hSphK2 activity being 36% at 1 μM. When the methyl is exchanged for bromine in **3.14c**, hSphK2 activity increases slightly to 40% at 1 μM. Compound **3.14d**, which contains a fluorine moiety, decreased hSphK2 activity to 66% at 1 μM. To determine the effect of an electron-donating group, methyl ether **3.14e** was tested with diminished activity (68% at 1 μM). Finally, dimethyl substituted derivative **3.14f** inhibited hSphK2 activity to 47% at 1 μM. These

results indicate that inhibitor **3.14a**, containing a trifluoromethyl moiety, shows a favorable interaction within the binding pocket. This could be attributed to its increased lipophilicity, strong electron withdrawing properties, or the ability to halogen bond.

With markedly improved inhibition with **3.14a**, an oxadiazole analog such as 1,3,4-thiadiazole (**3.18**) was synthesized. Not surprisingly, **3.18** showed comparable inhibition to lead compound **3.14a**. It inhibited hSphK2 to 33 and 54% activity at 1 and 0.3  $\mu\text{M}$  concentrations respectively. Because there is no observed inhibition with hSphK1, the data suggests that this compound is hSphK2 selective. The 1,2,4-oxadiazole linker in **3.14a** was investigated further due its slightly better inhibition values and ease of synthesis.

To determine the stereochemical preference of the enzyme, the enantiomer of **3.14a**, **3.20a**, bearing (*R*)-stereochemistry was synthesized. This compound showed little to no inhibition of hSphK1 or hSphK2, confirming the stereochemical preference of the enzyme for the (*S*)-enantiomer. Further, when exchanging the proline for an azetidine, as in **3.20b**, inhibition was as expected. With this information at hand, alkyl derivatives bearing the trifluoromethyl moiety were tested. Compound **3.23a**, with an octyl carbon tail, showed reasonable inhibition of hSphK2, limiting activity to 22% at a 1  $\mu\text{M}$  concentration. Compound **3.23a**'s ether counterpart, **3.27a**, did not inhibit hSphK2 as well, with activity reaching 42% at the same concentration. Compound **3.23b**, containing a nonyl carbon tail, showed comparable inhibition to its ether counterpart **3.14a**, with hSphK2 activity at 1  $\mu\text{M}$  being 33% versus 20%. These results suggest that both alkyl and ether tails are tolerated by the enzyme and that a length of 9 atoms affords optimal inhibition.

Analysis of tail branching and length in the next series of modifications, **3.27a-d**, led to a more potent inhibitor. Compounds **3.27a** and **3.27b** investigated the length of the ether tail

group. Compound **3.27a** (heptyloxy), at 1  $\mu\text{M}$ , inhibited hSphK2 activity to 42% and **3.27b** (nonyloxy) inhibited activity to 21%. Further, **3.27a** showed a decrease in selectivity by inhibiting hSphK1 to 65% at 1  $\mu\text{M}$ . The octyl and nonyl ether tails, **3.14a** and **3.27b**, appear to be the best lengths. Compound **3.27c** tested branching within the tail group. This compound showed little to no inhibition against either kinase, leading to the conclusion that branched alkyl tails are not as effective as straight chain alkyl groups. To probe the enzyme cavity further, compound **3.27d** with a benzyl ether tail with a trifluoromethyl moiety in the para position was synthesized. Compound **3.27d** decreased hSphK2 activity to 23% at 1  $\mu\text{M}$ . Because of its significantly improved activity, it was tested at a more stringent concentration of 0.3  $\mu\text{M}$ . At this concentration, **3.27d** was found to be more potent than **3.14a**, inhibiting hSphK2 activity to 35% versus 49%, suggesting a  $K_i$  value less than 300 nM. With this new information, an SAR was developed around **3.27d**.

The final group of modifications, **3.32a-m** and **3.35**, are derivatives of **3.27d**. They were designed to analyze the effect of different substituents attached to the benzyl ring. First, a non-substituted benzyl ring **3.32a** was tested. This modification led to a decrease in hSphK2 inhibition (58% activity at 1  $\mu\text{M}$ ) suggesting that a substituted benzyl ring provides better interactions within the binding pocket. Electron donating groups in the para position were tested next, **3.32b-d**. The alkyl derivatives **3.32b** (methyl) and **3.32c** (*tert*-butyl) showed slightly less inhibition than **3.27d**, resulting in activities around 40% at 1  $\mu\text{M}$ . Compound **3.32d**, containing a trifluoromethyl ether substituent, decreased hSphK2 activity to 21% at 1  $\mu\text{M}$ , suggesting that the  $-\text{OCF}_3$  moiety is a good substitution for  $-\text{CF}_3$  in this series. Furthermore, at a 0.3  $\mu\text{M}$  concentration, **3.32d** provides better inhibition compared to **3.27d**, with hSphK2 activities being 24% versus 35%, respectively. With a trifluoromethyl moiety in common, it can be concluded

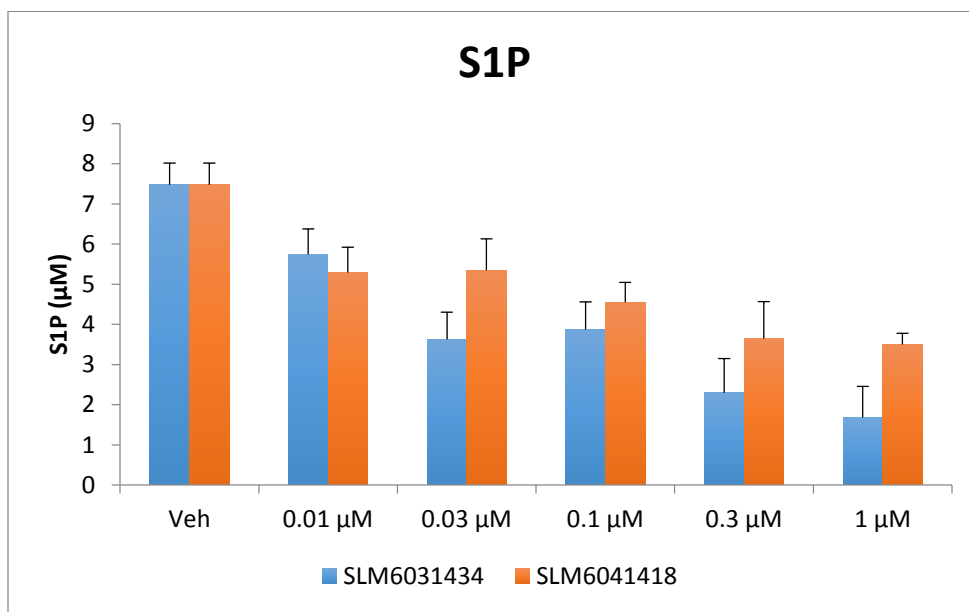
that the lipophilicity and/or its extra length fits in a favorable pocket in the binding site.

Compounds **3.32e-f** exchange the trifluoromethyl group for halogens, Br and F. They showed comparable inhibition to **3.27d**, both limiting SphK2 activity to 33% at 1  $\mu$ M.

Compounds **3.32g** and **3.35** probed the effects of size and hydrophobic interactions using a biphenyl group. The biphenyl derivative **3.32g** inhibited hSphK2 activity to 19% at 1  $\mu$ M and 26% at 0.3  $\mu$ M. The addition of a trifluoromethyl moiety on the para position of the biphenyl **3.35** resulted in 20% activity at 1  $\mu$ M and 39% at 0.3  $\mu$ M. In this particular case, the trifluoromethyl group did not improve inhibition. Next, we investigated moving the substituents from the para position to the meta and ortho position, **3.32h-j**. A trifluoromethyl **3.32h** and a phenyl **3.32i** moiety were tested in the meta position, but, unfortunately, no improvement of activity was observed. When a trifluoromethyl group was tested in the ortho position (**3.32j**), a drop in inhibition was also observed (61% activity at 1  $\mu$ M), leading to the conclusion that groups in the para position are favored. Next, a disubstituted benzyl tail was evaluated. Compound **3.32k** containing two trifluoromethyl groups in the meta positions of the phenyl ring was ineffective (52% activity at 1  $\mu$ M). Finally, we extended the methylene spacer of **3.27d** to an ethylene unit **3.32l** to evaluate the length dependency. The results showed a slight decrease in hSphK2 activity in the presence of **3.32l** (36% versus **3.27d** being 23%). Rigidity and inclusion of a hydrogen bond donor was probed by the installation of a ketone in the ethylene linker **3.32m**. Unfortunately, this derivative showed significantly diminished activity (60% at 1  $\mu$ M).

Compound **3.14a** (SLM6031434) and **3.18** (SLM6041418) were further evaluated in U937 full cell assays. The inhibitors were incubated with U937 cells expressing SphK1 and SphK2. After incubation, the cells were washed, lysed, and the amount of S1P was measured by LC-MS-MS. Figure 3.4 shows the effect of **SLM6031434** and **SLM6041418** on S1P levels in

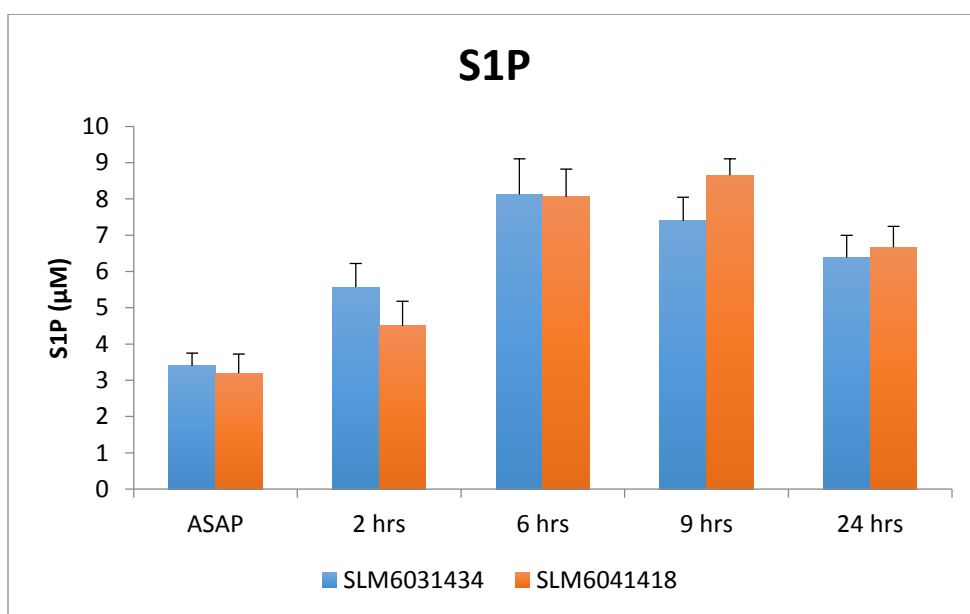
U937 cells. To our delight, we observe a dose-dependent decrease in S1P levels as a function of inhibitor concentration. Analysis of the data suggests that **SLM6031434** is more potent than **SLM6041418**. We then determined the inhibition constant of each inhibitor and found a  $K_i$  of 370 nM for **SLM6031434** and 23-fold selectivity for SphK2 over SphK1. **SLM6041418** had a  $K_i$  of 430 nM and 24-fold selectivity for SphK2 over SphK1. These compounds are a significant improvement over our lead SLR080811, suggesting that further structural manipulations can lead to better inhibitors.



**Figure 3.4.** Effect of **SLM6031434** and **SLM6041418** on S1P in U937 cells. After 2h of incubation, cells were harvested by centrifugation, lysed, and levels of S1P were measured using LC-MS-MS. Each value was determined in duplicate.

The encouraging activities of **SLM6031434** and **SLM6041418** prompted us to determine their effects *in vivo*. Figure 3.5 provides the data from these studies. The mice were injected

intraperitoneally with 5 mg/kg of each inhibitor and their S1P levels were monitored over a period of time. As shown in Figure 3.5, S1P levels increased after inhibitor administration. S1P levels peaked at 6 hours and remained elevated over 24 hours. This was the same response observed with **SLR080811**.<sup>16</sup> This increase in S1P levels is a pharmacodynamic marker for target engagement and is consistent with SphK2 inhibitors. The mechanism of S1P elevation is yet to be determined.



**Figure 3.5.** S1P levels in the blood of mice injected with **SLM6031434**. Wild-type mice were injected (i.p.) with 5 mg/kg of inhibitor and blood was drawn at time increments (0, 2, 6, 9, and 24 hrs). Levels of S1P from blood samples of WT mice were measured by LC-MS-MS. Each bar represents an average of 6 mice.

### 3.6. Conclusion

In conclusion, this chapter focused on the structure-activity studies in the tail region of sphingosine kinase inhibitors. A significant finding in our investigations was the effect of a trifluoromethyl group on the benzene ring which improved affinity and selectivity towards SphK2. In addition, we discovered that a para-(trifluoromethyl) benzyl group aided in SphK2 binding affinity. These studies suggest that the binding cavity in SphK2 is large and can accommodate a bulky, lipophilic para-(trifluoromethyl) benzyl group. Treatment of U937 cells with **SLM6031434** and **SLM6041418** demonstrated inhibition of SphK2 and decreased S1P levels as expected. Subsequent administration of inhibitors in mice increased S1P levels in blood, which is in contrast with whole cell assays but consistent with SphK2 knock-out studies. Our investigations also confirm our initial observation that SphK2 inhibition with a small molecule results in increased S1P levels in blood. The compounds reported herein are the most potent and selective SphK2 inhibitors discovered. Further, we provide a platform/scaffold that will aid in improving sphingosine kinase inhibitors.

### 3.7 References

1. Takabe, K.; Paugh, S. W.; Milstien, S.; Spiegel, S., "Inside-Out" signaling of sphingosine-1-phosphate: Therapeutic targets. *Pharmacol. Rev.* **2008**, *60*, 181-195.
2. Furuya, H.; Shimizu, Y.; Kawamori, T., Sphingolipids in cancer. *Cancer and Metastasis Rev.* **2011**, *30*, 567-576.
3. Takuwa, Y.; Ikeda, H.; Okamoto, Y.; Takuwa, N.; Yoshioka, K., Sphingosine-1-phosphate as a mediator involved in development of fibrotic diseases. *Biochem. Biophys. Acta* **2012**.
4. Maceyka, M.; Harikumar, K. B.; Milstien, S.; Spiegel, S., Sphingosine-1-phosphate signaling and its role in disease. *Trends Cell Biol.* **2012**, *22*, 50-60.

5. Pyne, N. J.; Dubois, G.; Pyne, S., Role of sphingosine 1-phosphate and lysophosphatidic acid in fibrosis. *Biochem. Biophys. Acta* **2012**.
6. Zhang, Y.; Berka, V.; Song, A.; Sun, K.; Wang, W.; Zhang, W.; Ning, C.; Li, C.; Zhang, Q.; Bogdanov, M.; Alexander, D. C.; Milburn, M. V.; Ahmed, M. H.; Lin, H.; Idowu, M.; Zhang, J.; Kato, G. J.; Abdulmalik, O. Y.; Zhang, W.; Dowhan, W.; Kellems, R. E.; Zhang, P.; Jin, J.; Safo, M.; Tsai, A.-L.; Juneja, H. S.; Xia, Y., Elevated sphingosine-1-phosphate promotes sickling and sickle cell disease progression. *J. Clin. Invest.* **2014**, *124*, 2750-2761.
7. Kihara, A.; Mitsutake, S.; Mizutani, Y.; Igarashi, Y., Metabolism and biological functions of two phosphorylated sphingolipids, sphingosine 1-phosphate and ceramide 1-phosphate. *Prog. Lipid. Res.* **2007**, *46*, 126-144.
8. Hait, N. C.; Allegood, J.; Maceyka, M.; Strub, G. M.; Harikumar, K. B.; Singh, S. K.; Luo, C.; Marmorstein, R.; Kordula, T.; Milstien, S.; Spiegel, S., Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. *Science* **2009**, *325*, 1254-1257.
9. Cuvillier, O., Sphingosine in apoptosis signaling. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **2002**, *1585*, 153-162.
10. Pettus, B. J.; Chalfant, C. E.; Hannun, Y. A., Ceramide in apoptosis: an overview and current perspectives. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **2002**, *1585*, 114-125.
11. Plano, D.; Amin, S.; Sharma, A. K., Importance of sphingosine kinase (SphK) as a target in developing cancer therapeutics and recent developments in the synthesis of novel SphK inhibitors. *J. Med. Chem.* **2014**, *57*, 5509-5524.
12. Spiegel, S.; Milstien, S., Sphingosine 1-phosphate, a key cell signaling molecule. *J. Biol. Chem.* **2002**, *277*, 25851-25854.



13. Pyne, N. J.; Pyne, S., Sphingosine 1-phosphate and cancer. *Nat. Rev. Cancer* **2010**, *10*, 489-503.
14. Kim, R. H.; Takabe, K.; Milstien, S.; Spiegel, S., Export and functions of sphingosine-1-phosphate. *Biochem. Biophys. Acta* **2009**, *1791*, 692-696.
15. Edmonds, Y.; Milstien, S.; Spiegel, S., Development of small-molecule inhibitors of sphingosine-1-phosphate signaling. *Pharmacol. Ther.* **2011**, *132*, 352-360.
16. Kharel, Y.; Raje, M. R.; Gao, M.; Gellett, A. M.; Tomsig, J. L.; Lynch, K. R.; Santos, W. L., Sphingosine kinase type 2 inhibition elevates circulating sphingosine 1-phosphate. *Biochem. J.* **2012**, 149-157.
17. Venkataraman, K.; Thangada, S.; Michaud, J.; Oo, M. L.; Ai, Y.; Lee, Y.-M.; Wu, M.; Parikh, N. S.; Khan, F.; Proia, R. L.; Hla, T., Extracellular export of sphingosine kinase-1a contributes to the vascular S1P gradient. *Biochem. J.* **2006**, *397*, 461-471.
18. Gustin, D. J.; Li, Y.; Brown, M. L.; Min, X.; Schmitt, M. J.; Wanska, M.; Wang, X.; Connors, R.; Johnstone, S.; Cardozo, M.; Cheng, A. C.; Jeffries, S.; Franks, B.; Li, S.; Shen, S.; Wong, M.; Wesche, H.; Xu, G.; Carlson, T. J.; Plant, M.; Morgenstern, K.; Rex, K.; Schmitt, J.; Coxon, A.; Walker, N.; Kayser, F.; Wang, Z., Structure guided design of a series of sphingosine kinase (SphK) inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4608-4616.
19. French, K. J.; Zhuang, Y.; Maines, L. W.; Gao, P.; Wang, W.; Beljanski, V.; Upson, J. J.; Green, C. L.; Keller, S. N.; Smith, C. D., Pharmacology and antitumor activity of ABC294640, a selective inhibitor of sphingosine kinase-2. *J. Pharmacol. Exp. Ther.* **2010**, *333*, 129-139.
20. Lim, K. G.; Sun, C.; Bittman, R.; Pyne, N. J.; Pyne, S., (R)-FTY720 methyl ether is a specific sphingosine kinase 2 inhibitor: Effect on sphingosine kinase 2 expression in HEK

- 293 cells and actin rearrangement and survival of MCF-7 breast cancer cells. *Cell Signal.* **2011**, *23*, 1590-1595.
21. Schnute, M. E.; McReynolds, M. D.; Kasten, T.; Yates, M.; Jerome, G.; Rains, J. W.; Hall, T.; Chrencik, J.; Kraust, M.; Cronin, C. N.; Saabye, M.; Highkin, M. K.; Broadus, R.; Ogawa, S.; Cukyne, K.; Zawadzke, L. E.; Peterkin, V.; Iyanar, K.; Scholten, J. A.; Wendling, J.; Fujiwara, H.; Nemirovskiy, O.; Wittwer, A. J.; Nagiec, M. M., Modulation of cellular S1P levels with a novel, potent and specific inhibitor of sphingosine kinase-1. *Biochem. J.* **2012**, *444*, 79-88.
22. Raje, M. R.; Knott, K.; Kharel, Y.; Bissel, P.; Lynch, K. R.; Santos, W. L., Design, synthesis and biological activity of sphingosine kinase 2 selective inhibitors. *Bioorg. Med. Chem.* **2012**, *20*, 183-194.
23. Patwardhan, N. N.; Morris, E. A.; Raje, M. R.; Gao, M.; Kharel, Y.; Tomsig, J. L.; Lynch, K. R.; Santos, W. L., Structure-activity relationship studies and in vivo activity of guanidine-based sphingosine kinase inhibitors: Discovery of SphK 1 and 2 selective inhibitors. *J. Med. Chem.* **2015**, *58*, 1879-1899.
24. Wang, Z.; Min, X.; Xiao, S.-H.; Johnstone, S.; Romanow, W.; Meininger, D.; Xu, H.; Liu, J.; Dai, J.; An, S.; Thibault, S.; Walker, N., Molecular basis of sphingosine kinase 1 substrate recognition and catalysis. *Structure* **2013**, *21*, 798-809.
25. Wang, J.; Knapp, S.; Pyne, N. J.; Pyne, S.; Elkins, J. M., Crystal structure of sphingosine kinase 1 with PF-543. *ACS Med. Chem. Lett.* **2014**, *5*, 1329-1333.
26. Deng, H.; Bernier, S. G.; Doyle, E.; Lorusso, J.; Morgan, B. A.; Westlin, W. F.; Evindar, G., Discovery of clinical candidate GSK1842799 as a selective S1P(1) receptor agonist (prodrug) for multiple sclerosis. *ACS Med. Chem. Lett.* **2013**, *4*, 942-947.

## Chapter 4 Experimental

### 4.1 General procedures

All reactions in Chapters 2 and 3 were conducted in oven-dried glassware under an inert atmosphere of nitrogen or argon using magnetic stirring, unless otherwise stated. Non-alcohol solvents were dried using an Innovative Technology Pure Solv-MD solvent purification system. Commercially available reagents were purchased and used without further purification. TLC analysis was performed on aluminum backed silica plates or aluminum oxide (neutral) plates. Column chromatography was performed either on flash grade silica gel ( $\text{SiO}_2$ , 32–63  $\mu\text{m}$ ) or neutral, activated aluminum oxide ( $\text{Al}_2\text{O}_3$ , ~150 mesh, 58 Å) as solid phase.

### 4.2 Instrumentation

$^1\text{H}$  NMR spectra were recorded on a Bruker Avance II-500 (500 MHz), Agilent U4-DD2-400 (400 MHz), or Agilent MR4-400 (400 MHz). Chemical shifts are reported in ppm with the solvent resonance as an internal standard (Ex: Chloroform-d: 7.26 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration.  $^{13}\text{C}$  NMR spectra were recorded on a Bruker Avance II-500 (125 MHz), Agilent U4-DD2-400 (101 MHz), or Agilent MR4-400 (101 MHz). Chemical shifts are reported in ppm with the solvent resonance as the internal standard (Chloroform-d: 77.16 ppm).  $^{19}\text{F}$  NMR spectra were recorded on an Agilent U4-DD2-400 (376 MHz) or Agilent MR4-400 (376 MHz). Fluorine NMR chemical shifts are reported in ppm with either trifluoroacetic acid (-76.55 ppm) or hexafluorobenzene (-164.9 ppm) as internal standards. Low-resolution mass spectrometry (ESI-MS) was performed on a Thermo Electron TSQ triple quadrupole mass spectrometer, equipped with an ESI source, which was used in the positive ion mode. High-resolution mass spectroscopy (HRMS) was performed on an Agilent 6220 LC/MS

time-of-flight mass spectrometer using either electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI). All melting points are reported without correction. HPLC analyses for Chapter 2 were performed by Dr. Neeraj Patwardhan on an Agilent XDB-C8 reverse phase column using water (with 0.1% v/v of TFA) and acetonitrile as eluents. HPLC analyses for Chapter 3 were performed by Dr. Mehdi Ashraf on an Agilent 6220 reverse phase column using water (with 0.1% v/v of formic acid) and acetonitrile as eluents. Optical rotations of final compounds were measured on a Jasco P-2000 polarimeter at room temperature (25 °C). All compounds tested in biological assays are >95% pure by <sup>1</sup>HNMR and HPLC analyses unless noted otherwise. Microwave reactions were performed with a CEM Discover SP microwave reactor with an Explorer Hybrid robot.

### **4.3 Biological evaluation procedures**

#### **4.3.1 Sphingosine Kinase assays**

Recombinant baculovirus encoding either SphK1 or SphK2 was expressed in Sf9 insect cells, cleared lysates were prepared after 48 hours and 1-2 μL (0.02-0.03 mg protein) was used in each assay. Alternately, plasmids encoding SphK1 or SphK2 were used to transfect HEK293T cells and cleared lysates were prepared after 48 hours. SphK activity was measured in kinase assay buffer that consisted of 20 mM Tris-Cl (pH 7.4), 1 mM 2-mercaptoethanol, 1mM EDTA, 5 mM sodium orthovanadate, 40 mM □-glycerophosphate, 15 mM NaF, 1 mM phenylmethylsulfonyl fluoride, 10 mM MgCl<sub>2</sub>, 0.5 mM 4-deoxypyridoxine, 10% glycerol, and 0.01 mg/ml each leupeptin, aprotinin, and soybean trypsin inhibitor. To achieve optimal activity of SphK1 or SphK2, the buffer was supplemented with either 0.5% Triton X-100 or 1 M KCl, respectively. To ascertain any inhibitory effect of compounds, the assay was supplemented with substrate (*D*-erythro-sphingosine, (10 μM for SphK1 and 5 μM for SphK2), appropriate amount

of compounds (to achieve 10-10,000 nM);  $\gamma$ - [ $^{32}\text{P}$ ] ATP (10  $\mu\text{M}$ , specific activity = 8.3 Ci/mmol), and recombinant enzyme (0.02–0.03 mg of total protein). After 20 min at 37 °C, the reaction mixture was extracted with 2 volumes of chloroform/methanol/1 N HCl (100:200:1), and the components in the organic phase were separated by thin layer chromatography using a 1-butanol/glacial acetic acid/water (3:1:1) solvent system. Radiolabeled enzyme products were detected by autoradiography and identified by migration relative to authentic standards. For quantification, the silica gel containing radiolabeled lipid was scraped into a scintillation vial and measured by liquid scintillation counting.

#### **4.3.2 Sample Preparation and LC-MS-MS Analysis**

To analyze the lipids and compounds by LC/MS, sample preparation protocols were adapted from a literature procedure,<sup>1</sup> with minor modifications. Cell pellets (2-4 x 10<sup>6</sup> cells), whole blood (20  $\mu\text{L}$ ) or plasma (50  $\mu\text{L}$ ) was mixed with 2 mL of a methanol: chloroform solution (3:1) and transferred to a capped glass vial. Suspensions were supplemented with 10  $\mu\text{L}$  of internal standard solution containing 10 pmoles each of deuterated (D7) S1P and deuterated (D7) sphingosine. The mixture was placed in a bath sonicator for 10 minutes and incubated at 48 °C for 16 hours. The mixture was then cooled to ambient temperature and mixed with 200  $\mu\text{L}$  of 1M KOH in methanol. The samples were again sonicated and incubated another 2 hours at 37 °C. Samples were then neutralized by the addition of 20  $\mu\text{L}$  of glacial acetic acid and transferred to 2 mL microcentrifuge tubes. Samples were then centrifuged at 12,000 x g for 12 minutes at 4 °C. The supernatant fluid was collected in a separate glass vial and evaporated under a stream of nitrogen gas. Immediately prior to LC-MS analysis, the dried material was dissolved in 0.3 mL of methanol and centrifuged at 12,000 x g for 12 minutes at 4 °C. Fifty microliters of the resulting supernatant fluid was analyzed.

Analyses were performed using Liquid Chromatography-ESI Mass Spectrometry (LC-MS) using a triple quadrupole mass spectrometer (AB-Sciex 4000 Q-Trap) coupled to a Shimadzu LC-20AD LC system. A binary solvent gradient with a flow rate of 1 mL/min was used to separate sphingolipids and drugs by reverse phase chromatography using a Supelco Discovery C18 column (50 mm × 2.1 mm, 5 µm bead size). Mobile phase A consisted of water:methanol:formic acid (79:20:1) while mobile phase B was methanol : formic acid (99:1). The run started with 100% A for 0.5 minutes. Solvent B was then increased linearly to 100% B in 5.1 minutes and held at 100% for 4.3 minutes. The column was finally re-equilibrated to 100% A for 1 min. Natural sphingolipids were detected using multiple reaction monitoring (MRM) protocols previously described as follows: S1P (380.4 → 264.4); deuterated (D7)C<sub>18</sub>S1P (387.4 → 271.3); sphingosine (300.5 → 264.4); deuterated (D7) sphingosine (307.5 → 271.3).<sup>1</sup> Retention times for all analytes under our experimental conditions were between 5.1 and 5.6 min. Quantification was carried out by measuring peak areas using commercially available software (Analyst 1.5.1).

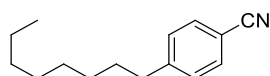
#### **4.3.3 U937 Cell Culture/Viability Assay**

U937 cells were grown in RPMI 1640 media supplemented with *L*-glutamate, 10% fetal bovine serum (FBS), and 1% penicillin/streptomycin at 37 °C in an atmosphere containing 5% CO<sub>2</sub>.<sup>2</sup> Twenty-four hours before adding inhibitors, the growth media was replaced with media containing 0.5% FBS. For viability studies, inhibitors were added at the indicated concentrations (0.1, 0.3, 1.0 and 3.0 µM) and after 24 hours, Trypan blue dye was used following the manufacturer instructions (Bio-RAD TC10 Automated Cell Counter).

#### 4.3.4 Pharmacokinetic Analysis

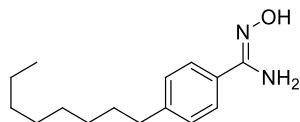
Groups of 8-20 week old mice (strain: C57BL6/j) were injected (intraperitoneal route) with either inhibitor (dose: 10 mg/kg) or an equal volume of vehicle (2% solution of hydroxypropyl- $\beta$ -cyclodextrin (Cargill Cavitron 82004)). For **SLP7111228**, 3-4 Sprague-Dawley strain rats (200-300 g) were injected with 10 mg/kg drug or an equal volume of vehicle for indicated time periods. After injection, animals were bled at the specified time points (ASAP time points were 1-2 minutes after dosing). Whole blood was processed immediately for LC-MS analysis as described above. Animal protocols were approved prior to experimentation by the University of Virginia's School of Medicine Animal Care and Use Committee.

#### 4.4 Synthetic procedures and characterization from Chapter 2



**4-Octylbenzonitrile (2.2).** Oct-1-ene (3 mL, 19.2 mmol) was added to a round bottom flask containing THF (8 mL). 9-BBN (42 mL, 21.0 mmol) was added as a 0.5 M solution in THF and the solution was stirred overnight at rt. To the above borane solution was added a solution of 4-iodobenzonitrile (4 g, 17.5 mmol) in DMF (50 mL). The reaction mixture was degassed for 10 min by bubbling N<sub>2</sub> through the solution. Cs<sub>2</sub>CO<sub>3</sub> (11.4 g, 34.9 mmol) and PdCl<sub>2</sub> (dppf) (383 mg, 0.52 mmol) were added together. The resulting reaction mixture was then stirred at 80 °C for 18 h, after which it was poured into a saturated solution of LiBr and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting brown residue was purified by flash

chromatography over silica gel (95/5 hexanes/EtOAc) to give the title compound (2.3 g, 62%) as a colorless oil. Analytical data matches with the literature.<sup>3</sup>



**(Z)-N'-Hydroxy-4-octylbenzimidamide (2.3).** Triethylamine (3.9 mL, 27.8 mmol) and hydroxylamine hydrochloride (1.7 g, 24.5 mmol) were added to a solution of **2** (2.4 g, 11.1 mmol) in 95% ethanol (30 mL). The colorless reaction mixture was then refluxed for 4 h. The organic solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (65/35 hexanes/EtOAc) to give the title compound (2.5 g, 92%) as a white solid. Analytical data matches with the literature.<sup>4</sup>

**General procedure 2-A: Coupling of amidoxime with amino acids.** DIEA (1.8 equiv) was added to a solution of amidoxime (1 equiv) and the appropriate Boc-protected amino acid (1.2 equiv) in DMF (0.2 M solution). HCTU (1.5 equiv) was then added to the resulting mixture at rt and stirred at 80 °C for 18h. At this time, TLC showed complete conversion of starting material. The solution was partitioned between ethyl acetate and water. The organic layer was collected and washed twice with a sat. LiBr. The aqueous solution was then back extracted with ethyl acetate. The organic layers were then combined and washed with sat. NaHCO<sub>3</sub> and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel to yield the desired product.

**General Procedure 2-B: Deprotection of *t*-Boc protecting groups using HCl (g).** Hydrochloric acid gas was bubbled through a solution of the N-Boc protected compound in methanol for 2-5 minutes, or until complete consumption of starting material was observed by



TLC. The reaction mixture was concentrated under reduced pressure and triturated with diethyl ether to yield the corresponding free amine hydrochloride salt, which was further purified by trituration with diethyl ether until satisfactory analytical data was obtained.

**General Procedure 2-C: Guanidylation of amines.** DIEA (3 equiv) was added to a solution of the corresponding amine hydrochloric acid salt and the reagent (*Z*)-*tert*-butyl (((*tert*-butoxycarbonyl) imino)(1*H*-pyrazol-1-yl) methyl) carbamate (1.05 equiv) in acetonitrile (20% vol/wt). The resulting reaction mixture was then stirred at RT until acceptable conversion of the starting amine was observed using TLC. The solvent was then removed under reduced pressure and the resulting colorless residue was purified by flash column chromatography over silica gel to yield the pure product.

**General Procedure 2-D: Deprotection of *t*-Boc protecting groups using TFA.** To a solution of Boc-protected intermediate in CH<sub>2</sub>Cl<sub>2</sub>, a 1N TFA solution in CH<sub>2</sub>Cl<sub>2</sub> was added. The resulting solution was stirred at room temperature until complete consumption of the starting material was observed using TLC. The reaction mixture was concentrated under reduced pressure and triturated with diethyl ether to yield the corresponding free amine TFA salt, which was purified by trituration with diethyl ether/hexanes (1/1) until satisfactory analytical data was obtained.

**General procedure 2-E: Inversion of hydroxyl group via Mitsunobu reaction.** PPh<sub>3</sub> (1 equiv), benzoic acid (1 equiv), and alcohol intermediate were added to THF (0.2 M solution) at room temperature. The solution was cooled to 0 °C and diisopropyl azo dicarboxylate (1 equiv) was added. The solution was warmed to room temperature and stirred overnight. At this time, TLC showed complete conversion of the starting material. The organic solvent was

removed under reduced pressure and the residue was purified by silica gel column chromatography to yield desired product.

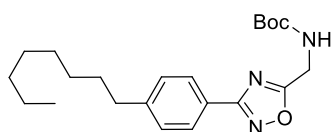
**General Procedure 2-F: Amide coupling of amino acids and amines.** The appropriate Boc-protected amino acid (1 equiv) and TEA (1 equiv) were dissolved in tetrahydrofuran (0.2 M solution) and then cooled to zero degrees Celsius. Ethyl chloroformate (1 equiv) was added dropwise and the solution was stirred for 30 minutes at 0 °C. The appropriate amine (1 equiv) was added dropwise. The reaction was stirred another 1 hour at 0 °C, 16 hours at rt, and 3 hours at reflux. After completion, the solution was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to yield the desired product.

**General procedure 2-G: Amide coupling of benzoic acids and amines.** Dissolve chosen benzoic acid derivative (1 equiv) in dichloromethane (0.2M solution). Add half the amount of TEA (0.75 equiv) and 1-hydroxypyrrolidine-2, 5-dione (1.5 equiv) with stirring at room temperature. In a separate flask, dissolve EDC (2 equiv) in dichloromethane (0.2M solution) with the other half of TEA (0.75 equiv). After the EDC is dissolved, add that into the reaction mixture dropwise over 15-20 minutes. Let the reaction stir for 6 hours at rt. After 6 hours, add (*S*)-*tert*-butyl 2-(aminomethyl) pyrrolidine-1-carboxylate (7 equiv) and let stir 16-60 hours. After completion, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to yield the desired product.

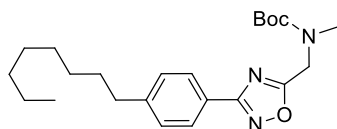
**General procedure 2-H: Suzuki coupling.** Chosen alkene (1.1 equiv) was added to a round bottom flask containing THF. 9-BBN (1.2 equiv) was added as a 0.5 M solution in THF

and the solution was stirred overnight at rt. To the above borane solution was added a solution of 4-iodobenzonitrile in DMF. The reaction mixture was degassed for 15 min by bubbling N<sub>2</sub> through the solution. Cs<sub>2</sub>CO<sub>3</sub> (2 equiv) and PdCl<sub>2</sub> (dppf) (0.03 equiv) were added together. The resulting reaction mixture was then stirred at 80 °C for 18 h, after which it was poured into a saturated solution of LiBr and extracted three times with hexane. The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting brown residue was purified by flash chromatography over silica gel to give the desired product.

**General procedure 2-I. Conversion of nitrile to amidoxime.** Triethylamine (3.3 equiv) and hydroxylamine hydrochloride (2 equiv) were added to a solution of chosen nitrile intermediate in 95% ethanol (0.2 M solution). The colorless reaction mixture was then refluxed for 2-3 h. The organic solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel to provide the desired product.

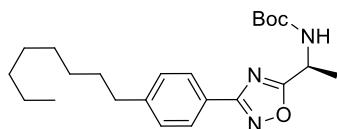


**Tert-butyl ((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) methyl) carbamate (2.4a).** Synthesized by author M.R.R. Synthesized by general procedure 2-A. 64% yield, yellow oil; <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 7.95 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.38 (br s, 1H), 4.61 (d, *J* = 5.2 Hz, 2H), 2.64 (t, *J* = 8.4 Hz, 2H), 1.66–1.56 (m, 2H), 1.46 (s, 9H), 1.36–1.19 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (126 MHz, Chloroform-d) δ 176.4, 168.5, 155.6, 146.8, 129.0, 127.5, 123.9, 80.7, 37.3, 36.0, 32.0, 31.3, 29.5, 29.4, 29.3, 28.4, 22.7, 14.2; HRMS (ESI<sup>+</sup>): Calcd for C<sub>22</sub>H<sub>33</sub>N<sub>3</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 410.2420, Found: 410.2451.



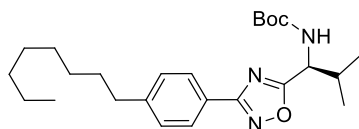
***Tert*-butyl methyl ((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) methyl) carbamate (2.4b).**

Synthesized by general procedure 2-A. 53% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.97 (d,  $J=8.2$  Hz, 2H), 7.26 (d,  $J=7.9$  Hz, 2H), 4.66 (d,  $J=41.5$  Hz, 2H), 3.03 (d,  $J=13.2$  Hz, 3H), 2.63 (t,  $J=7.4$  Hz, 2H), 1.62 (p,  $J=7.4$  Hz, 2H), 1.46 (d,  $J=29.3$  Hz, 9H), 1.32-1.21 (m, 10H), 0.87 (t,  $J=6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  176.2, 168.6, 146.8, 129.0, 127.5, 124.0, 81.0, 45.5, 36.1, 35.3, 32.0, 31.3, 29.6, 29.4, 29.3, 28.4, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{23}\text{H}_{36}\text{N}_3\text{O}_3$   $[\text{M}+\text{H}]^+$ : 402.2756, Found: 402.2742.



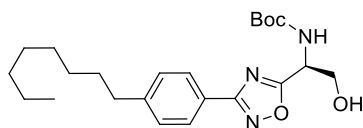
**(*S*)-*Tert*-butyl (1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) ethyl) carbamate (2.4c).**

Synthesized by author M.R.R. Synthesized by general procedure 2-A. 82% yield, yellow oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  7.96 (d,  $J = 8.0$  Hz, 2H), 7.26 (d,  $J = 8.0$  Hz, 2H), 5.29 (br s, 1H), 5.22–5.03 (m, 1H), 2.64 (t,  $J = 8.0$  Hz, 2H), 1.68–1.53 (m, 5H), 1.45 (s, 9H), 1.36–1.17 (m, 10H), 0.86 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  180.0, 168.4, 154.9, 146.7, 129.0, 127.5, 124.0, 80.5, 44.3, 36.0, 31.9, 31.3, 29.5, 29.3, 29.3, 28.4, 22.7, 20.2, 14.2; HRMS: Calcd for  $\text{C}_{23}\text{H}_{35}\text{N}_3\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 424.2576, Found: 424.2571.



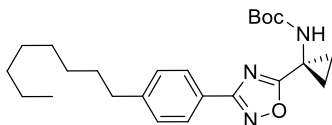
**(S)-Tert-butyl (2-methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) propyl) carbamate**

**(2.4d).** Synthesized by author M.R.R. Synthesized by general procedure 2-A. 77% yield, yellow oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  7.97 (d,  $J = 8.1$  Hz, 2H), 7.27 (d,  $J = 8.1$  Hz, 2H), 5.28–5.17 (m, 1H), 5.01–4.92 (m, 1H), 2.68–2.60 (m, 2H), 2.33–2.17 (m, 1H), 1.67–1.53 (m, 2H), 1.45 (s, 9H), 1.34–1.16 (m, 10H), 0.98 (d,  $J = 6.8$  Hz, 6H), 0.87 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  178.9, 168.3, 155.4, 146.7, 129.0, 127.5, 124.1, 80.4, 53.7, 36.0, 32.9, 31.9, 31.3, 29.5, 29.3, 28.4, 22.7, 18.7, 18.0, 14.2; HRMS: Calcd for  $\text{C}_{25}\text{H}_{39}\text{N}_3\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 452.2889, Found: 452.2884.



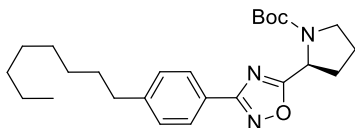
**(S)-Tert-butyl (2-hydroxy-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) ethyl) carbamate (2.4e).**

Synthesized by general procedure 2-A. 28% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.97 (d,  $J=8.3$  Hz, 2H), 7.28 (d,  $J=8.3$  Hz, 2H), 5.56 (s, 1H), 5.18 (s, 1H), 4.17 (d,  $J=8.9$  Hz, 1H), 4.04 (d,  $J=9.5$  Hz, 1H), 2.65 (t,  $J=7.6$  Hz, 2H), 2.51 (s, 1H), 1.63 (p,  $J=7.6$  Hz, 2H), 1.48 (s, 9H), 1.35-1.22 (m, 10H), 0.87 (t,  $J=6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  177.4, 168.4, 147.0, 129.1, 127.6, 123.8, 64.0, 50.2, 36.1, 32.0, 31.3, 29.6, 29.4, 29.3, 28.4, 22.8, 14.2; HRMS (Mixed ESI): Calcd for  $\text{C}_{23}\text{H}_{36}\text{N}_3\text{O}_4$   $[\text{M}+\text{H}]^+$ : 418.5505, Found: 418.2692.



***Tert*-butyl (1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) cyclopropyl) carbamate (2.4f).**

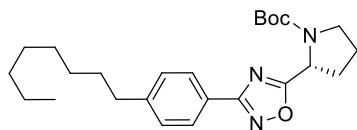
Synthesized by author M.G. Synthesized by general procedure 2-A. 62% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.91 (d,  $J = 7.5$  Hz, 2H), 7.24 (d,  $J = 8.0$  Hz, 2H), 5.53 (s, 1H), 2.70-2.57 (m, 2H), 1.77-1.73 (m, 2H), 1.67-1.56 (m, 2H), 1.49-1.45 (m, 11H), 1.35-1.18 (m, 10H), 0.92-0.82 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  180.8, 168.5, 155.6, 146.3, 128.8, 127.3, 124.2, 80.5, 35.9, 31.8, 31.2, 30.9, 29.4, 29.3, 29.2, 28.2, 22.6, 19.6, 14.1; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{24}\text{H}_{35}\text{N}_3\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 436.2576, Found: 436.2530.



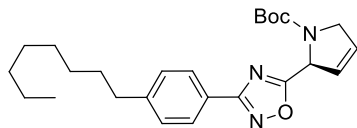
***(S)*-Tert-butyl 2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate (2.4g).**

Synthesized by author M.R.R. Synthesized by general procedure 2-A. 48% yield, yellow oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  7.96 (d,  $J = 7.8$  Hz, 2H), 7.33-7.18 (m, 2H), 5.21-5.14 (m, 1H, minor rotamer), 5.07-5.01 (m, 1H, major rotamer), 3.75-3.67 (m, 1H, major rotamer), 3.67-3.61 (m, 1H, minor rotamer), 3.59-3.50 (m, 1H, major rotamer), 3.50-3.41 (m, 1H, minor rotamer), 2.66-2.58 (m, 2H), 2.44-2.25 (m, 1H), 2.20-2.05 (m, 2H), 2.05-1.89 (m, 1H), 1.68-1.54 (m, 2H), 1.44 (s, 3H), 1.37-1.16 (m, 16H), 0.85 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ , rotamers)  $\delta$  180.5 (major), 180.1 (minor), 168.5 (major), 154.3 (minor), 153.6 (major), 146.7 (major), 146.4 (minor), 129.0 (major), 128.9 (minor), 127.5 (minor), 127.5 (major), 124.4 (minor), 124.2 (major), 80.5 (major), 80.4 (minor), 53.9 (major), 46.7 (minor),

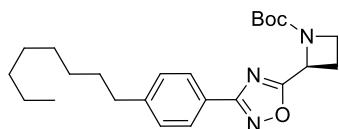
46.4 (major), 36.0 (major), 32.5 (major), 32.0 (major), 31.6 (minor), 31.3 (major), 29.5 (major), 29.3 (major), 29.2 (major), 28.5 (minor), 28.2 (major), 24.4 (minor), 23.8 (major), 22.7 (major), 14.2 (major). HRMS (ESI+): Calcd for C<sub>25</sub>H<sub>37</sub>N<sub>3</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 450.2733, Found: 450.2727.



**(R)-Tert-butyl 2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate ((R)-2.4h).** Synthesized by author M.G. Synthesized by general procedure 2-A. 73% yield, yellow oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 7.95 (d, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.10 – 4.94 (m, 1H), 3.68 (m, 1H), 3.52 (m, 1H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.36 (m, 1H), 2.12 (m, 2H), 2.02-1.87 (m, 1H), 1.61 (m, 2H), 1.44 (s, 3H), 1.34-1.15 (m, 16H), 0.85 (t, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 180.4, 168.3, 153.5, 146.5, 128.9, 128.7, 127.4, 127.3, 124.0, 80.4, 60.3, 53.8, 46.3, 35.9, 32.4, 31.8, 31.4, 31.2, 29.4, 29.3, 29.2, 28.4, 28.1, 23.7, 22.6, 21.0, 14.1, 14.0; HRMS (ESI+): Calcd for C<sub>25</sub>H<sub>38</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 428.2913, Found: 428.2908.

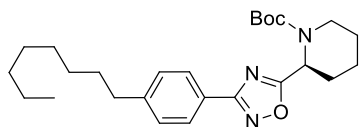


**(S)-Tert-butyl 2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (2.4i).** Synthesized by general procedure 2-A. 20% yield, yellow oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 7.97 (d, *J*=8.2 Hz, 2H), 7.29 (d, *J*=8.2 Hz, 2H), 6.09 (dd, *J*=24.9, 4.3 Hz, 1H), 5.87, (d, *J*=21.6 Hz, 1H), 5.87-5.77 (m, 1H), 4.49-4.30 (m, 2H), 2.65 (t, *J*=8 Hz, 2H), 1.63 (p, *J*=7.6 Hz, 2H), 1.48 (s, 3H), 1.28 (d, *J*=22.2 Hz, 16H), 0.88 (t, *J*=6.9 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 178.28, 177.80, 168.69, 153.26, 146.79, 129.89, 129.08, 127.54, 124.99, 124.14, 81.00, 60.85, 53.46, 36.12, 32.01, 31.37, 29.85, 29.58, 29.38, 28.28, 22.81, 14.24; HRMS (ESI+): Calcd for C<sub>25</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub>Na [M+Na]<sup>+</sup>: 448.2576, Found: 448.2595.



**(S)-Tert-butyl,2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) azetidine-1-carboxylate (2.4j).**

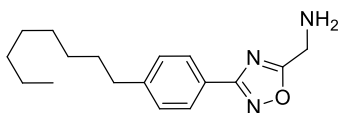
Synthesized by author N.N.P. Synthesized by general procedure 2-A. 73% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.97 (d,  $J = 8.2$  Hz, 2H), 7.38 – 7.15 (m, 2H), 4.60 (s, 1H), 4.19 (td,  $J = 9.4, 5.6$  Hz, 1H), 2.8 (p,  $J = 9.4$  Hz, 2H), 2.72 – 2.40 (m, 2H), 1.83 – 1.61 (m, 3H), 1.42 (s, 9H), 1.33 – 1.19 (m, 10H), 1.18 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  179.0, 168.2, 155.9, 132.0, 127.3, 127.2, 125.2, 93.3, 80.2, 80.1, 31.3, 28.6, 28.5, 28.3, 25.7, 22.5, 19.5, 14.1; HRMS (ESI+): Calcd for  $\text{C}_{24}\text{H}_{35}\text{N}_3\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 436.2576, Found: 436.2571.



**(S)-Tert-butyl 2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) piperidine-1-carboxylate (2.4k).**

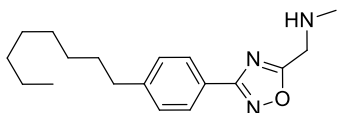
Synthesized by author N.N.P. Synthesized by general procedure 2-A. 77% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.97 (d,  $J = 8.1$  Hz, 2H), 7.25 (d,  $J = 8.4$  Hz, 2H), 5.55 (s, 1H), 4.07 (s, 1H), 3.02 (s, 1H), 2.63 (t,  $J = 8.1, 6.7$  Hz, 2H), 1.98 – 1.85 (m, 2H), 1.80 – 1.57 (m, 4H), 1.55 – 1.38 (m, 9H), 1.35 – 1.19 (m, 10H), 0.86 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  178.7, 168.3, 150.8, 146.4, 128.8, 127.4, 124.1, 80.5, 35.9, 31.8, 31.2, 29.4, 29.2, 29.2, 28.3, 27.9, 24.7, 22.6, 20.0, 14.0. HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{39}\text{N}_3\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 464.2889, Found: 436.2874





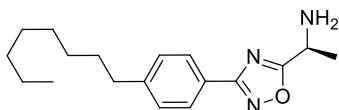
**3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl methanamine (2.5a).** Synthesized by author M.R.R.

Synthesized by general procedure 2-D. 99% yield, off-white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.08–7.92 (m, 2H), 7.34 (d,  $J = 8.4$  Hz, 2H), 4.86 (br s, 2H), 4.59 (s, 2H), 2.70–2.62 (m, 2H), 1.70–1.57 (m, 2H), 1.37–1.20 (m, 10H), 0.88 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  173.1, 168.5, 147.2, 128.9, 127.2, 123.4, 35.6, 34.9, 31.7, 31.1, 29.2, 29.1, 29.0, 22.4, 13.1; HRMS (ESI+): Calcd for  $\text{C}_{17}\text{H}_{26}\text{N}_3\text{O}^+$  [ $\text{M}^+$ ]: 288.2070, Found: 288.2067.



**N-Methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) methanamine (2.5b).** Synthesized by

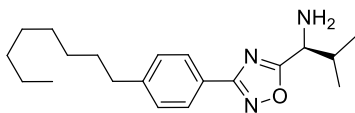
general procedure 2-B. 94% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.13 (d,  $J=8.3$  Hz, 2H), 7.48 (d,  $J=8.3$  Hz, 2H), 5.01 (s, 2H), 3.09 (s, 3H), 2.81 (t,  $J=7.8$ , 2H), 1.78 (p,  $J=7.3$  Hz, 2H), 1.51-1.38 (m, 10H), 1.01 (t,  $J=6.7$ , 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  173.2, 169.7, 148.5, 130.2, 128.5, 124.6, 44.4, 36.8, 34.2, 33.0, 32.4, 30.5, 30.3, 30.2, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{18}\text{H}_{28}\text{N}_3\text{O}$  [ $\text{M}+\text{H}$ ] $^+$ : 302.2232, Found: 302.2224.



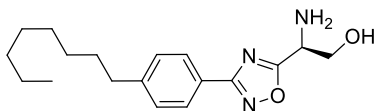
**(S)-1-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) ethanamine (2.5c).** Synthesized by author

M.R.R. Synthesized by general procedure 2-D. 89% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  8.06 – 7.89 (m, 2H), 7.35–7.19 (m, 2H), 4.33 (q,  $J = 6.9$  Hz, 1H), 2.70–2.55 (m, 2H), 1.81 (br s, 2H), 1.66–1.52 (m, 5H), 1.36–1.17 (m, 10H), 0.86 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR

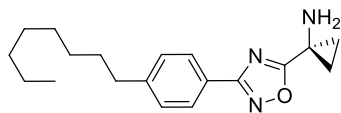
(126 MHz, Chloroform-d)  $\delta$  183.0, 168.3, 146.6, 129.0, 127.5, 124.2, 45.0, 36.0, 32.0, 31.3, 29.5, 29.4, 29.3, 22.7, 21.8, 14.2. HRMS (ESI+): Calcd for  $C_{18}H_{28}N_3O^+$  [ $M^+$ ]: 302.2227, Found: 302.2219.



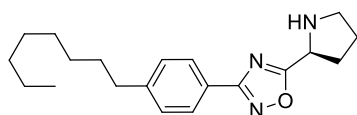
**(S)-2-Methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) propan-1-amine (2.5d).** Synthesized by author M.R.R. Synthesized by general procedure 2-D. 59% yield, white solid;  $^1H$  NMR (500 MHz, Chloroform-d)  $\delta$  8.01–7.92 (m, 2H), 7.30–7.19 (m, 2H), 4.00 (d,  $J = 5.8$  Hz, 1H), 2.61 (t,  $J = 8.0$  Hz, 2H), 2.23–2.11 (m, 1H), 1.73 (br s, 2H), 1.66–1.53 (m, 2H), 1.38–1.16 (m, 10H), 1.03–0.91 (m, 6H), 0.85 (t,  $J = 7.0$  Hz, 3H);  $^{13}C$  NMR (126 MHz, Chloroform-d)  $\delta$  182.2, 168.1, 146.6, 129.0, 127.5, 124.2, 55.1, 36.0, 33.6, 31.9, 31.3, 29.5, 29.3, 22.7, 19.0, 17.9, 14.2. HRMS (ESI+): Calcd for  $C_{20}H_{32}N_3O^+$  [ $M^+$ ]: 330.2540, Found: 330.2532.



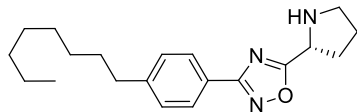
**(S)-2-Hydroxy-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) ethanaminium chloride (2.5e).** Synthesized by general procedure 2-B. 74% yield, white solid;  $^1H$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.05 (d,  $J=8.4$  Hz, 2H), 7.40 (d,  $J=8.4$  Hz, 2H), 4.99 (t,  $J=4.5$  Hz, 1H), 4.20 (d,  $J=4.5$  Hz, 2H), 2.73 (t,  $J=6.5$  Hz, 2H), 1.70 (p,  $J=7.3$  Hz, 2H), 1.43-1.28 (m, 10H), 0.93 (t,  $J=6.5$  Hz, 3H);  $^{13}C$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  175.3, 169.8, 148.6, 130.2, 128.5, 124.7, 61.4, 51.4, 36.9, 33.0, 32.4, 30.5, 30.4, 30.3, 23.7, 14.4; HRMS (ESI+): Calcd for  $C_{18}H_{28}N_3O_2^+$  [ $M^+$ ]: 318.2181, Found: 318.2174.



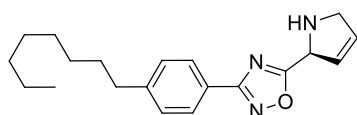
**1-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) cyclopropanamine (2.5f).** Synthesized by author M.G. Synthesized by general procedure 2-D. 100% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.94 (d,  $J = 8.2$  Hz, 2H), 7.27 (d,  $J = 8.0$  Hz, 2H), 2.70-2.59 (m, 2H), 2.38 (s, 2H), 1.69-1.55 (m, 2H), 1.54-1.46 (m, 2H), 1.36-1.19 (m, 12H), 0.87 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  183.8, 168.4, 146.4, 128.8, 127.3, 124.2, 35.9, 31.9, 31.8, 31.2, 29.4, 29.2, 29.2, 22.6, 19.8, 14.1; HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{19}\text{H}_{28}\text{N}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 314.2232, Found: 314.2208.



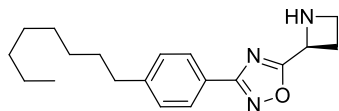
**(S)-3-(4-Octylphenyl)-5-(pyrrolidin-2-yl)-1,2,4-oxadiazole (2.5g).** Synthesized by author M.R.R. Synthesized by general procedure 2-D. 82% yield, off white solid;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  8.01–7.87 (m, 2H), 7.25–7.18 (m, 2H), 4.46 (dd,  $J = 8.3, 5.6$  Hz, 1H), 3.20–3.09 (m, 1H), 3.09–2.94 (m, 1H), 2.60 (t,  $J = 8.0$  Hz, 2H), 2.34 (br s, 1H), 2.29–2.17 (m, 1H), 2.14–2.00 (m, 1H), 1.96–1.76 (m, 2H), 1.65–1.51 (m, 2H), 1.34–1.13 (m, 10H), 0.83 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  181.9, 168.2, 146.5, 128.9, 127.5, 124.2, 54.4, 46.9, 36.0, 31.9, 31.3, 31.2, 29.5, 29.3, 29.3, 25.4, 22.7, 14.2; HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{20}\text{H}_{30}\text{N}_3\text{O}$   $[\text{M}^+]$ : 328.2389, Found 328.2354.



**(R)-3-(4-Octylphenyl)-5-(pyrrolidin-2-yl)-1,2,4-oxadiazole (2.5h).** Synthesized by author M.G. Synthesized by general procedure 2-D. 100% yield, off white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  7.97 (d,  $J = 8.0$  Hz, 2H), 7.32 (d,  $J = 7.6$  Hz, 2H), 4.65-4.44 (m, 1H), 3.34 (s, 1H), 3.12-3.18 (m, 2H), 2.67 (t,  $J = 7.6$  Hz, 2H), 2.35-2.31 (m, 1H), 2.18-2.14 (m, 1H), 2.05-1.91 (m, 2H), 1.68-1.62 (m, 2H), 1.38-1.25 (m, 10H), 0.90 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  182.8, 169.4, 148.0, 130.1, 128.4, 125.4, 55.3, 47.6, 36.9, 33.0, 32.4, 31.9, 30.6, 30.4, 30.3, 26.4, 23.7, 14.5; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{20}\text{H}_{30}\text{N}_3\text{O}$   $[\text{M}+\text{H}]^+$ : 328.2389, Found: 328.2383.

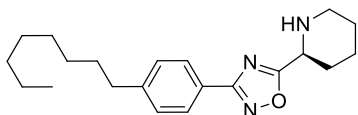


**(S)-2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl)-2,5-dihydro-1H-pyrrol-1-ium chloride (2.5i).** Synthesized by general procedure 2-B. 72% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  11.95 (d,  $J=8.3$  Hz, 2H), 11.31 (d,  $J=8.3$  Hz, 2H), 10.30 (d,  $J=4.5$  Hz, 1H), 10.20 (d,  $J=5.3$  Hz, 1H), 9.97 (s, 1H), 8.37-8.20 (m, 2H), 6.64 (t,  $J=7.0$  Hz, 2H), 5.61 (p,  $J=7.4$  Hz, 2H), 5.33-5.19 (m, 10H), 4.84 (t,  $J=6.4$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  174.7, 170.1, 148.7, 130.3, 130.2, 128.5, 125.2, 124.5, 61.6, 54.0, 36.9, 33.0, 32.4, 30.5, 30.4, 30.3, 23.7, 14.4; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{20}\text{H}_{28}\text{N}_3\text{O}^+$   $[\text{M}^+]$ : 326.2232, Found: 326.2240.

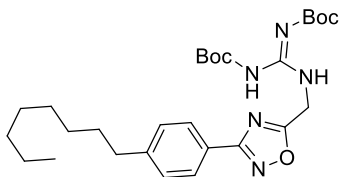


**(S)-2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) azetidinium (2.5j).** Synthesized by author N.N.P. Synthesized by general procedure 2-B. 94% yield, white solid;  $^1\text{H}$  NMR (400 MHz,

Methanol-d<sub>4</sub>)  $\delta$  8.00 (d,  $J = 8.4$  Hz, 1H), 7.35 (d,  $J = 8.5$  Hz, 2H), 5.93 (t,  $J = 8.5$  Hz, 1H), 4.39 – 4.26 (m, 1H), 4.17 (td,  $J = 10.0, 6.3$  Hz, 1H), 3.21 – 2.96 (m, 3H), 2.67 (t,  $J = 7.9, 7.4$  Hz, 2H), 1.64 (p,  $J = 7.3$  Hz, 2H), 1.43 – 1.16 (m, 10H), 0.87 (t,  $J = 6.7$  Hz, 3H). <sup>13</sup>C NMR (101 MHz, Methanol-d<sub>4</sub>)  $\delta$  173.8, 168.7, 147.2, 128.8, 127.1, 123.2, 52.8, 44.6, 35.4, 31.6, 31.0, 29.1, 28.9, 28.9, 23.9, 22.3, 13.0; HRMS (ESI<sup>+</sup>): Calcd for C<sub>19</sub>H<sub>29</sub>ClN<sub>3</sub>O [M+H]<sup>+</sup>: 350.1999, Found: 350.2017.

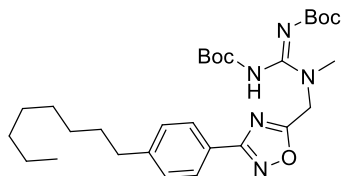


**(S)-2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) piperidin-1-ium chloride (2.5k).** Synthesized by author N.N.P. Synthesized by general procedure 2-B. 95% yield, white solid; <sup>1</sup>H NMR (500 MHz, Chloroform-d)  $\delta$  8.00 (d,  $J = 8.3$  Hz, 2H), 7.27 (d,  $J = 8.8$  Hz, 2H), 4.12 (dd,  $J = 9.8, 3.3$  Hz, 1H), 3.20 (dt,  $J = 12.2, 3.6$  Hz, 1H), 2.88 – 2.77 (m, 1H), 2.65 (t,  $J = 7.6$  Hz, 2H), 2.29 – 2.10 (m, 2H), 1.94 – 1.76 (m, 2H), 1.72 – 1.54 (m, 5H), 1.30 (ddt,  $J = 24.7, 9.8, 3.9$  Hz, 10H), 0.88 (t,  $J = 6.9$  Hz, 3H); <sup>13</sup>C NMR (126 MHz, Chloroform-d)  $\delta$  180.3, 168.2, 146.5, 128.9, 127.4, 124.1, 53.5, 46.0, 36.0, 31.9, 31.6, 31.2, 30.3, 29.4, 29.3, 29.2, 25.7, 23.6, 22.7, 14.1; HRMS (ESI<sup>+</sup>): Calcd for C<sub>21</sub>H<sub>32</sub>N<sub>3</sub>O<sup>+</sup> [M<sup>+</sup>]: 342.2540, Found: 342.2554.

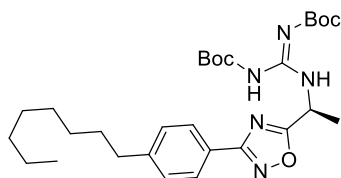


**Tert-butyl N-[[tert-butoxy]carbonyl]amino([3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl]methylamino)methylidene]carbamate (2.6a).** Synthesized by author M.R.R. Synthesized by general procedure 2-C. 78% yield, yellow oil; <sup>1</sup>H NMR (500 MHz, Chloroform-d)  $\delta$  11.47 (br s, 1H), 8.99

(t,  $J = 5.3$  Hz, 1H), 7.99–7.95 (m, 2H), 7.28 (d,  $J = 8.0$  Hz, 2H), 4.95 (d,  $J = 5.3$  Hz, 2H), 2.64 (t,  $J = 7.7$  Hz, 2H), 1.67–1.58 (m, 2H), 1.52 (s, 9H), 1.49 (s, 9H), 1.35–1.19 (m, 10H), 0.86 (t,  $J = 6.3$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  175.4, 168.5, 163.2, 156.3, 153.1, 146.8, 129.0, 127.6, 123.8, 83.8, 79.9, 37.3, 36.1, 31.9, 31.3, 29.5, 29.3, 29.3, 28.3, 28.1, 22.7, 14.2. HRMS (ESI+): Calcd for  $\text{C}_{28}\text{H}_{44}\text{N}_5\text{O}_5$   $[\text{M}+\text{H}]^+$ : 530.3342, Found: 530.3302.

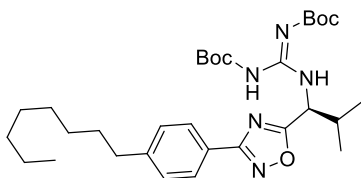


**Tert-butyl (((tert-butoxycarbonyl)amino)(methyl((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)amino)carbamate (2.6b).** Synthesized by general procedure 2-C. 34% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.98 (d,  $J=8.4$  Hz, 2H), 7.28 (d,  $J=8.7$  Hz, 2H), 4.96 (s, 2H), 3.18 (s, 3H), 2.65 (t,  $J=7.3$  Hz, 2H), 1.67-1.59 (m, 2H), 1.49 (s, 18H), 1.36-1.21 (m, 10H), 0.87 (t,  $J=7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  175.0, 168.6, 156.1, 146.8, 129.1, 127.6, 124.0, 77.4, 46.5, 38.0, 36.1, 32.0, 31.4, 29.9, 29.6, 29.4, 29.3, 28.2, 28.1, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{29}\text{H}_{46}\text{N}_5\text{O}_5$   $[\text{M}+\text{H}]^+$ : 544.3499, Found: 544.3453.

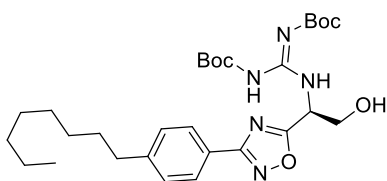


**Tert-butyl *N*-[[(tert-butoxy)carbonyl]amino([(1*S*)-1-[3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl]ethyl)amino)methylidene]carbamate (2.6c).** Synthesized by author M.R.R. Synthesized by general procedure 2-C. 81% yield, yellow solid;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  11.50 (br s, 1H), 8.97 (d,  $J = 8.1$  Hz, 1H), 8.00–7.92 (m, 2H), 7.30–7.23 (m, 2H), 5.82–5.72 (m, 1H), 2.70–2.55 (m, 2H), 1.71–1.36 (m, 5H), 1.51 (s, 9H), 1.47 (s, 9H), 1.36–1.10 (m, 10H), 0.86 (t,  $J$

= 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  179.2, 168.5, 163.4, 155.7, 153.1, 146.7, 129.0, 127.6, 124.0, 83.7, 79.7, 43.8, 36.0, 32.0, 31.3, 29.5, 29.3, 28.3, 28.2, 22.7, 20.1, 14.2.  
 HRMS (ESI+): Calcd for  $\text{C}_{29}\text{H}_{46}\text{N}_5\text{O}_5$   $[\text{M}+\text{H}]^+$ : 544.3499, Found: 544.3477.

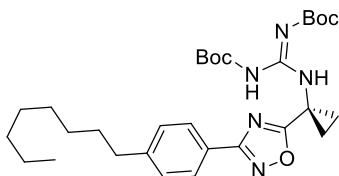


***Tert*-butyl *N*-[[(*tert*-butoxy)carbamoyl]amino(1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)propyl)amino)methylidene]carbamate (2.6d).** Synthesized by author M.R.R. Synthesized by general procedure 2-C. 43% yield, yellow oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  11.51 (br s, 1H), 9.05 (d,  $J = 8.5$  Hz, 1H), 7.98 (d,  $J = 7.3$  Hz, 2H), 7.26 (d,  $J = 7.6$  Hz, 2H), 5.59–5.55 (m, 1H), 2.64 (t,  $J = 7.6$  Hz, 2H), 2.43–2.35 (m, 1H), 1.66–1.57 (m, 2H), 1.52 (s, 9H), 1.44 (s, 9H), 1.34–1.19 (m, 10H), 1.05–0.99 (m, 6H), 0.86 (t,  $J = 6.5$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  178.2, 168.3, 163.4, 156.3, 153.2, 146.6, 129.0, 127.6, 124.2, 83.6, 79.6, 53.1, 36.0, 32.4, 31.9, 31.3, 29.5, 29.3, 29.3, 28.3, 28.2, 22.7, 18.6, 18.1, 14.2. HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{50}\text{N}_5\text{O}_5$   $[\text{M}+\text{H}]^+$ : 572.3812, Found: 572.3802.



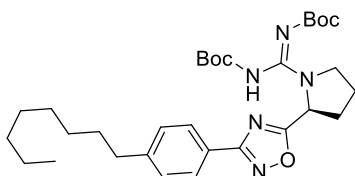
**(*S*)-*Tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-hydroxy-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate (2.6e).** Synthesized by general procedure 2-C. 32% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  11.49 (s, 1H), 9.36 (d,  $J=7.6$  Hz, 1H), 7.98 (d,  $J=8.2$  Hz, 2H), 7.29 (d,  $J=8.2$  Hz, 2H), 5.77 (dt,  $J=7.9, 4.1$  Hz, 1H), 4.14 (qd,  $J=$ , 2H), 2.65 (t,  $J=7.9$  Hz, 2H), 1.68-1.59 (m, 2H), 1.51 (d,  $J=14.0$  Hz, 18H), 1.29 (d,  $J=17.3$  Hz, 10H), 0.88 (t,

$J=6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  176.5, 168.5, 163.0, 156.4, 153.0, 147.0, 129.1, 127.7, 123.7, 84.0, 80.0, 64.6, 50.6, 36.1, 32.0, 31.3, 29.6, 29.4, 29.4, 28.4, 28.2, 22.8, 14.2; HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{29}\text{H}_{46}\text{N}_5\text{O}_6$   $[\text{M}+\text{H}]^{+}$ : 560.3448, Found: 560.3454.



**1,2-DiBoc-3-(1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) cyclopropyl) guanidine (2.6f).**

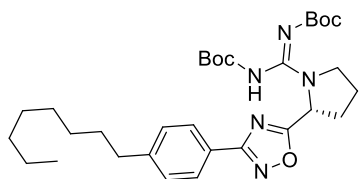
Synthesized by author M.G. Synthesized by general procedure 2-C. 35% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  11.50 (s, 1H), 8.92 (s, 1H), 7.86 (d,  $J = 8.3$  Hz, 2H), 7.18 (d,  $J = 8.2$  Hz, 2H), 2.57 (t,  $J = 7.5$  Hz, 2H), 1.79 (dd,  $J = 5.5, 8.5$  Hz, 2H), 1.60-1.53 (m, 2H), 1.51 (dd,  $J = 5.5, 8.5$  Hz, 2H), 1.45 (s, 9H), 1.32 (s, 9H), 1.26-1.12 (m, 10H), 0.80 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  180.0, 168.5, 163.3, 156.9, 153.2, 146.3, 128.8, 127.4, 124.3, 83.5, 79.6, 35.9, 31.9, 31.2, 30.7, 29.7, 29.4, 29.2, 28.2, 28.1, 22.7, 20.3, 14.1; HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{30}\text{H}_{46}\text{N}_5\text{O}_5$   $[\text{M}+\text{H}]^{+}$ : 556.3499.



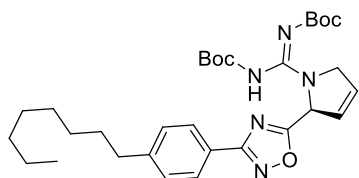
**(S)-Tert-butyl (((tert-butoxycarbonyl) imino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-yl) methyl) carbamate (2.6g).** Synthesized by author M.R.R. Synthesized by general procedure 2-C. 66% yield, yellow oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  7.96 (d,  $J = 8.2$  Hz, 2H), 7.26 (d,  $J = 8.0$  Hz, 2H), 5.62–5.54 (m, 1H), 3.93–3.83 (m, 1H), 3.83–3.71 (m, 1H), 2.64 (t,  $J = 7.9$  Hz, 2H), 2.48–2.36 (m, 1H), 2.30–2.09 (m, 2H), 2.08–1.98 (m, 1H), 1.95–1.86 (m, 1H), 1.67–1.57 (m, 2H), 1.54–1.18 (m, 28H), 0.86 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  178.7, 168.3, 161.9, 153.5, 150.3, 146.5, 128.8, 127.4, 123.9, 82.2, 79.5, 55.3,



49.4, 35.9, 31.8, 31.2, 29.4, 29.2, 28.1, 23.9, 22.6, 14.1; HRMS (ESI+): Calcd for C<sub>31</sub>H<sub>48</sub>N<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 570.3655, found 570.3605.

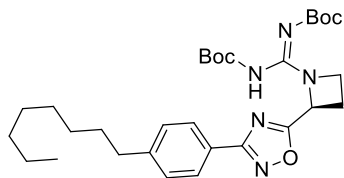


**(R)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (2.6h).** Synthesized by author M.G. Synthesized by general procedure 2-C. 55% yield, colorless oil; <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 10.10 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 5.71-5.53 (m, 1H), 3.98-3.87 (m, 1H), 3.84-3.80 (m, 1H), 2.75-2.63 (m, 2H), 2.48-2.44 (m, 1H), 2.35-2.13 (m, 2H), 2.08-2.04 (m, 1H), 1.74-1.61 (m, 2H), 1.48 (s, 18H), 1.38-1.21 (m, 10H), 0.89 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (126 MHz, Chloroform-d) δ 178.7, 168.4, 146.5, 129.6, 128.9, 127.5, 124.0, 82.2, 79.6, 55.3, 49.4, 35.9, 31.8, 31.4, 31.2, 29.7, 29.4, 29.2, 28.1, 23.9, 22.6, 14.1; HRMS (ESI+): Calcd for C<sub>31</sub>H<sub>48</sub>N<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 570.3655, Found: 570.3662.

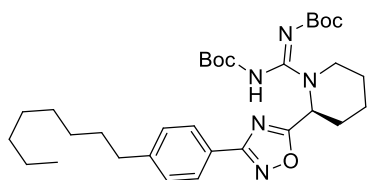


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)-2,5-dihydro-1H-pyrrol-1-yl)methylene)carbamate (2.6i).** Synthesized by general procedure 2-C. 22% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 7.97 (d, *J*=8.2 Hz, 2H), 7.27 (d, *J*=8.0 Hz, 2H), 6.42 (s, 1H), 6.13 (d, *J*=4.6 Hz, 1H), 5.90 (dd, *J*=6.4, 2.2 Hz, 1H), 2.65 (t, *J*=7.5 Hz, 2H), 1.67-1.59 (m, 2H), 1.50 (d, *J*=10.8 Hz, 18H), 1.35-1.22 (m, 10H), 0.88 (t, *J*=6.8 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 176.7, 168.6, 129.0, 128.9, 127.6, 124.3, 115.6, 110.2, 53.6,

36.1, 32.0, 31.4, 29.9, 29.6, 29.4, 29.3, 28.3, 22.8, 14.2; HRMS (ESI<sup>+</sup>): Calcd for C<sub>31</sub>H<sub>46</sub>N<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 568.7286, Found: 568.3478.

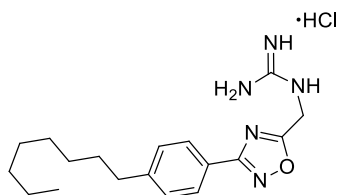


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methylene)carbamate (2.6j).** Synthesized by author N.N.P. Synthesized by general procedure 2-C. 58% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 7.99 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.63 (s, 1H), 4.20 (td, *J* = 9.4, 5.6 Hz, 1H), 2.85 (p, *J* = 9.4 Hz, 1H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.56 (dq, *J* = 10.4, 5.0 Hz, 1H), 1.74 (s, 1H), 1.64 (p, *J* = 7.4 Hz, 2H), 1.45 (s, 18H), 1.34 – 1.23 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H). <sup>13</sup>C NMR (126 MHz, Chloroform-d) δ 177.1, 171.1, 168.5, 146.7, 128.9, 127.5, 123.8, 60.4, 36.0, 31.8, 31.2, 29.4, 29.2, 29.2, 28.0, 22.6, 22.4, 21.0, 14.2, 14.1; HRMS (ESI<sup>+</sup>): Calcd for C<sub>30</sub>H<sub>46</sub>N<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 556.3499, Found: 556.3488



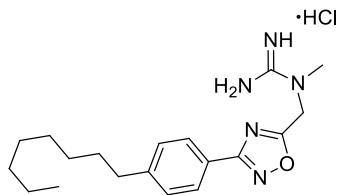
**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)methylene)carbamate (2.6k).** Synthesized by author N.N.P. To a microwave safe glass tube was added (S)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) piperidin-1-ium **2.5k** (0.04 g, 0.105 mmol), triethylamine (0.045 mL, 0.32 mmol), *tert*-butyl (((*tert*-butoxycarbonyl) amino) (1*H*-pyrazol-1-yl) methylene) carbamate (0.032 g, 0.105 mmol), and anhydrous

acetonitrile 2mL. The resulting reaction mixture was sealed and heated in a microwave reactor for 3h at 60 W. After 3h, the reaction flask was cooled and resulting colorless solution was concentrated *in-vacuo*. The resulting pale yellow oil was then purified by flash chromatography to yield product **2.6k** as colorless oil in 18% yield. <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 5.98 (bs, 1H), 3.99 (bs, 1H), 3.67 (s, 1H), 3.35 (t, *J* = 12.0 Hz, 1H), 3.10 (s, 1H), 2.66 (t, *J* = 7.9, 7.5 Hz, 2H), 2.41 (d, *J* = 13.4 Hz, 1H), 2.11 (s, 1H), 1.77 (m, 2H), 1.72 – 1.60 (m, 4H), 1.56 (d, *J* = 11.9 Hz, 4H), 1.49 (s, 18H), 1.37 – 1.21 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (126 MHz, Chloroform-d) δ 176.6, 167.3, 154.5, 145.5, 127.8, 126.5, 123.0, 52.8, 34.9, 30.8, 30.2, 28.4, 28.2, 27.1, 27.0, 23.7, 21.6, 19.1, 17.9, 16.6, 13.1; HRMS (ESI+): Calcd for C<sub>32</sub>H<sub>50</sub>N<sub>5</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 584.3734, Found: 584.3822

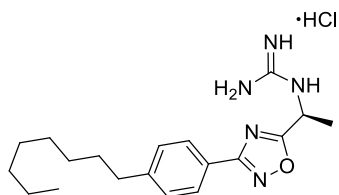


**1-((3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) methyl) guanidine hydrochloride (2.7a).**

Synthesized by author M.R.R. Synthesized by general procedure 2-B. 84% yield, white solid; <sup>1</sup>H NMR (500 MHz, Methanol-d<sub>4</sub>) δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 4.84 (s, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.71–1.54 (m, 2H), 1.38–1.19 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (126 MHz, Methanol-d<sub>4</sub>) δ 175.5, 168.4, 158.1, 147.0, 128.8, 127.1, 123.7, 37.4, 35.5, 31.7, 31.1, 29.2, 29.1, 29.0, 22.4, 13.1; HRMS (ESI+) *m/z* calcd for C<sub>18</sub>H<sub>28</sub>N<sub>5</sub>O [M+H]<sup>+</sup>: 330.2294, Found: 330.2269.

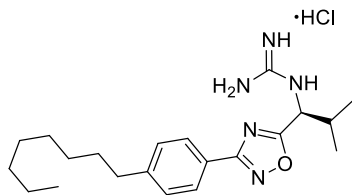


**1-Methyl-1-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) methyl) guanidine hydrochloride (2.7b).** Synthesized by general procedure 2-B. 15% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.00 (d,  $J=8.4$  Hz, 2H), 7.39 (d,  $J=8.5$  Hz, 2H), 5.04 (s, 2H), 3.27 (s, 3H), 2.72 (t,  $J=7.4$  Hz, 2H), 1.69 (p,  $J=7.3$  Hz, 2H), 1.43-1.26 (m, 10H), 0.93 (t,  $J=6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  175.9, 169.8, 159.6, 148.4, 130.2, 128.4, 125.0, 47.4, 37.8, 36.8, 33.0, 32.4, 30.5, 30.4, 30.3, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{19}\text{H}_{30}\text{N}_5\text{O}$   $[\text{M}+\text{H}]^+$ : 344.2450, Found: 344.2416.

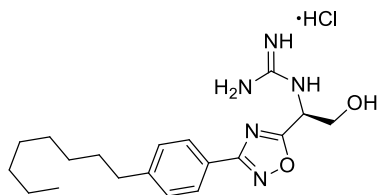


**(S)-1-(1-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) ethyl) guanidine hydrochloride (2.7c).**

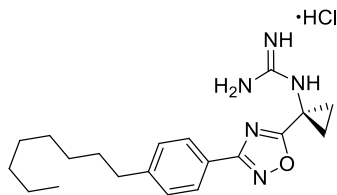
Synthesized by author M.R.R. Synthesized by general procedure 2-B. 82% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  7.96 (d,  $J = 8.1$  Hz, 2H), 7.32 (d,  $J = 8.0$  Hz, 2H), 5.28–5.14 (m, 1H), 2.75–2.56 (m, 2H), 1.75 (d,  $J = 6.9$  Hz, 3H), 1.68–1.56 (m, 2H), 1.39–1.17 (m, 10H), 0.88 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  178.5, 168.4, 157.3, 147.0, 128.8, 127.1, 123.8, 45.2, 35.6, 31.7, 31.1, 29.2, 29.1, 29.0, 22.4, 18.0, 13.1; HRMS (ESI+) calcd for  $\text{C}_{19}\text{H}_{30}\text{N}_5\text{O}$   $[\text{M}+\text{H}]^+$ : 344.2450, Found: 344.2407.  $[\alpha]_D^{20} = -148^\circ$  ( $c = 0.0005$ , methanol)



**(S)-1-(2-Methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) propyl) guanidine hydrochloride (2.7d).** Synthesized by author M.R.R. Synthesized by general procedure 2-B. 80% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  7.96 (d,  $J = 8.1$  Hz, 2H), 7.32 (d,  $J = 8.0$  Hz, 2H), 5.08–4.99 (m, 1H), 2.65 (t,  $J = 7.9$  Hz, 2H), 2.51–2.40 (m, 1H), 1.68–1.56 (m, 2H), 1.38–1.19 (m, 10H), 1.07 (dd,  $J = 15.1, 6.8$  Hz, 6H), 0.87 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  177.4, 168.4, 157.9, 147.0, 128.9, 127.1, 123.7, 54.7, 35.6, 32.4, 31.7, 31.1, 29.2, 29.1, 29.0, 22.4, 17.6, 16.9, 13.1; HRMS (ESI+) calcd for  $\text{C}_{21}\text{H}_{34}\text{N}_5\text{O}$   $[\text{M}+\text{H}]^+$ : 372.2763, Found: 372.2773.  $[\alpha]_D^{25} = -156^\circ$  ( $c = 0.0005$ , methanol)

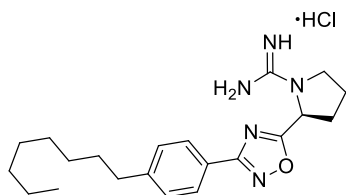


**(S)-Amino ((2-hydroxy-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) ethyl) amino) methaniminium chloride (2.7e).** Synthesized by general procedure 2-B. 12% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.00 (d,  $J=8.4$  Hz, 2H), 7.35 (d,  $J=8.4$  Hz, 2H), 4.90 (d,  $J=4.4$  Hz, 1H), 4.15-4.10 (m, 2H), 2.68 (t,  $J=7.6$  Hz, 2H), 1.71-1.55 (m, 2H), 1.39-1.22 (m, 10H), 0.88 (t,  $J=6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  177.8, 169.8, 159.2, 148.3, 130.2, 128.4, 125.1, 63.4, 53.1, 36.9, 33.0, 32.4, 30.5, 30.4, 30.3, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{19}\text{H}_{30}\text{N}_5\text{O}_2$   $[\text{M}^+]$ : 360.2399, Found: 360.2386.  $[\alpha]_D^{25} = +118^\circ$  ( $c = 0.00066$ , methanol).



**1-(1-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) cyclopropyl) guanidine hydrochloride (2.7f).**

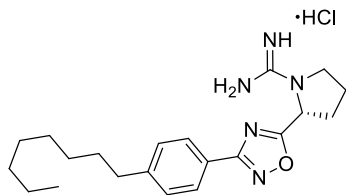
Synthesized by author M.G. Synthesized by general procedure 2-B. 99% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.63 (s, 1H), 7.92 (d,  $J = 8.2$  Hz, 2H), 7.32 (d,  $J = 8.2$  Hz, 2H), 2.67 (t,  $J = 7.6$  Hz, 2H), 1.92 (dd,  $J = 5.2, 8.4$  Hz, 2H), 1.72-1.58 (m, 4H), 1.38-1.24 (m, 10H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  180.6, 169.9, 159.8, 148.2, 130.1, 128.3, 125.2, 36.8, 33.0, 32.4, 31.6, 30.5, 30.4, 30.3, 23.7, 21.1, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{30}\text{N}_5\text{O}$   $[\text{M}+\text{H}]^+$ : 356.2445, Found 356.2439.



**(S)-2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboximidamide**

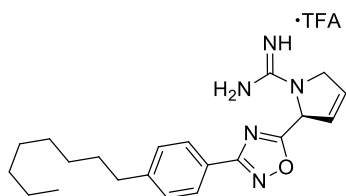
**hydrochloride (2.7g).** Synthesized by author M.R.R. Synthesized by general procedure 2-B.

80% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  7.94 (d,  $J = 8.2$  Hz, 2H), 7.33 (d,  $J = 8.2$  Hz, 2H), 5.50-5.38 (m, 1H), 3.80-3.70 (m, 1H), 3.67-3.54 (m, 1H), 2.70-2.39 (m, 4H), 2.28-2.16 (m, 1H), 2.16-1.98 (m, 1H), 1.70-1.55 (m, 2H), 1.39-1.15 (m, 10H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  177.5, 168.4, 155.8, 147.0, 128.8, 127.1, 123.6, 55.1, 35.5, 31.7, 31.4, 31.1, 29.2, 29.0, 28.9, 23.0, 22.4, 13.1; HRMS (ESI+) Calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_5\text{O}$   $[\text{M}+\text{H}]^+$ : 370.2601, Found: 370.2607.  $[\alpha]_D = -74.6^\circ$  ( $c = 0.005$ , methanol).



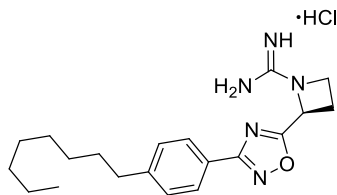
**(R)-2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboximidamide**

**hydrochloride (2.7h).** Synthesized by author M.G. Synthesized by general procedure 2-B. 99%, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.94 (d,  $J = 7.8$  Hz, 2H), 7.32 (d,  $J = 7.9$  Hz, 2H), 5.46-5.42 (m, 1H), 3.79-3.75 (m, 1H), 3.65-3.61 (m, 1H), 2.66 (t,  $J = 7.5$  Hz, 2H), 2.53-2.49 (m, 2H), 2.23-2.19 (m, 1H), 2.10=2.06 (m, 1H), 1.65-1.61 (m, 2H), 1.38-1.26 (m, 10H), 0.88 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  178.9, 169.7, 157.1, 148.3, 130.2, 128.5, 125.0, 56.6, 36.9, 33.0, 32.8, 32.4, 30.6, 30.4, 30.3, 24.4, 23.7, 14.5; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_5\text{O} [\text{M}^+]$ : 370.2601, Found: 370.2596.  $[\alpha]_D^{25} = +78.8^\circ$  ( $c = 0.00085$ , methanol).

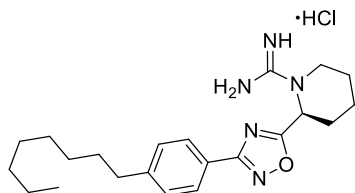


**(S)-Amino(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)-2,5-dihydro-1H-pyrrol-1-**

**yl)methaniminium 2,2,2-trifluoroacetate (2.7i).** Synthesized general procedure 2-D. 98% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  7.95 (d,  $J=8.4$  Hz, 2H), 7.34 (d,  $J=8.4$  Hz, 2H), 6.31-6.28 (m, 1H), 6.19-6.13 (m, 2H), 4.57-4.43 (m, 2H), 2.68 (t,  $J=5.9$  Hz, 2H), 1.69-1.60 (m, 2H), 1.38-1.24 (m, 10H), 0.89 (t,  $J=7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  169.9, 157.0, 148.5, 130.2, 129.8, 129.7, 128.4, 125.6, 125.5, 124.8, 56.1, 36.9, 33.0, 32.4, 30.5, 30.4, 30.3, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{30}\text{N}_5\text{O}^+ [\text{M}^+]$ : 368.2450, Found: 368.2454. *HPLC analysis shows 2.7i is 70% pure.*



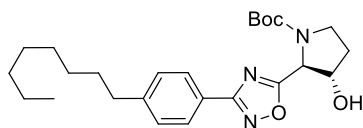
**(S)-2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) azetidine-1-carboximidamide hydrochloride (2.7j).** Synthesized by author N.N.P. Synthesized by general procedure 2-B. 95% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.98 (d,  $J = 8.2$  Hz, 2H), 7.34 (d,  $J = 8.2$  Hz, 2H), 5.83 (dd,  $J = 9.3, 5.2$  Hz, 1H), 4.37 (q,  $J = 8.6$  Hz, 1H), 4.27 (q,  $J = 8.7$  Hz, 1H), 3.18 – 2.93 (m, 1H), 2.76 – 2.55 (m, 3H), 1.64 (q,  $J = 7.3$  Hz, 2H), 1.40 – 1.19 (m, 12H), 0.88 (t,  $J = 7.2, 6.5$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  178.2, 169.8, 158.6, 148.4, 130.2, 128.4, 124.9, 58.4, 50.9, 36.9, 33.0, 32.4, 30.4, 23.7, 23.0, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{31}\text{N}_5\text{O}$  [ $\text{M}^+$ ]: 356.2450, Found: 356.2478.  $[\alpha]_D^{25} = -27.3^\circ$  ( $c = 0.00055$ , methanol).



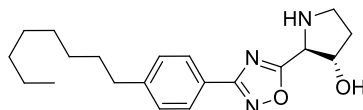
**(S)-Amino (2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) piperidin-1-yl) methaniminium chloride (2.7k).** Synthesized by author N.N.P. Synthesized by general procedure 2-B. 99% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  7.87 (d,  $J = 8.1$  Hz, 2H), 7.25 (d,  $J = 8.1$  Hz, 2H), 5.44 (d,  $J = 4.0$  Hz, 1H), 3.90-4.01 (m, 1H), 3.41-3.50 (m, 1H), 3.13 (d,  $J = 7.4$  Hz, 1H), 2.59 (t,  $J = 7.6$  Hz, 2H), 2.46 (d,  $J = 14.0$  Hz, 1H), 2.10 – 1.98 (m, 1H), 1.75 (m, 2H), 1.63 – 1.51 (m, 4H), 1.37 (m, 1H), 1.23 (m, 11H), 0.79 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  176.5, 168.5, 158.5, 147.0, 128.8, 127.0, 127.0, 123.6, 54.5, 51.7, 43.4, 42.5, 37.3, 35.4, 31.6, 31.0, 29.1, 29.0, 28.9, 27.3, 23.9, 22.3, 19.1, 17.9, 17.4, 15.9, 13.0, 11.8. HRMS (ESI+): Calcd for



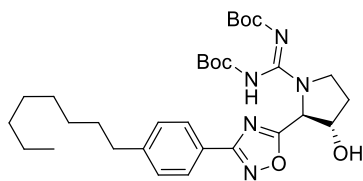
$C_{22}H_{34}N_5O^+$  [ $M^+$ ]: 384.2758, Found: 384.2759. HPLC analysis indicates that compound **2.7k** is 85% pure.



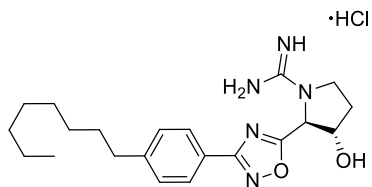
**(2S, 3S)-Tert-butyl-3-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate (2.8)**. Synthesized by general procedure 2-A. 46% yield, yellow oil;  $^1H$  NMR (500 MHz, Chloroform-d)  $\delta$  7.95 (d,  $J = 8.0$  Hz, 2H), 7.28 (d,  $J = 8.0$  Hz, 2H), 4.96 (s, 1H), 4.56 (s, 1H), 3.82-3.68 (m, 2H), 2.69-2.59 (m, 2H), 2.35-2.27 (m, 1H), 2.07-2.00 (m, 1H), 1.66-1.58 (m, 2H), 1.46 (s, 3H), 1.36-1.21 (m, 16H), 0.87 (t,  $J = 7.0$  Hz, 3H);  $^{13}C$  NMR (126 MHz, Chloroform-d)  $\delta$  178.3, 168.6, 154.0, 146.9, 129.1, 129.0, 127.5, 123.9, 81.0, 76.1, 62.4, 44.5, 36.1, 32.2, 32.0, 31.3, 29.5, 29.4, 29.3, 28.5, 28.3, 22.8, 14.2; HRMS (ESI+): Calcd for  $C_{25}H_{37}N_3O_4$  [ $M+H$ ] $^+$ : 444.2862, Found: 444.2883.



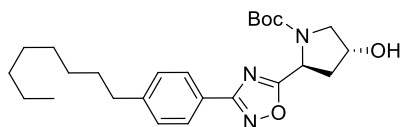
**(2S, 3S)-2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-3-ol (2.9)**. Synthesized by general procedure 2-D. 59% yield, clear oil;  $^1H$  NMR (500 MHz, Chloroform-d)  $\delta$  7.97 (d,  $J = 8.0$  Hz, 2H), 7.27 (d,  $J = 7.4$  Hz, 2H), 4.70 (s, 1H), 3.35 (s, 1H), 2.74-2.52 (m, 2H), 2.43-2.17 (m, 3H), 1.97 (s, 1H), 1.72-1.49 (m, 2H), 1.43-1.13 (m, 10H), 0.87 (t,  $J = 6.9$  Hz, 3H);  $^{13}C$  NMR (126 MHz, Chloroform-d)  $\delta$  179.4, 168.4, 146.8, 129.0, 127.6, 124.0, 76.5, 63.3, 45.1, 36.1, 34.4, 32.0, 31.3, 29.6, 29.4, 29.3, 22.8, 14.2; HRMS (ESI+): Calcd for  $C_{20}H_{30}N_3O_2$  [ $M+H$ ] $^+$ : 344.2338, Found: 344.2338.



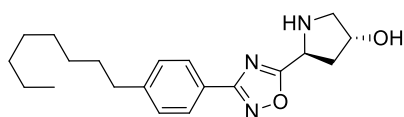
**Tert-butyl (((tert-butoxycarbonyl)amino)((2*S*, 3*S*)-3-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (2.10).** Synthesized by general procedure 2-C. 89% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-*d*)  $\delta$  7.95 (d,  $J = 8.2$  Hz, 2H), 7.25 (d,  $J = 7.9$  Hz, 2H), 5.52 (s, 1H), 4.64 (s, 1H), 4.06-3.86 (m, 2H), 3.18 (bs, 1H), 2.63 (t,  $J = 7.1$  Hz, 2H), 2.38-2.30 (m, 1H), 2.17-2.05 (m, 1H), 1.68-1.57 (m, 2H), 1.81 (bs, 1H), 1.49-1.40 (m, 18H), 1.33-1.23 (m, 10H), 0.87 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  177.1, 168.8, 147.2, 129.3, 127.9, 124.2, 75.1, 63.8, 47.4, 36.4, 32.3, 31.7, 30.2, 29.9, 29.7, 29.7, 28.5, 23.1, 14.6; HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{48}\text{N}_5\text{O}_6$   $[\text{M}+\text{H}]^+$ : 586.3604, Found: 586.3569.



**Amino ((1*S*, 3*S*)-3-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-yl) methaniminium chloride (2.11).** Synthesized by general procedure 2-B. 52% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  7.97 (d,  $J = 8.2$  Hz, 2H), 7.36 (d,  $J = 8.2$  Hz, 2H), 5.24 (s, 1H), 4.80 (d,  $J = 3.2$  Hz, 1H), 3.85-3.82 (m, 2H), 2.70 (t,  $J = 7.2$  Hz, 2H), 2.30-2.14 (m, 2H), 1.72-1.60 (m, 2H), 1.44-1.22 (m, 10H), 0.91 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol-*d*<sub>4</sub>)  $\delta$  176.65, 169.7, 157.5, 148.4, 130.1, 128.4, 124.7, 76.0, 64.1, 47.3, 36.8, 33.0, 32.5, 32.4, 30.5, 30.4, 30.3, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_5\text{O}_2$   $[\text{M}+\text{H}]^+$ : 386.2556, Found: 386.2576.

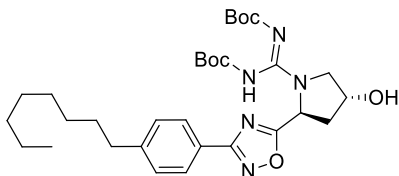


**(2S, 4R)-Tert-butyl 4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate (2.12).** Synthesized by author M.R.R. Synthesized by general procedure 2-A. 63% yield, yellow oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  7.99 (d,  $J = 7.9$  Hz, 2H), 7.31 (d,  $J = 7.9$  Hz, 2H), 5.42–5.30 (m, 1H, minor rotamer), 5.20 (m, 1H, major rotamer), 4.74–4.56 (m, 1H), 3.89–3.79 (m, 1H), 3.77–3.69 (m, 1H, major rotamer), 3.64–3.53 (m, 1H, minor rotamer), 2.74–2.61 (m, 2H), 2.59–2.40 (m, 1H), 2.38–2.28 (m, 1H), 1.74–1.58 (m, 2H), 1.56–1.16 (m, 19H), 0.90 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d, rotamers)  $\delta$  180.3 (major), 168.5 (major), 153.8 (major), 146.7 (major), 146.5 (minor), 129.0 (major), 128.8 (minor), 127.4 (major), 125.8 (minor), 123.9 (major), 81.0 (major), 80.8 (minor), 69.9 (minor), 69.3 (major), 54.8 (major), 52.6 (major), 40.9 (major), 40.2 (minor), 36.0 (major), 31.9 (major), 31.2 (major), 29.4 (major), 29.3 (major), 29.2 (major), 28.3 (minor), 28.1 (major), 22.7 (major), 14.1 (major). HRMS (ESI+): Calcd for  $\text{C}_{25}\text{H}_{37}\text{N}_3\text{NaO}_4$   $[\text{M}+\text{H}]^+$ : 466.2682, Found: 466.2720.



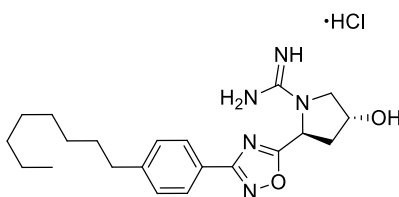
**(3R, 5S)-5-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-3-ol (2.13).** Synthesized by author M.R.R. Synthesized by general procedure 2-D. 95% yield, yellow solid;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  7.89 (d,  $J = 8.2$  Hz, 2H), 7.19 (d,  $J = 8.2$  Hz, 2H), 4.79–4.63 (m, 1H), 4.57–4.43 (m, 1H), 3.22–3.10 (m, 1H), 3.08–2.95 (m, 1H), 2.77 (br s, 2H), 2.56 (t,  $J = 7.7$  Hz, 2H), 2.35–2.18 (m, 2H), 1.63–1.48 (m, 2H), 1.33–1.10 (m, 10H), 0.80 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  181.3, 168.3, 146.6, 128.9, 127.4, 124.0, 72.2, 55.4, 53.0,

40.7, 36.0, 31.9, 31.2, 29.4, 29.3, 29.2, 22.7, 14.1. HRMS (ESI+): Calcd for C<sub>20</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 344.2333, Found: 344.2336.



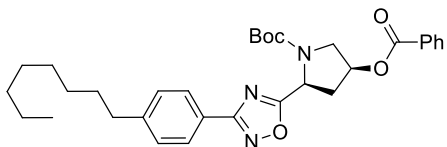
**Tert-butyl (((tert-butoxycarbonyl)imino)((2S, 4R)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methyl)carbamate (2.14).** Synthesized by author M.R.R.

Synthesized by general procedure 2-C. 53% yield, yellow solid; <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.83 (t, *J* = 8.2 Hz, 1H), 4.72–4.59 (m, 1H), 4.05 (dd, *J* = 12.5, 3.5 Hz, 1H), 3.85–3.69 (m, 1H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.63–2.53 (m, 1H), 2.45–2.32 (m, 1H), 1.74–1.60 (m, 2H), 1.47 (s, 18H), 1.39–1.24 (m, 10H), 0.90 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (126 MHz, ) δ 178.5, 168.5, 154.1, 146.6, 128.9, 127.5, 124.0, 69.3, 58.0, 53.7, 40.0, 36.0, 31.9, 31.2, 29.7, 29.4, 29.2, 28.1, 22.7, 14.1. HRMS (ESI+): Calcd for C<sub>31</sub>H<sub>48</sub>N<sub>5</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 586.3605, Found: 586.3557.

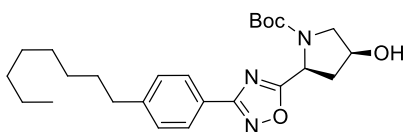


**Amino ((2S, 4R)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-yl) methaniminium chloride (2.15).** Synthesized by author M.R.R. Synthesized by general procedure 2-B. 79% yield, white solid; <sup>1</sup>H NMR (500 MHz, Methanol-d<sub>4</sub>) δ 8.01–7.93 (m, 2H), 7.41–7.31 (m, 2H), 5.66–5.54 (m, 1H), 4.67–4.58 (m, 1H), 3.96–3.85 (m, 1H), 3.65–3.58 (m, 1H), 2.74–2.61 (m, 3H), 2.58–2.49 (m, 1H), 1.73–1.61 (m, 2H), 1.42–1.24 (m, 10H), 0.91 (t, *J* =

7.0 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  178.9, 169.8, 157.7, 148.4, 130.2, 128.4, 124.9, 69.8, 57.1, 54.9, 41.1, 36.9, 33.0, 32.4, 30.5, 30.4, 30.3, 23.7, 14.5; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_5\text{O}_2$   $[\text{M}+\text{H}]^+$ : 386.2556, Found: 386.2596.  $[\alpha]_D^{25} = -45.5^\circ$  ( $c = 0.00055$ , methanol).

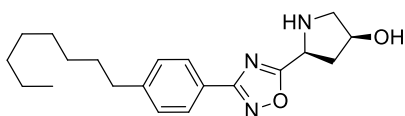


**(2S, 4S)-Tert-butyl 4-(benzoyloxy)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate (2.16).** Synthesized by general procedure 2-E. 75% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  7.93 (d,  $J=7.8$  Hz, 2H), 7.77 (d,  $J=7.6$  Hz, 1H), 7.71 (d,  $J=7.5$  Hz, 1H), 7.36 (t,  $J=7.9$  Hz, 1H), 7.24 (t,  $J=7.8$  Hz, 2H), 7.13 (t,  $J=7.0$  Hz, 2H), 5.65 (s, 1H), 5.28 (d,  $J=8.3$  Hz, 1H), 4.00-3.80 (m, 2H), 2.80-2.63 (m, 4H), 1.67-1.60 (m, 2H), 1.51 (s, 3H), 1.39 (s, 6H), 1.37-1.23 (m, 10H), 0.87 (t,  $J=6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  179.7, 168.5, 165.8, 153.6, 146.6, 133.2, 129.7, 129.4, 129.0, 128.3, 127.5, 124.1, 81.1, 72.4, 53.5, 52.6, 38.0, 36.0, 32.0, 31.3, 29.5, 29.3, 28.5, 28.3, 22.7, 14.2; HRMS (Mixed+): Calcd for  $\text{C}_{32}\text{H}_{41}\text{N}_3\text{O}_5\text{Na}$   $[\text{M}+\text{Na}]^+$ : 570.2944, Found: 570.2903.

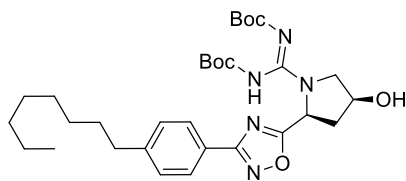


**(2S, 4S)-Tert-butyl 4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate.** Hydrolysis of 4-benzoyl ester protecting group in **2.16**. (2S, 4S)-Tert-butyl-4-(benzoyloxy)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.16** (85 mg, 0.16 mmol) was dissolved in equal parts of methanol (0.38 mL), THF (0.38 mL) and 2 M NaOH (0.15 mL, 2 M) and stirred for thirty minutes at room temperature under nitrogen. The solution was partitioned between ethyl acetate and water. The aqueous solution was extracted with ethyl

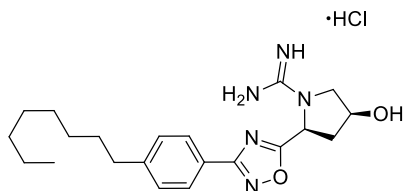
acetate and the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *via* vacuum to yield the product as colorless oil. 95% yield. <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 5.11 (d, *J* = 9.1 Hz, 1H), 4.51 (s, 1H), 3.87-3.63 (m, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.59-2.50 (m, 1H), 2.35-2.25 (m, 1H), 1.66-1.57 (m, 2H), 1.43 (s, 3H), 1.37-1.19 (m, 16H), 0.86 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (126 MHz, Chloroform-d) δ 181.5, 168.1, 153.5, 147.1, 129.1, 129.0, 127.5, 123.4, 81.2, 70.6, 56.0, 52.4, 39.6, 36.1, 31.9, 31.3, 29.5, 29.3, 29.3, 28.2, 22.7, 14.2; HRMS (ESI<sup>+</sup>): Calcd for C<sub>25</sub>H<sub>37</sub>N<sub>3</sub>O<sub>4</sub>Na [M+Na]<sup>+</sup>: 466.2681, Found: 466.2637.



**(2S, 4S)-2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-4-ol.** Deprotection of Boc group in (2S, 4S)-*tert*-butyl-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate. Synthesized by general procedure 2-D. 48% yield, colorless oil; <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 7.92 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 4.66 (d, *J* = 6.6 Hz, 1H), 4.53 (s, 1H), 3.91 (s, 2H), 3.27 (s, 2H), 2.67-2.60 (m, 2H), 2.56-2.50 (m, 1H), 2.29 (d, *J* = 13.8 Hz, 1H), 1.62 (p, *J* = 7.5 Hz, 2H), 1.38-1.19 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (126 MHz, Chloroform-d) δ 181.1, 168.2, 147.0, 129.0, 127.6, 123.7, 72.0, 56.0, 53.1, 40.2, 36.1, 32.0, 31.3, 29.6, 29.4, 29.4, 22.8, 14.2; HRMS (Mixed<sup>+</sup>): Calcd for C<sub>20</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 344.2338, Found: 344.2315.

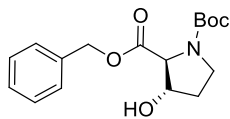


**Tert-butyl (((tert-butoxycarbonyl)amino)((2S, 4S)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.** Guanylation of (2S, 4S)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-4-ol. Synthesized by general procedure 2-C. 79% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.96 (d,  $J = 8.2$  Hz, 2H), 7.26 (d,  $J = 8.2$  Hz, 2H), 5.81 (t,  $J = 8.2$  Hz, 1H), 4.63 (s, 1H), 4.02 (dd,  $J = 12.5$  Hz, 1H), 3.79-3.70 (m, 1H), 2.65 (t,  $J = 7.3$  Hz, 2H), 2.57 (dd,  $J = 13.3, 7.7$  Hz, 1H), 2.41-2.29 (m, 1H), 1.62 (p,  $J = 7.5$  Hz, 2H), 1.45 (s, 18H), 1.35-1.20 (m, 10H), 0.87 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  178.6, 168.6, 154.2, 146.7, 129.0, 127.6, 124.1, 69.6, 58.1, 53.8, 40.2, 36.1, 32.0, 31.4, 29.6, 29.4, 28.2, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{48}\text{N}_5\text{O}_6$   $[\text{M}+\text{H}]^+$ : 586.3604, Found: 586.3603.

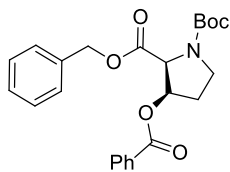


**Amino ((1S, 4S)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-yl) methaniminium chloride (2.17).** Synthesized by general procedure 2-B. 22% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.97 (d,  $J=8.4$  Hz, 2H), 7.36 (d,  $J=8.4$  Hz, 2H), 5.59 (dd,  $J=7.8, 6.7$  Hz, 1H), 4.64 (p,  $J=4.4$  Hz, 1H), 3.91 (dd,  $J=10.7, 4.7$  Hz, 1H), 3.62 (ddd,  $J=10.7, 2.9, 1.3$  Hz, 1H), 2.70 (t,  $J=7.4$  Hz, 2H), 2.65 (dtd,  $J=8.0, 4.8, 4.1, 1.3$  Hz, 1H), 2.54 (ddd,  $J=13.3, 6.4, 4.9$  Hz, 1H), 1.68 (p,  $J=7.3$  Hz, 2H), 1.42-1.21 (m, 10H), 0.91 (t,  $J=6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  178.9, 169.8, 157.6, 148.4, 130.2, 128.4, 125.0, 69.7, 57.1, 54.9, 41.0,

36.8, 33.0, 32.4, 30.5, 30.4, 30.3, 23.7, 14.4; HRMS (ESI+): Calcd for C<sub>21</sub>H<sub>32</sub>N<sub>5</sub>O<sub>2</sub> [M<sup>+</sup>]: 386.2556, Found: 386.2548. [ $\alpha$ ]<sup>D</sup> = -40.6° (c = 0.0015, methanol).



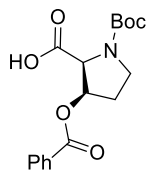
**(2S, 3S)-2-Benzyl 1-tert-butyl 3-hydroxypyrrolidine-1,2-dicarboxylate (2.20).** (2S, 3S)-1-(Tert-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid (1 equiv) was dissolved in methanol (0.2 M solution) and cooled to 0 °C. Cesium carbonate (0.5 equiv) was added and the reaction was stirred for 30 min. After 30 mins, the solution was concentrated under reduced pressure. The resulting white solid was then dissolved in DMF (0.2 M solution). The reaction mixture was cooled to 0 °C. Once cooled, benzyl bromide (1 equiv) was added. The reaction was warmed to rt and stirred vigorously overnight. Once complete, the reaction was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate and washed with water two times and brine two times. The organic layer was dried with sodium sulfate, filtered, and then the solvent was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (1:1 hexane:ethyl acetate) to produce a 51% yield. The proton matched published literature.<sup>5</sup>



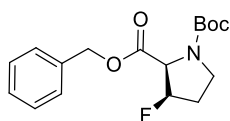
**(2S, 3R)-2-Benzyl 1-tert-butyl 3-(benzyloxy) pyrrolidine-1,2-dicarboxylate.** Synthesized by general procedure 2-E. 38% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  7.89 (dd, *J* = 13.3, 7.6 Hz, 2H), 7.55 (q, *J* = 7.6 Hz, 1H), 7.43-7.32 (m, 2H), 7.24-7.12 (m, 5H), 5.72 (q, *J* =



6.5 Hz, 1H), 5.15 (d,  $J= 12.1$  Hz, 1H), 5.09 (s, 1H), 4.91 (d,  $J= 12.1$  Hz, 1H), 4.67 (d,  $J= 7.0$  Hz, 1H), 3.81-3.55 (m, 2H), 2.31-2.20 (m, 2H), 1.49 (s, 3H), 1.35 (s, 2H).

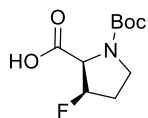


**(2S, 3R)-3-(Benzoyloxy)-1-(tert-butoxycarbonyl) pyrrolidine-2-carboxylic acid (2.21).** (2S, 3R)-2-Benzyl 1-*tert*-butyl 3-(benzoyloxy) pyrrolidine-1,2-dicarboxylate was dissolved in ethanol (0.2 M solution) and degassed with nitrogen for 15 min. Still under nitrogen flow, the Pd/C (0.02 equiv) was added, washing down any left on the sides with a small amount of DCM. The hydrogen filled balloon was attached and the reaction was stirred at rt overnight. Once complete, the solution was filtered over a celite plug. The solution was then concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give the product in a 62% yield.  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.94 (d,  $J = 7.5$  Hz, 2H), 7.54-7.57 (m, 1H), 7.36 (t,  $J= 7.5$  Hz, 2H), 5.68 (s, 1H), 4.64 (d,  $J= 6.8$  Hz, 1H), 3.72-3.50 (m, 2H), 2.32-2.15 (m, 2H), 1.40 (s, 9H).

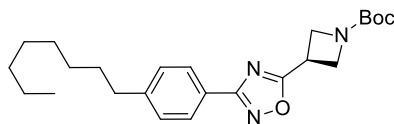


**(2R, 3R)-2-Benzyl 1-*tert*-butyl 3-fluoropyrrolidine-1,2-dicarboxylate.** DAST (5 equiv) was added dropwise to a solution of (2S, 3S)-2-benzyl 1-*tert*-butyl 3-hydroxypyrrolidine-1,2-dicarboxylate in dry DCM at  $-78$  °C under nitrogen. The reaction was then warmed to rt and stirred for 5 h. Once completed, the reaction was quenched with 1 M sodium bicarbonate. The aqueous layer was then washed with DCM and extracted. The organic layer was then washed with 10% acetic acid and brine. The organic layer was then dried with sodium sulfate, filtered, and

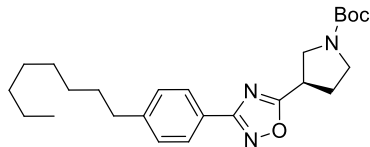
concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography producing a 69% yield. Taken to the next step with no further analysis.



**(2R, 3R)-1-(Tert-butoxycarbonyl)-3-fluoropyrrolidine-2-carboxylic acid (2.22).** (2R, 3R)-2-Benzyl 1-tert-butyl 3-fluoropyrrolidine-1,2-dicarboxylate was dissolved in ethanol (0.2 M solution) and degassed with nitrogen for 15 min. Still under nitrogen flow, the Pd/C (0.02 equiv) was added, washing down any left on the sides with a small amount of DCM. The hydrogen filled balloon was attached and the reaction was stirred at rt overnight. Once complete, the solution was filtered over a celite plug. The solution was then concentrated under reduced pressure and the residue was purified by silica gel column chromatography producing a 66% yield. Characterization matches the literature.<sup>6</sup>

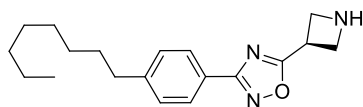


**Tert-butyl 3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) azetidine-1-carboxylate (2.24a).** Synthesized by author N.N.P. Synthesized by general procedure 2-A. 77% yield, yellow oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  7.96 (d,  $J = 8.4$  Hz, 2H), 7.27 (d,  $J = 8.5$  Hz, 2H), 4.48 – 4.21 (m, 4H), 4.15 – 3.92 (m, 1H), 2.64 (t,  $J = 7.5$  Hz, 2H), 1.63 (td,  $J = 15.9, 15.1, 8.5$  Hz, 2H), 1.45 (s, 9H), 1.36 – 1.19 (m, 10H), 0.86 (t,  $J = 7.0$  Hz, 3H). <sup>13</sup>C NMR (101 MHz, Chloroform-d)  $\delta$  178.7, 168.6, 155.9, 146.7, 128.9, 127.4, 123.8, 80.1, 35.9, 31.8, 31.2, 29.4, 29.2, 29.2, 28.3, 25.7, 22.6, 14.0; HRMS (ESI+): Calcd for C<sub>24</sub>H<sub>35</sub>N<sub>3</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 436.2576, Found: 436.2558.



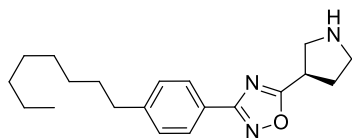
**(R)-Tert-butyl 3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate (2.24b).**

Synthesized by general procedure 2-A. 77% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  7.95 (d,  $J=8.2$  Hz, 2H), 7.25 (d,  $J=7.7$  Hz, 2H), 3.93-3.37 (m, 5H), 2.68-2.57 (m, 2H), 2.36 (dq,  $J=12.0, 6.9$  Hz, 2H), 1.61 (p,  $J=7.4$  Hz, 2H), 1.46 (s, 9H), 1.34-1.18 (m, 10H), 0.86 (t,  $J=6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  179.3, 168.5, 154.3, 146.7, 129.0, 127.4, 124.0, 79.8, 49.4, 45.1, 36.7, 36.0, 31.9, 31.3, 29.7, 29.5, 29.3, 29.3, 28.6, 22.7, 14.2; HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{25}\text{H}_{37}\text{N}_3\text{O}_3\text{Na}$  [ $\text{M}+\text{Na}$ ]<sup>+</sup>: 450.2732, Found: 450.2695.



**3-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) azetidinium chloride (2.25a).**

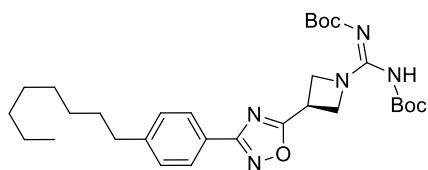
Synthesized by author N.N.P. Synthesized by general procedure 2-B. 94% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  7.97 (d,  $J = 8.4$  Hz, 2H), 7.33 (d,  $J = 8.4$  Hz, 2H), 4.64 – 4.31 (m, 5H), 2.67 (t,  $J = 7.5$  Hz, 2H), 1.64 (p,  $J = 7.4$  Hz, 2H), 1.42 – 1.17 (m, 10H), 0.87 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  178.9, 169.9, 148.3, 130.2, 128.4, 125.1, 51.0, 36.8, 33.0, 32.4, 30.5, 30.4, 30.3, 30.0, 23.7, 14.4. HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{19}\text{H}_{28}\text{N}_3\text{O}^+$  [ $\text{M}^+$ ]: 314.2227, Found: 314.2221.



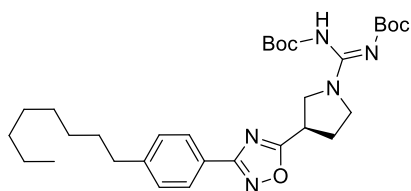
**(R)-3-(4-Octylphenyl)-5-(pyrrolidin-3-yl)-1,2,4-oxadiazole (2.25b).**

Synthesized by general procedure 2-B. 79%, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.95 (d,  $J = 8.2$  Hz, 2H),

7.25 (d,  $J = 8.4$  Hz, 2H), 3.57 (ddd,  $J = 12.7, 9.1, 6.3$  Hz, 1H), 3.29 (d,  $J = 5.9$  Hz, 2H), 3.25-3.16 (m, 1H), 3.06-2.96 (m, 1H), 2.67-2.57 (m, 2H), 2.34-2.08 (m, 3H), 1.68-1.55 (m, 2H), 1.27 (d,  $J = 19.6$  Hz, 10H), 0.86 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  182.1, 168.4, 146.5, 129.0, 127.4, 124.3, 52.6, 47.5, 37.3, 36.0, 32.0, 32.0, 31.3, 29.8, 29.5, 29.3, 29.3, 22.7, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 328.2383, Found: 328.2386.

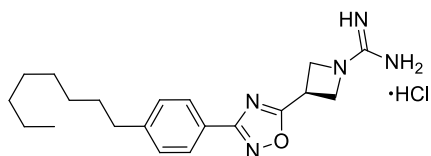


***Tert*-butyl (((*tert*-butoxycarbonyl) amino)(3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) azetid-1-yl) methylene) carbamate.** Synthesized by author N.N.P. Guanylation of 3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) azetid-1-ium chloride **2.25a**. Synthesized by general procedure 2-C. 57%, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  11.01 (s, 1H), 7.95 (d,  $J = 8.2$  Hz, 2H), 7.27 (d,  $J = 8.1$  Hz, 2H), 4.82 – 4.51 (m, 3H), 4.10 (ddd,  $J = 15.5, 8.9, 6.6$  Hz, 1H), 2.64 (t,  $J = 8.0, 7.4$  Hz, 2H), 1.61 (dt,  $J = 11.9, 7.1$  Hz, 2H), 1.48 (s, 18H), 1.36 – 1.20 (m, 10H), 0.85 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  178.2, 168.6, 156.2, 146.7, 128.9, 127.4, 123.7, 35.9, 31.8, 31.1, 29.4, 29.2, 29.2, 28.1, 26.5, 22.6, 14.0; HRMS (ESI+): Calcd for  $\text{C}_{30}\text{H}_{46}\text{N}_5\text{O}_5$   $[\text{M}+\text{H}]^+$ : 556.3499, Found: 556.3455.

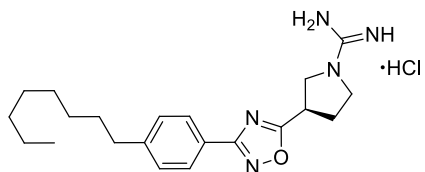


**(*R*)-*Tert*-butyl (((*tert*-butoxycarbonyl)imino)(3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methyl)carbamate.** Guanylation of (*R*)-3-(4-octylphenyl)-5-(pyrrolidin-3-yl)-1,2,4-oxadiazole **2.25b**. Synthesized by general procedure 2-C. 8% yield, colorless oil;  $^1\text{H}$  NMR

(400 MHz, Chloroform-d)  $\delta$  7.96 (d,  $J = 8.3$  Hz, 2H), 7.27 (d,  $J = 8.2$  Hz, 2H), 4.05 (s, 2H), 3.87-3.68 (m, 3H), 2.69-2.62 (m, 2H), 2.45 (dt,  $J = 13.4, 6.5$  Hz, 2H), 1.68-1.61 (m, 2H), 1.50 (s, 18H), 1.28 (d,  $J = 22.8$  Hz, 10H), 0.92-0.83 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  178.6, 171.3, 168.6, 154.4, 146.8, 129.1, 127.6, 124.0, 77.4, 66.0, 60.5, 36.1, 32.0, 31.7, 31.3, 29.8, 29.6, 29.4, 29.4, 28.3, 25.4, 22.8, 21.2, 15.4, 14.3, 14.3, 14.2, 11.6, 1.2; HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{48}\text{N}_5\text{O}_5$   $[\text{M}+\text{H}]^+$ : 570.3655, Found: 570.3690.

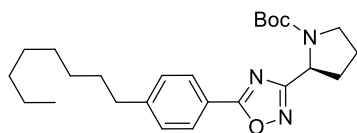


**Amino (3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) azetid-1-yl) methaniminium chloride (2.26a).** Synthesized by author N.N.P. Synthesized by general procedure 2-B. 82% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.96 (d,  $J = 8.3$  Hz, 2H), 7.32 (d,  $J = 8.3$  Hz, 2H), 4.63 (t,  $J = 8.9$  Hz, 2H), 4.50 – 4.33 (m, 3H), 2.66 (t,  $J = 7.5$  Hz, 2H), 1.62 (p,  $J = 7.3$  Hz, 2H), 1.42 – 1.18 (m, 10H), 0.87 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  180.0, 169.8, 158.3, 148.2, 130.1, 128.4, 125.2, 55.8, 36.8, 33.0, 32.4, 30.5, 30.4, 30.3, 27.2, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{30}\text{N}_5\text{O}^+$   $[\text{M}^+]$ : 356.2445, Found: 356.2418.



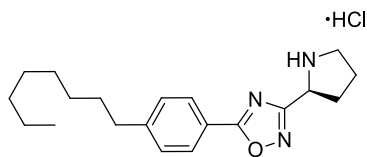
**(R)-Amino (3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-yl) methaniminium chloride (2.26b).** Synthesized by general procedure 2-B. 72% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.98 (d,  $J = 8.0$  Hz, 2H), 7.37 (d,  $J = 8.0$  Hz, 2H), 4.13-3.87 (m, 3H), 3.74-3.65 (m, 2H), 2.75-2.62 (m, 3H), 2.53 (s, 1H), 1.72-1.64 (m, 2H), 1.45-1.24 (m, 10H), 0.92 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  180.3, 169.6, 156.4, 148.2, 130.1, 128.3, 125.2,

51.4, 47.7, 37.3, 36.8, 33.0, 32.4, 30.6, 30.5, 30.3, 30.3, 23.7, 14.4; MS: Calcd for C<sub>21</sub>H<sub>32</sub>N<sub>5</sub>O [M<sup>+</sup>]: 370.2606, Found: 370.2586.



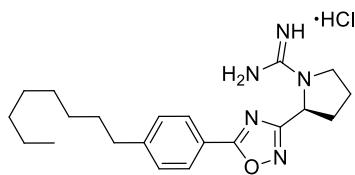
**(S)-Tert-butyl 2-(5-(4-octylphenyl)-1,2,4-oxadiazol-3-yl) pyrrolidine-1-carboxylate (2.28).**

Synthesized by general procedure 2-A. 19% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 8.02 (d, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 4.99 (d, *J* = 4.3 Hz, 1H), 3.73-3.52 (m, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.32 (s, 1H), 2.19-2.04 (m, 2H), 1.96 (d, *J* = 5.8 Hz, 1H), 1.69-1.59 (m, 2H), 1.46 (s, 3H), 1.37-1.22 (m, 16H), 0.91-0.85 (m, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 172.9, 159.8, 156.0, 148.6, 129.3, 128.2, 107.7, 80.0, 77.4, 53.5, 46.6, 36.2, 32.0, 31.3, 29.6, 29.4, 29.4, 28.4, 23.5, 22.8, 14.2; HRMS (ESI<sup>+</sup>): Calcd for C<sub>25</sub>H<sub>38</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 428.2913, Found: 428.2918.

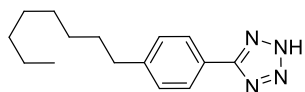


**(S)-2-(5-(4-Octylphenyl)-1,2,4-oxadiazol-3-yl) pyrrolidine-1-carboximidamide**

**hydrochloride.** Synthesized by general procedure 2-B. 89% yield, white solid; <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 5.02 (t, *J* = 7.7 Hz, 1H), 3.63-3.46 (m, 2H), 2.78-2.72 (m, 2H), 2.62 (m, 2H), 2.47-2.18 (m, 3H), 1.75-1.63 (m, 2H), 1.41-1.26 (m, 10H), 0.94-0.87 (m, 3H); <sup>13</sup>C NMR (101 MHz, Methanol-d<sub>4</sub>) δ 178.7, 168.6, 151.0, 130.6, 129.3, 122.1, 55.8, 47.2, 37.0, 33.0, 32.3, 30.5, 30.3, 30.3, 30.1, 24.5, 23.7, 14.4; HRMS (ESI<sup>+</sup>): Calcd for C<sub>20</sub>H<sub>30</sub>N<sub>3</sub>O [M+H]<sup>+</sup>: 328.2388, Found: 328.2386.

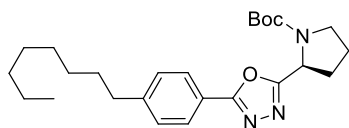


**(S)-Amino (2-(5-(4-octylphenyl)-1,2,4-oxadiazol-3-yl) pyrrolidin-1-yl) methaniminium chloride (2.29).** Synthesized by general procedure 2-B. 28% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.05 (d,  $J = 6.9$  Hz, 2H), 7.43 (d,  $J = 7.2$  Hz, 2H), 5.29 (d,  $J = 7.3$  Hz, 1H), 3.74-3.69 (m, 1H), 3.65-3.53 (m, 1H), 2.73 (t,  $J = 7.8$  Hz, 2H), 2.52-2.39 (m, 2H), 2.19 (s, 2H), 1.70-1.63 (m, 2H), 1.32 (d,  $J = 20$  Hz, 10H), 0.93-0.86 (m, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  178.2, 171.1, 156.9, 150.6, 130.5, 129.2, 122.4, 56.3, 37.0, 33.0, 32.4, 32.3, 30.5, 30.4, 30.3, 24.1, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_5\text{O}$   $[\text{M}+\text{H}]^+$ : 370.2606, Found: 370.2617.



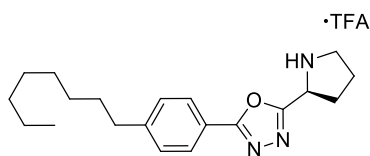
**5-(4-Octylphenyl)-2H-tetrazole (2.30).** To a solution of 4-octylbenzotrile **2.3** (120 mg, 0.557 mmol) in DMF (3 mL), ammonium chloride (54 mg, 1.003 mmol) and sodium azide (65 mg, 1.003 mmol) were added. The reaction was refluxed for ~4 hours. After the reaction was completed, the solution was cooled to room temperature, filtered, and the residue washed with acetone. The solvent was then evaporated *in vacuo*, and the residue was partitioned between equal volumes of hexanes and water. Organic layer was then separated, washed with sat. LiBr and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford **2.30** in a quantitative yield as colorless oil. The isolated product was sufficiently pure to use in the next reaction.  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.56 (d,  $J = 8.3$  Hz, 2H), 7.26 (d,  $J = 7.3$  Hz, 2H), 2.65 (t,  $J = 8.1$  Hz, 2H), 1.61 (p,  $J = 7.4$  Hz, 2H), 1.34-1.21 (m, 10H), 0.87 (t,  $J = 6.2$  Hz, 3H);  $^{13}\text{C}$

NMR (101 MHz, Chloroform-d)  $\delta$  148.8, 132.2, 129.3, 119.3, 109.6, 36.3, 32.0, 31.1, 29.5, 29.3, 22.8, 14.2; HRMS (ESI<sup>+</sup>): Calcd for C<sub>15</sub>H<sub>23</sub>N<sub>4</sub> [M+H]<sup>+</sup>: 259.1923, Found: 259.1931.



**(S)-Tert-butyl 2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl) pyrrolidine-1-carboxylate (2.31).**

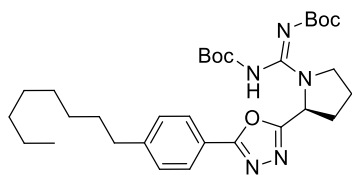
Synthesized by general procedure 2-A. 67% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  7.92 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 5.21-5.05 (m, 1H), 3.71-3.34 (m, 2H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.44-1.68 (m, 4H), 1.62 (q, *J* = 7.3 Hz, 2H), 1.44 (d, *J* = 8.6 Hz, 3H), 1.37-1.20 (m, 16H), 0.86 (t, *J* = 6.7 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d)  $\delta$  167.3, 164.8, 154.3, 147.4, 129.2, 126.9, 121.3, 80.3, 58.6, 53.0, 46.5, 36.1, 32.4, 32.0, 31.2, 29.5, 29.4, 29.3, 28.5, 28.4, 23.8, 22.8, 14.2; HRMS (ESI<sup>+</sup>): Calcd for C<sub>25</sub>H<sub>38</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 428.2913, Found: 428.2930.



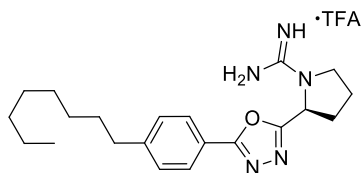
**(S)-2-(5-(4-Octylphenyl)-1,3,4-oxadiazol-2-yl) pyrrolidin-1-ium 2,2,2-trifluoroacetate.**

Deprotection of (S)-tert-butyl 2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl) pyrrolidine-1-carboxylate **2.31**. Synthesized by general procedure 2-D. 100 % yield, white solid; <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  8.00 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 5.17 (t, *J* = 7.7 Hz, 1H), 3.61-3.48 (m, 2H), 2.72 (t, *J* = 7.4 Hz, 2H), 2.68-2.59 (m, 1H), 2.58-2.46 (m, 2H), 2.36-2.22 (m, 2H), 1.68 (p, *J* = 7.3 Hz, 2H), 1.40-1.26 (m, 10H), 0.90 (t, *J* = 8.0 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Methanol-d<sub>4</sub>)  $\delta$  167.8, 163.3, 149.7, 130.5, 128.2, 121.7, 54.7, 47.3, 36.9, 33.0, 32.3, 30.5, 30.4, 30.3, 29.8, 24.6, 23.7, 14.4; HRMS (ESI<sup>+</sup>): Calcd for C<sub>20</sub>H<sub>30</sub>N<sub>3</sub>O<sup>+</sup> [M+H]<sup>+</sup>: 328.2388, Found: 328.2389.

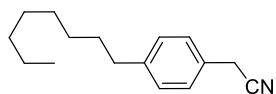




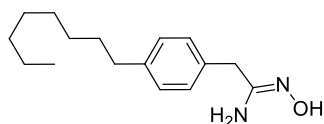
**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl)methylene)carbamate.** Guanylation of (S)-2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl) pyrrolidin-1-ium 2,2,2-trifluoroacetate. Synthesized by general procedure 2-C. 30% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.94 (d,  $J = 8.2$  Hz, 2H), 7.28 (d,  $J=8.2$  Hz, 2H), 5.64 (dd,  $J = 7.6, 5.3$  Hz, 1H), 3.95-3.70 (m, 2H), 2.65 (t,  $J = 7.4$  Hz, 2H), 2.48-2.39 (m, 1H), 2.34-2.16 (m, 2H), 2.07-1.98 (m, 1H), 1.68-1.57 (m, 2H), 1.48 (d,  $J = 19.1$  Hz, 18H), 1.31-1.24 (m, 10H), 0.87 (t,  $J=7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  171.7, 170.4, 165.9, 165.1, 147.3, 129.2, 127.1, 121.4, 54.3, 49.6, 36.1, 32.0, 31.3, 29.6, 29.4, 29.4, 28.3, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{48}\text{N}_5\text{O}_5$   $[\text{M}+\text{H}]^+$ : 570.3655, Found: 570.3656.



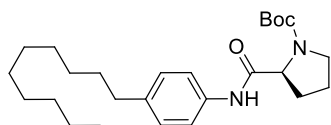
**(S)-Amino(2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate (2.32).** Deprotection of (S)-tert-butyl (((tert-butoxycarbonyl)amino)(2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl)methylene)carbamate by general procedure 2-D. 90% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  7.99 (d,  $J = 8.4$  Hz, 2H), 7.45 (d,  $J = 8.4$  Hz, 2H), 5.43 (dd,  $J = 7.3, 2.1$  Hz, 1H), 3.80 (td,  $J = 9.2, 2.3$  Hz, 1H), 3.63 (td,  $J = 9.8, 7.2$  Hz, 1H), 2.75 (t,  $J = 7.2$  Hz, 2H), 2.63-2.46 (m, 2H), 2.33-2.08 (m, 2H), 1.70 (p,  $J=7.3$  Hz, 2H), 1.43-1.27 (m, 10H), 0.92 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol-d<sub>4</sub>)  $\delta$  167.5, 165.8, 157.0, 149.4, 130.5, 128.0, 121.9, 55.7, 36.9, 33.0, 32.3, 32.1, 30.5, 30.4, 30.3, 24.1, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_5\text{O}^+$   $[\text{M}+\text{H}]^+$ : 370.2606, Found: 370.2618.



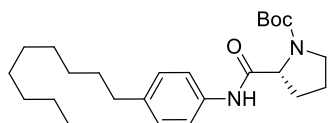
**2-(4-Octylphenyl) acetonitrile (2.33).** Synthesized using general procedure 2-H. 24% yield, colorless oil.  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  7.23 (d,  $J = 8.2$  Hz, 2H), 7.19 (d,  $J = 8.2$  Hz, 2H), 3.71 (s, 2H), 2.60 (t,  $J = 7.6$  Hz, 2H), 1.65-1.56 (m, 2H), 1.36-1.22 (m, 10H), 0.89 (t,  $J = 7.0$  Hz, 3H).



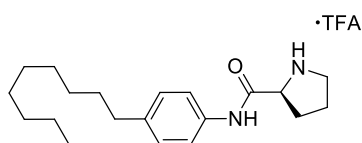
**(Z)-N'-Hydroxy-2-(4-octylphenyl) acetimidamide (2.34).** Synthesized by general procedure 2-I. 16% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.20 (d,  $J = 8.1$  Hz, 2H), 7.13 (d,  $J = 8.1$  Hz, 2H), 3.64 (d,  $J = 16.3$  Hz, 2H), 2.63-2.54 (m, 2H), 1.62-1.54 (m, 2H), 1.35-1.23 (m, 10H), 0.88 (t,  $J = 7.3$  Hz, 3H).



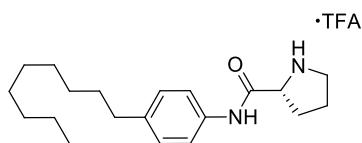
**(S)-Tert-butyl 2-((4-decylphenyl) carbamoyl) pyrrolidine-1-carboxylate (2.36a).** Synthesized using general procedure 2-F. 61% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  9.37 (s, 1H), 7.41 (d,  $J = 8.4$  Hz, 2H), 7.10 (s, 2H), 4.39 (m, 1H), 3.68-3.21 (m, 2H), 2.54 (t,  $J = 7.5$  Hz, 2H), 2.03-1.81 (m, 2H), 1.60-1.53 (m, 2H), 1.49 (s, 9H), 1.34-1.16 (m, 14H), 0.87 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  169.8, 156.5, 138.8, 136.1, 128.9, 119.8, 81.0, 60.6, 47.3, 35.5, 32.0, 31.7, 29.7, 29.6, 29.4, 29.4, 28.5, 27.2, 24.7, 22.8, 14.2. HRMS (ESI $^+$ ): Calcd for  $\text{C}_{26}\text{H}_{43}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 431.3273, Found: 431.3240.



**(R)-Tert-butyl 2-((4-decylphenyl) carbamoyl) pyrrolidine-1-carboxylate (2.36b).** Synthesized using general procedure 2-F. 95% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  9.39 (s, 1H), 7.40 (d,  $J = 8.5$  Hz, 2H), 7.07 (s, 2H), 4.38 (m, 1H), 3.43 (t,  $J = 45.4$  Hz, 2H), 2.59-2.48 (m, 2H), 2.21 (s, 1H), 2.05-1.84 (m, 3H), 1.52 (d,  $J = 35.8$  Hz, 11H), 1.27 (d,  $J = 19.0$  Hz, 14H), 0.87 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  169.8, 156.5, 138.5, 136.1, 128.8, 119.7, 80.8, 60.5, 47.3, 35.4, 32.0, 31.6, 29.7, 29.7, 29.6, 29.4, 29.3, 27.4, 24.7, 28.5, 22.8, 14.2. HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{42}\text{N}_2\text{O}_3\text{Na}$   $[\text{M}+\text{Na}]^+$ : 453.3093, Found: 453.3126.

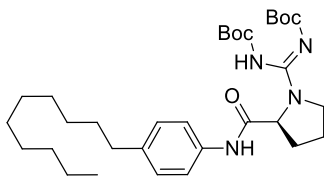


**(S)-2-((4-Decylphenyl) carbamoyl) pyrrolidin-1-ium 2,2,2-trifluoroacetate (2.37a).** Synthesized by general procedure 2-D. 73% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  10.22 (s, 1H), 7.38 (s, 2H), 7.06 (d,  $J = 6.3$  Hz, 2H), 4.6 (s, 1H), 3.39 (s, 2H), 2.53 (t,  $J = 8.0$  Hz, 2H), 2.20 – 1.91 (m, 4H), 1.55 (s, 2H), 1.37-1.18 (m, 14H), 0.88 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  166.6, 139.9, 135.0, 129.0, 120.3, 60.4, 46.7, 35.5, 32.1, 31.6, 30.3, 29.8, 29.8, 29.7, 29.5, 29.4, 24.9, 22.8, 14.3; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{35}\text{N}_2\text{O}^+$   $[\text{M}+\text{H}]^+$ : 331.2749, Found: 331.2716.

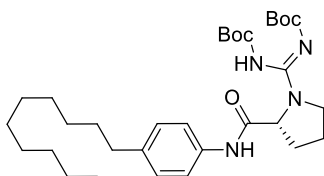


**(R)-2-((4-Decylphenyl) carbamoyl) pyrrolidin-1-ium 2,2,2-trifluoroacetate (2.37b).** Synthesized by general procedure 2-D. Quantitative yield, yellow oil;  $^1\text{H}$  NMR (400 MHz,

Chloroform-d)  $\delta$  10.26 (s, 1H), 7.37 (d,  $J = 7.9$  Hz, 2H), 7.04 (d,  $J = 7.9$  Hz, 2H), 4.80 (s, 1H), 3.34 (d,  $J = 26.2$  Hz, 2H), 2.51 (t,  $J = 7.9$  Hz, 2H), 2.44 (s, 1H), 2.08 (s, 1H), 1.95 (s, 2H), 1.54 (s, 2H), 1.32-1.22 (m, 14H), 0.87 (t,  $J = 6.6$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  166.7, 140.0, 135.1, 128.9, 120.5, 60.5, 46.6, 35.6, 32.1, 31.6, 30.2, 29.8, 29.8, 29.7, 29.5, 24.6, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{35}\text{N}_2\text{O}^+$   $[\text{M}+\text{H}]^+$ : 331.2749, Found: 331.2752.

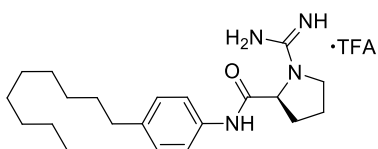


**(S)-Tert-butyl (((tert-butoxycarbonyl) imino)(2-((4-decylphenyl) carbamoyl) pyrrolidin-1-yl) methyl) carbamate.** Guanylation of (S)-2-((4-decylphenyl)carbamoyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate. Synthesized by general procedure 2-C. 55% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  9.75 (s, 1H), 7.57 (d,  $J = 8.5$  Hz, 2H), 7.11 (d,  $J = 8.5$  Hz, 2H), 5.10 (s, 1H), 3.71 (dt,  $J = 11.0, 7.3$  Hz, 1H), 3.55-3.50 (m, 1H), 2.54 (t,  $J = 7.9$  Hz, 2H), 2.41-2.34 (m, 1H), 2.22-2.15 (m, 1H), 2.06-1.99 (m, 1H), 1.91-1.83 (m, 1H), 1.65-1.53 (m, 2H), 1.51 (s, 18H), 1.31-1.21 (m, 14H), 0.87 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  171.0, 168.7, 161.9, 155.5, 138.7, 136.3, 128.8, 119.6, 61.8, 50.2, 50.2, 35.5, 32.0, 31.8, 29.8, 29.7, 29.7, 29.5, 29.4, 28.4, 28.3, 28.1, 24.7, 22.8; HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{52}\text{N}_4\text{O}_5$   $[\text{M}+\text{H}]^+$ : 573.4016, Found: 573.4011.

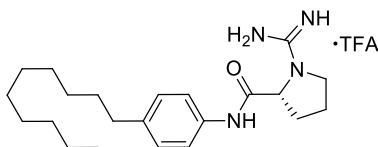


**(R)-Tert-butyl (((tert-butoxycarbonyl) imino)(2-((4-decylphenyl) carbamoyl) pyrrolidin-1-yl) methyl) carbamate.** Guanylation of (R)-2-((4-decylphenyl) carbamoyl) pyrrolidin-1-ium 2, 2,2-trifluoroacetate. Synthesized by general procedure 2-C. 85% yield, colorless oil;  $^1\text{H}$  NMR (500

MHz, Chloroform-d)  $\delta$  9.75 (s, 1H), 7.57 (d,  $J = 8.5$  Hz, 2H), 7.11 (d,  $J = 8.5$  Hz, 2H), 5.11 (s, 1H), 3.72 (dt,  $J = 10.9, 7.3$  Hz, 1H), 3.60-3.49 (m, 1H), 2.54 (t,  $J = 7.1$  Hz, 2H), 2.41-2.35 (m, 1H), 2.24-2.15 (m, 1H), 2.06-2.00 (m, 1H), 1.92-1.84 (m, 1H), 1.60-1.54 (m, 2H), 1.51 (s, 18H), 1.25 (s, 14H), 0.87 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  168.8, 155.4, 138.7, 136.2, 128.8, 119.5, 61.8, 50.3, 35.5, 32.0, 31.7, 29.8, 29.7, 29.7, 29.5, 29.4, 28.3, 28.1, 24.7, 22.8, 14.3; HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{53}\text{N}_4\text{O}_5$   $[\text{M}+\text{H}]^+$ : 573.4016, Found: 573.4011.

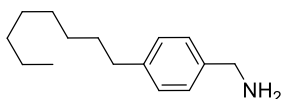


**(S)-Amino (2-((4-decylphenyl) carbamoyl) pyrrolidin-1-yl) methaniminium 2,2,2-trifluoroacetate (2.38a).** Synthesized by general procedure 2-D. 29% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  9.85 (s, 1H), 7.42 (d,  $J = 7.9$  Hz, 2H), 7.09 (d,  $J = 8.0$  Hz, 2H), 4.83 (s, 1H), 3.66 (s, 1H), 3.47 (s, 1H), 2.53 (t,  $J = 7.6$  Hz, 2H), 2.31 (s, 2H), 2.19 (s, 1H), 2.00 (s, 1H), 1.55 (s, 2H), 1.25 (s, 14H), 0.88 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  169.4, 155.4, 139.9, 135.2, 129.0, 120.3, 60.9, 48.4, 35.5, 32.0, 31.7, 31.4, 29.8, 29.8, 29.7, 29.5, 29.4, 24.1, 22.8, 14.3; HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{37}\text{N}_4\text{O}^+$   $[\text{M}+\text{H}]^+$ : 373.2967, Found: 373.2963.

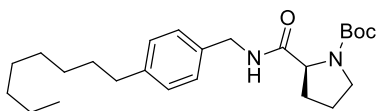


**(R)-Amino (2-((4-decylphenyl) carbamoyl) pyrrolidin-1-yl) methaniminium 2,2,2-trifluoroacetate (2.38b).** Synthesized by general procedure 2-D. 31% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  9.83 (s, 1H), 7.45 (d,  $J = 8.4$  Hz, 2H), 7.10 (d,  $J = 8.4$  Hz, 2H), 4.86 (s, 1H), 3.70-3.64 (m, 1H), 3.50-3.42 (m, 1H), 2.53 (t,  $J = 7.8$  Hz, 2H), 2.40-2.16 (m, 3H), 2.06-1.98 (m, 1H), 1.61-1.50 (m, 2H), 1.32-1.19 (m, 14H), 0.87 (t,  $J = 6.2$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,

Chloroform-d)  $\delta$  169.2, 155.3, 139.8, 135.3, 129.0, 120.3, 60.9, 48.3, 35.5, 32.1, 31.7, 31.4, 29.8, 29.8, 29.7, 29.5, 29.4, 22.8, 14.3; HRMS (ESI+): Calcd for  $C_{22}H_{37}N_4O^+$   $[M+H]^+$ : 373.2967, Found: 373.2949.

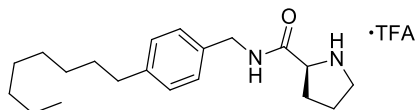


**(4-Octylphenyl) methanamine.** 4-Octylbenzylamine **2.2** (200 mg, 0.93 mmol) dissolved in tetrahydrofuran and added dropwise to a solution of lithium aluminum hydride (106 mg, 2.79 mmol) in tetrahydrofuran (9 mL) at zero degrees Celsius. After the addition, the mixture was warmed to room temperature and stirred for 0.5-1 hour. After completion, the reaction was cooled to zero degrees Celsius and diluted with diethyl ether. Next, 60  $\mu$ L of water, 60  $\mu$ L of 15% NaOH solution, and 180  $\mu$ L of water were added dropwise in that order. The reaction was heated back up to room temperature and stirred for 0.5 hour. After, the reaction was filtered through a celite plug and the aqueous layer was washed with diethyl ether x3 and separated. The organic layer was then washed with brine, dried with sodium sulfate, and concentrated *in vacuo* to give (4-octylphenyl) methanamine without further purification.  $^1H$  NMR (400 MHz, Chloroform-d)  $\delta$  7.22 (d,  $J = 8.1$  Hz, 2H), 7.15 (d,  $J = 8.1$  Hz, 2H), 3.83 (s, 1H), 2.59 (t,  $J = 7.6$  Hz, 2H), 1.66-1.54 (m, 2H), 1.37-1.24 (m, 10H), 0.89 (t,  $J = 6.8$  Hz, 3H).

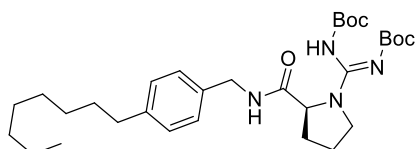


**(S)-Tert-butyl 2-((4-octylbenzyl) carbamoyl) pyrrolidine-1-carboxylate.** Synthesized using general procedure 2-E. Taken to the next step without further purification, colorless oil;  $^1H$  NMR (500 MHz, Chloroform-d)  $\delta$  7.16 (d,  $J = 7.9$  Hz, 2H), 7.11 (d,  $J = 7.8$  Hz, 2H), 4.62-16 (m, 3H), 3.50-3.26 (m, 2H), 2.55 (t,  $J = 7.4$  Hz, 2H), 2.40-2.10 (m, 1H), 1.96-1.80 (m, 3H), 1.56 (p,  $J = 7.4$

Hz, 2H), 1.49-1.19 (m, 19H), 0.87 (t,  $J=7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  172.4, 155.8, 142.5, 135.5, 128.8, 128.0, 80.7, 61.4, 60.2, 47.2, 43.3, 35.7, 32.0, 31.6, 29.6, 29.4, 29.3, 28.4, 22.8, 14.2. HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{25}\text{H}_{40}\text{N}_2\text{O}_3\text{Na}$   $[\text{M}+\text{Na}]^{+}$ : 439.2936, Found: 439.2937.

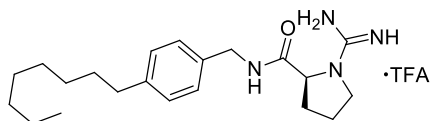


**(S)-2-((4-Octylbenzyl) carbamoyl) pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Deprotection of the Boc group in (*S*)-*tert*-butyl 2-((4-octylbenzyl) carbamoyl) pyrrolidine-1-carboxylate. Synthesized using general procedure 2-D. Taken to the next step without further purification, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.55 (s, 1H), 7.69 (s, 1H), 7.09 (dd,  $J=8.5, 2.9$  Hz, 4H), 4.58 (s, 1H), 4.33 (d,  $J=5.2$  Hz, 2H), 3.35-3.18 (m, 2H), 2.53 (t,  $J=7.7$  Hz, 2H), 2.37-2.25 (m, 1H), 2.00-1.84 (m, 3H), 1.55 (p,  $J=7.4$  Hz, 2H), 1.33-1.20 (m, 10H), 0.86 (t,  $J=6.6$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  168.62, 142.38, 134.87, 128.76, 127.52, 59.67, 46.33, 43.69, 35.73, 32.01, 31.68, 30.20, 29.60, 29.50, 29.40, 24.52, 22.80, 14.24; HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{20}\text{H}_{33}\text{N}_2\text{O}^{+}$   $[\text{M}+\text{H}]^{+}$ : 317.2592, Found: 317.2591.

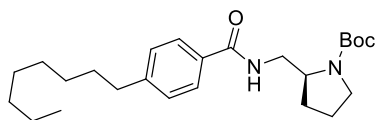


**(S)-Tert-butyl (((tert-butoxycarbonyl) imino)(2-((4-octylbenzyl) carbamoyl) pyrrolidin-1-yl) methyl) carbamate (2.39).** Guanylation of (*S*)-2-((4-octylbenzyl) carbamoyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate. Synthesized by general procedure 2-C. 46% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  10.02 (s, 1H), 7.61 (s, 1H), 7.15 (d,  $J=8.2$  Hz, 2H), 7.08 (d,  $J=8.2$  Hz, 2H), 4.98 (t,  $J=6.8$  Hz, 1H), 4.45 (dd,  $J=14.8, 6.0$  Hz, 1H), 4.32 (dd,  $J=14.8, 5.1$  Hz, 1H), 3.63 (dt,  $J=11.1, 7.3$  Hz, 1H), 3.51-3.44 (m, 1H), 3.54 (t,  $J=7.4$  Hz, 2H), 2.21 (q,  $J=7.0$  Hz, 1H), 2.03-1.79 (m, 3H), 1.56 (p,  $J=6.9$  Hz, 2H), 1.43 (s, 18H), 1.31-1.19 (m, 10H), 0.87 (t,  $J=6.7$  Hz,

3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  171.0, 155.1, 141.9, 135.4, 128.6, 127.7, 61.5, 49.8, 43.4, 35.7, 32.0, 31.6, 29.6, 29.5, 29.4, 29.0, 28.2, 24.6, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{51}\text{N}_4\text{O}_5$   $[\text{M}+\text{H}]^+$ : 559.3859, Found: 559.3832.

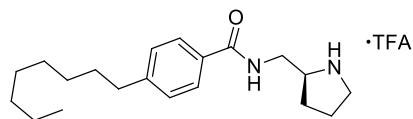


**(S)-Amino (2-((4-octylbenzyl) carbamoyl) pyrrolidin-1-yl) methaniminium 2,2,2-trifluoroacetate (2.40).** Synthesized by general procedure 2-D. 39% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.35 (s, 1H), 7.09 (s, 4H), 4.64 (s, 1H), 4.40 (dd,  $J= 14.5, 5.9$  Hz, 1H), 4.20 (dd,  $J= 9.6, 4.8$  Hz, 1H), 3.64 (s, 1H), 3.44 (s, 1H), 2.54 (t,  $J= 7.8$  Hz, 2H), 2.32-2.05 (m, 3H), 2.01-1.93 (m, 1H), 1.56 (p,  $J= 7.8$  Hz, 2H), 1.33-1.20 (m, 10H), 0.87 (t,  $J= 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  171.2, 155.6, 142.3, 135.0, 128.8, 127.5, 60.5, 48.3, 43.5, 35.7, 32.0, 31.7, 31.3, 29.6, 29.5, 29.4, 24.1, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{35}\text{N}_4\text{O}^+$   $[\text{M}+\text{H}]^+$ : 359.2810, Found: 359.2794.

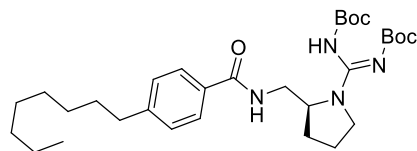


**(S)-Tert-butyl 2-((4-octylbenzamido) methyl) pyrrolidine-1-carboxylate (2.41).** Synthesized by general procedure 2-G. 85% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.30 (s, 1H), 7.77 (d,  $J= 7.8$  Hz, 2H), 7.18 (d,  $J= 8.2$  Hz, 2H), 4.17 (s, 1H), 3.51 (d,  $J= 13.3$  Hz, 1H), 3.41-3.31 (m, 3H), 2.60 (t,  $J= 7.5$  Hz, 2H), 2.08-1.79 (m, 3H), 1.72 (s, 1H), 1.59 (p,  $J= 7.2$  Hz, 2H), 1.45 (s, 9H), 1.32-1.18 (m, 10H), 0.85 (t,  $J= 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  167.5, 157.1, 146.4, 131.7, 128.4, 127.2, 80.2, 56.2, 47.2, 47.1, 35.9, 31.9, 31.3, 29.6, 29.5, 29.3, 28.5, 24.0, 22.7, 14.2. HRMS (ESI+): Calcd for  $\text{C}_{25}\text{H}_{41}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 417.3117, Found: 417.3088.

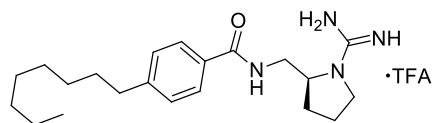




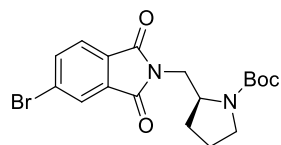
**(S)-2-((4-Octylbenzamido) methyl) pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Deprotection of Boc group in (*S*)-*tert*-butyl 2-((4-octylbenzamido) methyl) pyrrolidine-1-carboxylate. Synthesized by general procedure 2-D. 63% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.24 (s, 1H), 8.43 (s, 1H), 7.72 (d,  $J = 8.1$  Hz, 2H), 7.18 (d,  $J = 8.0$  Hz, 2H), 3.80 (s, 1H), 3.72-3.62 (m, 1H), 3.56 (d,  $J = 14.0$  Hz, 1H), 3.17 (s, 2H), 2.59 (t,  $J = 7.4$  Hz, 2H), 2.05-1.93 (m, 2H), 1.92-1.82 (m, 1H), 1.73-1.64 (m, 1H), 1.57 (p,  $J = 6.7$  Hz, 2H), 1.33-1.20 (m, 10H), 0.87 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  169.8, 147.9, 130.4, 128.8, 127.5, 60.7, 45.2, 41.4, 36.0, 32.0, 31.3, 29.5, 29.4, 29.4, 27.8, 24.1, 22.8, 14.2; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{20}\text{H}_{33}\text{N}_2\text{O}^+$  [ $\text{M}^+$ ] $^+$ : 317.2592, Found: 317.2564.



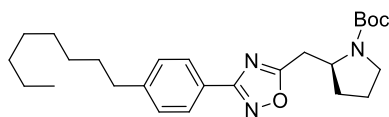
**(S)-*Tert*-butyl (((*tert*-butoxycarbonyl) amino)(2-((4-octylbenzamido) methyl) pyrrolidin-1-yl) methylene) carbamate.** Guanylation of (*S*)-2-((4-octylbenzamido) methyl) pyrrolidin-1-ium 2,2,2-trifluoroacetate. Synthesized by general procedure 2-C. 47% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.29 (s, 1H), 7.86 (d,  $J = 8.3$  Hz, 2H), 7.71 (s, 1H), 7.20 (d,  $J = 8.2$  Hz, 2H), 4.61-4.53 (m, 1H), 3.84 (dt,  $J = 14.0, 3.7$  Hz, 1H), 3.76-3.68 (m, 1H), 3.62-3.41 (m, 2H), 2.62 (t,  $J = 7.6$  Hz, 2H), 2.20-2.12 (m, 1H), 1.94-1.86 (m, 1H), 1.82-1.67 (m, 3H), 1.59 (p,  $J = 6.3$  Hz, 2H), 1.50 (s, 18H), 1.36-1.18 (m, 10H), 0.87 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  167.6, 155.1, 146.6, 131.8, 128.4, 127.5, 58.6, 50.8, 42.6, 36.0, 32.0, 31.4, 29.6, 29.4, 29.4, 28.9, 28.3, 24.9, 22.8, 14.2; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{31}\text{H}_{51}\text{N}_4\text{O}_5$  [ $\text{M}+\text{H}$ ] $^+$ : 559.3859, Found: 559.3813.



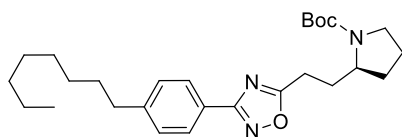
**(S)-Amino 2-((4-octylbenzamido) methyl) pyrrolidin-1-yl) methaniminium 2,2,2-trifluoroacetate (2.42).** Deprotection by general procedure 2-D. 47% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.02 (s, 1H), 7.72 (d,  $J = 8.1$  Hz, 2H), 7.21 (d,  $J = 8.1$  Hz, 2H), 4.05 (s, 1H), 3.54 (s, 1H), 3.35-3.09 (m, 1H), 2.60 (t,  $J = 7.4$  Hz, 2H), 2.13-1.92 (m, 3H), 1.58 (p,  $J = 6.9$  Hz, 2H), 1.50-1.36 (m, 1H), 1.32-1.22 (m, 10H), 0.87 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  169.2, 155.5, 147.7, 130.5, 128.8, 127.3, 57.9, 47.0, 42.7, 36.0, 32.0, 31.3, 29.8, 29.6, 29.6, 29.4, 29.4, 27.8, 22.8, 22.7, 14.2; HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{21}\text{H}_{35}\text{N}_4\text{O}^+ [\text{M}]^+$ : 359.2810, Found: 359.2817.



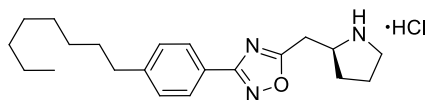
**(S)-Tert-butyl 2-((5-bromo-1,3-dioxisoindolin-2-yl)methyl)pyrrolidine-1-carboxylate (2.44).** Compound **2.43**, 5-bromoisoindoline-1,3-dione (1.3 equiv), and  $\text{PPh}_3$  (1.3 equiv) were dissolved in THF and cooled to zero degrees celsius. DIAD (1.3 equiv) was then added dropwise and the reaction was stirred for 1 hour. After an hour, the reaction was warmed to room temperature and stirred overnight. Once completion was observed, the reaction was concentrated under reduced pressure and purified by silica gel column chromatography to give compound **2.44** in 22% yield as an oil.  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  7.97 (d,  $J = 15.7$  Hz, 1H), 7.83 (dd,  $J = 29.5, 7.7$  Hz, 1H), 7.70 (dd,  $J = 17.0, 7.0$  Hz, 1H), 4.39-1.13 (m, 1H), 3.82-3.73 (m, 1H), 3.66-3.59 (m, 1H), 3.43-3.29 (m, 2H), 2.05-1.85 (m, 2H), 1.78-1.71 (m, 2H), 1.36 (s, 3H), 1.23 (s, 6H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  167.6, 167.1, 155.0, 136.6, 134.2, 131.1, 128.5, 126.6, 79.3, 54.8, 46.2, 41.4, 31.1, 29.0, 28.5, 28.3, 23.6.



**Tert-butyl (S)-2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) methyl) pyrrolidine-1-carboxylate (2.47a).** Synthesized by author N.N.P. Synthesized by general procedure 2-A. 56% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.95 (d,  $J = 8.3$  Hz, 2H), 7.25 (d,  $J = 7.9$  Hz, 2H), 4.39 – 4.16 (m, 1H), 3.48 – 3.22 (m, 3H), 3.15 – 2.94 (m, 1H), 2.63 (t,  $J = 7.9, 6.8$  Hz, 2H), 2.14 – 1.95 (m, 1H), 1.85 (m, 3H), 1.60 (dq,  $J = 12.9, 6.4, 5.4$  Hz, 2H), 1.45 (s, 9H), 1.36 – 1.17 (m, 18H), 0.85 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  177.0, 168.3, 154.1, 146.4, 128.8, 127.3, 124.1, 79.9, 55.1, 46.7, 46.3, 35.9, 31.8, 31.2, 29.4, 29.2, 29.2, 28.4, 22.6, 14.1. HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{26}\text{H}_{39}\text{N}_3\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 464.2889, Found: 464.2905.

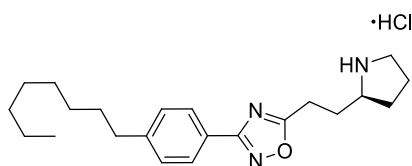


**Tert-butyl (S)-2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) ethyl) pyrrolidine-1-carboxylate (2.47b).** Synthesized by author N.N.P. Synthesized by general procedure 2-A. 63% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  7.97 (d,  $J = 8.2$  Hz, 2H), 7.28 (d,  $J = 8.0$  Hz, 2H), 3.94 (d,  $J = 51.5$  Hz, 1H), 3.45 (s, 0.5 H), 3.34 (s, 1H), 3.12 (q,  $J = 6.3$  Hz, 0.5 H), 2.95 (dq,  $J = 19.8, 8.5, 7.6$  Hz, 2H), 2.65 (t,  $J = 7.6$  Hz, 2H), 2.37 – 2.15 (m, 1H), 2.09 – 1.79 (m, 4H), 1.64 (tq,  $J = 20.6, 13.1, 9.4$  Hz, 4H), 1.45 (d,  $J = 6.8$  Hz, 9H), 1.36 – 1.20 (m, 10H), 0.88 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  179.6, 168.2, 154.6, 146.4, 128.9, 127.3, 124.3, 79.6, 56.4, 46.2, 40.4, 35.9, 31.8, 31.2, 29.9, 29.4, 29.2, 29.2, 28.7, 28.5, 28.4, 26.6, 26.5, 26.3, 22.6, 14.1. HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{27}\text{H}_{41}\text{N}_3\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 478.3046, Found: 478.3042.



**(S)-2-((3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) methyl) pyrrolidin-1-ium chloride.**

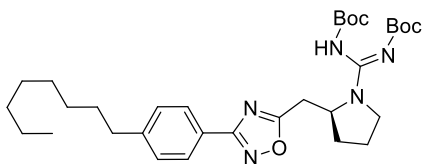
Synthesized by author N.N.P. Deprotection of Boc group in *tert*-butyl (S)-2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) methyl) pyrrolidine-1-carboxylate. Synthesized by general procedure 2-B. 85% yield, white solid; <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.00 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 4.18 (s, 1H), 3.61 – 3.47 (m, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 2.67 (t, *J* = 7.8 Hz, 2H), 2.47 – 2.36 (m, 1H), 2.12 (dd, *J* = 20.8, 13.5 Hz, 2H), 1.93 (d, *J* = 8.4 Hz, 1H), 1.71 – 1.57 (m, 2H), 1.39 – 1.22 (m, 10H), 0.88 (t, *J* = 7.2, 6.7 Hz, 3H). <sup>13</sup>C NMR (101 MHz, Methanol-d<sub>4</sub>) δ 177.4, 169.5, 148.1, 130.1, 128.4, 125.1, 58.4, 47.1, 36.8, 33.0, 32.4, 31.5, 30.5, 30.3, 30.3, 29.8, 24.7, 23.7, 14.4. HRMS (ESI<sup>+</sup>): Calcd for C<sub>21</sub>H<sub>32</sub>N<sub>3</sub>O [M+H]<sup>+</sup>: 342.2540, Found: 342.2537.



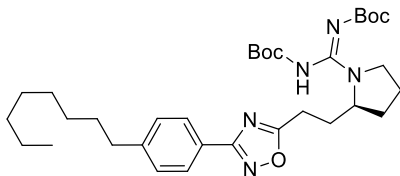
**(S)-2-(2-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl) ethyl) pyrrolidin-1-ium chloride.**

Synthesized by author N.N.P. Deprotection of Boc group in *tert*-butyl (S)-2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) ethyl) pyrrolidine-1-carboxylate. Synthesized by general procedure 2-B. 90% yield, white solid; <sup>1</sup>H NMR (500 MHz, Methanol-d<sub>4</sub>) δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 3.73 (q, *J* = 7.6, 6.9 Hz, 1H), 3.44 – 3.30 (m, 2H), 3.18 (t, *J* = 7.5 Hz, 2H), 2.98 (dt, *J* = 7.5 Hz, 1H), 2.68 (t, *J* = 7.8, 6.7 Hz, 2H), 2.36 (ddd, *J* = 14.1, 7.1 Hz, 2H), 2.10 (ddt, *J* = 37.7, 13.2, 8.2 Hz, 1.5H), 1.91 (q, *J* = 7.1 Hz, 0.5H), 1.84-1.57(m, 3.5H), 1.55 – 1.45 (m, 2H), 1.40 – 1.23 (m, 10H), 0.90 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C NMR (126 MHz, Methanol-d<sub>4</sub>) δ 180.2 (rotamer 1), 178.6 (rotamer 2), 168.1 (rotamer 1), 168.0 (rotamer 2), 146.6 (rotamer 1), 146.5 (rotamer 2), 128.7 (rotamer 1), 128.7 (rotamer 2), 126.9 (rotamer 1), 126.9 (rotamer 2), 124.1 (rotamer 1), 124.0

(rotamer 2), 59.7, 45.0, 39.3, 35.5, 31.6, 31.1, 29.6, 29.1 (rotamer 1), 29.0 (rotamer 2), 28.9, 28.2 (rotamer 1), 28.1 (rotamer 2), 26.9, 25.9, 25.7, 25.6, 23.2, 23.0, 22.3, 13.1. HRMS (ESI+): Calcd for C<sub>22</sub>H<sub>34</sub>N<sub>3</sub>O [M+H]<sup>+</sup>: 356.2696, Found: 356.2703.

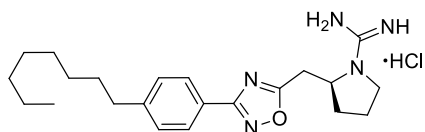


**Tert-butyl (S)-(((tert-butoxycarbonyl)amino)(2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methylene)carbamate.** Synthesized by author N.N.P. Guanylation of (S)-2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) methyl) pyrrolidin-1-ium chloride. Synthesized by general procedure 2-C. 71% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 10.28 (s, 2H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 6.1 Hz, 2H), 4.76 (dt, *J* = 11.3, 5.7 Hz, 1H), 3.72 – 3.58 (m, 2H), 3.48 (s, 1H), 3.12 (dd, *J* = 15.1, 8.4 Hz, 1H), 2.63 (t, *J* = 8.2, 6.5 Hz, 2H), 2.29 – 2.17 (m, 1H), 1.89 (ddd, *J* = 10.1, 7.4, 4.6 Hz, 1H), 1.85 – 1.74 (m, 2H), 1.61 (p, *J* = 7.3 Hz, 2H), 1.45 (s, 18H), 1.35 – 1.18 (m, 10H), 0.86 (t, *J* = 5.8 Hz, 3H). <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 176.9, 168.2, 154.0, 146.3, 128.8, 127.4, 124.2, 56.4, 50.0, 35.9, 31.8, 31.6, 31.2, 30.5, 30.3, 29.4, 29.2, 28.1, 25.2, 22.6, 14.1, 14.1. HRMS (ESI+): Calcd for C<sub>32</sub>H<sub>49</sub>N<sub>5</sub>NaO<sub>5</sub> [M+Na]<sup>+</sup>: 606.3631, Found: 606.3700.

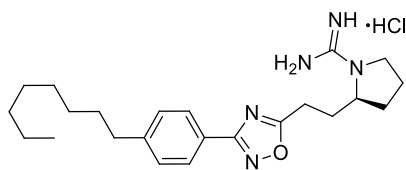


**Tert-butyl (S)-(((tert-butoxycarbonyl)imino)(2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)pyrrolidin-1-yl)methyl)carbamate.** Synthesized by author N.N.P. Guanylation of (S)-2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) ethyl) pyrrolidin-1-ium chloride. Synthesized by general procedure 2-C. 47% yield, colorless oil; <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 7.97 (d, *J*

= 8.3 Hz, 2H), 7.28 (d,  $J = 8.1$  Hz, 2H), 4.58 (s, 1H), 3.62 (ddd,  $J = 11.4, 9.2, 7.0$  Hz, 2H), 3.44 (m, 1H), 3.01 (m, 2H), 2.65 (t,  $J = 7.7$  Hz, 2H), 2.35 (m, 2H), 2.14 (m, 2H), 2.02 – 1.92 (m, 2H), 1.84 – 1.68 (m, 3H), 1.63 (m, 3H), 1.48 (s, 18H), 1.37 – 1.20 (m, 10H), 0.88 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  179.4, 168.2, 154.4, 146.3, 128.9, 127.3, 124.3, 57.7, 49.9, 35.9, 31.9, 31.2, 29.9, 29.4, 29.3, 29.2, 28.2, 22.9, 22.7, 14.1. HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{33}\text{H}_{51}\text{N}_5\text{NaO}_5$   $[\text{M}+\text{Na}]^{+}$ : 620.3788, Found: 620.3770.

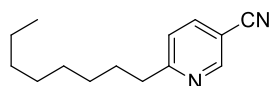


**(S)-Amino (2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) methyl) pyrrolidin-1-yl) methaniminium chloride (2.48a).** Synthesized by author N.N.P. Synthesized by general procedure 2-B. 83% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.94 (d,  $J = 8.3$  Hz, 2H), 7.31 (d,  $J = 8.4$  Hz, 2H), 4.52 (m, 1H), 3.53 (m, 1H), 3.48 – 3.40 (m, 1H), 2.66 (t,  $J = 7.9, 7.4$  Hz, 1H), 2.27 (m, 1H), 2.07 (m, 3H), 1.63 (m, 2H), 1.29 (m, 10H), 0.87 (t,  $J = 6.9$  Hz, 3H).  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.5, 168.2, 155.0, 146.7, 128.7, 126.9, 123.8, 55.8, 35.4, 31.6, 31.0, 30.2, 29.1, 28.9, 28.9, 28.7, 22.3, 22.2, 13.0. HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{22}\text{H}_{34}\text{N}_5\text{O}$   $[\text{M}+\text{H}]^{+}$ : 384.2758, Found: 384.2743.  $[\alpha]_D^{25} = -89.6^\circ$  ( $c = 0.005$ , methanol). *HPLC analysis indicates that compound 2.48a is 93% pure.*

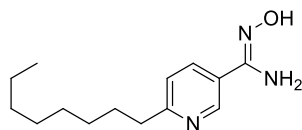


**(S)-Amino (2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl) ethyl) pyrrolidin-1-yl) methaniminium chloride (2.48b).** Synthesized by author N.N.P. Synthesized by general procedure 2-B. 95% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  7.80 (d,  $J = 8.3$  Hz,

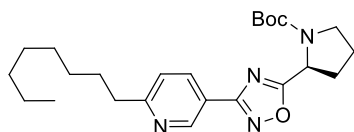
1H), 7.25 (d,  $J = 8.4$  Hz, 1H), 4.03 (m, 1H), 3.46 (m, 1H), 3.35 – 3.27 (m, 1H), 3.07 – 2.89 (m, 2H), 2.59 (t,  $J = 7.5$  Hz, 2H), 2.19 (m, 1H), 2.13 – 1.97 (m, 3H), 1.91 (m, 2H), 1.55 (m, 2H), 1.33 – 1.12 (m, 10H), 0.79 (t,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  179.8, 167.8, 154.8, 146.7, 128.8, 126.8, 123.8, 57.6, 35.4, 31.6, 31.0, 29.3, 29.1, 29.0, 28.9, 28.1, 22.4, 22.3, 22.2, 13.0. HRMS (ESI+): Calcd for  $\text{C}_{23}\text{H}_{36}\text{N}_5\text{O}$   $[\text{M}+\text{H}]^+$ : 398.2914, Found: 398.2905. *HPLC analysis indicates that compound 2.48b is 89% pure.*



**6-Octylnicotinonitrile (2.49).** Synthesized by general procedure 2-H. 56% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.79-8.77 (m, 1H), 7.83 (ddd,  $J = 8.1, 2.2, 0.7$  Hz, 1H), 7.25 (d,  $J = 8.1$  Hz, 1H), 2.84 (t,  $J = 7.4$  Hz, 2H), 1.71 (p,  $J = 7.3$  Hz, 2H), 1.36-1.18 (m, 10H), 0.88-0.81 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  167.3, 152.2, 139.3, 122.8, 117.1, 107.2, 38.8, 31.9, 29.5, 29.4, 29.4, 29.2, 22.7, 14.2.

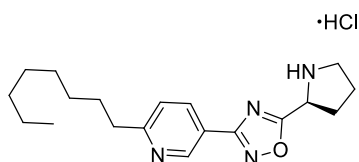


**(Z)-N'-Hydroxy-6-octylnicotinimidamide.** Synthesized by general procedure 2-I. 62% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.70 (dd,  $J = 2.3, 0.8$  Hz, 1H), 7.96 (dd,  $J = 8.1, 2.3$  Hz, 1H), 7.30 (dd,  $J = 8.2, 0.7$  Hz, 1H), 2.79 (t,  $J = 7.6$  Hz, 2H), 1.70 (p,  $J = 7.4$  Hz, 2H), 1.38-1.21 (m, 10H), 0.88 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  164.5, 152.6, 147.2, 136.0, 128.2, 124.0, 38.6, 33.0, 31.0, 30.5, 30.3, 30.3, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{14}\text{H}_{24}\text{N}_3\text{O}$   $[\text{M}+\text{H}]$ : 250.1919, Found 250.1919:



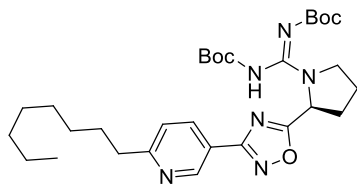
**(S)-Tert-butyl 2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate.**

Synthesized by general procedure 2-A. 49% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  9.17 (s, 1H), 8.21 (dd,  $J=8.1, 1.9$  Hz, 1H), 7.25 (d,  $J=9.2$  Hz, 1H), 5.22-5.01 (m, 1H), 3.74 – 3.61 (m, 1H), 3.59 – 3.43 (m, 1H), 2.83 (t,  $J=7.7$  Hz, 2H), 2.44 – 2.29 (m, 1H), 2.18 – 2.09 (m, 2H), 2.05-1.93 (m, 1H), 1.73 (p,  $J=7.6$  Hz, 2H), 1.44 (s, 3H), 1.39-1.19 (m, 16H), 0.85 (t,  $J=6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  181.1, 166.7, 165.8, 153.6, 148.2, 135.0, 122.8, 120.4, 80.6, 53.9, 46.5, 38.6, 32.5, 31.9, 29.8, 29.5, 29.5, 29.3, 28.3, 23.8, 22.7, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{24}\text{H}_{36}\text{N}_4\text{O}_3\text{Na}$  [ $\text{M}+\text{Na}$ ]: 451.2665, Found: 451.2685.

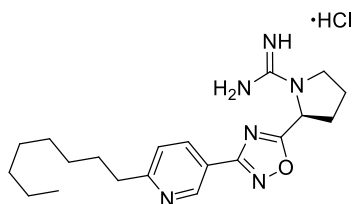


**(S)-2-(3-(6-Octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-ium chloride.** Synthesized by general procedure 2-B. 91% yield, colorless solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $\text{d}_4$ )  $\delta$  9.32 (d,  $J=1.5$  Hz, 1H), 9.05 (dd,  $J=8.4, 1.6$  Hz, 1H), 8.14 (d,  $J=8.4$  Hz, 1H), 5.29 (t,  $J=7.7$  Hz, 1H), 3.68 – 3.46 (m, 2H), 3.14 (t,  $J=7.7$  Hz, 2H), 2.73 - 2.64 (m, 1H), 2.51-2.41 (m, 1H), 2.35 – 2.19 (m, 2H), 1.85 (p,  $J=7.7$  Hz, 2H), 1.48-1.21 (m, 10H), 0.87 (t,  $J=6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $\text{d}_4$ )  $\delta$  177.5, 165.8, 162.4, 144.8, 141.8, 129.0, 125.1, 55.5, 47.5, 35.0, 32.9, 30.3, 30.3, 30.2, 30.2, 30.2, 24.5, 23.6, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{19}\text{H}_{29}\text{N}_4\text{O}^+$  [ $\text{M}^+$ ]: 329.2341, Found: 329.2311.

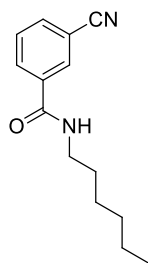




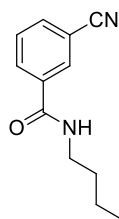
**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.** Synthesized by general procedure 2-C. 58% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  10.12 (s, 1H), 9.18 (d,  $J$ = 1.8 Hz, 1H), 8.22 (dd,  $J$  = 8.1, 2.2 Hz, 1H), 7.24 (d,  $J$  = 8.2 Hz, 1H), 5.61 (dd,  $J$  = 7.8, 4.5 Hz, 1H), 3.93-3.86 (m, 1H), 3.84 – 3.75 (m, 1H), 2.84 (t,  $J$ = 7.7 Hz, 2H), 2.48 – 2.40 (m, 1H), 2.24-2.12 (m, 2H), 2.07-1.98 (m, 1H), 1.74 (p,  $J$ = 7.7 Hz, 2H), 1.55-1.20 (m, 28H), 0.86 (t,  $J$ = 6.7 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  179.5, 166.7, 165.7, 162.1, 153.8, 150.5, 148.3, 135.2, 122.7, 120.4, 82.4, 79.7, 55.5, 49.6, 38.7, 32.0, 31.6, 29.9, 29.6, 29.5, 29.3, 28.2, 24.1, 22.8, 14.2; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{30}\text{H}_{47}\text{N}_6\text{O}_5$  [M+H]: 571.3608, Found: 571.3586.



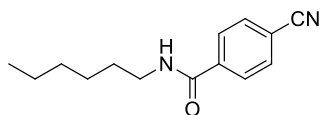
**(S)-Amino (2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-yl) methaniminium chloride (2.50).** Synthesized by general procedure 2-B. 91% yield, colorless solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  9.18 (s, 1H), 8.72 (s, 1H), 7.83 (d,  $J$ = 5.0 Hz, 1H), 5.49 (d,  $J$  = 5.5 Hz, 1H), 3.76 (s, 1H), 3.62 (s, 1H), 3.01 (t,  $J$ = 7.2 Hz, 2H), 2.57 (s, 1H), 2.48 (s, 1H), 2.22 (s, 1H), 2.08 (s, 1H), 1.80 (s, 2H), 1.45-1.22 (m, 10H), 0.87 (t,  $J$ = 6.4 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  180.2, 166.5, 164.3, 157.1, 144.7, 141.4, 127.3, 123.9, 56.6, 36.8, 33.0, 32.9, 30.7, 30.4, 30.3, 30.3, 24.4, 23.7, 14.4; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{20}\text{H}_{31}\text{N}_6\text{O}^+$  [M $^+$ ]: 371.2559, Found: 371.2529.



**3-Cyano-N-hexylbenzamide (2.52a).** Synthesized by general procedure 2-G. 63% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.08-8.06 (m, 1H), 8.02 (dt,  $J$ = 7.9, 1.2 Hz, 1H), 7.70 (dt,  $J$ = 7.7, 1.4 Hz, 1H), 7.50 (t,  $J$ = 7.8 Hz, 1H), 7.05 (t,  $J$ = 5.1 Hz, 1H), 3.38 (q,  $J$ = 7.2 Hz, 2H), 1.57 (p,  $J$ = 7.4 Hz, 2H), 1.35-1.16 (m, 6H), 0.83 (t,  $J$ = 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  165.5, 136.1, 134.4, 131.6, 130.8, 129.5, 118.2, 112.6, 40.4, 31.5, 29.4, 26.7, 22.5, 14.0.

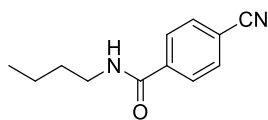


**N-Butyl-3-cyanobenzamide (2.52b).** Synthesized by general procedure 2-G. 62% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  8.05 (t,  $J$ = 1.5 Hz, 1H), 8.00 (dt,  $J$ = 7.9, 1.3 Hz, 1H), 7.66 (d,  $J$ = 7.7 Hz, 1H), 7.50-7.46 (m, 1H), 7.44 (t,  $J$ = 7.8 Hz, 1H), 3.33 (q,  $J$ = 6.7 Hz, 2H), 1.51 (p,  $J$ = 7.3 Hz, 2H), 1.29 (h,  $J$ = 7.4 Hz, 2H), 0.83 (t,  $J$ = 7.4 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  165.5, 135.9, 134.2, 131.5, 130.9, 129.3, 118.1, 112.2, 40.0, 31.3, 20.0, 13.6.

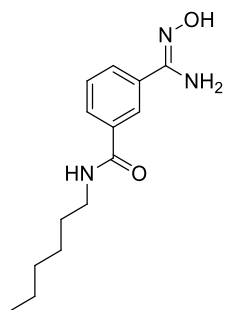


**4-Cyano-N-hexylbenzamide (2.52c).** Synthesized by general procedure 2-G. 20% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.85 (dt,  $J$ = 8.6, 1.9 Hz, 2H), 7.64 (dt,  $J$ = 8.6, 1.5 Hz, 2H), 6.96 (t,  $J$ = 5.2 Hz, 1H), 3.36 (q,  $J$ = 7.2 Hz, 2H), 1.55 (p,  $J$ = 7.4 Hz, 2H), 1.36-1.19 (m, 6H),

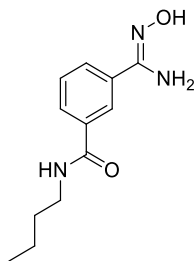
0.82 (t,  $J= 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  165.8, 138.8, 132.2, 127.8, 118.1, 114.7, 40.4, 31.4, 29.4, 26.6, 22.5, 14.0.



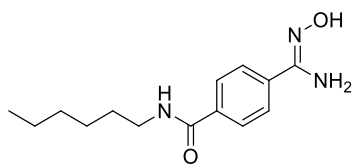
**N-Butyl-4-cyanobenzamide (2.52d).** Synthesized by general procedure 2-G. 86% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.83 (d,  $J= 7.9$  Hz, 2H), 7.57 (d,  $J= 7.9$  Hz, 2H), 7.49 (s, 1H), 3.29 (q,  $J= 6.2$  Hz, 2H), 1.47 (p,  $J= 7.1$  Hz, 2H), 1.25 (h,  $J= 7.4$  Hz, 2H), 0.80 (t,  $J= 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  165.8, 138.6, 132.0, 127.7, 117.9, 114.3, 39.9, 31.2, 19.9, 13.5.



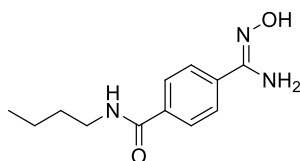
**(Z)-N-Hexyl-3-(N'-hydroxycarbamimidoyl) benzamide.** Synthesized by general procedure 2-I. 83%, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  8.04 (s, 1H), 7.77 (d,  $J= 7.8$  Hz, 1H), 7.71 (d,  $J= 7.8$  Hz, 1H), 7.38 (t,  $J= 7.8$  Hz, 1H), 3.28 (t,  $J= 7.2$  Hz, 2H), 1.52 (p,  $J= 7.2$  Hz, 2H), 1.36-1.16 (m, 6H), 0.82 (t,  $J= 6.6$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol-d<sub>4</sub>)  $\delta$  169.5, 154.5, 136.0, 134.5, 130.0, 129.6, 129.3, 126.0, 41.1, 32.6, 30.4, 27.7, 23.6, 14.4; HRMS (ESI<sup>+</sup>): Calcd for C<sub>14</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub> [M+H]: 264.1712, Found: 264.1702.



**(Z)-N-Butyl-3-(N'-hydroxycarbamimidoyl) benzamide.** Synthesized by general procedure 2-I. 85%, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.03 (s, 1H), 7.76 (d,  $J = 7.8$  Hz, 1H), 7.70 (d,  $J = 7.8$  Hz, 1H), 7.37 (t,  $J = 7.8$  Hz, 1H), 3.27 (t,  $J = 7.2$  Hz, 2H), 1.49 (p,  $J = 7.4$  Hz, 2H), 1.30 (h,  $J = 7.4$  Hz, 2H), 0.85 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  169.5, 154.5, 136.0, 134.4, 130.0, 129.6, 129.3, 126.0, 40.7, 32.5, 21.1, 14.1; HRMS (ESI+): Calcd for  $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}_2$  [M+H]: 236.1399, Found: 236.1390.

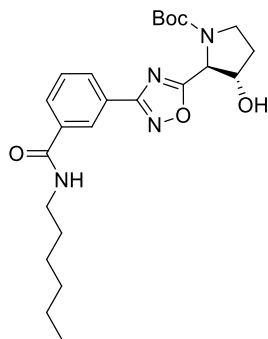


**(Z)-N-Hexyl-4-(N'-hydroxycarbamimidoyl) benzamide.** Synthesized by general procedure 2-I. 90%, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.85 (dt,  $J = 8.4, 2.0$  Hz, 2H), 7.75 (dt,  $J = 8.3, 1.8$  Hz, 2H), 3.39 (t,  $J = 7.2$  Hz, 2H), 1.64 (p,  $J = 7.2$  Hz, 2H), 1.45-1.32 (m, 6H), 0.93 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  169.5, 154.5, 137.1, 136.8, 128.3, 127.2, 41.1, 32.7, 30.4, 27.8, 23.6, 14.3; HRMS (ESI+): Calcd for  $\text{C}_{14}\text{H}_{22}\text{N}_3\text{O}_2$  [M+H]: 264.1712, Found: 264.1709.

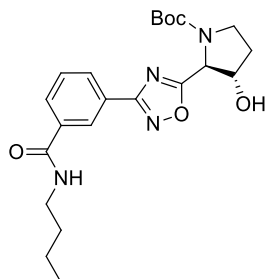


**(Z)-N-Butyl-4-(N'-hydroxycarbamimidoyl) benzamide.** Synthesized by general procedure 2-I. 80%, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.84 (dt,  $J = 8.7, 2.0$  Hz, 2H), 7.74 (dt,  $J$

= 8.7, 1.7 Hz, 2H), 3.40 (t,  $J= 7.2$  Hz, 2H), 1.62 (p,  $J= 7.2$  Hz, 2H), 1.43 (h,  $J= 7.4$  Hz, 2H), 0.99 (t,  $J= 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  169.5, 154.4, 136.8, 128.8, 128.3, 127.2, 40.8, 32.6, 21.2, 14.1; HRMS (ESI+): Calcd for  $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}_2$  [M+H]: 236.1399, Found: 236.1394.

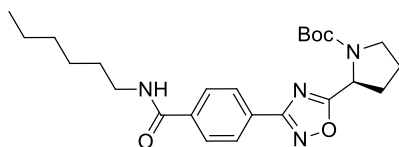


**(2S, 3S)-Tert-butyl 2-(3-(3-(hexylcarbamoyl) phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidine-1-carboxylate (2.53a).** Synthesized by general procedure 2-A. 45% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  8.28 (s, 1H), 8.17-8.03 (m, 1H), 7.91 (dd,  $J= 14.8, 7.6$  Hz, 1H), 7.54-7.44 (m, 1H), 6.52 (s, 1H), 4.95 (s, 1H), 4.51 (s, 1H), 3.78 – 3.68 (m, 2H), 3.48 – 3.40 (m, 2H), 2.36 – 2.21 (m, 1H), 2.09-2.00 (m, 1H), 1.62 (p,  $J= 7.3$  Hz, 2H), 1.45 (s, 3H), 1.41-1.21 (m, 12H), 0.88 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  179.0, 178.3, 167.9, 167.0, 153.9, 135.6, 130.2, 129.5, 127.0, 125.6, 80.9, 76.1, 75.1, 62.3, 44.5, 40.5, 36.8, 32.3, 31.6, 29.7, 28.3, 26.8, 24.8, 22.7, 14.1; HRMS (ESI+): Calcd for  $\text{C}_{24}\text{H}_{34}\text{N}_4\text{O}_5\text{Na}$  [M+Na]: 481.2427, Found: 481.2430.

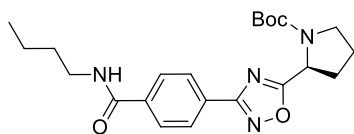


**(2S, 3S)-Tert-butyl 2-(3-(3-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidine-1-carboxylate (2.53b).** Synthesized by general procedure 2-A. 44% yield,

colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  8.27 (s, 1H), 8.03 (d,  $J=7.6$  Hz, 1H), 7.88 (d,  $J=7.7$  Hz, 1H), 7.43 (t,  $J=7.7$  Hz, 1H), 6.64 (t,  $J=5.2$  Hz, 1H), 4.93 (s, 1H), 4.58-4.27 (m, 2H), 3.74 – 3.69 (m, 2H), 3.46 – 3.41 (m, 2H), 2.31 – 2.22 (m, 1H), 2.06-1.99 (m, 1H), 1.60 (p,  $J=7.4$  Hz, 2H), 1.44 (s, 3H), 1.42-1.34 (m, 2H), 1.25 (s, 6H), 0.93 (t,  $J=7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  179.1, 178.3, 167.9, 167.0, 153.9, 135.6, 130.2, 129.4, 127.0, 125.6, 80.9, 76.0, 62.3, 60.6, 44.6, 40.2, 32.2, 31.7, 28.5, 28.2, 20.3, 13.9; HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_5\text{Na}$  [ $\text{M}+\text{Na}$ ]: 453.2114, Found: 453.2113.

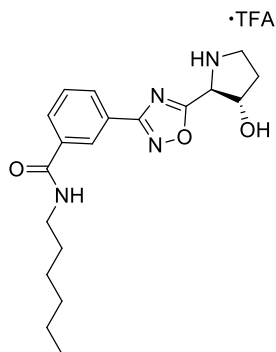


**(S)-Tert-butyl 2-(3-(4-(hexylcarbamoyl) phenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate (2.53c).** Synthesized by general procedure 2-A. 22% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.14 (d,  $J=8.1$  Hz, 2H), 7.85 (t,  $J=8.8$  Hz, 2H), 6.19 (t,  $J=5.5$  Hz, 1H), 5.22-5.03 (m, 1H), 3.76 – 3.64 (m, 1H), 3.61 – 3.51 (m, 1H), 3.47 (q,  $J=7.1$  Hz, 2H), 2.48 – 2.31 (m, 1H), 2.20 – 2.11 (m, 2H), 2.07-1.95 (m, 1H), 1.63 (p,  $J=7.4$  Hz, 2H), 1.46 (s, 3H), 1.43-1.31 (m, 6H), 1.29 (s, 6H), 0.89 (t,  $J=7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  181.2, 167.8, 166.8, 153.6, 137.4, 129.5, 127.8, 127.5, 80.6, 77.4, 54.0, 46.5, 40.4, 32.5, 31.6, 29.8, 28.5, 28.3, 26.8, 23.9, 22.7, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{24}\text{H}_{34}\text{N}_4\text{O}_4\text{Na}$  [ $\text{M}+\text{Na}$ ]: 465.2478, Found: 465.2507.

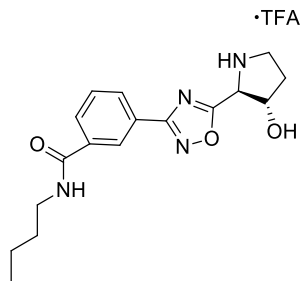


**(S)-Tert-butyl 2-(3-(4-(butylcarbamoyl) phenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate (2.53d).** Synthesized by general procedure 2-A. 12% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.13 (d,  $J=7.9$  Hz, 2H), 7.85 (t,  $J=9.3$  Hz, 2H), 6.25 (s, 1H), 5.22-

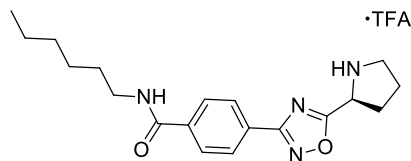
5.00 (m, 1H), 3.75 – 3.63 (m, 1H), 3.60 – 3.51 (m, 1H), 3.47 (q,  $J = 6.9$  Hz, 2H), 2.47 – 2.33 (m, 1H), 2.22 – 2.09 (m, 2H), 2.07-1.96 (m, 1H), 1.61 (p,  $J = 7.4$  Hz, 2H), 1.45 (s, 3H), 1.44-1.35 (m, 2H), 1.28 (s, 6H), 0.96 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  181.1, 167.8, 166.8, 153.6, 137.4, 129.5, 127.8, 127.5, 80.6, 53.9, 46.5, 40.1, 32.5, 31.9, 28.3, 23.8, 20.3, 13.9; HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_4\text{Na}$  [ $2\text{M} + \text{Na}$ ]: 851.4534, Found: 851.4461.



**(2S, 3S)-2-(3-(3-(Hexylcarbamoyl) phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 2-D. 94% yield, yellow oil;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.55 (t,  $J = 1.4$  Hz, 1H), 8.25 (d,  $J = 7.8$  Hz, 1H), 8.01 (d,  $J = 7.9$  Hz, 1H), 7.65 (t,  $J = 7.8$  Hz, 1H), 5.09 (d,  $J = 1.9$  Hz, 1H), 4.85-4.78 (m, 1H), 3.79 – 3.69 (m, 2H), 3.40 (t,  $J = 7.2$  Hz, 2H), 2.44-2.39 (m, 1H), 2.26-2.17 (m, 1H), 1.64 (p,  $J = 7.4$  Hz, 2H), 1.46-1.29 (m, 6H), 0.92 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  174.9, 169.3, 168.9, 137.0, 131.3, 131.2, 130.5, 127.6, 127.6, 75.1, 62.8, 45.8, 41.2, 33.0, 32.7, 30.4, 27.8, 23.6, 14.4; HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{19}\text{H}_{27}\text{N}_4\text{O}_3 + [\text{M}^{+}]$ : 359.2083, Found: 359.2087.

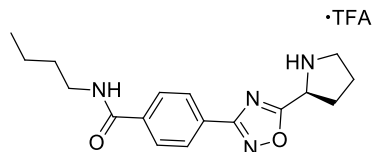


**(2*S*, 3*S*)-2-(3-(3-(Butylcarbamoyl) phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 2-D. 100% yield, yellow oil;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.54 (t,  $J$  = 1.6 Hz, 1H), 8.24 (dt,  $J$  = 7.8, 1.2 Hz, 1H), 8.00 (dt,  $J$  = 8.3, 1.1 Hz, 1H), 7.64 (t,  $J$  = 7.8 Hz, 1H), 5.09 (d,  $J$  = 1.9 Hz, 1H), 4.84-4.82 (m, 1H), 3.80 – 3.67 (m, 2H), 3.40 (t,  $J$  = 7.2 Hz, 2H), 2.46-2.38 (m, 1H), 2.24-2.19 (m, 1H), 1.62 (p,  $J$  = 7.3 Hz, 2H), 1.42 (h,  $J$  = 7.4 Hz, 2H), 0.97 (t,  $J$  = 7.4 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  174.9, 169.3, 168.9, 136.9, 131.3, 131.2, 130.5, 127.6, 127.6, 75.1, 62.8, 45.8, 40.9, 33.0, 32.6, 21.2, 14.1; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{17}\text{H}_{23}\text{N}_4\text{O}_3$  + [M $^+$ ]: 331.1770, Found: 331.1784.

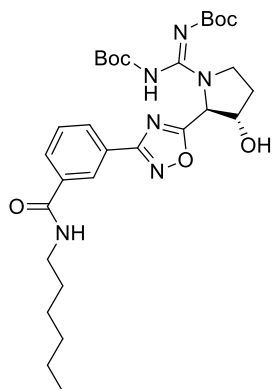


**(*S*)-2-(3-(4-(Hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 2-D. 78% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.21 (d,  $J$  = 8.0 Hz, 2H), 7.99 (d,  $J$  = 8.0 Hz, 2H), 5.24 (s, 1H), 3.68 – 3.52 (m, 2H), 3.41 (t,  $J$  = 7.1 Hz, 2H), 2.71 (s, 1H), 2.47 (s, 1H), 2.31 (s, 2H), 1.66 (p,  $J$  = 6.9 Hz, 2H), 1.48-1.33 (m, 6H), 0.94 (t,  $J$  = 6.7 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.4, 169.2, 169.0, 139.0, 129.8, 129.0, 128.6, 55.7, 47.6, 41.2, 32.7, 30.4, 30.3, 27.8, 24.6, 23.6, 14.3; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{19}\text{H}_{27}\text{N}_4\text{O}_2$  + [M $^+$ ]: 343.2134, Found: 343.2161.



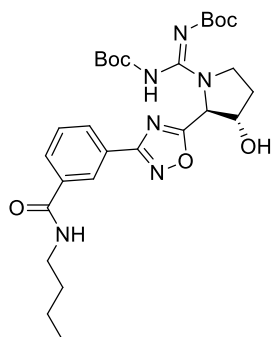


**(S)-2-(3-(4-(Butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 2-D. 79% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.20 (d,  $J = 7.8$  Hz, 2H), 7.99 (d,  $J = 7.8$  Hz, 2H), 5.25 (s, 1H), 3.69 – 3.52 (m, 2H), 3.42 (t,  $J = 7.0$  Hz, 2H), 2.71 (s, 1H), 2.48 (s, 1H), 2.32 (s, 2H), 1.65 (p,  $J = 7.2$  Hz, 2H), 1.45 (h,  $J = 7.4$  Hz, 2H), 1.00 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.3, 169.2, 169.0, 138.9, 129.8, 129.0, 128.6, 55.7, 47.7, 40.9, 32.6, 30.3, 24.7, 21.2, 14.1; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{17}\text{H}_{23}\text{N}_4\text{O}_2 + [\text{M}^+]$ : 315.1821, Found: 315.1633.

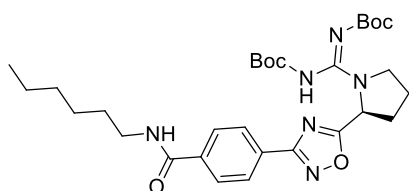


**Tert-butyl (((tert-butoxycarbonyl)amino)((2S, 3S)-2-(3-(3-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl)methylene)carbamate (2.54a).** Synthesized by general procedure 2-C. 35% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  9.61 (s, 1H), 8.35 (s, 1H), 8.12 (d,  $J = 7.7$  Hz, 1H), 7.99 (d,  $J = 7.8$  Hz, 1H), 7.52 (t,  $J = 7.8$  Hz, 1H), 5.73 (s, 1H), 4.58 (s, 1H), 3.97 (t,  $J = 6.7$  Hz, 2H), 3.43-3.35 (m, 1H), 3.30 (s, 1H), 2.42-2.34 (m, 1H), 2.16-2.08 (m, 1H), 1.77 (s, 1H), 1.61 (p,  $J = 5.8$  Hz, 2H), 1.54-1.25 (m, 24H), 0.89 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  177.4, 168.1, 166.8, 161.8, 154.0, 150.3, 135.7, 130.7,

130.0, 129.3, 126.7, 126.0, 82.7, 80.2, 74.8, 63.7, 47.2, 40.5, 32.2, 31.7, 29.6, 28.2, 26.9, 22.7, 14.2; HRMS (ESI+): Calcd for C<sub>30</sub>H<sub>44</sub>N<sub>6</sub>O<sub>7</sub> [M+H]: 601.3350, Found: 601.3386.

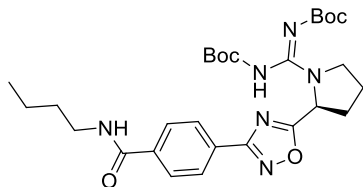


**Tert-butyl (((tert-butoxycarbonyl)amino)((2S, 3S)-2-(3-(3-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl)methylene)carbamate (2.54b).** Synthesized by general procedure 2-C. 24% yield, colorless oil; <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 9.84 (s, 1H), 8.36 (s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.99 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 5.63 (s, 1H), 4.61 (s, 1H), 3.99 (t, *J* = 6.8 Hz, 2H), 3.49-3.36 (m, 2H), 2.44-2.33 (m, 1H), 2.17-2.10 (m, 1H), 1.62 (p, *J* = 6.0 Hz, 2H), 1.54-1.29 (m, 20H), 0.96 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (151 MHz, Chloroform-d) δ 177.3, 168.1, 166.9, 153.8, 135.7, 130.7, 130.0, 129.3, 126.6, 126.0, 81.8, 74.7, 63.7, 47.5, 40.2, 32.1, 31.7, 31.4, 28.2, 20.4, 13.9; HRMS (ESI+): Calcd for C<sub>28</sub>H<sub>41</sub>N<sub>6</sub>O<sub>7</sub> [M+H]: 573.3037, Found: 573.3081.

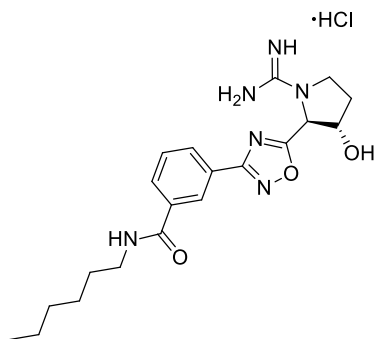


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (2.54c).** Synthesized by general procedure 2-C. 17% yield, colorless oil; <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 6.17 (t, *J* = 5.5 Hz, 1H), 5.61 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.92-3.87 (m,

1H), 3.81 (s, 1H), 3.50-3.45 (m, 2H), 2.49 – 2.43 (m, 1H), 2.27-2.14 (m, 2H), 2.08-2.01 (m, 1H), 1.63 (p,  $J = 7.5$  Hz, 2H), 1.45 (s, 18H), 1.38-1.31 (m, 6H), 0.90 (t,  $J = 7.0$  Hz, 3H); HRMS (ESI+): Calcd for  $C_{30}H_{45}N_6O_6$  [M+H]: 585.3401, Found: 585.3391.

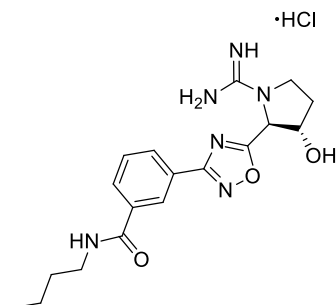


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (2.54d).** Synthesized by general procedure 2-C. 46% yield, colorless oil;  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  10.13 (s, 1H), 8.13 (d,  $J = 8.2$  Hz, 2H), 7.85 (d,  $J = 8.2$  Hz, 2H), 6.19 (s, 1H), 5.61 (dd,  $J = 7.4, 4.4$  Hz, 1H), 3.93-3.87 (m, 1H), 3.81 (s, 1H), 3.48 (q,  $J = 6.8$  Hz, 2H), 2.51 – 2.39 (m, 1H), 2.27-2.13 (m, 2H), 2.09-2.01 (m, 1H), 1.62 (p,  $J = 7.1$  Hz, 2H), 1.45 (s, 20H), 0.97 (t,  $J = 7.3$  Hz, 3H); HRMS (ESI+): Calcd for  $C_{28}H_{41}N_6O_6$  [M+H]: 557.3088, Found: 557.3055.

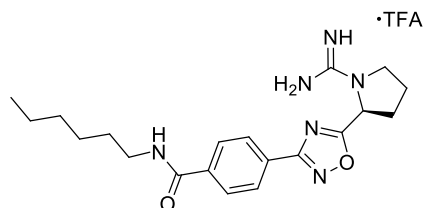


**Amino ((2S, 3S)-2-(3-(3-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl) methaniminium chloride (2.55a).** Synthesized by general procedure 2-B. 17% yield, white solid;  $^1H$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.50 (t,  $J = 1.5$  Hz, 1H), 8.21 (dt,  $J = 7.8, 1.3$  Hz, 1H), 7.98 (dt,  $J = 7.8, 1.1$  Hz, 1H), 7.63 (t,  $J = 7.8$  Hz, 1H), 5.23 (s, 1H), 4.79 (d,  $J = 3.4$  Hz, 1H), 3.85-3.79 (m, 2H), 3.39 (t,  $J = 7.2$  Hz, 1H), 2.26-2.15 (m, 2H), 1.63 (p,  $J = 7.4$  Hz,

2H), 1.44-1.29 (m, 6H), 0.91 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  177.1, 169.3, 169.0, 157.6, 137.0, 131.1, 131.1, 130.4, 128.0, 127.5, 76.0, 64.8, 47.4, 41.2, 32.7, 32.5, 30.4, 27.8, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{29}\text{N}_6\text{O}_3 + [\text{M}^+]$ : 401.2301, Found: 401.2305.

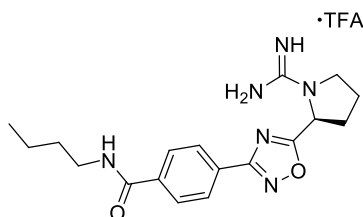


**Amino ((2S, 3S)-2-(3-(3-(butylcarbamoyl) phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl) methaniminium chloride (2.55b).** Synthesized by general procedure 2-B. 52% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.50 (t,  $J = 1.6$  Hz, 1H), 8.20 (dt,  $J = 7.8, 1.3$  Hz, 1H), 7.98 (dt,  $J = 7.8, 1.4$  Hz, 1H), 7.62 (t,  $J = 7.8$  Hz, 1H), 5.23 (s, 1H), 4.78 (d,  $J = 3.4$  Hz, 1H), 3.86-3.78 (m, 2H), 3.39 (t,  $J = 7.2$  Hz, 1H), 2.29-2.12 (m, 2H), 1.61 (p,  $J = 7.3$  Hz, 2H), 1.42 (h,  $J = 7.6$  Hz, 2H), 0.97 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  177.1, 169.3, 169.0, 157.6, 137.0, 131.1, 131.1, 130.4, 128.0, 127.5, 76.0, 64.8, 47.4, 40.9, 32.6, 32.5, 21.2, 14.1; HRMS (ESI+): Calcd for  $\text{C}_{18}\text{H}_{25}\text{N}_6\text{O}_3 + [\text{M}^+]$ : 373.1988, Found: 373.1986.

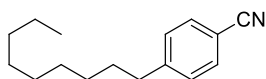


**(S)-Amino(2-(3-(4-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate (2.55c).** Synthesized by general procedure 2-D. 30% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.13 (d,  $J = 8.5$  Hz, 2H), 7.94 (d,  $J = 8.5$  Hz, 2H), 5.44 (dd,  $J = 7.9, 1.6$  Hz, 1H), 3.76 (td,  $J = 9.4, 2.4$  Hz, 1H), 3.60 (q,  $J = 9.6$  Hz, 1H), 3.38

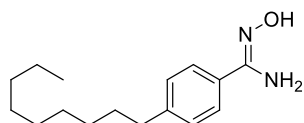
(q,  $J = 7.0$  Hz, 2H), 2.62 – 2.44 (m, 2H), 2.26-2.17 (m, 1H), 2.14 – 2.02 (m, 1H), 1.62 (p,  $J = 7.4$  Hz, 2H), 1.44-1.29 (m, 6H), 0.91 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  179.4, 169.1, 169.1, 157.1, 138.8, 130.2, 129.0, 128.5, 56.5, 41.2, 32.7, 30.4, 27.8, 24.3, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{29}\text{N}_6\text{O}_2 + [\text{M}^+]$ : 385.2352, Found: 385.2370.



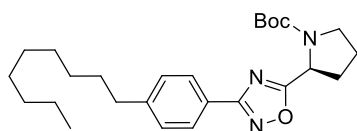
**(S)-Amino(2-(3-(4-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate (2.55d).** Synthesized by general procedure 2-D. 65% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.17 (d,  $J = 8.6$  Hz, 2H), 7.97 (d,  $J = 8.6$  Hz, 2H), 5.48 (dd,  $J = 7.9, 1.8$  Hz, 1H), 3.80 (td,  $J = 9.2, 2.4$  Hz, 1H), 3.65 (q,  $J = 9.6$  Hz, 1H), 3.43 (t,  $J = 7.2$  Hz, 2H), 2.67 – 2.45 (m, 2H), 2.31-2.20 (m, 1H), 2.18 – 2.05 (m, 1H), 1.65 (p,  $J = 7.8$  Hz, 2H), 1.51-1.36 (m, 2H), 1.01 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  179.4, 169.1, 169.1, 157.1, 138.8, 130.2, 129.0, 128.5, 56.5, 40.9, 32.7, 32.6, 24.3, 21.2, 14.1; HRMS (ESI+): Calcd for  $\text{C}_{18}\text{H}_{25}\text{N}_6\text{O}_2 + [\text{M}^+]$ : 357.2039, Found: 357.2017.



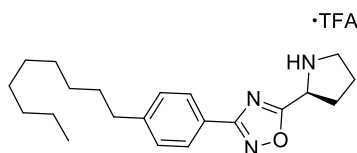
**4-Nonylbenzotrile (2.57).** Synthesized by general procedure 2-H. 24% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.52 (dt,  $J = 8.4, 1.6$  Hz, 2H), 7.25 (dq,  $J = 7.9, 1.6$  Hz, 2H), 2.63 (t,  $J = 7.6$  Hz, 2H), 1.59 (p,  $J = 7.4$  Hz, 2H), 1.33-1.19 (m, 12H), 0.86 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  148.6, 132.0, 129.2, 119.1, 109.5, 36.1, 31.9, 31.0, 29.5, 29.4, 29.3, 29.2, 22.7, 14.1.



**(Z)-N'-Hydroxy-4-nonylbenzimidamide.** Synthesized by general procedure 2-I. 61% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.54 (dt,  $J = 8.4, 2.0$  Hz, 2H), 7.20 (d,  $J = 8.4$  Hz, 2H), 4.89 (s, 2H), 2.62 (t,  $J = 7.6$  Hz, 2H), 1.61 (p,  $J = 7.4$  Hz, 2H), 1.37-1.20 (m, 12H), 0.88 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  152.8, 145.3, 129.8, 128.8, 125.9, 35.9, 32.0, 31.4, 29.7, 29.6, 29.5, 29.4, 22.8, 14.3.

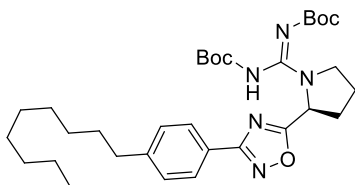


**(S)-Tert-butyl 2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate.** Synthesized by general procedure 2-A. 54% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.97 (d,  $J = 8.1$  Hz, 2H), 7.28 (d,  $J = 8.1$  Hz, 2H), 5.24-5.02 (m, 1H), 3.74 – 3.63 (m, 1H), 3.58 – 3.46 (m, 1H), 2.64 (t,  $J = 7.5$  Hz, 2H), 2.43 – 2.34 (m, 1H), 2.20 – 2.09 (m, 2H), 2.04-1.94 (m, 1H), 1.67-1.57 (m, 2H), 1.45 (s, 3H), 1.27 (d,  $J = 15.1$  Hz, 18H), 0.86 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  180.5, 168.4, 153.6, 146.7, 129.0, 127.5, 124.2, 80.5, 53.9, 46.4, 36.1, 32.5, 32.0, 31.3, 29.6, 29.6, 29.4, 29.4, 28.2, 24.4, 23.8, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{39}\text{N}_3\text{O}_3\text{Na}$  [ $\text{M}+\text{Na}$ ]: 464.2889, Found: 464.2861.

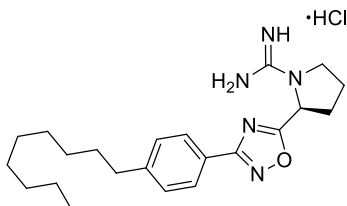


**(S)-2-(3-(4-Nonylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 2-D. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz,

Chloroform-d)  $\delta$  7.89 (d,  $J=8.2$  Hz, 2H), 7.25 (d,  $J = 8.5$  Hz, 2H), 5.10 (t,  $J = 6.6$  Hz, 1H), 3.67 – 3.48 (m, 2H), 2.64 (t,  $J= 7.6$  Hz, 2H), 2.61 - 2.52 (m, 1H), 2.45-2.37 (m, 1H), 2.26 – 2.15 (m, 2H), 1.62 (p,  $J= 7.3$  Hz, 2H), 1.35-1.19 (m, 12H), 0.88 (t,  $J= 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  174.2, 168.6, 147.3, 129.1, 127.6, 123.0, 54.0, 46.1, 36.1, 32.0, 31.3, 29.9, 29.7, 29.6, 29.4, 29.4, 23.8, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_3\text{O}^+$  [ $\text{M}^+$ ]: 342.2545, Found: 342.2517.



**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.** Synthesized by general procedure 2-C. 49% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  10.07 (s, 1H), 7.96 (d,  $J = 8.4$  Hz, 2H), 7.26 (d,  $J = 8.4$  Hz, 2H), 5.59 (dd,  $J = 7.8, 4.5$  Hz, 1H), 3.91-3.85 (m, 1H), 3.84 – 3.75 (m, 1H), 2.64 (t,  $J= 7.5$  Hz, 2H), 2.45 – 2.40 (m, 1H), 2.28-2.11 (m, 2H), 2.07-1.99 (m, 1H), 1.62 (p,  $J= 7.4$  Hz, 2H), 1.45 (s, 18H), 1.35-1.16 (m, 12H), 0.86 (t,  $J= 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  178.8, 168.4, 162.0, 153.5, 150.5, 146.6, 128.9, 127.6, 124.1, 82.3, 79.5, 55.4, 49.5, 36.0, 32.0, 31.5, 31.3, 29.6, 29.6, 29.4, 29.3, 28.2, 24.0, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{50}\text{N}_5\text{O}_5$  [ $\text{M}+\text{H}$ ]: 584.3812, Found: 584.3811.



**(S)-Amino (2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-yl) methaniminium chloride (2.58).** Synthesized by general procedure 2-B. 63% yield, white solid;  $^1\text{H}$  NMR (400

MHz, Methanol-d<sub>4</sub>)  $\delta$  7.96 (d,  $J$ = 8.2 Hz, 2H), 7.34 (d,  $J$  = 8.2 Hz, 2H), 5.48 (d,  $J$  = 7.1 Hz, 1H), 3.79 (t,  $J$  = 8.1 Hz, 1H), 3.64 (q,  $J$ = 9.5 Hz, 1H), 2.68 (t,  $J$ = 7.5 Hz, 2H), 2.61 – 2.53 (m, 1H), 2.49-2.45 (m, 1H), 2.29-2.19 (m, 1H), 2.15 – 2.03 (m, 1H), 1.65 (p,  $J$ = 7.2 Hz, 2H), 1.39-1.24 (m, 12H), 0.89 (t,  $J$ = 6.7 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Methanol-d<sub>4</sub>)  $\delta$  178.8, 169.6, 157.0, 148.2, 130.1, 128.4, 124.9, 56.4, 36.8, 33.0, 32.7, 32.4, 30.6, 30.5, 30.4, 30.3, 24.3, 23.7, 14.4; HRMS (ESI+): Calcd for C<sub>22</sub>H<sub>34</sub>N<sub>5</sub>O<sup>+</sup> [M<sup>+</sup>]: 384.2763, Found: 384.2772.

#### 4.5 Synthetic procedures and characterization for Chapter 3

**General procedure 3-A. Nucleophilic aromatic substitution.** To a roundbottom, the alkyl alcohol (1 equiv) and potassium *tert*-butoxide (2.5 equiv) were added and dissolved in THF. The solution was then refluxed for 30 minutes. After 30 minutes, the solution was cooled to room temperature. Once cool, 4-fluorobenzonitrile was added to the reaction and the solution was refluxed for 18 h. Once completion was observed, the reaction was cooled to rt. The reaction was the partitioned between dichloromethane and water. The organic layer was subsequently washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to yield the desired product.

**General procedure 3-B. Conversion of nitrile to amidoxime.** Triethylamine (3.3 equiv) and hydroxylamine hydrochloride (2 equiv) were added to a solution of chosen nitrile intermediate in 95% ethanol (0.2 M solution). The reaction mixture was then refluxed for 2-3 h. The organic solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel to provide the desired product.

**General procedure 3-C. Coupling of amidoxime with amino acids.** DIEA (1.8 equiv) was added to a solution of amidoxime (1 equiv) and the appropriate Boc-protected amino acid



(1.2 equiv) in DMF (0.2 M solution). HCTU (1.5 equiv) was then added to the resulting mixture at rt and stirred at 80 °C for 18h. At this time, TLC showed complete conversion of starting material. The solution was partitioned between ethyl acetate and water. The organic layer was collected and washed twice with a sat. LiBr. The aqueous solution was then back extracted with ethyl acetate. The organic layers were then combined and washed with sat. NaHCO<sub>3</sub> and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel to yield the desired product.

**General Procedure 3-D: Deprotection of *t*-Boc protecting groups using TFA.** To a solution of Boc-protected intermediate in CH<sub>2</sub>Cl<sub>2</sub>, a 1N TFA solution in CH<sub>2</sub>Cl<sub>2</sub> was added. The resulting solution was stirred at room temperature until complete consumption of the starting material was observed using TLC. The reaction mixture was concentrated under reduced pressure and triturated with diethyl ether to yield the corresponding free amine TFA salt.

**General Procedure 3-E: Guanidylation of amines using the microwave.** DIEA (3 equiv) was added to a solution of the corresponding amine hydrochloric acid salt and the reagent (*Z*)-*tert*-butyl (((*tert*-butoxycarbonyl) imino)(1H-pyrazol-1-yl) methyl) carbamate (1.05 equiv) in a reaction tube with acetonitrile (20% vol/wt). The resulting reaction mixture was then placed in the microwave reactor and stirred for 2 hours at 50 degrees Celsius at 200 W. The solvent was then removed under reduced pressure and the resulting colorless residue was purified by flash column chromatography over silica gel to yield the pure product.

**General Procedure 3-F: Deprotection of *t*-Boc protecting groups using HCl gas.** Hydrochloric acid gas was bubbled through a solution of the N-Boc protected compound in methanol for 2-5 minutes, or until complete consumption of starting material was observed by

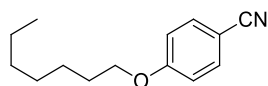
TLC. The reaction mixture was concentrated under reduced pressure and triturated with diethyl ether to yield the corresponding free amine hydrochloride salt, which was further purified by trituration with diethyl ether until satisfactory analytical data was obtained.

**General procedure 3-G. Williamson ether synthesis with alkyl bromides.** To a roundbottom, 1-bromooctane (1.2 equiv), potassium carbonate (4 equiv), and chosen substituted 4-hydroxybenzotrile were dissolved in ACN. The reaction was then refluxed for 18 h. Once the reaction was complete, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was then washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by silica gel column chromatography to yield the desired product.

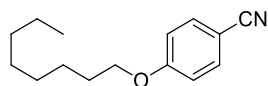
**General procedure 3-H. Williamson ether reaction with benzyl bromides.** Chosen benzyl bromide (1.2 equiv), potassium carbonate (2 equiv), and common intermediate **3.29** were dissolved in acetone. The reaction was refluxed for 1-2 h. Once the reaction was complete, the mixture was filtered and the resulting solvent was concentrated under reduced pressure. The resulting residue was then purified by silica gel column chromatography to yield the product.

**General procedure 3-I: Suzuki coupling.** Chosen alkene (1.1 equiv) was added to a round bottom flask containing THF. 9-BBN (1.2 equiv) was added as a 0.5 M solution in THF and the solution was stirred overnight at rt. To the above borane solution was added a solution of 4-iodobenzotrile in DMF. The reaction mixture was degassed for 15 min by bubbling N<sub>2</sub> through the solution. Cs<sub>2</sub>CO<sub>3</sub> (2 equiv) and PdCl<sub>2</sub> (dppf) (0.03 equiv) were added together. The resulting reaction mixture was then stirred at 80 °C for 18 h, after which it was poured into a saturated solution of LiBr and extracted three times with hexane. The combined organic extracts were

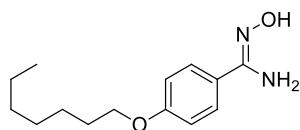
washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting brown residue was purified by flash chromatography over silica gel to give the desired product.



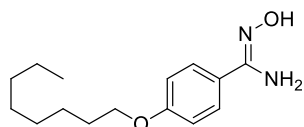
**4-(Heptyloxy)benzonitrile (3.2a).** Synthesized by general procedure 3-A. 66% yield, colorless oil; <sup>1</sup>H NMR (500 MHz, Chloroform-d) δ 7.51 (dt, *J* = 9.5, 3.0 Hz, 2H), 6.89 (dt, *J* = 9.0, 2.0 Hz, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 1.76 (p, *J* = 5.5 Hz, 2H), 1.41 (p, *J* = 6.5 Hz, 2H), 1.35-1.22 (m, 6H), 0.86 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (126 MHz, Chloroform-d) δ 162.4, 133.8, 119.2, 115.1, 103.5, 68.4, 31.7, 28.9, 25.8, 22.5, 14.0.



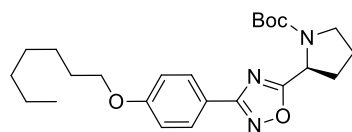
**4-(Octyloxy)benzonitrile (3.2b).** Synthesized by general procedure 3-A. 81% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 7.51 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.89 (dt, *J* = 9.0, 2.2 Hz, 2H), 3.96 (t, *J* = 6.6 Hz, 2H), 1.76 (p, *J* = 6.2 Hz, 2H), 1.42 (p, *J* = 8.0 Hz, 2H), 1.37-1.15 (m, 8H), 0.85 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 162.4, 133.8, 119.2, 115.1, 103.5, 68.4, 31.7, 29.2, 29.2, 28.9, 25.9, 22.6, 14.0.



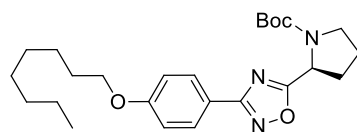
**(Z)-4-(Heptyloxy)-N'-hydroxybenzimidamide (3.3a).** Synthesized by general procedure 3-B. 72% yield, white solid; <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 7.54 (dt, *J* = 8.8, 2.4 Hz, 2H), 6.88 (dt, *J* = 9.2, 2.4 Hz, 2H), 3.96 (t, *J* = 6.5 Hz, 2H), 1.75 (p, *J* = 6.8 Hz, 2H), 1.45 (p, *J* = 6.4 Hz, 2H), 1.40-1.20 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Methanol-d<sub>4</sub>) δ 161.8, 155.5, 128.6, 126.2, 115.3, 69.0, 33.0, 30.3, 30.2, 27.1, 23.6, 14.4; HRMS (ESI<sup>+</sup>): Calcd for C<sub>14</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> [M+H]: 251.1760, Found: 251.1753.



**(Z)-N'-Hydroxy-4-(octyloxy) benzimidamide (3.3b).** Synthesized by general procedure 3-B. 44% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  7.52 (dt,  $J = 8.9, 2.1$  Hz, 2H), 6.88 (dt,  $J = 8.9, 2.1$  Hz, 2H), 3.94 (t,  $J = 6.5$  Hz, 2H), 1.74 (p,  $J = 6.5$  Hz, 2H), 1.44 (p,  $J = 7.1$  Hz, 2H), 1.37-1.22 (m, 8H), 0.88 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  161.8, 155.5, 128.6, 126.2, 115.3, 69.0, 33.0, 30.5, 30.4, 30.3, 27.1, 23.7, 14.4; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_2$  [M+H]: 265.1916, Found: 265.1929.

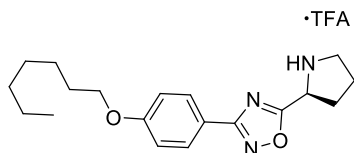


**(S)-Tert-butyl 2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.4a).** Synthesized by general procedure 3-C. 69% yield, yellow oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  7.97 (d,  $J = 8.7$  Hz, 2H), 6.93 (t,  $J = 10.4$  Hz, 2H), 5.22-4.92 (m, 1H), 3.97 (t,  $J = 6.4$  Hz, 2H), 3.76 – 3.58 (m, 1H), 3.57 – 3.36 (m, 1H), 2.40 – 2.24 (m, 1H), 2.19 – 2.03 (m, 2H), 2.01-1.90 (m, 1H), 1.77 (p,  $J = 6.7$  Hz, 2H), 1.43 (s, 5H), 1.38-1.20 (m, 12H), 0.86 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  180.3, 168.1, 161.6, 153.6, 129.0, 118.9, 114.8, 80.4, 68.2, 53.8, 46.4, 32.4, 31.8, 31.5, 29.2, 29.1, 28.2, 26.0, 24.4, 23.7, 22.6, 14.1; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{24}\text{H}_{35}\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 452.2525, Found: 452.2539.

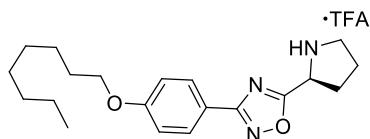


**(S)-Tert-butyl 2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.4b).** Synthesized by general procedure 3-C. 59% yield, yellow oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  7.98 (d,  $J = 8.7$  Hz, 2H), 6.94 (t,  $J = 10.4$  Hz, 2H), 5.22-4.96 (m, 1H), 3.99 (t,  $J$

= 6.4 Hz, 2H), 3.76 – 3.59 (m, 1H), 3.58 – 3.41 (m, 1H), 2.49 – 2.25 (m, 1H), 2.18 – 2.07 (m, 2H), 2.02-1.92 (m, 1H), 1.78 (p,  $J= 6.7$  Hz, 2H), 1.44 (s, 5H), 1.40-1.20 (m, 14H), 0.87 (t,  $J= 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  180.4, 168.1, 161.6, 153.6, 129.1, 119.0, 114.8, 80.5, 68.2, 53.9, 46.4, 32.5, 31.9, 31.6, 29.4, 29.3, 29.2, 28.2, 26.1, 24.4, 23.8, 22.7, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{25}\text{H}_{37}\text{N}_3\text{O}_4\text{Na}$  [ $\text{M}+\text{Na}$ ]: 466.2682, Found: 466.2685.

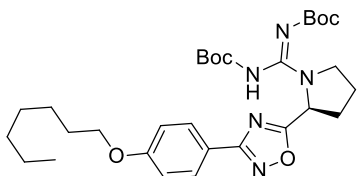


**(S)-2-(3-(4-(Heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.5a).** Synthesized by general procedure 3-D. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.94 (d,  $J=8.8$  Hz, 2H), 6.97 (d,  $J = 8.8$  Hz, 2H), 5.10 (t,  $J = 7.7$  Hz, 1H), 3.97 (t,  $J= 6.4$  Hz, 2H), 3.57 – 3.41 (m, 2H), 2.59 (hex,  $J= 5.0$  Hz, 1H), 2.40-2.28 (m, 1H), 2.26 – 2.13 (m, 2H), 1.72 (p,  $J= 6.5$  Hz, 2H), 1.41 (p,  $J= 8.2$  Hz, 2H), 1.37-1.16 (m, 6H), 0.84 (t,  $J= 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  175.7, 169.5, 163.5, 130.2, 119.2, 116.0, 69.3, 55.5, 47.2, 32.9, 30.3, 30.2, 30.2, 27.1, 24.5, 23.6, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{19}\text{H}_{28}\text{N}_3\text{O}_2^+$  [ $\text{M}^+$ ]: 330.2182, Found: 330.2177.

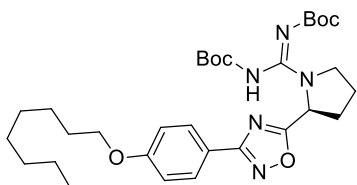


**(S)-2-(3-(4-(Octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.5b).** Synthesized by general procedure 3-D. 100% conversion, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  7.89 (d,  $J=8.8$  Hz, 2H), 6.92 (d,  $J = 8.8$  Hz, 2H), 5.06 (t,  $J = 7.7$  Hz, 1H), 3.91 (t,  $J= 6.4$  Hz, 2H), 3.58 – 3.31 (m, 2H), 2.57 - 2.48 (m, 1H), 2.33-2.25 (m, 1H), 2.22 – 2.02 (m, 2H), 1.67 (p,  $J= 6.0$  Hz, 2H), 1.36 (p,  $J= 7.0$  Hz, 2H), 1.29-1.13 (m, 8H), 0.78 (t,  $J= 6.8$  Hz, 3H);  $^{13}\text{C}$

NMR (126 MHz, Methanol-d<sub>4</sub>)  $\delta$  175.7, 169.5, 163.4, 130.1, 119.2, 116.0, 69.2, 55.4, 47.2, 32.9, 30.4, 30.4, 30.3, 30.2, 27.1, 24.5, 23.7, 14.4; HRMS (ESI<sup>+</sup>): Calcd for C<sub>20</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 344.2338, Found: 344.2360.

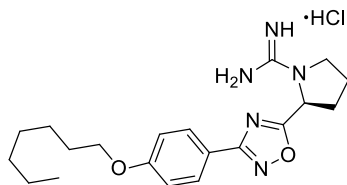


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.6a).** Synthesized by general procedure 3-E. 39% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  10.07 (s, 1H), 7.98 (dt, *J* = 8.9, 2.2 Hz, 2H), 6.95 (dt, *J* = 8.8, 2.0 Hz, 2H), 5.58 (dd, *J* = 7.7, 4.6 Hz, 1H), 4.01 (t, *J* = 6.6 Hz, 2H), 3.91-3.84 (m, 1H), 3.83 – 3.69 (m, 1H), 2.48 – 2.37 (m, 1H), 2.27-2.12 (m, 2H), 2.09-1.98 (m, 1H), 1.80 (p, *J* = 6.5 Hz, 2H), 1.54-1.26 (m, 26H), 0.89 (t, *J* = 6.5 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d)  $\delta$  178.7, 168.2, 162.0, 161.7, 153.6, 150.5, 129.2, 118.9, 114.8, 82.3, 79.7, 68.3, 55.4, 49.5, 31.9, 31.5, 29.3, 29.2, 28.2, 26.1, 24.0, 22.7, 14.2; HRMS (ESI<sup>+</sup>): Calcd for C<sub>30</sub>H<sub>46</sub>N<sub>5</sub>O<sub>6</sub> [M+H]: 572.3448, Found: 572.3451.

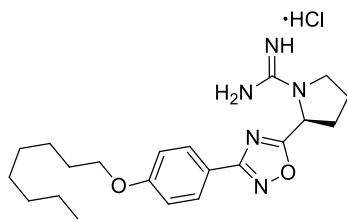


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.6b).** Synthesized by general procedure 3-E. 96% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  10.07 (s, 1H), 7.98 (dt, *J* = 9.1, 2.1 Hz, 2H), 6.95 (dt, *J* = 8.9, 2.1 Hz, 2H), 5.57 (dd, *J* = 7.7, 4.5 Hz, 1H), 4.00 (t, *J* = 6.6 Hz, 2H), 3.91-3.83 (m, 1H), 3.83 – 3.74 (m, 1H), 2.47 – 2.37 (m, 1H), 2.30-2.10 (m, 2H), 2.07-1.98 (m, 1H), 1.80 (p, *J* = 6.5 Hz, 2H), 1.56-1.39 (m, 20H), 1.37-1.19 (m, 8H), 0.88 (t, *J* = 6.6 Hz, 3H); <sup>13</sup>C NMR

(101 MHz, Chloroform-d)  $\delta$  178.7, 168.2, 162.1, 161.7, 153.5, 150.5, 129.2, 118.9, 114.8, 82.3, 79.7, 68.3, 55.4, 49.5, 31.9, 31.5, 29.5, 29.4, 29.3, 28.2, 28.1, 26.1, 24.1, 22.8, 14.2; HRMS (ESI+): Calcd for C<sub>31</sub>H<sub>48</sub>N<sub>5</sub>O<sub>6</sub> [M+H]: 586.3605, Found: 586.3611.

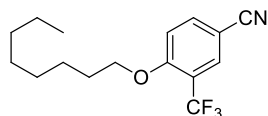


**(S)-Amino(2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.7a).** Synthesized by general procedure 2-F. 72% yield, white solid; <sup>1</sup>H NMR (500 MHz, Methanol-d<sub>4</sub>)  $\delta$  7.95 (dt, *J* = 8.8, 1.9 Hz, 2H), 7.02 (dt, *J* = 8.9, 2.0 Hz, 2H), 5.40 (d, *J* = 7.9, 1.7 Hz, 1H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.75 (td, *J* = 9.3, 2.5 Hz, 1H), 3.59 (q, *J* = 7.0 Hz, 1H), 2.58-2.49 (m, 1H), 2.48 – 2.38 (m, 1H), 2.24-2.18 (m, 1H), 2.12– 2.01 (m, 1H), 1.78 (p, *J* = 6.0 Hz, 2H), 1.56-1.43 (m, 2H), 1.42-1.28 (m, 6H), 0.90 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (126 MHz, Methanol-d<sub>4</sub>)  $\delta$  178.6, 169.4, 163.4, 157.1, 130.1, 119.6, 115.9, 69.3, 56.4, 33.0, 32.7, 30.3, 30.2, 27.1, 24.3, 23.7, 14.4; HRMS (ESI+): Calcd for C<sub>20</sub>H<sub>30</sub>N<sub>5</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 372.2400, Found: 372.2382.

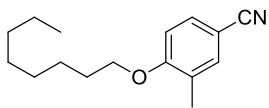


**(S)-Amino(2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.7b).** Synthesized by general procedure 2-F. 45% yield, white solid; <sup>1</sup>H NMR (500 MHz, Methanol-d<sub>4</sub>)  $\delta$  7.95 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 5.41 (d, *J* = 7.0 Hz, 1H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.75 (t, *J* = 8.5 Hz, 1H), 3.60 (q, *J* = 8.9 Hz, 1H), 2.54 (s, 1H), 2.48 – 2.39 (m, 1H), 2.22 (s, 1H), 2.13– 2.02 (m, 1H), 1.78 (p, *J* = 6.4 Hz, 2H), 1.54-1.43 (m, 2H), 1.40-1.26 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (126 MHz, Methanol-d<sub>4</sub>)  $\delta$  178.6, 169.4, 163.4, 157.1,

130.1, 119.6, 116.0, 69.3, 56.5, 33.0, 32.7, 30.5, 30.4, 30.3, 28.1, 27.1, 24.3, 23.7, 14.4; HRMS (ESI+): Calcd for  $C_{21}H_{32}N_5O_2 + [M]^+$ : 386.2556, Found: 386.2554. HPLC analysis shows **3.7b** is 81% pure

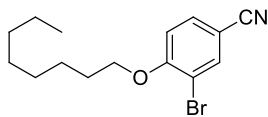


**4-(Octyloxy)-3-(trifluoromethyl) benzonitrile (3.9a).** Synthesized by general procedure 3-G. 94% yield, white solid;  $^1H$  NMR (400 MHz, Chloroform-d)  $\delta$  7.80 (d,  $J = 2.0$  Hz, 1H), 7.75 (dd,  $J = 8.7, 2.1$  Hz, 1H), 7.06 (d,  $J = 8.7$  Hz, 1H), 4.10 (t,  $J = 6.4$  Hz, 2H), 1.87-1.77 (m, 2H), 1.46 (p,  $J = 7.1$  Hz, 2H), 1.38-1.14 (m, 8H), 0.85 (t,  $J = 6.1$  Hz, 3H);  $^{13}C$  NMR (101 MHz, Chloroform-d)  $\delta$  160.3, 137.5, 131.3 ( $^3 J_{CF} = 4.7$  Hz), 122.4 ( $^1 J_{CF} = 273.4$  Hz), 120.0 (q,  $^2 J_{CF} = 31.3$  Hz), 117.9, 113.5, 103.4, 69.5, 31.7, 29.1, 29.1, 28.7, 25.7, 22.6, 14.0;  $^{19}F$  NMR (376 MHz, Chloroform-d)  $\delta$  -66.4 (s, 3F).

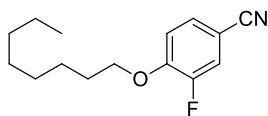


**3-Methyl-4-(octyloxy)benzonitrile (3.9b).** Synthesized by general procedure 3-G. 44% yield, clear solid;  $^1H$  NMR (400 MHz, Chloroform-d)  $\delta$  7.43 (ddd,  $J = 8.6, 2.0, 0.5$  Hz, 1H), 7.36 (dd,  $J = 2.0, 0.8$  Hz, 1H), 6.81 (d,  $J = 8.5$  Hz, 1H), 3.98 (t,  $J = 6.4$  Hz, 2H), 2.20 (s, 3H), 1.80 (p,  $J = 6.6$  Hz, 2H), 1.46 (p,  $J = 6.1$  Hz, 2H), 1.39-1.13 (m, 8H), 0.87 (t,  $J = 6.8$  Hz, 3H);  $^{13}C$  NMR (101 MHz, Chloroform-d)  $\delta$  160.7, 133.8, 131.9, 128.2, 119.6, 110.9, 103.0, 68.3, 31.8, 29.3, 29.2, 29.1, 26.1, 22.7, 16.1, 14.1.

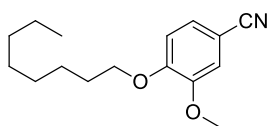




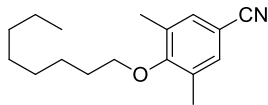
**3-Bromo-4-(octyloxy)benzonitrile (3.9c).** Synthesized by general procedure 3-G. 91% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.74 (d,  $J = 2.0$  Hz, 1H), 7.51 (dd,  $J = 8.6, 2.1$  Hz, 1H), 6.88 (d,  $J = 8.6$  Hz, 1H), 4.03 (t,  $J = 6.5$  Hz, 2H), 1.90-1.73 (m, 2H), 1.46 (p,  $J = 7.1$  Hz, 2H), 1.38-1.13 (m, 8H), 0.85 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  159.0, 136.4, 132.9, 117.7, 112.6, 112.5, 104.7, 69.5, 31.7, 29.1, 29.1, 28.7, 25.8, 22.6, 14.1.



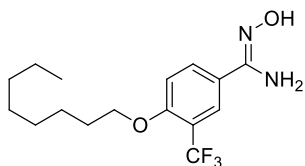
**3-Fluoro-4-(octyloxy)benzonitrile (3.9d).** Synthesized by general procedure 3-G. 99% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.39-7.32 (m, 1H), 7.31-7.26 (m, 1H), 6.97 (t,  $J = 8.4$  Hz, 1H), 4.04 (t,  $J = 6.6$  Hz, 2H), 1.80 (p,  $J = 6.6$  Hz, 2H), 1.43 (p,  $J = 7.0$  Hz, 2H), 1.37-1.17 (m, 8H), 0.84 (t,  $J = 6.6$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  151.8 (d,  $^1J_{\text{CF}} = 251.1$  Hz), 151.4 (d,  $^2J_{\text{CF}} = 10.3$  Hz), 129.6 (d,  $^3J_{\text{CF}} = 3.8$  Hz), 119.4 (d,  $^2J_{\text{CF}} = 21.5$  Hz), 118.0 (d,  $^3J_{\text{CF}} = 2.4$  Hz), 114.4 (d,  $^3J_{\text{CF}} = 2.6$  Hz), 103.5 (d,  $^2J_{\text{CF}} = 8.3$  Hz), 69.5, 31.7, 29.2, 29.1, 28.8, 25.8, 22.6, 14.0;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -134.5- -134.6 (m, 1F).



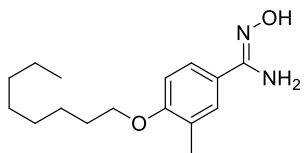
**3-Methoxy-4-(octyloxy)benzonitrile (3.9e).** Synthesized by general procedure 3-G. 100% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.17 (dd,  $J = 8.3, 1.9$  Hz, 1H), 7.00 (d,  $J = 1.9$  Hz, 1H), 6.82 (d,  $J = 8.4$  Hz, 1H), 3.97 (t,  $J = 6.8$  Hz, 2H), 3.80 (s, 3H), 1.82-1.74 (m, 2H), 1.39 (p,  $J = 7.8$  Hz, 2H), 1.32-1.16 (m, 8H), 0.81 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  152.4, 149.3, 126.2, 119.2, 114.1, 112.1, 103.3, 68.9, 56.0, 31.6, 29.1, 29.0, 28.8, 25.7, 22.5, 13.9.



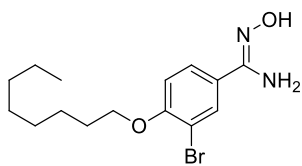
**3,5-Dimethyl-4-(octyloxy)benzonitrile (3.9f).** Synthesized by general procedure 3-G. 98% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.26 (s, 2H), 3.75 (t,  $J=6.6$  Hz, 2H), 2.25 (s, 6H), 1.78 (p,  $J=6.4$  Hz, 2H), 1.47 (p,  $J=7.0$  Hz, 2H), 1.38-1.22 (m, 8H), 0.87 (t,  $J=7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  160.0, 132.6, 132.5, 119.0, 107.0, 72.5, 31.8, 30.3, 29.4, 29.2, 26.0, 22.6, 16.1, 14.0.



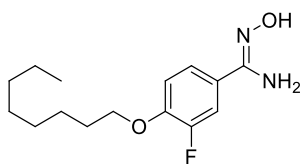
**(Z)-N'-Hydroxy-4-(octyloxy)-3-(trifluoromethyl) benzimidamide (3.10a).** Synthesized by general procedure 3-B. 84% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.89 (d,  $J=2.1$  Hz, 1H), 7.82 (dd,  $J=8.7, 2.2$  Hz, 1H), 7.15 (d,  $J=8.7$  Hz, 1H), 4.17 (t,  $J=6.2$  Hz, 2H), 1.86-1.75 (m, 2H), 1.51 (p,  $J=7.1$  Hz, 2H), 1.41-1.23 (m, 8H), 0.91 (t,  $J=6.6$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  159.3, 154.1, 132.4, 125.9 (q,  $^3J_{\text{CF}}=5.3$  Hz), 125.0 (q,  $^1J_{\text{CF}}=273.1$  Hz), 119.6 (q,  $^2J_{\text{CF}}=30.9$  Hz), 113.9, 69.9, 32.9, 30.3, 30.3, 30.1, 26.9, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.2 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{16}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_2$  [M+H]: 333.1789, Found: 333.1778.



**(Z)-N'-Hydroxy-3-methyl-4-(octyloxy)benzimidamide (3.10b).** Synthesized by general procedure 3-B. 46% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.41 (dd,  $J$  = 6.3, 2.3 Hz, 2H), 6.83-6.74 (m, 1H), 4.87 (s, 2H), 3.97 (t,  $J$  = 6.4 Hz, 2H), 2.23 (s, 3H), 1.80 (p,  $J$  = 5.4 Hz, 2H), 1.48 (p,  $J$  = 7.0 Hz, 2H), 1.41-1.23 (m, 8H), 0.90 (t,  $J$  = 6.7 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  158.8, 152.8, 128.2, 127.1, 124.6, 124.2, 110.7, 68.2, 31.9, 29.5, 29.4, 26.2, 22.8, 16.4, 14.2; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_2$  [M+H]: 279.2073, Found: 279.2053.

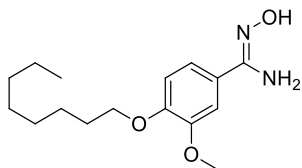


**(Z)-3-Bromo-N'-hydroxy-4-(octyloxy)benzimidamide (3.10c).** Synthesized by general procedure 3-B. 34% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.82 (d,  $J$  = 2.1 Hz, 1H), 7.55 (dd,  $J$  = 8.6, 2.1 Hz, 1H), 6.98 (d,  $J$  = 8.6 Hz, 1H), 4.03 (t,  $J$  = 6.3 Hz, 2H), 1.79 (p,  $J$  = 7.1 Hz, 2H), 1.50 (p,  $J$  = 7.0 Hz, 2H), 1.43-1.18 (m, 8H), 0.89 (t,  $J$  = 6.9 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  157.9, 154.1, 132.0, 127.6, 127.6, 113.7, 112.7, 70.2, 33.0, 30.4, 30.1, 27.1, 23.7, 14.5; HRMS (ESI $^+$ ): Calcd for  $\text{C}_{15}\text{H}_{24}\text{BrN}_2\text{O}_2$  [M+H]: 343.1021, Found: 343.1019.

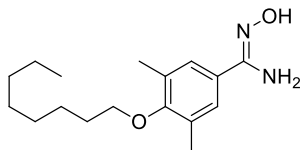


**(Z)-3-Fluoro-N'-hydroxy-4-(octyloxy)benzimidamide (3.10d).** Synthesized by general procedure 3-B. 44% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.39-7.36 (m, 1H), 7.35 (t,  $J$  = 2.5 Hz, 1H), 7.03 (t,  $J$  = 8.7 Hz, 1H), 4.02 (t,  $J$  = 6.4 Hz, 2H), 1.76 (p,  $J$  = 7.6 Hz, 2H), 1.45 (p,  $J$  = 6.4 Hz, 2H), 1.37-1.22 (m, 8H), 0.88 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  154.2 (d,  $^3J_{\text{CF}}$  = 2.2 Hz), 153.4 (d,  $^1J_{\text{CF}}$  = 245.7 Hz), 149.7 (d,  $^2J_{\text{CF}}$  = 10.9 Hz), 126.8 (d,  $^3J_{\text{CF}}$  = 6.8 Hz), 123.4 (d,  $^3J_{\text{CF}}$  = 3.6 Hz), 115.3 (d,  $^3J_{\text{CF}}$  = 2.2 Hz), 114.8 (d,  $^2J_{\text{CF}}$  = 20.6 Hz), 70.3, 33.0,

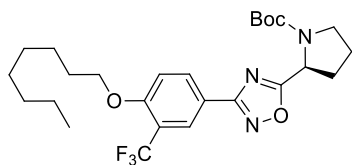
30.4, 30.4, 30.2, 27.0, 23.7, 14.5;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -135.8- -135.9 (m, 1F); HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{15}\text{H}_{24}\text{FN}_2\text{O}_2$  [M+H]: 283.1822, Found: 283.1825.



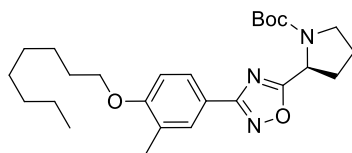
**(Z)-N'-Hydroxy-3-methoxy-4-(octyloxy)benzimidamide (3.10e).** Synthesized by general procedure 3-B. 40% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.26 (d,  $J$  = 2.1 Hz, 1H), 7.21 (dd,  $J$  = 8.4, 2.1 Hz, 1H), 6.94 (d,  $J$  = 8.4 Hz, 1H), 4.02 (t,  $J$  = 6.5 Hz, 2H), 3.87 (s, 3H), 1.89-1.68 (m, 2H), 1.49 (p,  $J$  = 6.9 Hz, 2H), 1.43-1.27 (m, 8H), 0.92 (t,  $J$  = 6.8 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  155.5, 151.4, 150.6, 126.7, 120.2, 113.8, 111.3, 70.1, 56.5, 33.0, 30.5, 30.4, 30.3, 27.1, 23.7, 14.4; HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_3$  [M+H]: 295.2022, Found: 295.2024.



**(Z)-N'-Hydroxy-3,5-dimethyl-4-(octyloxy)benzimidamide (3.10f).** Synthesized by general procedure 3-B. 74% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.23 (s, 2H), 3.70 (t,  $J$  = 6.4 Hz, 2H), 2.20 (s, 6H), 1.73 (p,  $J$  = 6.3 Hz, 2H), 1.47 (p,  $J$  = 7.2 Hz, 2H), 1.37-1.23 (m, 8H), 0.86 (t,  $J$  = 6.3 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  158.6, 155.4, 132.0, 129.3, 127.8, 73.3, 33.0, 31.5, 30.6, 30.4, 27.3, 23.7, 16.5, 14.5; HRMS (ESI $^{+}$ ): Calcd for  $\text{C}_{17}\text{H}_{29}\text{N}_2\text{O}_2$  [M+H]: 293.2229, Found: 293.2240.

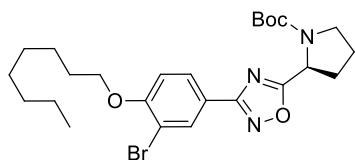


**(S)-Tert-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.11a).** Synthesized by general procedure 3-C. 64% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.28 (s, 1H), 8.18 (d,  $J = 8.7$  Hz, 1H), 7.07 (d,  $J = 8.6$  Hz, 1H), 5.26-4.85 (m, 1H), 4.11 (t,  $J = 6.2$  Hz, 2H), 3.76 – 3.64 (m, 1H), 3.62 – 3.44 (m, 1H), 2.48 – 2.31 (m, 1H), 2.21 – 2.10 (m, 2H), 2.07-1.96 (m, 1H), 1.84 (p,  $J = 6.7$  Hz, 2H), 1.53-1.43 (m, 5H), 1.39-1.22 (m, 14H), 0.88 (t,  $J = 6.5$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  180.9, 167.4, 159.4, 153.6, 132.5, 126.5, 123.6 (q,  $^1J_{\text{CF}} = 275.9$  Hz), 119.8, 118.6, 113.0, 80.6, 69.2, 53.9, 46.5, 32.5, 31.9, 31.6, 29.3, 29.0, 28.3, 25.9, 24.5, 23.8, 22.8, 14.2.;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.8 (d,  $J = 15.1$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{36}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [ $\text{M} + \text{Na}$ ]: 534.2555, Found: 534.2506.

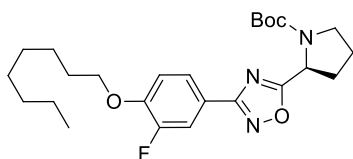


**(S)-Tert-butyl 2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.11b).** Synthesized by general procedure 3-C. 30% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  7.86 (d,  $J = 9.9$  Hz, 2H), 6.86 (t,  $J = 9.8$  Hz, 1H), 5.23-4.98 (m, 1H), 4.01 (t,  $J = 6.3$  Hz, 2H), 3.80 – 3.61 (m, 1H), 3.61 – 3.36 (m, 1H), 2.43 – 2.31 (m, 1H), 2.27 (s, 3H), 2.18 – 2.09 (m, 2H), 2.05-1.92 (m, 1H), 1.82 (p,  $J = 6.6$  Hz, 2H), 1.55-1.41 (m, 5H), 1.41-1.21 (m, 14H), 0.88 (t,  $J = 5.5$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-d)  $\delta$  180.3, 168.4, 159.9, 153.7, 129.7, 127.6, 126.7, 118.4, 110.8, 80.5, 68.2, 54.0, 46.5, 32.5, 31.9, 29.5, 29.4, 29.4, 28.3,

26.2, 23.8, 22.8, 16.3, 14.2; HRMS (ESI+): Calcd for C<sub>26</sub>H<sub>39</sub>N<sub>3</sub>O<sub>4</sub>Na [M+Na]: 480.2838, Found: 480.2832.

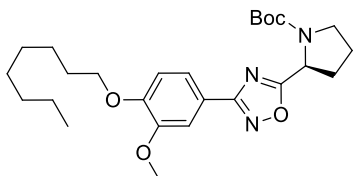


**(S)-Tert-butyl 2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.11c).** Synthesized by general procedure 3-C. 50% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 8.25 (d, *J* = 1.8 Hz, 1H), 7.95 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.93 (t, *J* = 8.2 Hz, 1H), 5.23-4.97 (m, 1H), 4.07 (t, *J* = 6.4 Hz, 2H), 3.75 – 3.62 (m, 1H), 3.61 – 3.41 (m, 1H), 2.44 – 2.29 (m, 1H), 2.22 – 2.07 (m, 2H), 2.04-1.96 (m, 1H), 1.85 (p, *J* = 7.3 Hz, 2H), 1.57-1.47 (m, 2H), 1.45 (s, 3H), 1.41-1.21 (m, 14H), 0.87 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 180.7, 167.2, 157.9, 153.6, 132.5, 127.9, 120.2, 112.8, 112.7, 80.6, 69.4, 53.9, 46.5, 32.5, 31.9, 31.6, 29.4, 29.3, 29.1, 28.3, 26.0, 24.5, 23.8, 22.8, 14.2; HRMS (ESI+): Calcd for C<sub>25</sub>H<sub>36</sub>BrN<sub>3</sub>O<sub>4</sub>Na [M+Na]: 544.1787, Found: 544.1786.

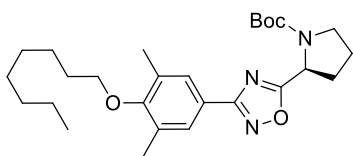


**(S)-Tert-butyl 2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.11d).** Synthesized by general procedure 3-C. 38% yield, yellow oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 7.81-7.81 (m, 2H), 7.01 (t, *J* = 8.5 Hz, 1H), 5.27-4.95 (m, 1H), 4.07 (t, *J* = 6.6 Hz, 2H), 3.74 – 3.63 (m, 1H), 3.59 – 3.43 (m, 1H), 2.47 – 2.28 (m, 1H), 2.21 – 2.06 (m, 2H), 2.05-1.95 (m, 1H), 1.83 (p, *J* = 8.0 Hz, 2H), 1.50-1.41 (m, 5H), 1.40-1.21 (m, 14H), 0.87 (t, *J* = 7.0 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 180.7, 167.5 (d, <sup>3</sup>*J*<sub>CF</sub> = 2.6 Hz), 154.4, 152.5 (d, <sup>1</sup>*J*<sub>CF</sub> = 247.9 Hz), 153.6, 149.9 (d, <sup>2</sup>*J*<sub>CF</sub> = 10.5 Hz), 124.0 (d, <sup>3</sup>*J*<sub>CF</sub> = 3.5 Hz), 119.3 (d, <sup>2</sup>*J*<sub>CF</sub> = 7.7

Hz), 115.3 (d,  $^2J_{CF} = 20.7$  Hz), 114.4, 80.6, 69.5, 53.9, 46.4, 32.5, 31.9, 31.6, 29.8, 29.4, 29.3, 29.2, 28.5, 28.2, 26.0, 24.5, 23.8, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -136.7 (dt,  $J = 11.8$ , 9.7 Hz, 1F); HRMS (ESI+): Calcd for  $\text{C}_{25}\text{H}_{36}\text{FN}_3\text{O}_4\text{Na}$  [M+Na]: 484.2588, Found: 484.2622.

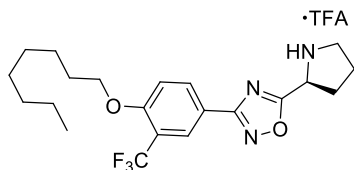


**(S)-Tert-butyl 2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.11e).** Synthesized by general procedure 3-C. 47% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.63 (d,  $J = 8.3$  Hz, 1H), 7.53 (d,  $J = 1.6$  Hz, 1H), 6.91 (d,  $J = 8.3$  Hz, 1H), 5.24-4.97 (m, 1H), 4.04 (t,  $J = 6.7$  Hz, 2H), 3.91 (s, 3H), 3.75 – 3.58 (m, 1H), 3.57 – 3.38 (m, 1H), 2.42 – 2.30 (m, 1H), 2.18 – 2.06 (m, 2H), 2.01-1.93 (m, 1H), 1.84 (p,  $J = 6.9$  Hz, 2H), 1.43 (s, 5H), 1.36-1.21 (m, 14H), 0.85 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  180.4, 168.2, 153.6, 151.2, 149.5, 120.9, 119.0, 112.3, 110.2, 80.4, 69.0, 56.1, 53.9, 46.4, 32.4, 31.8, 31.5, 29.4, 29.2, 29.1, 28.2, 26.0, 24.4, 23.8, 22.7, 14.1; HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{39}\text{N}_3\text{O}_5\text{Na}$  [M+Na]: 496.2788, Found: 496.2775.



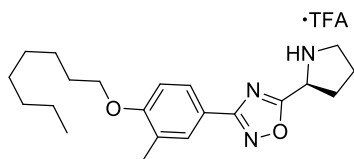
**(S)-Tert-butyl 2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.11f).** Synthesized by general procedure 3-C. 42% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.72 (s, 2H), 5.26-4.92 (m, 1H), 3.79 (t,  $J = 6.6$  Hz, 2H), 3.76 – 3.62 (m, 1H), 3.61 – 3.43 (m, 1H), 2.43 – 2.35 (m, 1H), 2.32 (s, 6H), 2.22 – 2.07 (m, 2H), 2.03-1.95 (m, 1H), 1.81 (p,  $J = 7.9$  Hz, 2H), 1.57-1.42 (m, 5H), 1.41-1.23 (m, 14H), 0.89 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  180.5, 168.3, 158.9, 153.7, 131.9, 128.1, 121.9, 80.6, 72.6, 54.0,

46.5, 32.6, 32.0, 30.5, 29.6, 29.4, 28.3, 26.3, 23.8, 22.8, 16.5, 14.2; HRMS (ESI<sup>+</sup>): Calcd for C<sub>27</sub>H<sub>41</sub>N<sub>3</sub>O<sub>4</sub>Na [M+Na]: 494.2995, Found: 494.3028.



**(S)-2-(3-(4-(Octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium**

**2,2,2-trifluoroacetate (3.12a).** Synthesized by general procedure 3-D. Quantitative yield, yellow oil; <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.26 (d, *J*=7.4 Hz, 2H), 7.32 (d, *J* = 9.4 Hz, 1H), 5.18 (t, *J* = 7.8 Hz, 1H), 4.17 (t, *J*= 6.2 Hz, 2H), 3.67 – 3.45 (m, 2H), 2.65 (dtd, *J* = 13.5, 7.8, 5.9 Hz, 1H), 2.48-2.34 (m, 1H), 2.33 – 2.16 (m, 2H), 1.88-1.76 (m, 2H), 1.50 (p, *J* = 7.1 Hz, 2H), 1.41-1.22 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Methanol-d<sub>4</sub>) δ 176.3, 168.7, 161.0, 134.0, 127.3 (q, <sup>3</sup>*J*<sub>CF</sub> = 5.5 Hz), 124.6 (q, <sup>1</sup>*J*<sub>CF</sub> = 274.9 Hz), 120.3 (q, <sup>2</sup>*J*<sub>CF</sub> = 39.0 Hz), 119.0, 114.9, 70.3, 55.5, 47.3, 32.9, 30.3, 30.2, 30.0, 26.9, 24.5, 23.7, 14.4; <sup>19</sup>F NMR (376 MHz, Chloroform-d) δ -63.9 (s, 3F); HRMS (ESI<sup>+</sup>): Calcd for C<sub>21</sub>H<sub>29</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 412.2211, Found: 412.2215.

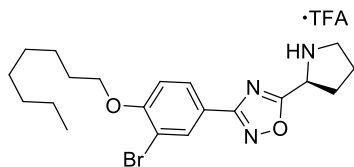


**(S)-2-(3-(3-Methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium** **2,2,2-**

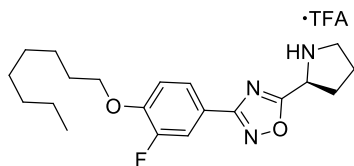
**trifluoroacetate (3.12b).** Synthesized by general procedure 3-D. 100% conversion, white solid; <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 7.87 (ddd, *J*= 8.5, 2.5, 0.5 Hz, 1H), 7.83 (dd, *J*= 2.1, 0.8 Hz, 1H), 6.98 (d, *J*= 8.6 Hz, 1H), 5.14 (t, *J* = 7.7 Hz, 1H), 4.03 (t, *J*= 6.3 Hz, 2H), 3.66 – 3.41 (m, 2H), 2.68 - 2.58 (m, 1H), 2.44-2.34 (m, 1H), 2.32-2.14 (m, 5H), 1.81 (p, *J*= 6.8 Hz, 2H), 1.50 (p, *J*= 5.9 Hz, 2H), 1.42-1.24 (m, 8H), 0.88 (t, *J*= 6.9 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Methanol-d<sub>4</sub>) δ 175.6,



169.7, 161.5, 130.4, 128.6, 128.0, 118.7, 112.1, 69.3, 55.5, 47.3, 33.0, 30.4, 30.4, 30.3, 30.2, 27.2, 24.5, 23.7, 16.4, 14.4; HRMS (ESI+): Calcd for C<sub>21</sub>H<sub>32</sub>N<sub>3</sub>O<sub>2</sub>+ [M<sup>+</sup>]: 358.2495, Found: 358.2485.

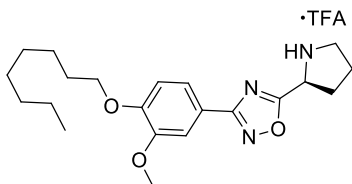


**(S)-2-(3-(3-Bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.12c).** Synthesized by general procedure 3-D. 100% conversion, yellow oil; <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.20 (d, *J* = 2.1 Hz, 1H), 7.99 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 5.16 (t, *J* = 7.7 Hz, 1H), 4.10 (t, *J* = 6.3 Hz, 2H), 3.66 – 3.45 (m, 2H), 2.68 - 2.58 (m, 1H), 2.44-2.34 (m, 1H), 2.31 – 2.13 (m, 2H), 1.84-1.77 (m, 2H), 1.51 (p, *J* = 7.2 Hz, 2H), 1.42-1.19 (m, 8H), 0.87 (t, *J* = 7.6 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Methanol-d<sub>4</sub>) δ 176.0, 168.5, 159.6, 133.2, 129.3, 120.4, 114.3, 113.3, 70.5, 55.4, 47.3, 32.9, 30.4, 30.3, 30.2, 30.1, 27.1, 24.5, 23.7, 14.4; HRMS (ESI+): Calcd for C<sub>20</sub>H<sub>29</sub>BrN<sub>3</sub>O<sub>2</sub>+ [M<sup>+</sup>]: 422.1443, Found: 422.1444.

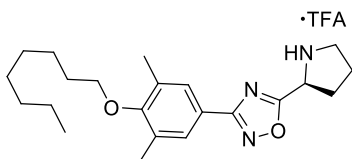


**(S)-2-(3-(3-Fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.12d).** Synthesized by general procedure 3-D. 100% conversion, white solid; <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 7.82 (ddd, *J* = 8.6, 2.0, 1.3 Hz, 1H), 7.74 (dd, *J* = 11.8, 2.1 Hz, 1H), 7.19 (t, *J* = 8.5 Hz, 1H), 5.15 (t, *J* = 7.7 Hz, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.65 – 3.39 (m, 2H), 2.68 - 2.58 (m, 1H), 2.43-2.34 (m, 1H), 2.30 – 2.12 (m, 2H), 1.79 (p, *J* = 6.4 Hz, 2H), 1.47 (p, *J* = 7.9 Hz, 2H), 1.41-1.09 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (126 MHz, Methanol-d<sub>4</sub>) δ 176.0, 168.8, 153.7 (d, <sup>1</sup>*J*<sub>CF</sub> = 246.7 Hz), 151.6 (d, <sup>2</sup>*J*<sub>CF</sub> = 10.6 Hz), 125.4 (d, <sup>3</sup>*J*<sub>CF</sub> = 3.6 Hz), 119.6 (d, <sup>2</sup>*J*<sub>CF</sub> = 7.4 Hz), 115.9 (d, <sup>2</sup>*J*<sub>CF</sub> = 20.9 Hz), 115.8, 70.4, 55.5, 47.3, 32.9, 30.4, 30.3, 30.2, 30.1,

27.0, 24.5, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -135.1 (dd,  $J$ = 11.4, 8.4 Hz, 1F); HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{29}\text{FN}_3\text{O}_2 + [\text{M}^+]$ : 362.2244, Found: 362.2254.

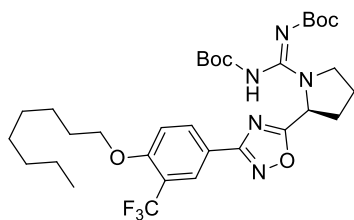


**(S)-2-(3-(3-Methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.12e).** Synthesized by general procedure 3-D. 100% conversion, yellow oil;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.57 (dd,  $J$ =8.4, 1.9 Hz, 1H), 7.50 (d,  $J$  = 1.8 Hz, 1H), 6.95 (d,  $J$ = 8.4 Hz, 1H), 5.09 (t,  $J$  = 7.8 Hz, 1H), 3.95 (t,  $J$ = 6.5 Hz, 2H), 3.80 (s, 3H), 3.58 – 3.36 (m, 2H), 2.64 - 2.50 (m, 1H), 2.39-2.26 (m, 1H), 2.24 – 2.11 (m, 2H), 1.71 (p,  $J$ = 6.0 Hz, 2H), 1.39 (p,  $J$ = 6.9 Hz, 2H), 1.31-1.17 (m, 8H), 0.80 (t,  $J$ = 6.7 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  175.7, 169.6, 153.2, 151.0, 122.3, 119.4, 113.8, 111.5, 70.0, 56.5, 55.4, 47.2, 33.0, 30.4, 30.4, 30.2, 30.2, 27.1, 24.5, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{32}\text{N}_3\text{O}_3 + [\text{M}^+]$ : 374.2444, Found: 374.2436.

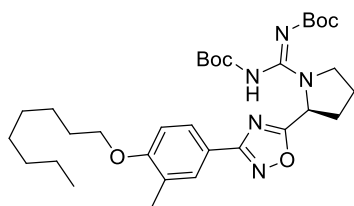


**(S)-2-(3-(3,5-Dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.12f).** Synthesized by general procedure 3-D. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.76 (s, 2H), 5.18 (t,  $J$  = 7.7 Hz, 1H), 3.83 (t,  $J$ = 6.4 Hz, 2H), 3.66 – 3.49 (m, 2H), 2.72 - 2.62 (m, 1H), 2.49-2.37 (m, 1H), 2.32 (s, 6H), 2.31 – 2.20 (m, 2H), 1.82 (p,  $J$ = 6.8 Hz, 2H), 1.55 (p,  $J$ = 6.8 Hz, 2H), 1.46-1.26 (m, 8H), 0.92 (t,  $J$ = 6.1 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  175.8, 169.6, 160.5, 133.2, 129.1, 122.3, 73.5, 55.5, 47.3, 33.0,

31.5, 30.6, 30.4, 30.2, 27.2, 24.5, 23.7, 16.5, 14.4; HRMS (ESI<sup>+</sup>): Calcd for C<sub>22</sub>H<sub>34</sub>N<sub>3</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 372.2651, Found: 372.2636.

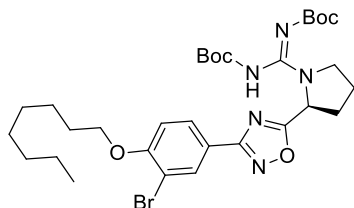


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.13a).** Synthesized by general procedure 3-E. 45% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 8.28 (d, *J* = 2.0 Hz, 1H), 8.18 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 5.60 (dd, *J* = 7.8, 4.5 Hz, 1H), 4.11 (t, *J* = 6.4 Hz, 2H), 3.94 – 3.75 (m, 2H), 2.45 (dq, *J* = 15.9, 8.4, 7.9 Hz, 1H), 2.30-2.12 (m, 2H), 2.03 (dq, *J* = 12.7, 6.7 Hz, 1H), 1.89-1.77 (m, 2H), 1.56-1.22 (m, 27H), 0.88 (t, *J* = 6.4 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 179.3, 167.4, 162.1, 159.4, 153.8, 150.5, 132.6, 126.9 (q, <sup>3</sup>*J*<sub>CF</sub> = 5.0 Hz), 123.4 (q, <sup>1</sup>*J*<sub>CF</sub> = 276.7 Hz), 119.5 (q, <sup>2</sup>*J*<sub>CF</sub> = 33.3 Hz), 113.0, 110.2, 82.4, 79.7, 69.2, 55.4, 49.6, 31.9, 29.8, 29.3, 29.0, 28.2, 28.1, 25.9, 22.8, 14.2; <sup>19</sup>F NMR (376 MHz, Chloroform-d) δ -65.8 (s, 3F); HRMS (ESI<sup>+</sup>): Calcd for C<sub>32</sub>H<sub>47</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub> [M+H]: 654.3478, Found: 654.3506.

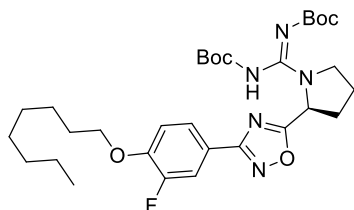


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.13b).** Synthesized by general procedure 3-E. 57% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 10.05 (s, 1H), 7.89-7.78 (m, 2H), 6.85 (d, *J* = 8.3 Hz, 1H), 5.57 (dd, *J* = 7.7, 4.5 Hz, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.92-

3.84 (m, 1H), 3.83-3.74 (m, 1H), 2.47 – 2.37 (m, 1H), 2.26 (s, 3H), 2.23-2.11 (m, 2H), 2.07-1.98 (m, 1H), 1.82 (p,  $J = 6.5$  Hz, 2H), 1.54-1.23 (m, 28H), 0.89 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  178.6, 168.4, 162.0, 159.9, 153.5, 150.6, 129.8, 127.5, 126.8, 118.3, 110.8, 82.3, 79.8, 68.2, 55.4, 49.5, 31.9, 31.5, 29.5, 29.4, 29.4, 28.3, 28.1, 26.2, 24.0, 22.8, 16.3, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{50}\text{N}_5\text{O}_6$  [M+H]: 600.3761, Found: 600.3733.

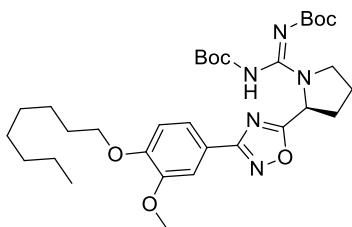


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.13c).** Synthesized by general procedure 3-E. 46% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  10.13 (s, 1H), 8.25 (d,  $J = 2.0$  Hz, 1H), 7.96 (dd,  $J = 8.6, 2.1$  Hz, 1H), 6.93 (d,  $J = 8.7$  Hz, 1H), 5.57 (dd,  $J = 7.7, 4.5$  Hz, 1H), 4.07 (t,  $J = 6.5$  Hz, 2H), 3.91-3.85 (m, 1H), 3.79 (s, 1H), 2.47 – 2.39 (m, 1H), 2.25-2.12 (m, 2H), 2.06-1.99 (m, 1H), 1.85 (p,  $J = 6.5$  Hz, 2H), 1.57-1.24 (m, 28H), 0.88 (t,  $J = 6.5$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  179.0, 167.2, 162.0, 157.8, 153.6, 150.4, 132.6, 128.0, 120.2, 112.8, 112.6, 82.4, 79.8, 69.5, 55.4, 49.6, 31.9, 31.4, 29.4, 29.3, 29.1, 28.2, 28.1, 26.1, 24.1, 22.8, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{47}\text{BrN}_5\text{O}_6$  [M+H]: 664.2710, Found: 664.2719.

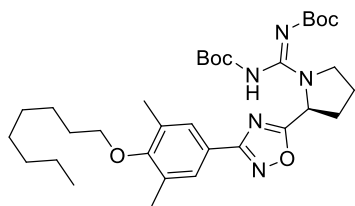


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.13d).** Synthesized by general

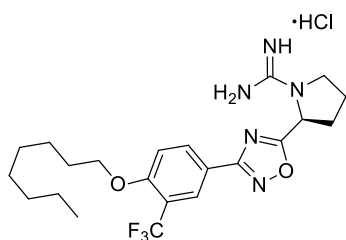
procedure 3-E. 44% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.10 (s, 1H), 7.87-7.65 (m, 2H), 7.01 (d,  $J = 8.5$  Hz, 1H), 5.58 (dd,  $J = 7.8, 4.5$  Hz, 1H), 4.08 (t,  $J = 6.6$  Hz, 2H), 3.92-3.84 (m, 1H), 3.80 (s, 1H), 2.48 – 2.38 (m, 1H), 2.27-2.13 (m, 2H), 2.09-1.98 (m, 1H), 1.84 (p,  $J = 7.3$  Hz, 2H), 1.55-1.22 (m, 28H), 0.88 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*)  $\delta$  179.1, 167.5, 162.0, 152.5 (d,  $^1J_{\text{CF}} = 247.6$  Hz), 150.5, 149.9 (d,  $^2J_{\text{CF}} = 10.5$  Hz), 124.1 (d,  $^3J_{\text{CF}} = 3.0$  Hz), 119.4, 115.5 (d,  $^2J_{\text{CF}} = 20.8$  Hz), 114.4, 82.4, 79.7, 69.5, 55.4, 49.8, 31.9, 31.4, 29.8, 29.4, 29.3, 29.2, 28.2, 26.0, 24.1, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -136.7 (s, 1F); HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{31}\text{H}_{47}\text{FN}_5\text{O}_6$  [M+H]: 604.3512, Found: 604.3534.



**(*S*)-Tert-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.13e).** Synthesized by general procedure 3-E. 51% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.08 (s, 1H), 7.64 (dd,  $J = 8.4, 1.9$  Hz, 1H), 7.54 (d,  $J = 1.9$  Hz, 1H), 6.91 (d,  $J = 8.5$  Hz, 1H), 5.57 (dd,  $J = 7.8, 4.6$  Hz, 1H), 4.05 (t,  $J = 6.9$  Hz, 2H), 3.92 (s, 3H), 3.90-3.82 (m, 1H), 3.79 (s, 1H), 2.48 – 2.39 (m, 1H), 2.26-2.11 (m, 2H), 2.08-1.95 (m, 1H), 1.85 (p,  $J = 6.9$  Hz, 2H), 1.51-1.20 (m, 28H), 0.86 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  178.7, 168.2, 162.0, 153.6, 151.2, 150.3, 149.5, 121.1, 119.0, 112.3, 110.3, 82.3, 79.7, 69.1, 56.2, 55.4, 49.6, 31.9, 31.7, 29.4, 29.3, 29.1, 28.2, 28.1, 26.0, 24.0, 22.7, 14.2; HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{32}\text{H}_{50}\text{N}_5\text{O}_7$  [M+H]: 616.3712, Found: 616.3703.

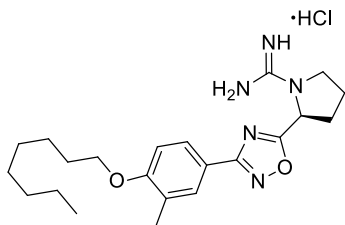


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.13f).** Synthesized by general procedure 3-E. 48% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  10.06 (s, 1H), 7.71 (s, 2H), 5.57 (dd,  $J = 7.7, 4.5$  Hz, 1H), 3.91-3.84 (m, 1H), 3.78 (t,  $J = 6.6$  Hz, 3H), 2.48 – 2.38 (m, 1H), 2.31 (s, 6H), 2.23-2.12 (m, 2H), 2.06-1.98 (m, 1H), 1.80 (p,  $J = 6.9$  Hz, 2H), 1.55-1.22 (m, 28H), 0.88 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  178.8, 168.3, 162.1, 158.9, 153.6, 150.5, 131.8, 128.2, 121.8, 82.2, 79.6, 72.6, 55.4, 49.5, 31.9, 31.5, 30.5, 29.6, 29.4, 28.2, 26.2, 24.0, 22.8, 16.4, 14.2; HRMS (ESI+): Calcd for  $\text{C}_{33}\text{H}_{52}\text{N}_5\text{O}_6$  [M+H]: 614.3918, Found: 614.3906.

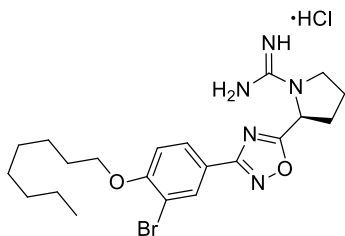


**(S)-Amino (2-(3-(4-(octyloxy)-3-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-yl) methaniminium chloride (3.14a).** Synthesized by general procedure 3-F. 80% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  8.27 (dd,  $J = 8.6, 2.1$  Hz, 2H), 8.24 (d,  $J = 2.0$  Hz, 1H), 7.35 (d,  $J = 8.7$  Hz, 1H), 5.46 (dd,  $J = 7.9, 1.7$  Hz, 1H), 4.20 (t,  $J = 6.2$  Hz, 2H), 3.80 (td,  $J = 9.5, 2.5$  Hz, 1H), 3.64 (td,  $J = 9.6, 7.4$  Hz, 1H), 2.65 – 2.47 (m, 2H), 2.30-2.21 (m, 1H), 2.19 – 2.04 (m, 1H), 1.90-1.81 (m, 2H), 1.54 (p,  $J = 6.7$  Hz, 2H), 1.46-1.30 (m, 8H), 0.92 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol-d<sub>4</sub>)  $\delta$  179.2, 168.6, 160.9, 157.1, 133.9, 127.1 (q,  $^3J_{\text{CF}} = 5.5$  Hz), 124.8 (q,  $^1J_{\text{CF}} = 272.8$  Hz), 120.3 (q,  $^2J_{\text{CF}} = 29.9$  Hz), 119.3, 114.8, 70.3, 56.5, 32.9, 32.7, 30.3,

30.2, 30.0, 26.9, 24.3, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{31}\text{F}_3\text{N}_5\text{O}_2 + [\text{M}^+]$ : 454.2429, Found: 454.2435.

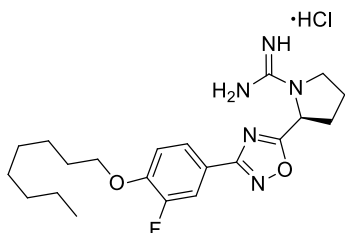


**(S)-Amino(2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.14b).** Synthesized by general procedure 3-F. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.88 (ddd,  $J$ = 8.4, 2.4, 0.4 Hz, 1H), 7.84 (dd,  $J$ = 2.1, 0.8 Hz, 1H), 7.44 (s, 1H), 7.04 (d,  $J$ =8.6 Hz, 1H), 5.47 (dd,  $J$  = 7.9, 1.8 Hz, 1H), 4.10 (t,  $J$ = 6.3 Hz, 2H), 3.82 (td,  $J$ = 9.3, 2.6 Hz, 1H), 3.66 (q,  $J$  = 9.1 Hz, 1H), 2.69– 2.45 (m, 2H), 2.29 (s, 3H), 2.28-2.21 (m, 1H), 2.20-2.06 (m, 1H), 1.87 (p,  $J$ = 6.3 Hz, 2H), 1.56 (p,  $J$ = 6.7 Hz, 2H), 1.49-1.27 (m, 8H), 0.94 (t,  $J$ = 7.0 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  178.5, 169.6, 161.4, 157.1, 130.4, 128.5, 127.9, 119.0, 112.1, 69.3, 56.4, 33.0, 32.7, 30.4, 30.4, 30.3, 27.2, 24.3, 23.7, 16.3, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{34}\text{N}_5\text{O}_2 + [\text{M}^+]$ : 400.2713, Found: 400.2690.



**(S)-Amino(2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.14c).** Synthesized by general procedure 3-F. 73% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.17 (d,  $J$  = 2.0 Hz, 1H), 7.98 (dd,  $J$ = 8.6, 1.9 Hz, 1H),

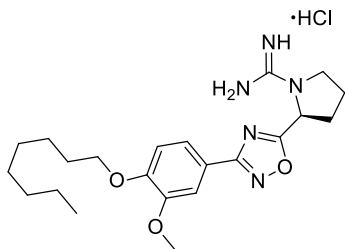
7.42 (s, 1H), 7.14 (d,  $J = 8.6$  Hz, 1H), 5.44 (d,  $J = 7.3$  Hz, 1H), 4.12 (t,  $J = 6.2$  Hz, 2H), 3.77 (t,  $J = 8.3$  Hz, 1H), 3.61 (q,  $J = 9.3$  Hz, 1H), 2.59–2.52 (m, 1H), 2.46 (dd,  $J = 12.4, 6.1$  Hz, 1H), 2.22 (s, 1H), 2.08 (s, 1H), 1.83 (p,  $J = 6.0$  Hz, 2H), 1.53 (p,  $J = 7.2$  Hz, 2H), 1.43–1.25 (m, 8H), 0.89 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  179.0, 168.4, 159.4, 157.1, 133.1, 129.2, 120.8, 114.3, 113.3, 70.5, 56.5, 32.9, 32.7, 30.3, 30.3, 30.1, 27.1, 24.3, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{31}\text{BrN}_5\text{O}_2 + [\text{M}^+]$ : 464.1661, Found: 464.1700.



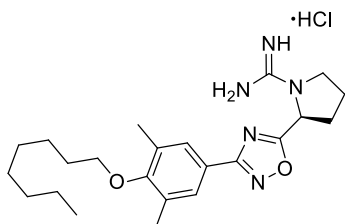
**(S)-Amino(2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-**

**yl)methaniminium chloride (3.14d).** Synthesized by general procedure 3-F. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.81 (d,  $J = 8.2$  Hz, 1H), 7.73 (dd,  $J = 11.8, 1.7$  Hz, 1H), 7.21 (t,  $J = 8.5$  Hz, 1H), 5.43 (d,  $J = 6.4$  Hz, 1H), 4.12 (t,  $J = 6.3$  Hz, 2H), 3.77 (t,  $J = 8.4$  Hz, 1H), 3.61 (q,  $J = 7.4$  Hz, 1H), 2.56 (s, 1H), 2.50–2.42 (m, 1H), 2.21 (s, 1H), 2.08 (s, 1H), 1.82 (p,  $J = 6.5$  Hz, 2H), 1.50 (p,  $J = 7.0$  Hz, 2H), 1.43–1.25 (m, 8H), 0.90 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.0, 168.7, 157.0, 153.6 (d,  $^1J_{\text{CF}} = 247.1$  Hz), 151.4 (d,  $^2J_{\text{CF}} = 10.6$  Hz), 125.3 (d,  $^3J_{\text{CF}} = 3.6$  Hz), 119.9 (d,  $^2J_{\text{CF}} = 7.4$  Hz), 115.8 (d,  $^3J_{\text{CF}} = 2.1$  Hz), 115.7 (d,  $^2J_{\text{CF}} = 20.9$  Hz), 70.4, 56.5, 32.9, 32.7, 30.4, 30.4, 30.2, 27.0, 24.3, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -135.1 (dd,  $J = 11.7, 8.4$  Hz, 1F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{31}\text{FN}_5\text{O}_2 + [\text{M}^+]$ : 404.2462, Found: 404.2449.



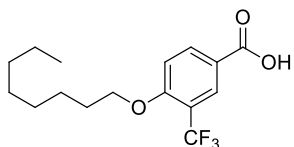


**(S)-Amino(2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.14e).** Synthesized by general procedure 3-F. 95% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.64 (dd,  $J = 8.3, 1.7$  Hz, 1H), 7.57 (d,  $J = 1.8$  Hz, 1H), 7.05 (d,  $J = 8.4$  Hz, 1H), 5.45 (d,  $J = 7.0$  Hz, 1H), 4.06 (t,  $J = 6.4$  Hz, 2H), 3.90 (s, 3H), 3.78 (t,  $J = 8.4$  Hz, 1H), 3.63 (q,  $J = 9.0$  Hz, 1H), 2.63– 2.52 (m, 1H), 2.52-2.41 (m, 1H), 2.23 (s, 1H), 2.10 (s, 1H), 1.82 (p,  $J = 6.6$  Hz, 2H), 1.50 (p,  $J = 7.0$  Hz, 2H), 1.44-1.25 (m, 8H), 0.91 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  178.7, 169.5, 157.0, 153.1, 151.1, 122.2, 119.7, 113.8, 111.5, 70.0, 56.6, 56.5, 33.0, 32.8, 30.5, 30.4, 30.2, 27.1, 24.4, 23.7, 14.4; HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{34}\text{N}_5\text{O}_3 + [\text{M}^+]$ : 416.2662, Found: 416.2661.

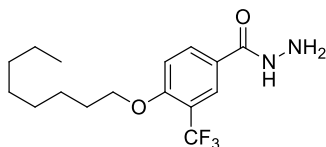


**(S)-Amino(2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.14f).** Synthesized by general procedure 3-F. 86% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.71 (s, 2H), 5.46 (d,  $J = 6.7$  Hz, 1H), 3.82 (t,  $J = 6.4$  Hz, 2H), 3.78 (dd,  $J = 9.1, 1.9$  Hz, 1H), 3.63 (q,  $J = 9.0$  Hz, 1H), 2.67– 2.51 (m, 1H), 2.47 (dd,  $J = 12.9, 6.4$  Hz, 1H), 2.32 (s, 6H), 2.30-2.19 (m, 1H), 2.16-2.02 (m, 1H), 1.82 (p,  $J = 6.8$  Hz, 2H), 1.55 (p,  $J = 7.1$  Hz, 2H), 1.45-1.27 (m, 8H), 0.89 (t,  $J = 6.6$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )

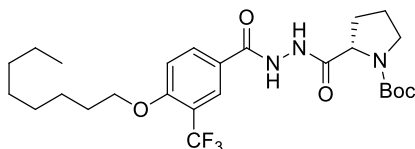
$\delta$  178.7, 169.4, 160.3, 157.1, 133.1, 129.0, 122.7, 73.5, 56.4, 33.0, 32.7, 31.5, 30.6, 30.4, 27.2, 24.3, 23.7, 16.5, 14.4; HRMS (ESI+): Calcd for  $C_{23}H_{36}N_5O_2 + [M]^+$ : 414.2869, Found: 414.2851.



**4-(Octyloxy)-3-(trifluoromethyl) benzoic acid.** Synthesized by general procedure 3-G, omitting purification by silica gel column chromatography. The product was taken to the next step with no further purification or analysis was performed.

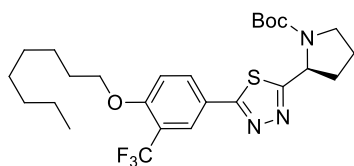


**4-(Octyloxy)-3-(trifluoromethyl) benzohydrazide.** 4-(octyloxy)-3-(trifluoromethyl) benzoic acid was dissolved in 4:1 DCM:DMF. HCTU (1.2 equiv) and DIEA (6.6 equiv) were added to the reaction mixture. Subsequently, hydrazine (4.65 equiv) was added dropwise and the reaction was allowed to stir at room temperature for 2 hours. Once complete, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The resulting organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was taken to the next reaction without further purification.



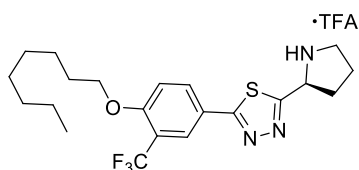
**(S)-Tert-butyl 2-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)pyrrolidine-1-carboxylate (3.16).** (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (1 equiv) was dissolved in 2:1 DCM:DMF. HCTU

(1.2 equiv) and DIEA (5 equiv) were added to the reaction mixture and stirred for 10 min. Next, 4-(octyloxy)-3-(trifluoromethyl)benzohydrazide was added and the reaction mixture was stirred another 2 hours at room temperature. Once complete, the mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (50% ethyl acetate/hexane) yielding product **3.16** as a colorless oil in a 32% yield.  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  10.05-9.17 (m, 2H), 8.05 (d,  $J$  = 1.4 Hz, 1H), 7.92 (dd,  $J$  = 8.7, 2.2 Hz, 1H), 6.88 (d,  $J$  = 8.8 Hz, 1H), 4.42 (s, 1H), 4.02 (t,  $J$  = 6.4 Hz, 2H), 3.55-3.31 (m, 2H), 2.30 (s, 1H), 2.16 (s, 1H), 2.04-1.95 (m, 1H), 1.92-1.84 (m, 1H), 1.79 (p,  $J$  = 6.4 Hz, 2H), 1.46 (s, 11H), 1.39-1.18 (m, 8H), 0.87 (t,  $J$  = 6.8 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  171.0, 163.5, 160.0, 155.9, 132.7, 127.1 (q,  $^3J_{\text{CF}}$  = 4.6 Hz), 123.2 (q,  $^1J_{\text{CF}}$  = 274.1 Hz), 123.1, 118.9 (q,  $^2J_{\text{CF}}$  = 31.5 Hz), 112.3, 81.0, 69.2, 59.8, 58.8, 47.3, 31.9, 31.3, 29.3, 28.9, 28.5, 25.8, 24.6, 23.8, 22.7, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.9 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{26}\text{H}_{38}\text{F}_3\text{N}_3\text{O}_5\text{Na}$  [ $\text{M}+\text{Na}$ ]: 552.2661, Found: 552.2656.



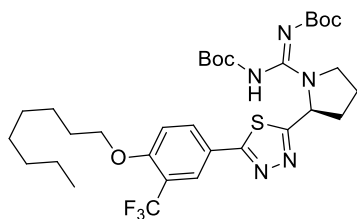
**(S)-Tert-butyl 2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidine-1-carboxylate (3.17).** Compound **3.16** was dissolved in toluene. Lawesson's reagent (3 equiv) was then added and the reaction was refluxed for 2 hours. Once the reaction was complete, the reaction was washed with diethyl ether and water. The resulting organic layer was further washed with brine, dried over sodium sulfate, filtered, and evaporated under reduced

pressure. The resulting residue was purified with silica gel column chromatography (100% dichloromethane for 3 column volumes then switched to 30% ethyl acetate/hexane) to yield **3.17** as a colorless oil in a 32% yield.  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.11 (s, 1H), 8.06 (d,  $J$  = 8.7 Hz, 1H), 7.06 (d,  $J$  = 8.5 Hz, 1H), 5.29 (s, 1H), 4.10 (t,  $J$  = 6.4 Hz, 2H), 3.65 – 3.38 (m, 2H), 2.65 – 2.37 (m, 1H), 2.32 (s, 1H), 2.16 – 1.96 (m, 2H), 1.84 (p,  $J$  = 6.4 Hz, 2H), 1.54-1.22 (m, 19H), 0.88 (t,  $J$  = 6.8 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  174.5, 159.0, 132.5, 126.8, 123.1 (q,  $^1J_{\text{CF}}$  = 275.0 Hz), 122.1, 119.6 (q,  $^2J_{\text{CF}}$  = 38.0 Hz), 113.1, 80.7, 69.1, 57.1, 56.4, 46.5, 33.9, 31.7, 31.6, 29.1, 28.8, 28.3, 25.7, 24.3, 23.4, 22.6, 14.0;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.9 (d,  $J$  = 16.7 Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{36}\text{F}_3\text{N}_3\text{O}_3\text{SNa}$  [ $\text{M}+\text{Na}$ ]: 550.2327, Found: 550.2324.

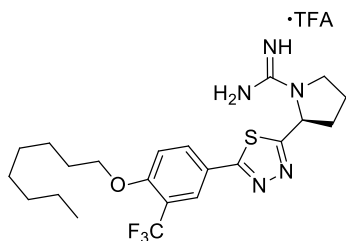


**(S)-2-(5-(4-(Octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-ium**

**2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, yellow oil;  $^1\text{H}$  NMR (500 MHz, Methanol- $\text{d}_4$ )  $\delta$  8.17 (s, 1H), 8.11 (d,  $J$  = 8.2 Hz, 1H), 7.30 (d,  $J$  = 8.6 Hz, 1H), 5.28 (s, 1H), 4.15 (t,  $J$  = 6.1 Hz, 2H), 3.61 – 3.45 (m, 2H), 2.64 (s, 1H), 2.36-2.14 (m, 3H), 1.80 (p,  $J$  = 6.3 Hz, 2H), 1.48 (p,  $J$  = 7.2 Hz, 2H), 1.38-1.20 (m, 8H), 0.86 (t,  $J$  = 6.9 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $\text{d}_4$ )  $\delta$  171.0, 165.6, 161.0, 134.7, 127.3 (q,  $^3J_{\text{CF}}$  = 5.4 Hz), 124.5 (q,  $^1J_{\text{CF}}$  = 272.5 Hz), 122.4, 120.6 (q,  $^2J_{\text{CF}}$  = 31.4 Hz), 115.1, 70.4, 58.5, 46.9, 32.8, 32.6, 30.3, 30.2, 29.9, 26.8, 24.4, 23.6, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $\text{d}_4$ )  $\delta$  -63.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{29}\text{F}_3\text{N}_3\text{OS}^+$  [ $\text{M}^+$ ]: 428.1983, Found: 428.2000.

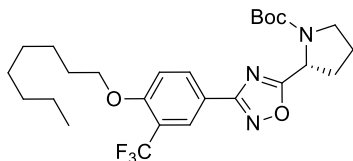


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-yl)methylene)carbamate.** Synthesized by general procedure 3-E. 51% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  10.15 (s, 1H), 8.09 (d,  $J = 6.6$  Hz, 2H), 7.06 (d,  $J = 9.3$  Hz, 1H), 5.79 (t,  $J = 6.8$  Hz, 1H), 4.10 (t,  $J = 6.4$  Hz, 2H), 3.85-3.78 (m, 1H), 3.64 (s, 1H), 2.65 (s, 1H), 2.53 – 2.43 (m, 1H), 2.20-2.13 (m, 1H), 2.04-1.95 (m, 1H), 1.84 (p,  $J = 6.4$  Hz, 2H), 1.48 (s, 18H), 1.39-1.25 (m, 10H), 0.88 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  169.7, 168.3, 159.1, 154.1, 132.6, 127.2 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 274.1$  Hz), 122.4, 119.7 (q,  $^2J_{\text{CF}} = 31.6$  Hz), 119.2, 113.3, 82.1, 80.0, 69.3, 58.3, 50.1, 29.8, 29.3, 29.0, 28.3, 25.9, 24.7, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.9 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{47}\text{F}_3\text{N}_5\text{O}_5\text{S}$  [M+H]: 670.3250, Found: 670.3253.

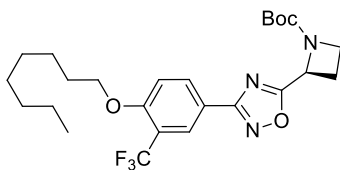


**(S)-Amino(2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate (3.18).** Synthesized by general procedure 3-D. 71% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  8.15 (d,  $J = 2.1$  Hz, 1H), 8.10 (dd,  $J = 8.7$ , 2.2 Hz, 1H), 7.30 (d,  $J = 8.8$  Hz, 1H), 5.49 (d,  $J = 6.7$  Hz, 1H), 4.17 (t,  $J = 6.2$  Hz, 2H), 3.78 (td,  $J = 9.7$ , 2.4 Hz, 1H), 3.61 (td,  $J = 9.6$ , 7.5 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.36 (dd,  $J = 12.9$ , 6.1 Hz,

1H), 2.23-2.06 (m, 2H), 1.82 (p,  $J = 6.4$  Hz, 2H), 1.51 (p,  $J = 7.1$  Hz, 2H), 1.41-1.27 (m, 8H), 0.89 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  171.1, 170.2, 160.9, 157.9, 134.6, 127.3 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 124.6 (q,  $^1J_{\text{CF}} = 272.4$  Hz), 122.7, 120.6 (q,  $^2J_{\text{CF}} = 31.3$  Hz), 115.1, 70.4, 59.0, 35.1, 32.9, 30.3, 30.2, 30.0, 26.9, 24.0, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{31}\text{F}_3\text{N}_5\text{OS}^+$  [M+]: 470.2201, Found: 470.2196.

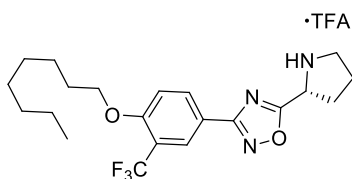


**(R)-Tert-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.19a).** Synthesized by general procedure 3-C. 50% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.27 (s, 1H), 8.17 (d,  $J = 8.5$  Hz, 1H), 7.06 (t,  $J = 8.6$  Hz, 1H), 5.22-5.00 (m, 1H), 4.09 (t,  $J = 6.2$  Hz, 2H), 3.75 – 3.62 (m, 1H), 3.61 – 3.41 (m, 1H), 2.46 – 2.31 (m, 1H), 2.20 – 2.07 (m, 2H), 2.06-1.94 (m, 1H), 1.82 (p,  $J = 6.6$  Hz, 2H), 1.53-1.41 (m, 5H), 1.38-1.21 (m, 14H), 0.87 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  180.9, 167.4, 159.4, 153.6, 132.5, 126.7, 123.4 (q,  $^1J_{\text{CF}} = 274.0$  Hz), 119.6 (q,  $^2J_{\text{CF}} = 31.1$  Hz), 118.6, 113.0, 80.6, 69.2, 53.9, 46.5, 32.5, 31.9, 29.3, 29.0, 28.2, 25.9, 24.5, 23.8, 22.7, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.8 (d,  $J = 14.6$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{36}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 534.2556, Found: 534.2539.

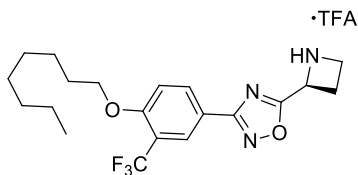


**(S)-Tert-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (3.19b).** Synthesized by general procedure 3-C. 57% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.30 (d,  $J = 2.0$  Hz, 1H), 8.20 (dd,  $J = 8.7, 2.1$  Hz, 1H), 7.06 (d,  $J =$

8.7 Hz, 1H), 5.41 (dd,  $J = 8.8, 5.7$  Hz, 1H), 4.24-4.14 (m, 1H), 4.10 (t,  $J = 6.4$  Hz, 2H), 4.08 – 4.02 (m, 1H), 2.76 – 2.67 (m, 1H), 2.59 – 2.50 (m, 1H), 1.89 – 1.78 (m, 2H), 1.48 (p,  $J = 6.9$  Hz, 2H), 1.41-1.23 (m, 17H), 0.87 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  178.6, 167.6, 159.4, 155.4, 132.5, 126.8 (q,  $^3J_{\text{CF}} = 5.0$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 275.0$  Hz), 119.6 (q,  $^2J_{\text{CF}} = 30.5$  Hz), 118.5, 113.0, 110.1, 80.8, 69.2, 55.2, 47.5, 31.9, 29.3, 29.0, 28.3, 25.9, 22.8, 21.9, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{25}\text{H}_{34}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 520.2399, Found: 520.2420.

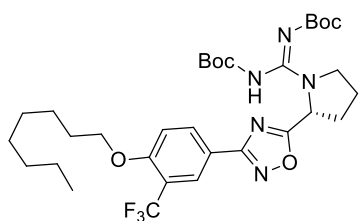


**(R)-2-(3-(4-(Octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 93% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.20 (d,  $J = 6.7$  Hz, 2H), 7.25 (d,  $J = 9.4$  Hz, 1H), 5.15 (t,  $J = 7.8$  Hz, 1H), 4.11 (t,  $J = 6.2$  Hz, 2H), 3.59 – 3.44 (m, 2H), 2.65 - 2.58 (m, 1H), 2.41-2.33 (m, 1H), 2.28 – 2.15 (m, 2H), 1.77 (p,  $J = 6.5$  Hz, 2H), 1.45 (p,  $J = 7.2$  Hz, 2H), 1.36-1.18 (m, 8H), 0.83 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  176.2, 168.7, 161.0, 134.0, 127.2 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 272.3$  Hz), 120.3 (q,  $^2J_{\text{CF}} = 31.3$  Hz), 118.9, 114.8, 70.3, 55.4, 47.3, 32.9, 30.3, 30.2, 30.2, 30.0, 26.9, 24.5, 23.6, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.5 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{29}\text{F}_3\text{N}_3\text{O}_2^+$  [M+]: 412.2212, Found: 412.2198.



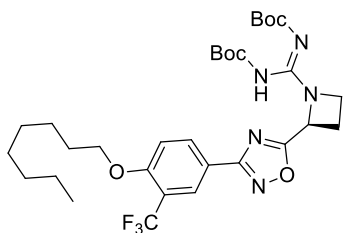
**(S)-2-(3-(4-(Octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 98% yield, yellow oil;  $^1\text{H}$  NMR (400

MHz, Methanol-d<sub>4</sub>)  $\delta$  8.25 (dd,  $J$ = 5.9, 2.1 Hz, 2H), 7.29 (d,  $J$  = 9.3 Hz, 1H), 5.90 (t,  $J$  = 8.5 Hz, 1H), 4.33-4.23 (m, 1H), 4.20 – 4.11 (m, 3H), 3.15-2.93 (m, 2H), 1.84-1.73 (m, 2H), 1.47 (p,  $J$ = 7.1 Hz, 2H), 1.39-1.19 (m, 8H), 0.85 (t,  $J$ = 7.0 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Methanol-d<sub>4</sub>)  $\delta$  175.6, 168.9, 161.0, 134.0, 127.3 (q, <sup>3</sup> $J_{CF}$  = 5.4 Hz), 124.7 (q, <sup>1</sup> $J_{CF}$  = 272.4 Hz), 120.3 (q, <sup>2</sup> $J_{CF}$  = 31.2 Hz), 119.0, 114.8, 70.3, 54.1, 45.9, 32.9, 30.3, 30.2, 30.0, 26.9, 25.3, 23.7, 14.4; <sup>19</sup>F NMR (376 MHz, Methanol-d<sub>4</sub>)  $\delta$  -63.7 (s, 3F); HRMS (ESI<sup>+</sup>): Calcd for C<sub>20</sub>H<sub>27</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 398.2055, Found: 398.2085.

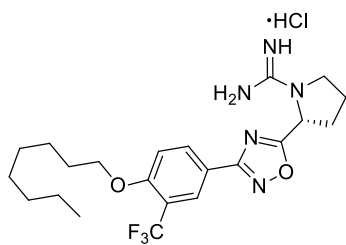


**(R)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.** Synthesized by general procedure 3-E. 51% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  8.28 (d,  $J$  = 2.0 Hz, 1H), 8.18 (dd,  $J$  = 8.7, 2.1 Hz, 1H), 7.05 (d,  $J$  = 8.8 Hz, 1H), 5.62 (dd,  $J$  = 7.7, 4.5 Hz, 1H), 4.11 (t,  $J$ = 6.4 Hz, 2H), 3.96-3.86 (m, 1H), 3.84 – 3.77 (m, 1H), 2.49 – 2.40 (m, 1H), 2.25-2.15 (m, 2H), 2.08-2.00 (m, 1H), 1.84 (p,  $J$ = 6.3 Hz, 2H), 1.52-1.42 (m, 20H), 1.38-1.24 (m, 8H), 0.88 (t,  $J$ = 6.4 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d)  $\delta$  178.9, 167.4, 159.4, 155.5, 153.6, 132.6, 126.9 (q, <sup>3</sup> $J_{CF}$  = 5.2 Hz), 123.4 (q, <sup>1</sup> $J_{CF}$  = 273.9 Hz), 119.5 (q, <sup>2</sup> $J_{CF}$  = 31.5 Hz), 118.5, 113.0, 81.5, 69.2, 55.6, 49.9, 31.9, 31.5, 29.3, 29.0, 28.2, 28.1, 25.9, 24.2, 22.8, 14.2; <sup>19</sup>F NMR (376 MHz, Chloroform-d)  $\delta$  -65.7 (s, 3F); HRMS (ESI<sup>+</sup>): Calcd for C<sub>32</sub>H<sub>47</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub> [M+H]: 654.3479, Found: 654.3471.



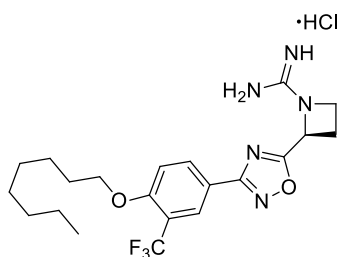


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetid-1-yl)methylene)carbamate.** Synthesized by general procedure 3-E. 59% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  10.85 (s, 1H), 8.29 (d,  $J = 1.9$  Hz, 1H), 8.19 (dd,  $J = 8.7, 2.1$  Hz, 1H), 7.06 (d,  $J = 8.8$  Hz, 1H), 4.64 (d,  $J = 7.5$  Hz, 1H), 4.23-4.16 (m, 1H), 4.11 (t,  $J = 6.4$  Hz, 2H), 2.90-2.79 (m, 1H), 2.62 – 2.52 (m, 1H), 1.92-1.76 (m, 2H), 1.54-1.22 (m, 28H), 0.88 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  177.5, 167.6, 162.8, 159.4, 155.4, 149.7, 132.6, 126.9, 123.3 (q,  $^1J_{\text{CF}} = 275.9$  Hz), 119.5 (q,  $^2J_{\text{CF}} = 31.2$  Hz), 118.3, 113.0, 82.6, 79.9, 69.2, 58.2, 50.0, 31.9, 29.3, 29.0, 28.2, 25.9, 22.7, 22.5, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{45}\text{F}_3\text{N}_5\text{O}_6$  [M+H]: 640.3322, Found: 640.3383.

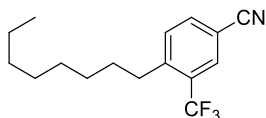


**(R)-Amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.20a).** Synthesized by general procedure 3-F. 62% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.28 (dd,  $J = 8.7, 2.1$  Hz, 1H), 8.26 (d,  $J = 2.0$  Hz, 1H), 7.37 (d,  $J = 8.7$  Hz, 1H), 5.49 (dd,  $J = 7.9, 1.7$  Hz, 1H), 4.22 (t,  $J = 6.2$  Hz, 2H), 3.82 (td,  $J = 7.3, 2.4$  Hz, 1H), 3.66 (q,  $J = 9.0$  Hz, 1H), 2.68 – 2.46 (m, 2H), 2.34-2.22 (m, 1H), 2.20 – 2.07 (m, 1H), 1.88 (p,  $J = 6.1$  Hz, 2H), 1.56 (p,  $J = 7.0$  Hz, 2H), 1.48-1.30 (m, 8H), 0.94 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$

NMR (101 MHz, Methanol-d<sub>4</sub>)  $\delta$  179.2, 168.6, 160.9, 157.1, 133.9, 127.1 (q,  $^3J_{CF} = 5.4$  Hz), 124.7 (q,  $^1J_{CF} = 273.1$  Hz), 120.3 (q,  $^2J_{CF} = 31.4$  Hz), 119.3, 114.8, 70.3, 56.5, 32.9, 32.7, 30.3, 30.2, 30.0, 26.9, 24.3, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol-d<sub>4</sub>)  $\delta$  -63.7 (s, 3F); HRMS (ESI<sup>+</sup>): Calcd for C<sub>22</sub>H<sub>31</sub>F<sub>3</sub>N<sub>5</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 454.2430, Found: 454.2430.

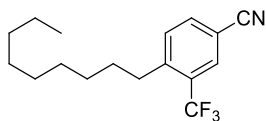


**(S)-Amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methaniminium chloride (3.20b).** Synthesized by general procedure 3-F. 89% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  8.30 (m, 2H), 7.34 (d,  $J = 8.6$  Hz, 1H), 5.86 (dd,  $J = 9.1, 5.0$  Hz, 1H), 4.39 (q,  $J = 8.3$  Hz, 1H), 4.28 (q,  $J = 8.4$  Hz, 1H), 4.18 (t,  $J = 6.1$  Hz, 2H), 3.16-3.00 (m, 1H), 2.70 – 2.57 (m, 1H), 1.91-1.78 (m, 2H), 1.52 (p,  $J = 7.1$  Hz, 2H), 1.44-1.23 (m, 8H), 0.90 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol-d<sub>4</sub>)  $\delta$  178.5, 168.7, 160.9, 158.5, 134.0, 127.1 (q,  $^3J_{CF} = 5.4$  Hz), 124.7 (q,  $^1J_{CF} = 273.1$  Hz), 120.3 (q,  $^2J_{CF} = 32.1$  Hz), 119.3, 114.9, 70.3, 58.4, 51.0, 32.9, 30.3, 30.2, 30.0, 26.9, 23.7, 23.0, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol-d<sub>4</sub>)  $\delta$  -63.7 (s, 3F); HRMS (ESI<sup>+</sup>): Calcd for C<sub>21</sub>H<sub>29</sub>F<sub>3</sub>N<sub>5</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 440.2273, Found: 440.2270.

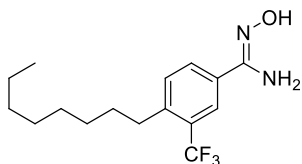


**4-Octyl-3-(trifluoromethyl)benzonitrile (3.22a).** Synthesized by general procedure 3-I. 47% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.89 (d,  $J = 1.2$  Hz, 1H), 7.74 (dd,  $J = 8.0, 1.6$  Hz, 1H), 7.47 (d,  $J = 8.0$  Hz, 1H), 2.82 (t,  $J = 7.6$  Hz, 2H), 1.62 (p,  $J = 8.0$  Hz, 2H), 1.39 (p,  $J = 6.8$  Hz, 2H), 1.35-1.22 (m, 8H), 0.88 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  147.7

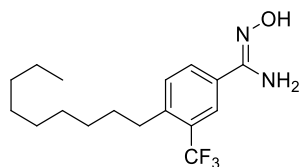
(q,  $^4 J_{CF} = 1.5$  Hz), 135.0, 132.1, 129.9 (q,  $^3 J_{CF} = 5.9$  Hz), 129.8 (q,  $^2 J_{CF} = 31.2$  Hz), 123.5 (q,  $^1 J_{CF} = 276.5$  Hz), 117.9, 110.3, 33.0 (q,  $^4 J_{CF} = 1.8$  Hz), 31.9, 31.5, 31.5, 29.7, 29.4, 29.3, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -63.5 (s, 3F).



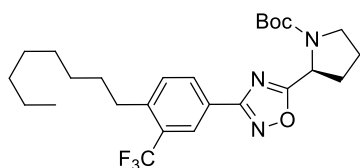
**4-Nonyl-3-(trifluoromethyl)benzonitrile (3.22b).** Synthesized by general procedure 3-I. 19% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.89 (s, 1H), 7.74 (dd,  $J = 8.4, 0.4$  Hz, 1H), 7.47 (d,  $J=8.0$  Hz, 1H), 2.82 (t,  $J= 8.4$  Hz, 2H), 1.61 (p,  $J= 8.0$  Hz, 2H), 1.45-1.20 (m, 12H), 0.87 (t,  $J= 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  147.7, 135.0, 132.1, 129.9 (q,  $^3 J_{CF} = 6.0$  Hz), 129.7, 123.5 (q,  $^1 J_{CF} = 275.5$  Hz), 117.8, 110.3, 33.0, 32.0, 31.5, 29.7, 29.6, 29.4, 29.4, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -63.5 (s, 3F).



**(Z)-Hydroxy-4-octyl-3-(trifluoromethyl)benzimidamide.** Synthesized by general procedure 3-B. 84% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.92 (d,  $J = 1.8$  Hz, 1H), 7.78 (dd,  $J = 8.1, 1.5$  Hz, 1H), 7.44 (d,  $J = 8.1$  Hz, 1H), 2.78 (t,  $J= 7.9$  Hz, 2H), 1.61 (p,  $J= 8.2$  Hz, 2H), 1.45-1.24 (m, 10H), 0.89 (t,  $J= 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  154.1, 147.7 (q,  $^4 J_{CF} = 1.4$  Hz), 132.5, 132.3, 130.6, 130.0, 129.3 (q,  $^2 J_{CF} = 29.7$  Hz), 128.5 (q,  $^1 J_{CF} = 274.5$  Hz), 124.7 (q,  $^3 J_{CF} = 5.9$  Hz), 33.5, 33.0, 32.9, 30.8, 30.5, 30.3, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -60.5 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{16}\text{H}_{24}\text{F}_3\text{N}_2\text{O}$  [M+H]: 317.1841, Found: 317.1836.

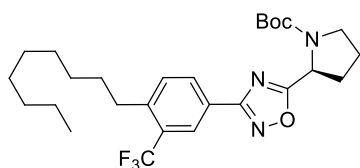


**(Z)-N'-Hydroxy-4-nonyl-3-(trifluoromethyl)benzimidamide.** Synthesized by general procedure 3-B. 86% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.92 (s, 1H), 7.79 (d,  $J = 8.0$  Hz, 1H), 7.44 (d,  $J = 8.1$  Hz, 1H), 2.78 (t,  $J = 8.0$  Hz, 2H), 1.62 (p,  $J = 8.5$  Hz, 2H), 1.46-1.22 (m, 12H), 0.90 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  154.1, 144.3 (q,  $^4J_{\text{CF}} = 1.6$  Hz), 132.5, 132.3, 130.6 (q,  $^4J_{\text{CF}} = 0.9$  Hz), 129.3 (q,  $^2J_{\text{CF}} = 29.9$  Hz), 128.7 (q,  $^1J_{\text{CF}} = 274.6$  Hz), 124.7 (q,  $^3J_{\text{CF}} = 5.9$  Hz), 33.5, 33.0, 32.9, 30.7, 30.6, 30.5, 30.4, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -60.5 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{17}\text{H}_{26}\text{F}_3\text{N}_2\text{O}$  [M+H]: 331.1997, Found: 331.1974.

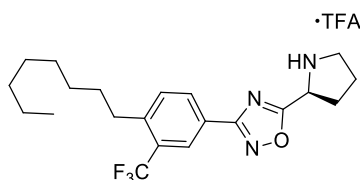


**(S)-Tert-butyl 2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate.** Synthesized by general procedure 3-C. 65% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.31 (s, 1H), 8.14 (d,  $J = 7.8$  Hz, 1H), 7.44 (t,  $J = 9.3$  Hz, 1H), 5.27-5.00 (m, 1H), 3.78 – 3.63 (m, 1H), 3.60 – 3.47 (m, 1H), 2.81 (t,  $J = 8.2$  Hz, 2H), 2.46 – 2.32 (m, 1H), 2.22 – 2.08 (m, 2H), 2.08-1.94 (m, 1H), 1.63 (p,  $J = 7.3$  Hz, 2H), 1.46 (s, 3H), 1.43-1.23 (m, 18H), 0.87 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  181.1, 167.6, 153.6, 145.3, 131.8, 130.4, 129.3 (q,  $^2J_{\text{CF}} = 30.7$  Hz), 127.0 (q,  $^1J_{\text{CF}} = 274.8$  Hz), 125.2 (q,  $^3J_{\text{CF}} = 5.8$  Hz), 124.9, 124.6, 122.9, 110.2, 80.6, 53.9, 46.5, 32.9, 32.5, 32.0, 31.7, 31.6, 29.8, 29.5, 29.3, 28.5, 28.3, 24.5, 23.8, 22.8, 14.2;  $^{19}\text{F}$

NMR (376 MHz, Chloroform-d)  $\delta$  -63.0 (d,  $J=11.9$  Hz, 3F); HRMS (ESI+): Calcd for  $C_{26}H_{36}F_3N_3O_3Na$  [M+Na]: 518.2606, Found: 518.2594.

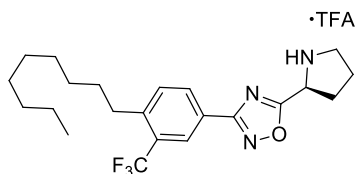


**(S)-Tert-butyl 2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate.** Synthesized by general procedure 3-C. 54% yield, colorless oil;  $^1H$  NMR (400 MHz, Chloroform-d)  $\delta$  8.32 (s, 1H), 8.15 (d,  $J=7.7$  Hz, 1H), 7.45 (d,  $J=8.2$  Hz, 1H), 5.22-5.04 (m, 1H), 3.76 – 3.63 (m, 1H), 3.61 – 3.45 (m, 1H), 2.81 (t,  $J=7.0$  Hz, 2H), 2.46 – 2.33 (m, 1H), 2.22 – 2.09 (m, 2H), 2.08-1.96 (m, 1H), 1.68-1.58 (m, 2H), 1.46 (s, 3H), 1.35-1.21 (m, 18H), 0.88 (t,  $J=6.7$  Hz, 3H);  $^{13}C$  NMR (101 MHz, Chloroform-d)  $\delta$  181.1, 167.6, 153.6, 145.4, 131.8, 130.4, 125.2 (q,  $^3J_{CF}=5.3$  Hz), 125.6 (q,  $^3J_{CF}=6.1$  Hz), 124.9, 124.3 (q,  $^1J_{CF}=274.8$  Hz), 124.1, 119.2, 80.7, 53.9, 46.5, 32.9, 32.6, 32.0, 31.7, 30.3, 29.8, 29.6, 29.5, 29.4, 28.3, 23.9, 22.8, 14.3;  $^{19}F$  NMR (376 MHz, Chloroform-d)  $\delta$  -63.0 (d,  $J=11.8$  Hz, 3F); HRMS (ESI+): Calcd for  $C_{27}H_{38}F_3N_3O_3Na$  [M+Na]: 532.2763, Found: 532.2763.

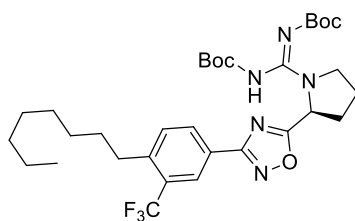


**(S)-2-(3-(4-Octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, yellow oil;  $^1H$  NMR (400 MHz, Chloroform-d)  $\delta$  8.24 (s, 1H), 8.07 (d,  $J=8.1$  Hz, 1H), 7.44 (d,  $J=8.1$  Hz, 1H), 5.19 (t,  $J=7.8$  Hz, 1H), 3.76 – 3.56 (m, 2H), 2.81 (t,  $J=7.4$  Hz, 1H), 2.73 - 2.64 (m, 1H), 2.51-2.43 (m, 1H), 2.35 – 2.22 (m, 2H), 1.63 (p,  $J=7.8$  Hz, 2H), 1.46-1.20 (m, 10H), 0.88 (t,  $J=6.8$  Hz, 3H);  $^{13}C$  NMR (101 MHz, Chloroform-d)  $\delta$  174.6, 167.7, 146.2, 131.9, 130.5, 129.4 (q,  $^2J_{CF}=30.7$  Hz),

125.3 (q,  $^3J_{CF} = 5.7$  Hz), 124.2 (q,  $^1J_{CF} = 275.1$  Hz), 123.3, 77.4, 54.3, 46.5, 32.9, 32.0, 31.6, 30.1, 29.8, 29.5, 29.3, 24.0, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -60.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{29}\text{F}_3\text{N}_3\text{O}^+ [\text{M}^+]$ : 396.2262, Found: 396.2271.

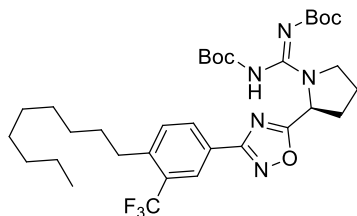


**(S)-2-(3-(4-Nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, colorless oil;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.32 (s, 1H), 8.24 (d,  $J=8.0$  Hz, 1H), 7.62 (d,  $J = 8.1$  Hz, 1H), 5.18 (t,  $J = 7.8$  Hz, 1H), 3.62 – 3.48 (m, 2H), 2.84 (t,  $J= 7.9$  Hz, 2H), 2.71 - 2.60 (m, 1H), 2.47-2.35 (m, 1H), 2.31 – 2.18 (m, 2H), 1.65 (p,  $J= 6.6$  Hz, 2H), 1.48-1.21 (m, 12H), 0.88 (t,  $J= 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.6, 168.8, 147.1, 133.6, 131.7, 130.2 (q,  $^2J_{CF} = 30.6$  Hz), 125.9 (q,  $^3J_{CF} = 5.8$  Hz), 125.6 (q,  $^1J_{CF} = 274.3$  Hz), 125.4, 125.2, 120.0, 55.5, 47.4, 33.7, 33.0, 32.8, 31.8, 30.7, 30.6, 30.5, 30.4, 30.2, 24.6, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -61.0 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{31}\text{F}_3\text{N}_3\text{O}^+ [\text{M}^+]$ : 410.2419, Found: 410.2451.

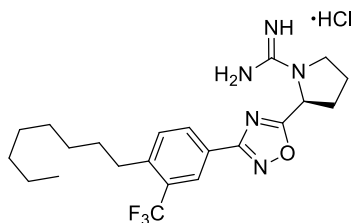


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.** Synthesized by general procedure 3-E. 56% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  10.11 (s, 1H), 8.31 (d,  $J = 1.6$  Hz, 1H), 8.14 (dd,  $J = 8.0, 1.6$  Hz, 1H), 7.43 (d,  $J = 8.1$  Hz, 1H), 5.61 (dd,  $J = 7.8, 4.5$  Hz, 1H), 3.94-3.87 (m, 1H), 3.84 – 3.75 (m, 1H), 2.81 (t,  $J= 7.1$  Hz, 2H), 2.50 – 2.40 (m, 1H), 2.27-2.13 (m, 2H),

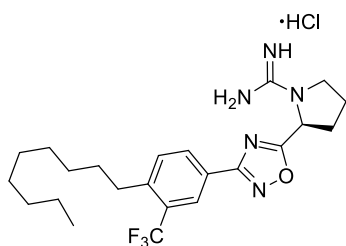
2.12-1.98 (m, 1H), 1.63 (p,  $J = 8.8$  Hz, 2H), 1.51-1.19 (m, 28H), 0.88 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  179.5, 167.6, 162.0, 159.4, 153.8, 150.5, 145.3, 131.7, 130.5, 129.2 (q,  $^2J_{\text{CF}} = 30.5$  Hz), 125.4 (q,  $^3J_{\text{CF}} = 5.8$  Hz), 124.7, 124.3 (q,  $^1J_{\text{CF}} = 275.3$  Hz), 82.4, 79.7, 55.4, 49.6, 32.9, 32.0, 31.7, 29.8, 29.5, 29.3, 28.2, 24.1, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -62.9 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{47}\text{F}_3\text{N}_5\text{O}_5$  [M+H]: 638.3529, Found: 638.3507.



**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.** Synthesized by general procedure 3-E. 50% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  10.11 (s, 1H), 8.31 (s, 1H), 8.14 (d,  $J = 8.0$  Hz, 1H), 7.44 (d,  $J = 8.1$  Hz, 1H), 5.61 (dd,  $J = 7.7, 4.5$  Hz, 1H), 3.95-3.85 (m, 1H), 3.84 – 3.75 (m, 1H), 2.81 (t,  $J = 7.8$  Hz, 2H), 2.52 – 2.40 (m, 1H), 2.27-2.14 (m, 2H), 2.09-1.99 (m, 1H), 1.68-1.19 (m, 31H), 0.88 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  179.5, 167.6, 162.6, 158.9, 153.8, 150.5, 145.3, 131.7, 130.5, 129.2 (q,  $^2J_{\text{CF}} = 30.2$  Hz), 125.4 (q,  $^3J_{\text{CF}} = 5.7$  Hz), 124.6, 124.3 (q,  $^1J_{\text{CF}} = 275.1$  Hz), 82.5, 79.8, 55.4, 49.6, 32.9, 32.0, 31.7, 29.8, 29.6, 29.5, 29.4, 28.2, 24.3, 22.8, 14.3;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -62.9 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{33}\text{H}_{49}\text{F}_3\text{N}_5\text{O}_5$  [M+H]: 652.3686, Found: 652.3743.

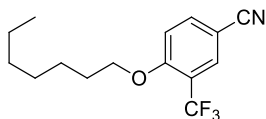


**(S)-Amino(2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.23a).** Synthesized by general procedure 3-F. 89% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.30 (s, 1H), 8.23 (d,  $J = 7.9$  Hz, 1H), 7.62 (d,  $J = 8.0$  Hz, 1H), 5.60 (d,  $J = 7.6$  Hz, 1H), 3.86 (t,  $J = 8.5$  Hz, 1H), 3.71 (q,  $J = 9.2$  Hz, 1H), 2.86 (t,  $J = 8.8$  Hz, 2H), 2.70 – 2.61 (m, 1H), 2.56-2.49 (m, 1H), 2.39-2.24 (m, 1H), 2.22 – 2.07 (m, 1H), 1.68 (p,  $J = 7.6$  Hz, 2H), 1.51-1.25 (m, 10H), 0.93 (t,  $J = 6.5$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.4, 168.5, 157.1, 146.6, 133.3, 131.7, 129.9 (q,  $^2J_{\text{CF}} = 30.3$  Hz), 125.7, 125.7 (q,  $^3J_{\text{CF}} = 5.9$  Hz), 125.6 (q,  $^1J_{\text{CF}} = 274.7$  Hz), 56.4, 49.1, 33.7, 32.9, 32.7, 30.7, 30.4, 30.3, 24.3, 23.6, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -60.6 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{22}\text{H}_{31}\text{F}_3\text{N}_5\text{O}^+ [\text{M}^+]$ : 438.2481, Found: 438.2484.

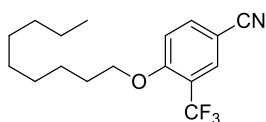


**(S)-Amino(2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.23b).** Synthesized by general procedure 3-F. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.28 (s, 1H), 8.21 (dd,  $J = 8.1, 1.5$  Hz, 1H), 7.62 (d,  $J = 8.1$  Hz, 1H), 5.46 (dd,  $J = 7.9, 1.8$  Hz, 1H), 3.79 (td,  $J = 9.4, 2.5$  Hz, 1H), 3.67-3.58 (m, 1H), 2.85 (t,  $J = 8.1$  Hz, 2H), 2.63 – 2.47 (m, 2H), 2.28-2.19 (m, 1H), 2.15 – 2.05 (m, 1H), 1.66 (p,  $J = 7.1$  Hz, 2H), 1.49-1.24 (m, 12H), 0.90 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  179.4, 168.7, 157.1, 146.9, 133.5, 131.7, 130.1 (q,  $^2J_{\text{CF}} = 30.2$  Hz), 125.7 (q,  $^3J_{\text{CF}} = 5.2$  Hz), 125.7 (q,  $^1J_{\text{CF}} = 273.8$  Hz), 56.5, 33.7, 33.0, 32.8, 32.7, 30.7, 30.6, 30.4, 30.4, 28.1, 24.3, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -60.8 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{23}\text{H}_{33}\text{F}_3\text{N}_5\text{O}^+ [\text{M}^+]$ : 452.2637, Found: 452.2626.

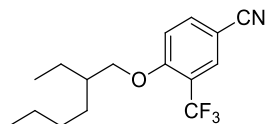




**4-(Heptyloxy)-3-(trifluoromethyl)benzonitrile (3.25a).** Synthesized by general procedure 3-G. 62% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.81 (d,  $J = 1.9$  Hz, 1H), 7.75 (dd,  $J = 8.7, 2.1$  Hz, 1H), 7.06 (d,  $J=8.7$  Hz, 1H), 4.11 (t,  $J=6.3$  Hz, 2H), 1.88-1.77 (m, 2H), 1.46 (p,  $J=6.7$  Hz, 2H), 1.40-1.21 (m, 6H), 0.86 (t,  $J=6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  160.3, 137.5, 131.3 (q,  $^3 J_{\text{CF}} = 5.3$  Hz), 122.4 (q,  $^1 J_{\text{CF}} = 272.8$  Hz), 120.1 (q,  $^2 J_{\text{CF}} = 32.1$  Hz), 117.9, 113.5, 103.5, 69.5, 31.7, 28.8, 28.7, 25.6, 22.5, 14.0;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -66.4 (s, 3F).

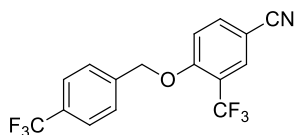


**4-(Nonyloxy)-3-(trifluoromethyl)benzonitrile (3.25b).** Synthesized by general procedure 3-A. 100% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.84 (d,  $J = 2.0$  Hz, 1H), 7.77 (dd,  $J = 8.6, 2.1$  Hz, 1H), 7.05 (d,  $J=8.7$  Hz, 1H), 4.11 (t,  $J=6.4$  Hz, 2H), 1.89-1.78 (m, 2H), 1.47 (p,  $J=7.3$  Hz, 2H), 1.39-1.15 (m, 10H), 0.87 (t,  $J=6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  160.4, 137.6, 131.5 (q,  $^3 J_{\text{CF}} = 5.4$  Hz), 122.4 (q,  $^1 J_{\text{CF}} = 274.8$  Hz), 120.2 (q,  $^2 J_{\text{CF}} = 32.1$  Hz), 118.1, 113.4, 103.6, 69.6, 32.0, 29.5, 29.3, 29.3, 28.8, 25.8, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -66.4 (s, 3F).



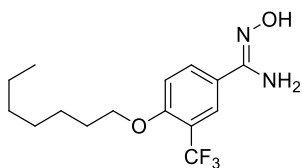
**4-((2-Ethylhexyl)oxy)-3-(trifluoromethyl)benzonitrile (3.25c).** Synthesized by general procedure 3-G. 78% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.80 (d,  $J = 1.9$  Hz, 1H), 7.76 (dd,  $J = 8.7, 2.1$  Hz, 1H), 7.09 (d,  $J = 8.7$  Hz, 1H), 4.00 (d,  $J = 5.3$  Hz, 2H), 1.78-1.72 (m,

1H), 1.52-1.37 (m, 4H), 1.31-1.26 (m, 4H), 0.88 (dt,  $J = 14.6, 7.3$  Hz, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  160.4, 137.5, 131.2 (q,  $^3 J_{\text{CF}} = 5.4$  Hz), 122.5 (q,  $^1 J_{\text{CF}} = 274.2$  Hz), 119.9 (q,  $^2 J_{\text{CF}} = 32.2$  Hz), 118.0, 113.3, 103.3, 71.4, 39.2, 30.1, 28.9, 23.6, 22.9, 13.9, 11.0;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -66.4 (s, 3F).

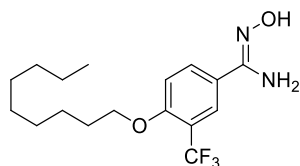


**3-(Trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)benzonitrile (3.25d).** (4-

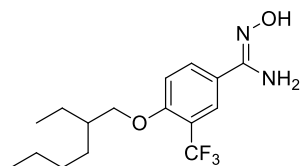
(Trifluoromethyl)phenyl)methanol (100 mg, 0.57 mmol) was stirred in THF (3 mL). Triphenylphosphine (194 mg, 0.74 mmol) and 4-hydroxy-3-(trifluoromethyl)benzonitrile **1** (319 mg, 1.70 mmol) were added to the solution. The mixture was then cooled to 0 °C. Once cooled, DIAD (1.42 mL, 0.57 mmol) was added dropwise (40% in toluene). The mixture was refluxed 3-4 hours. Reaction was checked for completion. After completed, the mixture was cooled to room temperature and concentrated *via* vacuum. The residue was purified by silica gel column chromatography (15%, ethyl acetate/ hexanes) to yield **3.25c** (152 mg, 78%) as an oil.  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.90 (d,  $J = 1.8$  Hz, 1H), 7.79 (dd,  $J = 8.7, 2.1$  Hz, 1H), 7.67 (d,  $J = 8.4$  Hz, 2H), 7.55 (d,  $J = 8.7$  Hz, 2H), 7.12 (d,  $J = 8.7$  Hz, 1H), 5.31 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  159.23, 138.96, 137.72, 131.7 ( $^3 J_{\text{CF}} = 5.3$  Hz), 130.8 ( $^2 J_{\text{CF}} = 30.2$  Hz), 126.9, 125.9 ( $^3 J_{\text{CF}} = 3.8$  Hz), 123.7 ( $^1 J_{\text{CF}} = 274.7$  Hz), 122.2 ( $^1 J_{\text{CF}} = 274.3$  Hz), 120.5 (q,  $^2 J_{\text{CF}} = 33.4$  Hz), 117.7, 113.9, 110.0, 104.8, 70.1;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.7 (s, 3F), -66.2 (s, 3F).



**(Z)-4-(Heptyloxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide (3.26a).** Synthesized by general procedure 3-B. 83% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.03 (d,  $J$  = 2.0 Hz, 1H), 7.97 (dd,  $J$  = 8.7, 2.2 Hz, 1H), 6.99 (d,  $J$  = 8.7 Hz, 1H), 6.30 (s, 2H), 4.08 (t,  $J$  = 6.4 Hz, 2H), 1.85-1.78 (m, 2H), 1.46 (p,  $J$  = 7.2 Hz, 2H), 1.40-1.22 (m, 6H), 0.88 (t,  $J$  = 6.8 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  158.4, 151.9, 131.0, 125.1 (q,  $^3J_{\text{CF}}$  = 5.3 Hz), 124.2, 123.6 (q,  $^1J_{\text{CF}}$  = 274.2 Hz), 119.1 (q,  $^2J_{\text{CF}}$  = 31.2 Hz), 112.9, 69.1, 31.8, 29.1, 29.0, 25.9, 22.7, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -62.3 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{15}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_2$  [M+H]: 319.1633, Found: 319.1635.

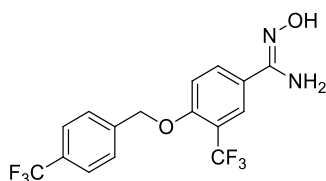


**(Z)-Hydroxy-4-(nonyloxy)-3-(trifluoromethyl)benzimidamide (3.26b).** Synthesized by general procedure 3-B. 61% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.89 (d,  $J$  = 2.3 Hz, 1H), 7.83 (dd,  $J$  = 8.7, 2.3 Hz, 1H), 7.18 (d,  $J$  = 8.7 Hz, 1H), 4.13 (t,  $J$  = 6.2 Hz, 2H), 1.88-1.76 (m, 2H), 1.52 (p,  $J$  = 7.3 Hz, 2H), 1.44-1.28 (m, 10H), 0.92 (t,  $J$  = 6.9 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  159.3, 154.1, 132.4, 125.9 (q,  $^3J_{\text{CF}}$  = 5.5 Hz), 124.9 (q,  $^1J_{\text{CF}}$  = 271.4 Hz), 119.5 (q,  $^2J_{\text{CF}}$  = 30.7 Hz), 113.9, 69.9, 33.0, 30.6, 30.3, 30.1, 26.9, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.3 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{17}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_2$  [M+H]: 347.1946, Found: 347.1929.

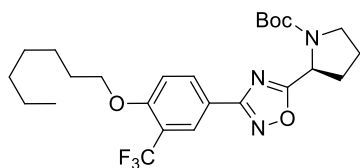


**(Z)-4-((2-Ethylhexyl)oxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide (3.26c).** Synthesized by general procedure 3-B. 54% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )

$\delta$  7.85 (d,  $J = 2.1$  Hz, 1H), 7.78 (dd,  $J = 8.7, 2.2$  Hz, 1H), 7.10 (d,  $J = 8.7$  Hz, 1H), 3.95 (d,  $J = 5.1$  Hz, 2H), 1.70-1.64 (m, 1H), 1.52-1.35 (m, 4H), 1.30-1.23 (m, 4H), 0.92-0.82 (m, 6H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  159.4, 154.1, 132.5, 125.9 (q,  $^3J_{\text{CF}} = 5.0$  Hz), 125.9, 124.9 (q,  $^1J_{\text{CF}} = 272.2$  Hz), 119.4 (q,  $^2J_{\text{CF}} = 30.1$  Hz), 113.7, 71.8, 49.8, 40.7, 31.4, 30.1, 24.8, 24.0, 14.3, 11.5; HRMS (ESI+): Calcd for  $\text{C}_{16}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_2$  [M+H]: 333.1790, Found: 333.1774.

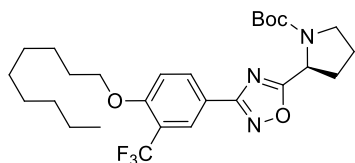


**(Z)-N'-Hydroxy-3-(trifluoromethyl)-4-((4-(trifluoromethyl) benzyl) oxy) benzimidamide (3.26d).** Synthesized by general procedure 3-B. 72% yield, white solid;  $^1\text{H}$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  7.93 (d,  $J = 2.1$  Hz, 1H), 7.83 (dd,  $J = 8.7, 2.2$  Hz, 1H), 7.69 (d,  $J = 8.3$  Hz, 2H), 7.65 (d,  $J = 8.3$  Hz, 2H), 7.25 (d,  $J = 8.7$  Hz, 1H), 5.34 (s, 2H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  158.4, 154.0, 142.3, 132.6, 131.1 (q,  $^2J_{\text{CF}} = 32.3$  Hz), 128.4, 127.0, 126.5 (q,  $^3J_{\text{CF}} = 3.8$  Hz), 126.2 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 125.6 (q,  $^1J_{\text{CF}} = 264$  Hz), 124.9 (q,  $^1J_{\text{CF}} = 277$  Hz), 119.9 (q,  $^2J_{\text{CF}} = 30.9$  Hz), 114.6; HRMS (ESI+): Calcd for  $\text{C}_{16}\text{H}_{13}\text{F}_6\text{N}_2\text{O}_2$  [M+H]: 379.0802, Found: 379.0905.

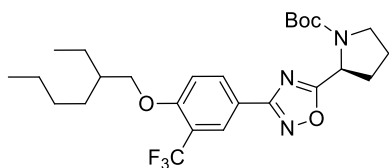


**(S)-Tert-butyl 2-(3-(4-(heptyloxy)-3-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate.** Synthesized by general procedure 3-C. 55% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.27 (s, 1H), 8.16 (d,  $J = 8.6$  Hz, 1H), 7.04 (t,  $J = 8.6$  Hz, 1H), 5.20-5.01 (m, 1H), 4.09 (t,  $J = 6.3$  Hz, 2H), 3.77 – 3.61 (m, 1H), 3.61 – 3.40 (m, 1H), 2.46 – 2.29 (m, 1H), 2.19 – 2.07 (m, 2H), 2.05-1.93 (m, 1H), 1.82 (p,  $J = 6.2$  Hz, 2H), 1.52-1.40 (m, 5H), 1.39-

1.23 (m, 12H), 0.87 (t,  $J=6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  180.9, 167.4, 159.3, 153.6, 132.5, 126.6, 123.3 (q,  $^1J_{\text{CF}}=274.3$  Hz), 119.5 (q,  $^2J_{\text{CF}}=31.7$  Hz), 118.6, 113.0, 80.5, 69.1, 53.9, 46.5, 32.5, 31.8, 29.0, 29.0, 28.2, 25.8, 24.5, 23.8, 22.6, 14.1.;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.8 (d,  $J=14.9$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{25}\text{H}_{34}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 520.2399, Found: 520.2419.

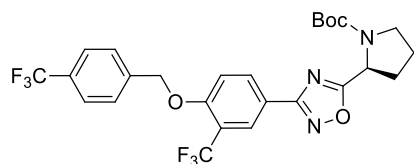


**(S)-Tert-butyl 2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate.** Synthesized by general procedure 3-C. 60% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.27 (s, 1H), 8.17 (d,  $J=8.6$  Hz, 1H), 7.05 (t,  $J=8.5$  Hz, 1H), 5.26-4.98 (m, 1H), 4.09 (t,  $J=6.3$  Hz, 2H), 3.77 – 3.61 (m, 1H), 3.60 – 3.41 (m, 1H), 2.45 – 2.28 (m, 1H), 2.21 – 2.07 (m, 2H), 2.04-1.94 (m, 1H), 1.82 (p,  $J=7.7$  Hz, 2H), 1.53-1.38 (m, 6H), 1.37-1.21 (m, 15H), 0.86 (t,  $J=6.6$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  180.9, 167.4, 159.3, 153.6, 132.5, 126.7, 123.3 (q,  $^1J_{\text{CF}}=273.3$  Hz), 119.6 (q,  $^2J_{\text{CF}}=31.9$  Hz), 118.6, 113.0, 80.6, 69.1, 53.9, 46.5, 32.0, 31.6, 29.6, 29.3, 29.3, 29.0, 28.5, 28.2, 25.8, 24.5, 23.8, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.8 (d,  $J=14.9$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{27}\text{H}_{38}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 548.2712, Found: 548.2705.

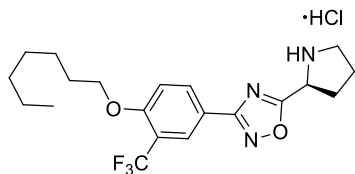


**(2S)-Tert-butyl 2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate.** Synthesized by general procedure 3-C. 66% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.26 (s, 1H), 8.17 (d,  $J=8.5$  Hz, 1H), 7.05 (t,  $J=9.1$  Hz, 1H),

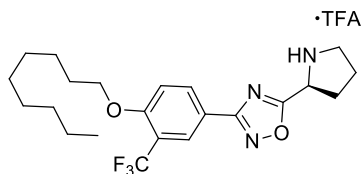
5.25-4.97 (m, 1H), 3.98 (d,  $J = 5.0$  Hz, 2H), 3.74 – 3.63 (m, 1H), 3.60 – 3.41 (m, 1H), 2.48 – 2.27 (m, 1H), 2.18 – 2.07 (m, 2H), 2.02-1.90 (m, 1H), 1.75 (p,  $J = 6.1$  Hz, 1H), 1.56-1.35 (m, 8H), 1.36-1.21 (m, 9H), 0.96-0.83 (m, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  180.9, 167.4, 159.5, 153.6, 132.5, 126.6 (q,  $^3J_{\text{CF}} = 5.5$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 273.5$  Hz), 119.4 (q,  $^2J_{\text{CF}} = 31.4$  Hz), 118.5, 112.8, 80.5, 71.0, 59.2, 53.9, 46.4, 39.4, 32.5, 31.6, 30.3, 29.0, 28.4, 28.4, 28.2, 24.5, 23.7, 23.0, 14.1, 11.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.8 (d,  $J = 15.5$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{36}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 534.2556, Found: 534.2600.



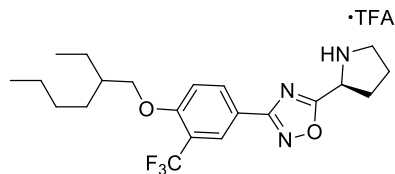
**(S)-Tert-butyl 2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate.** Synthesized by general procedure 3-C. 64% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.34 (s, 1H), 8.20 (d,  $J = 8.6$  Hz, 1H), 7.67 (d,  $J = 8.2$  Hz, 2H), 7.57 (d,  $J = 8.1$  Hz, 2H), 7.11 (t,  $J = 8.7$  Hz, 1H), 5.31 (s, 2H), 5.06 (dd,  $J = 8.1$ , 3.5 Hz, 1H), 3.77 – 3.63 (m, 1H), 3.62 – 3.42 (m, 1H), 2.49 – 2.31 (m, 1H), 2.22 – 1.96 (m, 3H), 1.46 (s, 3H), 1.30 (s, 6H).;  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  181.13, 167.22, 158.21, 153.63, 139.76, 132.66, 130.5 (q,  $^2J_{\text{CF}} = 30.3$  Hz), 127.0, 125.82 (t,  $^3J_{\text{CF}} = 3.8$  Hz), 124.3 (q,  $^1J_{\text{CF}} = 282.8$  Hz), 123.2 (q,  $^1J_{\text{CF}} = 363.6$  Hz), 119.7, 113.4, 80.6, 69.7, 53.9, 46.8, 46.5, 32.5, 31.6, 29.8, 28.5, 28.3, 24.5, 23.8, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.6 (d,  $J = 13.0$  Hz, 3F), -65.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{25}\text{F}_6\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 580.1646, Found: 580.1697.



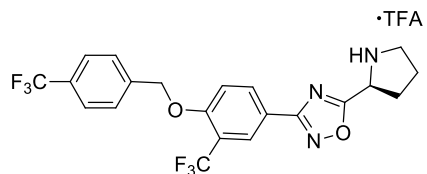
**(S)-2-(3-(4-(Heptyloxy)-3-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-ium chloride.** Synthesized by general procedure 3-F. 81% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.28 (d,  $J=8.8$  Hz, 2H), 7.35 (d,  $J = 8.5$  Hz, 1H), 5.23 (t,  $J = 7.8$  Hz, 1H), 4.19 (t,  $J= 6.2$  Hz, 2H), 3.67 – 3.50 (m, 2H), 2.74 - 2.65 (m, 1H), 2.48-2.39 (m, 1H), 2.33 – 2.24 (m, 2H), 1.87-1.80 (m, 2H), 1.52 (p,  $J= 7.8$  Hz, 2H), 1.44-1.28 (m, 6H), 0.91 (t,  $J= 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.2, 168.7, 161.0, 134.0, 127.2 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 273.0$  Hz), 120.3 (q,  $^2J_{\text{CF}} = 31.4$  Hz), 119.0, 114.9, 70.4, 55.6, 47.4, 32.9, 30.2, 30.0, 29.9, 26.9, 24.5, 23.6, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{27}\text{F}_3\text{N}_3\text{O}_2^+$  [M+]: 398.2055, Found: 398.2021.



**(S)-2-(3-(4-(Nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, clear solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.22 (d,  $J=6.5$  Hz, 2H), 7.27 (d,  $J = 9.1$  Hz, 1H), 5.15 (t,  $J = 7.7$  Hz, 1H), 4.12 (t,  $J= 4.9$  Hz, 2H), 3.59 – 3.45 (m, 2H), 2.66 - 2.57 (m, 1H), 2.43-2.32 (m, 1H), 2.27 – 2.15 (m, 2H), 1.84-1.71 (m, 2H), 1.51-1.40 (m, 2H), 1.25 (s, 10H), 0.87-0.80 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.3, 168.7, 161.0, 134.0, 127.2 (q,  $^3J_{\text{CF}} = 5.2$  Hz), 124.6 (q,  $^1J_{\text{CF}} = 273.4$  Hz), 120.3 (q,  $^2J_{\text{CF}} = 31.1$  Hz), 119.0, 114.8, 70.3, 55.4, 47.3, 33.0, 30.6, 30.2, 30.0, 26.9, 24.5, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.9 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{31}\text{F}_3\text{N}_3\text{O}_2^+$  [M+]: 426.2368, Found: 426.2350.



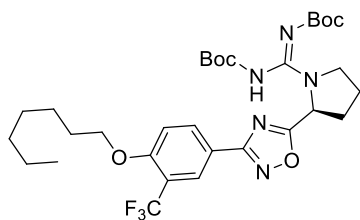
**(2S)-2-(3-(4-((2-Ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.18 (s, 1H), 8.10 (d,  $J = 8.4$  Hz, 1H), 7.04 (d,  $J = 8.7$  Hz, 1H), 5.13 (s, 1H), 3.99 (d,  $J = 5.3$  Hz, 2H), 3.65 (s, 1H), 3.59 (s, 1H), 2.68 - 2.58 (m, 1H), 2.50-2.40 (m, 1H), 2.26 (s, 2H), 1.77 (hep,  $J = 5.8$  Hz, 1H), 1.57-1.39 (m, 4H), 1.37-1.27 (m, 4H), 0.97-0.85 (m, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  174.4, 167.6, 159.9, 132.8, 126.7 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 273.9$  Hz), 119.5 (q,  $^2J_{\text{CF}} = 31.6$  Hz), 117.2, 112.9, 71.2, 59.4, 54.0, 53.7, 46.2, 39.4, 30.3, 30.0, 29.1, 28.8, 23.9, 23.8, 23.1, 14.1, 11.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -63.6 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{29}\text{F}_3\text{N}_3\text{O}_2 + [\text{M}^+]$ : 412.2212, Found: 412.2217.



**(S)-2-(3-(3-(Trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, yellow oil;  $^1\text{H}$  NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  8.31 – 8.25 (m, 2H), 7.66 (q,  $J = 8.4$  Hz, 4H), 7.42 (d,  $J = 8.6$  Hz, 1H), 5.39 (s, 2H), 5.18 (t,  $J = 7.8$  Hz, 1H), 3.65 – 3.42 (m, 2H), 2.65 (dtd,  $J = 13.5, 7.9, 5.8$  Hz, 1H), 2.40 (dq,  $J = 13.3, 7.7$  Hz, 1H), 2.31 – 2.15 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol-d<sub>4</sub>)  $\delta$  176.4, 168.6, 160.0, 141.9, 134.1, 131.25 (q,  $^2J_{\text{CF}} = 32.3$  Hz), 128.5, 127.4 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 126.5 (q,  $^3J_{\text{CF}} = 3.8$  Hz), 125.5 (q,  $^1J_{\text{CF}} = 272.7$  Hz), 124.6 (q,  $^1J_{\text{CF}} = 272.7$  Hz), 120.6 (q,  $^2J_{\text{CF}} = 31.5$  Hz), 119.9, 115.5, 70.9, 55.5, 47.3, 30.2, 24.5;  $^{19}\text{F}$  NMR (376 MHz,

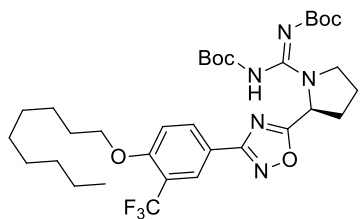


Methanol-d<sub>4</sub>)  $\delta$  -63.7 (s, 3F), -63.7 (s, 3F); HRMS (ESI<sup>+</sup>): Calcd for C<sub>21</sub>H<sub>18</sub>F<sub>6</sub>N<sub>3</sub>O<sub>2</sub><sup>+</sup> [M<sup>+</sup>]: 458.1303, Found: 458.1341.



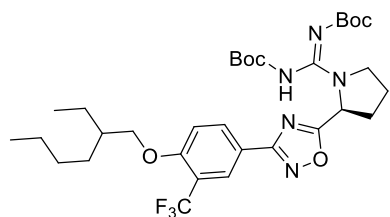
**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.**

Synthesized by general procedure 3-E. 71% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  10.10 (s, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 8.18 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 5.60 (dd, *J* = 7.8, 4.5 Hz, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 3.93-3.86 (m, 1H), 3.83 – 3.75 (m, 1H), 2.49 – 2.39 (m, 1H), 2.25-2.14 (m, 2H), 2.08-1.99 (m, 1H), 1.87-1.80 (m, 2H), 1.55-1.25 (m, 26H), 0.89 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-d)  $\delta$  179.3, 167.4, 162.1, 159.4, 153.8, 150.5, 132.6, 126.9 (q, <sup>3</sup>*J*<sub>CF</sub> = 5.2 Hz), 123.3 (q, <sup>1</sup>*J*<sub>CF</sub> = 273.4 Hz), 119.5 (q, <sup>2</sup>*J*<sub>CF</sub> = 31.6 Hz), 118.6, 113.0, 82.4, 79.7, 69.2, 55.4, 49.6, 31.8, 29.0, 29.0, 28.2, 28.2, 25.9, 22.7, 14.2; <sup>19</sup>F NMR (376 MHz, Chloroform-d)  $\delta$  -65.8 (s, 3F); HRMS (ESI<sup>+</sup>): Calcd for C<sub>31</sub>H<sub>45</sub>F<sub>3</sub>N<sub>5</sub>O<sub>6</sub> [M+H]: 640.3322, Found: 640.3321.



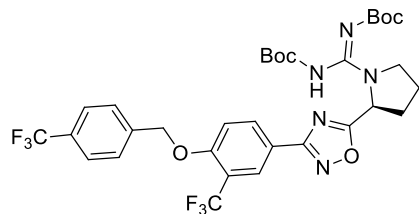
**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.** Synthesized by general procedure 3-E. 46% yield, colorless oil; <sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  10.09 (s, 1H), 8.28 (d, *J* = 1.6 Hz, 1H), 8.18 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 5.60 (dd, *J* = 7.7, 4.5 Hz, 1H),

4.11 (t,  $J= 6.3$  Hz, 2H), 3.93-3.86 (m, 1H), 3.81 (s, 1H), 2.49 – 2.40 (m, 1H), 2.26-2.15 (m, 2H), 2.08-2.00 (m, 1H), 1.84 (p,  $J= 7.0$  Hz, 2H), 1.46 (s, 19H), 1.39-1.23 (m, 11H), 0.88 (t,  $J= 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  179.3, 167.4, 162.1, 159.4, 153.8, 150.5, 132.6, 126.9 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 273.5$  Hz), 119.5 (q,  $^2J_{\text{CF}} = 32.2$  Hz), 118.6, 113.0, 82.4, 79.7, 69.2, 55.4, 49.6, 32.0, 31.62, 29.6, 29.3, 29.0, 28.2, 25.9, 24.2, 22.8, 14.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{33}\text{H}_{49}\text{F}_3\text{N}_5\text{O}_6$  [M+H]: 668.3635, Found: 668.3608.



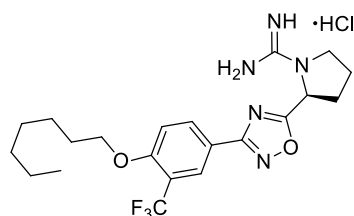
**Tert-butyl (((tert-butoxycarbonyl)amino)((2S)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.**

Synthesized by general procedure 3-E. 79% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  10.11 (s, 1H), 8.27 (d,  $J= 2.0$  Hz, 1H), 8.18 (dd,  $J = 8.7, 2.1$  Hz, 1H), 7.06 (d,  $J= 8.8$  Hz, 1H), 5.59 (dd,  $J= 7.8, 4.6$  Hz, 1H), 3.99 (d,  $J= 5.3$  Hz, 2H), 3.93 – 3.86 (m, 1H), 3.83-3.74 (m, 1H), 2.49 – 2.38 (m, 1H), 2.27 – 2.13 (m, 2H), 2.09-1.99 (m, 1H), 1.76 (p,  $J= 6.0$  Hz, 1H), 1.58-1.22 (m, 26H), 0.97-0.84 (m, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  179.2, 167.4, 162.2, 159.5, 153.8, 150.4, 132.6, 126.9 (q,  $^3J_{\text{CF}} = 5.2$  Hz), 123.4 (q,  $^1J_{\text{CF}} = 274.0$  Hz), 119.4 (q,  $^2J_{\text{CF}} = 31.5$  Hz), 118.5, 112.7, 82.3, 79.8, 71.1, 55.4, 49.6, 31.5, 30.4, 29.1, 28.2, 28.1, 24.1, 23.8, 23.1, 14.1, 11.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{47}\text{F}_3\text{N}_5\text{O}_6$  [M+H]: 654.3479, Found: 654.3480.



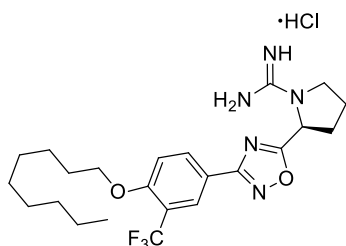
**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-**

**yl)methylene)carbamate.** Synthesized by general procedure 2-E. 80% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.34 (d,  $J = 2.0$  Hz, 1H), 8.20 (dd,  $J = 8.7, 2.1$  Hz, 1H), 7.67 (d,  $J = 8.3$  Hz, 2H), 7.57 (d,  $J = 8.1$  Hz, 2H), 7.10 (d,  $J = 8.7$  Hz, 1H), 5.60 (dd,  $J = 7.8, 4.6$  Hz, 1H), 5.31 (s, 2H), 3.99 – 3.73 (m, 2H), 2.45 (dd,  $J = 12.5, 7.5$  Hz, 1H), 2.19 (dq,  $J = 13.0, 6.6$  Hz, 2H), 2.04 (p,  $J = 6.8$  Hz, 1H), 1.48 (d,  $J = 20.2$  Hz, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  179.5, 167.2, 162.2, 158.2, 153.8, 150.5, 139.8, 132.7, 130.6 (q,  $^2J_{\text{CF}} = 30.3$  Hz), 127.1 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 127.0, 125.8 (q,  $^3J_{\text{CF}} = 3.6$  Hz), 124.1 (q,  $^1J_{\text{CF}} = 271.2$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 273.3$  Hz), 119.9 (q,  $^2J_{\text{CF}} = 28.9$  Hz), 113.4, 82.3, 79.9, 69.8, 55.4, 49.6, 36.8, 31.6, 29.8, 28.2, 24.1;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.6 (s, 3F), -65.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{36}\text{F}_6\text{N}_5\text{O}_6$  [M+H]: 700.2569, Found: 700.2631.

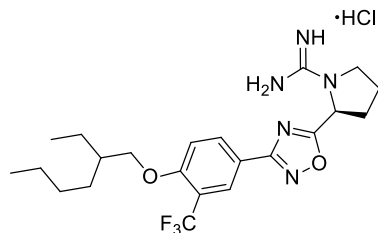


**(S)-Amino (2-(3-(4-(heptyloxy)-3-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5-yl) pyrrolidin-1-yl) methaniminium chloride (3.27a).** Synthesized by general procedure 3-F. 53% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.27 (dd,  $J = 8.7, 2.2$  Hz, 1H), 8.24 (d,  $J = 2.2$  Hz, 1H), 7.35 (d,  $J = 8.7$  Hz, 1H), 5.47 (dd,  $J = 7.9, 1.9$  Hz, 1H), 4.21 (t,  $J = 6.2$  Hz, 2H), 3.81 (td,  $J = 9.2, 2.6$  Hz, 1H), 3.65 (td,  $J = 9.7, 7.3$  Hz, 1H), 2.68 – 2.44 (m, 2H), 2.29-2.22 (m, 1H), 2.19 – 2.04

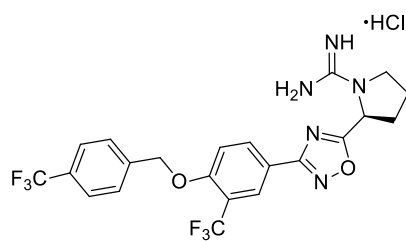
(m, 1H), 1.92-1.81 (m, 2H), 1.58-1.50 (m, 2H), 1.48-1.32 (m, 6H), 0.94 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.6, 160.9, 157.0, 133.9, 127.1 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 124.8 (q,  $^1J_{\text{CF}} = 271.6$  Hz), 120.3 (q,  $^2J_{\text{CF}} = 30.7$  Hz), 119.3, 114.8, 70.3, 56.5, 32.9, 32.7, 30.0, 30.0, 26.9, 24.3, 23.6, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{29}\text{F}_3\text{N}_5\text{O}_2 + [\text{M}^+]$ : 440.2273, Found: 440.2254.



**(S)-Amino(2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.27b).** Synthesized by general procedure 3-F. 100% conversion, white solid;  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  8.25 (dd,  $J = 8.7, 2.0$  Hz, 1H), 8.22 (d,  $J = 1.8$  Hz, 1H), 7.33 (d,  $J = 8.7$  Hz, 1H), 5.45 (d,  $J = 6.9$  Hz, 1H), 4.18 (t,  $J = 6.2$  Hz, 2H), 3.82-3.74 (m, 1H), 3.62 (q,  $J = 9.5$  Hz, 1H), 2.61–2.54 (m, 1H), 2.50-2.45 (m, 1H), 2.30-2.19 (m, 1H), 2.16 – 2.01 (m, 1H), 1.86-1.81 (m, 2H), 1.52 (p,  $J = 7.2$  Hz, 2H), 1.41-1.27 (m, 10H), 0.90 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.6, 160.9, 157.1, 133.9, 127.1 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 271.8$  Hz), 120.3 (q,  $^2J_{\text{CF}} = 31.5$  Hz), 119.3, 114.8, 70.3, 56.5, 33.0, 32.7, 30.6, 30.3, 30.3, 30.0, 26.9, 24.3, 23.7, 14.4;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{23}\text{H}_{33}\text{F}_3\text{N}_5\text{O}_2 + [\text{M}^+]$ : 468.2586, Found: 468.2562.

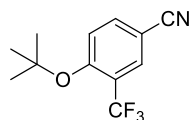


**Amino((2*S*)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.27d).** Synthesized by general procedure 3-F. 50% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.25 (dd,  $J$  = 8.7, 1.9 Hz, 1H), 8.21 (d,  $J$  = 1.8 Hz, 1H), 7.34 (d,  $J$  = 8.7 Hz, 1H), 5.47 (d,  $J$  = 7.2 Hz, 1H), 4.09 (d,  $J$  = 5.1 Hz, 2H), 3.79 (t,  $J$  = 9.1 Hz, 1H), 3.63 (q,  $J$  = 9.5 Hz, 1H), 3.61-3.54 (m, 1H), 2.48 (dd,  $J$  = 12.8, 6.3 Hz, 1H), 2.31-2.18 (m, 1H), 2.17-2.04 (m, 1H), 1.76 (p,  $J$  = 6.2 Hz, 1H), 1.62-1.42 (m, 4H), 1.38-1.32 (m, 4H), 0.98-0.89 (m, 6H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.5, 160.9, 157.1, 134.0, 127.0 (q,  $^3J_{\text{CF}}$  = 5.4 Hz), 124.7 (q,  $^1J_{\text{CF}}$  = 273.0 Hz), 120.1 (q,  $^2J_{\text{CF}}$  = 31.4 Hz), 119.3, 114.6, 72.2, 56.5, 49.0, 40.7, 32.7, 31.4, 30.1, 24.8, 24.3, 24.0, 14.3, 11.5;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{22}\text{H}_{31}\text{F}_3\text{N}_5\text{O}_2 + [\text{M}^+]$ : 454.2430, Found: 454.2421.

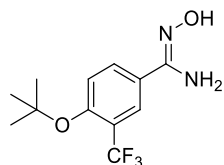


**(*S*)-Amino(2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.27c).** Synthesized by general procedure 3-F. 80% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.25 (dd,  $J$  = 4.4, 2.5 Hz, 2H), 7.67 (q,  $J$  = 8.4 Hz, 4H), 7.42 (d,  $J$  = 9.3 Hz, 1H), 5.43 (dd,  $J$  = 7.9, 1.7 Hz, 1H), 5.40 (s, 2H), 3.76 (td,  $J$  = 9.4, 2.5 Hz, 1H), 3.60 (td,  $J$  = 9.6, 7.3 Hz, 1H), 2.61 – 2.41 (m, 2H), 2.21 (ddt,  $J$  = 9.7, 7.0, 3.4 Hz, 1H), 2.13 – 2.00 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  177.9, 167.0,

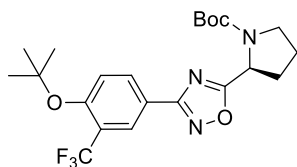
158.5, 155.7, 140.5, 132.6, 129.8 (q,  $^2J_{CF} = 32.5$  Hz), 127.1, 125.8 (q,  $^3J_{CF} = 5.2$  Hz), 125.1 (q,  $^3J_{CF} = 3.9$  Hz), 124.2 (q,  $^1J_{CF} = 271.9$  Hz), 123.4 (q,  $^1J_{CF} = 271.9$  Hz), 119.1 (q,  $^2J_{CF} = 30.9$  Hz), 118.8, 114.0, 69.5, 55.0, 31.3, 22.9;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.6 (s, 3F), -63.6 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{22}\text{H}_{20}\text{F}_6\text{N}_5\text{O}_2 + [\text{M}^+]$ : 500.1521, Found: 500.1518.



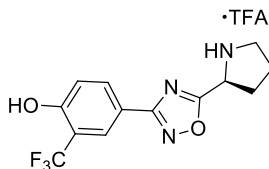
**4-(*Tert*-butoxy)-3-(trifluoromethyl) benzonitrile.** Synthesized by general procedure 3-A, omitting the primary alcohol. 77% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.82 (d,  $J = 2.2$  Hz, 1H), 7.70 (dd,  $J = 8.8, 2.3$  Hz, 1H), 7.25 (d,  $J = 8.6$  Hz, 1H), 1.53 (s, 9H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  158.9, 136.5, 131.6 (q,  $^3J_{CF} = 5.4$  Hz), 123.4 (q,  $^2J_{CF} = 31.1$  Hz), 122.6 (q,  $^1J_{CF} = 274.1$  Hz), 119.4, 118.1, 103.9, 82.7, 28.9;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -66.1 (s, 3F).



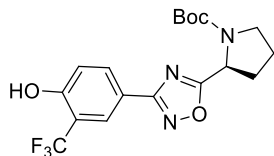
**(*Z*)-4-(*Tert*-butoxy)-*N'*-hydroxy-3-(trifluoromethyl) benzimidamide.** Synthesized by general procedure 3-B. 77% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  7.87 (d,  $J = 2.3$  Hz, 1H), 7.76 (dd,  $J = 8.6, 2.0$  Hz, 1H), 7.32 (d,  $J = 8.7$  Hz, 1H), 1.48 (s, 9H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  157.4, 154.1, 131.6, 127.0, 126.0 (q,  $^3J_{CF} = 5.4$  Hz), 125.0 (q,  $^1J_{CF} = 273.2$  Hz), 123.4 (q,  $^2J_{CF} = 29.9$  Hz), 121.1, 82.0, 29.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -62.6 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{12}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_2 + [\text{M}+\text{H}]$ : 277.1164, Found: 277.1153.



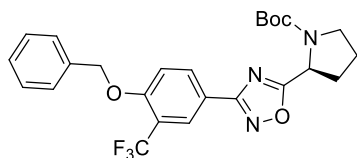
**(S)-Tert-butyl 2-(3-(4-(tert-butoxy)-3-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate.** Synthesized by general procedure 3-C. 29% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.26 (d,  $J$  = 2.1 Hz, 1H), 8.11 (dd,  $J$  = 8.7, 1.7 Hz, 1H), 7.25 (t,  $J$  = 8.4 Hz, 1H), 5.21-5.01 (m, 1H), 3.73 – 3.67 (m, 1H), 3.61 – 3.42 (m, 1H), 2.45 – 2.31 (m, 1H), 2.17 – 2.09 (m, 2H), 2.06-1.94 (m, 1H), 1.51 (s, 9H), 1.45 (s, 3H), 1.29 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  181.0, 167.4, 157.7, 153.6, 131.6, 126.8 (q,  $^3J_{\text{CF}}$  = 5.1 Hz), 123.4 (q,  $^1J_{\text{CF}}$  = 273.3 Hz), 123.3 (q,  $^2J_{\text{CF}}$  = 30.4 Hz), 120.1, 119.5, 81.6, 80.6, 53.9, 46.5, 32.5, 31.6, 29.2, 28.3, 24.5, 23.8;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.2 (d,  $J$  = 36.7 Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 478.1930, Found: 478.1925.



**(S)-2-(3-(4-Hydroxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.28).** Synthesized by general procedure 3-D. 100% conversion, yellow oil;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.11 (s, 1H), 8.02 (d,  $J$  = 8.5 Hz, 1H), 7.00 (d,  $J$  = 8.6 Hz, 1H), 5.08 (t,  $J$  = 7.7 Hz, 1H), 3.57 – 3.44 (m, 2H), 2.60 - 2.52 (m, 1H), 2.37-2.27 (m, 1H), 2.22 – 2.10 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.1, 168.8, 160.3, 133.5, 127.4 (q,  $^3J_{\text{CF}}$  = 5.3 Hz), 124.9 (q,  $^1J_{\text{CF}}$  = 272.7 Hz), 118.6 (q,  $^2J_{\text{CF}}$  = 31.4 Hz), 118.5, 117.9, 55.5, 47.3, 30.2, 24.5;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -64.0 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{13}\text{H}_{13}\text{F}_3\text{N}_3\text{O}_2^+$  [M+]: 300.0960, Found: 300.0941.



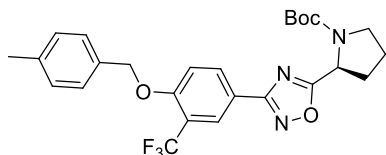
**(S)-Tert-butyl 2-(3-(4-hydroxy-3-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate (3.29).** Compound **3.28** was dissolved in 1,4-dioxane and was cooled to zero degrees Celsius. TEA (2.6 equiv), di-*tert*-butyl dicarbonate (1.2 equiv), 1,4-dioxane were mixed in an addition funnel and added dropwise into the reaction. The reaction was warmed to room temperature and stirred for another 3-4 hours. After completion, the reaction was concentrated under reduced pressure and purified by silica gel column chromatography (50% ethyl acetate/hexane). The product was obtained in a 55% yield as a white solid.  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.16 (s, 1H), 8.08 (d,  $J = 6.8$  Hz, 1H), 7.07 (dd,  $J = 8.4, 4.2$  Hz, 1H), 5.17-5.07 (m, 1H), 3.71 – 3.62 (m, 1H), 3.56 – 3.49 (m, 1H), 2.52 – 2.39 (m, 1H), 2.18 – 2.01 (m, 3H), 1.46 (s, 3H), 1.28 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  182.5, 168.6, 160.1, 155.4, 133.3, 127.2 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 124.9 (q,  $^1J_{\text{CF}} = 272.4$  Hz), 118.8, 118.6, 118.5, 118.4, 81.9, 55.2, 47.6, 33.2, 32.4, 28.6, 28.4, 25.3, 24.7;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.9 (d,  $J = 10.4$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{18}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 422.1304, Found: 422.1294.



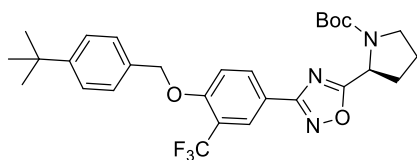
**(S)-Tert-butyl 2-(3-(4-(benzyloxy)-3-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5-yl) pyrrolidine-1-carboxylate (3.30a).** Synthesized by general procedure 3-H. 75% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.33 (d,  $J = 1.5$  Hz, 1H), 8.18 (d,  $J = 8.7$  Hz, 1H), 7.47-7.37 (m, 4H), 7.36-7.30 (m, 1H), 7.13 (t,  $J = 8.7$  Hz, 1H), 5.27 (s, 2H), 5.06 (dd,  $J = 8.0, 3.3$  Hz, 1H), 3.80 – 3.61 (m, 1H), 3.59 – 3.46 (m, 1H), 2.47 – 2.30 (m, 1H), 2.22 – 2.08 (m, 2H), 2.07-1.94



(m, 1H), 1.47 (s, 3H), 1.30 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  181.0, 167.3, 158.7, 153.6, 135.8, 132.6, 128.8, 128.3, 126.9, 123.4 (q,  $^1J_{\text{CF}} = 273.8$  Hz), 119.7 (q,  $^2J_{\text{CF}} = 37.6$  Hz), 119.2, 113.7, 80.6, 70.6, 53.9, 46.5, 32.5, 31.6, 29.8, 28.3, 24.5, 23.8;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -63.6 (d,  $J=14.7$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{25}\text{H}_{26}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 512.1773, Found: 512.1771.

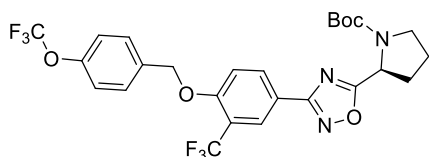


**(S)-Tert-butyl 2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30b).** Synthesized by general procedure 3-H. 76% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.31 (s, 1H), 8.17 (d,  $J = 8.7$  Hz, 1H), 7.33 (d,  $J=8.0$  Hz, 2H), 7.20 (d,  $J= 7.9$  Hz, 2H), 7.12 (t,  $J= 8.6$  Hz, 1H), 5.22 (s, 2H), 5.06 (dd,  $J= 8.1, 3.6$  Hz, 1H), 3.76 – 3.64 (m, 1H), 3.62 – 3.42 (m, 1H), 2.45 – 2.37 (m, 1H), 2.36 (s, 3H), 2.21 – 2.08 (m, 2H), 2.08-1.93 (m, 1H), 1.46 (s, 3H), 1.30 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  181.0, 167.3, 158.7, 153.6, 138.1, 132.5, 129.5, 127.1, 126.8 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 274.2$  Hz), 119.9 (q,  $^2J_{\text{CF}} = 32.1$  Hz), 119.1, 113.7, 80.6, 70.6, 53.9, 46.5, 32.5, 31.6, 28.5, 28.3, 24.5, 23.8, 21.3;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.7 (d,  $J=15.2$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 526.1930, Found: 526.1898.

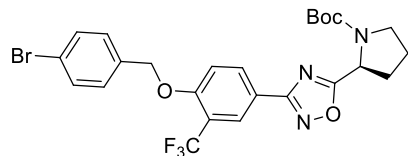


**(S)-Tert-butyl 2-(3-(4-((tert-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30c).** Synthesized by general procedure 3-H. 73% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.32 (s, 1H), 8.18 (d,  $J = 8.5$  Hz, 1H), 7.40 (q,

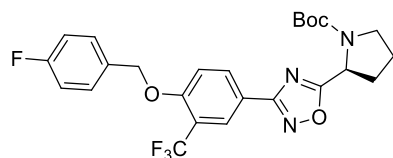
$J= 8.3$  Hz, 4H), 7.13 (t,  $J= 8.7$  Hz, 1H), 5.24 (s, 2H), 5.06 (dd,  $J= 7.9, 3.2$  Hz, 1H), 3.81 – 3.63 (m, 1H), 3.61 – 3.43 (m, 1H), 2.47 – 2.32 (m, 1H), 2.22 – 2.09 (m, 2H), 2.05-1.96 (m, 1H), 1.46 (s, 3H), 1.31 (d,  $J= 11.4$  Hz, 15H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  181.0, 167.3, 158.8, 153.6, 151.3, 132.7, 132.5, 129.5, 126.8, 125.7, 123.4 (q,  $^1J_{\text{CF}} = 274.2$  Hz), 120.0 (q,  $^2J_{\text{CF}} = 31.0$  Hz), 119.3, 119.1, 113.7, 80.6, 70.5, 53.9, 46.5, 34.7, 32.5, 31.4, 28.5, 28.3, 24.5, 23.8, 22.5;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.6 (d,  $J=15.0$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{29}\text{H}_{34}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 568.2399, Found: 568.2367.



**(S)-Tert-butyl 2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30d).** Synthesized by general procedure 3-H. 85% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.33 (s, 1H), 8.20 (d,  $J = 8.6$  Hz, 1H), 7.48 (d,  $J= 8.7$  Hz, 2H), 7.25 (d,  $J= 7.6$  Hz, 2H), 7.11 (t,  $J = 8.7$  Hz, 1H), 5.25 (s, 2H), 5.06 (dd,  $J= 8.1, 3.6$  Hz, 1H), 3.75 – 3.63 (m, 1H), 3.60 – 3.41 (m, 1H), 2.48 – 2.31 (m, 1H), 2.20 – 2.09 (m, 2H), 2.07-1.93 (m, 1H), 1.46 (s, 3H), 1.30 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  181.1, 167.2, 158.3, 153.6, 149.1, 134.4, 132.6, 128.3, 126.9, 123.2 (q,  $^1J_{\text{CF}} = 274.5$  Hz), 121.34, 120.6 (q,  $^1J_{\text{CF}} = 257.3$  Hz), 120.1, 119.8, 119.5, 113.5, 80.6, 69.7, 53.9, 46.5, 32.5, 31.6, 28.5, 28.3, 24.5, 23.8;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -60.9 (s, 3F), -65.6 (d,  $J=13.8$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{25}\text{F}_6\text{N}_3\text{O}_5\text{Na}$  [M+Na]: 596.1596, Found: 596.1588.

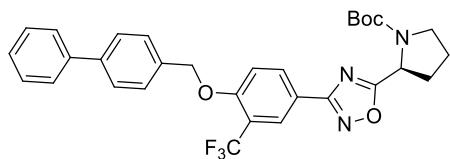


**(S)-Tert-butyl 2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30e).** Synthesized by general procedure 3-H. 77% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.32 (s, 1H), 8.18 (d,  $J = 8.6$  Hz, 1H), 7.52 (d,  $J = 8.4$  Hz, 2H), 7.32 (d,  $J = 8.4$  Hz, 2H), 7.10 (d,  $J = 8.4$  Hz, 1H), 5.19 (s, 2H), 5.06 (dd,  $J = 8.0$ , 3.3 Hz, 1H), 3.79 – 3.64 (m, 1H), 3.61 – 3.41 (m, 1H), 2.49 – 2.31 (m, 1H), 2.24 – 2.07 (m, 2H), 2.05-1.96 (m, 1H), 1.46 (s, 3H), 1.30 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  181.1, 167.2, 158.3, 153.6, 149.1, 134.8, 132.6, 132.0, 128.6, 126.9, 123.3 (q,  $^1J_{\text{CF}} = 273.7$  Hz), 122.3, 119.5, 113.6, 80.6, 70.0, 53.9, 46.5, 36.8, 32.5, 31.5, 29.8, 28.3, 24.5, 23.8;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.6 (d,  $J = 13.5$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{25}\text{H}_{25}\text{BrF}_3\text{N}_3\text{O}_4\text{K}$  [M+K]: 606.0618, Found: 606.0596.

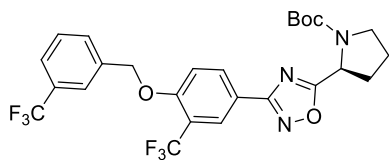


**(S)-Tert-butyl 2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30f).** Synthesized by general procedure 3-H. 79% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.32 (s, 1H), 8.19 (d,  $J = 8.5$  Hz, 1H), 7.42 (dd,  $J = 8.4$ , 5.4 Hz, 2H), 7.10 (q,  $J = 9.5$ , 8.6 Hz, 3H), 5.21 (s, 2H), 5.06 (d,  $J = 4.8$  Hz, 1H), 3.79 – 3.61 (m, 1H), 3.61 – 3.46 (m, 1H), 2.50 – 2.30 (m, 1H), 2.24 – 2.07 (m, 2H), 2.06-1.97 (m, 1H), 1.46 (s, 3H), 1.30 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  181.1, 167.3, 162.7 (d,  $^1J = 247.9$  Hz), 158.5, 153.6, 132.6, 131.5, 128.9, 128.8, 126.9, 123.3 (q,  $^1J_{\text{CF}} = 273.7$  Hz), 119.4, 115.8 (d,

$^2J = 21.8$  Hz), 113.6, 80.6, 70.1, 53.9, 46.5, 32.5, 31.6, 28.5, 28.3, 23.9;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -65.7 (d,  $J = 13.8$  Hz, 3F), -116.8 (d,  $J = 39.8$  Hz, 1F); HRMS (ESI+): Calcd for  $\text{C}_{25}\text{H}_{25}\text{F}_4\text{N}_3\text{O}_4\text{Na}$  [ $\text{M} + \text{Na}$ ]: 530.1679, Found: 530.1660. HPLC analysis shows **3.30f** is 92% pure.

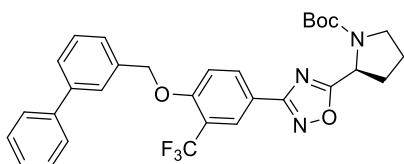


**(S)-Tert-butyl 2-(3-(4-((1,1'-biphenyl)-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30g).** Synthesized by general procedure 3-H. 71% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.34 (s, 1H), 8.20 (d,  $J = 8.6$  Hz, 1H), 7.66-7.57 (m, 4H), 7.52 (d,  $J = 8.3$  Hz, 2H), 7.45 (t,  $J = 7.9$  Hz, 2H), 7.36 (t,  $J = 7.2$  Hz, 1H), 7.16 (t,  $J = 8.7$  Hz, 1H), 5.31 (s, 2H), 5.25-5.01 (m, 1H), 3.79 – 3.64 (m, 1H), 3.61 – 3.46 (m, 1H), 2.46 – 2.32 (m, 1H), 2.22 – 2.08 (m, 2H), 2.06-1.97 (m, 1H), 1.47 (s, 3H), 1.31 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  181.0, 167.3, 158.7, 153.6, 141.3, 140.7, 134.8, 132.6, 128.9, 127.6, 127.4, 127.2, 126.9, 123.4 (q,  $^1J_{\text{CF}} = 272.1$  Hz), 120.0 (q,  $^2J_{\text{CF}} = 32.5$  Hz), 119.5, 119.3, 113.7, 80.6, 70.5, 53.9, 46.5, 32.5, 31.6, 28.3, 24.5, 23.8;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -65.6 (d,  $J = 14.8$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{30}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [ $\text{M} + \text{Na}$ ]: 588.2086, Found: 588.2072.

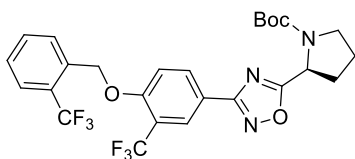


**(S)-Tert-butyl 2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30h).** Synthesized by general procedure 3-H. 88% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.34 (s, 1H), 8.21 (d,  $J = 8.6$  Hz, 1H), 7.72 (s, 1H), 7.66 (d,  $J = 7.6$  Hz, 1H), 7.60 (d,  $J = 7.8$  Hz, 1H), 7.53 (t,  $J = 7.7$  Hz, 1H), 7.12 (d,  $J = 8.7$  Hz, 1H), 5.30 (s, 2H), 5.24-5.02 (m, 1H), 3.75 – 3.65 (m, 1H), 3.62 – 3.44 (m, 1H), 2.48 – 2.29

(m, 1H), 2.23 – 2.07 (m, 2H), 2.06-1.91 (m, 1H), 1.46 (s, 3H), 1.30 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  181.1, 167.2, 158.2, 153.6, 136.8, 132.7, 131.2 (q,  $^2J_{\text{CF}} = 32.4$  Hz), 130.1, 129.4, 126.9 (q,  $^3J_{\text{CF}} = 5.1$  Hz), 125.1 (q,  $^3J_{\text{CF}} = 3.4$  Hz), 124.1 (q,  $^1J_{\text{CF}} = 273.5$  Hz), 123.7 (q,  $^3J_{\text{CF}} = 3.8$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 273.9$  Hz), 119.9, 119.7, 113.5, 80.6, 69.8, 53.9, 46.5, 32.5, 31.6, 28.5, 28.3, 24.5, 23.8;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.6 (d,  $J=12.8$  Hz, 3F), -65.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{25}\text{F}_6\text{N}_3\text{O}_4\text{K}$  [M+K]: 596.1386, Found: 596.1377.

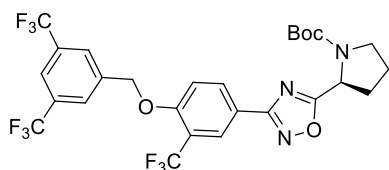


**(S)-Tert-butyl 2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30i).** Synthesized by general procedure 3-H. 58% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.35 (s, 1H), 8.20 (d,  $J = 8.5$  Hz, 1H), 7.70 (s, 1H), 7.63-7.54 (m, 3H), 7.46 (p,  $J = 7.4$  Hz, 4H), 7.37 (tt,  $J = 7.3, 1.2$  Hz, 1H), 7.17 (d,  $J = 8.5$  Hz, 1H), 5.33 (s, 2H), 5.25-4.95 (m, 1H), 3.76 – 3.65 (m, 1H), 3.63 – 3.45 (m, 1H), 2.47 – 2.31 (m, 1H), 2.20 – 2.09 (m, 2H), 2.05-1.96 (m, 1H), 1.48 (s, 3H), 1.31 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  181.0, 167.3, 158.6, 153.6, 141.8, 140.8, 136.3, 132.6, 129.3, 129.0, 127.6, 127.2, 127.1, 125.8, 126.9, 125.7, 123.4 (q,  $^1J_{\text{CF}} = 273.7$  Hz), 120.0 (q,  $^2J_{\text{CF}} = 32.7$  Hz), 119.3, 113.7, 80.6, 70.6, 53.9, 46.5, 32.5, 31.6, 28.2, 24.5, 23.8;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.5 (d,  $J=13.8$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{30}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 588.2086, Found: 588.2077.

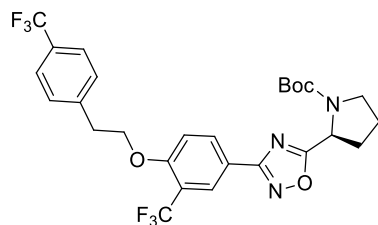


**(S)-Tert-butyl 2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30j).** Synthesized by general procedure 3-H. 77%

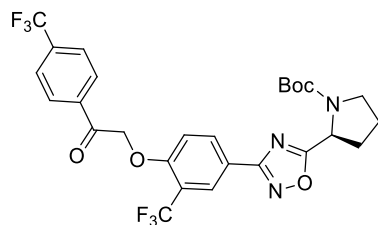
yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.35 (s, 1H), 8.20 (d,  $J = 8.5$  Hz, 1H), 7.81 (d,  $J = 7.8$  Hz, 1H), 7.71 (d,  $J = 7.8$  Hz, 1H), 7.61 (t,  $J = 7.6$  Hz, 1H), 7.44 (t,  $J = 7.6$  Hz, 1H), 7.10 (t,  $J = 8.7$  Hz, 1H), 5.45 (s, 2H), 5.23-5.03 (m, 1H), 3.76 – 3.64 (m, 1H), 3.61 – 3.46 (m, 1H), 2.47 – 2.32 (m, 1H), 2.21 – 2.08 (m, 2H), 2.05-1.97 (m, 1H), 1.46 (s, 3H), 1.30 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  181.1, 167.2, 158.1, 153.6, 134.3, 132.8, 132.6, 128.5, 128.1, 127.9, 127.1, 126.9 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 126.1 (q,  $^3J_{\text{CF}} = 5.2$  Hz), 124.4 (q,  $^1J_{\text{CF}} = 274.8$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 273.6$  Hz), 120.1, 119.9, 119.7, 113.4, 80.6, 66.6, 53.9, 46.5, 32.5, 28.3, 23.9;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -63.6 (d,  $J = 8.1$  Hz, 3F), -65.6 (d,  $J = 13.2$  Hz, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{25}\text{F}_6\text{N}_3\text{O}_4\text{Na}$  [ $\text{M}+\text{Na}$ ]: 580.1647, Found: 580.1631.



**(S)-Tert-butyl 2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30k).** Synthesized by general procedure 3-H. 81% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.37 (s, 1H), 8.24 (t,  $J = 6.8$  Hz, 1H), 7.95 (s, 2H), 7.87 (s, 1H), 7.14 (t,  $J = 9.4$  Hz, 1H), 5.35 (s, 2H), 5.22-5.03 (m, 1H), 3.75 – 3.65 (m, 1H), 3.61 – 3.45 (m, 1H), 2.45 – 2.32 (m, 1H), 2.22 – 2.10 (m, 2H), 2.07-1.96 (m, 1H), 1.46 (s, 3H), 1.30 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  181.2, 167.1, 157.8, 153.6, 138.4, 132.8, 132.3 (q,  $^2J_{\text{CF}} = 33.7$  Hz), 127.3, 127.1, 127.1, 126.9 (q,  $^3J_{\text{CF}} = 3.1$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 273.9$  Hz), 123.2 (q,  $^1J_{\text{CF}} = 273.8$  Hz), 122.3, 120.4, 120.2 (q,  $^2J_{\text{CF}} = 31.9$  Hz), 120.2, 119.2, 113.3, 80.6, 69.1, 53.9, 46.5, 32.5, 31.6, 28.3, 24.5, 23.9;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.7 (d,  $J = 10.3$  Hz, 3F), -66.1 (s, 6F); HRMS (ESI+): Calcd for  $\text{C}_{27}\text{H}_{24}\text{F}_9\text{N}_3\text{O}_4\text{Na}$  [ $\text{M}+\text{Na}$ ]: 648.1521, Found: 648.1469.

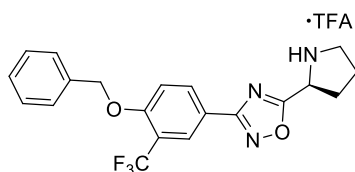


**(S)-Tert-butyl 2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenethoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30l).** Synthesized by general procedure 3-H. 25% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.29 (s, 1H), 8.18 (d,  $J = 8.6$  Hz, 1H), 7.58 (d,  $J = 8.1$  Hz, 2H), 7.44 (d,  $J = 8.1$  Hz, 2H), 7.04 (d,  $J = 8.3$  Hz, 1H), 5.23-5.00 (m, 1H), 4.32 (t,  $J = 6.3$  Hz, 2H), 3.70 (s, 1H), 3.61 – 3.42 (m, 1H), 3.22 (t,  $J = 6.2$  Hz, 2H), 2.48 – 2.32 (m, 1H), 2.23 – 2.07 (m, 2H), 2.06-1.96 (m, 1H), 1.46 (s, 3H), 1.27 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  181.1, 167.3, 158.7, 153.6, 142.1, 132.6, 129.7, 129.3 (q,  $^2J_{\text{CF}} = 32.5$  Hz), 126.9, 125.5 (q,  $^3J_{\text{CF}} = 3.7$  Hz), 124.4 (q,  $^1J_{\text{CF}} = 273.3$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 274.9$  Hz), 119.7 (q,  $^2J_{\text{CF}} = 34.0$  Hz), 119.3, 112.9, 80.6, 69.4, 53.9, 46.5, 35.6, 32.5, 31.6, 29.9, 28.3, 23.9;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.5 (d,  $J = 15.0$  Hz, 6F); HRMS (ESI+): Calcd for  $\text{C}_{27}\text{H}_{27}\text{F}_6\text{N}_3\text{O}_4\text{Na}$  [M+Na]: 594.1803, Found: 594.1803.

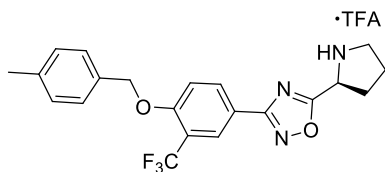


**(S)-Tert-butyl 2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.30m).** Synthesized by general procedure 3-H. 47% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.33 (s, 1H), 8.17 (d,  $J = 8.7$  Hz, 1H), 8.13 (d,  $J = 8.2$  Hz, 2H), 7.77 (d,  $J = 8.2$  Hz, 2H), 6.97 (d,  $J = 8.7$  Hz, 1H), 5.41 (d,  $J = 9.8$  Hz, 2H), 5.21-5.02 (m, 1H), 3.76 – 3.63 (m, 1H), 3.60 – 3.46

(m, 1H), 2.47 – 2.31 (m, 1H), 2.20 – 2.07 (m, 2H), 2.06-1.95 (m, 1H), 1.45 (s, 3H), 1.29 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  193.1, 181.2, 167.1, 157.7, 153.6, 136.7, 135.5 (q,  $^2J_{\text{CF}} = 33.3$  Hz), 132.6, 129.0, 127.2, 126.1, 123.5 (q,  $^1J_{\text{CF}} = 274.0$  Hz), 123.1 (q,  $^1J_{\text{CF}} = 273.8$  Hz), 120.3, 113.1, 80.7, 71.6, 53.9, 46.5, 36.8, 32.5, 31.6, 28.5, 28.3, 24.5, 23.8;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.4 (d,  $J=15.6$  Hz, 3F), -66.3 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{27}\text{H}_{25}\text{F}_6\text{N}_3\text{O}_5\text{K}$  [M+K]: 624.1336, Found: 624.1336.



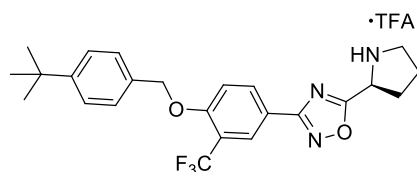
**(S)-2-(3-(4-Benzyloxy)-3-(trifluoromethyl) phenyl)-1,2,4-oxadiazol-5-yl pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, yellow oil;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.28 (d,  $J = 2.1$  Hz, 1H), 8.25 (dd,  $J = 8.7, 2.1$  Hz, 1H), 7.47-7.43 (m, 2H), 7.42-7.34 (m, 3H), 7.33-7.27 (m, 1H), 5.30 (s, 2H), 5.17 (t,  $J = 7.8$  Hz, 1H), 3.63-3.46 (m, 2H), 2.69 – 2.60 (m, 1H), 2.44 – 2.35 (m, 1H), 2.29-2.18 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.3, 168.6, 160.4, 137.3, 133.9, 129.6, 129.2, 128.2, 127.3 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 124.6 (q,  $^1J_{\text{CF}} = 273.1$  Hz), 120.6 (q,  $^2J_{\text{CF}} = 31.9$  Hz), 119.4, 115.5, 71.8, 55.5, 47.3, 30.2, 24.5;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.6 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_3\text{O}_2 + [\text{M}^+]$ : 390.1429, Found: 390.1431.



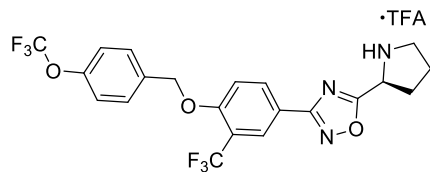
**(S)-2-(3-(4-((4-Methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 93% yield,



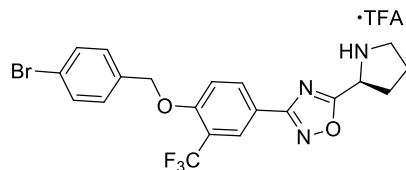
yellow oil;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.26 (d,  $J=2.1$  Hz, 1H), 8.23 (dd,  $J= 8.7, 2.2$  Hz, 1H), 7.37 (d,  $J= 8.7$  Hz, 1H), 7.31 (d,  $J=8.0$  Hz, 2H), 7.17 (d,  $J= 7.8$  Hz, 2H), 5.24 (s, 2H), 5.15 (t,  $J=7.8$  Hz, 1H), 3.65-3.40 (m, 2H), 2.68-2.58 (m, 1H), 2.43 – 2.34 (m, 1H), 2.31 (s, 3H), 2.28-2.14 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.3, 168.6, 160.5, 139.2, 134.2, 133.9, 130.2, 128.4, 127.3 (q,  $^3J_{\text{CF}} = 5.5$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 273.1$  Hz), 120.6 (q,  $^2J_{\text{CF}} = 31.5$  Hz), 119.3, 115.6, 71.8, 55.5, 47.3, 30.2, 24.5, 21.2;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{21}\text{F}_3\text{N}_3\text{O}_2 + [\text{M}^+]$ : 404.1586, Found: 404.1578.



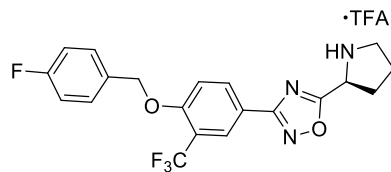
**(S)-2-(3-(4-((4-(Tert-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.21 (s, 1H), 8.08 (d,  $J= 7.9$  Hz, 1H), 7.43 (dd,  $J= 8.5, 2.3$  Hz, 2H), 7.39-7.31 (m, 2H), 7.10 (d,  $J= 8.7$  Hz, 1H), 5.33 (s, 1H), 5.21 (s, 1H), 5.12 (s, 1H), 3.65 (s, 1H), 3.59 (s, 1H), 2.68-2.56 (m, 1H), 2.50 – 2.39 (m, 1H), 2.30-2.22 (m, 2H), 1.33 (d,  $J= 1.1$  Hz, 9H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  174.5, 167.5, 159.2, 152.6, 151.4, 132.8, 132.6, 130.4, 128.8, 126.9, 126.8, 125.9, 125.8, 123.2 (q,  $^1J_{\text{CF}} = 273.9$  Hz), 119.9 (q,  $^2J_{\text{CF}} = 31.7$  Hz), 117.8, 113.7, 70.6, 69.7, 54.1, 46.2, 34.9, 34.7, 31.4, 31.4, 30.0, 23.9;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -63.5 (s, 2F), -75.7 (s, 1F); HRMS (ESI+): Calcd for  $\text{C}_{24}\text{H}_{27}\text{F}_3\text{N}_3\text{O}_2 + [\text{M}^+]$ : 446.2055, Found: 446.2041.



**(S)-2-(3-(4-((4-(Trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.31 (d,  $J$  = 9.1 Hz, 2H), 7.59 (d,  $J$  = 8.5 Hz, 2H), 7.44 (d,  $J$  = 8.5 Hz, 1H), 7.31 (d,  $J$  = 8.2 Hz, 2H), 5.36 (s, 2H), 5.20 (t,  $J$  = 7.8 Hz, 1H), 3.64-3.50 (m, 2H), 2.72 – 2.62 (m, 1H), 2.48 – 2.39 (m, 1H), 2.33-2.21 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.4, 168.6, 160.1, 150.2, 136.6, 134.0, 130.0, 129.6, 127.4 (q,  $^3J_{\text{CF}}$  = 5.4 Hz), 124.7 (q,  $^1J_{\text{CF}}$  = 273.1 Hz), 122.2, 121.8 (q,  $^1J_{\text{CF}}$  = 265.6 Hz), 120.9, 120.6, 119.7, 115.5, 70.9, 55.5, 47.4, 30.2, 24.5;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -59.1 (s, 3H), -63.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{18}\text{F}_6\text{N}_3\text{O}_3^+$  [M+]: 474.1252, Found: 474.1243.

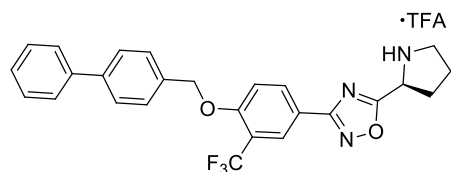


**(S)-2-(3-(4-((4-Bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 75% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.29 (d,  $J$  = 10.7 Hz, 2H), 7.56 (d,  $J$  = 8.4 Hz, 2H), 7.41 (t,  $J$  = 8.1 Hz, 3H), 5.29 (s, 2H), 5.20 (t,  $J$  = 7.8 Hz, 1H), 3.64-3.49 (m, 2H), 2.75 – 2.59 (m, 1H), 2.49 – 2.37 (m, 1H), 2.35-2.18 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.4, 168.6, 160.2, 150.2, 136.6, 134.0, 132.8, 130.1, 127.4 (q,  $^3J_{\text{CF}}$  = 6.1 Hz), 124.6 (q,  $^1J_{\text{CF}}$  = 273.0 Hz), 123.0, 120.7 (q,  $^2J_{\text{CF}}$  = 31.2 Hz), 119.7, 115.5, 71.0, 55.5, 47.4, 30.2, 24.5;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{18}\text{BrF}_3\text{N}_3\text{O}_2^+$  [M+]: 468.0534, Found: 468.0528.



**(S)-2-(3-(4-((4-Fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-**

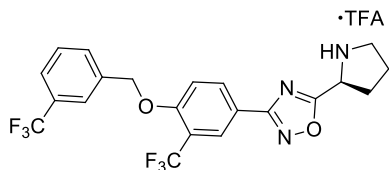
**yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.31 (d,  $J$ = 8.7 Hz, 2H), 7.52 (dd,  $J$ = 8.3, 5.5 Hz, 2H), 7.46 (d,  $J$ = 8.5 Hz, 1H), 7.15 (t,  $J$ = 8.7 Hz, 2H), 5.32 (s, 2H), 5.21 (t,  $J$ = 7.8 Hz, 1H), 3.66-3.50 (m, 2H), 2.69 (hex,  $J$ = 6.0 Hz, 1H), 2.49 – 2.39 (m, 1H), 2.34-2.21 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.4, 168.6, 164.0 (d,  $^1J$ = 246.3 Hz), 160.3, 134.0, 133.3 (d,  $^4J$ = 3.3 Hz), 130.4 (d,  $^3J$ = 8.3 Hz), 127.4 (q,  $^3J_{\text{CF}}$  = 5.4 Hz), 124.7 (q,  $^1J_{\text{CF}}$  = 273.1 Hz), 120.7 (q,  $^2J_{\text{CF}}$  = 31.6 Hz), 119.6, 116.4 (d,  $^2J$ = 22.0 Hz), 115.6, 71.2, 55.5, 47.4, 30.2, 24.5;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.8 (s, 3F), -115.7- -115.8 (m, 1F); HRMS (ESI+): Calcd for  $\text{C}_{20}\text{H}_{18}\text{F}_4\text{N}_3\text{O}_2 + [\text{M}^+]$ : 408.1335, Found: 408.1330.



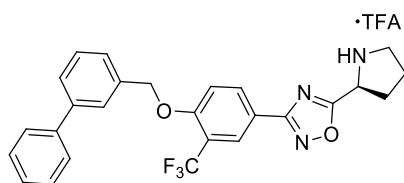
**(S)-2-(3-(4-([1,1'-Biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-**

**yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 95% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.33-8.23 (m, 2H), 7.62 (dd,  $J$ = 13.3, 7.8 Hz, 4H), 7.53 (d,  $J$ = 8.0 Hz, 2H), 7.42 (q,  $J$ = 6.8 Hz, 3H), 7.31 (t,  $J$ = 7.3 Hz, 1H), 5.36 (s, 2H), 5.17 (t,  $J$ = 7.8 Hz, 1H), 3.66-3.40 (m, 2H), 2.64 (hex,  $J$ = 6.2 Hz, 1H), 2.45 – 2.35 (m, 1H), 2.30-2.17 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.3, 168.6, 160.4, 142.4, 141.9, 136.3, 134.0, 129.9, 128.8, 128.5, 128.2, 128.0, 127.4 (q,  $^3J_{\text{CF}}$  = 5.5 Hz), 124.7 (q,  $^1J_{\text{CF}}$  = 273.0 Hz), 120.7 (q,

$^2J_{CF} = 31.6$  Hz), 119.5, 115.6, 71.5, 55.5, 47.4, 30.2, 24.5;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{23}\text{F}_3\text{N}_3\text{O}_2 + [\text{M}^+]$ : 466.1742, Found: 466.1734.

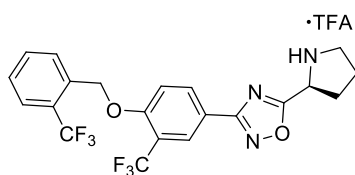


**(S)-2-(3-(3-(Trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.23 (s, 1H), 8.11 (d,  $J = 7.7$  Hz, 1H), 7.70 (d,  $J = 5.6$  Hz, 1H), 7.62 (dd,  $J = 14.5, 7.5$  Hz, 2H), 7.52 (t,  $J = 7.5$  Hz, 1H), 7.09 (d,  $J = 8.0$  Hz, 1H), 5.24 (d,  $J = 13.4$  Hz, 2H), 5.12 (s, 1H), 3.62 (d,  $J = 31.1$  Hz, 2H), 2.63 (s, 1H), 2.47 (s, 1H), 2.27 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  174.6, 167.4, 158.6, 136.6, 132.9, 131.2 (q,  $^2J_{CF} = 32.6$  Hz), 130.1, 129.4, 127.0 (q,  $^3J_{CF} = 5.3$  Hz), 125.2 (q,  $^3J_{CF} = 3.7$  Hz), 124.1 (q,  $^1J_{CF} = 273.4$  Hz), 123.6 (q,  $^3J_{CF} = 3.9$  Hz), 123.1 (q,  $^1J_{CF} = 273.9$  Hz), 120.0 (q,  $^2J_{CF} = 31.9$  Hz), 118.4, 113.5, 69.8, 54.0, 46.3, 30.0, 23.9;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -63.5 (s, 3F), -63.5 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{18}\text{F}_6\text{N}_3\text{O}_2 + [\text{M}^+]$ : 458.1303, Found: 458.1302.

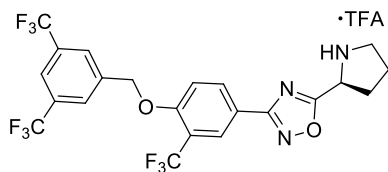


**(S)-2-(3-(4-([1,1'-Biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 99% yield, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.24 (d,  $J = 1.9$  Hz, 1H), 8.10 (dd,  $J = 8.7, 2.0$  Hz, 1H), 7.69 (s, 1H), 7.64-7.54 (m, 3H), 7.50-7.39 (m, 4H), 7.36 (tt,  $J = 7.4, 1.3$  Hz, 1H), 7.13 (d,  $J = 8.8$  Hz, 1H), 5.30 (s, 2H), 5.13 (t,  $J = 7.0$  Hz, 1H), 3.76-3.48 (m, 2H), 2.68 – 2.59 (m, 1H), 2.48 – 2.40 (m, 1H), 2.25 (p,  $J = 6.9$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  174.4, 167.5, 159.1,

141.8, 140.8, 136.2, 132.8, 129.3, 129.0, 127.7, 127.2, 127.1, 126.9 (q,  $^3J_{CF} = 5.3$  Hz), 125.8, 125.7, 123.2 (q,  $^1J_{CF} = 274.0$  Hz), 120.1 (q,  $^2J_{CF} = 31.8$  Hz), 117.9, 113.7, 70.7, 54.2, 46.4, 30.0, 23.9;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -63.3 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{26}\text{H}_{23}\text{F}_3\text{N}_3\text{O}_2 + [\text{M}^+]$ : 466.1742, Found: 466.1744.

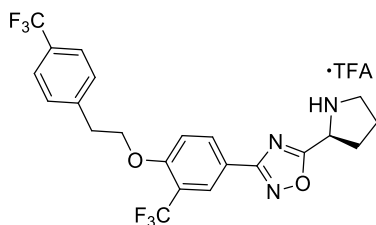


**(S)-2-(3-(3-(Trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.30-8.26 (m, 2H), 7.74 (t,  $J = 8.8$  Hz, 2H), 7.63 (t,  $J = 7.4$  Hz, 1H), 7.50 (t,  $J = 7.6$  Hz, 1H), 7.37 (d,  $J = 9.5$  Hz, 1H), 5.42 (s, 2H), 5.16 (t,  $J = 7.8$  Hz, 1H), 3.60-3.44 (m, 2H), 2.67-2.58 (m, 1H), 2.41-2.34 (m, 1H), 2.29-2.15 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.4, 168.6, 159.9, 135.3, 134.2, 133.7, 130.4, 129.7, 128.7 (q,  $^2J_{CF} = 31.0$  Hz), 127.5 (q,  $^3J_{CF} = 5.4$  Hz), 127.1 (q,  $^3J_{CF} = 5.7$  Hz), 125.8 (q,  $^1J_{CF} = 274.3$  Hz), 124.6 (q,  $^1J_{CF} = 273.1$  Hz), 120.7 (q,  $^2J_{CF} = 31.7$  Hz), 120.0, 115.2, 68.4, 55.5, 47.4, 30.3, 24.5;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -61.0 (s, 3F), -63.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{18}\text{F}_6\text{N}_3\text{O}_2 + [\text{M}^+]$ : 458.1303, Found: 458.1301.

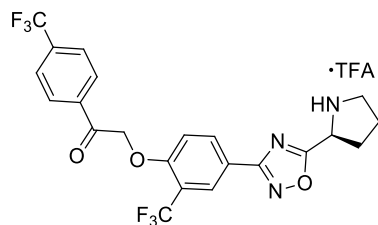


**(S)-2-(3-(4-((3,5-Bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.35 (d,  $J = 6.5$  Hz, 2H), 8.12 (s, 2H), 7.96 (s, 1H), 7.51 (d,  $J = 9.3$  Hz, 1H), 5.52 (s, 2H), 5.21 (t,  $J = 7.8$  Hz, 1H), 3.65-3.49 (m,

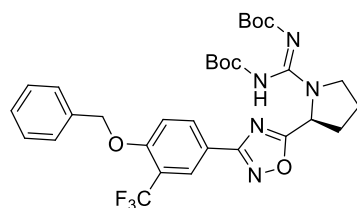
2H), 2.73-2.63 (m, 1H), 2.50-2.38 (m, 1H), 2.37-2.20 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $\text{d}_4$ )  $\delta$  176.4, 168.6, 159.7, 140.9, 134.2, 133.0 (q,  $^2J_{\text{CF}} = 33.6$  Hz), 128.4 (q,  $^4J_{\text{CF}} = 3.6$  Hz), 127.5 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 273.1$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 273.1$  Hz), 122.8, 120.7 (q,  $^2J_{\text{CF}} = 31.7$  Hz), 120.3, 115.5, 70.0, 55.5, 47.4, 30.2, 24.5;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $\text{d}_4$ )  $\delta$  -63.8 (s, 3F), -64.1 (s, 6F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{17}\text{F}_9\text{N}_3\text{O}_2 + [\text{M}^+]$ : 526.1177, Found: 526.1186.



**(S)-2-(3-(3-(Trifluoromethyl)-4-(4-(trifluoromethyl)phenethoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $\text{d}$ )  $\delta$  8.18 (s, 1H), 8.08 (d,  $J = 8.3$  Hz, 1H), 7.58 (d,  $J = 8.0$  Hz, 2H), 7.43 (d,  $J = 8.0$  Hz, 2H), 7.00 ( $J = 8.5$  Hz, 1H), 5.12 (s, 1H), 4.31 (t,  $J = 6.3$  Hz, 2H), 3.62 (d,  $J = 23.8$  Hz, 2H), 3.21 (t,  $J = 6.1$  Hz, 2H), 2.64 (s, 1H), 2.45 (s, 1H), 2.26 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $\text{d}$ )  $\delta$  174.5, 167.4, 159.1, 142.0, 132.8, 129.7, 129.2 (q,  $^2J_{\text{CF}} = 32.6$  Hz), 126.9 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 125.5 (q,  $^3J_{\text{CF}} = 3.8$  Hz), 124.4 (q,  $^1J_{\text{CF}} = 273.0$  Hz), 123.1 (q,  $^1J_{\text{CF}} = 274.1$  Hz), 119.6 (q,  $^2J_{\text{CF}} = 31.9$  Hz), 117.8, 113.0, 76.8, 69.4, 54.1, 46.3, 35.5, 30.1, 24.0;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $\text{d}$ )  $\delta$  -63.1 (s, 3F), -63.4 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{20}\text{F}_6\text{N}_3\text{O}_2 + [\text{M}^+]$ : 472.1460, Found: 472.1452.

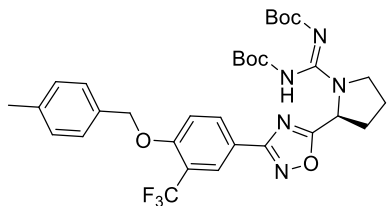


**(S)-2-(3-(4-(2-Oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, yellow oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.21 (s, 1H), 8.10 (d,  $J$  = 8.1 Hz, 3H), 7.77 (d,  $J$  = 8.1 Hz, 2H), 6.94 (s, 1H), 5.43 (s, 2H), 5.13 (s, 1H), 3.65 (s, 2H), 2.64 (s, 1H), 2.45 (s, 1H), 2.26 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  192.9, 174.6, 167.2, 158.1, 136.7, 135.6 (q,  $^2J_{\text{CF}}$  = 33.0 Hz), 132.8, 128.9, 127.1 (q,  $^3J_{\text{CF}}$  = 5.2 Hz), 126.1 (q,  $^3J_{\text{CF}}$  = 3.3 Hz), 123.5 (q,  $^1J_{\text{CF}}$  = 274.1 Hz), 122.9 (q,  $^1J_{\text{CF}}$  = 274.1 Hz), 120.0 (q,  $^2J_{\text{CF}}$  = 31.8 Hz), 118.9, 113.3, 71.5, 54.2, 46.4, 30.0, 23.9;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -63.4 (s, 3F), -64.1 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{18}\text{F}_6\text{N}_3\text{O}_3$  + [M+]: 486.1252, Found: 486.1255.



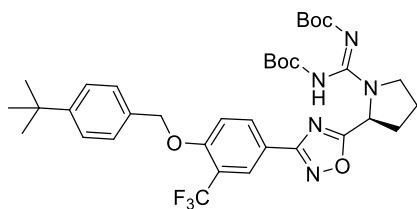
**(S)-Tert-butyl ((2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((tert-butoxycarbonyl)amino)methylene)carbamate (3.31a).** Synthesized by general procedure 3-E. 45% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.31 (d,  $J$  = 2.0 Hz, 1H), 8.17 (dd,  $J$  = 8.7, 2.1 Hz, 1H), 7.46-7.36 (m, 4H), 7.36-7.29 (m, 1H), 7.11 (t,  $J$  = 8.8 Hz, 1H), 5.60 (dd,  $J$  = 7.8, 4.6 Hz, 1H), 5.26 (s, 2H), 3.93 – 3.86 (m, 1H), 3.83 – 3.73 (m, 1H), 2.47 – 2.39 (m, 1H), 2.24 – 2.14 (m, 2H), 2.07-1.98 (m, 1H), 1.53-1.39 (m, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  179.3, 167.3, 162.2, 158.6, 153.7, 150.5, 148.8, 135.8, 132.6, 128.8, 128.3, 127.0, 126.9, 123.3 (q,  $^1J_{\text{CF}}$  = 273.2 Hz), 119.8 (q,  $^2J_{\text{CF}}$  = 32.2 Hz), 119.2, 113.6, 82.4, 79.8, 70.6,

55.4, 49.6, 36.7, 31.5, 29.8, 28.2, 28.1, 24.8, 24.1;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.6 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{37}\text{F}_3\text{N}_5\text{O}_6$  [M+H]: 632.2696, Found: 632.2701.



**(S)-Tert-butyl**                      **(((tert-butoxycarbonyl)amino)(2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.31b).**

Synthesized by general procedure 3-E. 34% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  10.10 (s, 1H), 8.31 (d,  $J$  = 1.6 Hz, 1H), 8.16 (dd,  $J$  = 8.7, 1.9 Hz, 1H), 7.33 (d,  $J$  = 7.9 Hz, 2H), 7.20 (d,  $J$  = 7.9 Hz, 2H), 7.11 (d,  $J$  = 8.8 Hz, 1H), 5.61 (dd,  $J$  = 7.7, 4.5 Hz, 1H), 5.22 (s, 2H), 3.94-3.86 (m, 1H), 3.85-3.72 (m, 1H), 2.48-2.40 (m, 1H), 2.36 (s, 3H), 2.26-2.14 (m, 2H), 2.08-1.99 (m, 1H), 1.48 (d,  $J$  = 20.8 Hz, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  179.3, 167.3, 158.7, 153.8, 150.9, 138.1, 132.8, 132.6, 129.5, 127.1, 127.0 (q,  $^3J_{\text{CF}}$  = 5.1 Hz), 123.4 (q,  $^1J_{\text{CF}}$  = 274.0 Hz), 119.9 (q,  $^2J_{\text{CF}}$  = 31.6 Hz), 119.1, 113.7, 81.3, 70.7, 55.5, 49.7, 31.6, 28.2, 28.1, 24.1, 21.3;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.6 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{39}\text{F}_3\text{N}_5\text{O}_6$  [M+H]: 646.2853, Found: 646.2832.

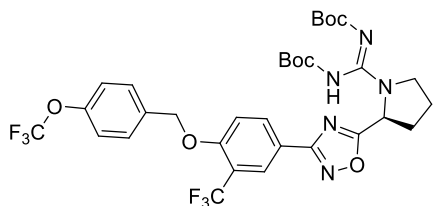


**(S)-Tert-butyl**                      **(((tert-butoxycarbonyl)amino)(2-(3-(4-((4-(tert-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.31c).**

Synthesized by general procedure 3-E. 44% yield, colorless oil;  $^1\text{H}$  NMR (500 MHz, Chloroform-d)  $\delta$  8.31 (d,  $J$  = 1.6 Hz, 1H), 8.17 (dd,  $J$  = 8.7, 1.8 Hz, 1H), 7.42 (d,  $J$  = 8.4 Hz, 2H), 7.37 (d,  $J$  =

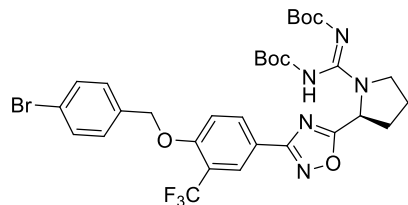


8.3 Hz, 2H), 7.13 (d,  $J = 8.7$  Hz, 1H), 5.61 (dd,  $J = 7.5, 4.5$  Hz, 1H), 5.24 (s, 2H), 3.93-3.87 (m, 1H), 3.81 (s, 1H), 2.48-2.40 (m, 1H), 2.24-2.14 (m, 2H), 2.08-1.98 (m, 1H), 1.45 (s, 18H), 1.33 (s, 9H);  $^{13}\text{C}$  NMR (126 MHz, Chloroform- $d$ )  $\delta$  179.3, 167.3, 158.8, 153.7, 151.3, 132.8, 132.6, 129.5, 127.0 (q,  $^3J_{\text{CF}} = 5.0$  Hz), 126.8, 125.7, 123.4 (q,  $^1J_{\text{CF}} = 273.2$  Hz), 119.9 (q,  $^2J_{\text{CF}} = 31.6$  Hz), 119.1, 113.7, 82.1, 79.9, 70.5, 55.5, 49.6, 34.7, 31.5, 29.8, 28.2, 24.1;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.6 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{35}\text{H}_{45}\text{F}_3\text{N}_5\text{O}_6$  [M+H]: 688.3322, Found: 688.3287.

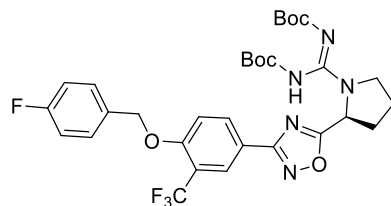


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.31d).**

Synthesized by general procedure 3-E. 55% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  10.11 (s, 1H), 8.33 (s, 1H), 8.20 (dd,  $J = 8.7, 1.8$  Hz, 1H), 7.48 (d,  $J = 8.6$  Hz, 2H), 7.25 (d,  $J = 7.9$  Hz, 2H), 7.11 (t,  $J = 8.7$  Hz, 1H), 5.61 (dd,  $J = 7.6, 4.5$  Hz, 1H), 5.25 (s, 2H), 3.94 – 3.87 (m, 1H), 3.85 – 3.73 (m, 1H), 2.48 – 2.41 (m, 1H), 2.30 – 2.12 (m, 2H), 2.09-2.00 (m, 1H), 1.53-1.38 (m, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  179.4, 167.2, 162.0, 158.3, 153.8, 150.4, 149.1, 134.5, 132.7, 128.4, 127.1 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 123.3 (q,  $^1J_{\text{CF}} = 274.0$  Hz), 121.3, 120.6 (q,  $^1J_{\text{CF}} = 258.6$  Hz), 119.9 (q,  $^2J_{\text{CF}} = 31.0$  Hz), 119.6, 113.5, 82.1, 79.9, 69.8, 55.4, 49.6, 36.8, 31.4, 29.8, 28.2, 28.1, 24.1;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -60.9 (s, 3F), -65.6 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{32}\text{H}_{36}\text{F}_6\text{N}_5\text{O}_7$  [M+H]: 716.2519, Found: 716.2496.

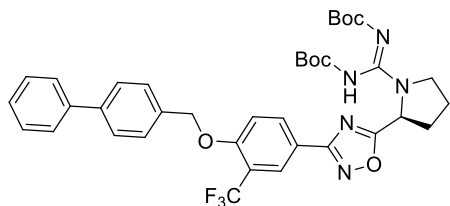


**(S)-Tert-butyl ((2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((tert-butoxycarbonyl)amino)methylene)carbamate (3.31e).** Synthesized by general procedure 3-E. 73% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  10.13 (s, 1H), 8.32 (d,  $J=2.0$  Hz, 1H), 8.19 (dd,  $J=8.7, 2.1$  Hz, 1H), 7.53 (dt,  $J=8.5, 2.5$  Hz, 2H), 7.33 (d,  $J=8.5$  Hz, 2H), 7.09 (t,  $J=8.8$  Hz, 1H), 5.61 (dd,  $J=7.7, 4.5$  Hz, 1H), 5.20 (s, 2H), 3.94–3.86 (m, 1H), 3.83–3.76 (m, 1H), 2.50–2.39 (m, 1H), 2.25–2.13 (m, 2H), 2.09–2.00 (m, 1H), 1.52–1.38 (m, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  179.4, 167.2, 158.3, 153.8, 134.8, 132.7, 132.0, 128.6, 127.1 (q,  $^3J_{\text{CF}}=5.3$  Hz), 123.3 (q,  $^1J_{\text{CF}}=274.0$  Hz), 122.3, 119.9 (q,  $^2J_{\text{CF}}=31.7$  Hz), 119.5, 113.5, 69.9, 55.4, 49.6, 31.7, 31.4, 29.8, 28.2, 28.1, 24.1;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.6 (s, 3F); HRMS (ESI<sup>+</sup>): Calcd for  $\text{C}_{31}\text{H}_{36}\text{BrF}_3\text{N}_5\text{O}_6$  [M+H]: 710.1801, Found: 710.1807.



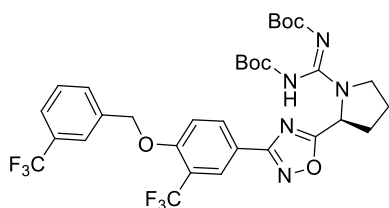
**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.31f).** Synthesized by general procedure 3-E. 44% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.32 (d,  $J=1.6$  Hz, 1H), 8.19 (dd,  $J=8.7, 1.9$  Hz, 1H), 7.42 (dd,  $J=8.5, 5.4$  Hz, 2H), 7.14–7.03 (m, 3H), 5.61 (dd,  $J=7.7, 4.5$  Hz, 1H), 5.21 (s, 2H), 3.94–3.87 (m, 1H), 3.85–3.75 (m, 1H), 2.48–2.41 (m, 1H), 2.25–2.15 (m, 2H), 2.04 (p,  $J=6.7$  Hz, 1H), 1.45 (s, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  179.4, 167.3, 162.7 (d,  $^1J=247.9$  Hz), 158.4, 153.8, 132.6, 131.5 (d,  $^4J=3.1$  Hz),

128.9 (d,  $^3J = 8.3$  Hz), 127.0 (q,  $^3J = 5.2$  Hz), 123.3 (q,  $^1J_{CF} = 274.0$  Hz), 120.0 (q,  $^2J_{CF} = 31.7$  Hz), 119.4, 115.8 (d,  $^2J = 21.7$  Hz) 113.6, 81.5, 70.1, 55.5, 49.7, 31.5, 28.2, 28.1, 24.1;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.6 (s, 3F), -116.8- -116.9 (m, 1F); HRMS (ESI+): Calcd for  $\text{C}_{31}\text{H}_{36}\text{F}_4\text{N}_5\text{O}_6$  [M+H]: 650.2602, Found: 650.2607.



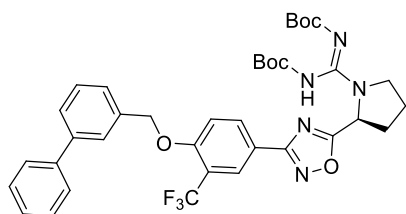
**(S)-Tert-butyl ((2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((tert-butoxycarbonyl)amino)methylene)carbamate (3.31g).**

Synthesized by general procedure 3-E. 36% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  8.31 (s, 1H), 8.19 (d,  $J = 8.6$  Hz, 1H), 7.65-7.56 (m, 4H), 7.52 (d,  $J = 8.2$  Hz, 2H), 7.44 (t,  $J = 7.6$  Hz, 2H), 7.35 (t,  $J = 7.3$  Hz, 1H), 7.16 (d,  $J = 8.7$  Hz, 1H), 6.12 (s, 1H), 5.31 (s, 2H), 4.14-4.05 (m, 1H), 3.94 (s, 1H), 2.60 (s, 1H), 2.35 (s, 1H), 2.18 (s, 2H), 1.48 (s, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  167.3, 158.7, 153.4, 141.3, 140.8, 134.7, 132.7, 128.9, 127.6, 127.5, 127.2, 127.1, 125.0, 123.4 (q,  $^1J_{CF} = 273.7$  Hz), 120.0 (q,  $^2J_{CF} = 32.7$  Hz), 113.7, 82.6, 70.5, 56.1, 51.1, 34.6, 31.4, 28.2, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.6 (s, 2F), -65.6 (s, 1F); HRMS (ESI+): Calcd for  $\text{C}_{37}\text{H}_{41}\text{F}_3\text{N}_5\text{O}_6$  [M+H]: 708.3009, Found: 708.3008.



**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.**

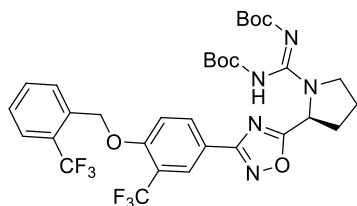
**yl)methylene)carbamate (3.31h).** Synthesized by general procedure 3-E. 64% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  10.12 (s, 1H), 8.34 (d,  $J$ = 2.0 Hz, 1H), 8.21 (dd,  $J$ = 8.7, 2.1 Hz, 1H), 7.72 (s, 1H), 7.66 (d,  $J$ = 7.7 Hz, 1H), 7.60 (d,  $J$ = 7.8 Hz, 1H), 7.53 (t,  $J$ = 7.7 Hz, 1H), 7.12 (d,  $J$ = 8.8 Hz, 1H), 5.60 (dd,  $J$ = 7.8, 4.6 Hz, 1H), 5.30 (s, 2H), 3.93 – 3.86 (m, 1H), 3.83-3.76 (m, 1H), 2.49 – 2.40 (m, 1H), 2.28 – 2.13 (m, 2H), 2.04 (p,  $J$ = 6.8 Hz, 1H), 1.53-1.40 (m, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  179.5, 167.2, 158.2, 153.8, 150.3, 136.8, 132.7, 131.3 (q,  $^2J_{\text{CF}}$  = 32.7 Hz), 130.2, 129.4, 127.1 (q,  $^3J_{\text{CF}}$  = 5.3 Hz), 125.2 (q,  $^3J_{\text{CF}}$  = 3.8 Hz), 124.1 (q,  $^1J_{\text{CF}}$  = 273.7 Hz), 123.7 (q,  $^3J_{\text{CF}}$  = 3.9 Hz), 123.3 (q,  $^1J_{\text{CF}}$  = 274.0 Hz), 120.2, 119.8, 119.8, 113.4, 82.4, 79.8, 69.8, 55.4, 49.6, 36.8, 31.5, 28.2, 28.1, 24.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.6 (s, 3F), -65.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{36}\text{F}_6\text{N}_5\text{O}_6$  [M+H]: 700.2570, Found: 700.2603.



**(S)-Tert-butyl ((2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((tert-butoxycarbonyl)amino)methylene)carbamate (3.31i).**

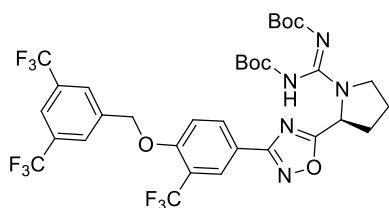
Synthesized by general procedure 3-E. 56% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  10.10 (s, 1H), 8.34 (d,  $J$ = 2.0 Hz, 1H), 8.19 (dd,  $J$ = 8.7, 2.1 Hz, 1H), 7.72-7.67 (m, 1H), 7.63-7.54 (m, 3H), 7.52-7.40 (m, 4H), 7.36 (tt,  $J$ = 7.4, 1.1 Hz, 1H), 7.16 (d,  $J$ = 8.8 Hz, 1H), 5.61 (dd,  $J$ = 7.8, 4.5 Hz, 1H), 5.33 (s, 2H), 3.94 – 3.87 (m, 1H), 3.84 – 3.77 (m, 1H), 2.49 – 2.41 (m, 1H), 2.24 – 2.15 (m, 2H), 2.10-1.98 (m, 1H), 1.51-1.40 (m, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  179.4, 167.3, 158.6, 153.7, 141.8, 140.8, 136.3, 132.7, 129.3, 129.0, 127.6, 127.2, 127.1, 125.8, 125.7, 123.4 (q,  $^1J_{\text{CF}}$  = 273.9 Hz), 119.9 (q,  $^2J_{\text{CF}}$  = 31.8 Hz), 119.3, 113.6, 70.6, 55.4, 49.6, 31.5,

28.2, 28.1, 24.1;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.5 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{37}\text{H}_{41}\text{F}_3\text{N}_5\text{O}_6$  [M+H]: 708.3009, Found: 708.2955.



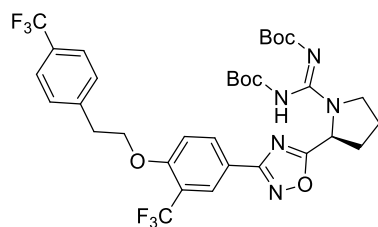
**(S)-Tert-butyl** (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-

**yl)methylene)carbamate (3.31j).** Synthesized by general procedure 3-E. 59% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  10.12 (s, 1H), 8.34 (d,  $J$  = 1.6 Hz, 1H), 8.20 (dd,  $J$  = 8.7, 1.8 Hz, 1H), 7.81 (d,  $J$  = 7.8 Hz, 1H), 7.70 (d,  $J$  = 7.8 Hz, 1H), 7.60 (t,  $J$  = 7.6 Hz, 1H), 7.44 (t,  $J$  = 7.6 Hz, 1H), 7.09 (d,  $J$  = 8.8 Hz, 1H), 5.60 (dd,  $J$  = 7.7, 4.5 Hz, 1H), 5.45 (s, 2H), 3.93 – 3.87 (m, 1H), 3.85-3.74 (m, 1H), 2.47 – 2.41 (m, 1H), 2.25 – 2.12 (m, 2H), 2.07-2.00 (m, 1H), 1.45 (s, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  179.4, 167.2, 161.9, 158.0, 153.9, 150.2, 134.4, 132.8, 132.6, 128.0, 127.9, 127.4, 127.1 (q,  $^3J_{\text{CF}}$  = 5.3 Hz), 126.8, 126.0 (q,  $^3J_{\text{CF}}$  = 5.6 Hz), 124.4 (q,  $^1J_{\text{CF}}$  = 274.8 Hz), 123.3 (q,  $^1J_{\text{CF}}$  = 273.9 Hz), 119.8 (q,  $^2J_{\text{CF}}$  = 31.6 Hz), 119.7, 119.6, 119.3, 113.4, 82.4, 79.8, 66.6, 55.4, 49.6, 31.6, 28.2, 24.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -63.6 (s, 3F), -65.6 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{32}\text{H}_{36}\text{F}_6\text{N}_5\text{O}_6$  [M+H]: 700.2570, Found: 700.2596.



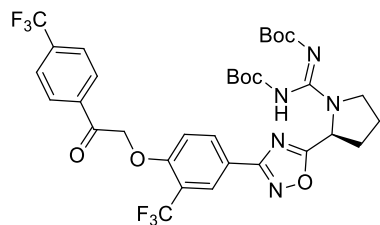
**(S)-Tert-butyl** ((2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate

**(3.31k)**. Synthesized by general procedure 3-E. 67% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  10.10 (s, 1H), 8.36 (s, 1H), 8.24 (dd,  $J$ = 8.6, 1.7 Hz, 1H), 7.95 (s, 2H), 7.87 (s, 1H), 7.13 (d,  $J$  = 8.7 Hz, 1H), 5.61 (dd,  $J$ = 7.7, 4.5 Hz, 1H), 5.34 (s, 2H), 3.94 – 3.86 (m, 1H), 3.84-3.76 (m, 1H), 2.50 – 2.39 (m, 1H), 2.26 – 2.13 (m, 2H), 2.10-1.99 (m, 1H), 1.45 (s, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  179.6, 167.1, 162.3, 157.7, 153.9, 150.6, 138.4, 132.8, 132.3 (q,  $^2J_{\text{CF}}$  = 33.7 Hz), 127.3 (q,  $^3J_{\text{CF}}$  = 5.1 Hz), 127.0, 123.3 (q,  $^1J_{\text{CF}}$  = 273.9 Hz), 123.2 (q,  $^1J_{\text{CF}}$  = 274.0 Hz), 122.3, 120.3, 120.0, 119.2, 113.3, 82.4, 79.7, 69.1, 55.5, 49.6, 31.5, 28.2, 24.1;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.6 (s, 3F), -66.1 (s, 6F); HRMS (ESI+): Calcd for  $\text{C}_{33}\text{H}_{35}\text{F}_9\text{N}_5\text{O}_6$  [M+H]: 768.2444, Found: 768.2439.

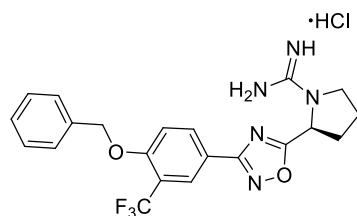


**(S)-Tert-butyl** **(((tert-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-(trifluoromethyl)phenethoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-**

**yl)methylene)carbamate (3.31l)**. Synthesized by general procedure 3-E. 33% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.28 (s, 1H), 8.18 (d,  $J$ = 8.6 Hz, 1H), 7.58 (d,  $J$ = 7.9 Hz, 2H), 7.44 (d,  $J$ = 7.9 Hz, 2H), 7.03 (d,  $J$  = 8.7 Hz, 1H), 5.68 (dd,  $J$ = 7.2, 5.0 Hz, 1H), 4.32 (t,  $J$ = 6.3 Hz, 2H), 3.97 – 3.87 (m, 1H), 3.86-3.77 (m, 1H), 3.22 (t,  $J$ = 6.2 Hz, 2H), 2.53 – 2.42 (m, 1H), 2.29 – 2.15 (m, 2H), 2.10-2.01 (m, 1H), 1.45 (s, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  179.1, 167.3, 158.7, 153.7, 142.0, 132.7, 129.7, 127.0, 125.5, 123.9 123.3 (q,  $^1J_{\text{CF}}$  = 273.9 Hz), 123.0, 119.6 (q,  $^2J_{\text{CF}}$  = 31.7 Hz), 112.9, 81.4, 69.4, 55.6, 49.9, 35.6, 31.5, 31.4, 29.9, 28.2, 24.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.5 (s, 3F), -65.5 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{33}\text{H}_{38}\text{F}_6\text{N}_5\text{O}_6$  [M+H]: 714.2726, Found: 714.2699.

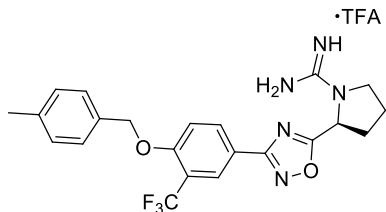


**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate (3.31m).** Synthesized by general procedure 3-E. 31% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  10.12 (s, 1H), 8.33 (d,  $J = 2.0$  Hz, 1H), 8.18 (dd,  $J = 8.7, 2.2$  Hz, 1H), 8.14 (d,  $J = 8.1$  Hz, 2H), 7.77 (d,  $J = 8.2$  Hz, 2H), 6.97 (d,  $J = 8.8$  Hz, 1H), 5.60 (dd,  $J = 7.8, 4.6$  Hz, 1H), 5.40 (s, 2H), 3.94 – 3.85 (m, 1H), 3.81 (s, 1H), 2.49 – 2.40 (m, 1H), 2.23 – 2.15 (m, 2H), 2.09-1.99 (m, 1H), 1.51-1.42 (m, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  193.3, 179.6, 167.1, 157.6, 153.8, 136.8, 135.6 (q,  $^2J_{\text{CF}} = 33.0$  Hz), 132.7, 129.1, 127.3 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 126.1 (q,  $^3J_{\text{CF}} = 3.8$  Hz), 123.5 (q,  $^1J_{\text{CF}} = 274.4$  Hz), 123.1 (q,  $^1J_{\text{CF}} = 274.2$  Hz), 120.4, 120.0 (q,  $^2J_{\text{CF}} = 32.1$  Hz), 113.1, 71.8, 55.4, 48.3, 31.5, 28.2, 28.1, 24.1;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.4 (s, 3F), -66.3 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{33}\text{H}_{36}\text{F}_6\text{N}_5\text{O}_7$  [M+H]: 728.2519, Found: 728.2524.

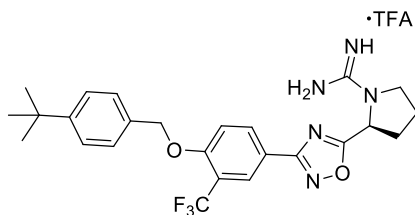


**(S)-Amino (2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.32a).** Synthesized by general procedure F. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.24 (d,  $J = 7.4$  Hz, 2H), 7.47 (d,  $J = 7.3$  Hz, 2H), 7.44-7.37 (m, 3H), 7.33 (t,  $J = 7.2$  Hz, 1H), 5.46 (d,  $J = 6.7$  Hz, 1H), 5.32 (s, 2H), 3.78 (td,  $J = 9.5,$

2.2 Hz, 1H), 3.63 (q,  $J=9.6$  Hz, 1H), 2.65 – 2.52 (m, 1H), 2.50 – 2.44 (m, 1H), 2.30-2.18 (m, 1H), 2.14-2.04 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.5, 160.2, 157.1, 137.3, 133.9, 129.6, 129.2, 128.2, 127.1 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 272.4$  Hz), 120.5 (q,  $^2J_{\text{CF}} = 31.7$  Hz), 119.8, 115.5, 71.7, 56.5, 49.0, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.6 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{21}\text{F}_3\text{N}_5\text{O}_2 + [\text{M}^+]$ : 432.1647, Found: 432.1626.



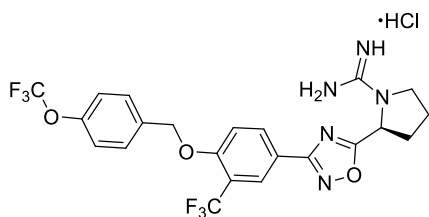
**(S)-Amino(2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate (3.32b).** Synthesized by general procedure 3-D. 68% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.27 (dd,  $J=9.1, 1.2$  Hz, 2H), 7.44 (d,  $J=8.4$  Hz, 1H), 7.38 (d,  $J=8.0$  Hz, 2H), 7.25 (d,  $J=7.8$  Hz, 2H), 5.48 (dd,  $J=7.9, 1.9$  Hz, 1H), 5.31 (s, 2H), 3.82 (td,  $J=9.2, 2.6$  Hz, 1H), 3.65 (q,  $J=7.6$  Hz, 1H), 2.67 – 2.46 (m, 2H), 2.38 (s, 3H), 2.31 – 2.23 (m, 1H), 2.18-2.08 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.5, 160.4, 157.1, 139.2, 134.3, 133.8, 130.2, 128.4, 127.2 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 273.1$  Hz), 120.6 (q,  $^2J_{\text{CF}} = 31.4$  Hz), 119.7, 115.6, 71.8, 56.5, 32.7, 24.3, 21.2;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{23}\text{F}_3\text{N}_5\text{O}_2 + [\text{M}^+]$ : 446.1804, Found: 446.1818.



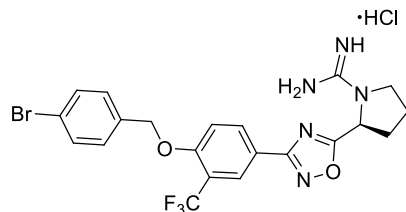
**(S)-Amino(2-(3-(4-((tert-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate (3.32c).** Synthesized by general



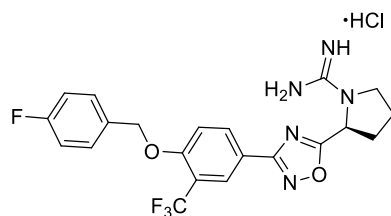
procedure 3-E. 70% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.27 (d,  $J= 8.2$  Hz, 2H), 7.50-7.38 (m, 5H), 5.48 (dd,  $J= 6.0, 2.0$  Hz, 1H), 5.33 (s, 2H), 3.82 (td,  $J= 9.4, 2.4$  Hz, 1H), 3.65 (q,  $J= 9.5$  Hz, 1H), 2.69 – 2.43 (m, 2H), 2.30 – 2.21 (m, 1H), 2.17-2.07 (m, 1H), 1.37 (s, 9H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.5, 157.1, 152.4, 134.3, 133.8, 133.4, 128.2, 127.2 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 273.1$  Hz), 120.6 (q,  $^2J_{\text{CF}} = 31.4$  Hz), 119.7, 118.5, 115.5, 71.7, 56.5, 35.4, 32.7, 31.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 2F), -64.0 (s, 1F); HRMS (ESI+): Calcd for  $\text{C}_{25}\text{H}_{29}\text{F}_3\text{N}_5\text{O}_2 + [\text{M}^+]$ : 488.2273, Found: 488.2270.



**(S)-Amino(2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.32d).** Synthesized by general procedure 3-F. 64% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.33-8.29 (m, 2H), 7.63 (d,  $J= 8.8$  Hz, 2H), 7.48 (d,  $J= 9.3$  Hz, 1H), 7.36 (d,  $J= 7.9$  Hz, 2H), 5.49 (dd,  $J= 7.9, 1.8$  Hz, 1H), 5.40 (s, 2H), 3.82 (td,  $J= 9.3, 2.6$  Hz, 1H), 3.66 (q,  $J= 9.4$  Hz, 1H), 2.66 – 2.48 (m, 2H), 2.34 – 2.22 (m, 1H), 2.19-2.07 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.3, 168.5, 160.0, 157.1, 150.3, 136.6, 134.0, 130.0, 127.2 (q,  $^3J_{\text{CF}} = 5.2$  Hz), 124.6 (q,  $^1J_{\text{CF}} = 273.0$  Hz), 122.2, 121.7 (q,  $^1J_{\text{CF}} = 256.9$  Hz), 120.6 (q,  $^2J_{\text{CF}} = 31.5$  Hz), 120.1, 115.5, 70.9, 56.5, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -59.0 (s, 3F), -63.6 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{20}\text{F}_6\text{N}_5\text{O}_3 + [\text{M}^+]$ : 516.1470, Found: 516.1460.

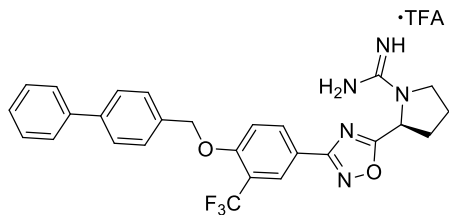


**(S)-Amino(2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.32e).** Synthesized by general procedure 3-F. 96% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.29-8.21 (m, 2H), 7.56 (d,  $J$ = 8.4 Hz, 2H), 7.41 (dd,  $J$ = 8.8, 4.0 Hz, 3H), 5.45 (d,  $J$ = 6.5 Hz, 1H), 5.30 (s, 2H), 3.78 (td,  $J$ = 9.4, 2.2 Hz, 1H), 3.62 (q,  $J$ = 9.5 Hz, 1H), 2.62 – 2.45 (m, 2H), 2.28 – 2.18 (m, 1H), 2.14-2.01 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.5, 160.0, 157.1, 136.6, 133.9, 132.8, 130.1, 127.2 (q,  $^3J_{\text{CF}}$  = 5.4 Hz), 124.7 (q,  $^1J_{\text{CF}}$  = 273.1 Hz), 123.0, 120.6 (q,  $^2J_{\text{CF}}$  = 31.5 Hz), 120.1, 115.5, 71.0, 56.5, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.6 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{20}\text{BrF}_3\text{N}_5\text{O}_2 + [\text{M}^+]$ : 510.0752, Found: 510.0746.

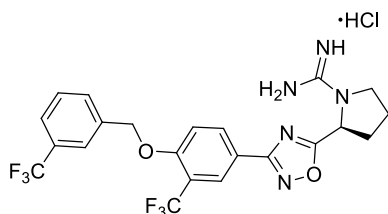


**(S)-Amino(2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.32f).** Synthesized by general procedure 3-F. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.26 (d,  $J$ = 7.0 Hz, 2H), 7.50 (dd,  $J$ = 8.5, 5.4 Hz, 2H), 7.43 (d,  $J$ = 9.3 Hz, 1H), 7.13 (t,  $J$ = 8.8 Hz, 2H), 5.45 (d,  $J$ = 6.7 Hz, 1H), 5.30 (s, 2H), 3.78 (td,  $J$ = 9.5, 2.3 Hz, 1H), 3.62 (q,  $J$ = 9.6 Hz, 1H), 2.62 – 2.43 (m, 2H), 2.27 – 2.19 (m, 1H), 2.13-2.03 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.5, 164.0 (d,  $^1J$ = 246.4 Hz), 160.1, 157.1, 133.9, 133.4 (d,  $^4J$ = 3.3 Hz), 130.5 (d,  $^3J$ = 8.3 Hz), 127.2 (q,  $^3J_{\text{CF}}$  = 5.4 Hz), 124.7 (q,  $^1J_{\text{CF}}$  = 273.1 Hz), 120.6 (q,  $^2J_{\text{CF}}$  = 31.5 Hz), 120.0, 116.4 (d,  $^2J$ = 22.1 Hz), 115.5,

71.2, 56.5, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.6 (s, 3F), -115.6- -115.8 (m, 1F); HRMS (ESI+): Calcd for  $\text{C}_{21}\text{H}_{20}\text{F}_4\text{N}_5\text{O}_2 + [\text{M}^+]$ : 450.1553, Found: 450.1533.

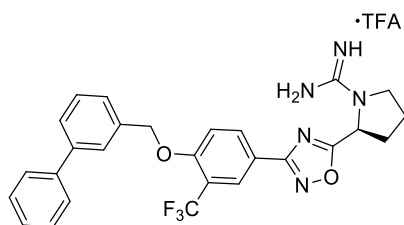


**(S)-2-(2-(3-(4-((1,1'-Biphenyl)-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)(amino)methaniminium 2,2,2-trifluoroacetate (3.32g).** Synthesized by general procedure 3-D. 84% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.30 (d,  $J$ = 7.6 Hz, 2H), 7.68 (dd,  $J$ = 13.3, 7.8 Hz, 4H), 7.60 (d,  $J$ = 8.2 Hz, 2H), 7.47 (t,  $J$ = 7.7 Hz, 3H), 7.38 (t,  $J$ = 7.4 Hz, 1H), 5.48 (dd,  $J$ = 7.8, 1.6 Hz, 1H), 5.42 (s, 2H), 3.82 (td,  $J$ = 9.4, 2.5 Hz, 1H), 3.72-3.59 (m, 1H), 2.66 – 2.49 (m, 2H), 2.34 – 2.22 (m, 1H), 2.21-2.07 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.5, 160.3, 157.1, 142.5, 141.9, 136.4, 133.9, 129.9, 128.8, 128.5, 128.2, 128.0, 127.2 (q,  $^3J_{\text{CF}}$  = 5.4 Hz), 124.7 (q,  $^1J_{\text{CF}}$  = 273.1 Hz), 120.7 (q,  $^2J_{\text{CF}}$  = 31.6 Hz), 119.9, 115.6, 71.6, 56.5, 32.7, 28.1, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{27}\text{H}_{25}\text{F}_3\text{N}_5\text{O}_2 + [\text{M}^+]$ : 508.1960, Found: 508.1974.

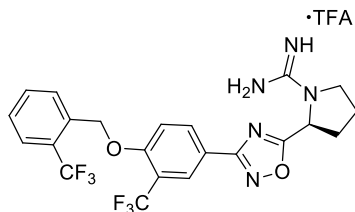


**(S)-Amino(2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.32h).** Synthesized by general procedure 3-F. 99% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.28 (d,  $J$ = 6.5 Hz, 2H), 7.82 (s, 1H), 7.75 (d,  $J$ = 7.4 Hz, 1H), 7.65 (d,  $J$ = 7.8 Hz, 1H), 7.61 (t,  $J$ = 7.8 Hz, 1H), 7.44 (t,  $J$ = 9.2 Hz, 1H), 5.45 (d,  $J$ = 7.1 Hz, 1H), 5.42 (s, 2H), 3.78 (t,  $J$ = 8.3 Hz, 1H), 3.62 (q,  $J$ = 9.0

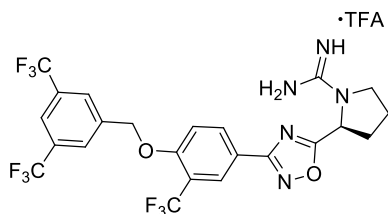
Hz, 1H), 3.62-3.53 (m, 1H), 2.52 – 2.41 (m, 1H), 2.22 (s, 1H), 2.09 (s, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.3, 168.4, 159.9, 157.1, 138.8, 134.0, 132.0 (q,  $^2J_{\text{CF}} = 32.5$  Hz), 131.7, 130.5, 127.2 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 125.8 (q,  $^3J_{\text{CF}} = 3.8$  Hz), 125.5 (q,  $^1J_{\text{CF}} = 272.6$  Hz), 124.7 (q,  $^3J_{\text{CF}} = 3.9$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 273.1$  Hz), 120.6 (q,  $^2J_{\text{CF}} = 31.6$  Hz), 120.2, 115.5, 70.9, 56.5, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 3F), -63.8 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{22}\text{H}_{20}\text{F}_6\text{N}_5\text{O}_2 + [\text{M}^+]$ : 500.1521, Found: 500.1514.



**(S)-2-(2-(3-(4-([1,1'-Biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)(amino)methaniminium 2,2,2-trifluoroacetate (3.32i).** Synthesized by general procedure 3-D. 50% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.30 (s, 1H), 8.28 (d,  $J = 2.1$  Hz, 1H), 7.78 (s, 1H), 7.64 (tt,  $J = 7.1, 1.6$  Hz, 3H), 7.55-7.45 (m, 4H), 7.38 (tt,  $J = 7.3, 1.5$  Hz, 1H), 5.48 (dd,  $J = 7.9, 1.9$  Hz, 1H), 5.44 (s, 2H), 3.81 (td,  $J = 9.42, 2.6$  Hz, 1H), 3.69-3.62 (m, 1H), 2.68 – 2.46 (m, 2H), 2.30 – 2.22 (m, 1H), 2.20-2.04 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.5, 160.2, 157.1, 142.9, 142.1, 138.0, 133.9, 130.2, 129.9, 128.5, 128.0, 127.8, 127.2 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 127.0, 126.8, 124.8 (q,  $^1J_{\text{CF}} = 273.1$  Hz), 120.6 (q,  $^2J_{\text{CF}} = 31.5$  Hz), 119.9, 115.5, 71.7, 56.4, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.6 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{27}\text{H}_{25}\text{F}_3\text{N}_5\text{O}_2 + [\text{M}^+]$ : 508.1960, Found: 508.1952.

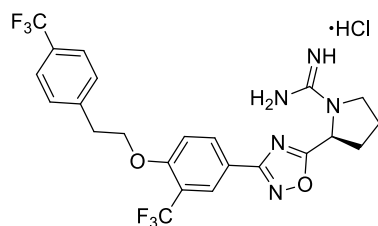


**(S)-Amino(2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate (3.32j).** Synthesized by general procedure 3-D. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.33 (d,  $J = 7.3$  Hz, 2H), 7.83 (t,  $J = 8.5$  Hz, 2H), 7.73 (t,  $J = 7.4$  Hz, 1H), 7.60 (t,  $J = 7.7$  Hz, 1H), 7.44 (d,  $J = 9.5$  Hz, 1H), 5.51 (s, 2H), 5.50-5.47 (m, 1H) 3.82 (td,  $J = 9.3, 2.6$  Hz, 1H), 3.66 (q,  $J = 7.5$  Hz, 1H), 3.68-3.47 (m, 2H), 2.31-2.23 (m, 1H), 2.21-2.06 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.3, 168.5, 159.8, 157.1, 135.4, 134.1, 133.7, 130.5, 129.7, 128.8 (q,  $^2J_{\text{CF}} = 31.1$  Hz), 127.3 (q,  $^3J_{\text{CF}} = 5.4$  Hz), 127.2 (q,  $^3J_{\text{CF}} = 5.6$  Hz), 125.8 (q,  $^1J_{\text{CF}} = 274.3$  Hz), 124.6 (q,  $^1J_{\text{CF}} = 273.1$  Hz), 120.6 (q,  $^2J_{\text{CF}} = 31.7$  Hz), 120.4, 115.2, 68.4, 56.5, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -60.9 (s, 3F), -63.6 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{22}\text{H}_{20}\text{F}_6\text{N}_5\text{O}_2$  + [M $^+$ ]: 500.1521, Found: 500.1538.

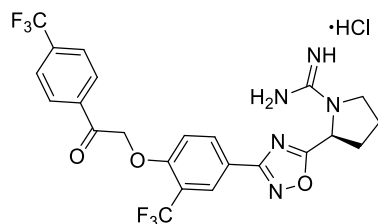


**(S)-Amino(2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate (3.32k).** Synthesized by general procedure 3-D. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.34 (d,  $J = 7.7$  Hz, 2H), 8.15 (s, 2H), 7.99 (s, 1H), 7.52 (d,  $J = 9.2$  Hz, 1H), 5.54 (s, 2H), 5.50 (dd,  $J = 7.9, 1.8$  Hz, 1H), 3.82 (td,  $J = 9.3, 2.6$  Hz, 1H), 3.66 (q,  $J = 8.6$  Hz, 1H), 3.67-3.49 (m, 2H), 2.31-2.23 (m, 1H), 2.18-2.08 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.4, 168.4, 159.5, 157.1,

140.9, 134.1, 133.0 (q,  $^2J_{CF} = 33.5$  Hz), 128.4 (q,  $^4J_{CF} = 3.0$  Hz), 127.3 (q,  $^3J_{CF} = 5.4$  Hz), 124.8 (q,  $^1J_{CF} = 273.1$  Hz), 124.7 (q,  $^1J_{CF} = 273.1$  Hz), 122.8, 120.7 (q,  $^2J_{CF} = 31.6$  Hz), 120.6, 115.5, 70.0, 56.4, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.7 (s, 3F), -64.1 (s, 6F); HRMS (ESI+): Calcd for  $\text{C}_{23}\text{H}_{19}\text{F}_9\text{N}_5\text{O}_2 + [\text{M}^+]$ : 568.1395, Found: 568.1406.

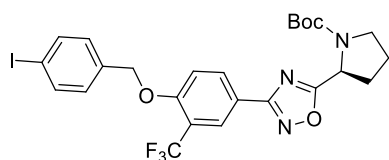


**(S)-Amino(2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenethoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.32l).** Synthesized by general procedure 3-F. 30% yield, clear solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.28 (d,  $J = 8.7$  Hz, 1H), 8.25 (s, 1H), 7.63 (d,  $J = 8.2$  Hz, 2H), 7.57 (d,  $J = 8.1$  Hz, 2H), 7.38 (d,  $J = 8.7$  Hz, 1H), 5.48 (d,  $J = 6.4$  Hz, 1H), 4.48 (t,  $J = 6.2$  Hz, 1H), 3.81 (td,  $J = 9.3, 2.5$  Hz, 1H), 3.66 (q,  $J = 9.5$  Hz, 1H), 3.28 (t,  $J = 6.1$  Hz, 2H), 2.64 – 2.46 (m, 2H), 2.30 – 2.23 (m, 1H), 2.19-2.05 (m, 1H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.5, 160.4, 157.1, 144.2, 133.9, 130.9, 127.2, 126.2 (q,  $^3J_{CF} = 3.7$  Hz), 125.8 (q,  $^1J_{CF} = 271.3$  Hz), 125.7, 120.3 (q,  $^2J_{CF} = 32.6$  Hz), 119.7, 114.9, 70.7, 56.5, 36.2, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.5 (s, 3F), -63.5 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{23}\text{H}_{22}\text{F}_6\text{N}_5\text{O}_2 + [\text{M}^+]$ : 514.1678, Found: 514.1668.

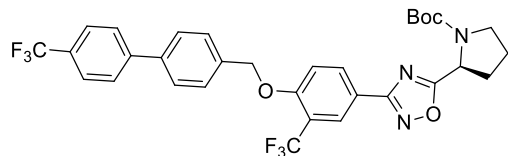


**(S)-Amino(2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride (3.32m).** Synthesized by general

procedure 3-F. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.29-8.14 (m, 3H), 7.88 (d,  $J$ = 8.2 Hz, 1H), 7.79 (d,  $J$ = 8.2 Hz, 1H), 7.66 (d,  $J$ = 8.2 Hz, 1H), 7.40 (s, 1H), 7.27 (dd,  $J$ = 8.7, 5.0 Hz, 1H), 5.79 (s, 1H), 5.44 (td,  $J$ = 8.3, 1.8 Hz, 1H), 5.43 (s, 1H), 3.82-3.74 (m, 1H), 3.67-3.57 (m, 1H), 2.66 – 2.40 (m, 2H), 2.28 – 2.18 (m, 1H), 2.14-2.01 (m, 1H);  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )  $\delta$  194.2, 179.2, 168.4, 159.6, 157.1, 144.7, 133.8, 129.9, 129.5, 126.9, 125.8 (q,  $^3J_{\text{CF}}$  = 3.8 Hz), 124.6, 123.3, 120.4, 120.3, 120.1, 115.3, 115.0, 114.9, 102.1, 72.3, 71.1, 56.5, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.5 (d,  $J$ = 7.5 Hz, 3F), -63.6 (s, 2F), -64.3 (s, 1F); HRMS (ESI+): Calcd for  $\text{C}_{23}\text{H}_{20}\text{F}_6\text{N}_5\text{O}_3$  +  $[\text{M}^+]$ : 528.1470, Found: 528.1456.

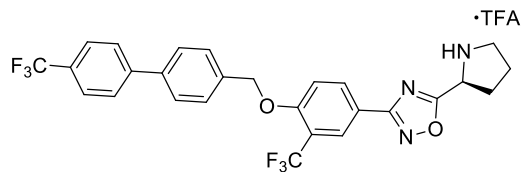


**(S)-Tert-butyl 2-(3-(4-((4-iodobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.33).** Synthesized by general procedure 3-H. 70% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.32 (s, 1H), 8.18 (d,  $J$  = 8.5 Hz, 1H), 7.72 (d,  $J$ = 8.2 Hz, 2H), 7.19 (d,  $J$ = 8.2 Hz, 2H), 7.09 (t,  $J$  = 8.0 Hz, 1H), 5.19 (s, 2H), 5.06 (dd,  $J$ = 7.9, 3.3 Hz, 1H), 3.77 – 3.63 (m, 1H), 3.60 – 3.46 (m, 1H), 2.45 – 2.36 (m, 1H), 2.20 – 2.09 (m, 2H), 2.06-1.96 (m, 1H), 1.46 (s, 3H), 1.29 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )  $\delta$  181.1, 167.2, 158.3, 153.6, 137.9, 135.4, 132.6, 128.8, 126.9 (q,  $^3J_{\text{CF}}$  = 4.9 Hz), 123.3 (q,  $^1J_{\text{CF}}$  = 274.1 Hz), 120.1, 119.7, 119.5, 113.5, 93.9, 80.6, 69.9, 53.9, 46.5, 32.5, 31.6, 28.5, 28.3, 24.5, 23.8;  $^{19}\text{F}$  NMR (376 MHz, Chloroform- $d$ )  $\delta$  -65.6 (d,  $J$ = 14.4 Hz, 3F).

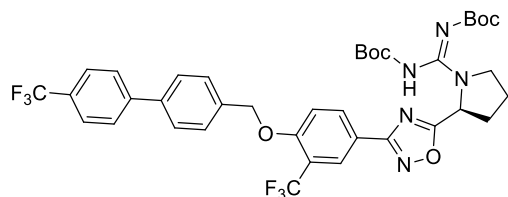


**(S)-Tert-butyl 2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate (3.34).** Compound **3.33** and 4-(trifluoromethyl)phenyl boronic acid (1.1 equiv) were added to a round bottom flask and dissolved in THF. The reaction mixture was degassed for 15 min by bubbling N<sub>2</sub> through the solution. Cs<sub>2</sub>CO<sub>3</sub> (2 equiv) and PdCl<sub>2</sub> (dppf) (0.03 equiv) were added to the reaction mixture. The resulting reaction mixture was then stirred at 80 °C for 18 h, after which it was poured into a saturated solution of LiBr and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting brown residue was purified by flash chromatography over silica gel (30% ethyl acetate/hexane) to give the desired product **3.34** in a 46% yield as a colorless oil. <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 8.34 (s, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 7.70 (m, 4H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.15 (t, *J* = 8.9 Hz, 1H), 5.32 (s, 2H), 5.22-5.04 (m, 1H), 3.75 – 3.66 (m, 1H), 3.62 – 3.47 (m, 1H), 2.46 – 2.33 (m, 1H), 2.21 – 2.09 (m, 2H), 2.05-1.96 (m, 1H), 1.46 (s, 3H), 1.30 (s, 6H); <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 191.6, 181.1, 167.3, 158.6, 153.6, 144.3, 139.8, 135.9, 132.6, 129.7 (q, <sup>2</sup>*J*<sub>CF</sub> = 33.1 Hz), 128.8, 127.7, 127.6, 127.5, 127.0, 125.9 (q, <sup>3</sup>*J*<sub>CF</sub> = 3.6 Hz), 124.4 (q, <sup>1</sup>*J*<sub>CF</sub> = 273.1 Hz), 123.4 (q, <sup>1</sup>*J*<sub>CF</sub> = 273.7 Hz), 119.6 (q, <sup>2</sup>*J*<sub>CF</sub> = 24.9 Hz), 113.7, 80.7, 70.3, 53.9, 46.5, 32.6, 31.6, 29.9, 28.3, 24.5, 23.9; <sup>19</sup>F NMR (376 MHz, Chloroform-d) δ -65.5 (s, 3F), -65.6 (d, *J* = 14.4 Hz, 3F); HRMS (ESI<sup>+</sup>): Calcd for C<sub>32</sub>H<sub>29</sub>F<sub>6</sub>N<sub>3</sub>O<sub>4</sub>Na [M+Na]: 656.1960, Found: 656.1933.



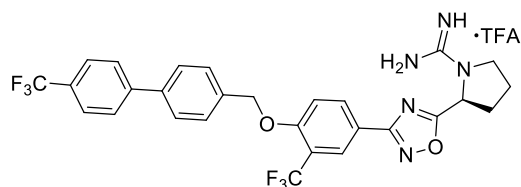


**(S)-2-(3-(3-(Trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate.** Synthesized by general procedure 3-D. 100% conversion, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.32 (d,  $J$  = 1.9 Hz, 1H), 8.30 (dd,  $J$  = 8.6, 2.1 Hz, 1H), 7.82 (d,  $J$  = 8.2 Hz, 2H), 7.73 (dd,  $J$  = 8.4, 2.0 Hz, 4H), 7.60 (d,  $J$  = 8.3 Hz, 2H), 7.46 (d,  $J$  = 8.7 Hz, 1H), 5.40 (s, 2H), 5.19 (t,  $J$  = 7.8 Hz, 1H), 3.66-3.45 (m, 2H), 2.71-2.62 (m, 1H), 2.48 – 2.36 (m, 1H), 2.34-2.21 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  176.3, 168.6, 160.4, 145.7, 140.7, 137.5, 134.0, 130.4 (q,  $^2J_{\text{CF}}$  = 32.5 Hz), 129.0, 128.6, 128.5, 127.4 (q,  $^3J_{\text{CF}}$  = 5.5 Hz), 126.8 (q,  $^3J_{\text{CF}}$  = 3.9 Hz), 125.8 (q,  $^1J_{\text{CF}}$  = 272.1 Hz), 124.7 (q,  $^1J_{\text{CF}}$  = 273.1 Hz), 120.7 (q,  $^2J_{\text{CF}}$  = 31.6 Hz), 119.6, 115.6, 71.4, 55.5, 47.4, 30.2, 24.5;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.6 (s, 3F), -63.7 (s, 3F); HRMS (ESI $^+$ ): Calcd for  $\text{C}_{27}\text{H}_{22}\text{F}_6\text{N}_3\text{O}_2^+$  [ $\text{M}^+$ ]: 534.1616, Found: 534.1608.



**(S)-Tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate.** Synthesized by general procedure 3-E. 37% yield, colorless oil;  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.34 (s, 1H), 8.20 (d,  $J$  = 8.6 Hz, 1H), 7.70 (s, 4H), 7.64 (d,  $J$  = 8.1 Hz, 2H), 7.56 (d,  $J$  = 8.1 Hz, 2H), 7.16 (d,  $J$  = 8.7 Hz, 1H), 5.62 (dd,  $J$  = 7.3, 4.4 Hz, 1H), 5.32 (s, 2H), 3.96-3.85 (m, 1H), 3.86-3.76 (m, 1H), 2.51-2.39 (m, 1H), 2.27-2.13 (m, 2H), 2.10-1.99

(m, 1H), 1.46 (s, 18H);  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  179.4, 167.3, 158.5, 153.8, 151.3, 144.3, 139.8, 135.9, 132.7, 129.7 (q,  $^2J_{\text{CF}} = 32.7$  Hz), 127.7, 127.6, 127.5, 127.1 (q,  $^3J_{\text{CF}} = 5.0$  Hz), 125.9 (q,  $^3J_{\text{CF}} = 3.6$  Hz), 124.4 (q,  $^1J_{\text{CF}} = 273.4$  Hz), 123.4 (q,  $^1J_{\text{CF}} = 274.4$  Hz), 120.0 (q,  $^2J_{\text{CF}} = 31.8$  Hz), 119.5, 113.6, 70.3, 55.5, 49.7, 31.7, 28.2, 24.2;  $^{19}\text{F}$  NMR (376 MHz, Chloroform-d)  $\delta$  -65.5 (s, 3F), -65.5 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{38}\text{H}_{40}\text{F}_6\text{N}_5\text{O}_6$  [M+H]: 776.2883, Found: 776.2868.

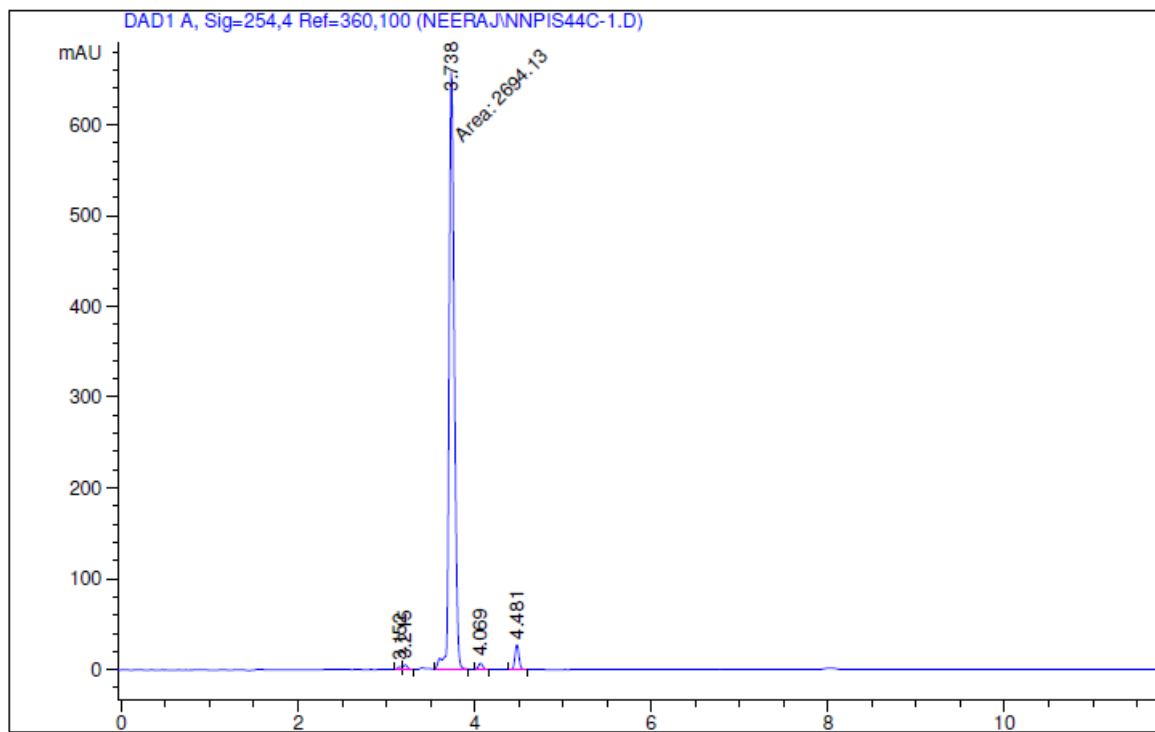


**(S)-Amino(2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate (3.35).** Synthesized by general procedure 3-D. 87% yield, white solid;  $^1\text{H}$  NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.30 (d,  $J = 7.4$  Hz, 2H), 7.88 (d,  $J = 8.3$  Hz, 2H), 7.78 (dd,  $J = 8.4, 2.0$  Hz, 4H), 7.65 (d,  $J = 8.3$  Hz, 2H), 7.49 (d,  $J = 9.5$  Hz, 1H), 5.48 (dd,  $J = 7.9, 1.8$  Hz, 1H), 5.44 (s, 2H), 3.82 (td,  $J = 9.0, 2.6$  Hz, 1H), 3.69-3.62 (m, 1H), 2.67 – 2.48 (m, 2H), 2.33 – 2.21 (m, 1H), 2.20-2.06 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  179.2, 168.5, 160.2, 157.1, 156.1, 145.8, 140.8, 137.6, 133.9, 130.5 (q,  $^2J_{\text{CF}} = 32.4$  Hz), 129.0, 128.6, 128.5, 127.2 (q,  $^3J_{\text{CF}} = 5.3$  Hz), 126.8 (q,  $^3J_{\text{CF}} = 3.7$  Hz), 125.8 (q,  $^1J_{\text{CF}} = 271.6$  Hz), 124.7 (q,  $^1J_{\text{CF}} = 273.0$  Hz), 120.7 (q,  $^2J_{\text{CF}} = 31.5$  Hz), 120.0, 115.6, 71.4, 56.5, 32.7, 24.3;  $^{19}\text{F}$  NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -63.6 (s, 3F), -63.7 (s, 3F); HRMS (ESI+): Calcd for  $\text{C}_{28}\text{H}_{24}\text{F}_6\text{N}_5\text{O}_2+$  [M+]: 576.1834, Found: 576.1827.

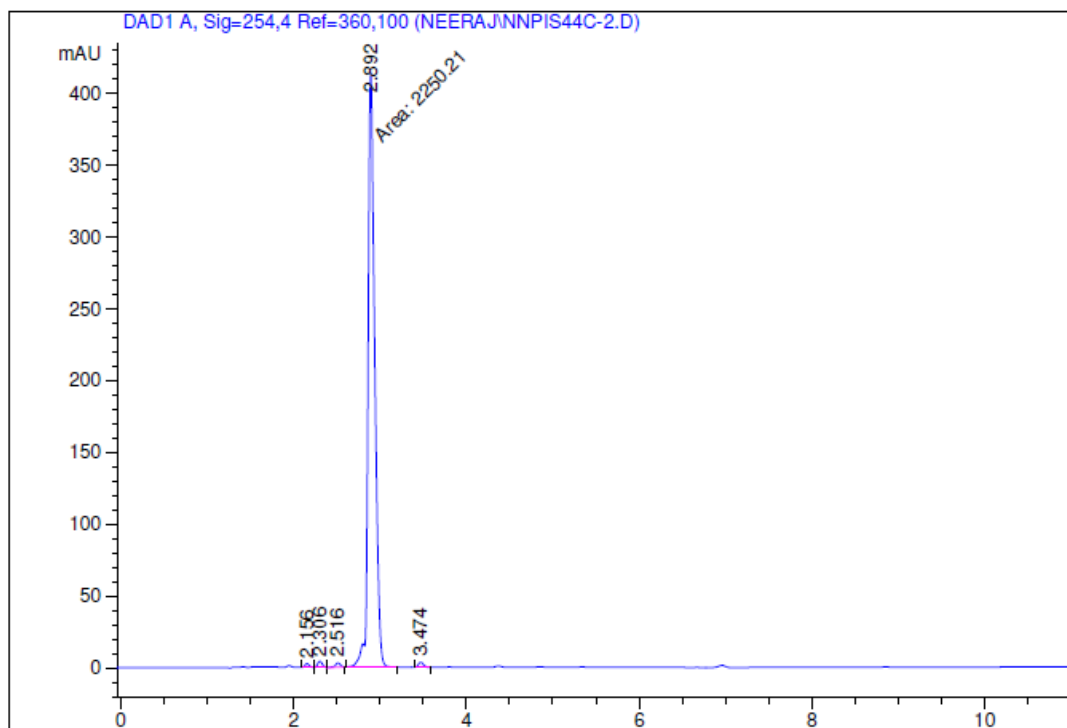
## 4.6 HPLC traces

### 4.6.1 Chapter 2 HPLC traces

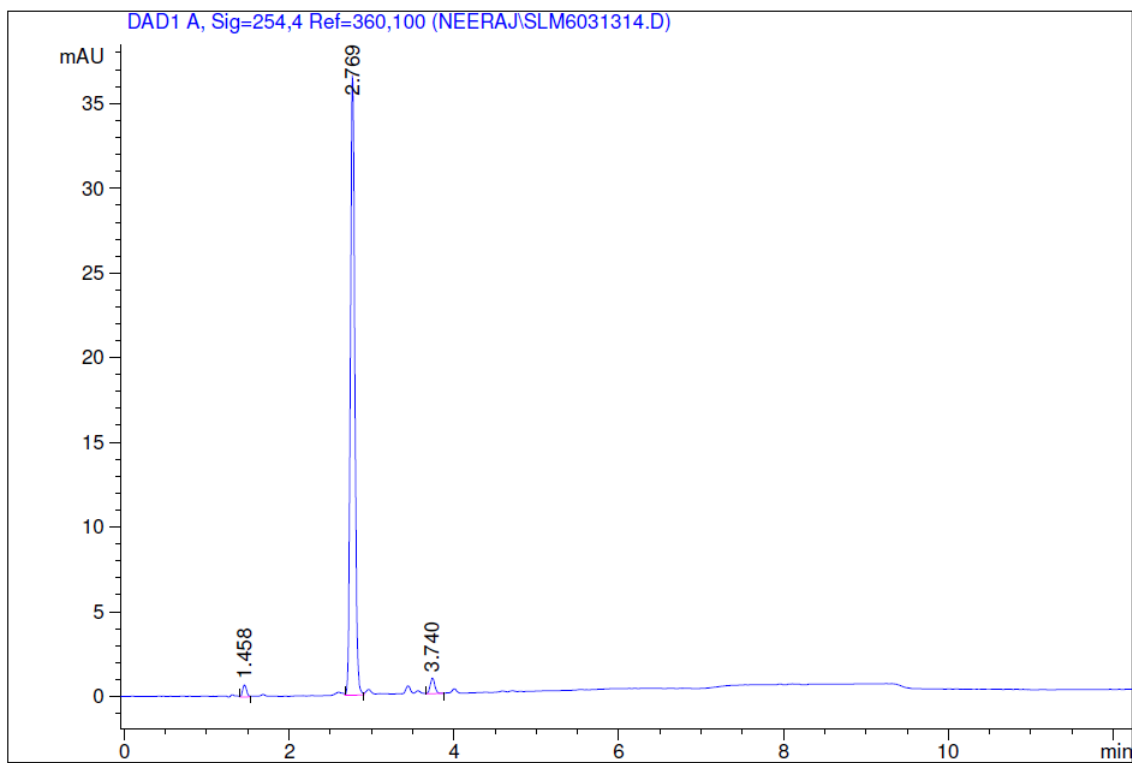
#### Compound 2.7c



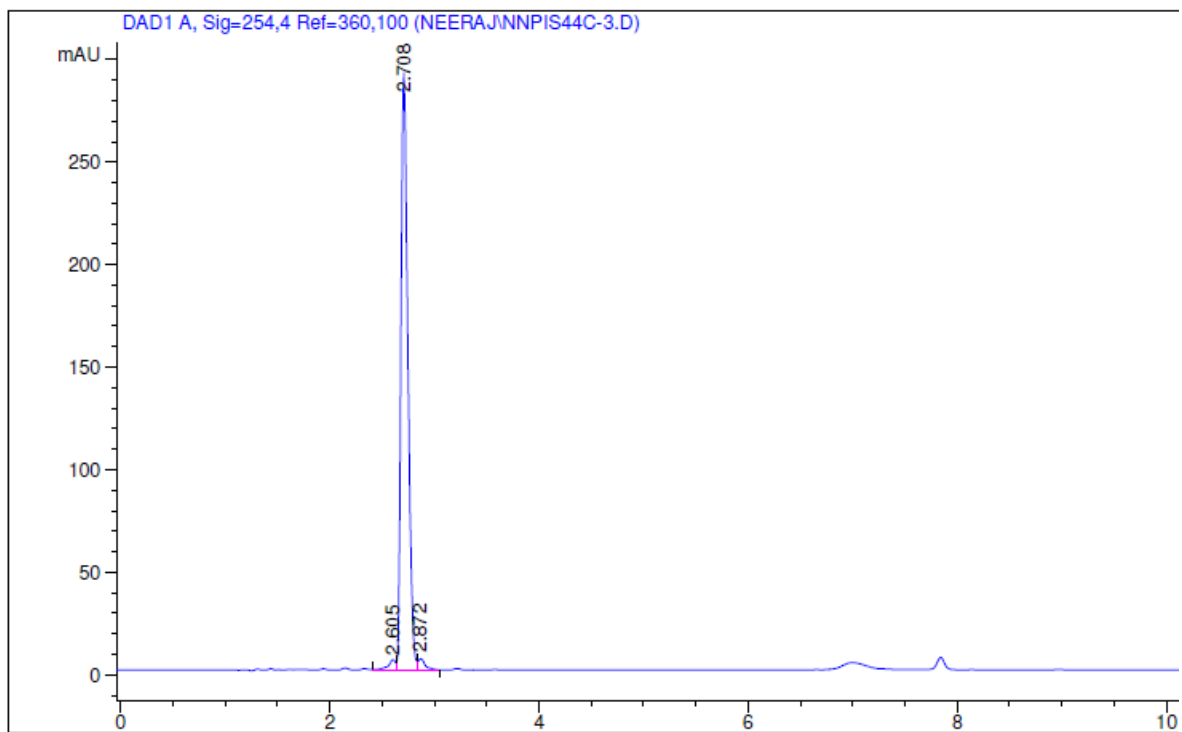
### Compound 2.7d



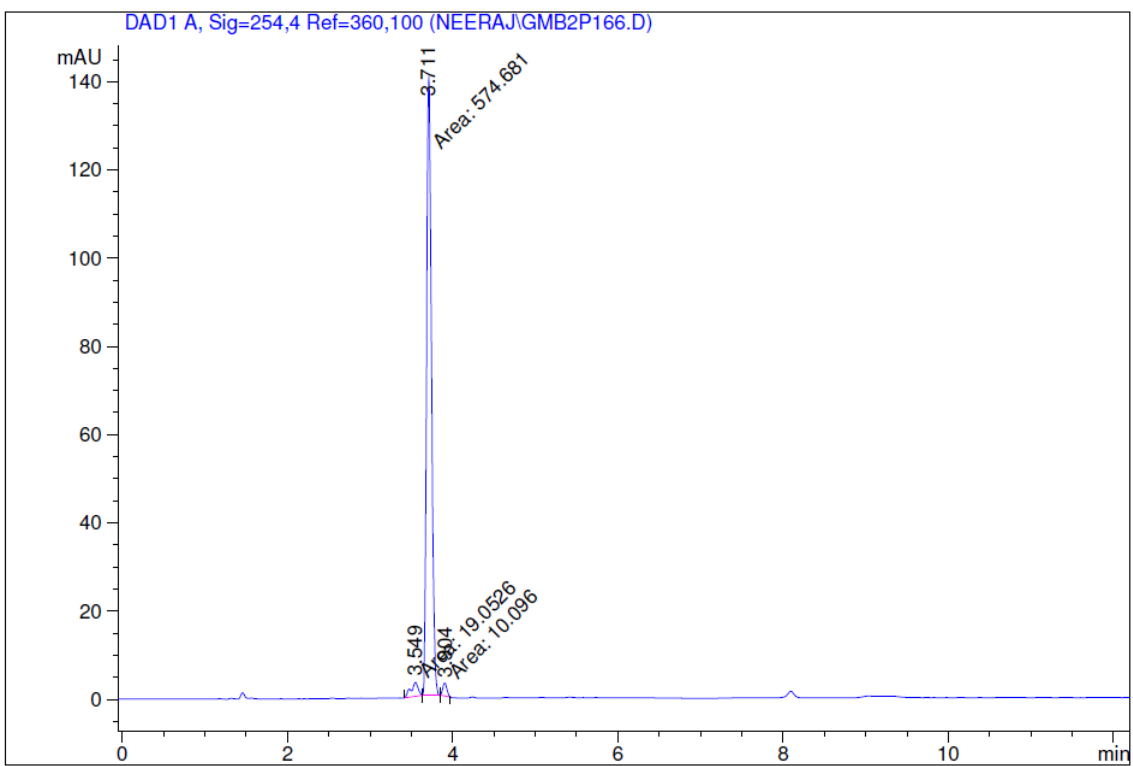
### Compound 2.7e



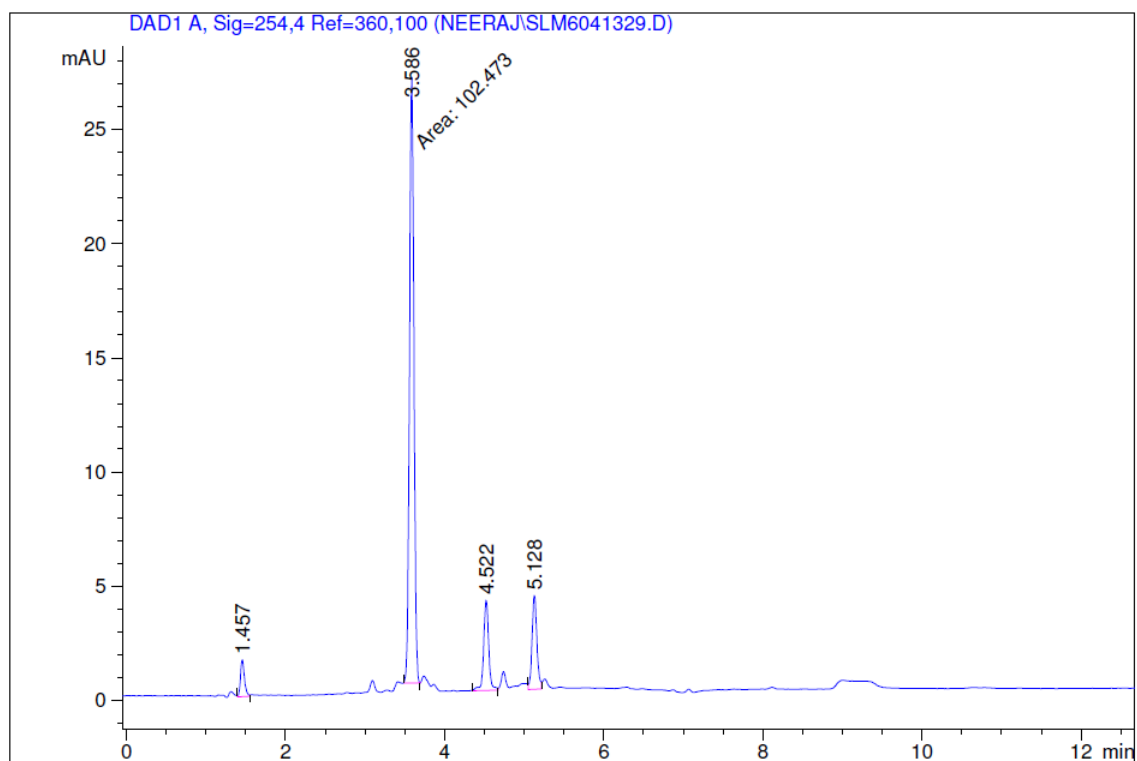
### Compound 2.7g



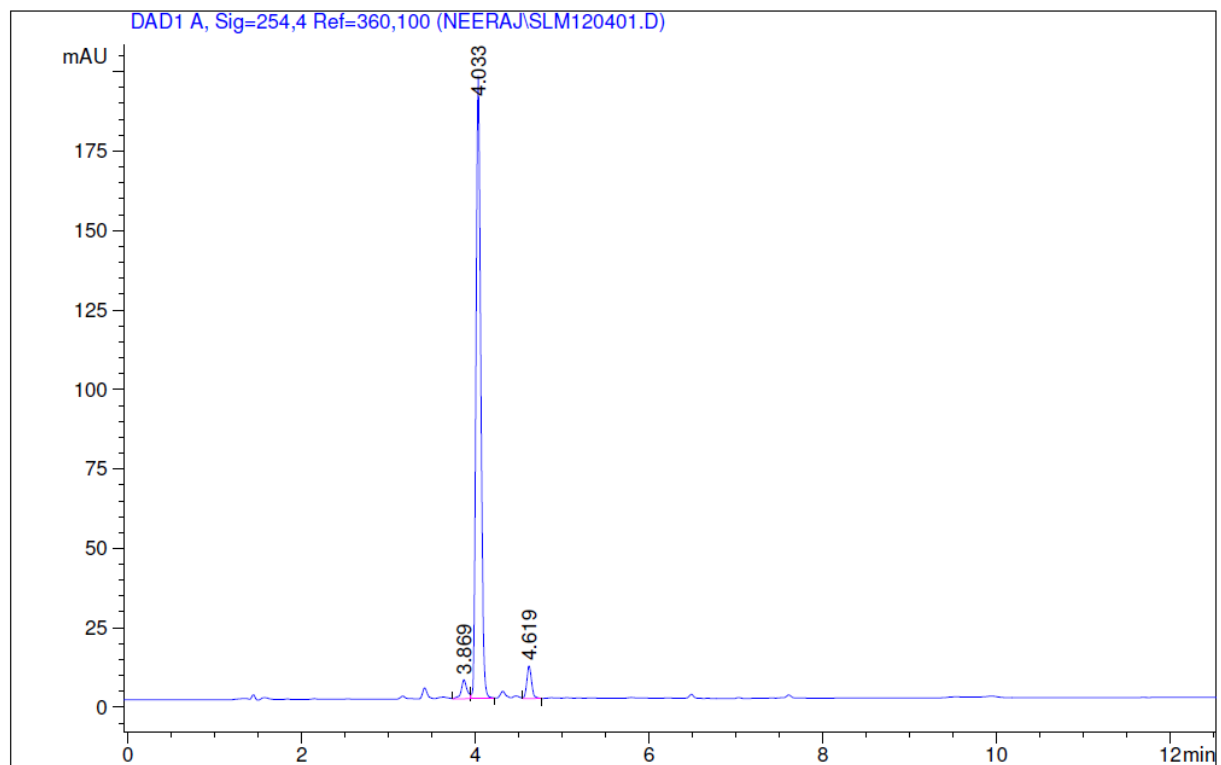
### Compound 2.7h



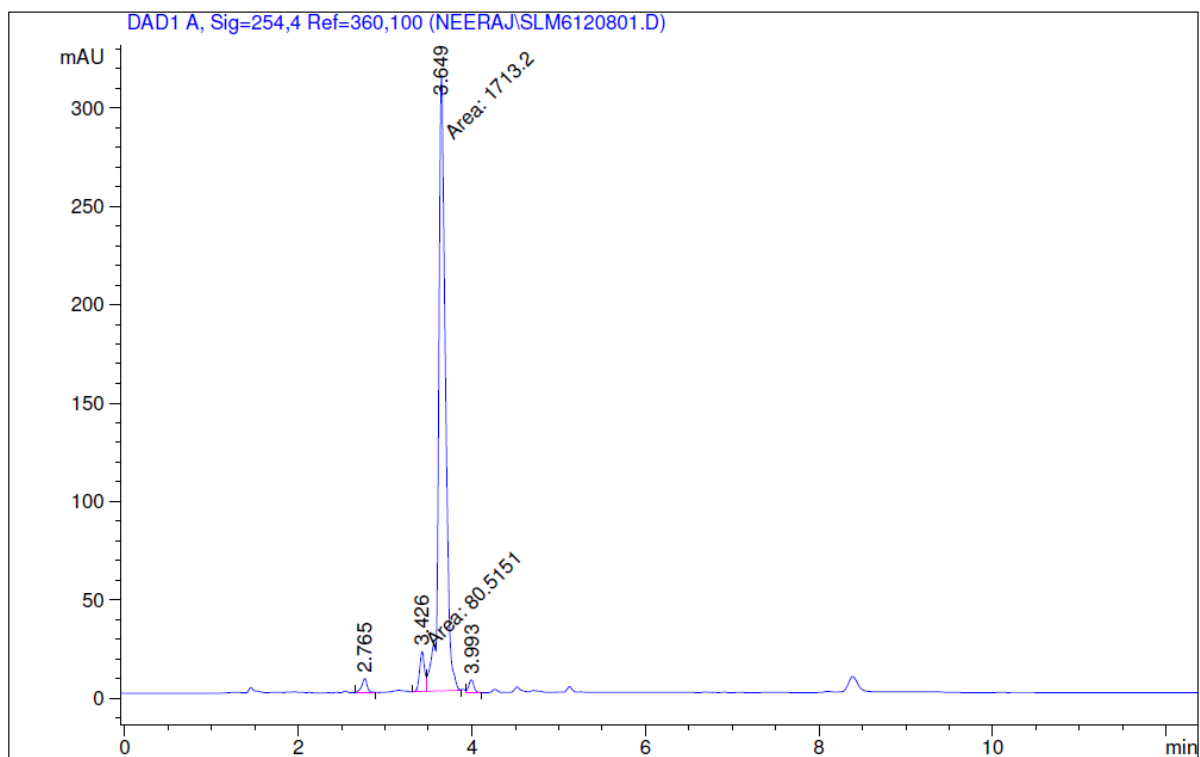
## Compound 2.7i



## Compound 2.11

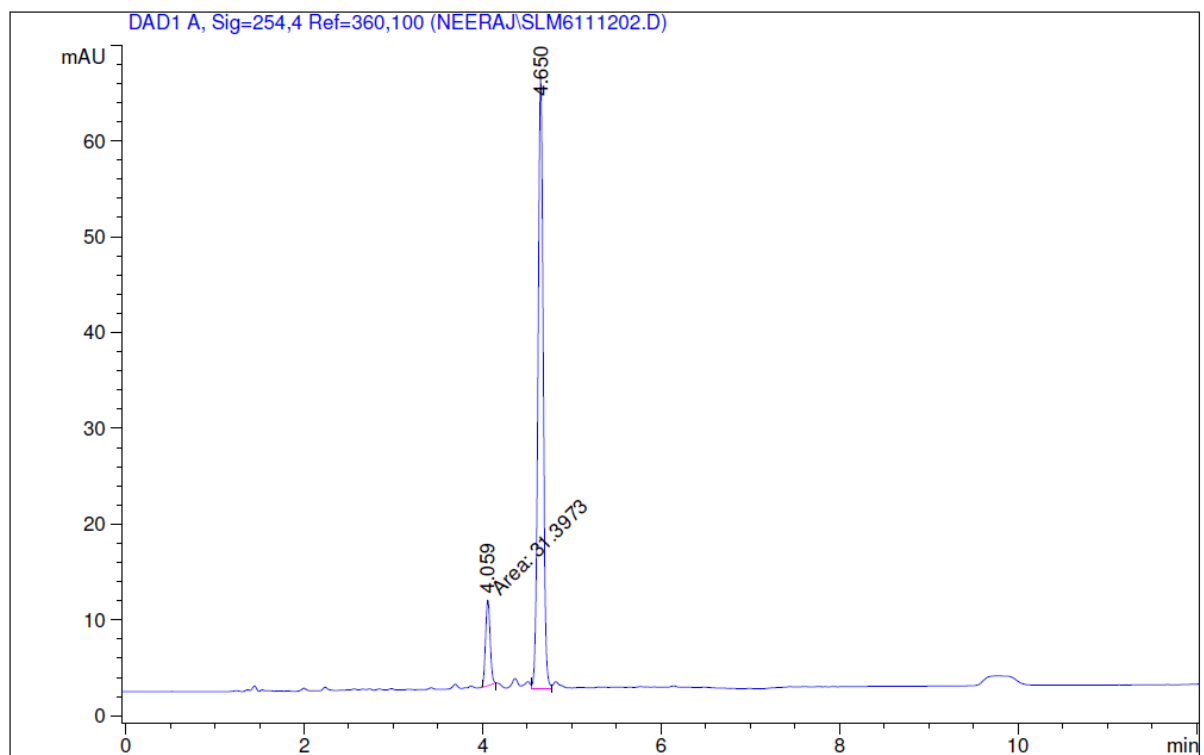


## Compound 2.26b

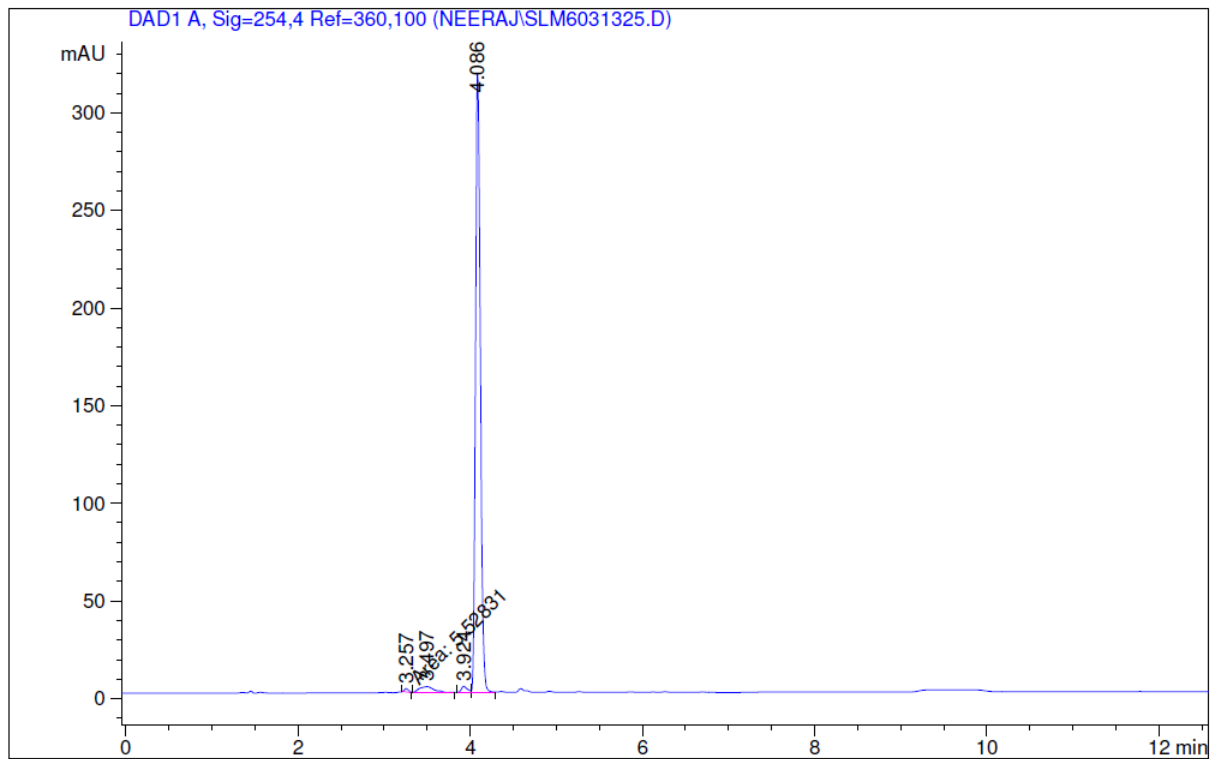




## Compound 2.29



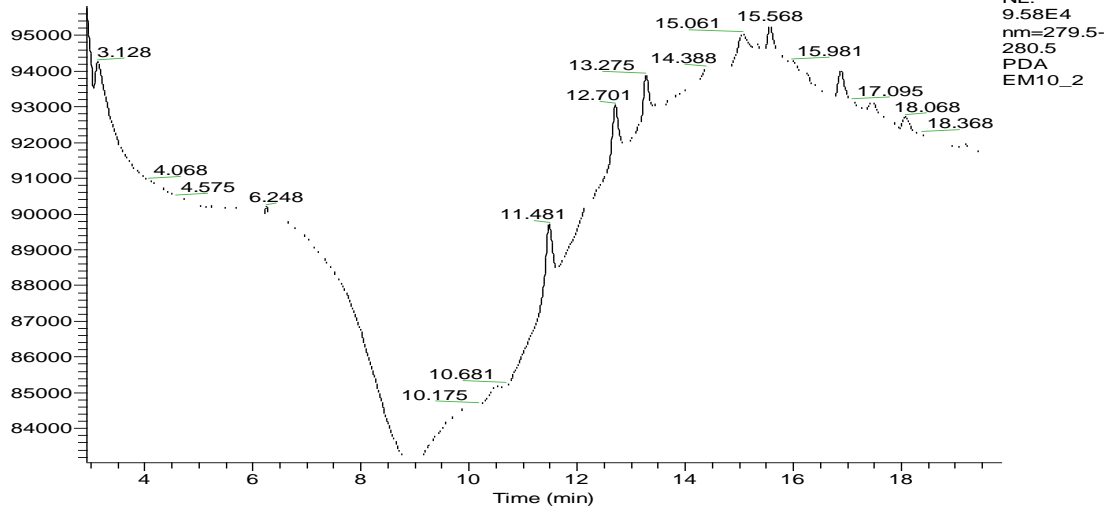
## Compound 2.32



# Compound 2.38a

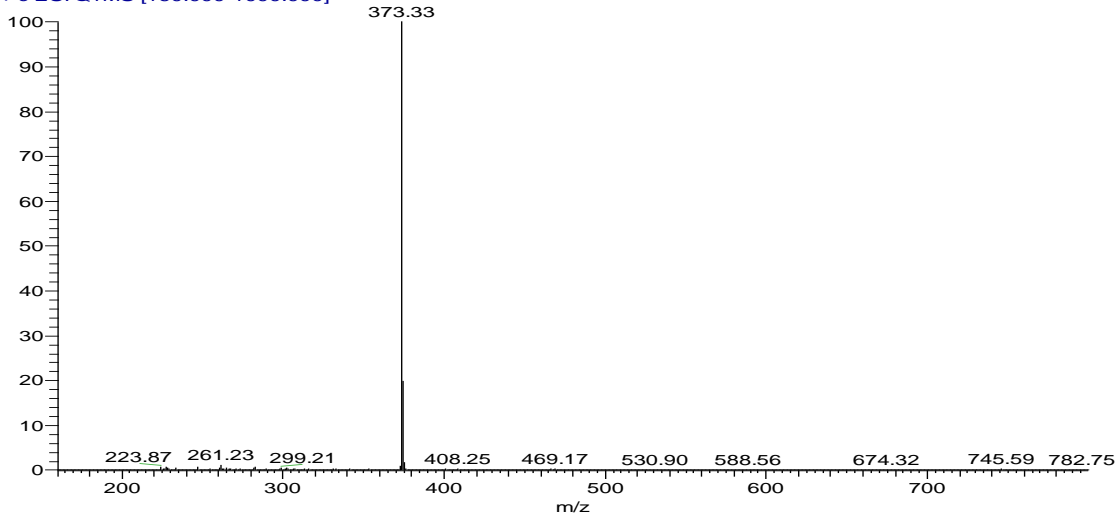
LC/UV: product peak 13.275 min. Extra peaks from Blank 1.

RT: 2.915 - 19.862



Spectrum of peak with retention time of 13.3 min

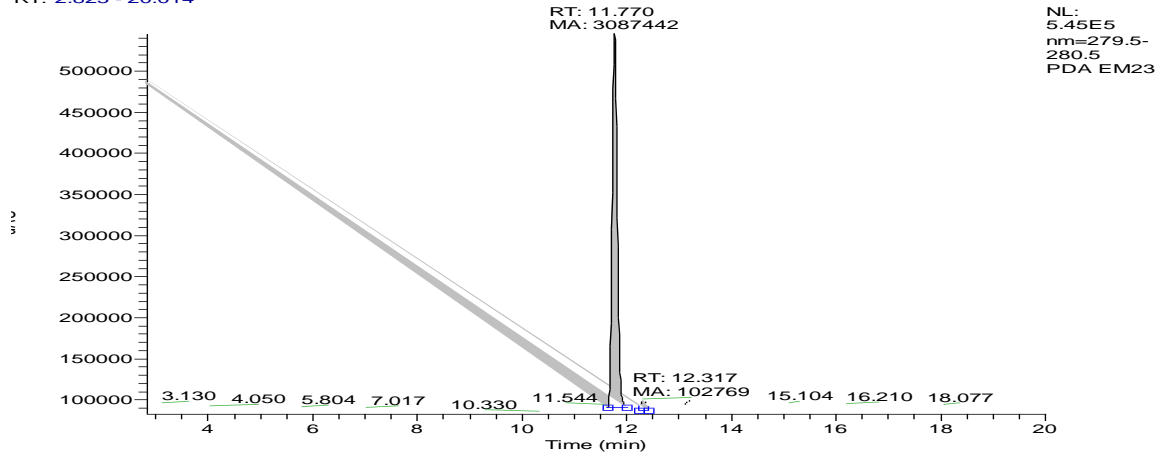
EM10\_2 #1083-1106 RT: 13.288-13.570 AV: 24 NL: 2.11E5  
T: + c ESI Q1 MS [160.000-1000.000]



# Compound 2.50

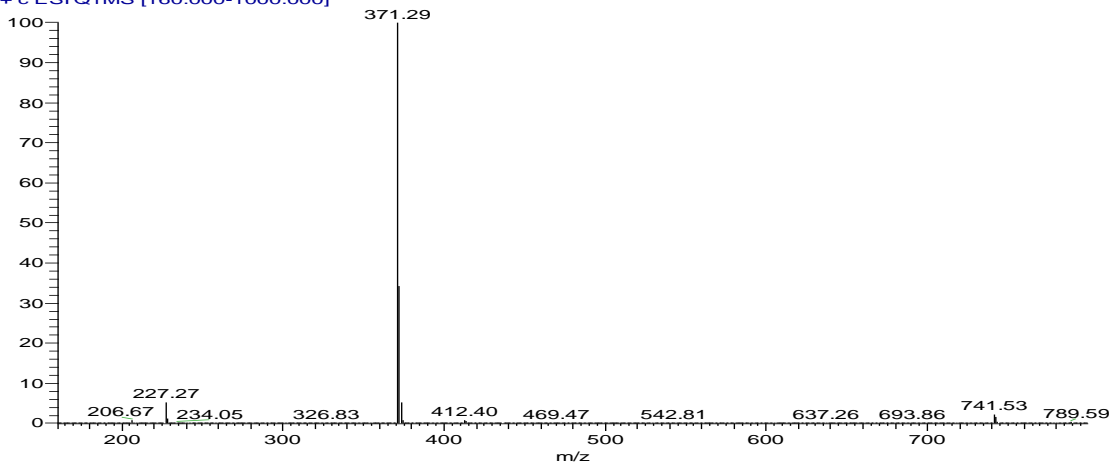
LC/UV

RT: 2.825 - 20.014



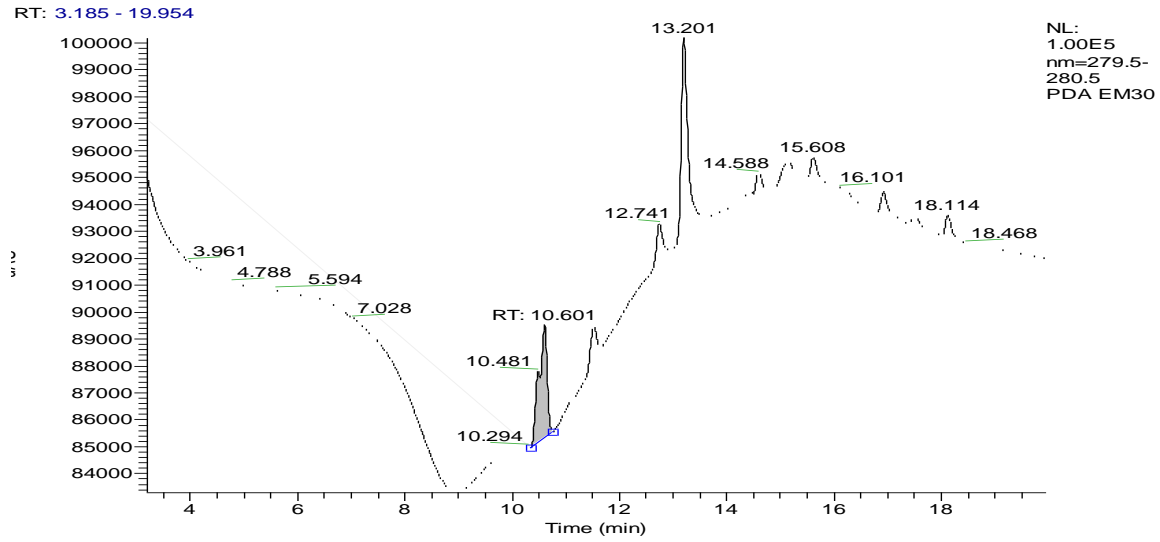
MS spectrum of peak with retention time of 11.8 min

EM23 #969 RT: 11.893 AV: 1 NL: 7.13E6  
T: + c ESI Q1 MS [160.000-1000.000]

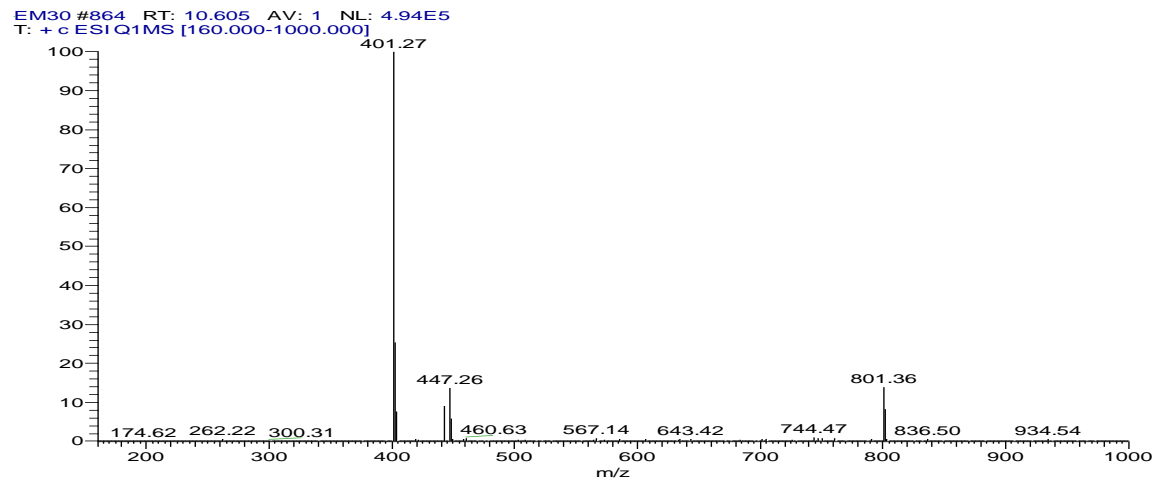


# Compound 2.55a

LC/UV: product peak 10.6 min. Run with Blank 2.



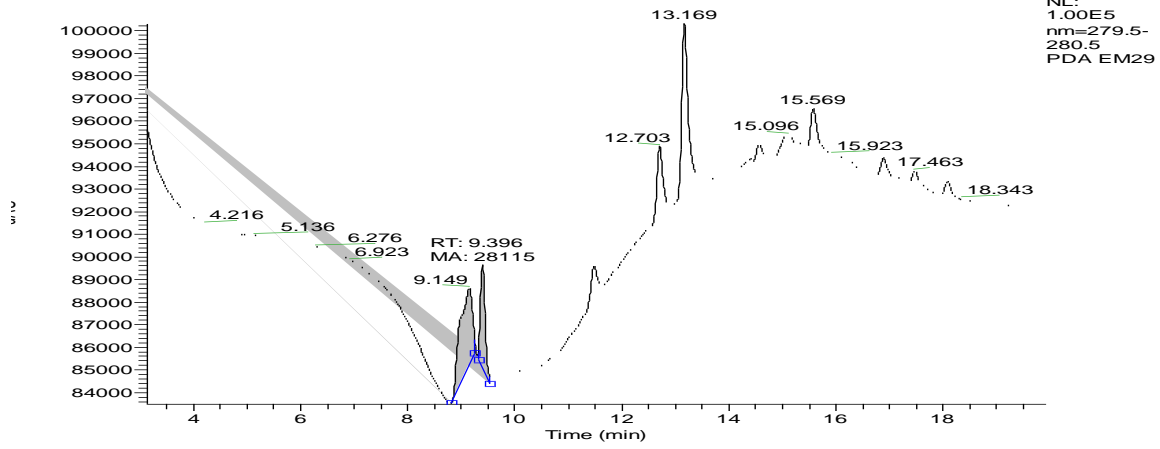
MS spectrum of peak with retention time of 10.6 min



# Compound 2.55b

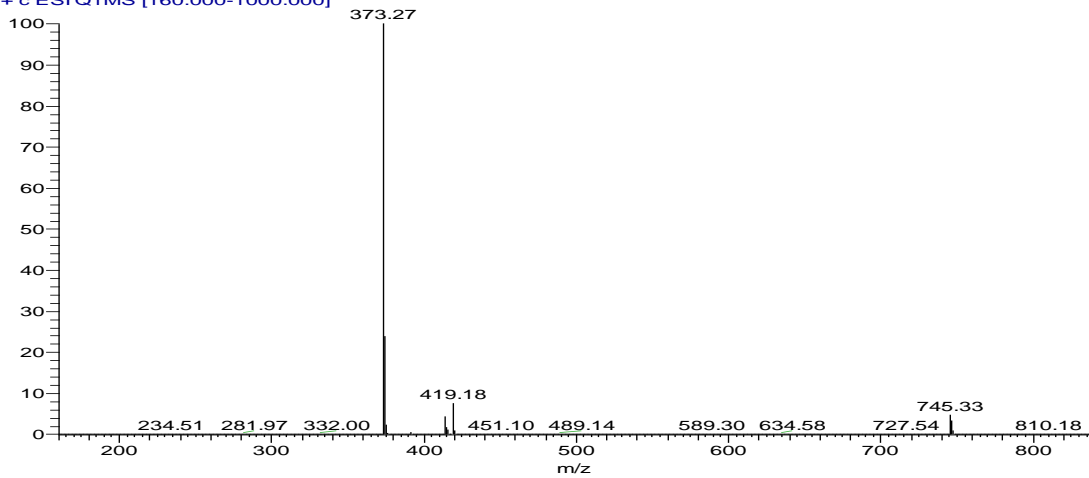
LC/UV: product peak 9.2. Run with Blank 2.

RT: 3.125 - 19.922



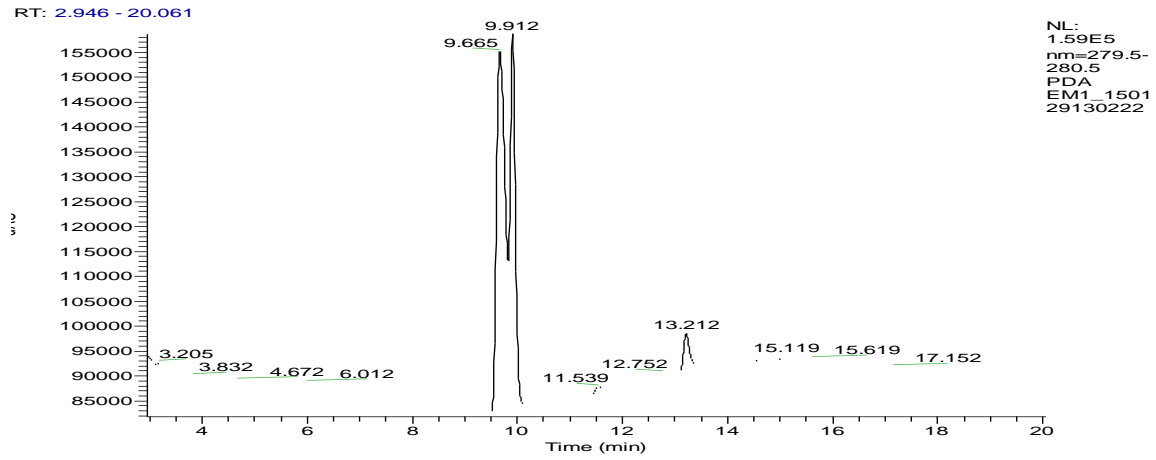
MS spectrum of peak with retention time of 9.2 min

EM29 #740-754 RT: 9.086-9.257 AV: 15 NL: 5.46E5  
T: + c ESI Q1 MS [160.000-1000.000]

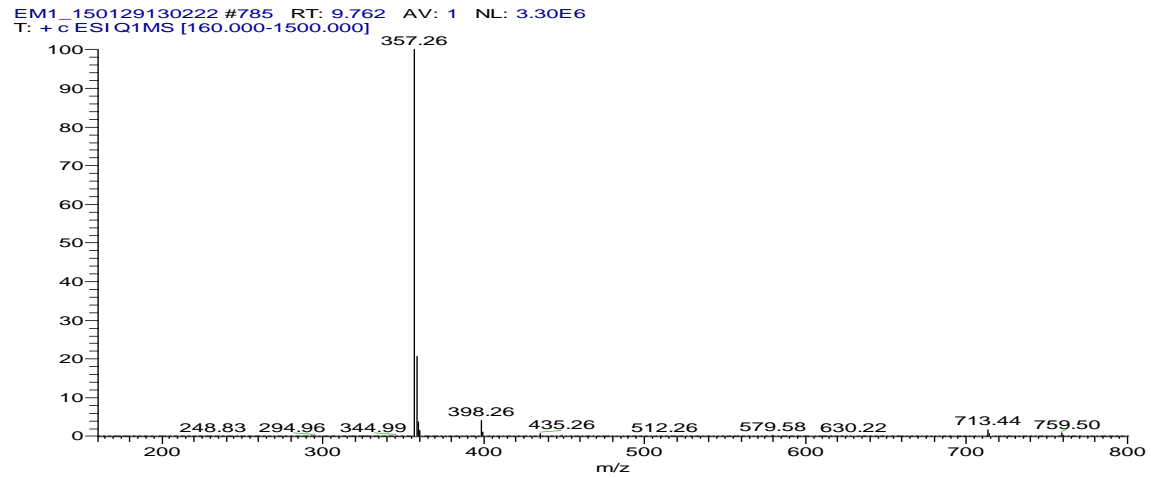


# Compound 2.55d

LC/UV: product peak 9.7. Other peaks present in Blank 1.



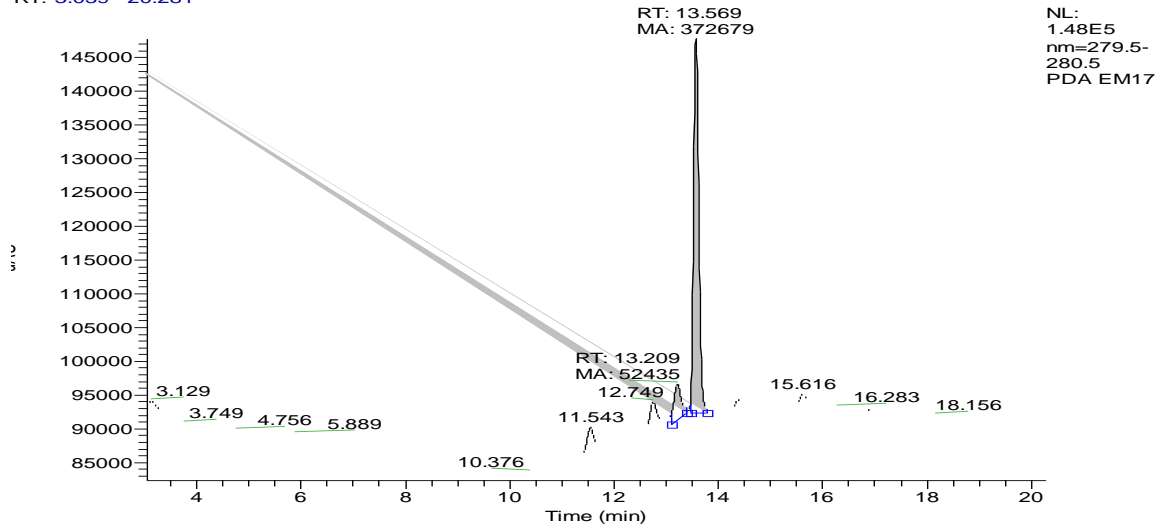
MS spectrum of peak with retention time of 9.75 min



# Compound 2.58

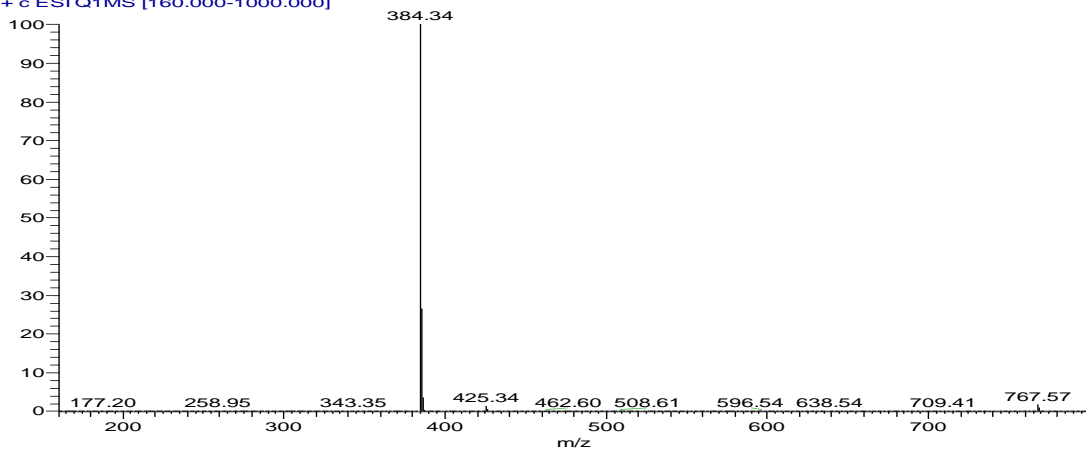
LC/UV: product peak 13.6 min. Other peaks present in Blank 2.

RT: 3.039 - 20.281



MS spectrum of peak with retention time of 13.69 min

EM17 #1117 RT: 13.705 AV: 1 NL: 4.86E7  
T: + c ESI Q1MS [160.000-1000.000]

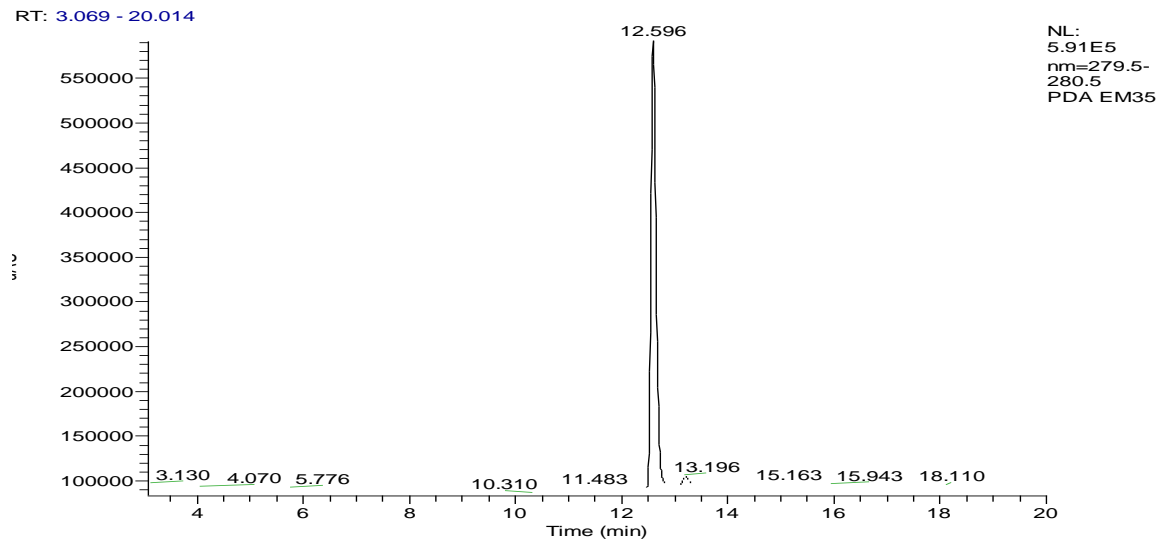




## 4.6.2 Chapter 3 HPLC traces

### Compound 3.7a

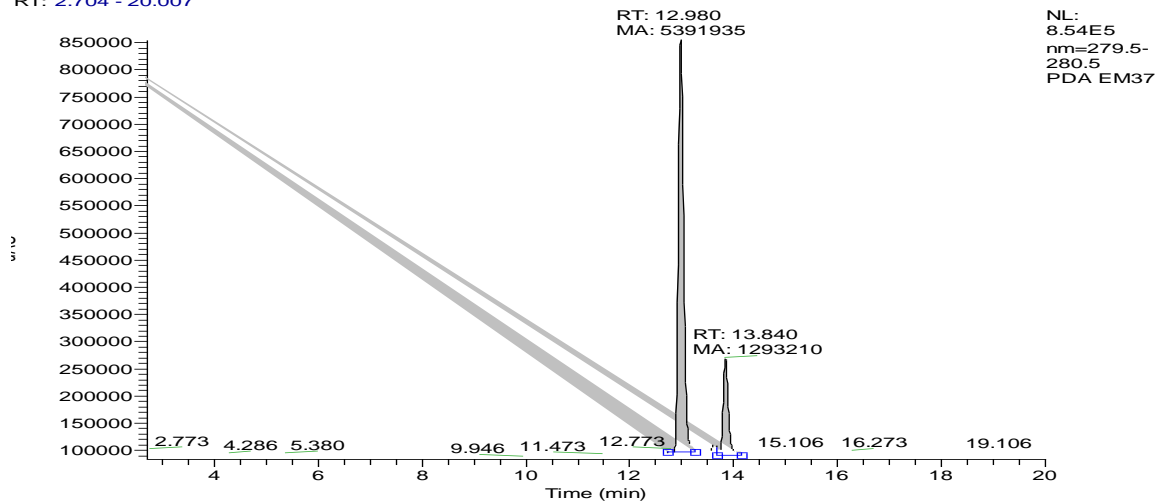
LC/UV



# Compound 3.7b

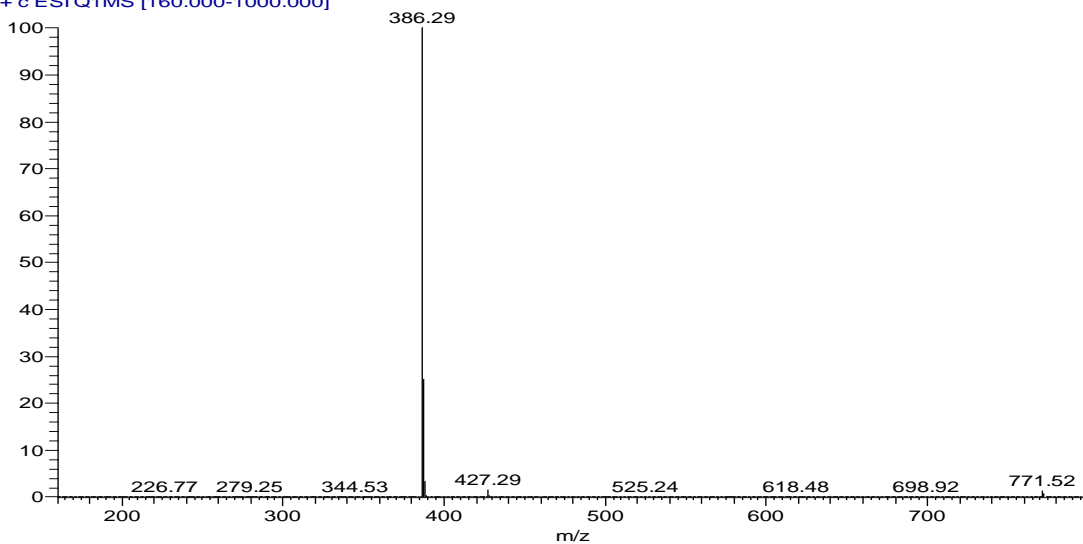
## LC/UV

RT: 2.704 - 20.007



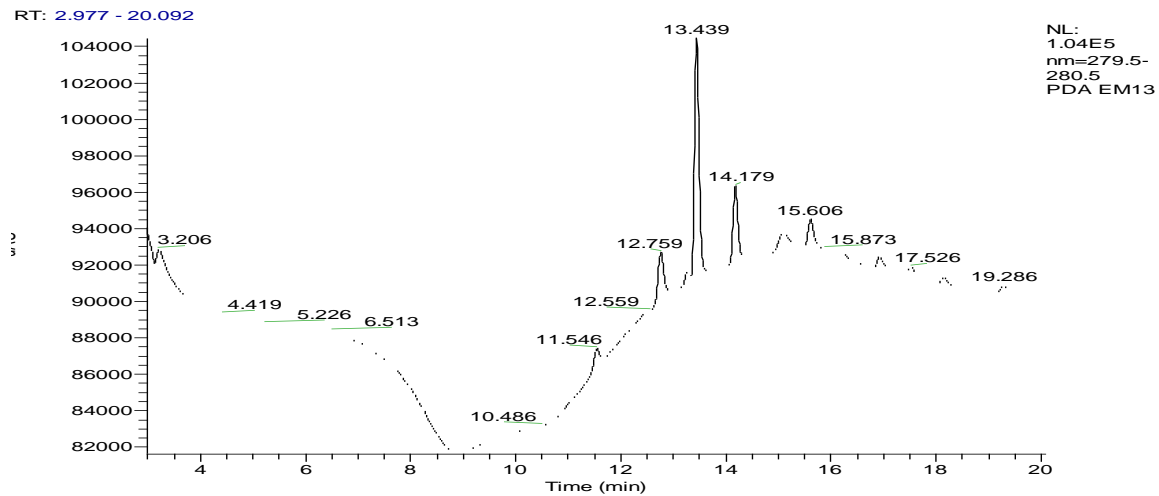
## MS spectrum of peak with retention time of 12.9 min

EM37 #1070 RT: 13.134 AV: 1 NL: 6.96E7  
T: + c ESI Q1 MS [160.000-1000.000]

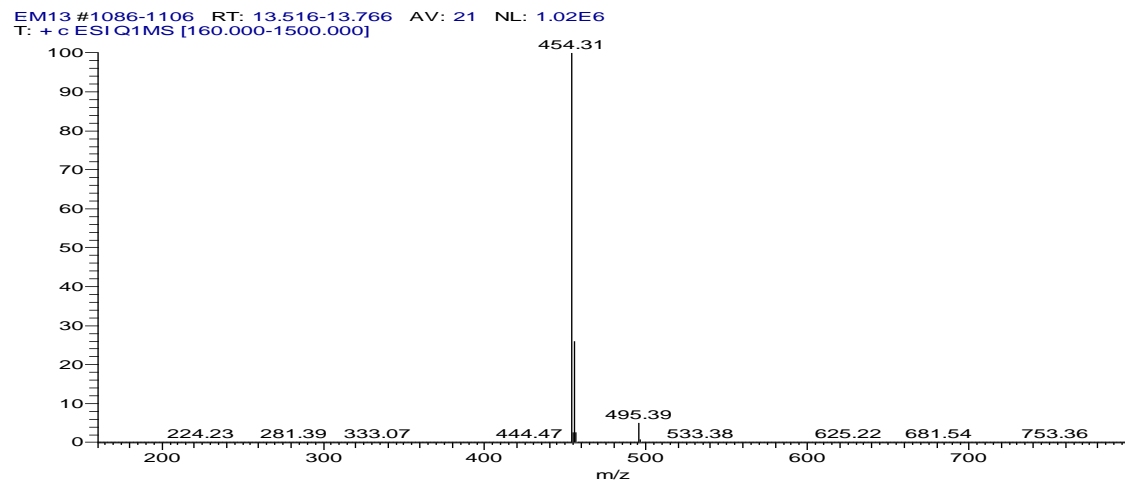


## Compound 3.14a

LC/UV: product 13.4 min. Other peaks present in Blank 1.



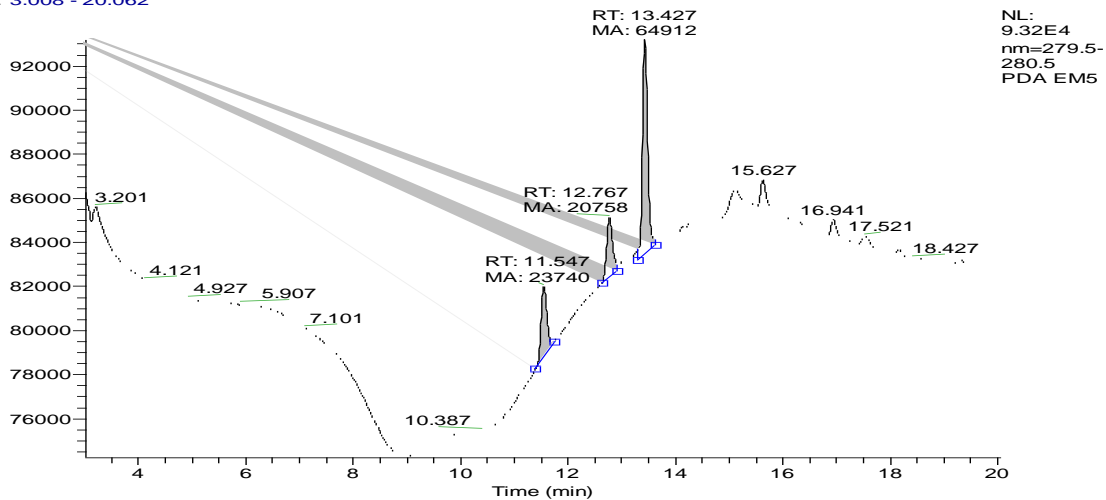
Spectrum of Peak with retention time of 13.4 min



# Compound 3.14b

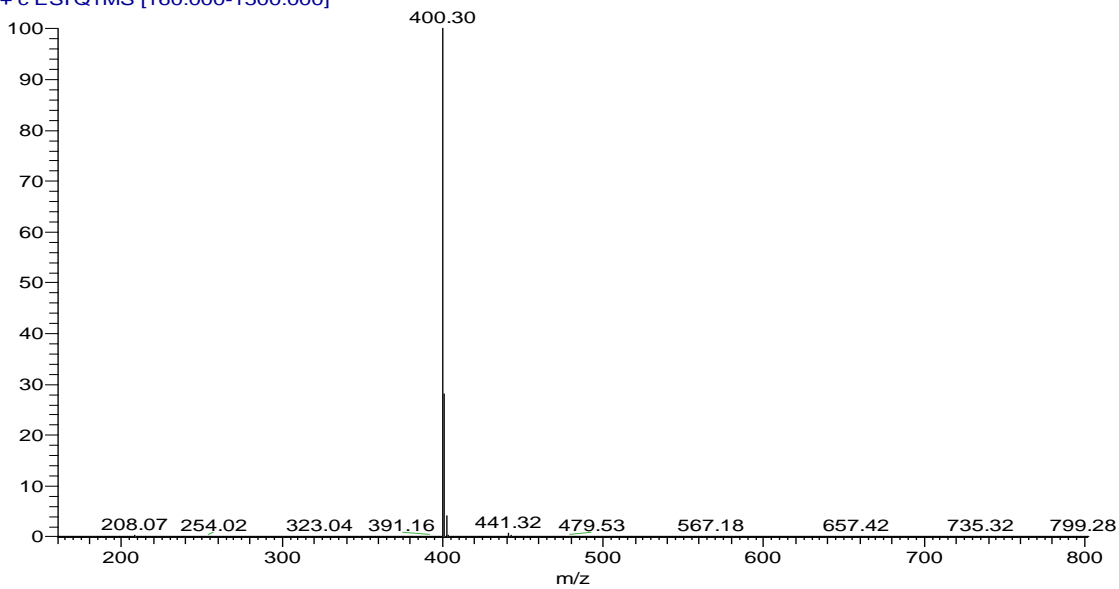
LC/UV: product peak 13.4 min. Run with Blank 1.

RT: 3.008 - 20.062



MS spectrum of peak with retention time of 13.548 min

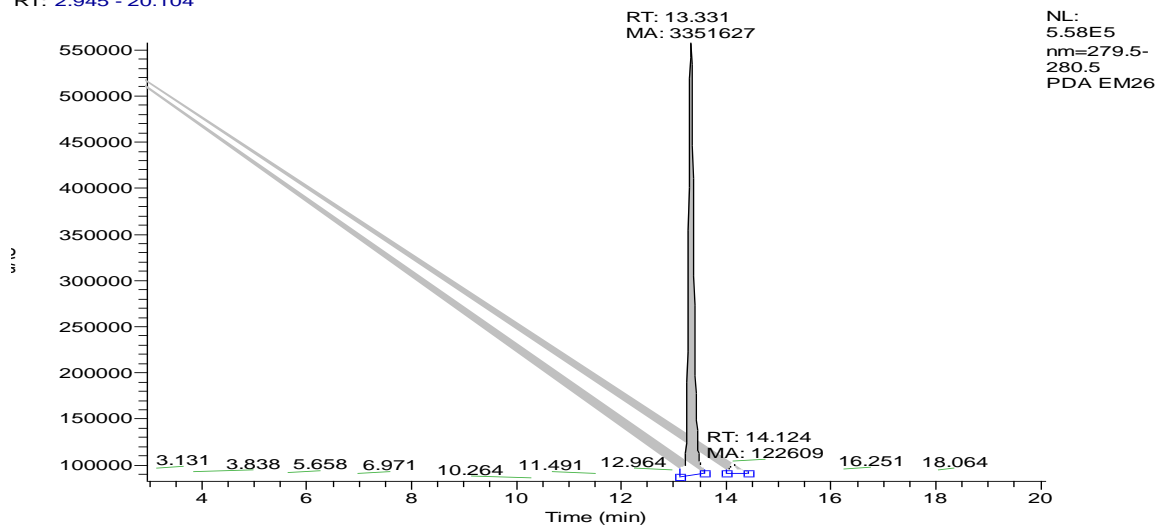
EM5 #1076-1097 RT: 13.423-13.685 AV: 22 NL: 5.03E6  
T: + c ESI Q1 MS [160.000-1500.000]



# Compound 3.14c

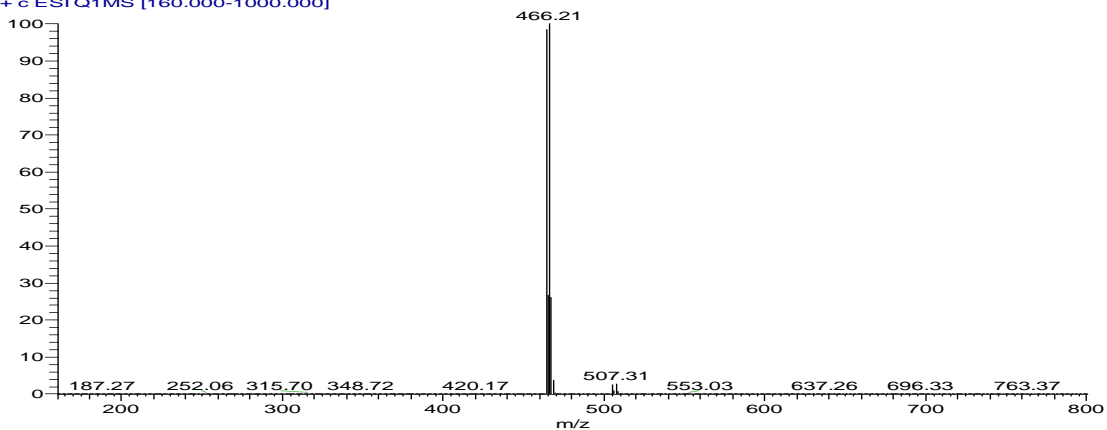
## LC/UV

RT: 2.945 - 20.104



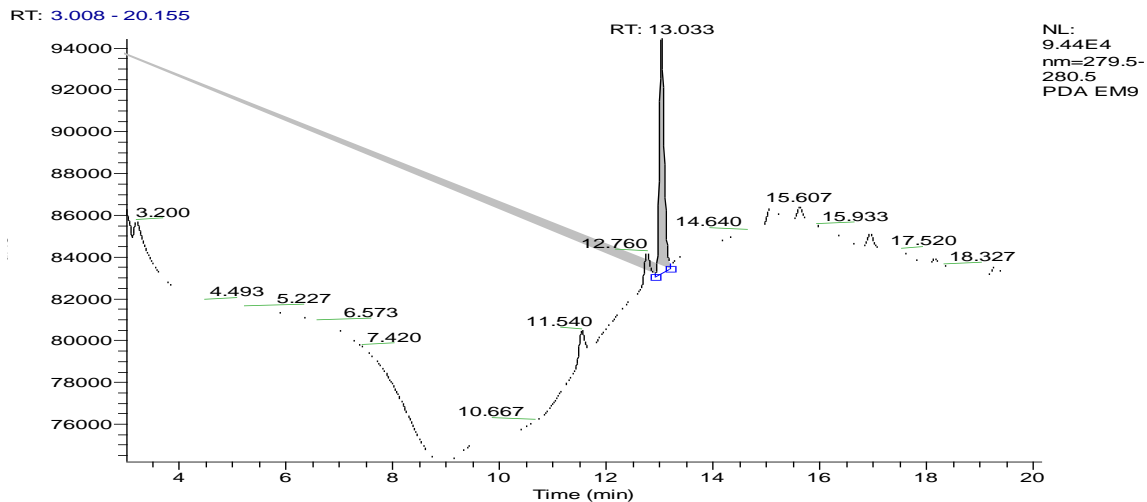
## MS spectrum of peak with retention time of 13.3 min.

EM26 #1096 RT: 13.449 AV: 1 NL: 2.76E7  
T: + c ESI Q1 MS [160.000-1000.000]

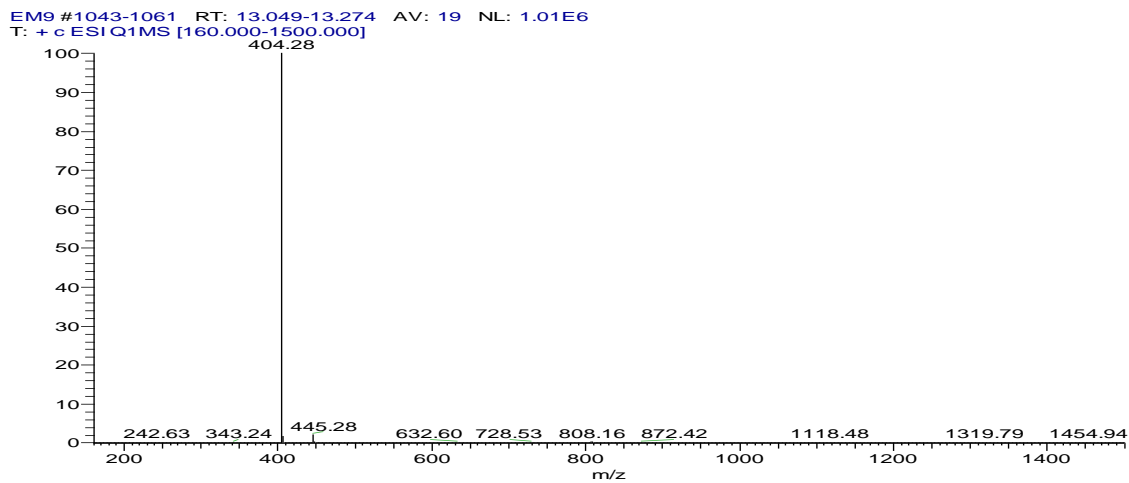


# Compound 3.14d

LC/UV: product peak 13.0 min. Run with Blank 1.



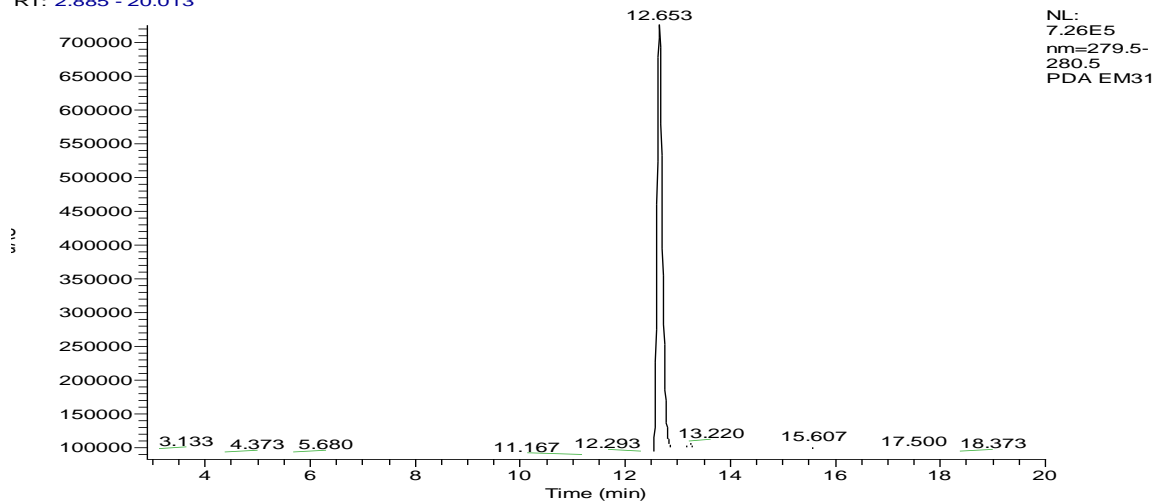
MS spectrum of peak with retention time of 13.0 min



# Compound 3.14e

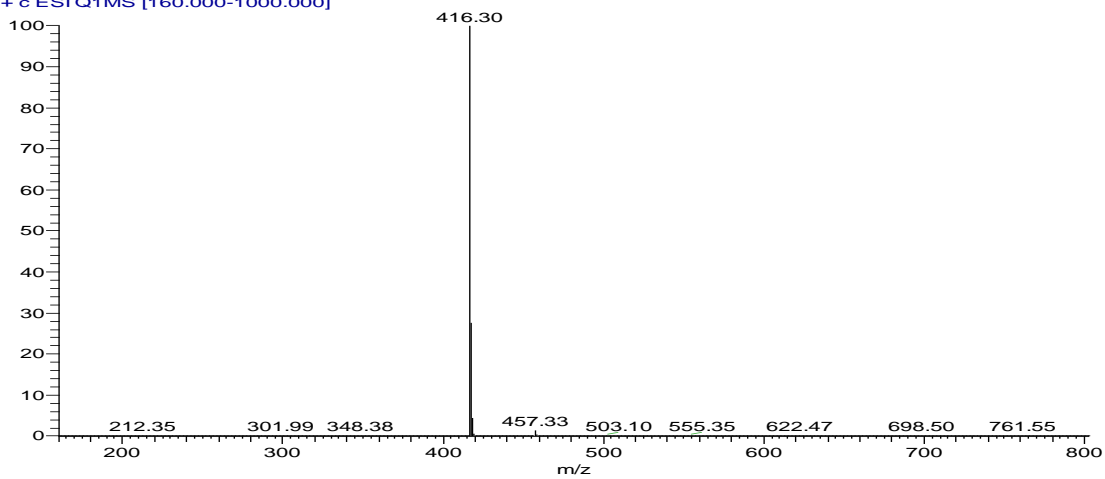
## LC/UV

RT: 2.885 - 20.013



## MS spectrum of peak with retention time of 12.6 min

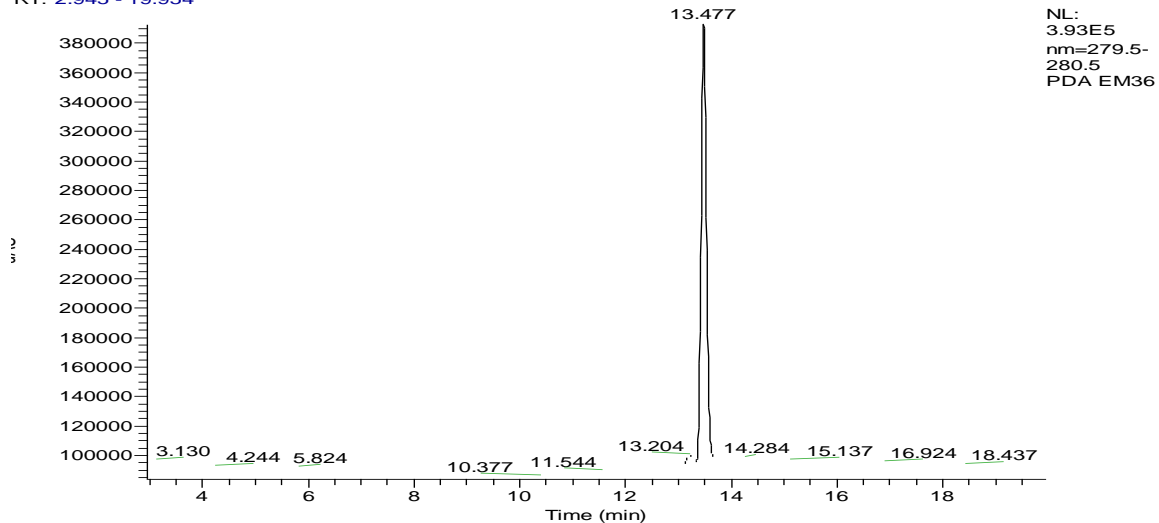
EM31 #1036-1047 RT: 12.713-12.848 AV: 12 NL: 5.26E7  
T: + c ESI Q1MS [160.000-1000.000]



# Compound 3.14f

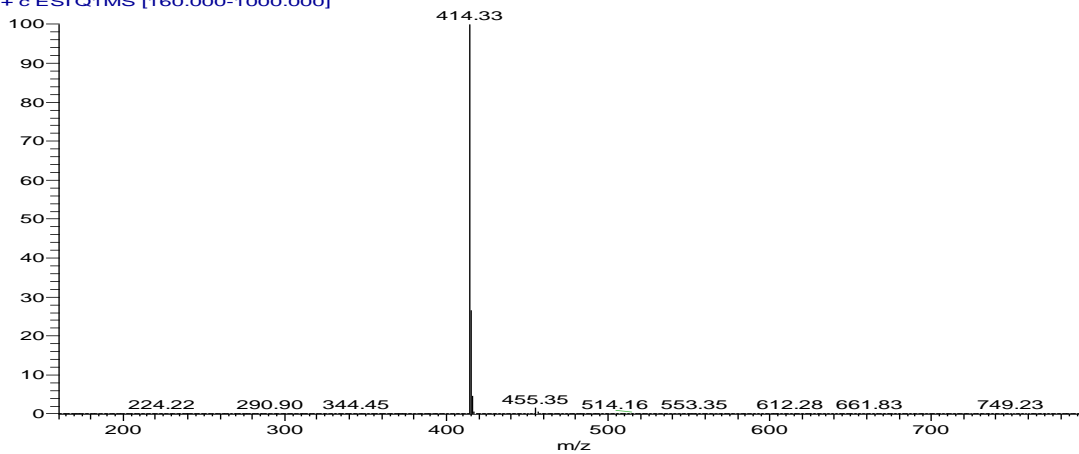
## LC/UV

RT: 2.945 - 19.954



## MS spectrum of peak with retention time of 13.4 min

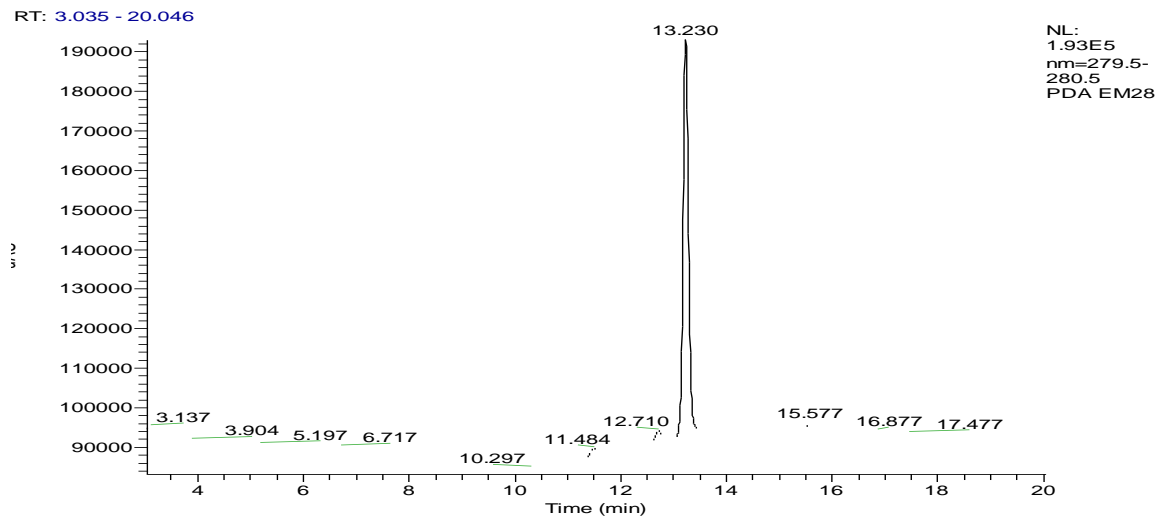
EM36 #1115 RT: 13.681 AV: 1 NL: 5.53E7  
T: + c ESI Q1MS [160.000-1000.000]



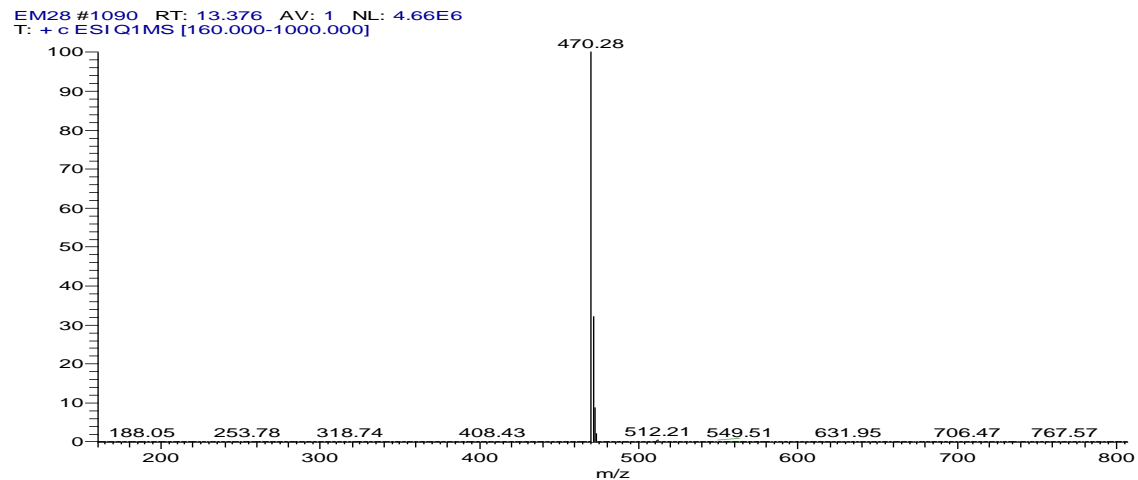


# Compound 3.18

## LC/UV

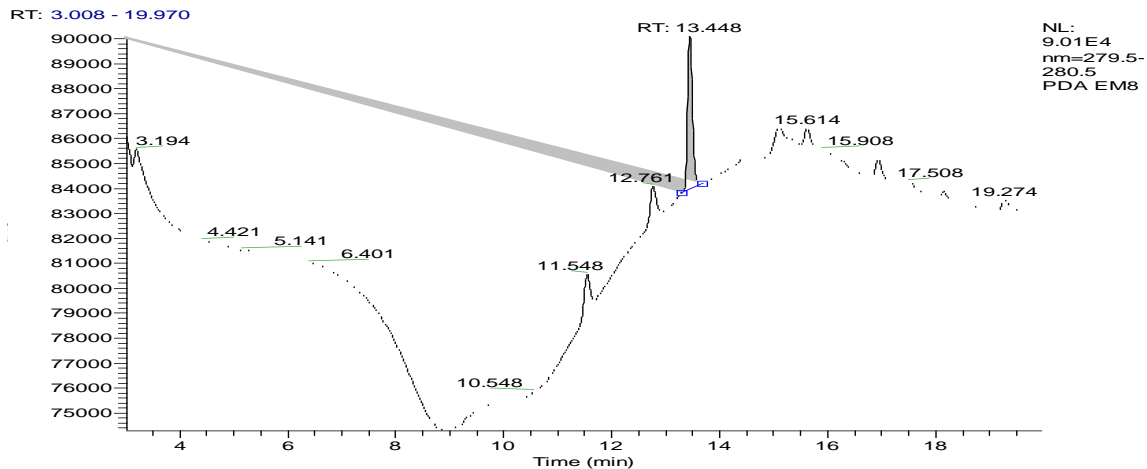


MS spectrum of peak with retention time of 13.2 min.

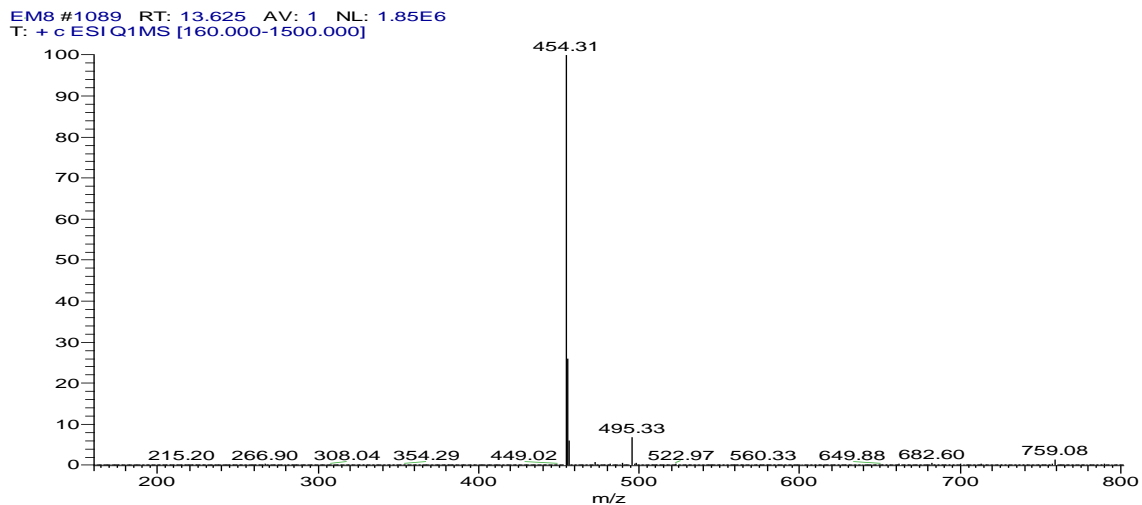


## Compound 3.20a

LC/UV: product peak 13.4 min. Run with Blank 1.

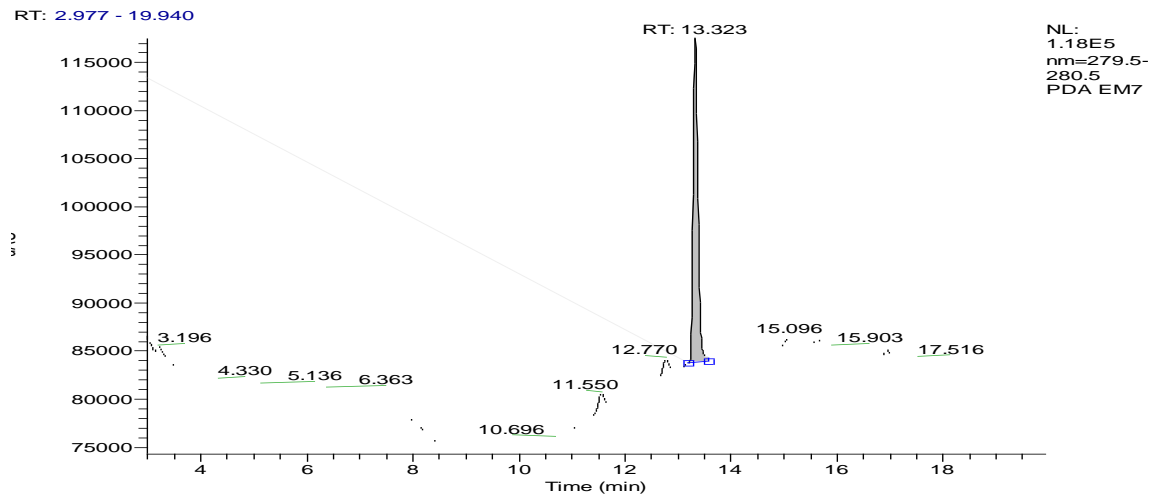


MS spectrum of peak with retention time of 13.4 min

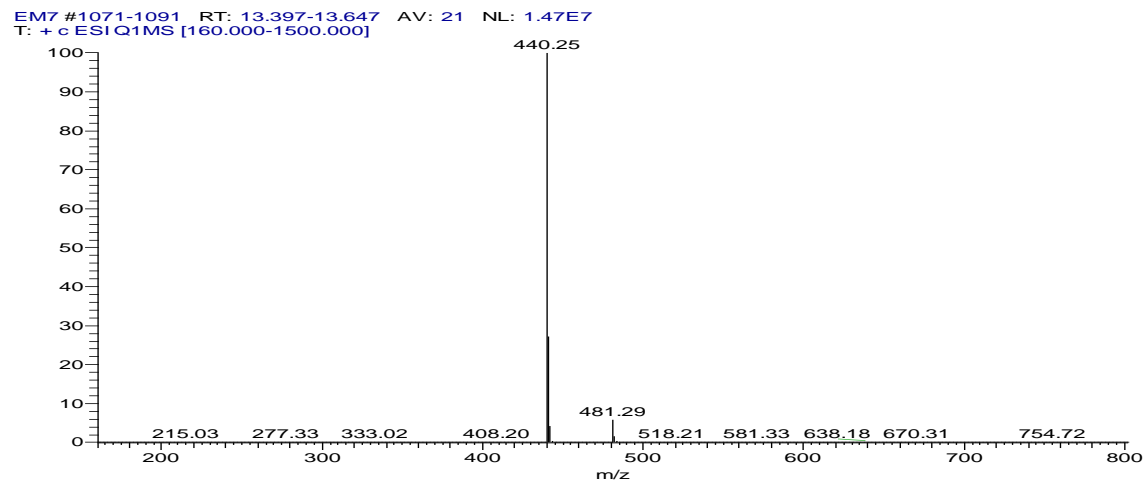


## Compound 3.20b

LC/UV: product peak 13.3 min. Run with Blank 1.



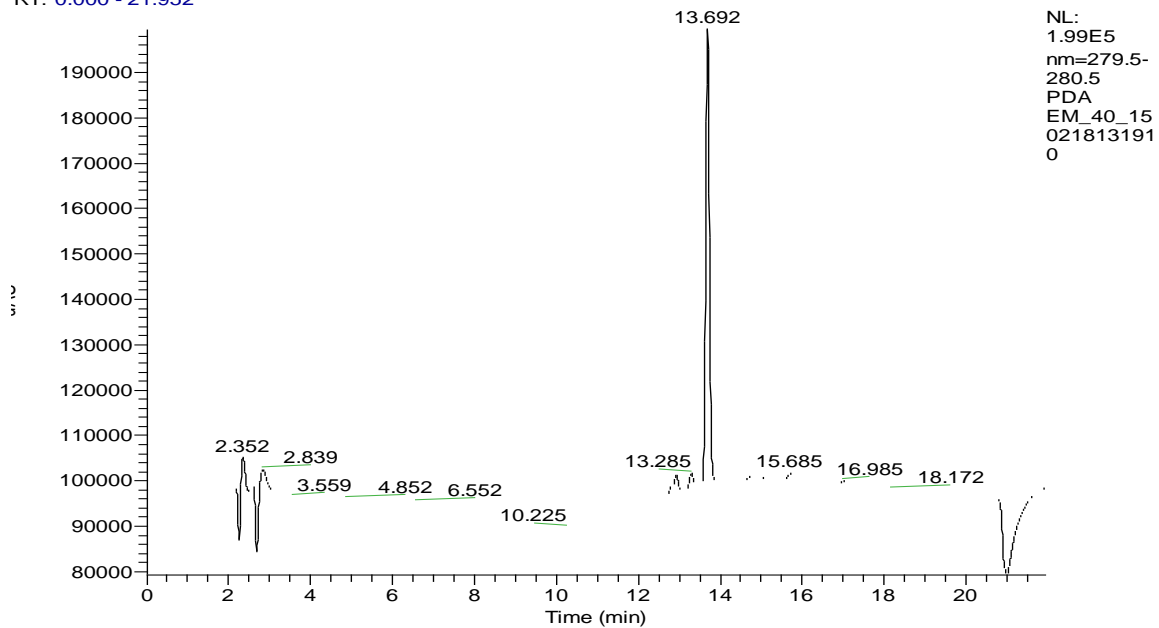
MS spectrum of peak with retention time of 13.3 min



# Compound 3.23a

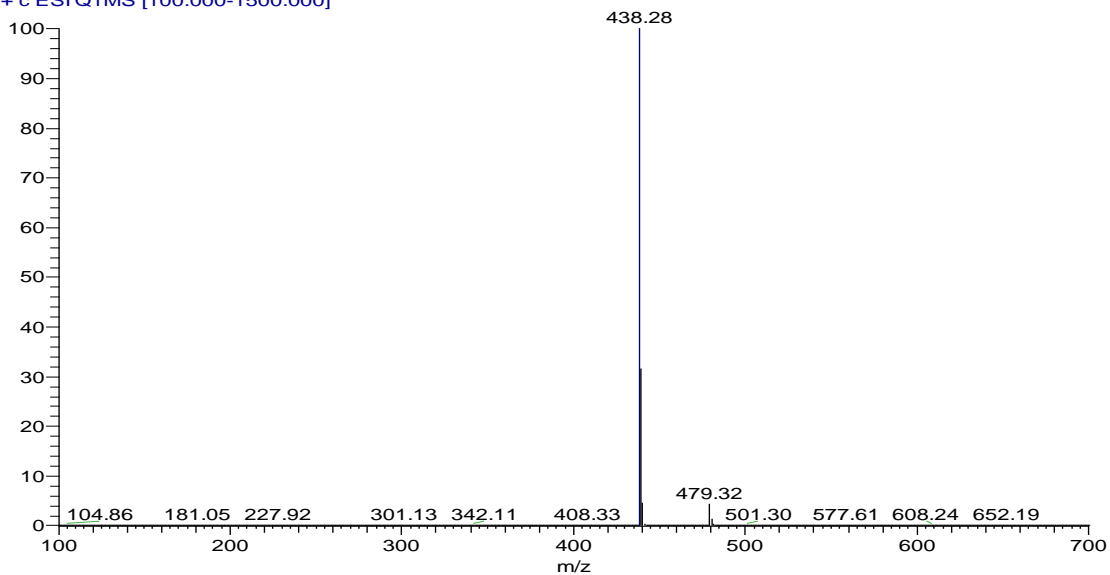
## LC/UV

RT: 0.000 - 21.952



## MS spectrum of peak with retention time of 13.7 min

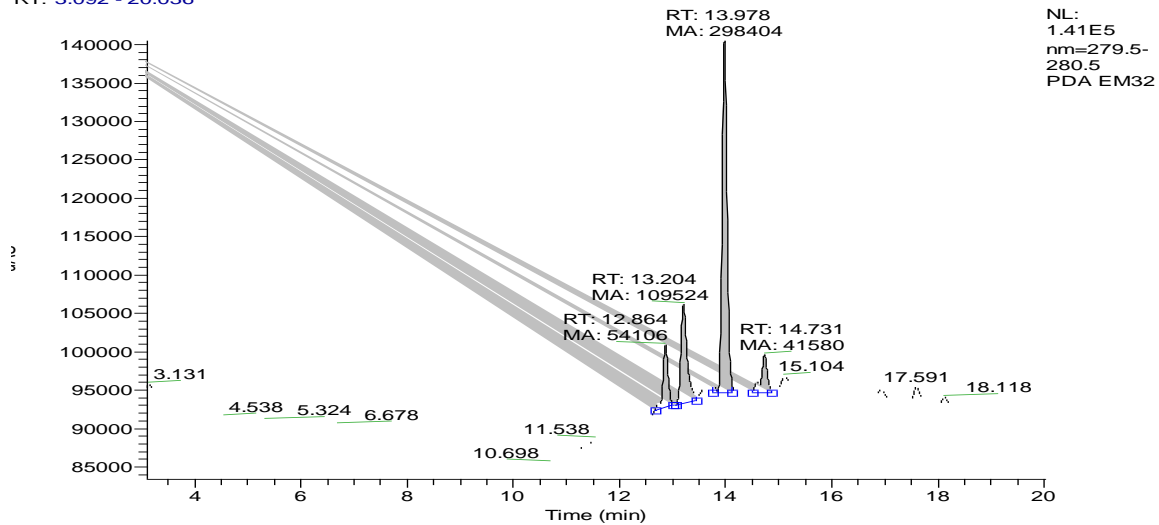
EM\_40\_150218131910 #1101-1113 RT: 13.817-13.968 AV: 13 NL: 2.11E8  
T: + c ESI Q1 MS [100.000-1500.000]



## Compound 3.23b

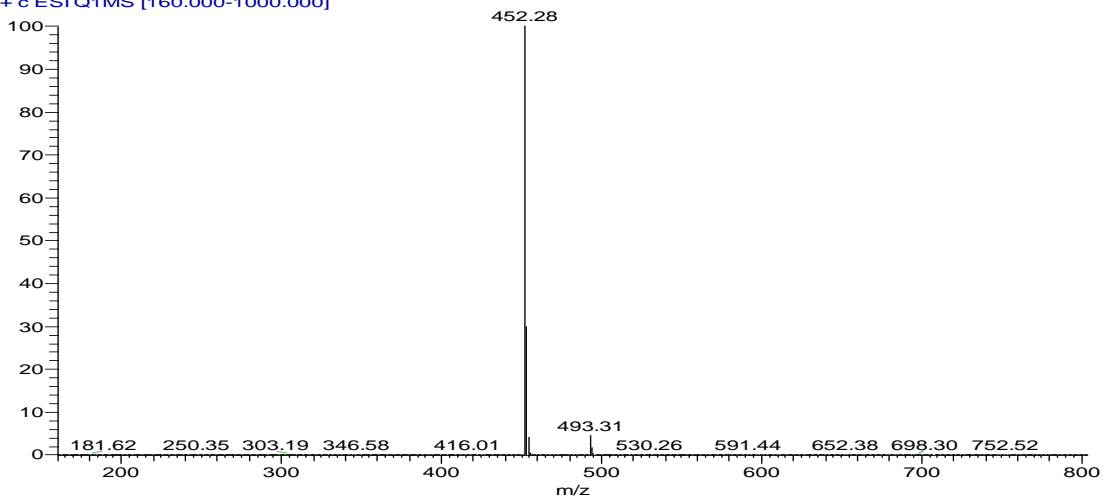
LC/UV: product peak 13.9 mins. Run with Blank 2.

RT: 3.092 - 20.036



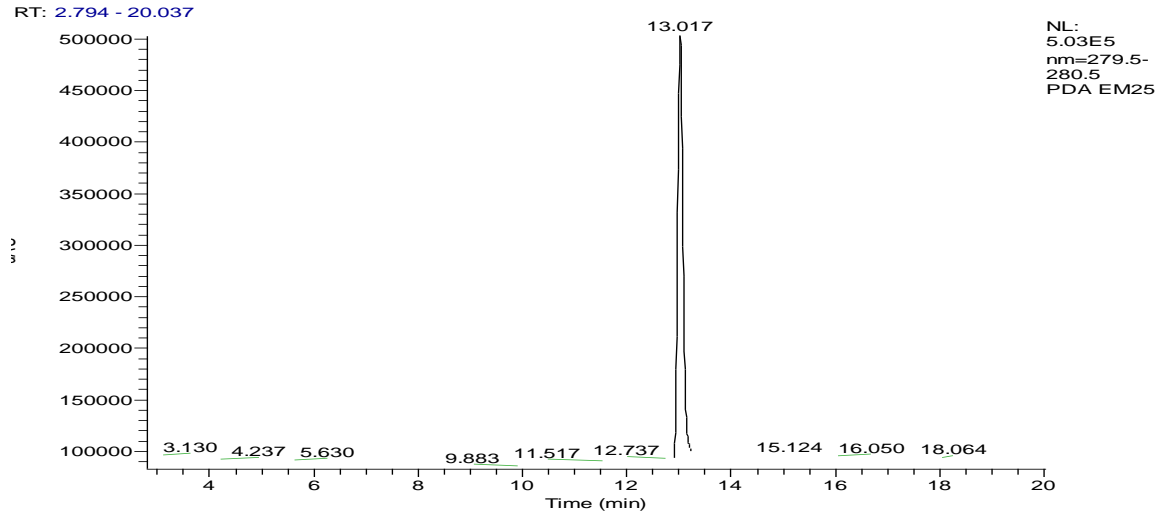
MS spectrum of peak with retention time of 13.9 min

EM32 #1151 RT: 14.123 AV: 1 NL: 4.07E7  
T: + c ESI Q1MS [160.000-1000.000]

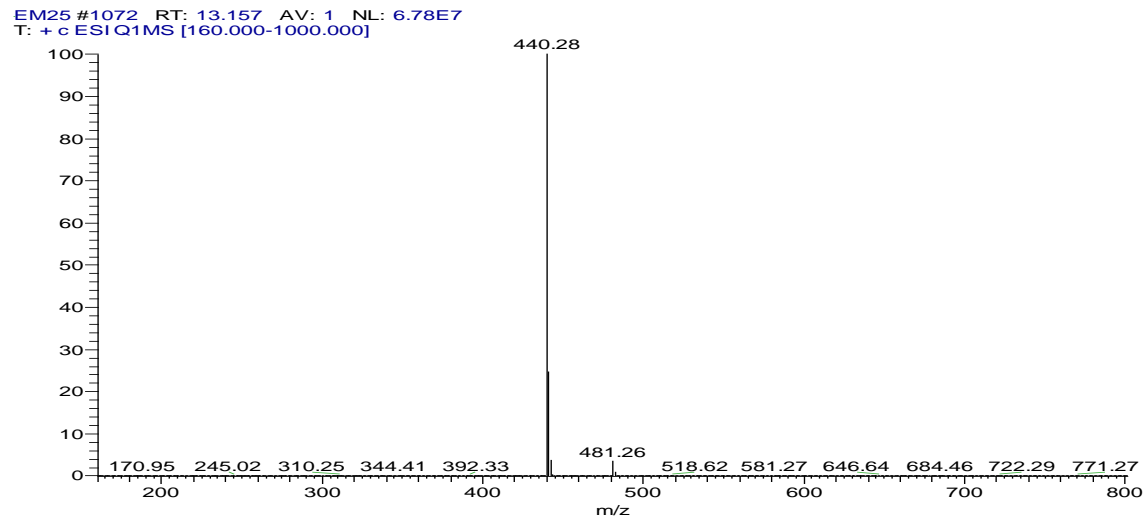


# Compound 3.27a

LC/UV

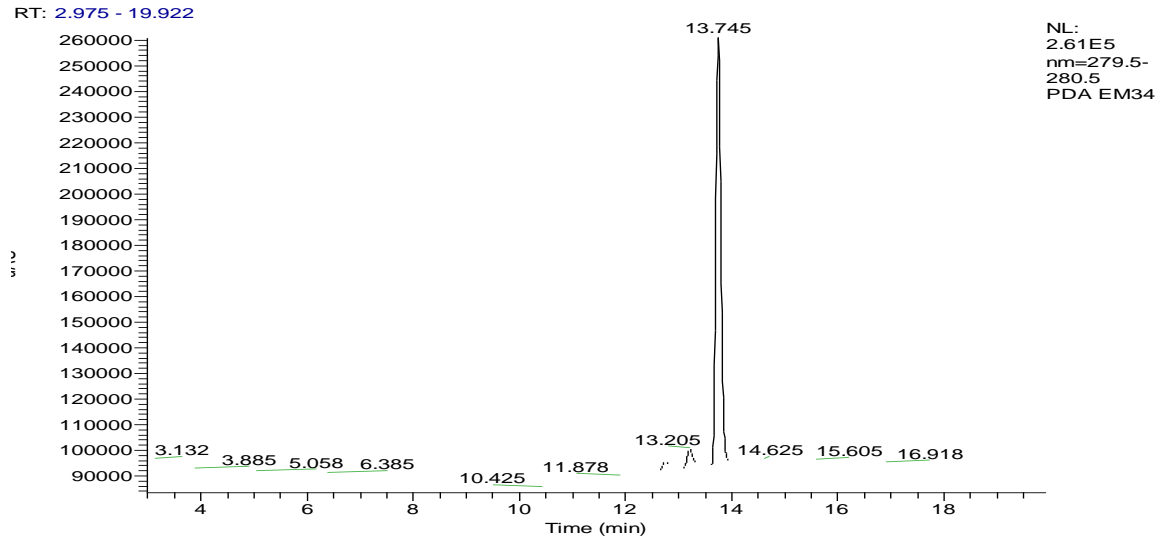


MS spectrum of peak with retention time of 13.0 min.

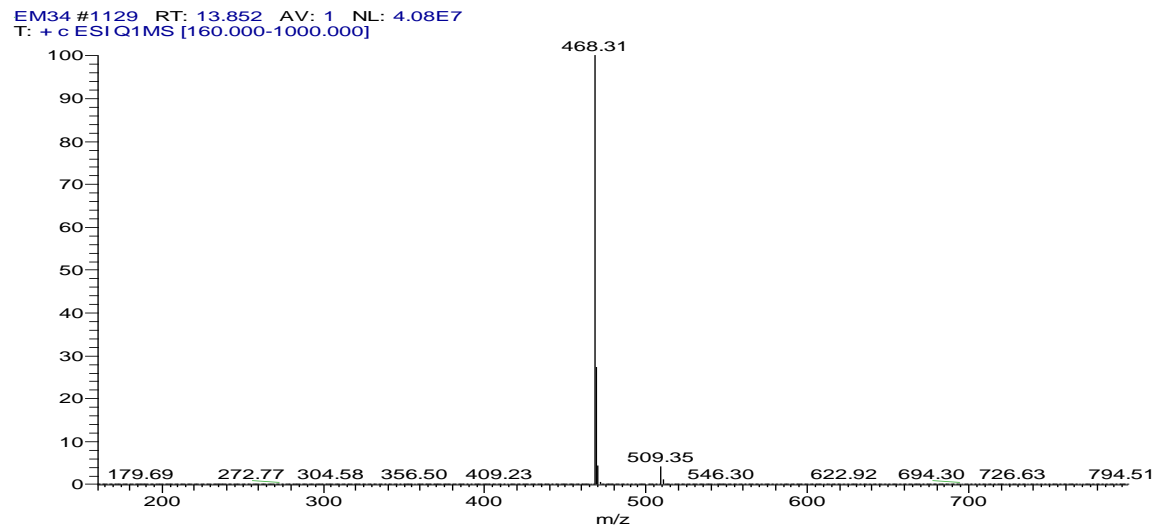


# Compound 3.27b

LC/UV

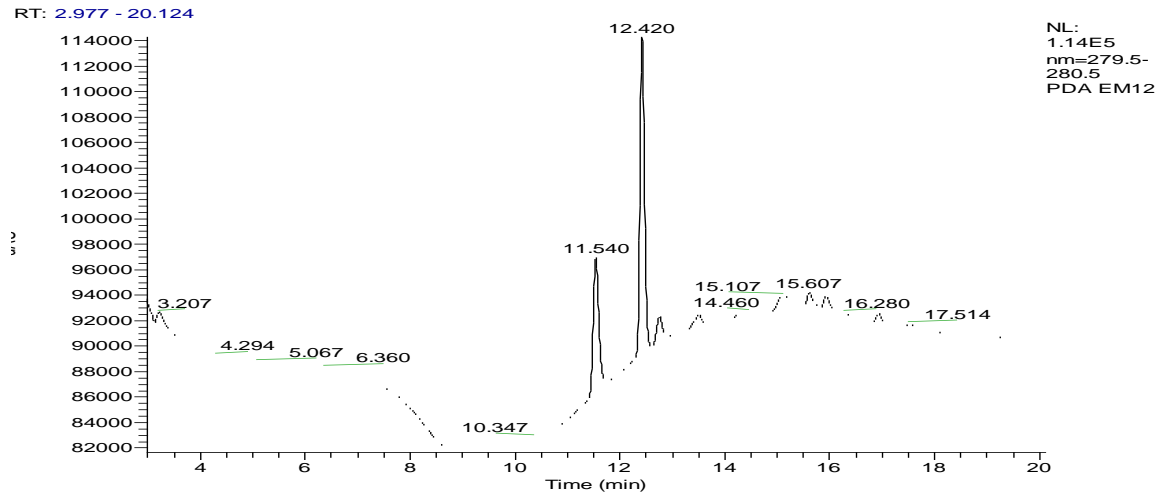


MS spectrum of peak with retention time of 13.7 min.

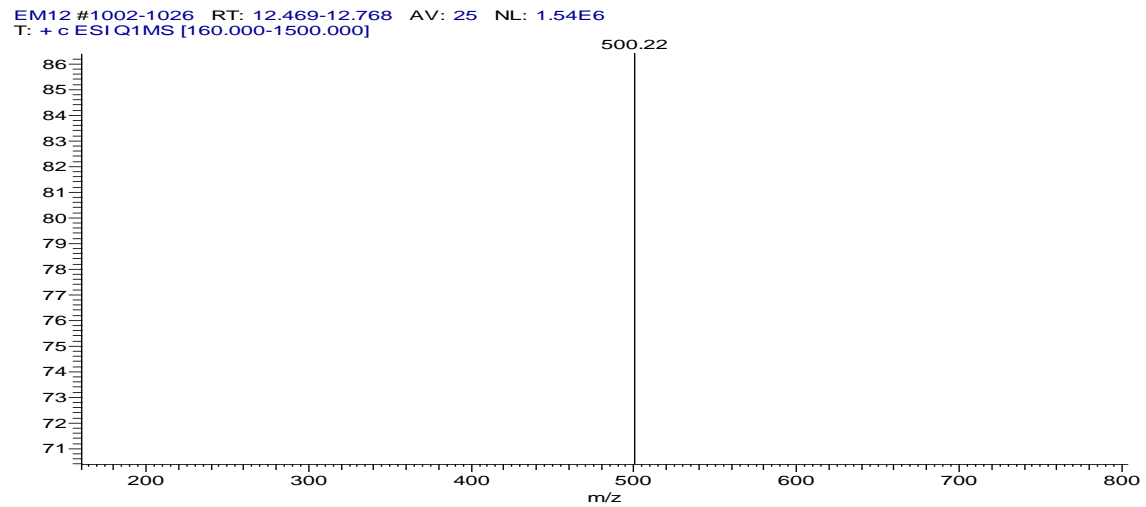


# Compound 3.27c

LC/UV: product peak 12.4 min. Extra peaks from Blank 1.



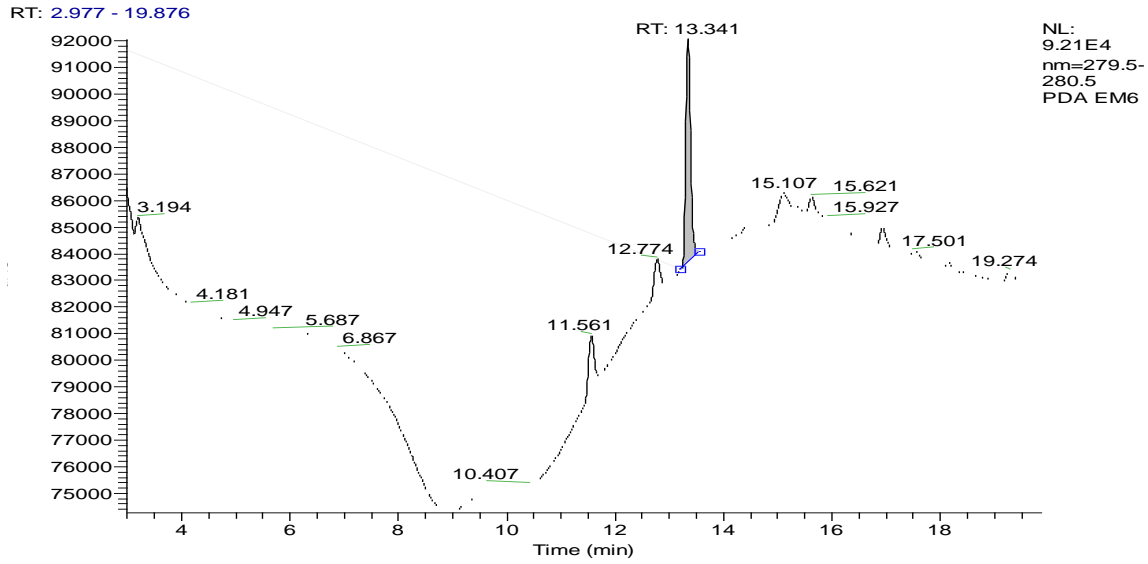
Spectrum of peak with retention time of 12.4 min



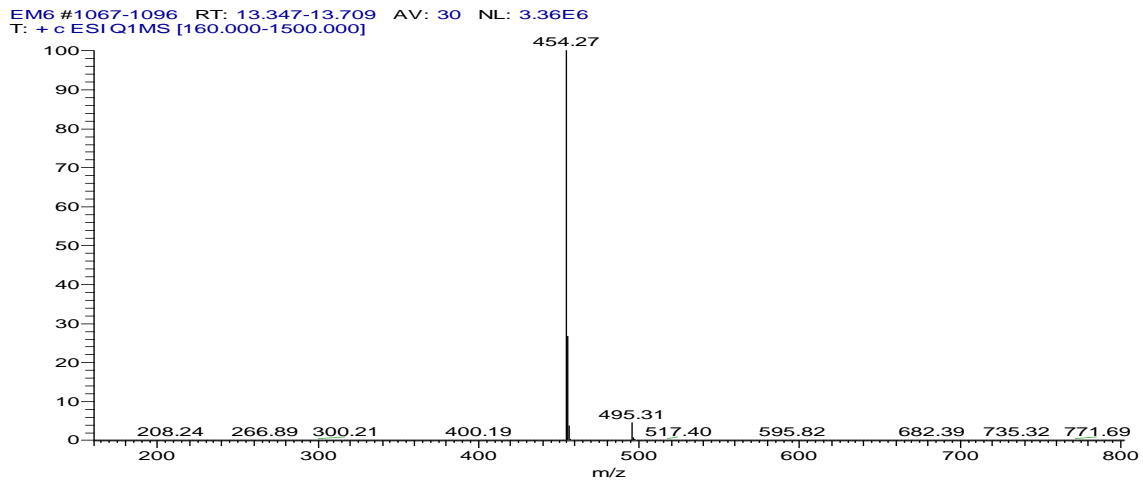


# Compound 3.27d

LC/UV: product peak at 13.3 min. Extra peaks from Blank 1.



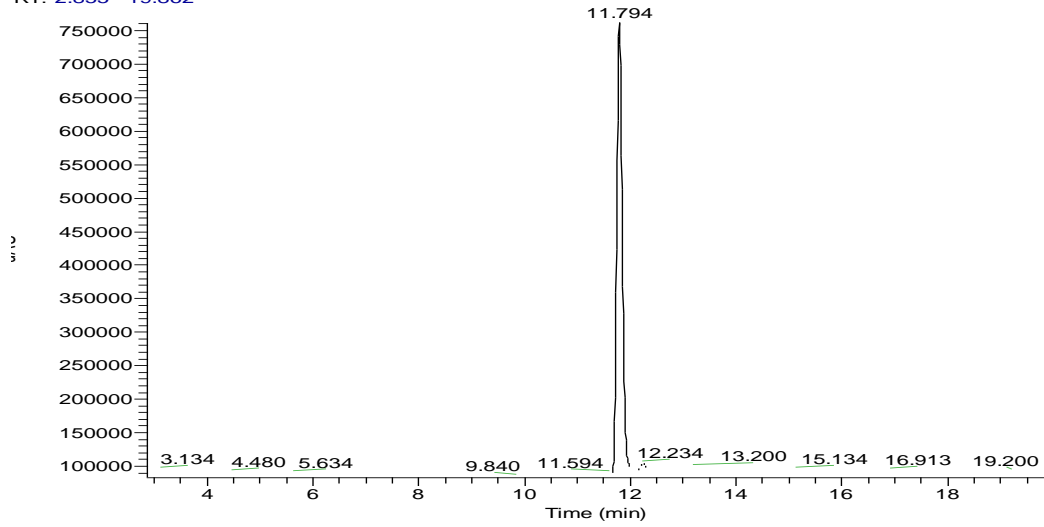
MS spectrum of peak with retention time of 13.3 min



# Compound 3.32a

LC/UV

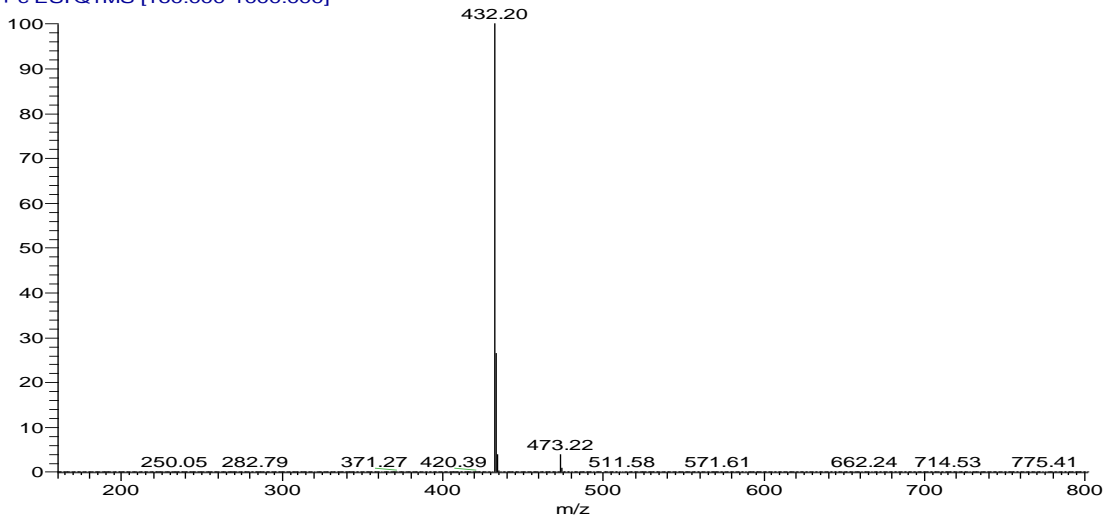
RT: 2.855 - 19.862



NL:  
7.61E5  
nm=279.5-  
280.5  
PDA EM33

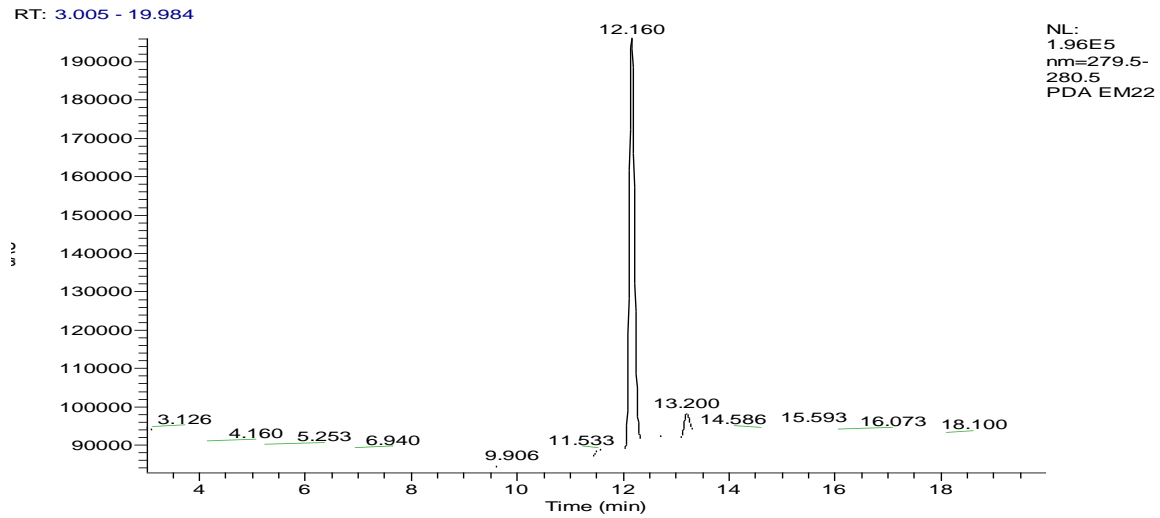
MS spectrum of peak with retention time of 11.8 min

EM33 #973 RT: 11.941 AV: 1 NL: 4.88E7  
T: + c ESI Q1 MS [160.000-1000.000]

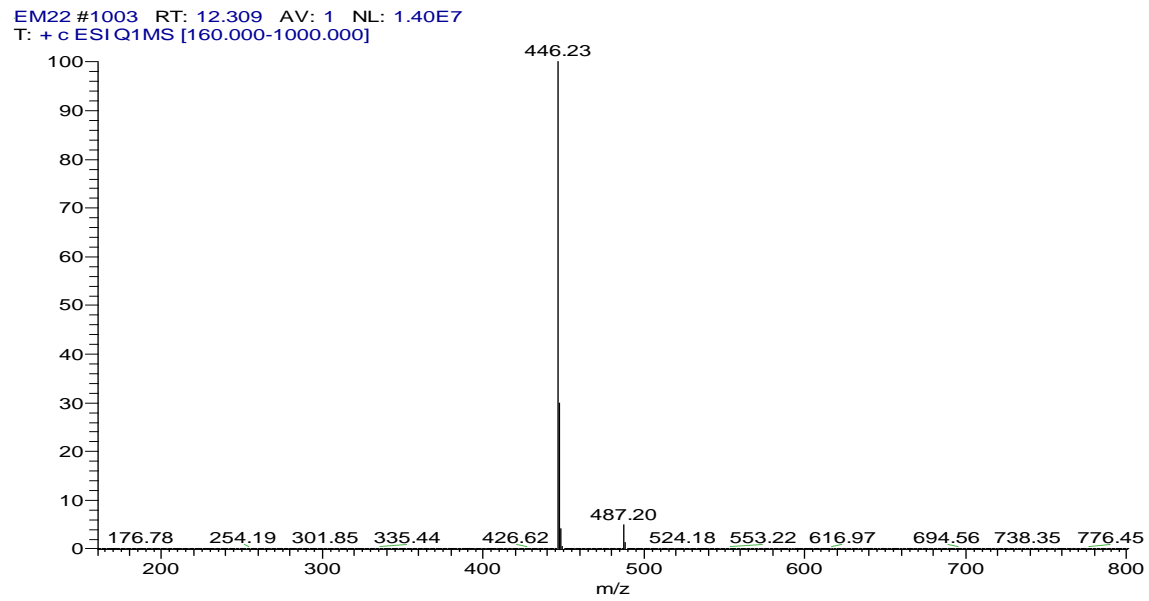


# Compound 3.32b

LC/UV



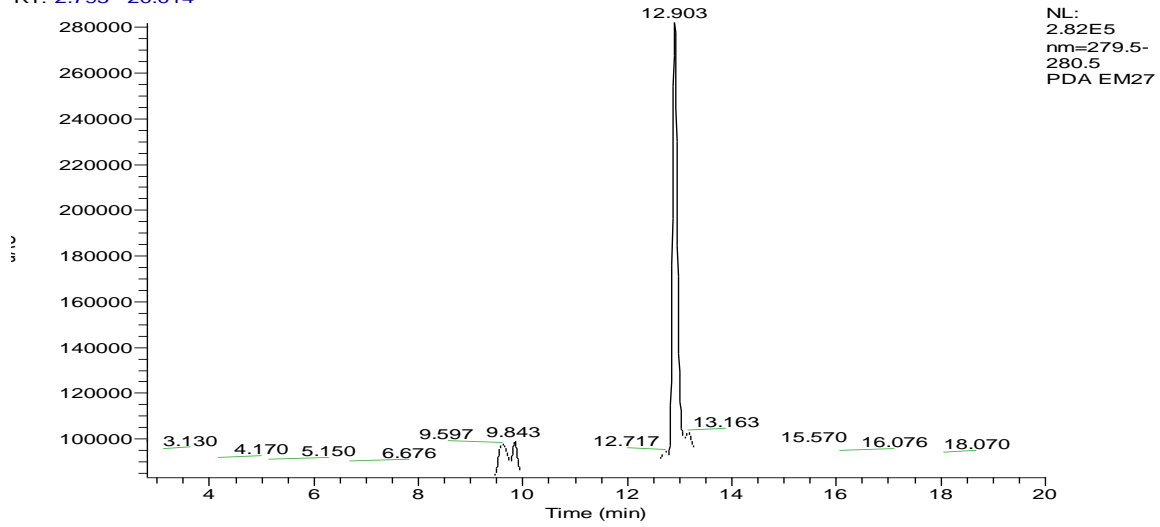
MS spectrum of peak with retention time of 12.1 min.



# Compound 3.32c

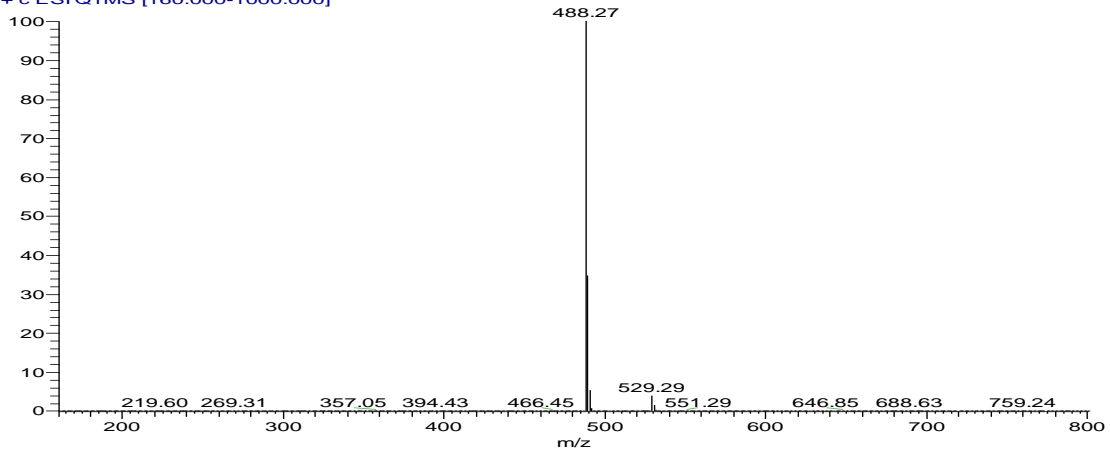
## LC/UV

RT: 2.795 - 20.014



MS spectrum of peak with retention time of 12.9 min.

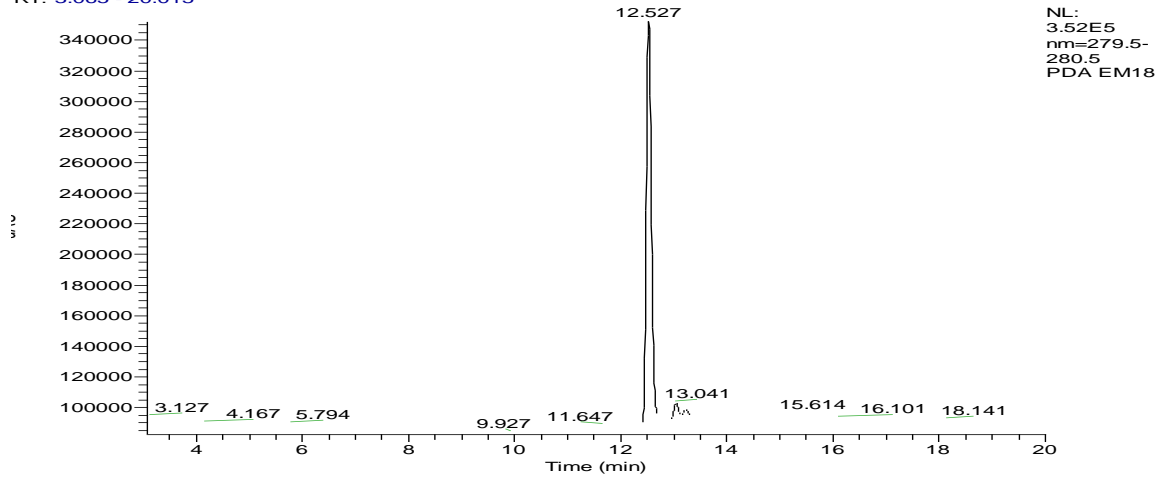
EM27 #1065 RT: 13.068 AV: 1 NL: 3.74E7  
T: + c ESI Q1 MS [160.000-1000.000]



# Compound 3.32d

LC/UV

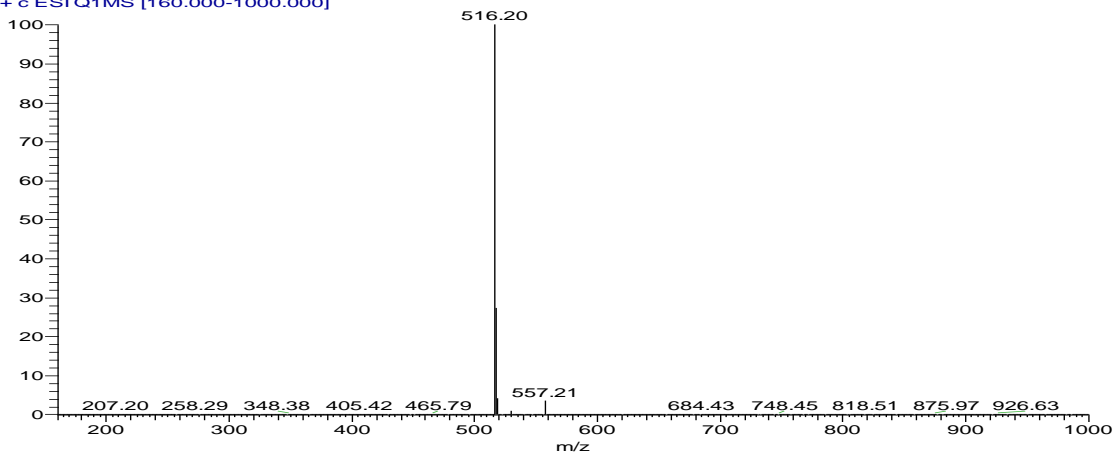
RT: 3.065 - 20.015



NL:  
3.52E5  
nm=279.5-  
280.5  
PDA EM18

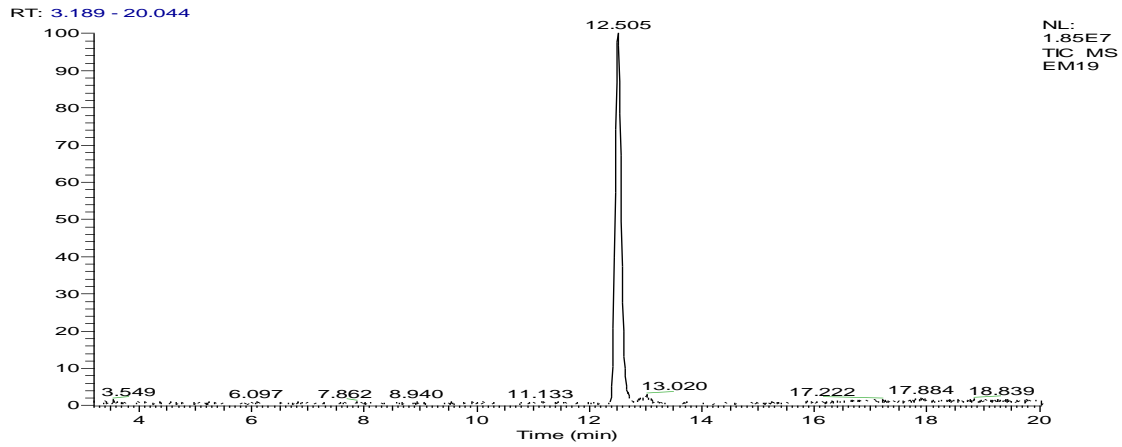
MS spectrum of peak with retention time of 12.5 min

EM18 #1031 RT: 12.653 AV: 1 NL: 4.75E7  
T: + c ESI Q1MS [160.000-1000.000]

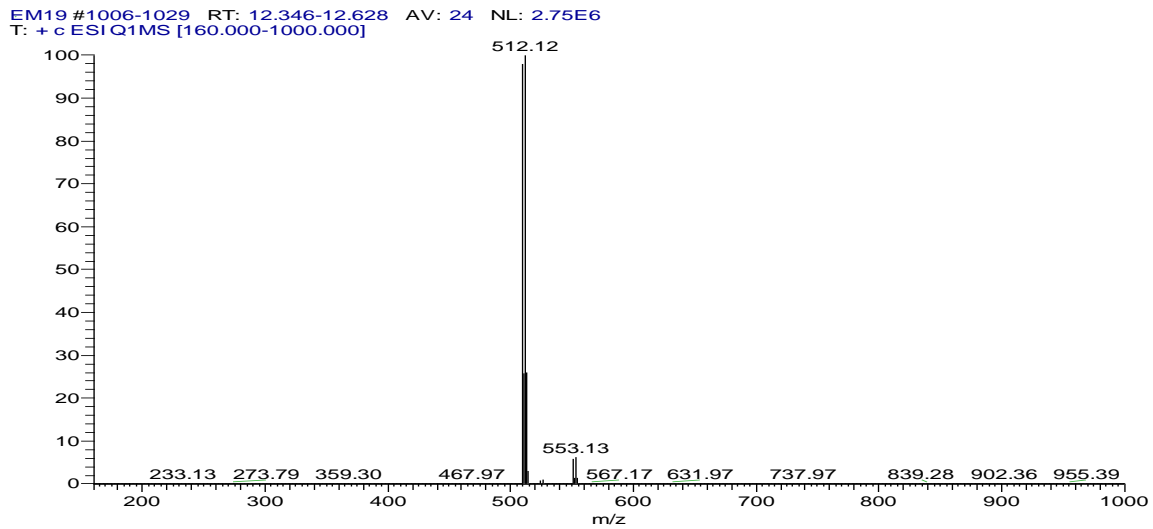


# Compound 3.32e

LC/UV



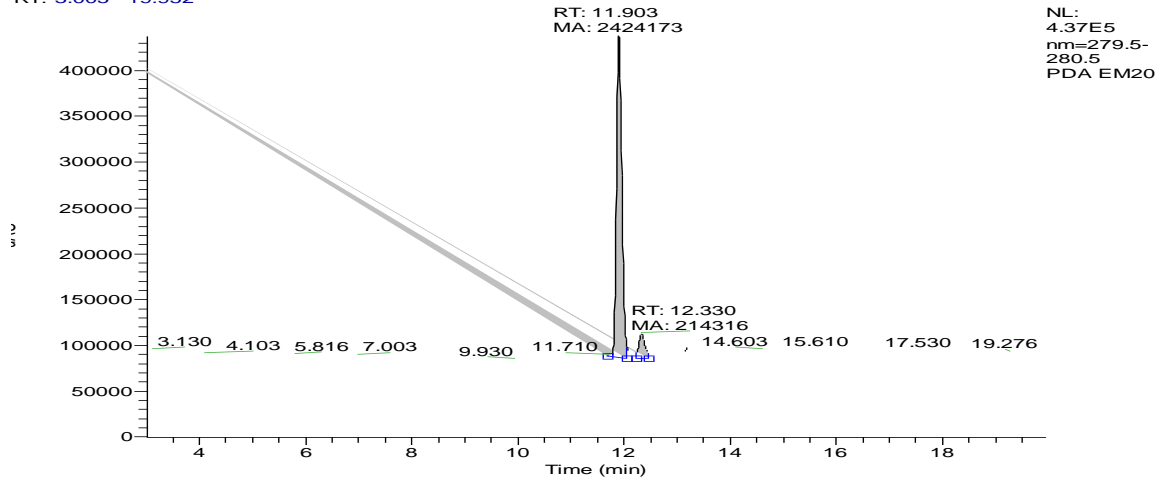
MS spectrum of peak with retention time of 12.505 min



# Compound 3.32f

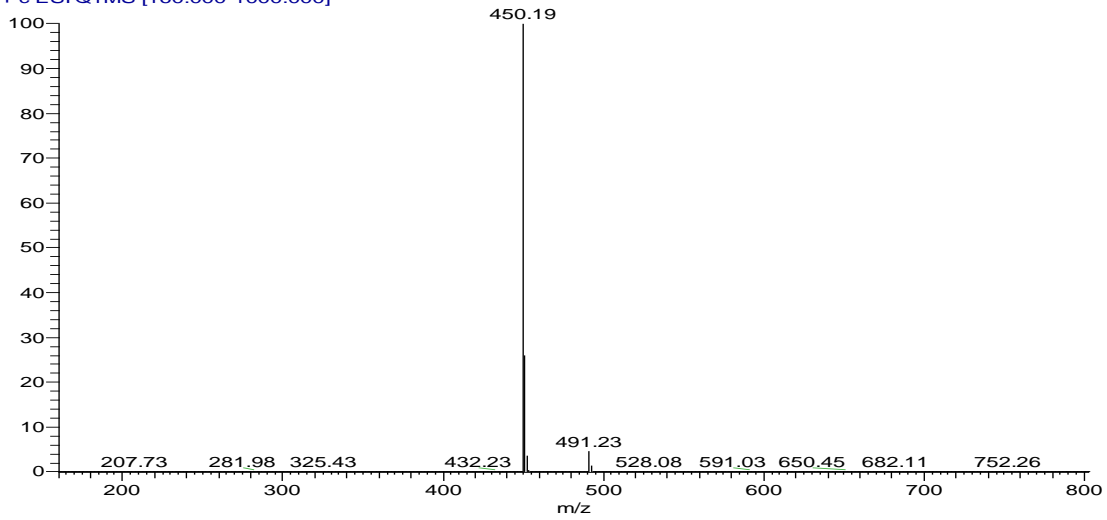
LC/UV

RT: 3.005 - 19.952



MS spectrum of peak with retention time of 11.9 min

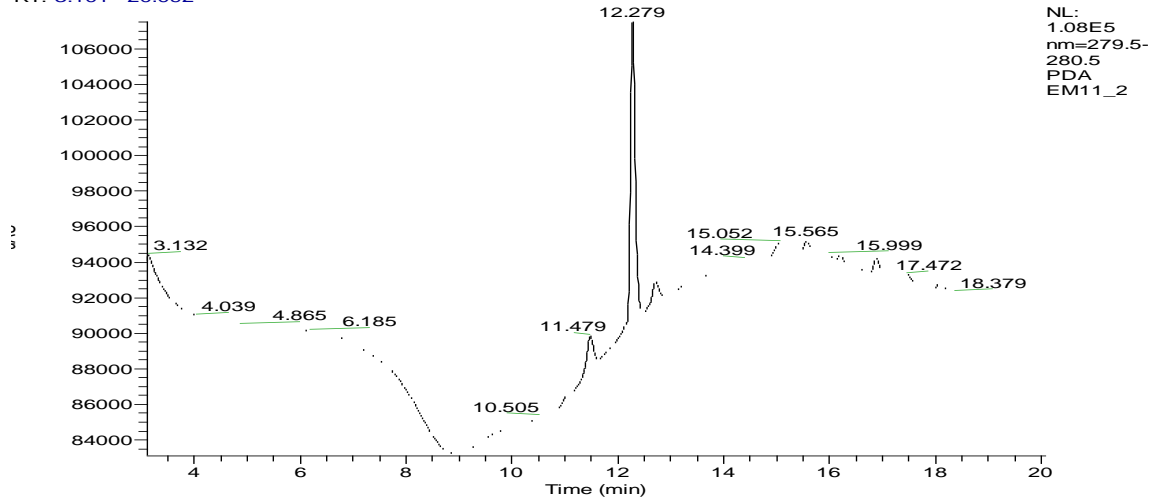
EM20 #977-992 RT: 11.988-12.172 AV: 16 NL: 2.39E7  
T: + c ESI Q1MS [160.000-1000.000]



# Compound 3.32h

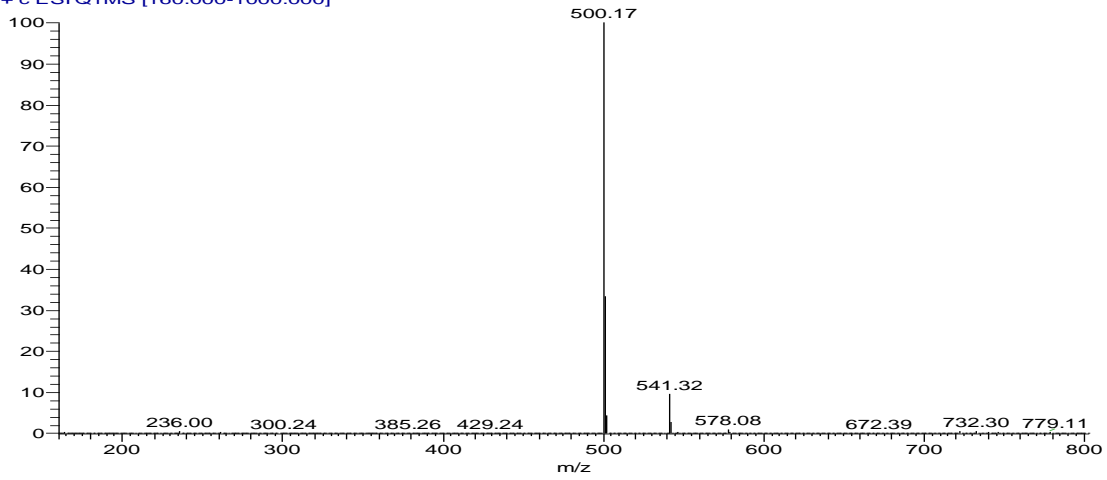
LC/UV

RT: 3.101 - 20.092



Spectrum of peak with retention time of 12.2 min

EM11\_2 #1012 RT: 12.421 AV: 1 NL: 1.31E6  
T: + c ESI Q1MS [160.000-1000.000]

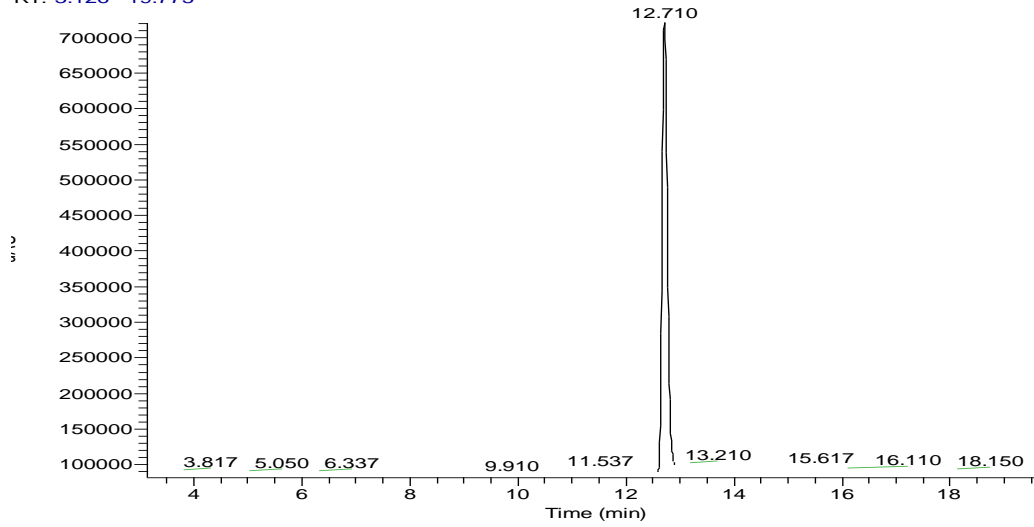




# Compound 3.32i

LC/UV

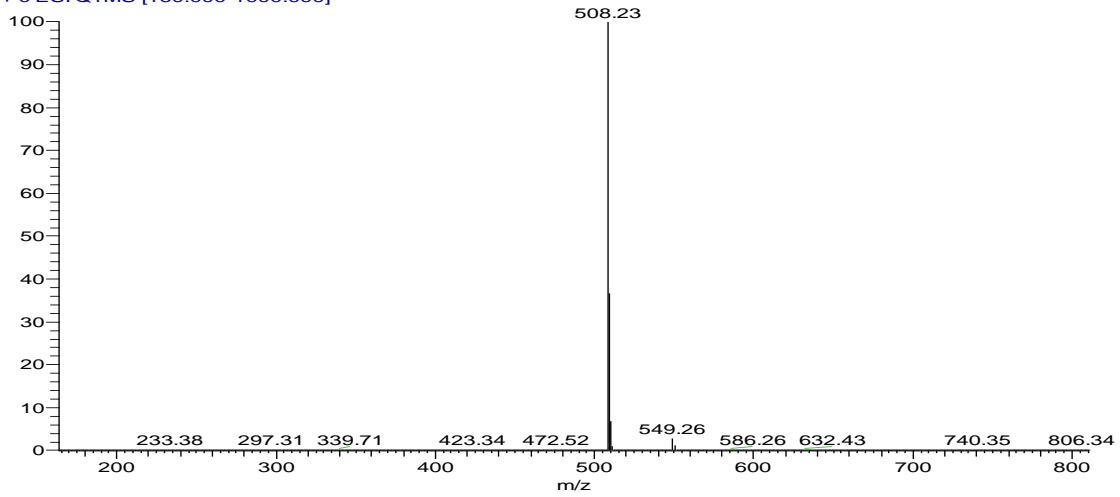
RT: 3.126 - 19.775



NL:  
7.20E5  
nm=279.5-  
280.5  
PDA EM16

MS spectrum of peak with retention time of 12.7 min.

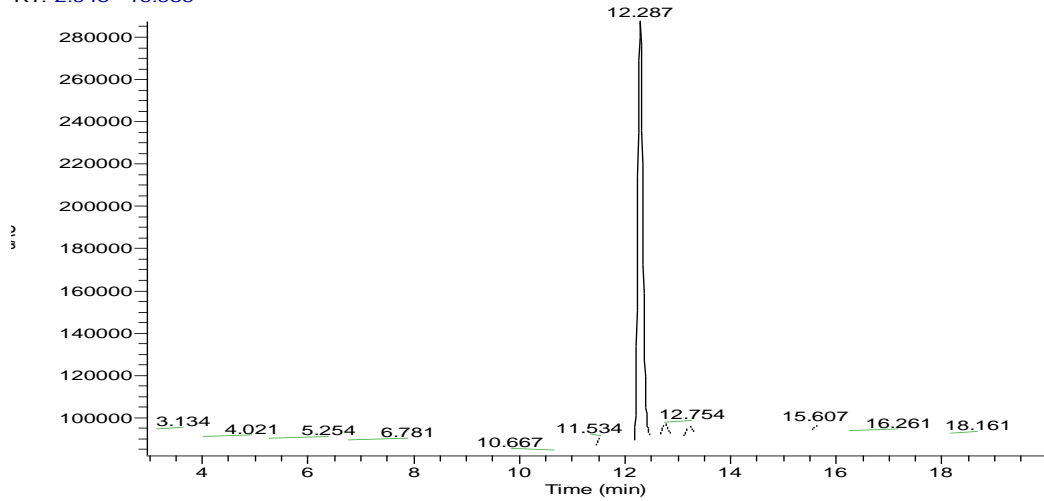
EM16 #1041-1063 RT: 12.776-13.045 AV: 23 NL: 2.80E7  
T: + c ESI Q1MS [160.000-1000.000]



# Compound 3.32j

LC/UV

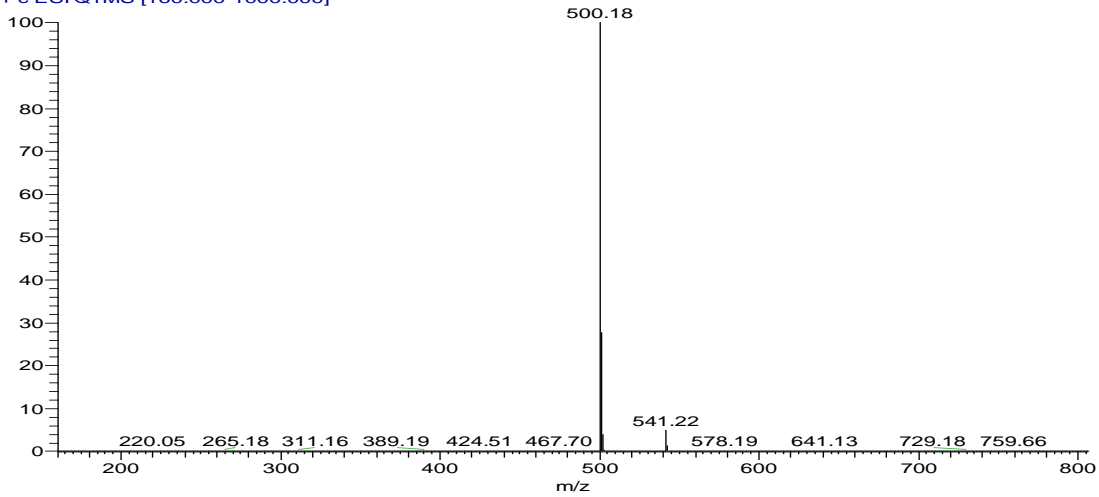
RT: 2.946 - 19.969



NL:  
2.87E5  
nm=279.5-  
280.5  
PDA EM14

MS spectrum of peak with retention time of 12.28 min

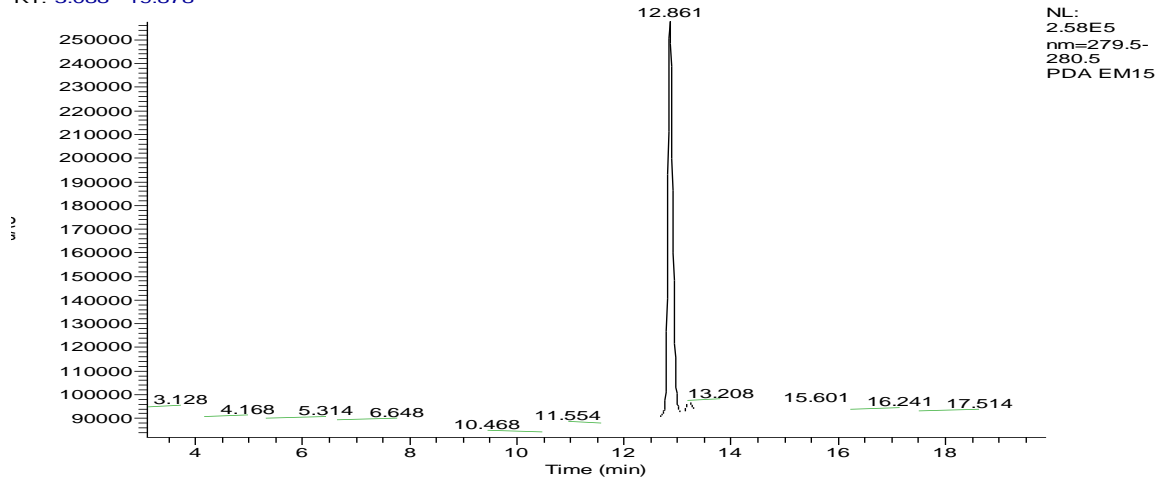
EM14 #1016-1026 RT: 12.468-12.591 AV: 11 NL: 9.62E6  
T: + c ESI Q1MS [160.000-1000.000]



# Compound 3.32k

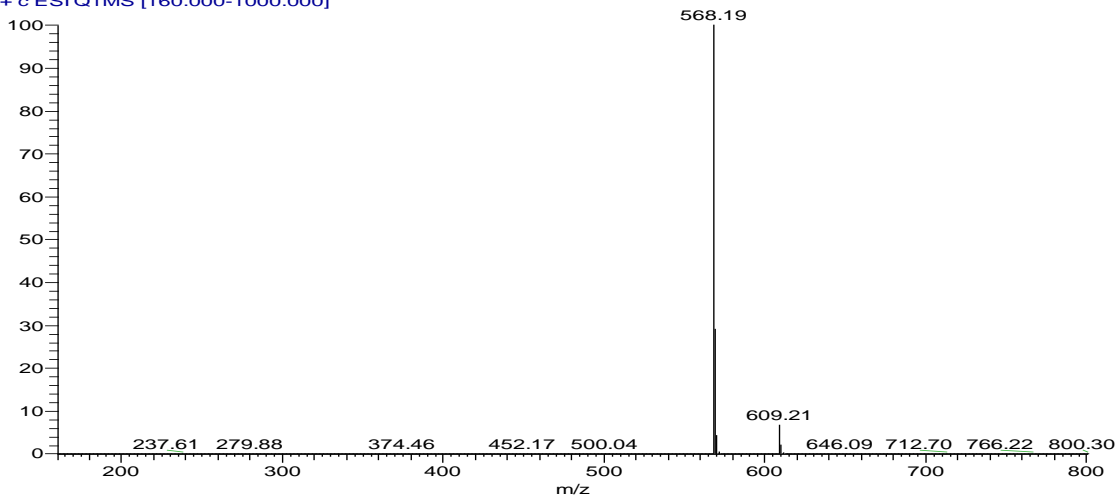
LC/UV

RT: 3.088 - 19.878



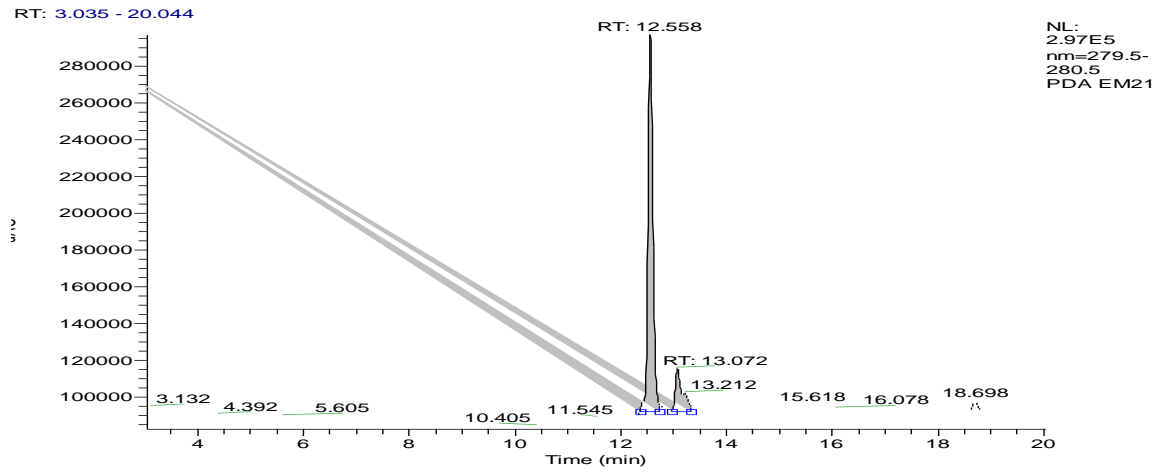
MS spectrum of peak with retention time of 12.86 min

EM15 #1057-1074 RT: 12.969-13.177 AV: 18 NL: 2.03E7  
T: + c ESI Q1 MS [160.000-1000.000]

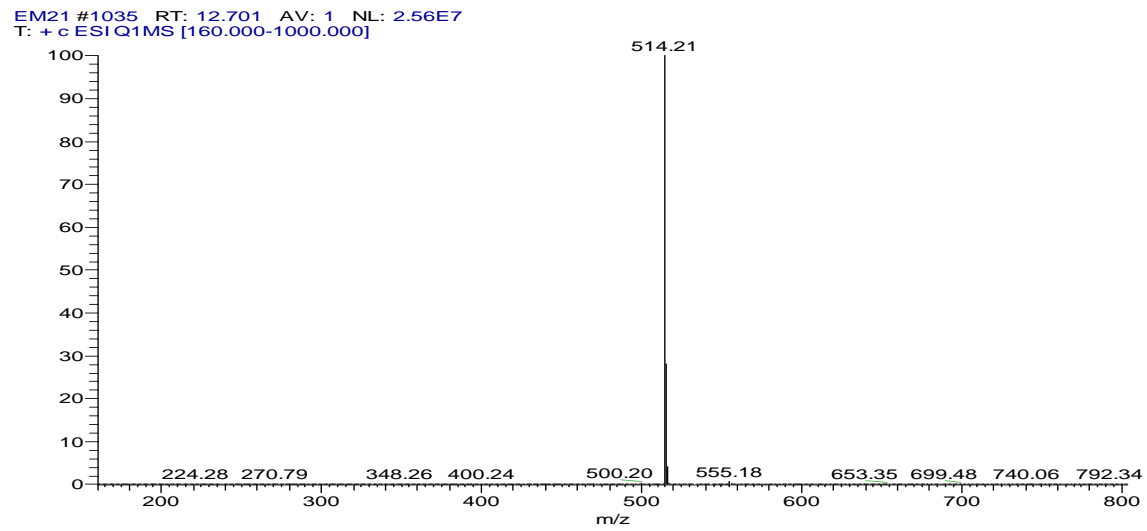


# Compound 3.321

LC/UV: product peak 12.5 min. Run with Blank 2.



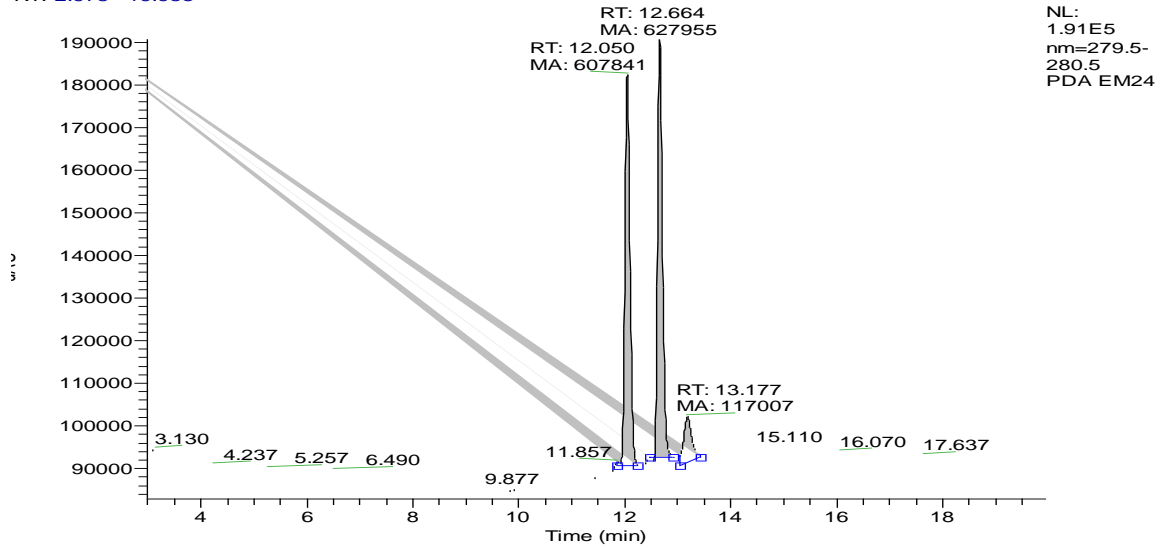
MS spectrum of peak with retention time of 12.55 min



# Compound 3.32m

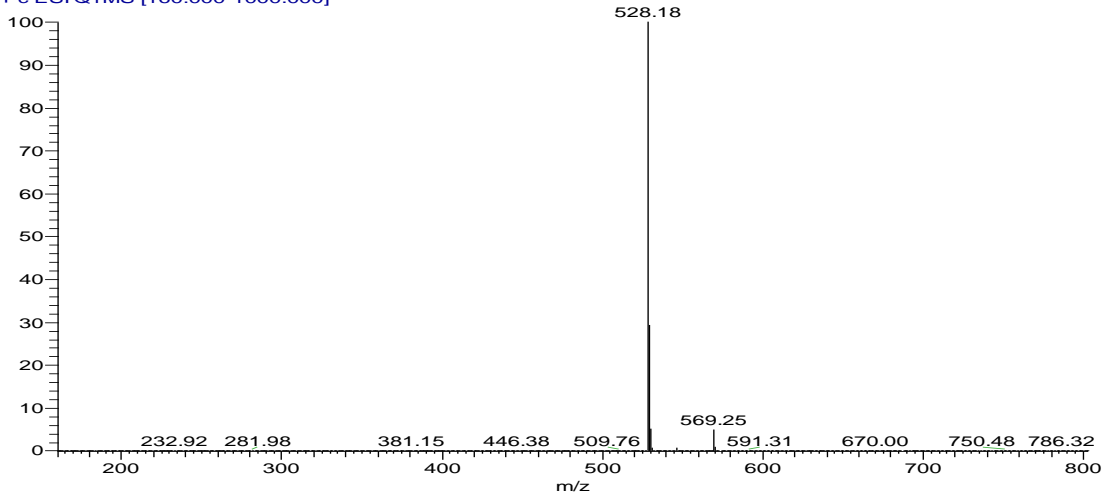
LC/UV: product peak 12.0 min. Run with Blank 2.

RT: 2.975 - 19.953



MS spectrum of peak with retention time of 12.0 min

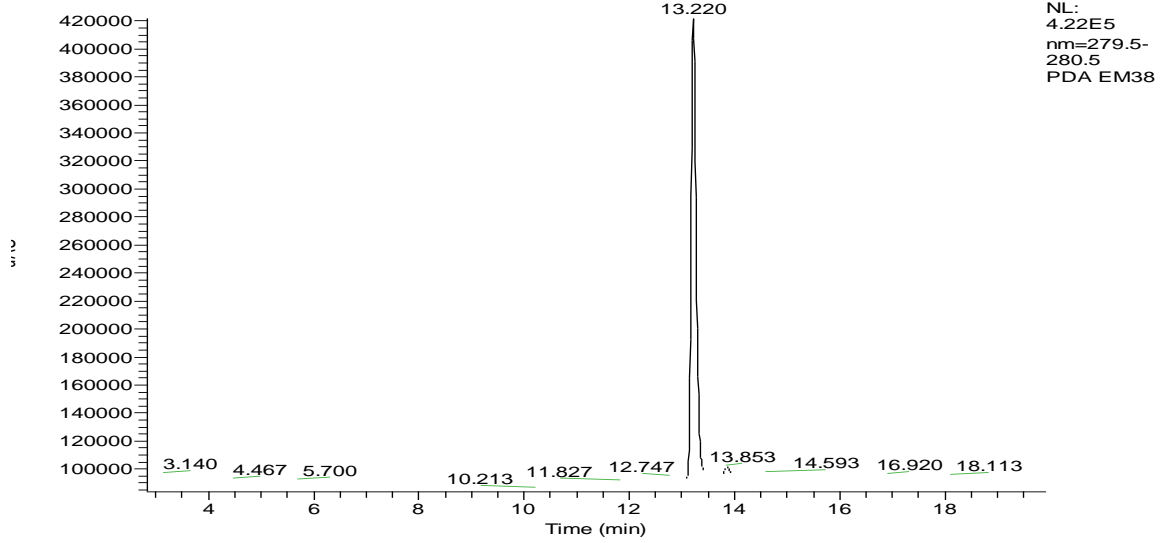
EM24 #993 RT: 12.187 AV: 1 NL: 1.23E7  
T: + c ESI Q1MS [160.000-1000.000]



# Compound 3.35

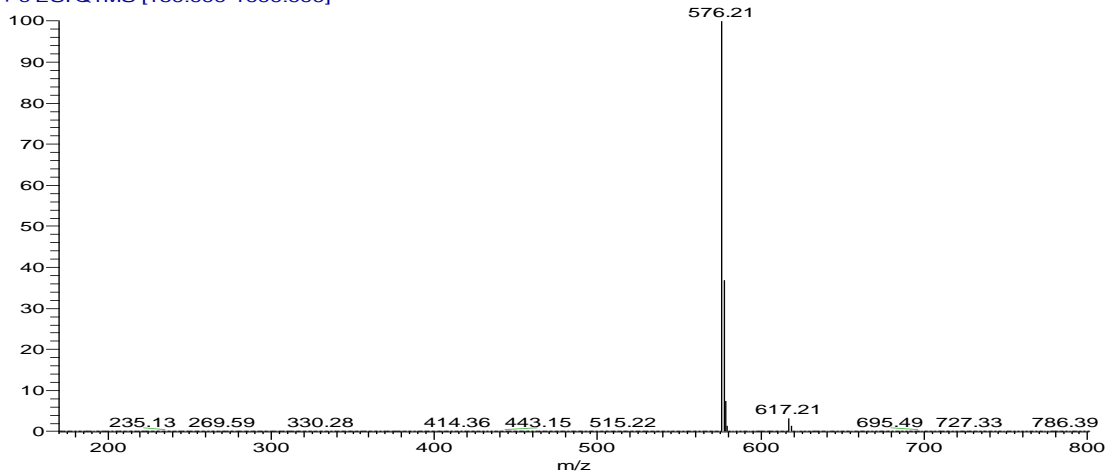
LC/UV

RT: 2.825 - 19.923



MS spectrum of peak with retention time of 13.22 min

EM38 #1089 RT: 13.363 AV: 1 NL: 2.88E7  
T: + c ESI Q1 MS [160.000-1000.000]

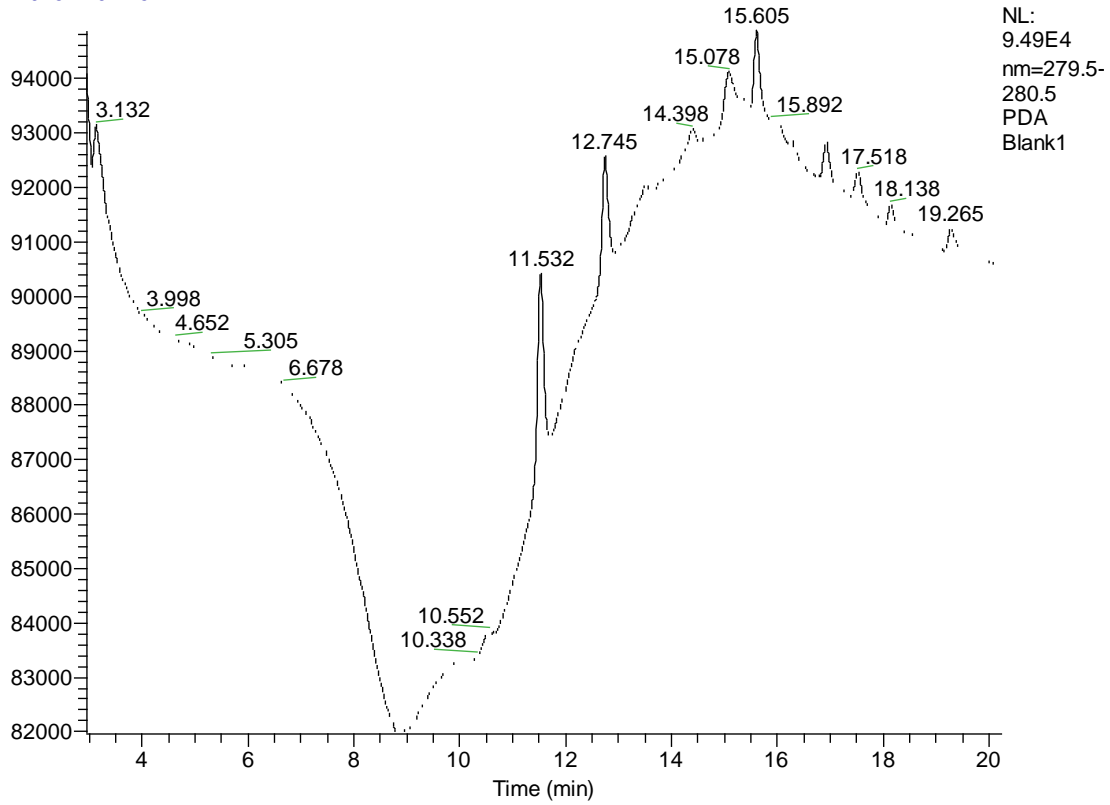


### 4.6.3 HPLC blank traces

#### Blank 1

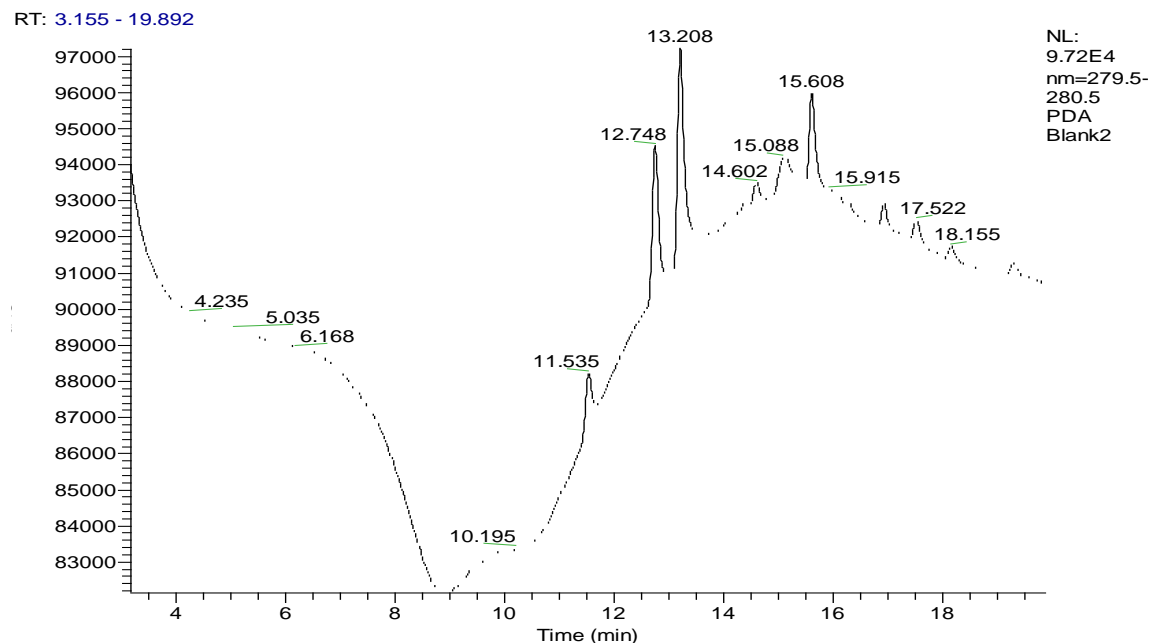
LC/UV of Blank 1.

RT: 2.945 - 20.246



## Blank 2

LC/UV of Blank 2.



## 4.7 References

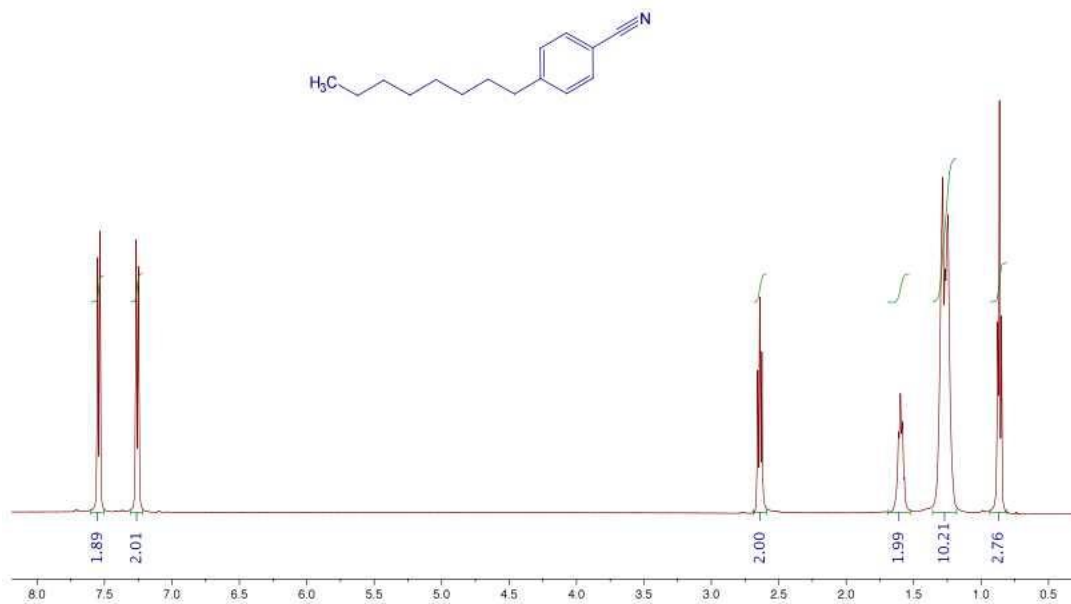
1. Shaner, R. L.; Allegood, J. C.; Park, H.; Wang, E.; Kelly, S.; Haynes, C. A.; Sullards, M. C.; Merrill, A. H., Quantitative analysis of sphingolipids for lipidomics using triple quadrupole and quadrupole linear ion trap mass spectrometers. *J. Lipid Res.* **2009**, *50*, 1692-1707.
2. Paugh, S. W.; Paugh, B. S.; Rahmani, M.; Kapitonov, D.; Almenara, J. A.; Kordula, T.; Milstien, S.; Adams, J. K.; Zipkin, R. E.; Grant, S.; Spiegel, S., A selective sphingosine kinase 1 inhibitor integrates multiple molecular therapeutic targets in human leukemia. *Blood* **2008**, *112*, 1382-1391.
3. Everson, D. A.; Shrestha, R.; Weix, D. J., Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 920-921.



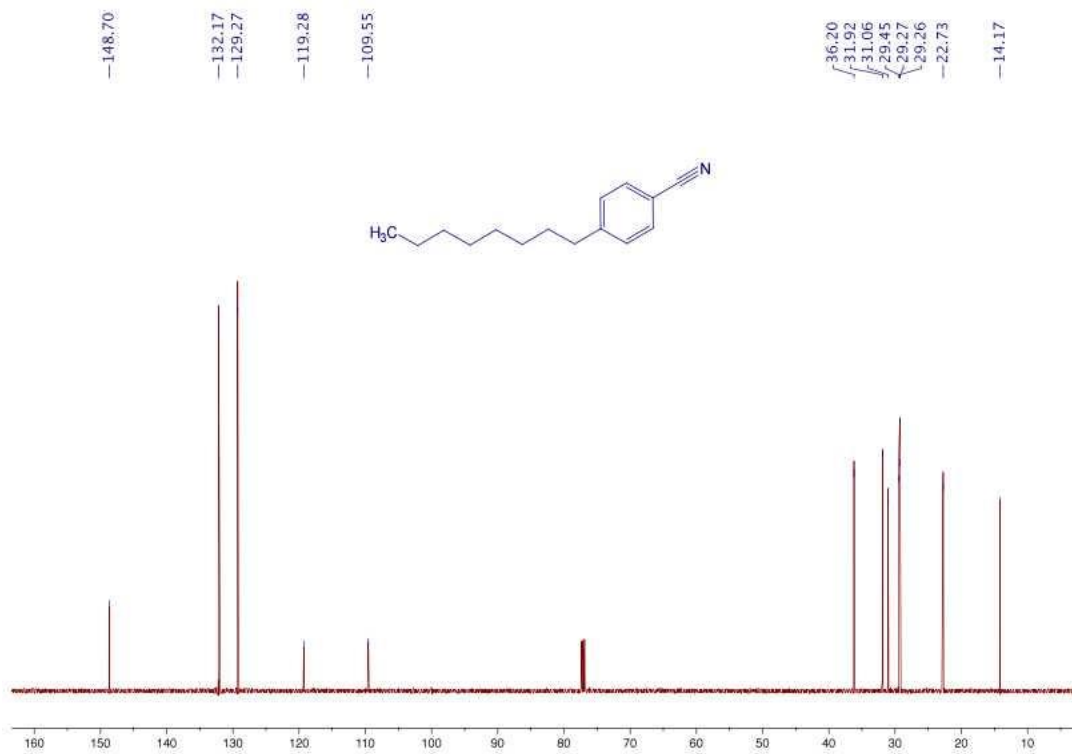
4. Foss Jr, F. W.; Mathews, T. P.; Kharel, Y.; Kennedy, P. C.; Snyder, A. H.; Davis, M. D.; Lynch, K. R.; Macdonald, T. L., Synthesis and biological evaluation of sphingosine kinase substrates as sphingosine-1-phosphate receptor prodrugs. *Bioorg. Med. Chem.* **2009**, *17*, 6123-6136.
5. Hodges, J. A.; Raines, R. T., Stereoelectronic and steric effects in the collagen triple helix: Toward a code for strand association. *J. Am. Chem. Soc.* **2005**, *127*, 15923-15932.
6. Demange, L.; Cluzeau, J.; Menez, A.; Dugave, C., Synthesis of optically pure N-Boc-protected (2R,3R)- and (2R,3S)-3-fluoroprolines. *Tetrahedron Lett.* **2001**, *42*, 651-653.

## Appendix

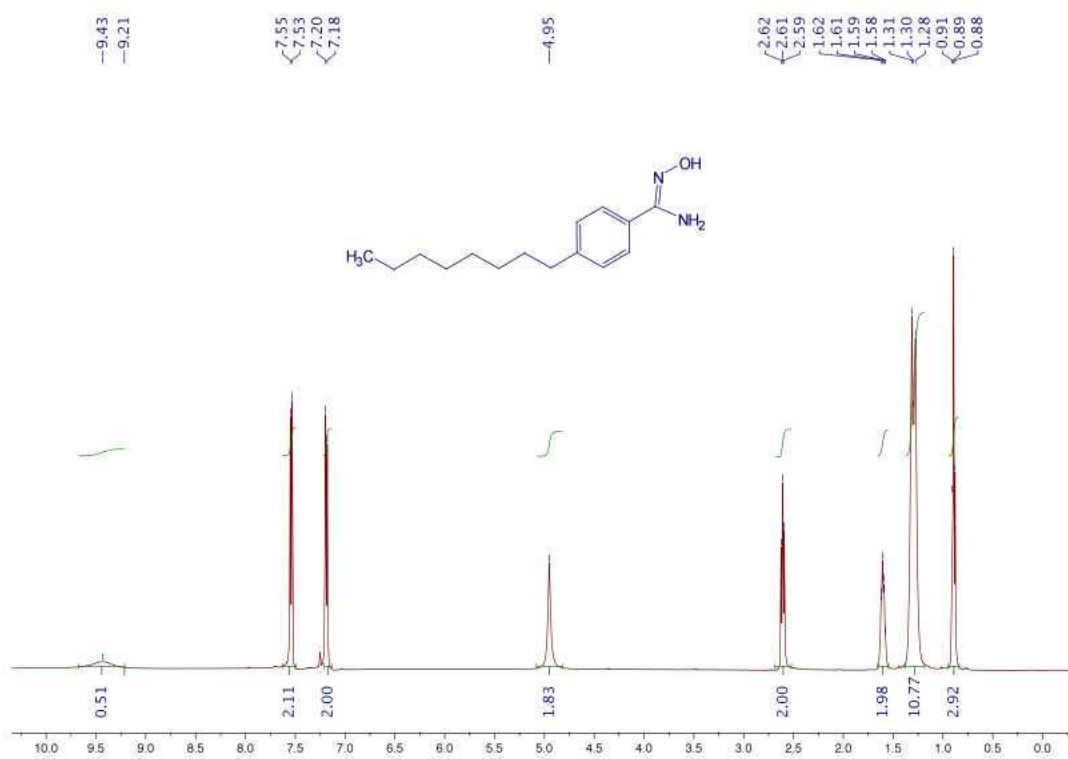
$^1\text{H-NMR}$  Spectrum for 4-octylbenzonitrile **2.2** -



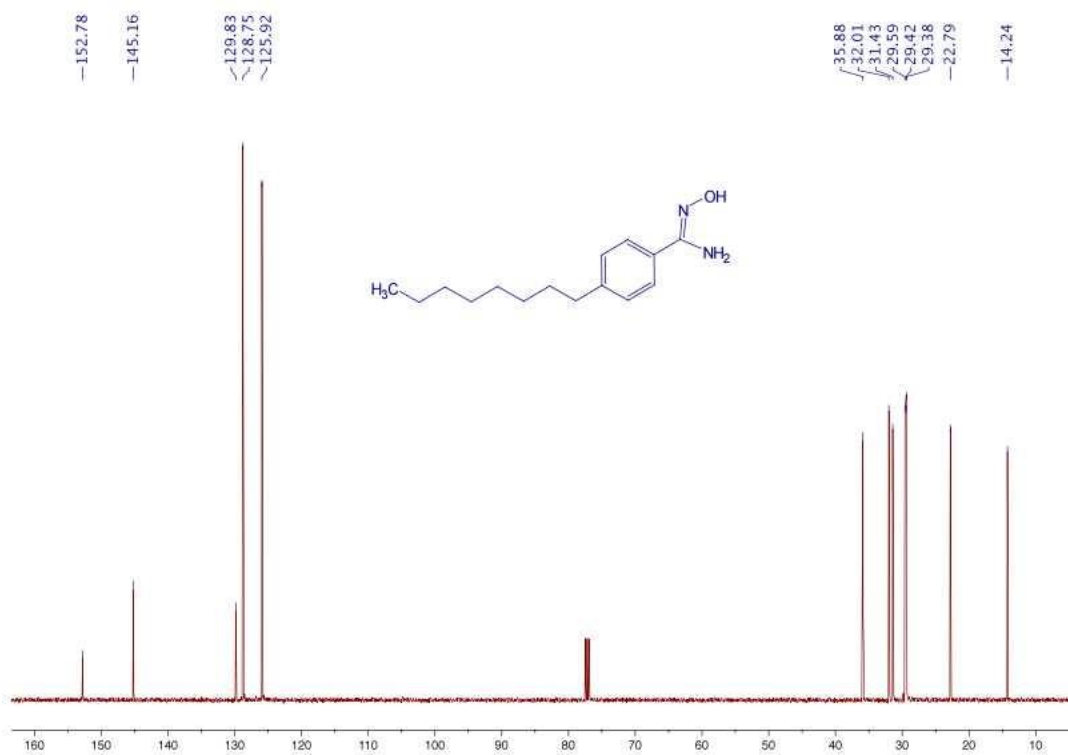
$^{13}\text{C-NMR}$  Spectrum for 4-octylbenzonitrile **2.2** -



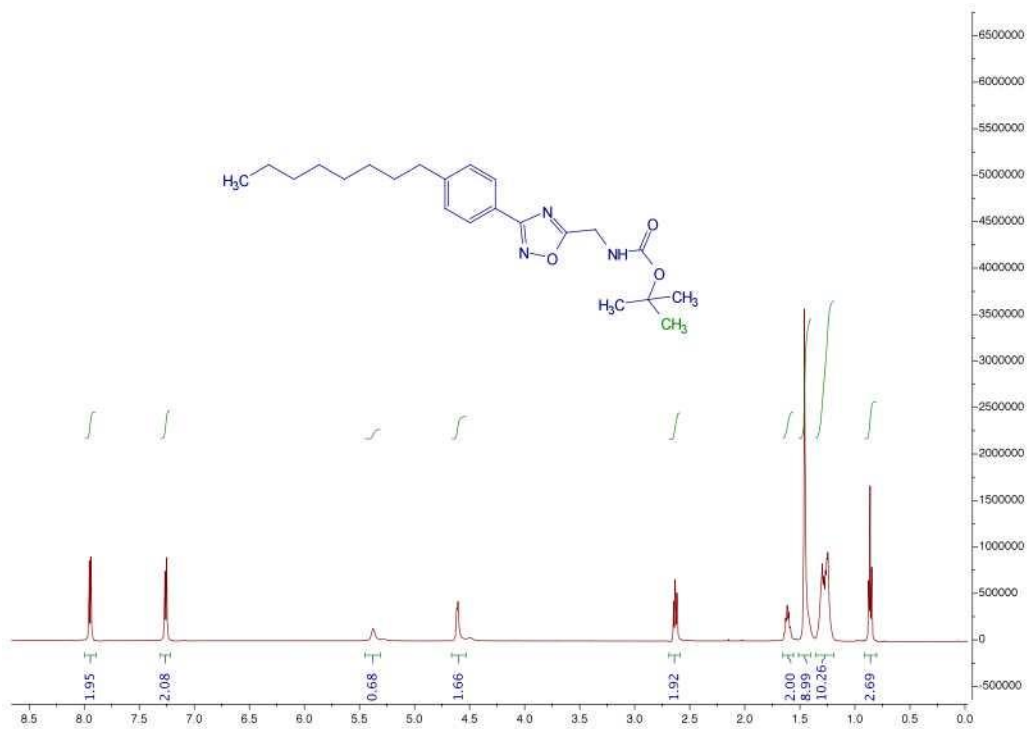
<sup>1</sup>H-NMR Spectrum for (Z)-N'-hydroxy-4-octylbenzimidamide **2.3** –



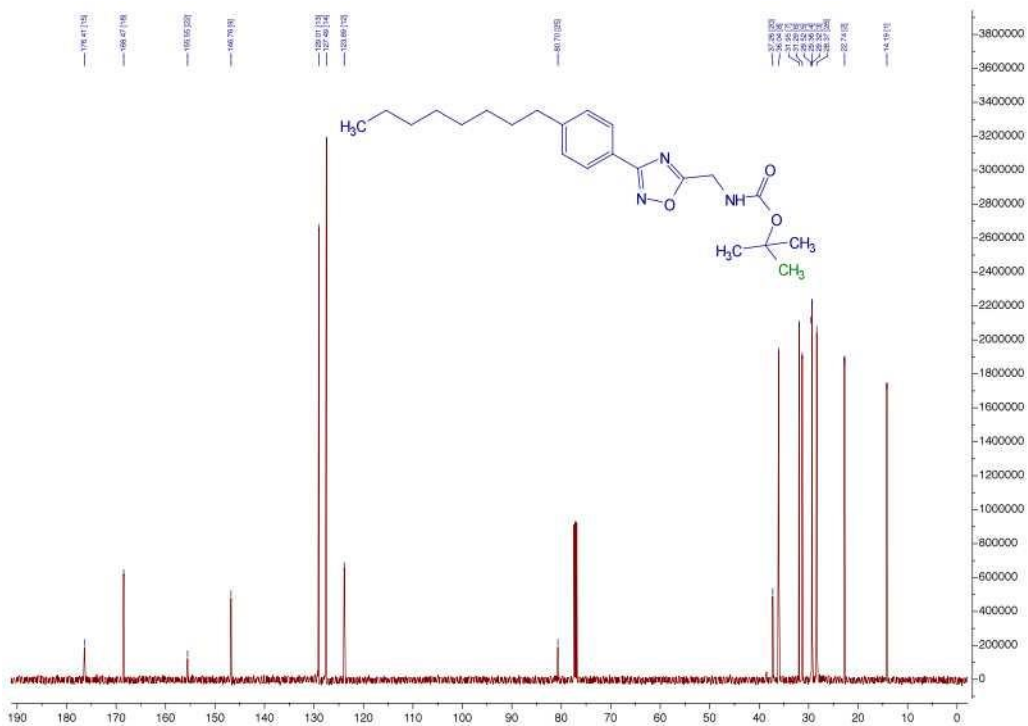
<sup>13</sup>C-NMR Spectrum for (Z)-N'-hydroxy-4-octylbenzimidamide **2.3**–



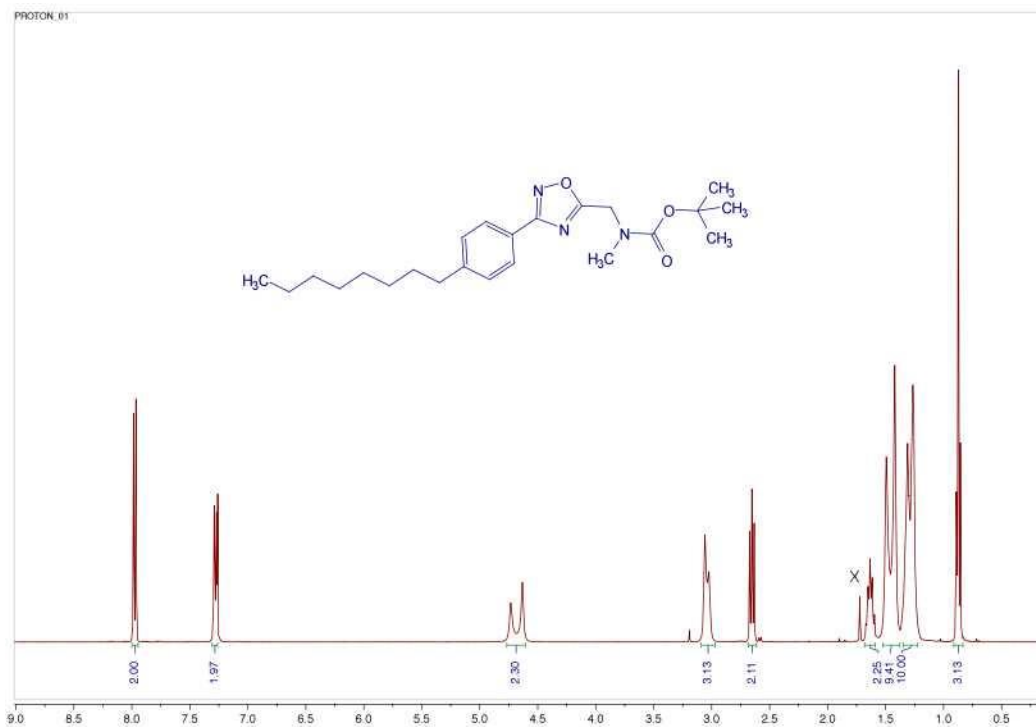
<sup>1</sup>H-NMR Spectrum for *tert*-butyl ((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)carbamate **2.4a**



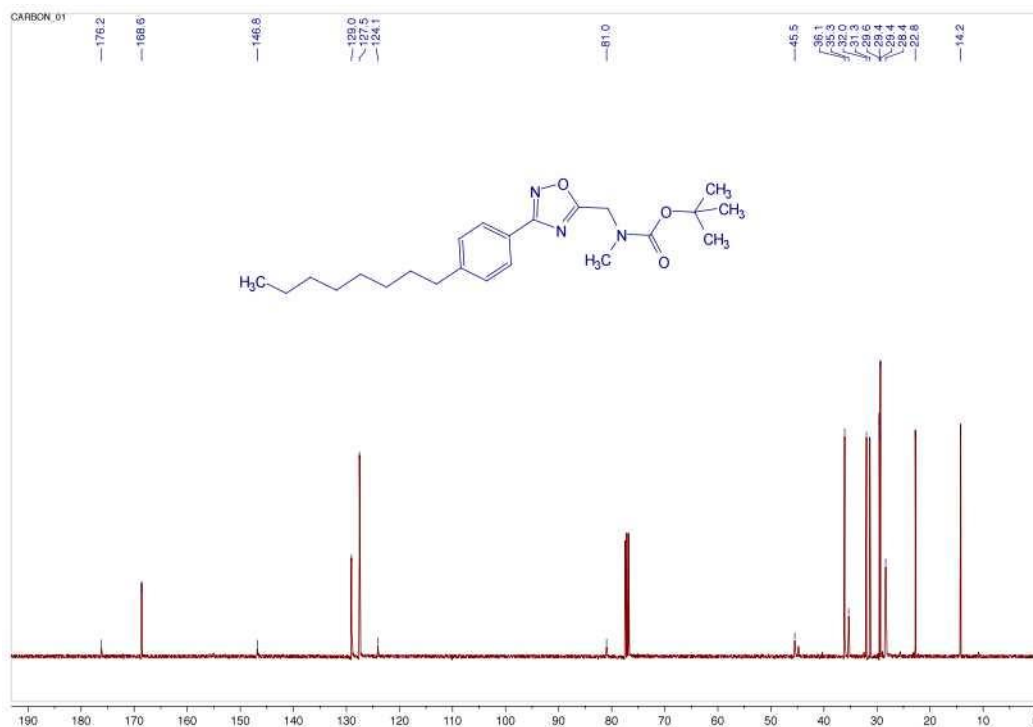
<sup>13</sup>C-NMR Spectrum for *tert*-butyl ((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)carbamate **2.4a**



$^1\text{H-NMR}$  Spectrum for *tert*-butyl methyl((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)carbamate **2.4b** –

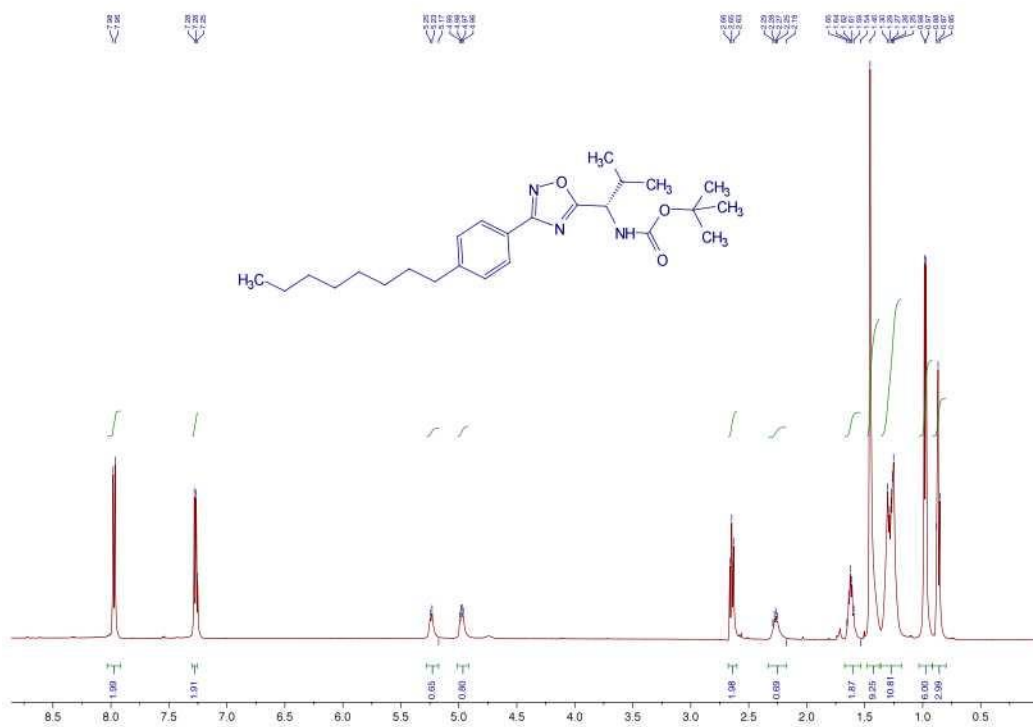


$^{13}\text{C-NMR}$  Spectrum for *tert*-butyl methyl((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)carbamate **2.4b**–

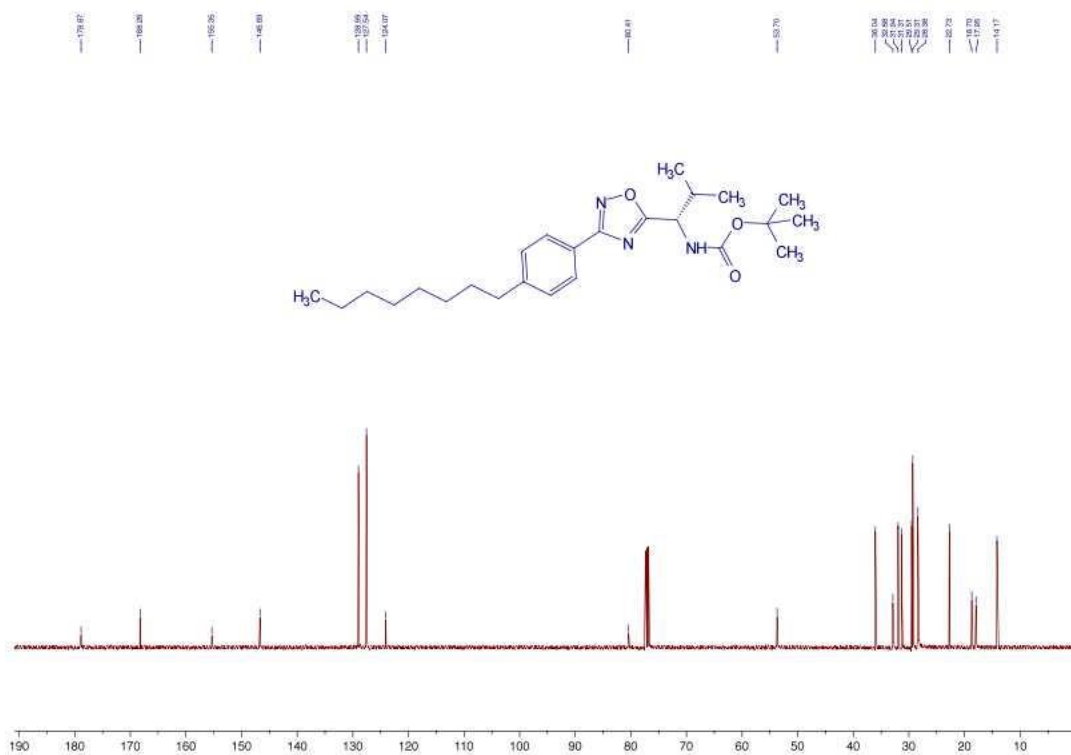




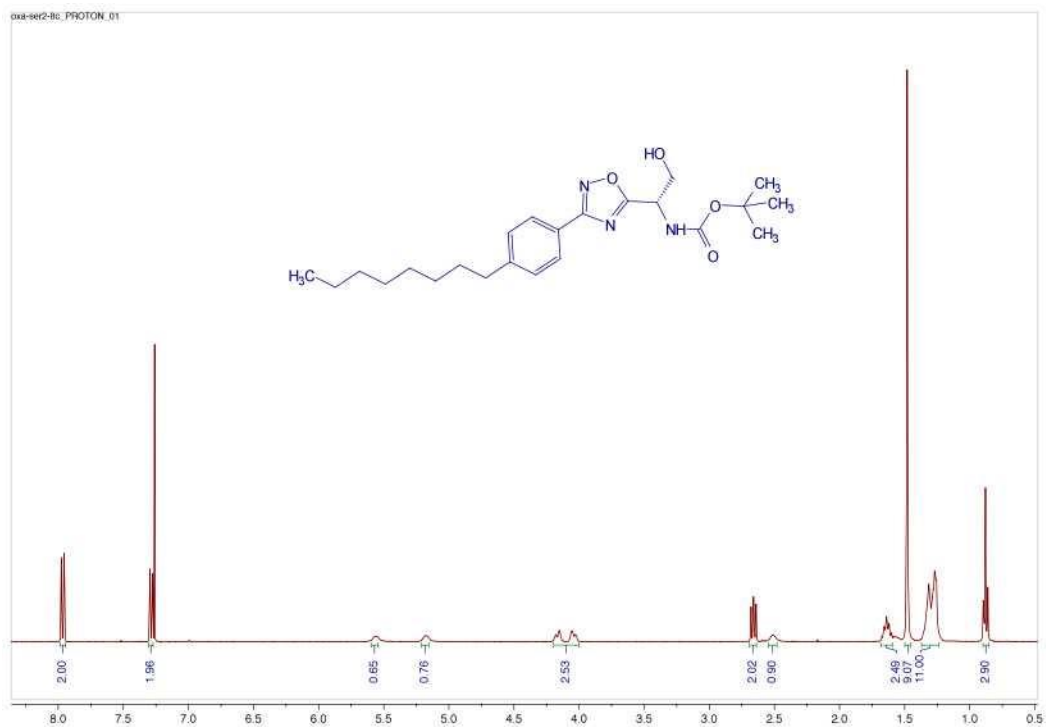
$^1\text{H-NMR}$  Spectrum for *tert*-butyl (*S*)-(2-methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)propyl)carbamate **2.4d** –



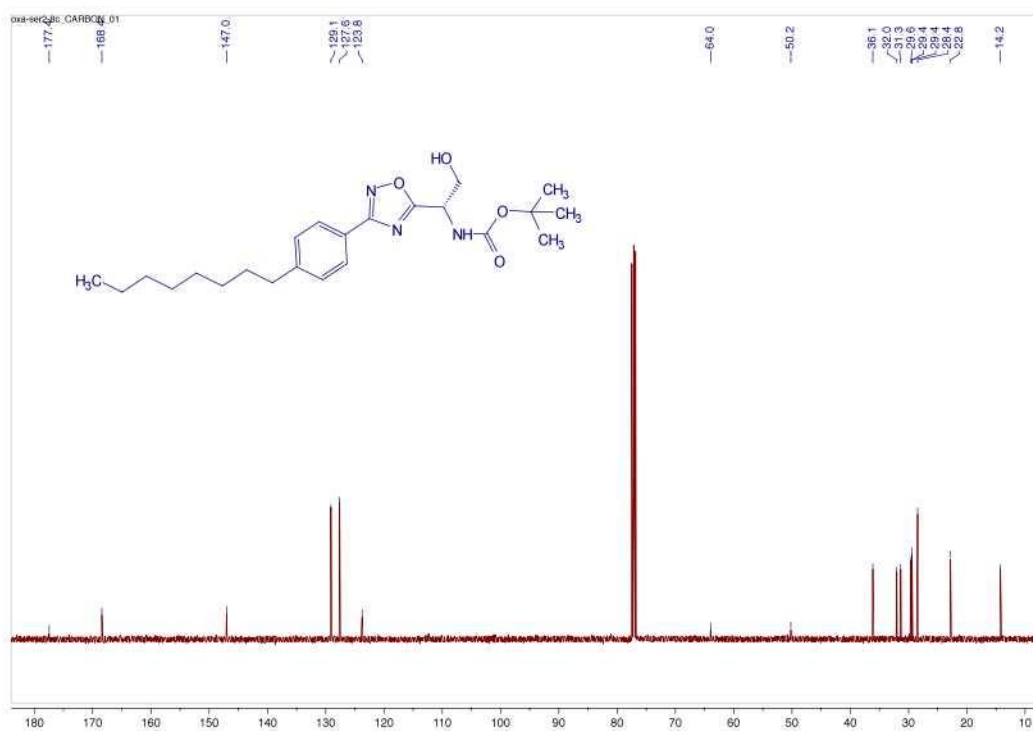
$^{13}\text{C-NMR}$  Spectrum for *tert*-butyl (*S*)-(2-methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)propyl)carbamate **2.4d** –



<sup>1</sup>H-NMR Spectrum for *tert*-butyl (*S*)-(2-hydroxy-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate **2.4e** –

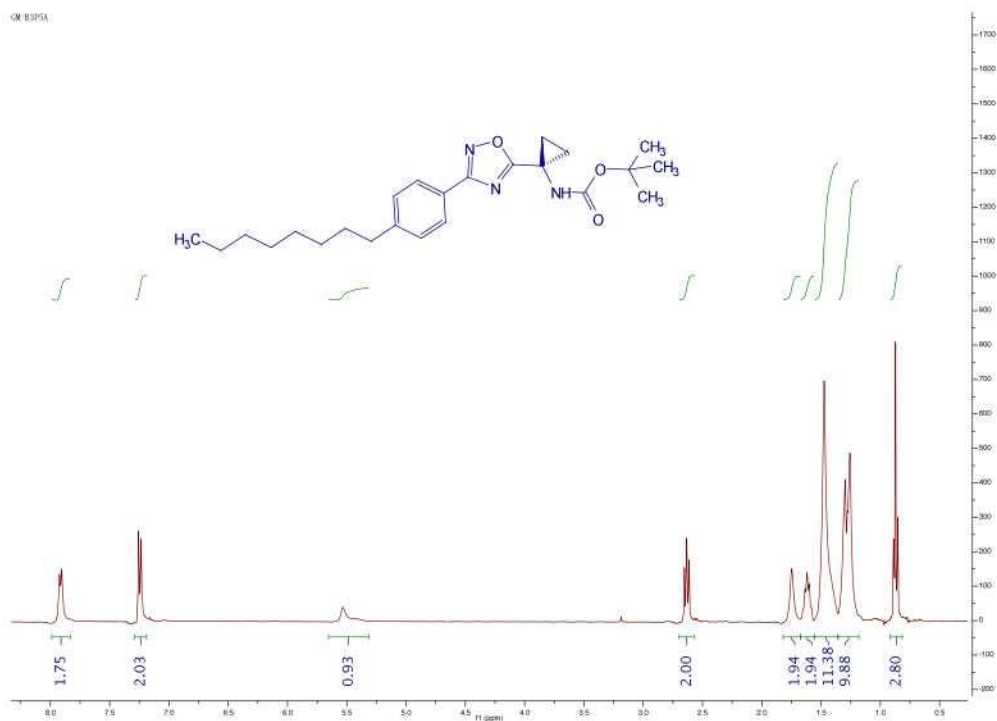


<sup>13</sup>C-NMR Spectrum for *tert*-butyl (*S*)-(2-hydroxy-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate **2.4e** –

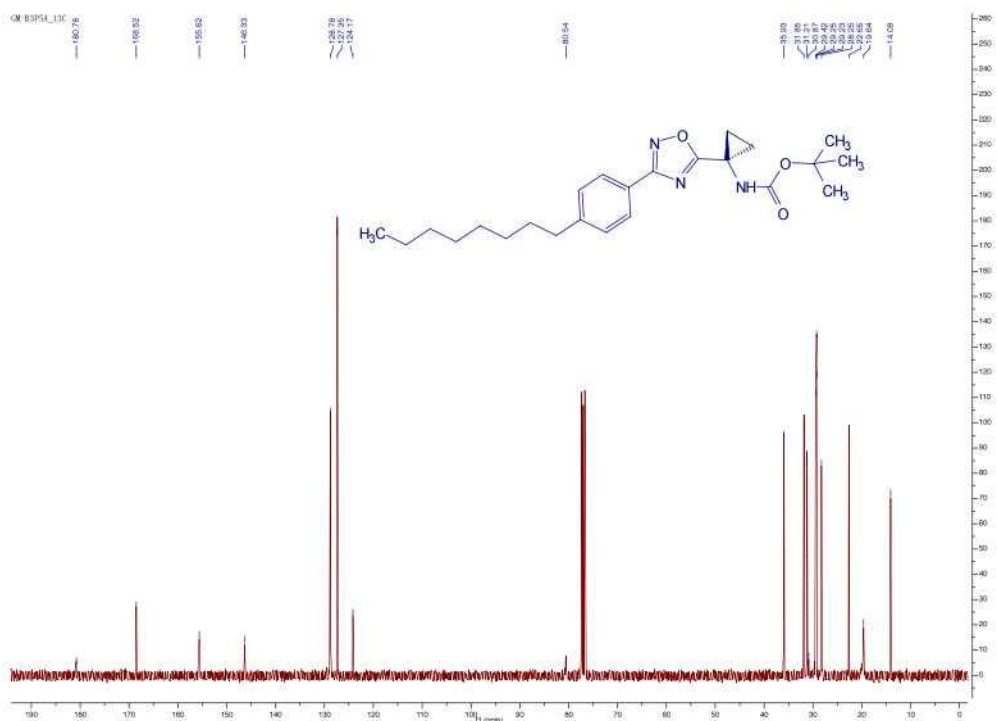




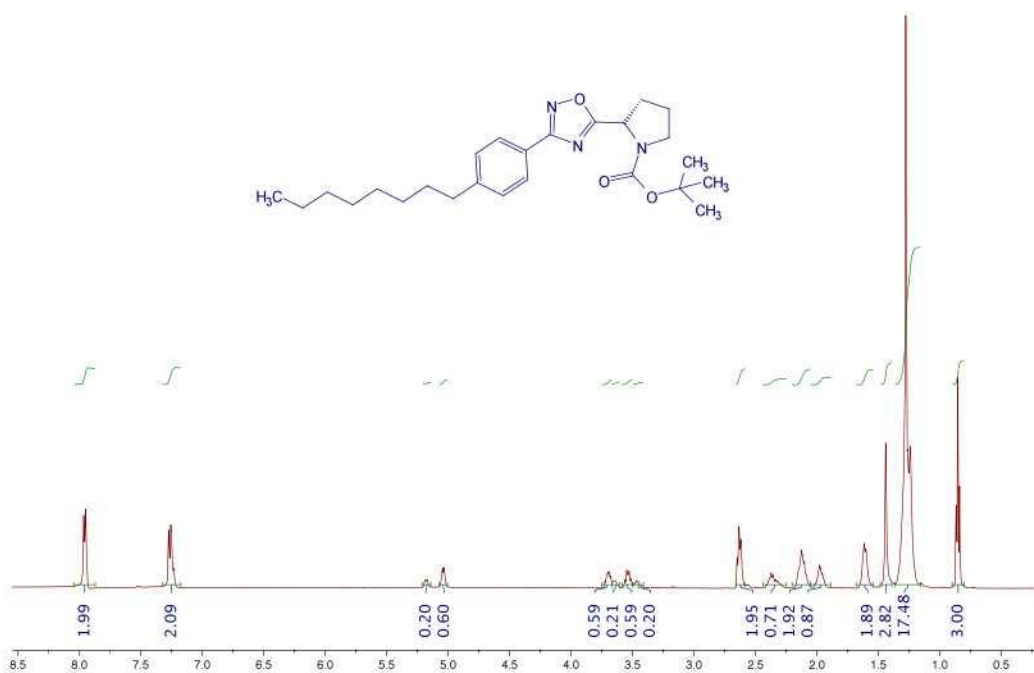
<sup>1</sup>H-NMR Spectrum for *tert*-butyl (1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropyl)carbamate **2.4f** –



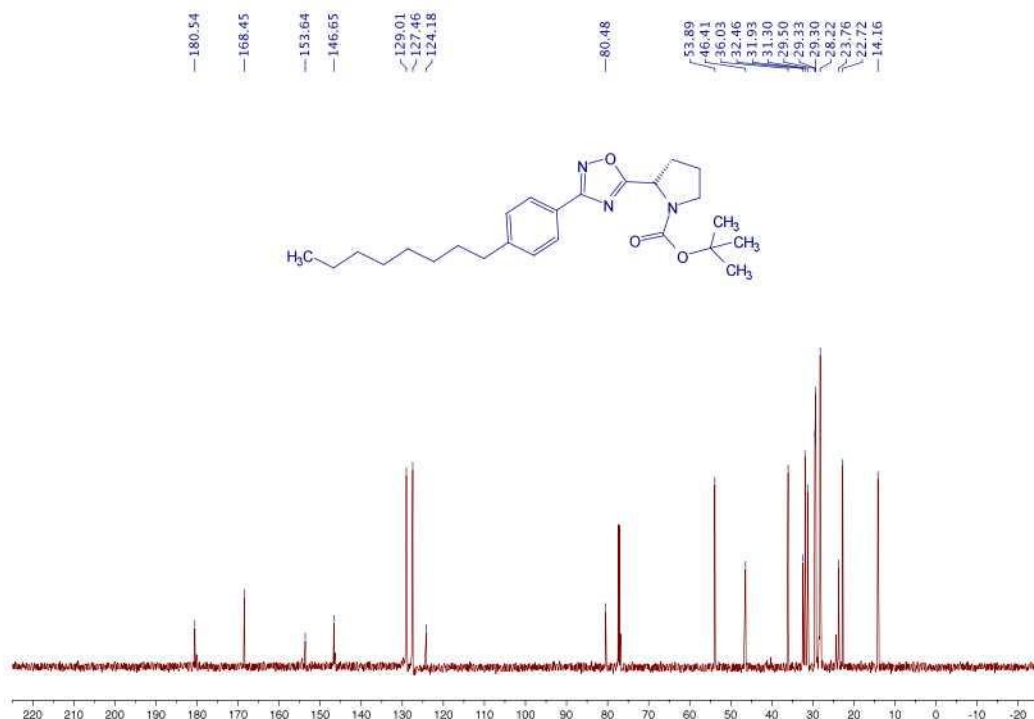
<sup>13</sup>C-NMR Spectrum for *tert*-butyl (1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropyl)carbamate **2.4f** –



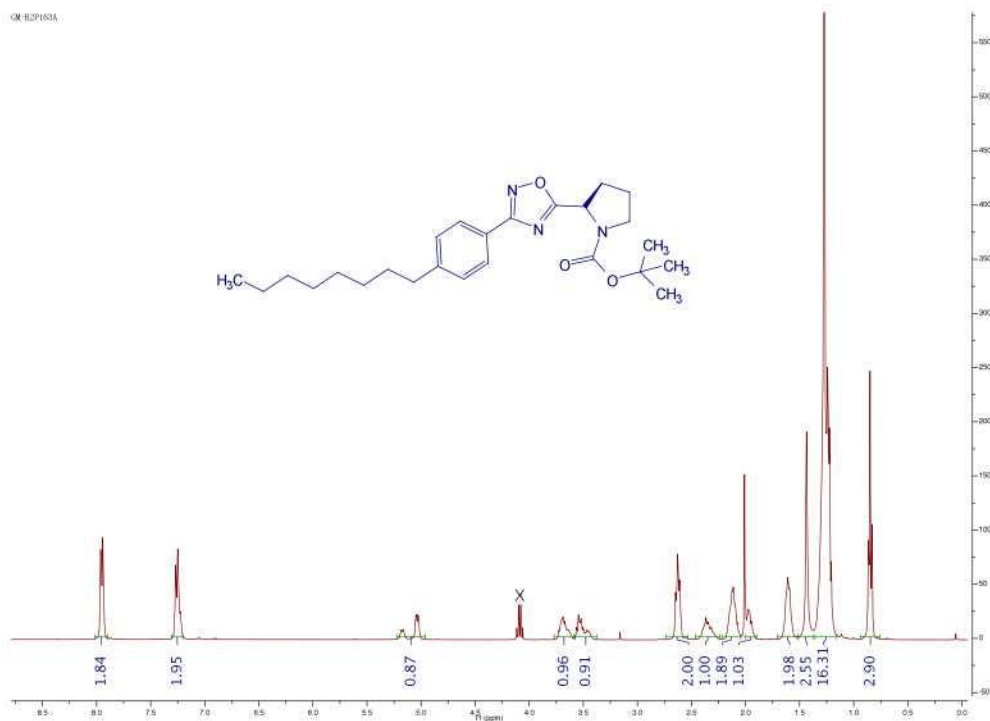
<sup>1</sup>H-NMR Spectrum for *tert*-butyl (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.4g** –



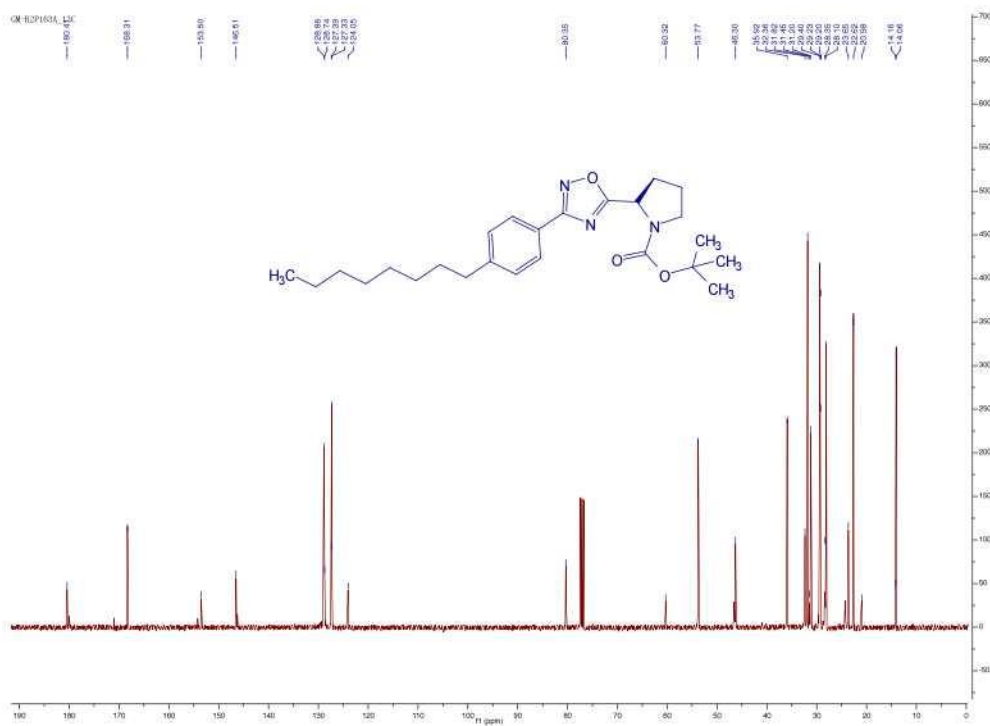
<sup>13</sup>C-NMR Spectrum for *tert*-butyl (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.4g** –



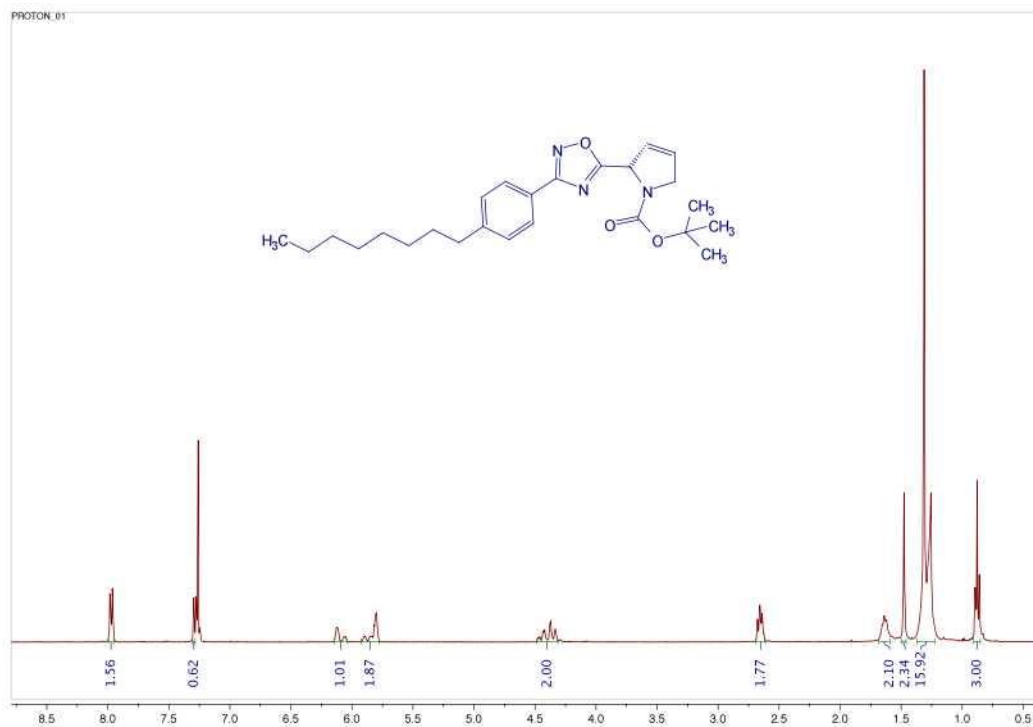
$^1\text{H-NMR}$  Spectrum for *tert*-butyl (*R*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.4h** –



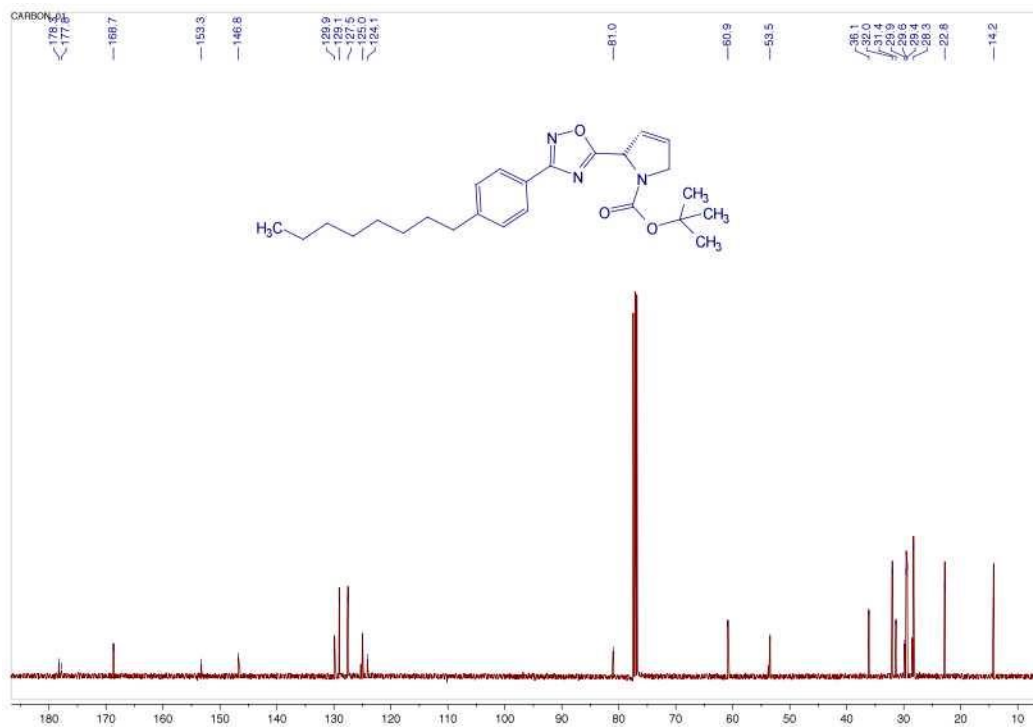
$^{13}\text{C-NMR}$  Spectrum for *tert*-butyl (*R*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.4h** –



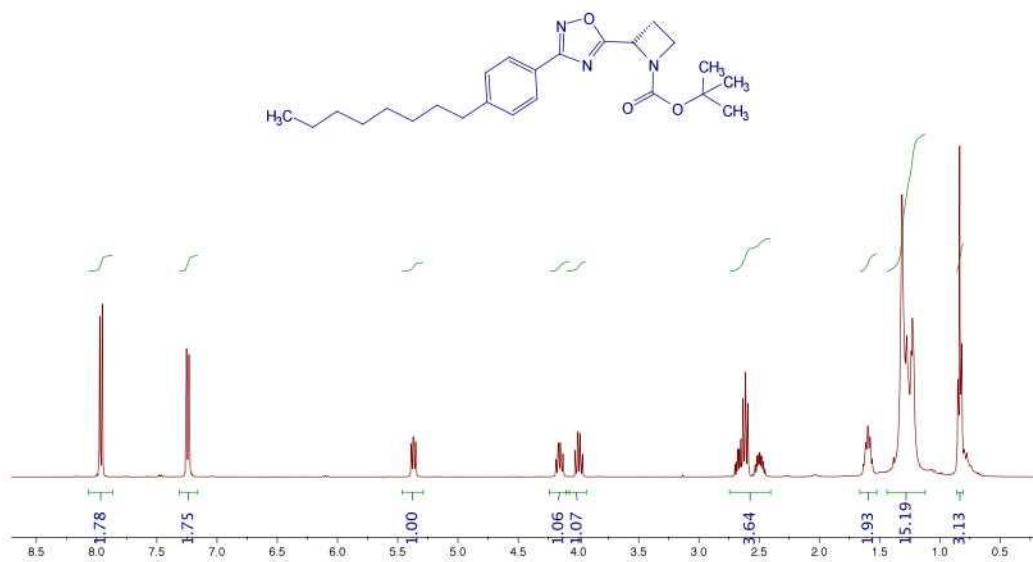
$^1\text{H-NMR}$  Spectrum for *tert*-butyl (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate **2.4i** –



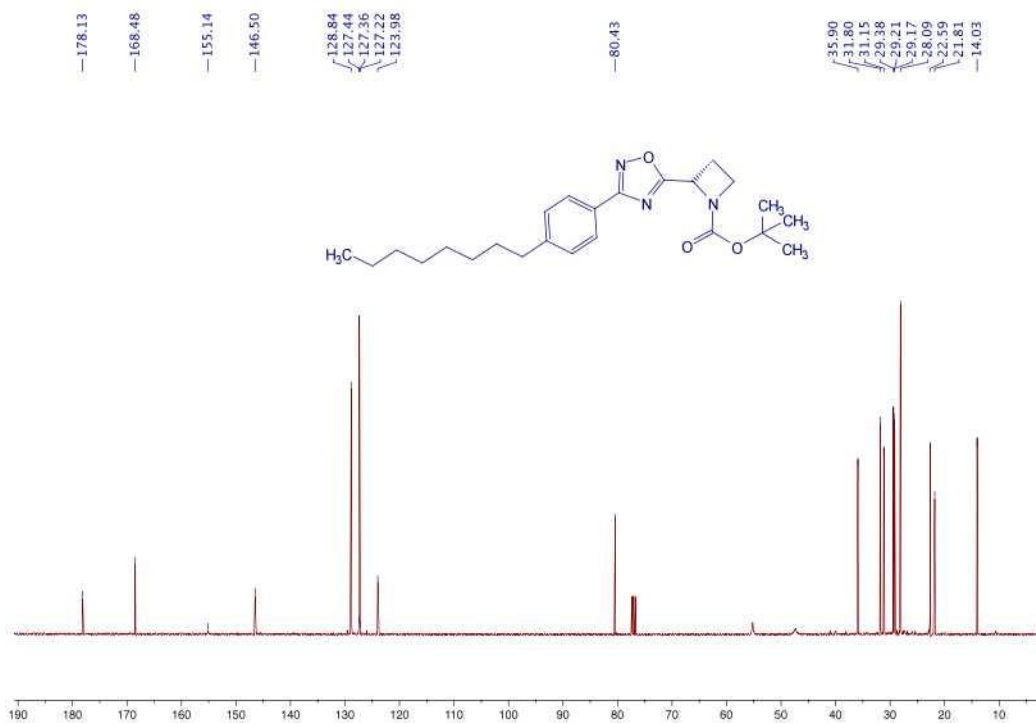
$^{13}\text{C-NMR}$  Spectrum *tert*-butyl (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate **2.4i** –



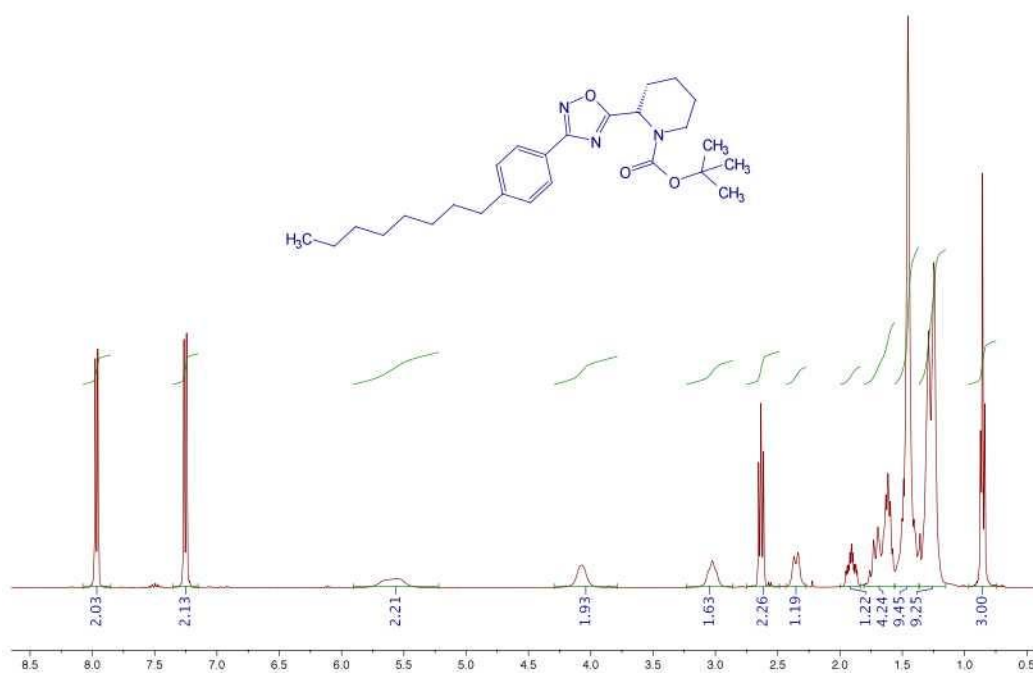
$^1\text{H-NMR}$  Spectrum for *tert*-butyl (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate **2.4j** –



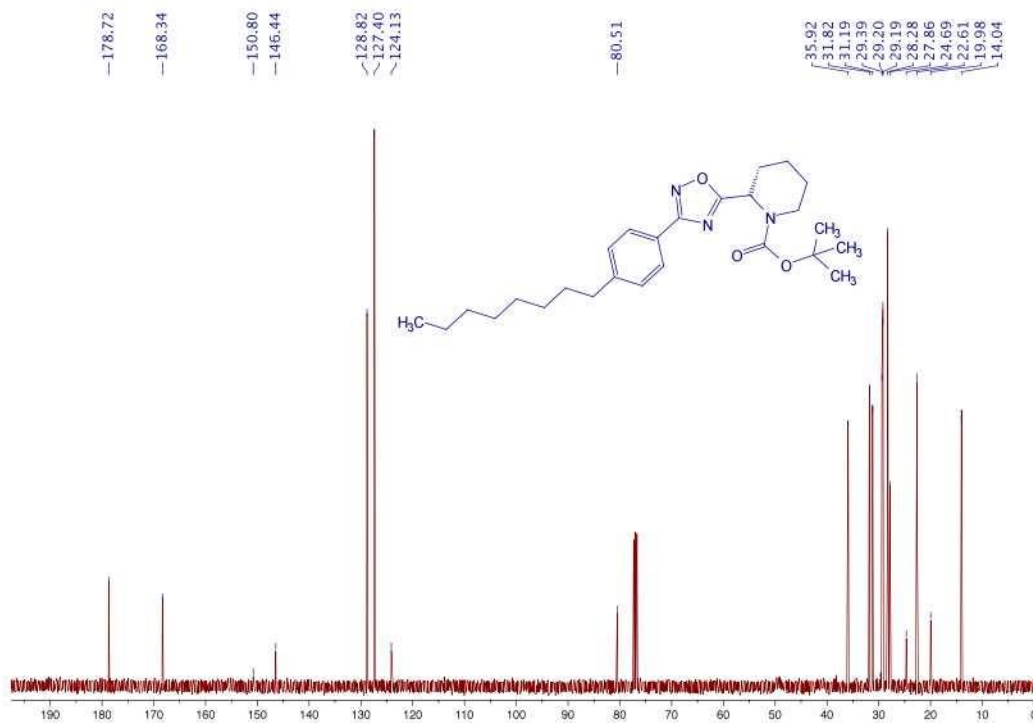
$^{13}\text{C-NMR}$  Spectrum for *tert*-butyl (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate **2.4j** –



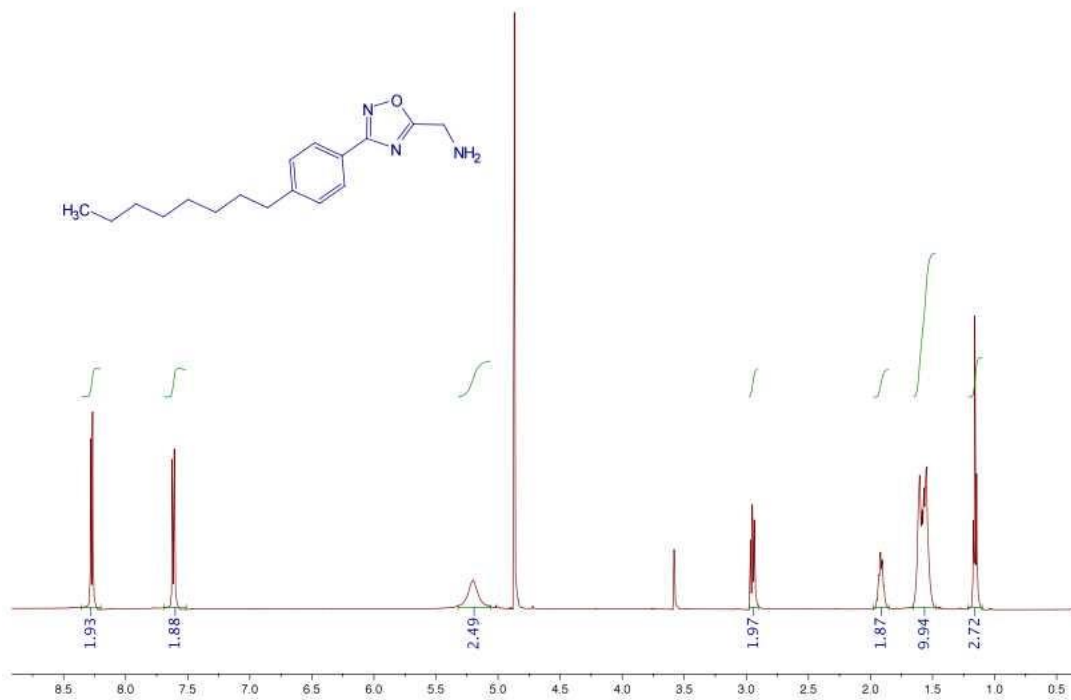
$^1\text{H-NMR}$  Spectrum for *tert*-butyl (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate **2.4k** –



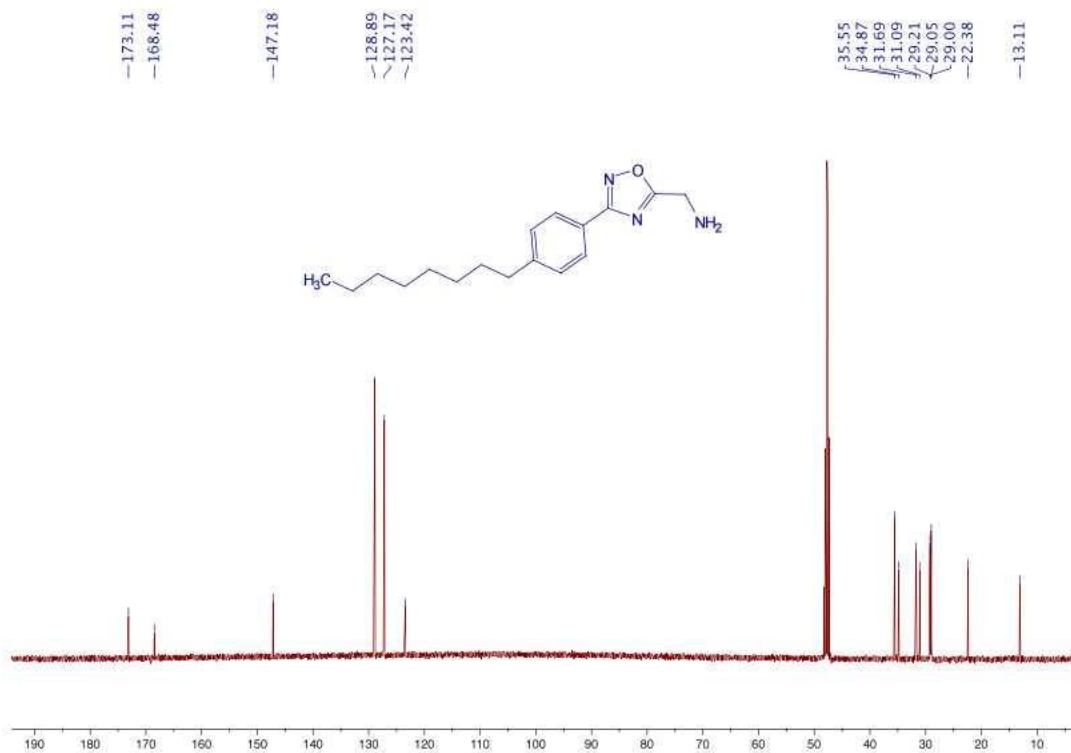
$^{13}\text{C-NMR}$  Spectrum for *tert*-butyl (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate **2.4k** –



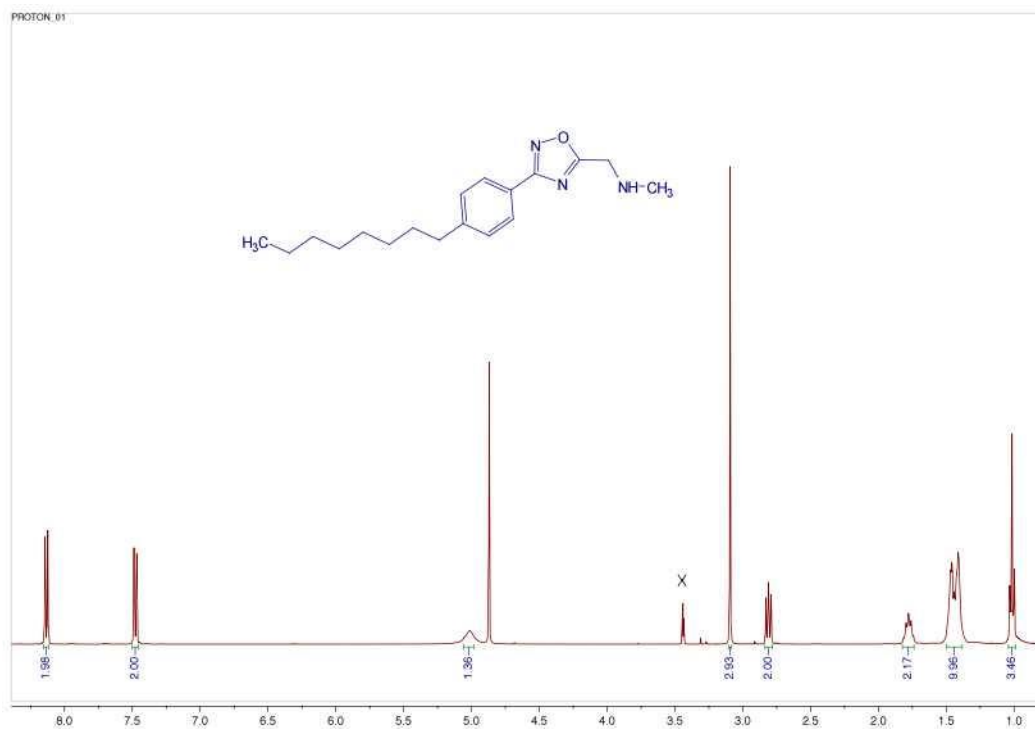
<sup>1</sup>H-NMR Spectrum for (3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methanamine **2.5a** –



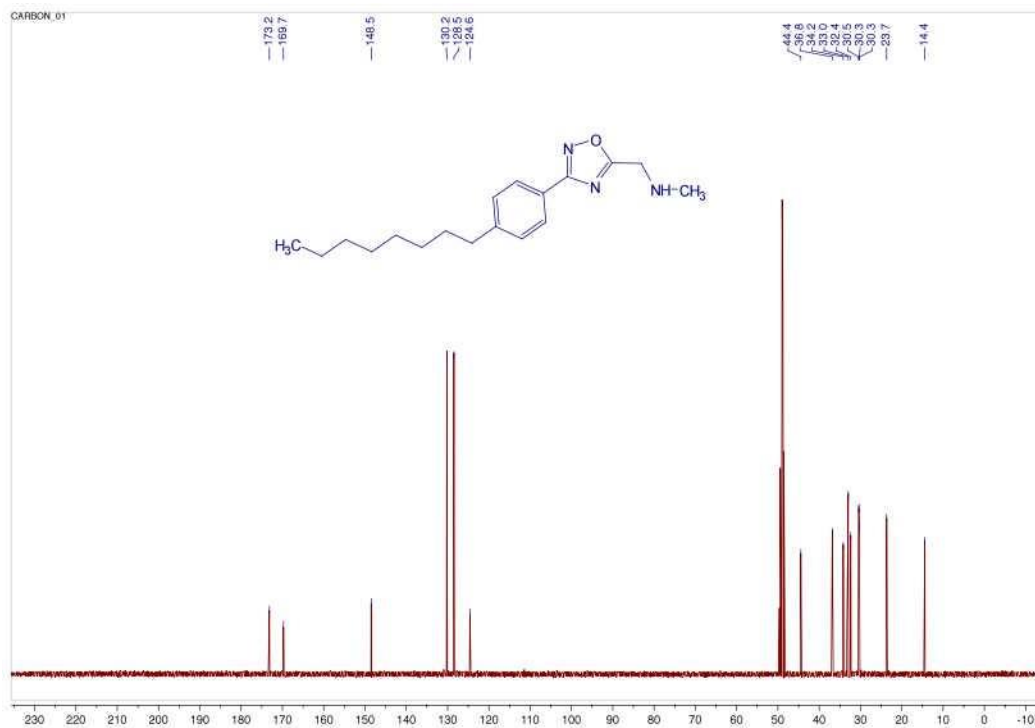
<sup>13</sup>C-NMR Spectrum of (3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methanamine **2.5a** –



<sup>1</sup>H-NMR Spectrum for *N*-methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methanamine **2.5b** –

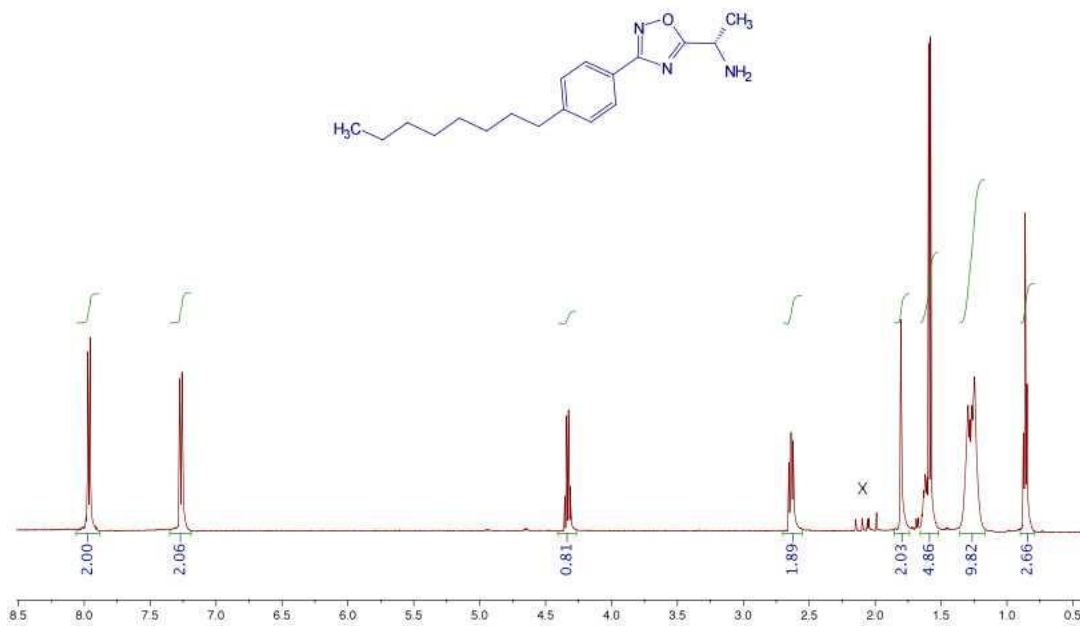


<sup>13</sup>C-NMR Spectrum for *N*-methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methanamine **2.5b** –

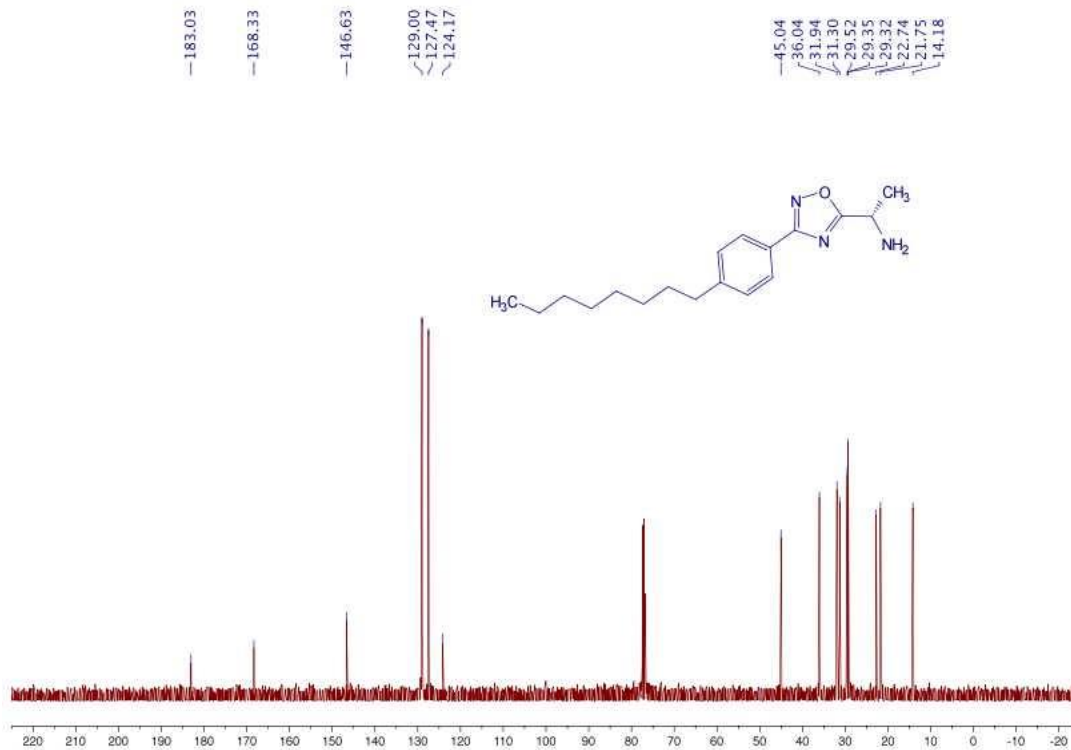




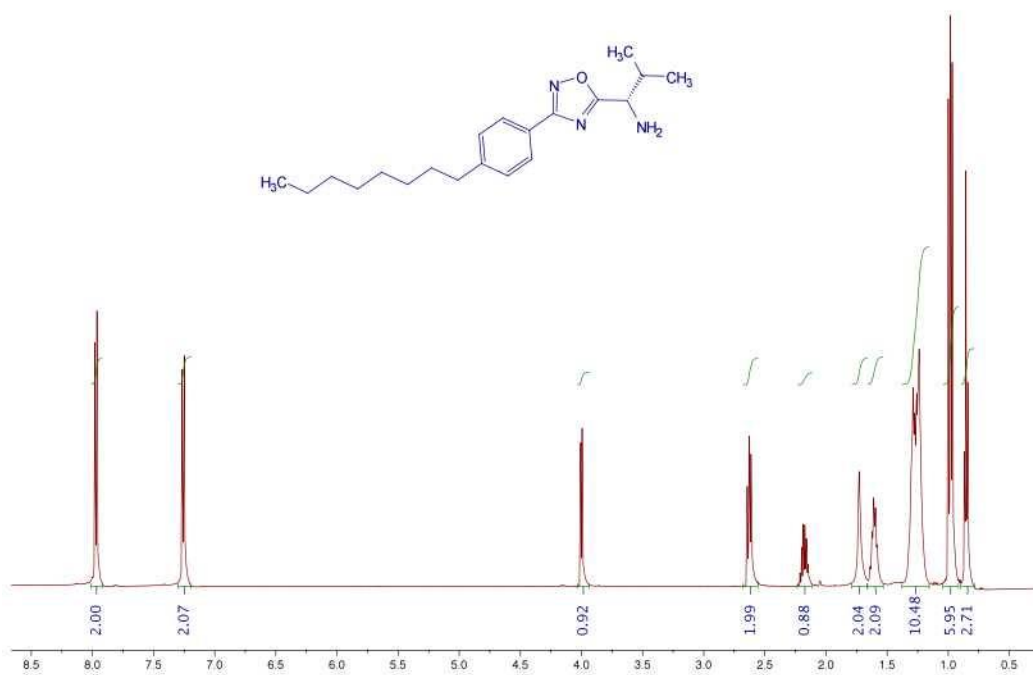
<sup>1</sup>H-NMR Spectrum for (S)-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethan-1-amine **2.5c** –



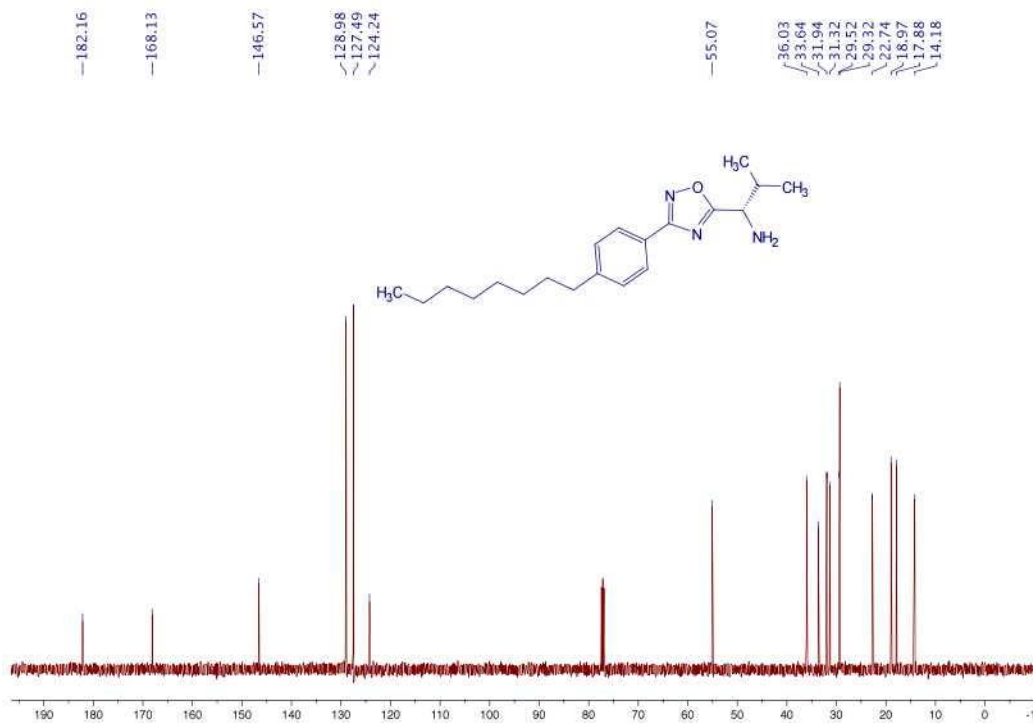
<sup>13</sup>C-NMR Spectrum for (S)-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethan-1-amine **2.5c** –



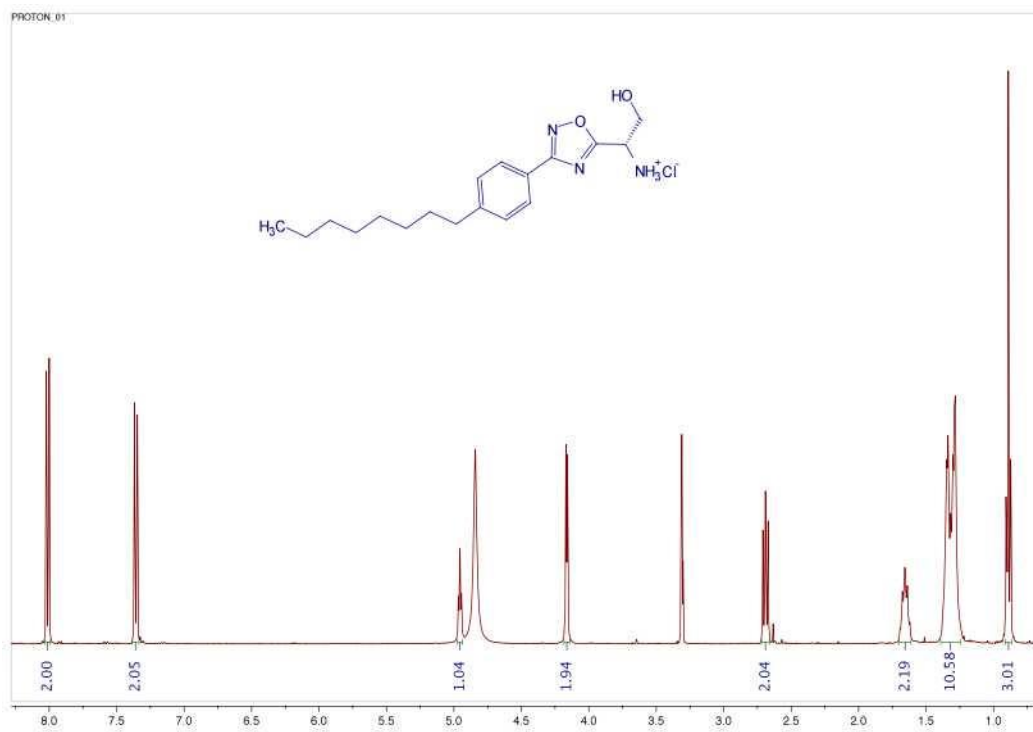
<sup>1</sup>H-NMR Spectrum for (*S*)-2-methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine  
**2.5d** –



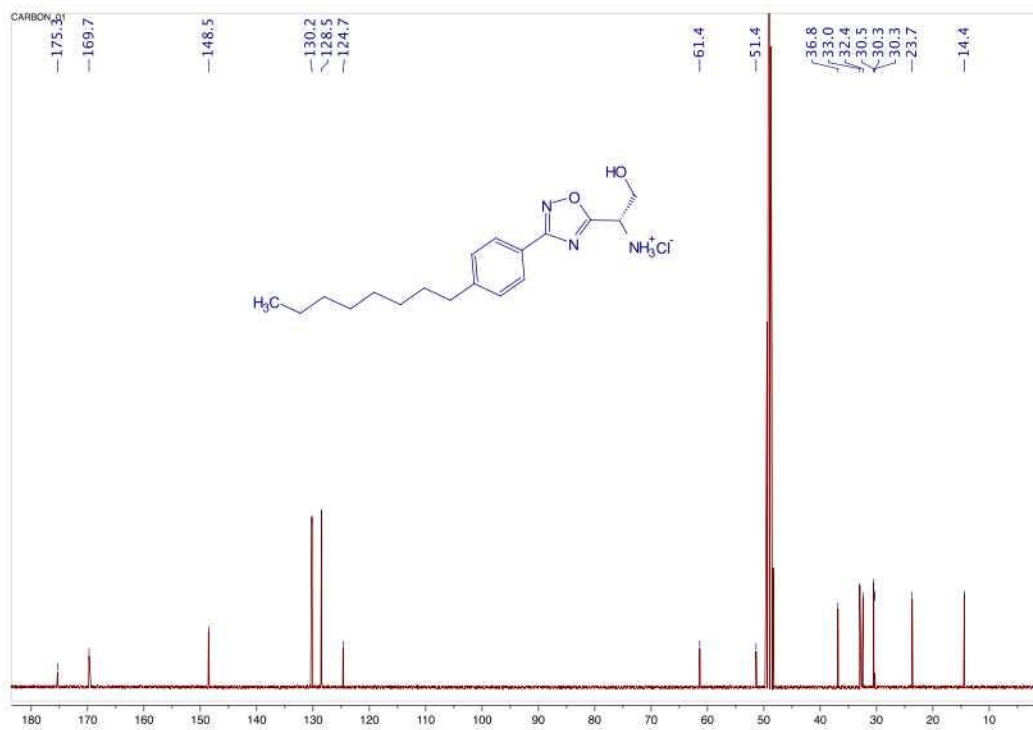
<sup>13</sup>C-NMR Spectrum for (*S*)-2-methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)propan-1-amine  
**2.5d** –



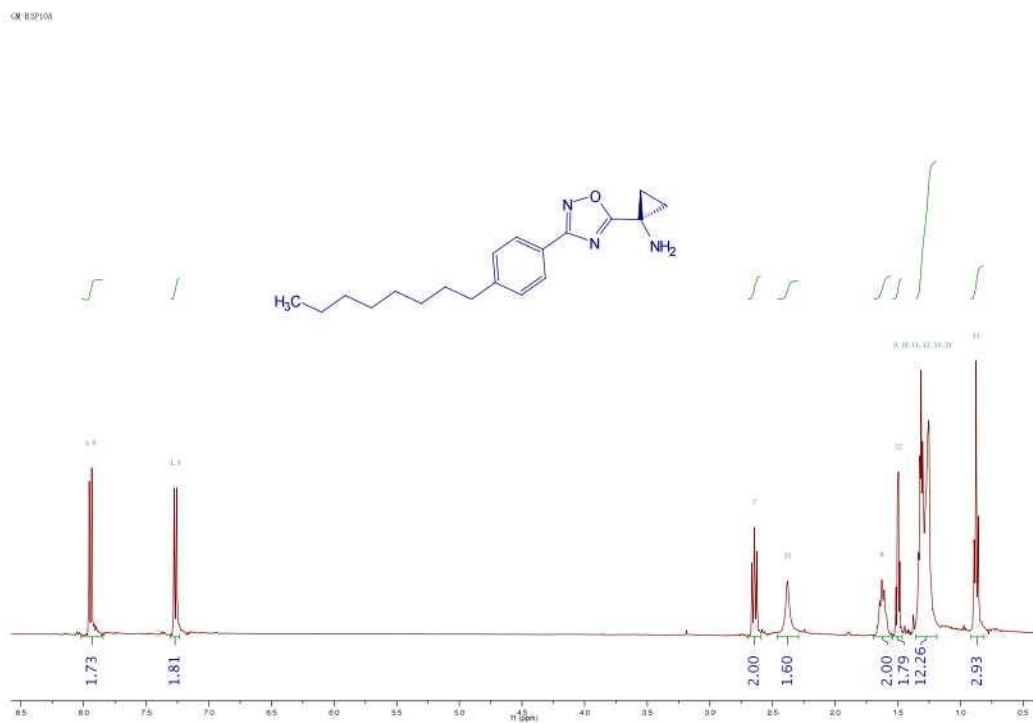
<sup>1</sup>H-NMR Spectrum for (S)-2-amino-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethan-1-ol **2.5e** –



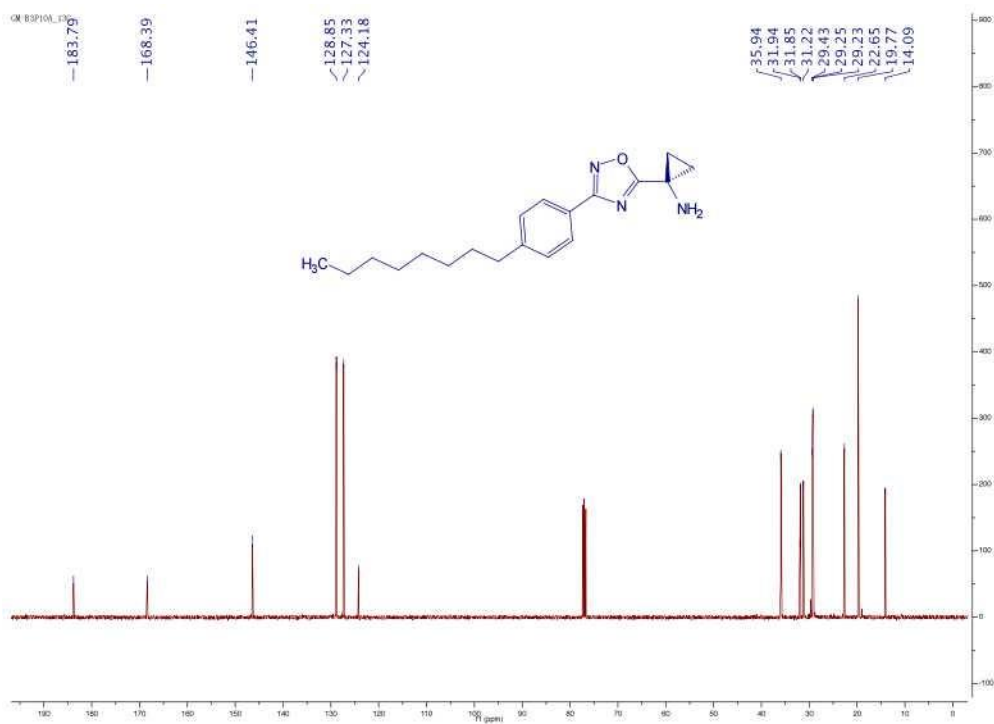
<sup>13</sup>C-NMR Spectrum for (S)-2-amino-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethan-1-ol **2.5e** –



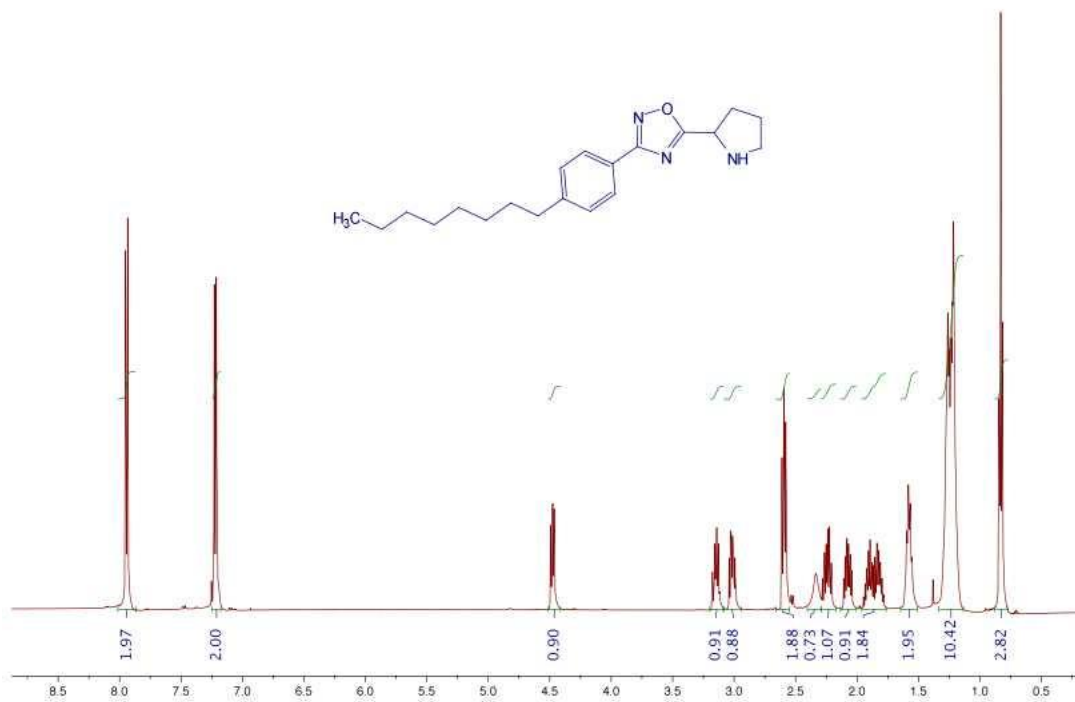
<sup>1</sup>H-NMR Spectrum for 1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropan-1-amine **2.5f** –



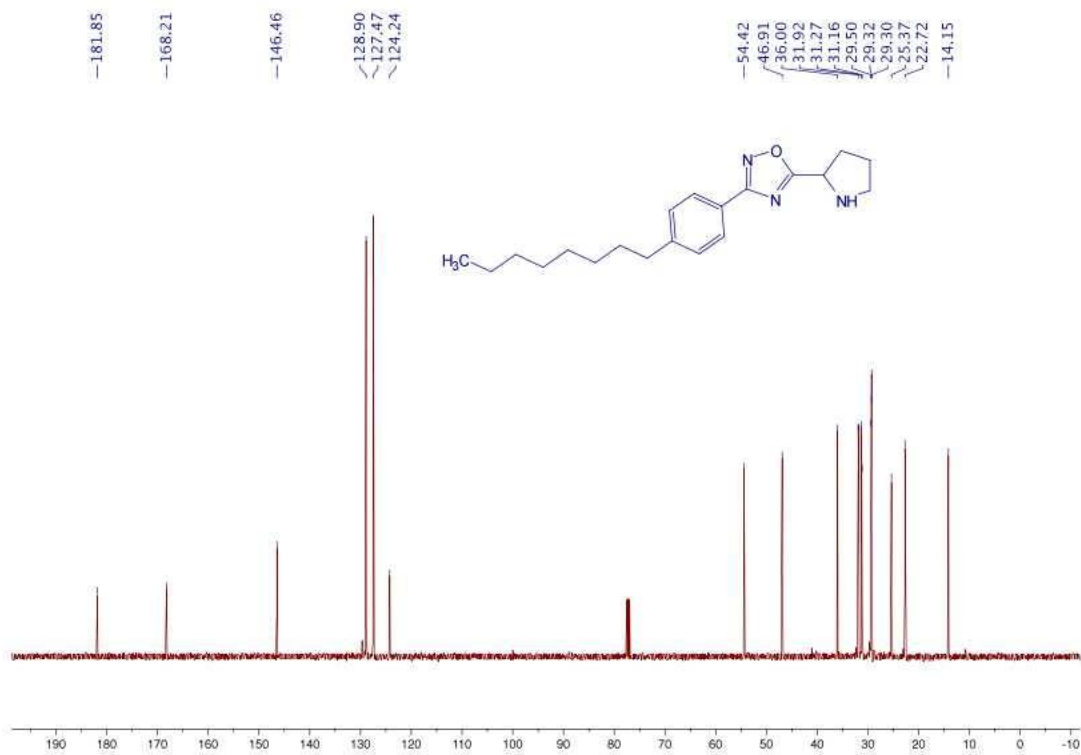
<sup>13</sup>C-NMR Spectrum for 1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropan-1-amine **2.5f** –



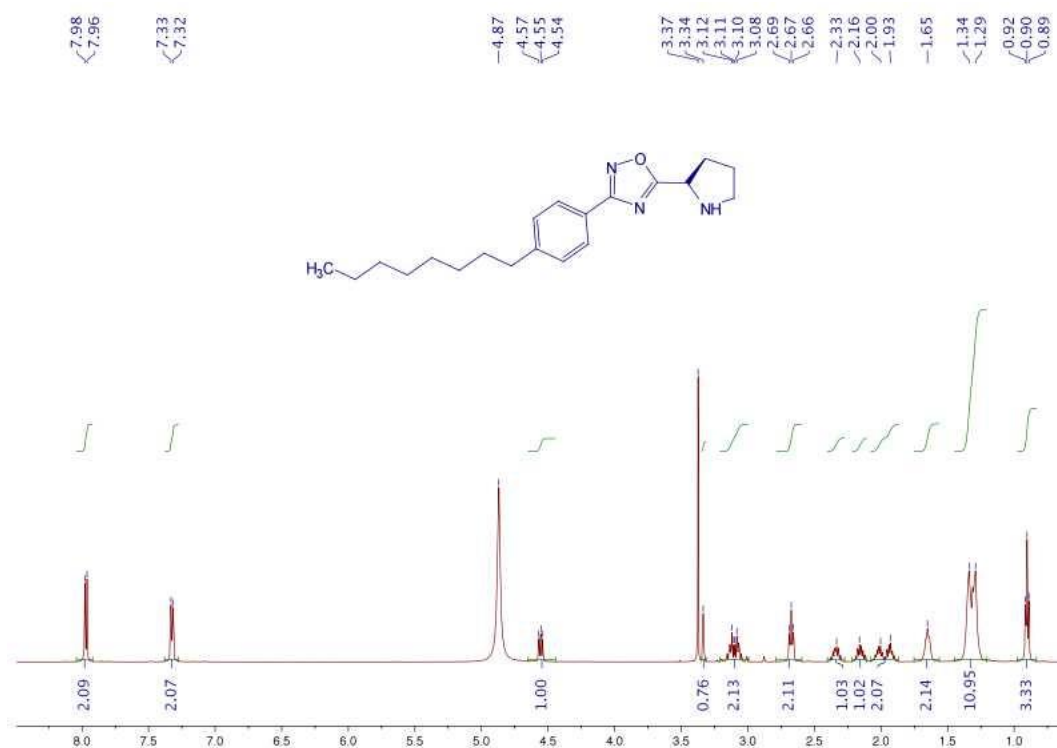
$^1\text{H-NMR}$  Spectrum for (*S*)-3-(4-octylphenyl)-5-(pyrrolidin-2-yl)-1,2,4-oxadiazole **2.5g** –



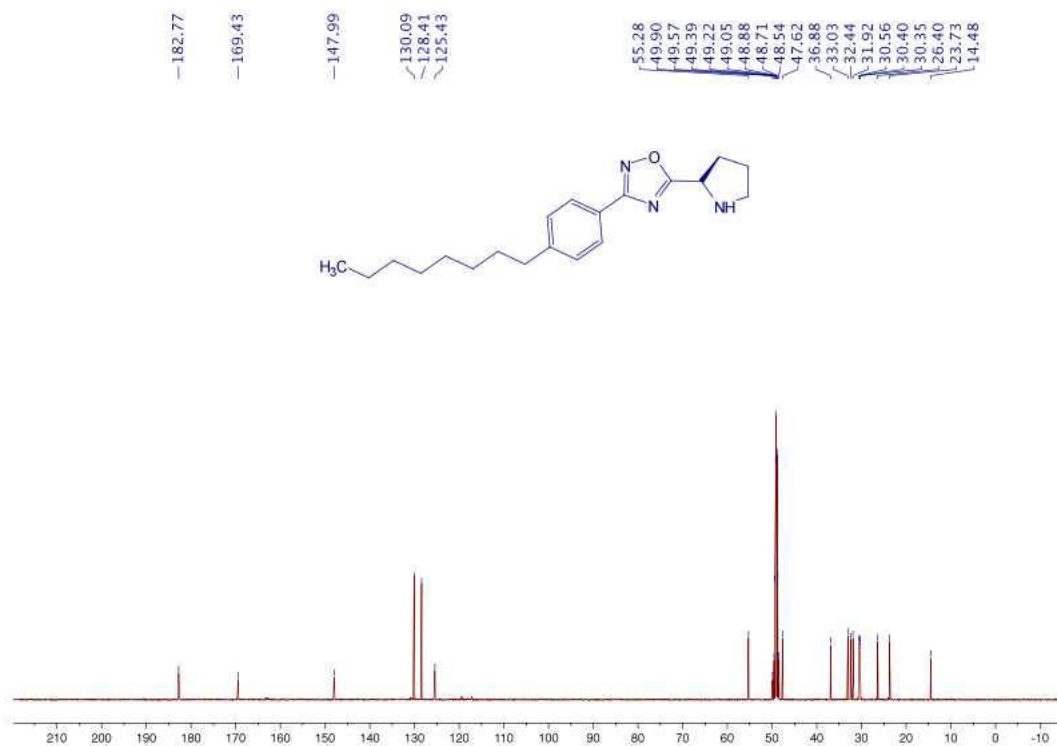
$^{13}\text{C-NMR}$  Spectrum for (*S*)-3-(4-octylphenyl)-5-(pyrrolidin-2-yl)-1,2,4-oxadiazole **2.5g** –



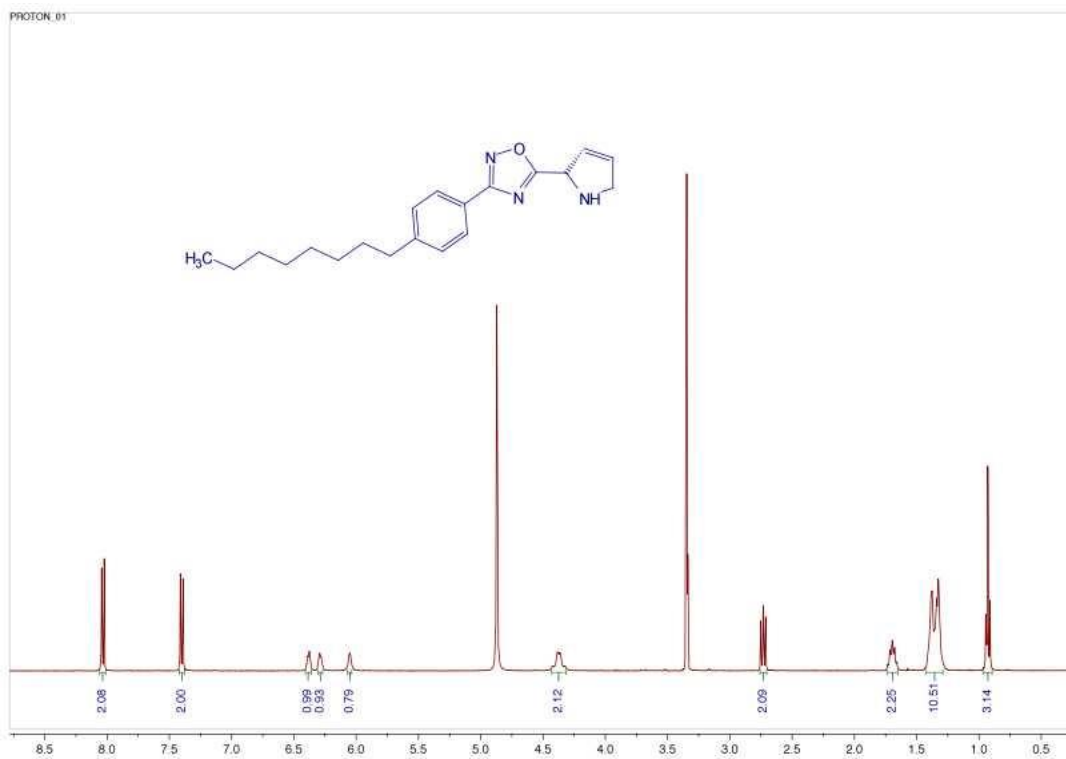
<sup>1</sup>H-NMR Spectrum for (*R*)-3-(4-octylphenyl)-5-(pyrrolidin-2-yl)-1,2,4-oxadiazole **2.5h** –



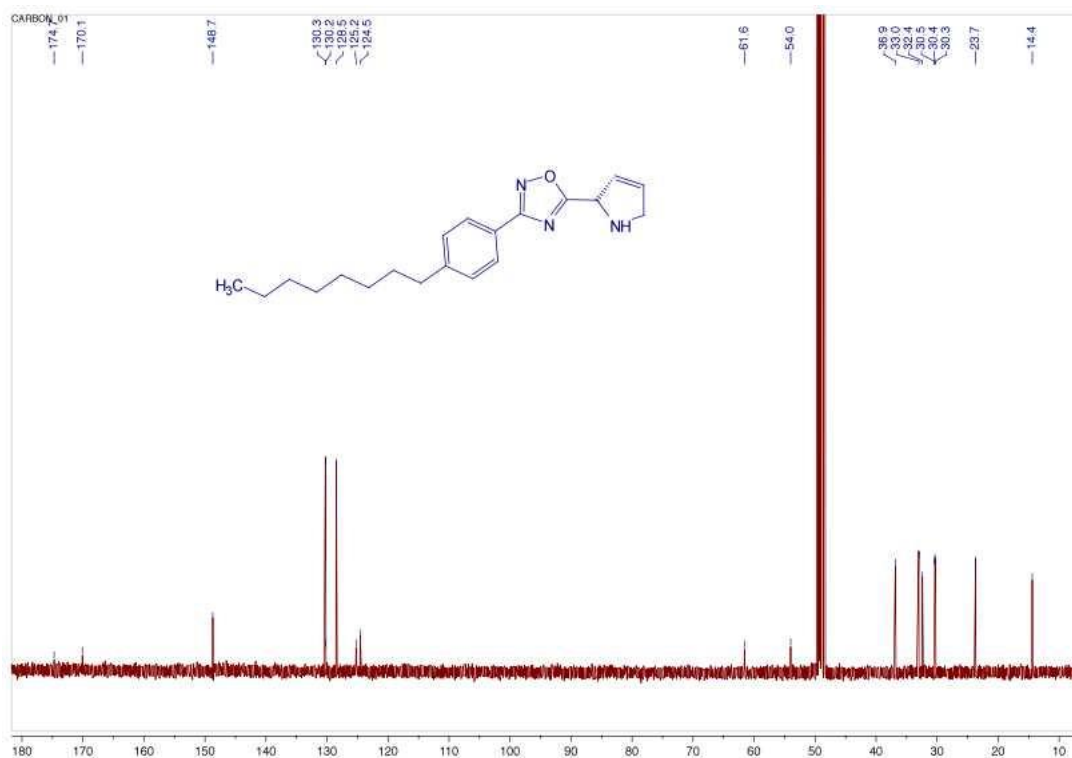
<sup>13</sup>C-NMR Spectrum for (*R*)-3-(4-octylphenyl)-5-(pyrrolidin-2-yl)-1,2,4-oxadiazole **2.5h** –



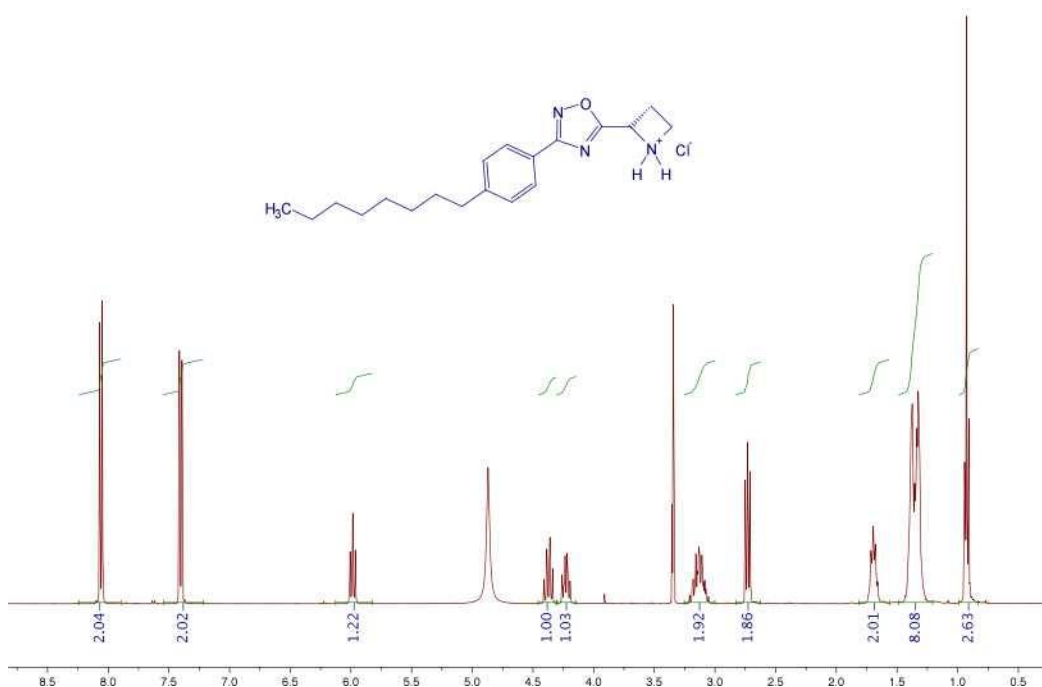
<sup>1</sup>H-NMR Spectrum for (S)-5-(2,5-dihydro-1H-pyrrol-2-yl)-3-(4-octylphenyl)-1,2,4-oxadiazole **2.5i** –



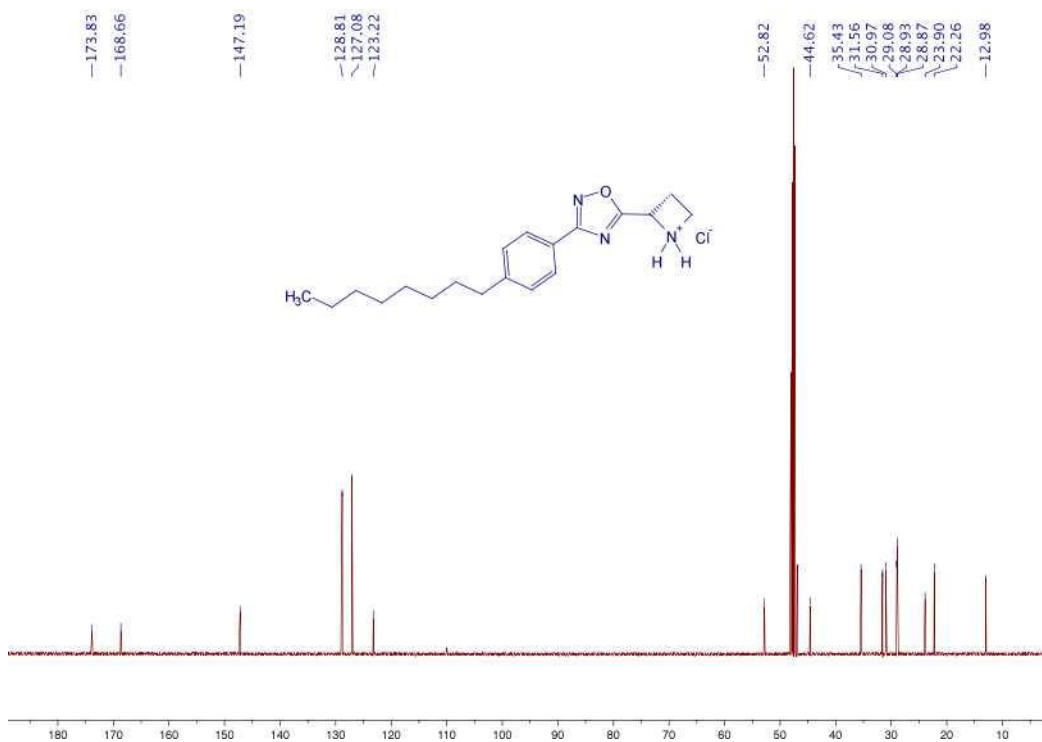
<sup>13</sup>C-NMR Spectrum for (S)-5-(2,5-dihydro-1H-pyrrol-2-yl)-3-(4-octylphenyl)-1,2,4-oxadiazole **2.5i** –



<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidinium chloride **2.5j**

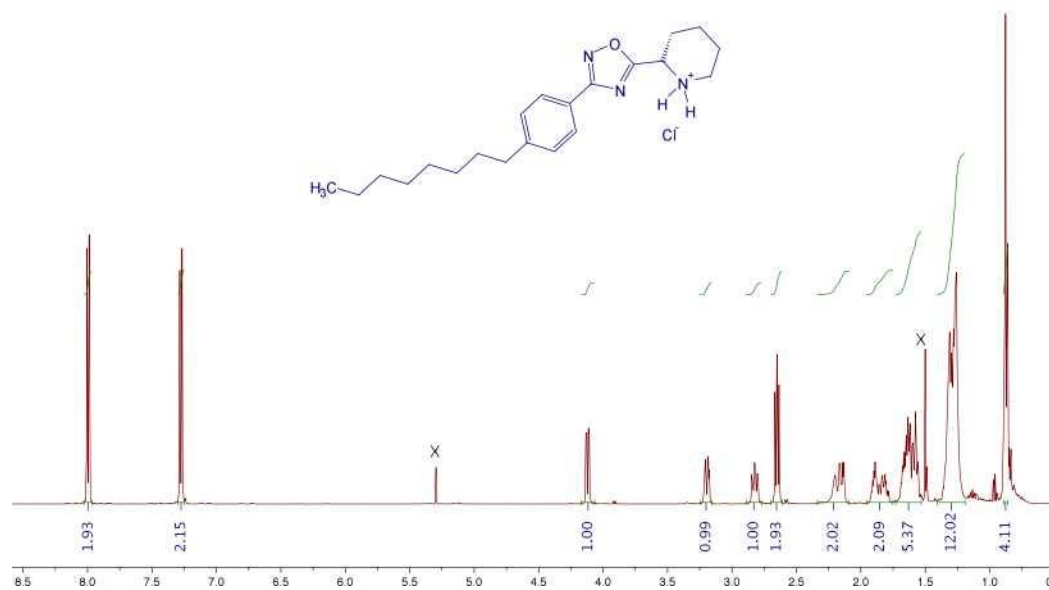


<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidinium chloride **2.5j**

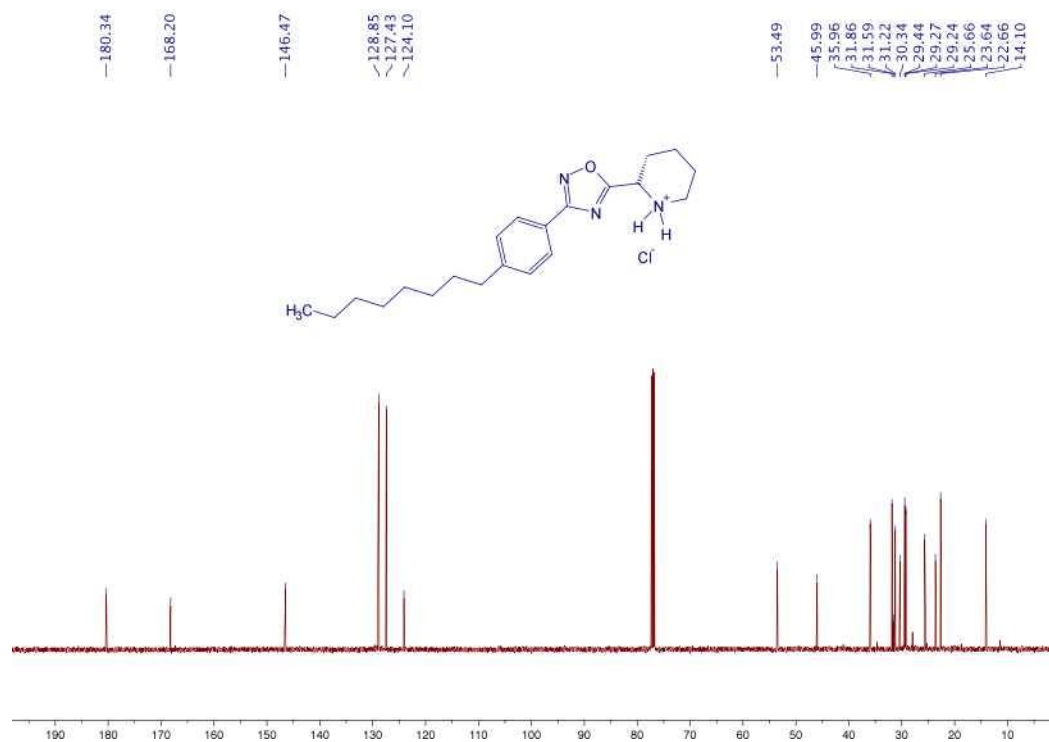




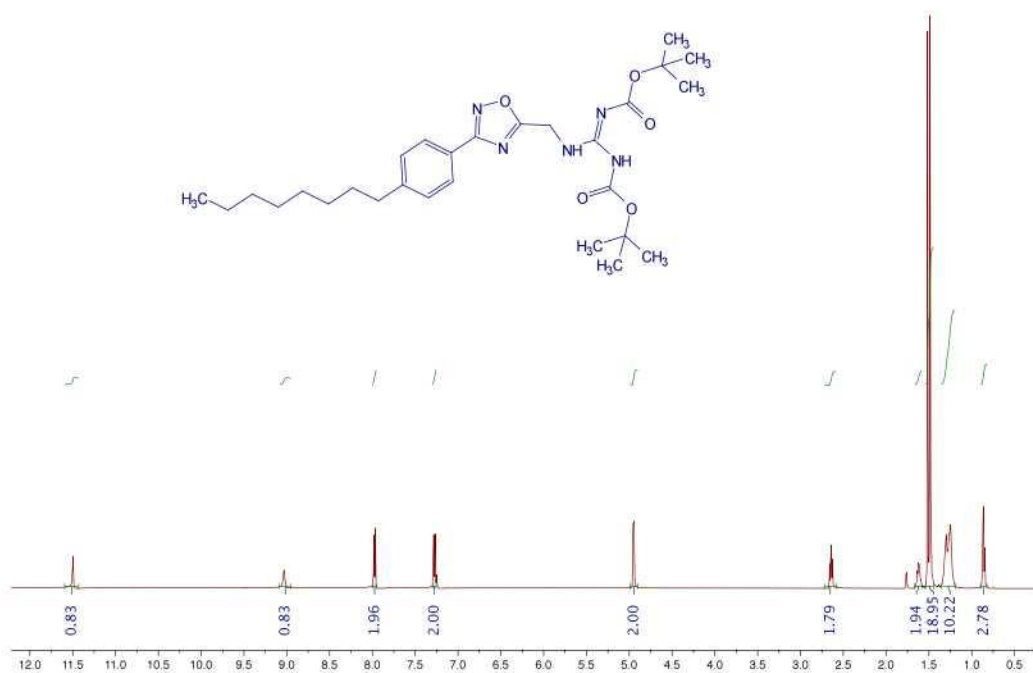
<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-ium chloride **2.5k** –



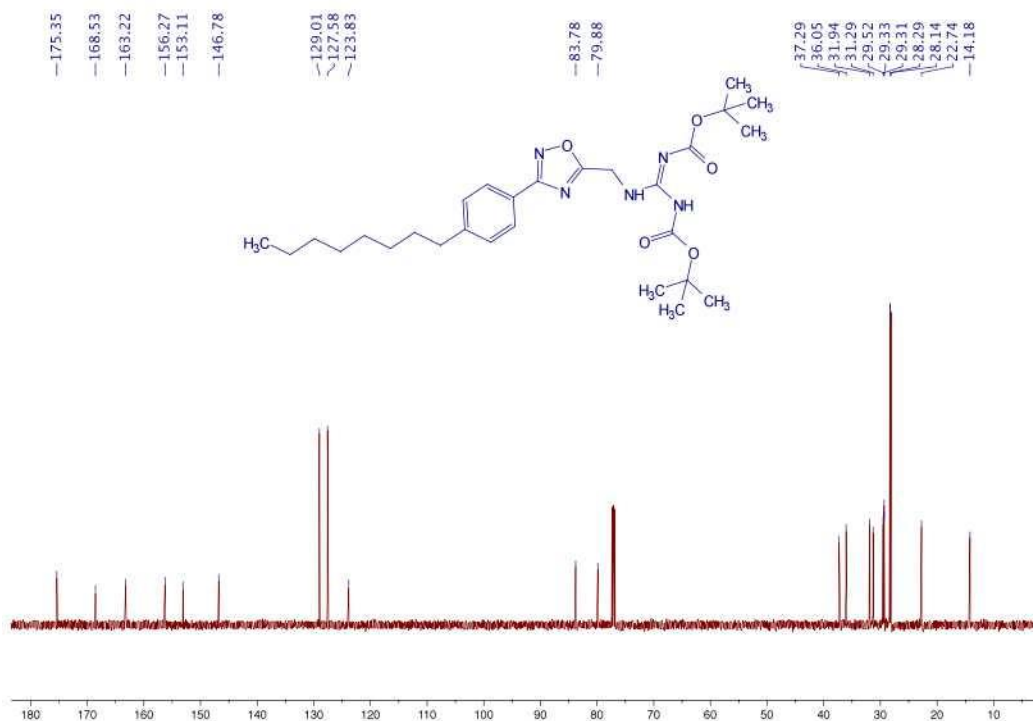
<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-ium chloride **2.5k** –



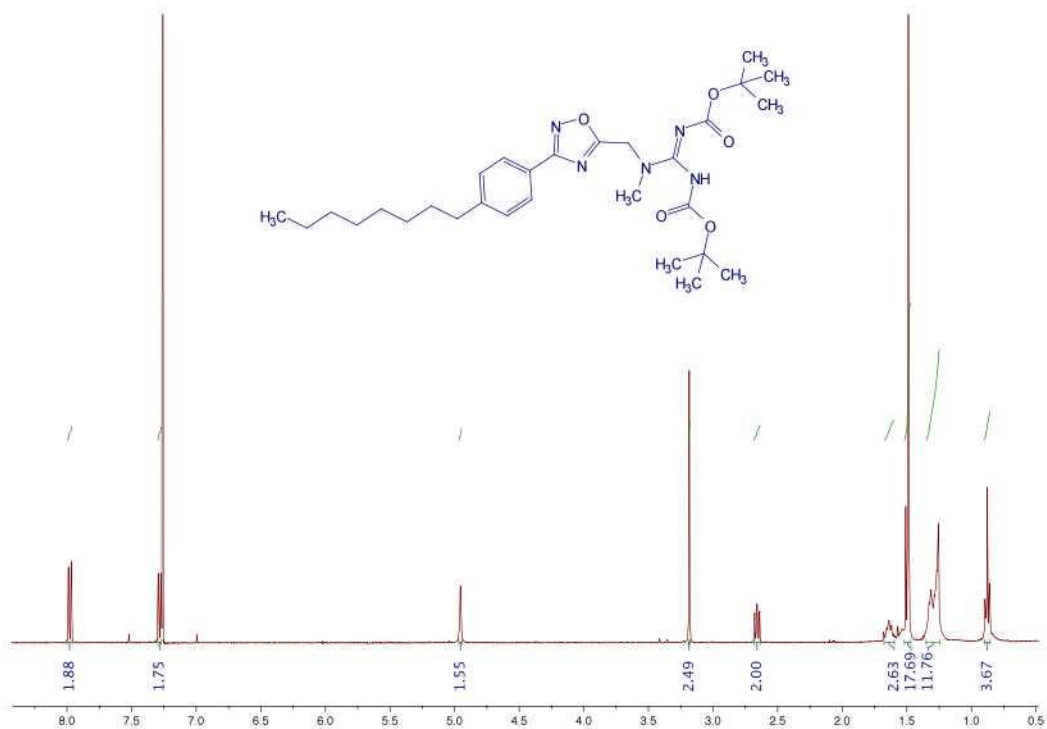
$^1\text{H-NMR}$  Spectrum for *tert*-butyl *N*-[[*tert*-butoxy]carbonyl]amino({[3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl]methyl} amino)methylidene]carbamate **2.6a** –



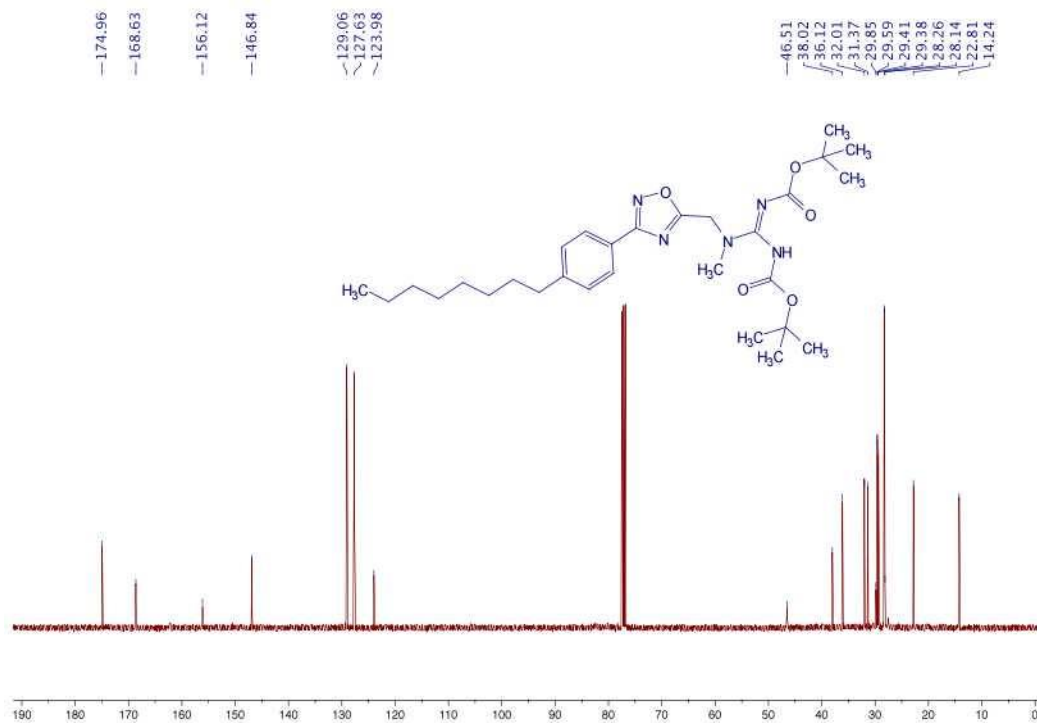
$^{13}\text{C-NMR}$  Spectrum for *tert*-butyl *N*-[[*tert*-butoxy]carbonyl]amino({[3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl]methyl} amino)methylidene]carbamate **2.6a** –



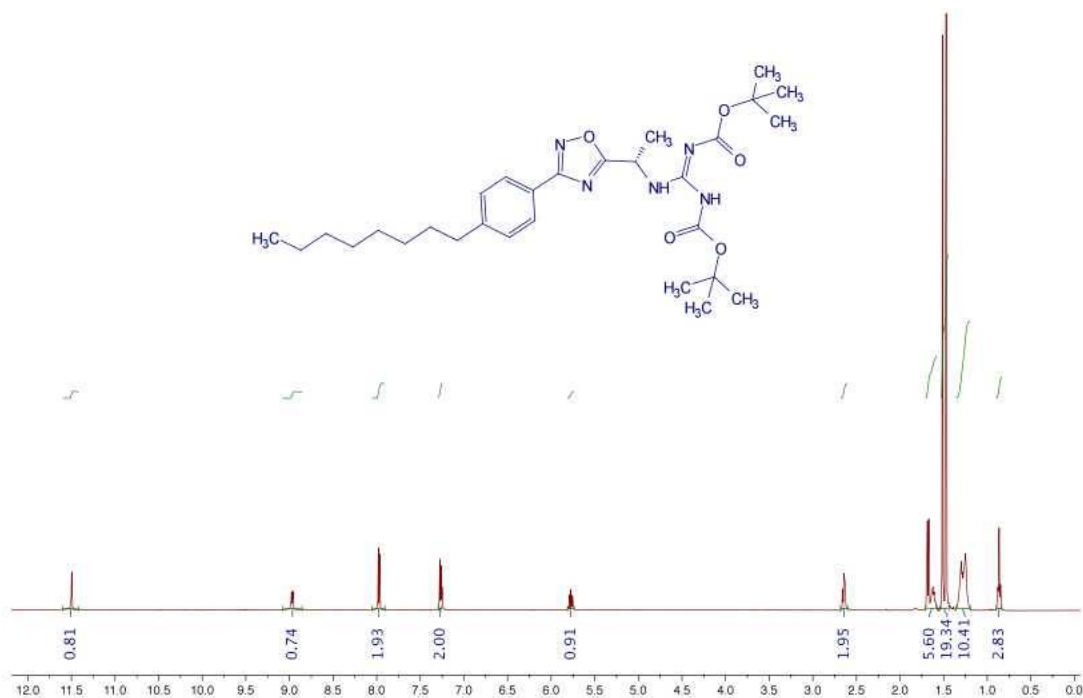
$^1\text{H-NMR}$  Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)(methyl((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)amino)carbamate **2.6b** –



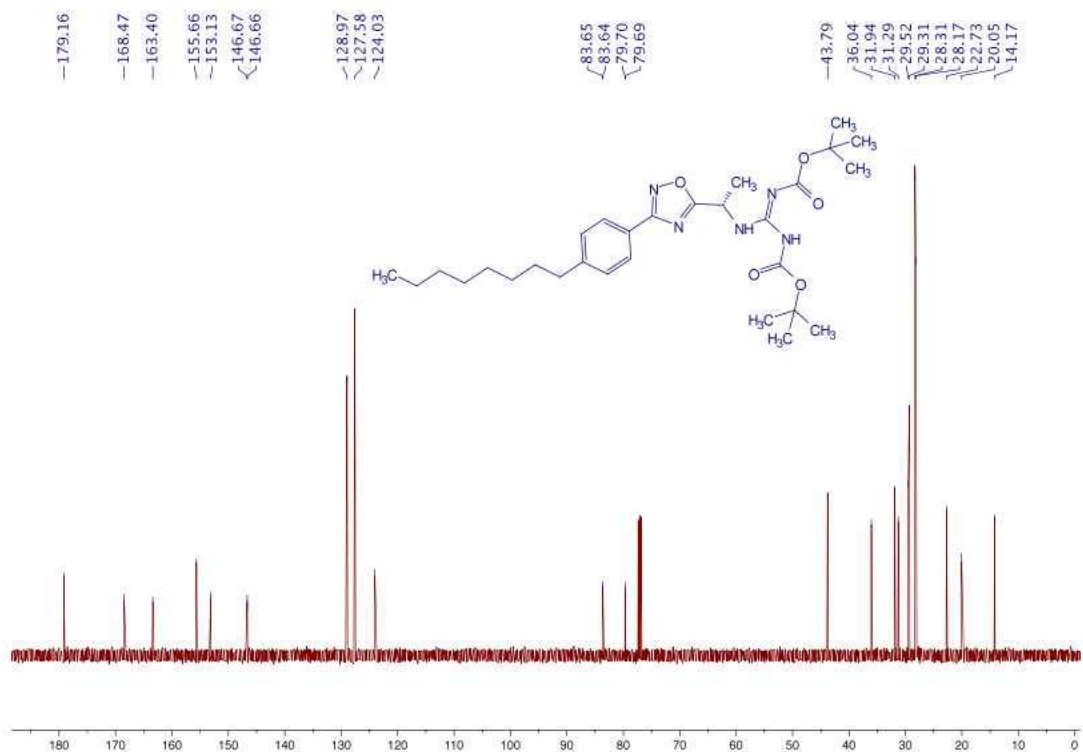
$^{13}\text{C-NMR}$  Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)(methyl((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)amino)carbamate **2.6b** –



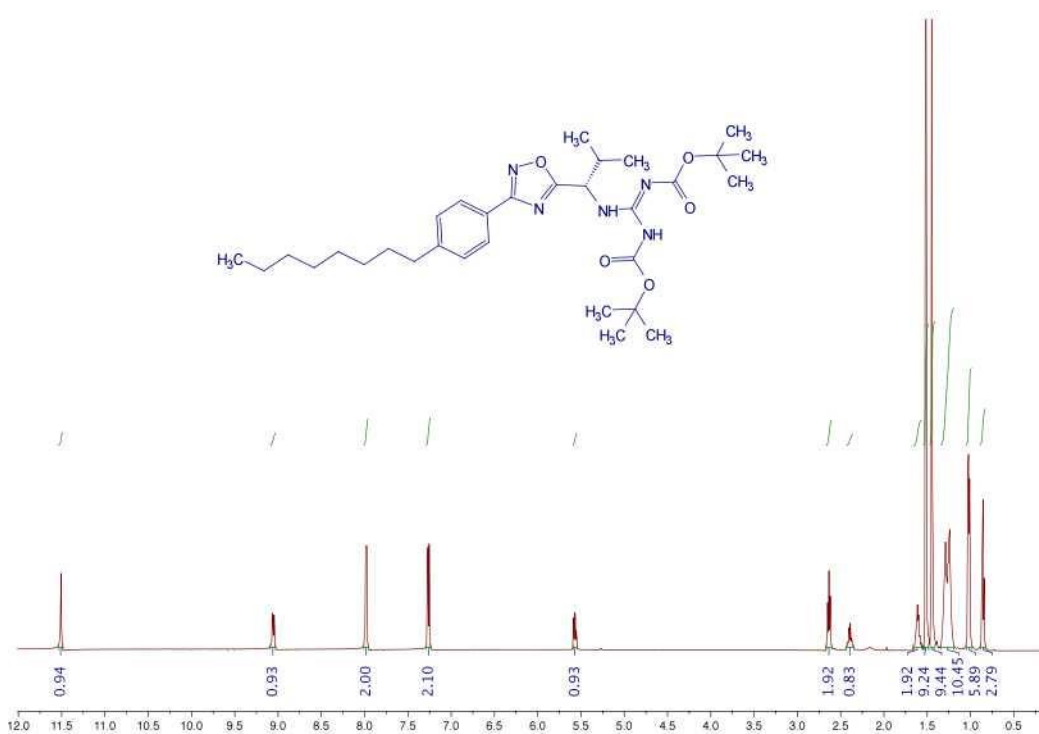
<sup>1</sup>H-NMR Spectrum for *tert*-butyl *N*-[[*tert*-butoxy]carbonyl]amino({[(1*S*)-1-[3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl]ethyl]amino})methylidene]carbamate **2.6c** –



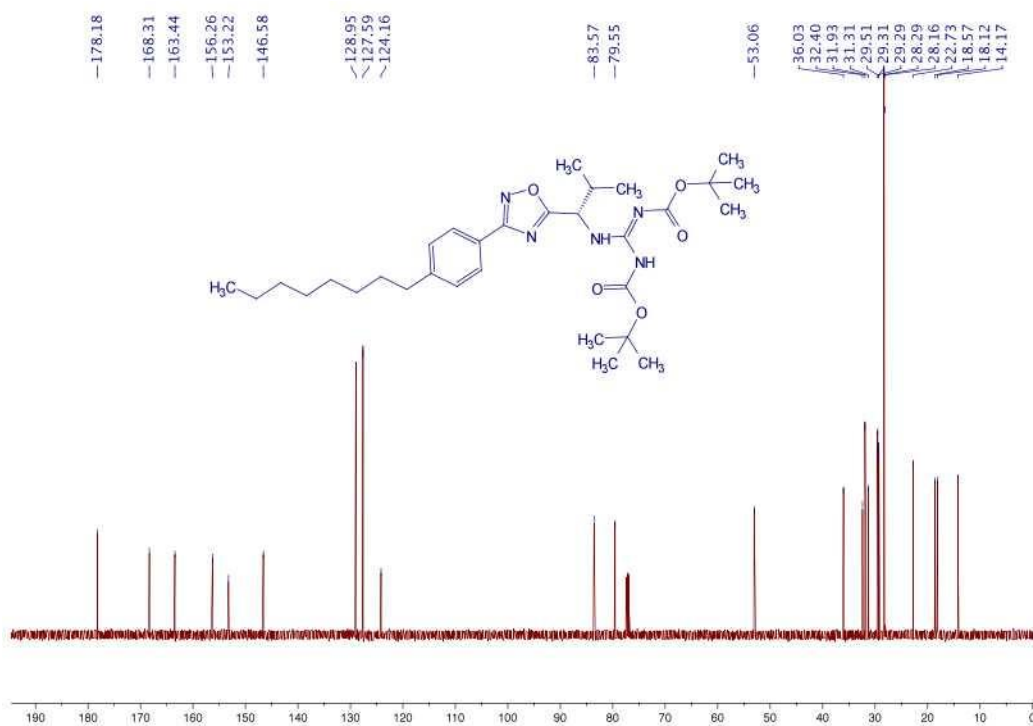
<sup>13</sup>C-NMR Spectrum for *tert*-butyl *N*-[[*tert*-butoxy]carbonyl]amino({[(1*S*)-1-[3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl]ethyl]amino})methylidene]carbamate **2.6c**–



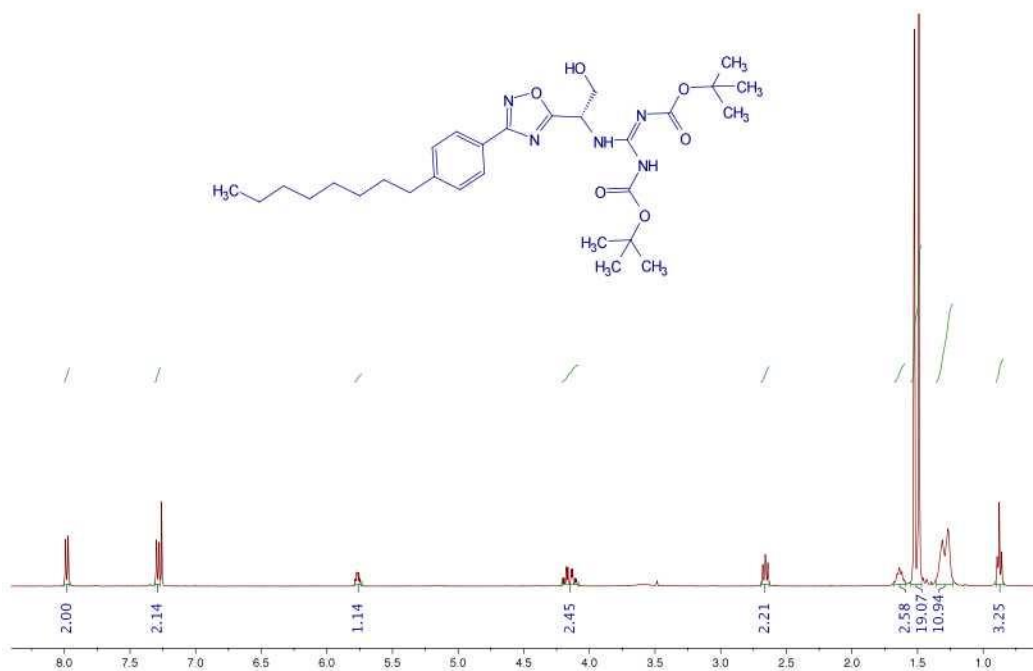
$^1\text{H-NMR}$  Spectrum for *tert*-butyl-*N*-[[*tert*-butoxy]carbonyl]amino({[(1*S*)-2-methyl-1-[3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl]propyl]amino})methylidene]carbamate **2.6d** –



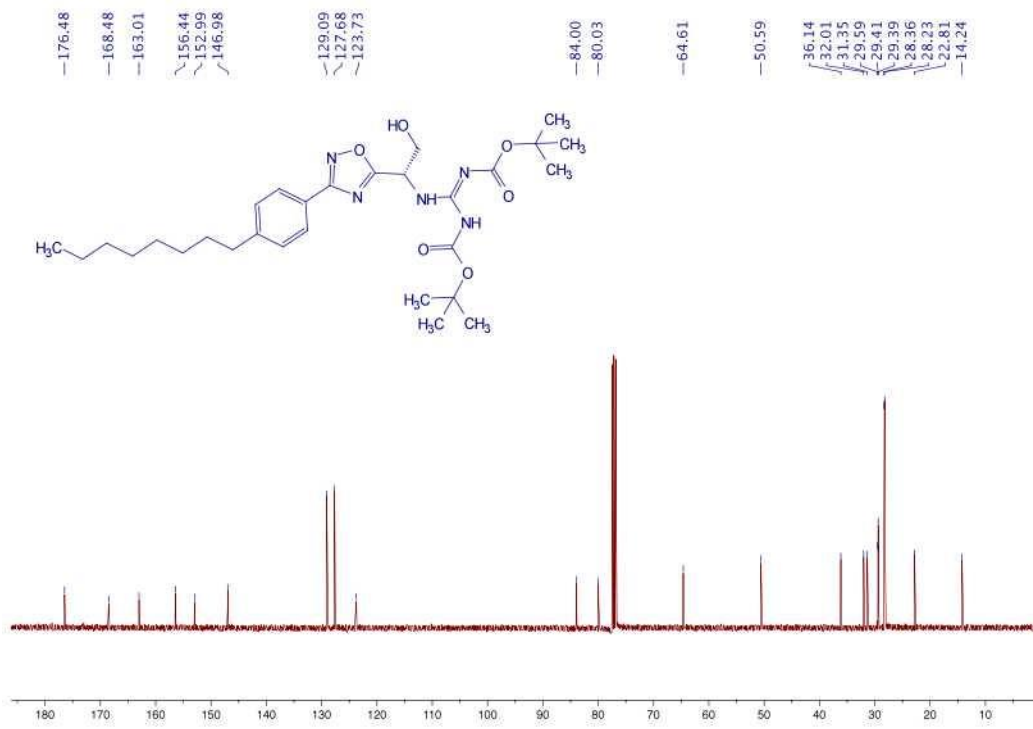
$^{13}\text{C-NMR}$  Spectrum for *tert*-butyl-*N*-[[*tert*-butoxy]carbonyl]amino({[(1*S*)-2-methyl-1-[3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl]propyl]amino})methylidene]carbamate **2.6d** –



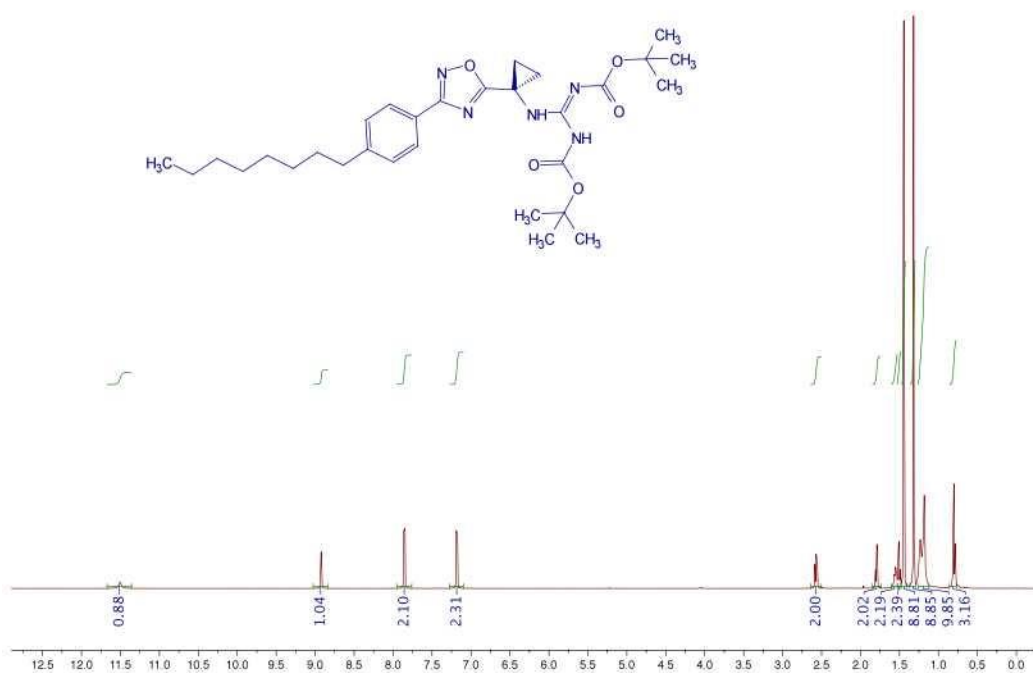
$^1\text{H-NMR}$  Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-hydroxy-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate **2.6e** –



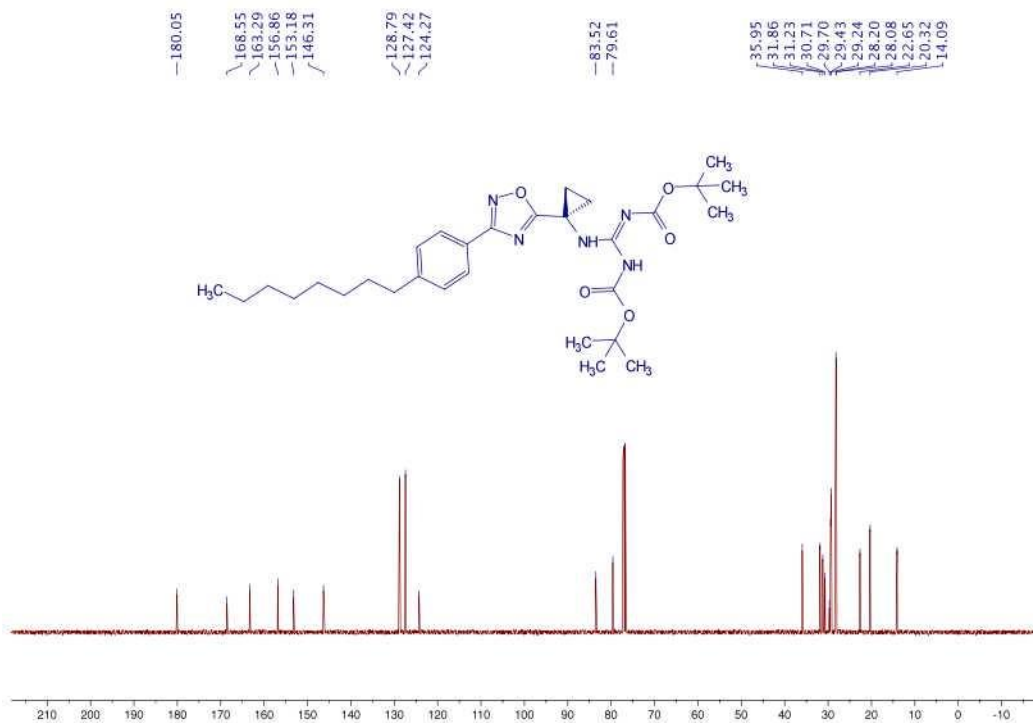
$^{13}\text{C-NMR}$  Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-hydroxy-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate **2.6e** –



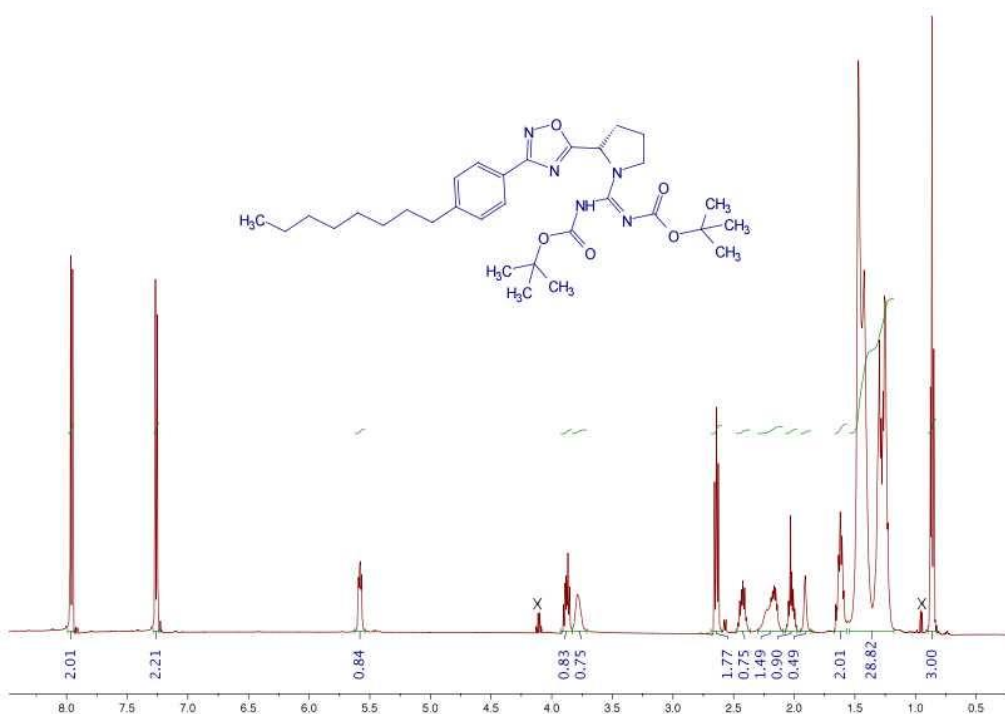
$^1\text{H-NMR}$  Spectrum for 1,2-diBoc-3-(1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropyl)guanidine **2.6f** –



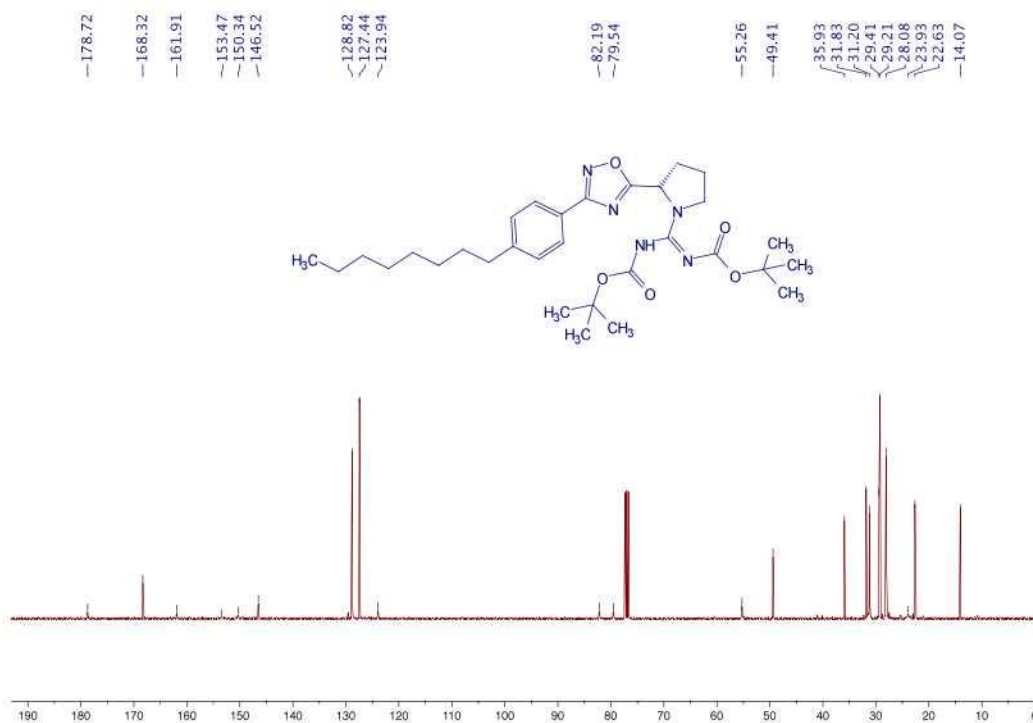
$^{13}\text{C-NMR}$  Spectrum for 1,2-diBoc-3-(1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropyl)guanidine **2.6f** –



$^1\text{H-NMR}$  Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)imino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methyl) carbamate **2.6g** –

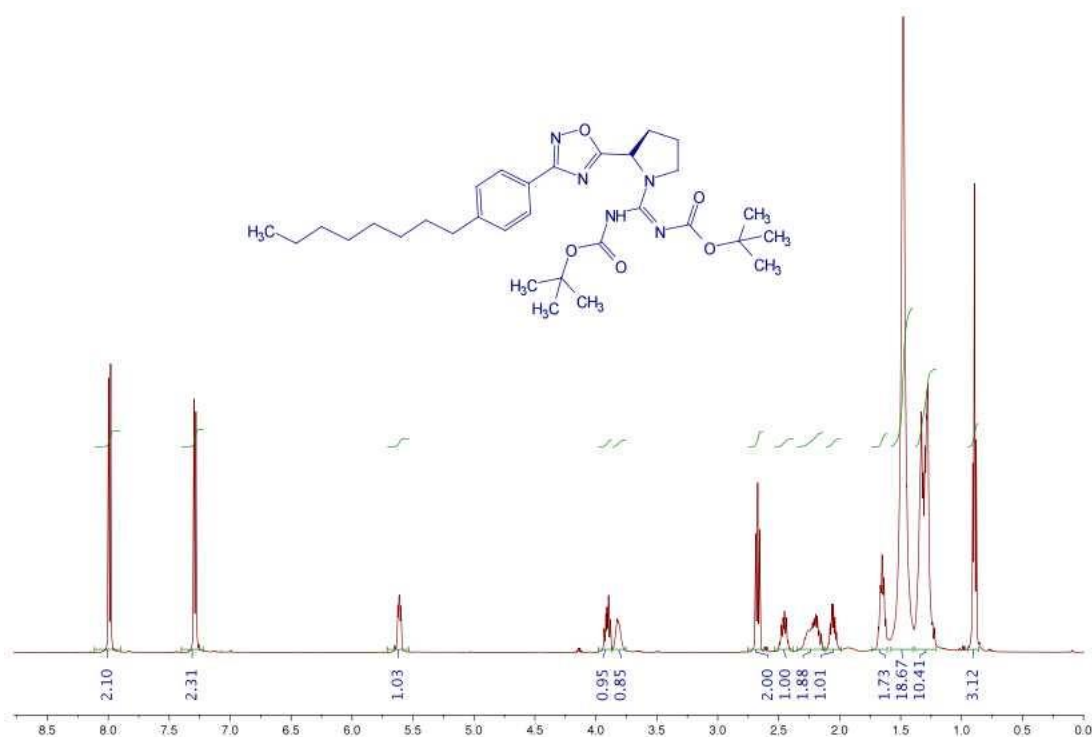


$^{13}\text{C-NMR}$  Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)imino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methyl) carbamate **2.6g** –

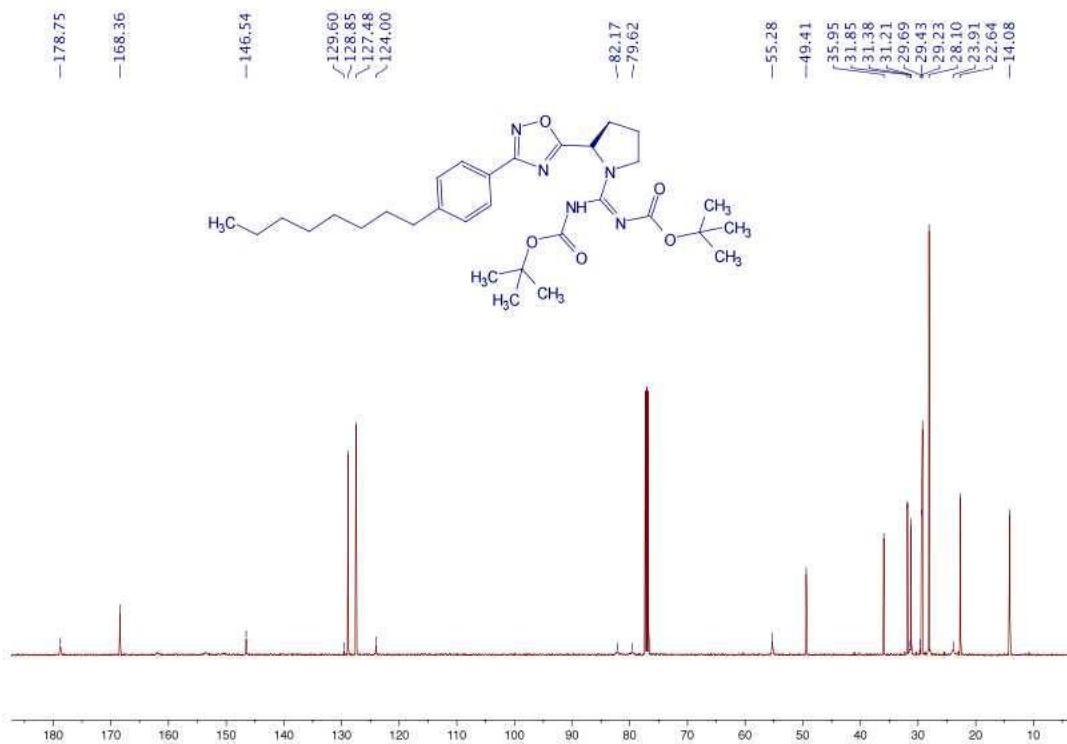




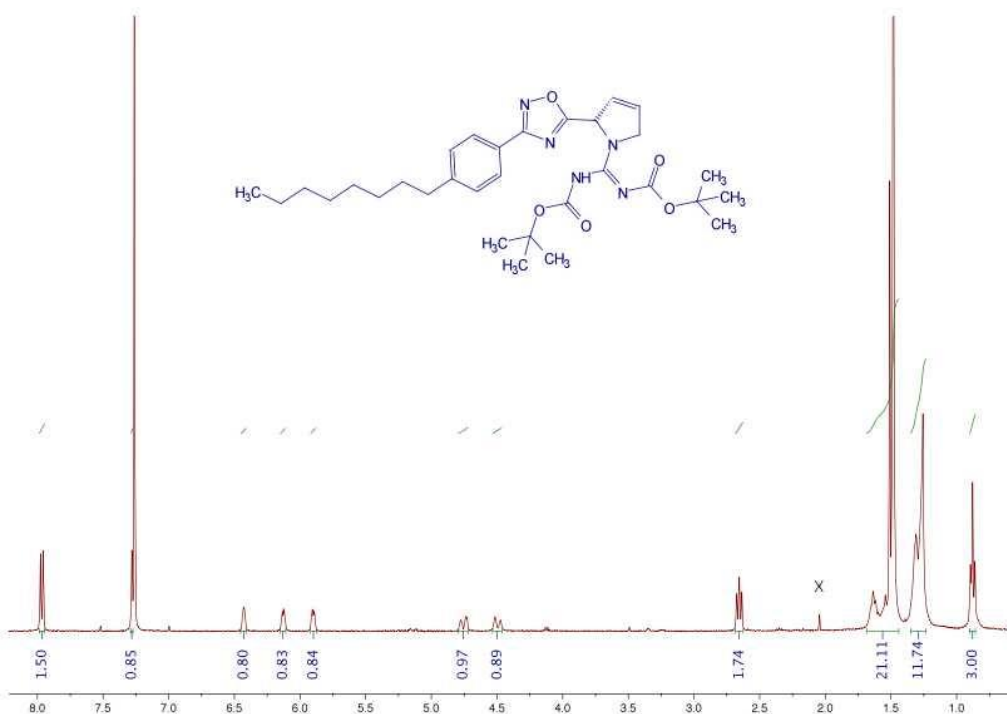
<sup>1</sup>H-NMR Spectrum for (*R*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **2.6h** –



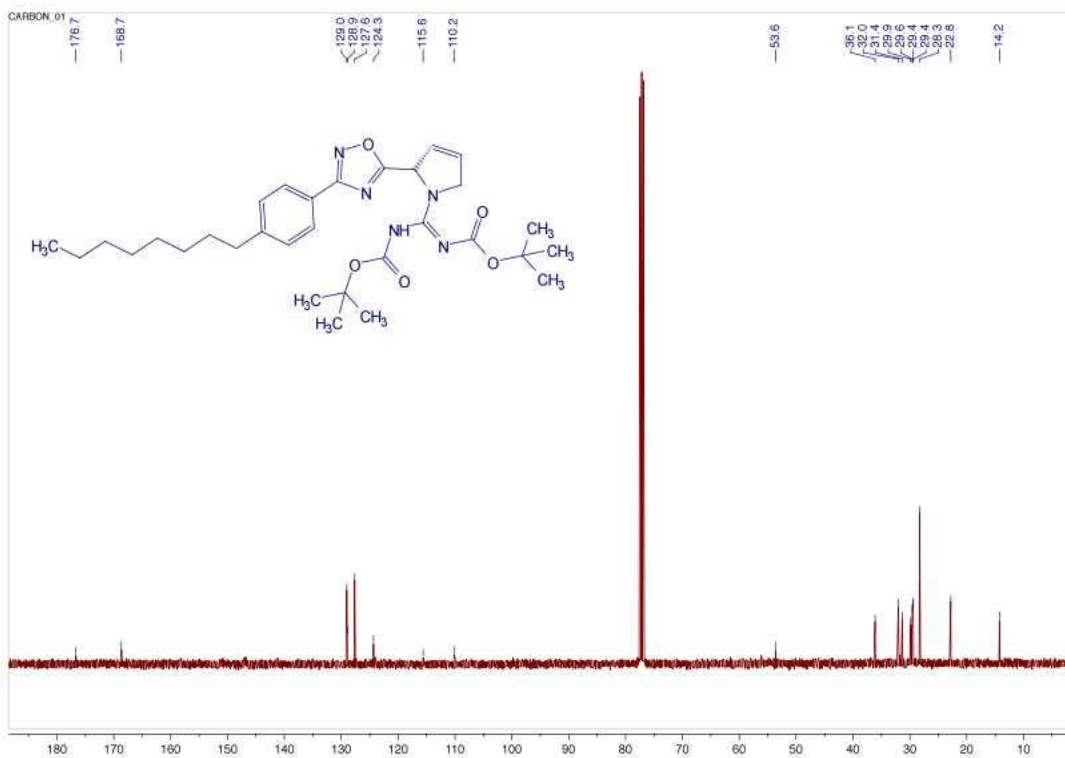
<sup>13</sup>C-NMR Spectrum for (*R*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **2.6h**–



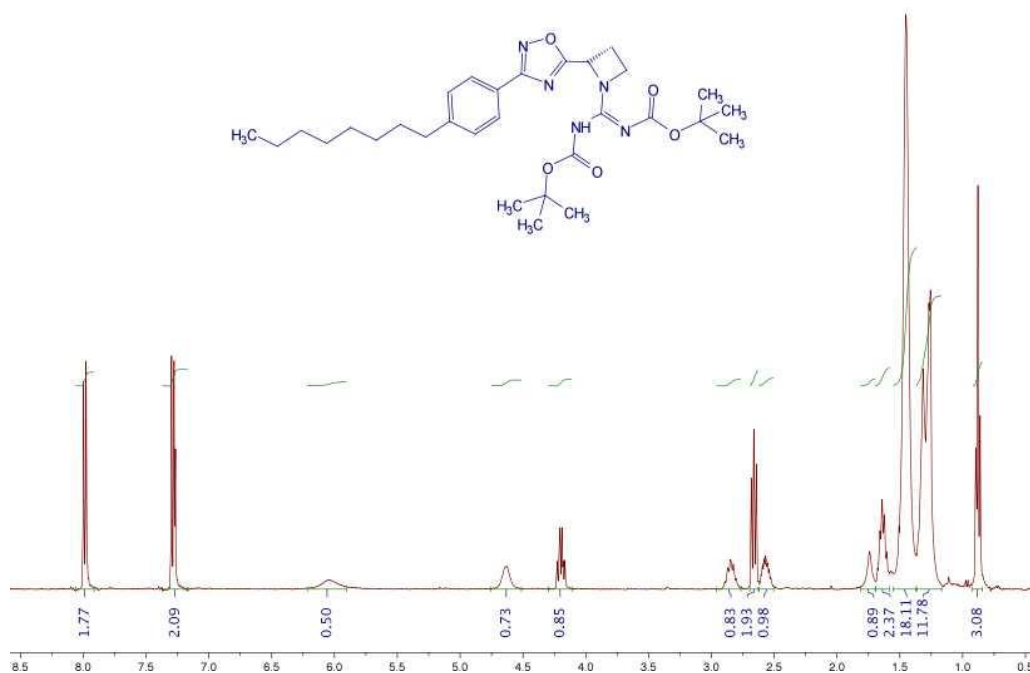
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)-2,5-dihydro-1H-pyrrol-1-yl)methylene)carbamate **2.6i**-



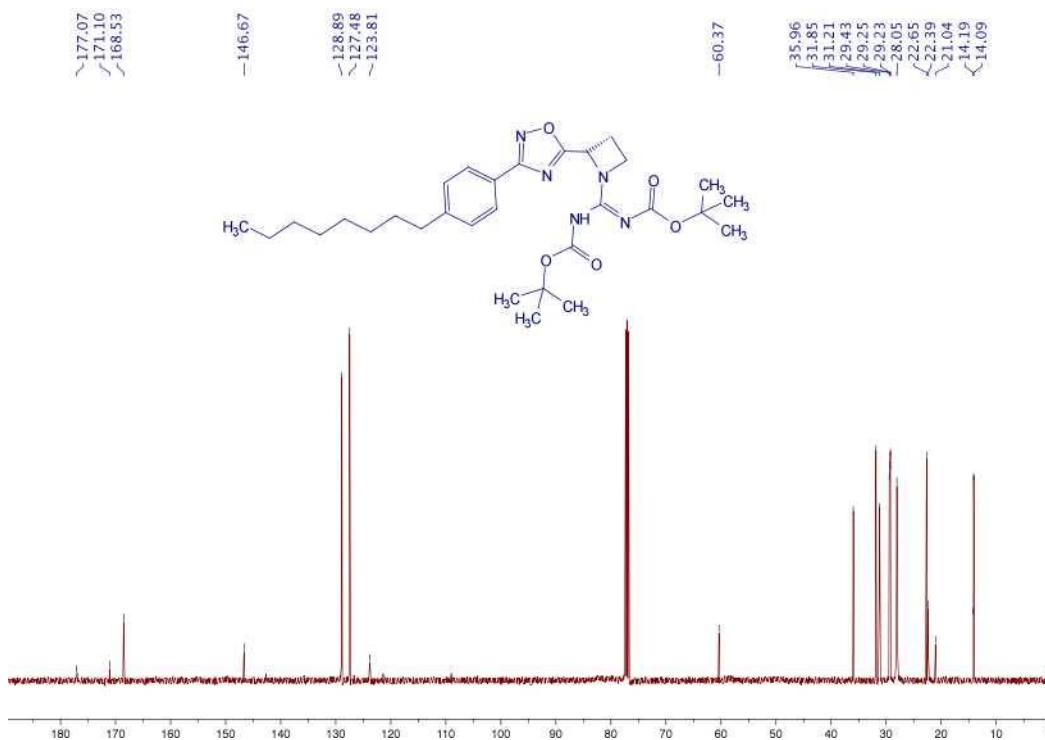
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)-2,5-dihydro-1H-pyrrol-1-yl)methylene)carbamate **2.6i**-



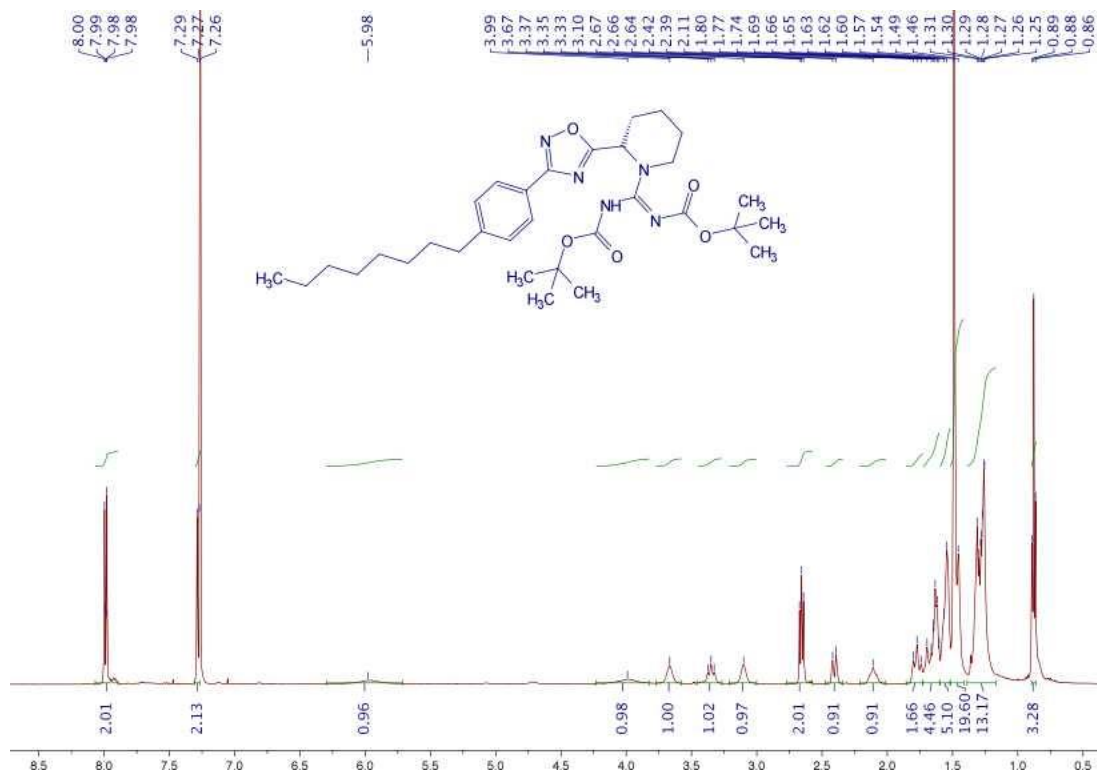
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methylene)carbamate **2.6j** –



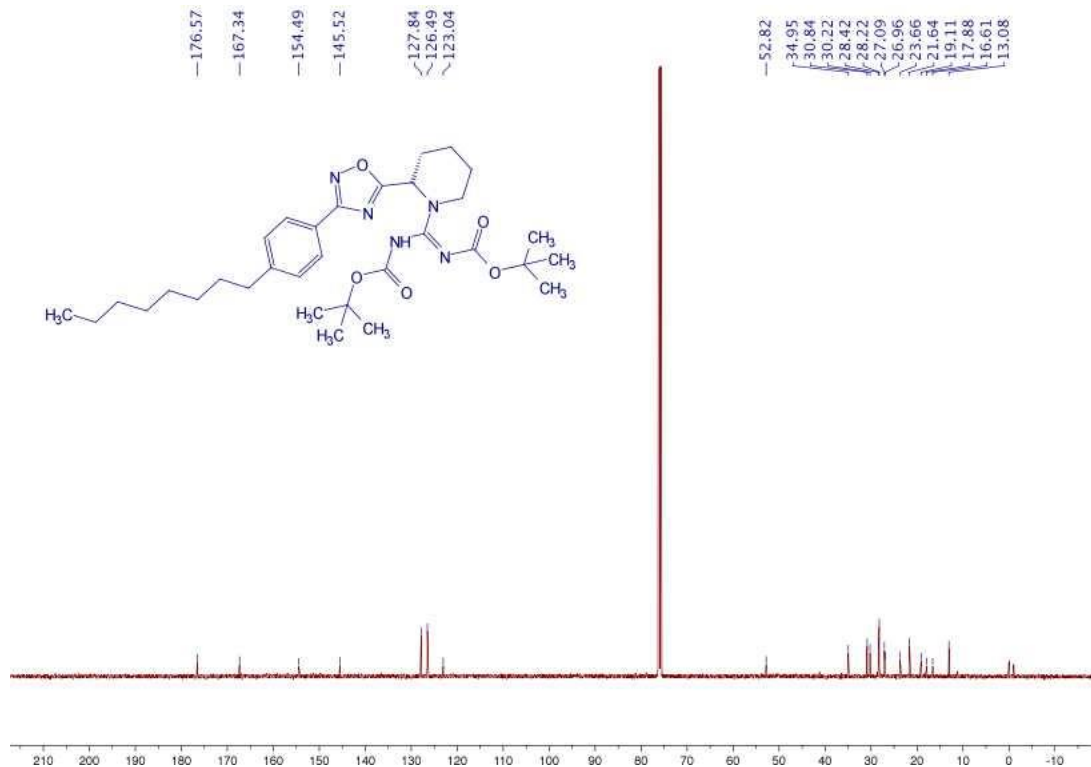
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methylene)carbamate **2.6j** –



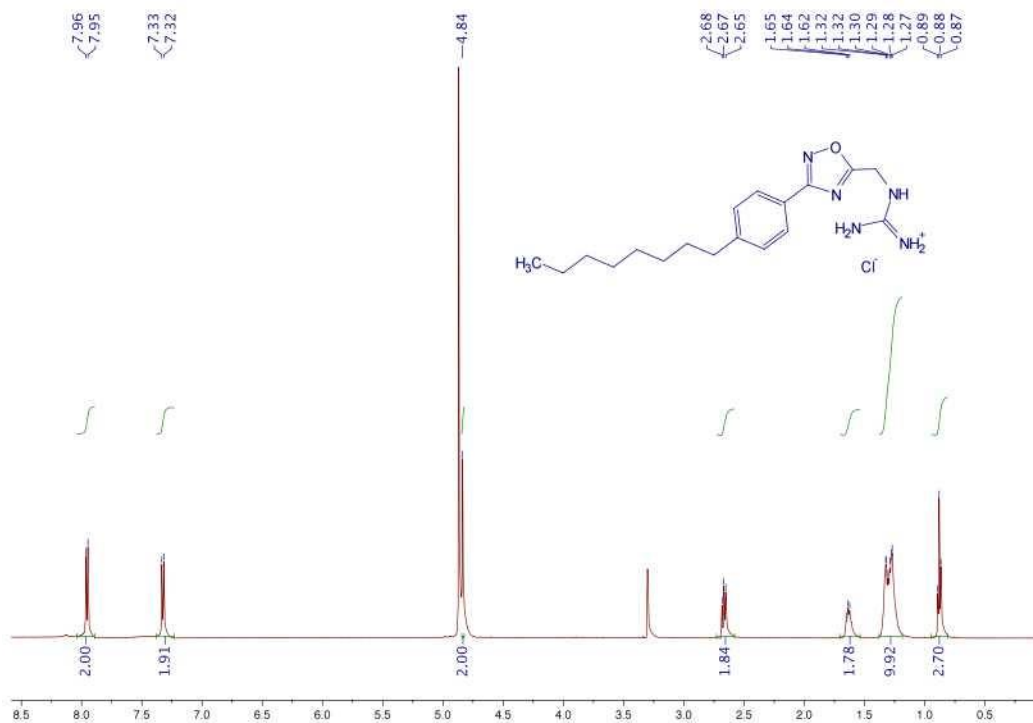
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)methylene)carbamate **2.6k** –



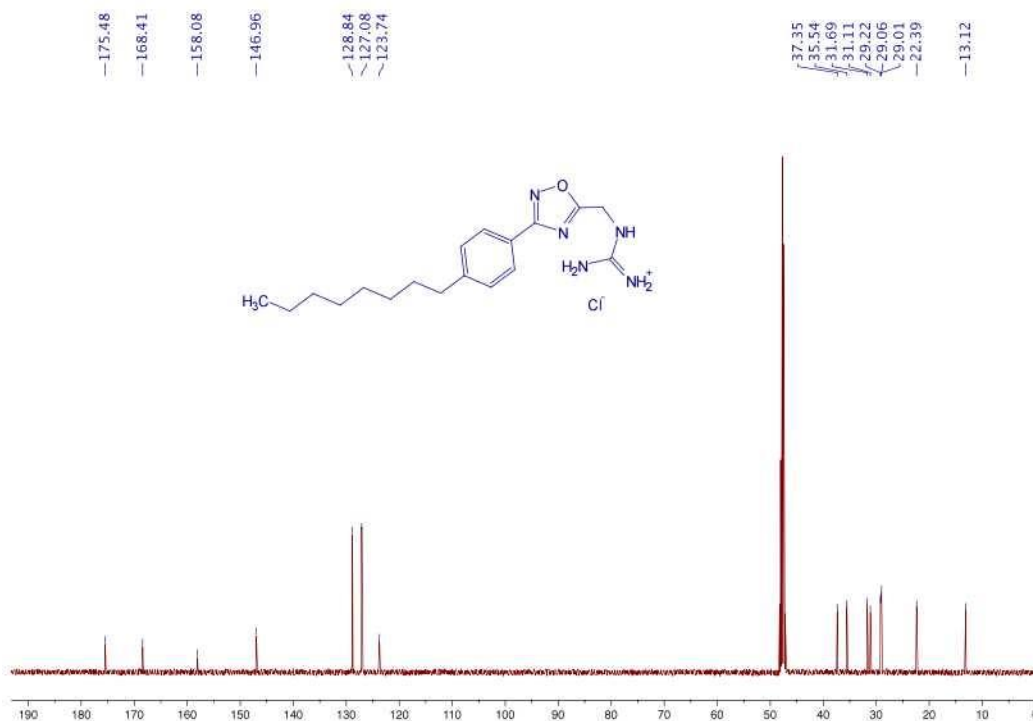
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)methylene)carbamate **2.6k** –



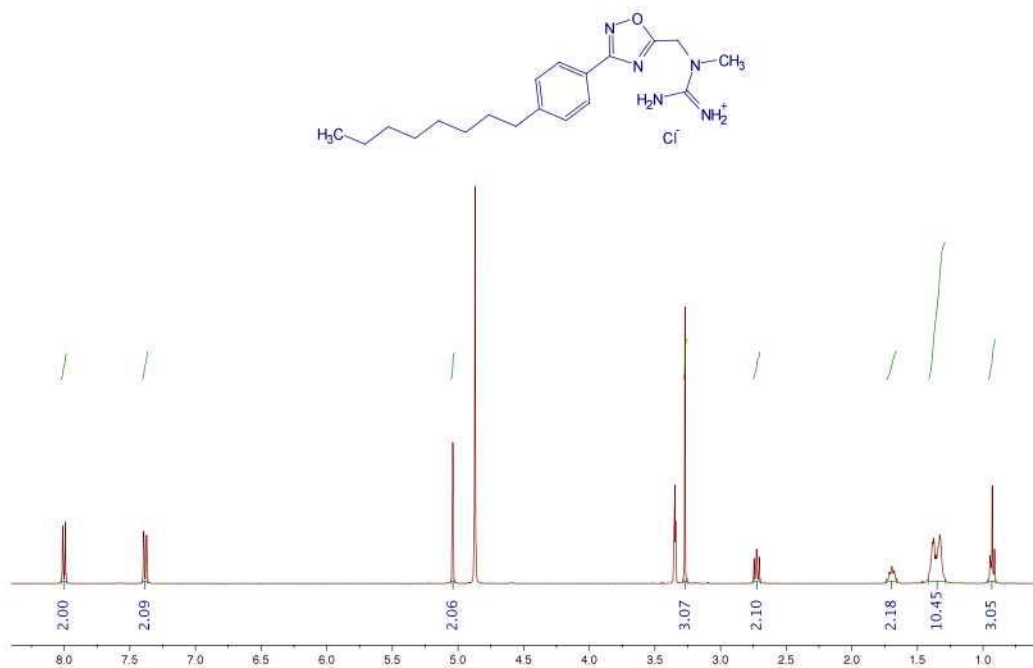
$^1\text{H-NMR}$  Spectrum for 1-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)guanidine hydrochloride **2.7a** –



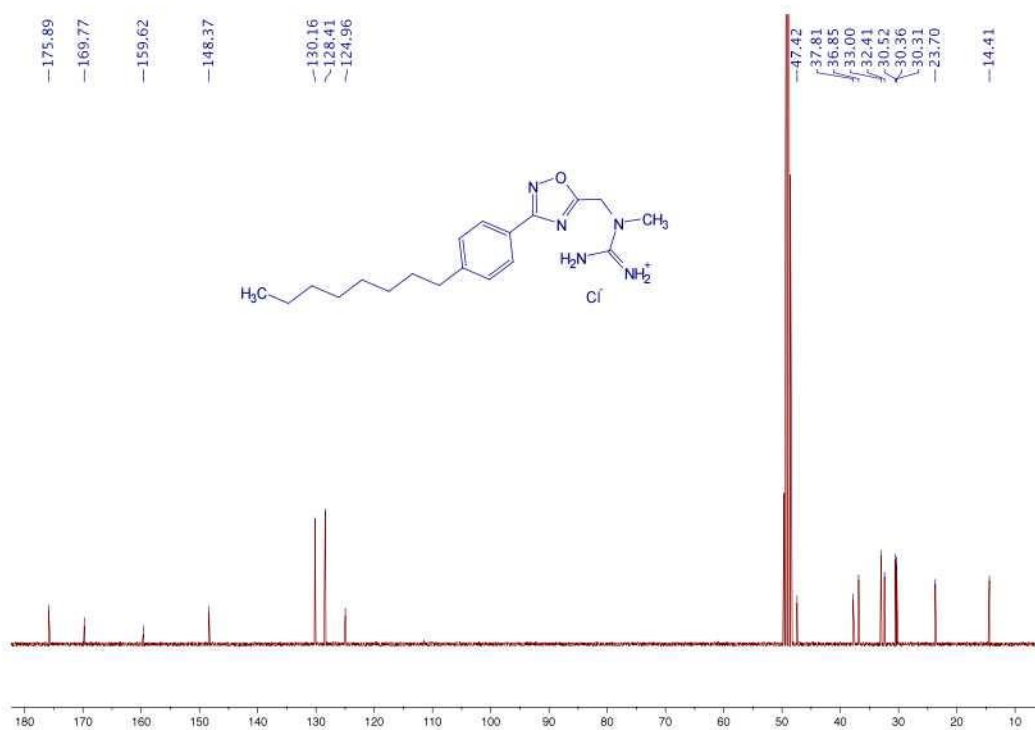
$^{13}\text{C-NMR}$  Spectrum for 1-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)guanidine hydrochloride **2.7a** –



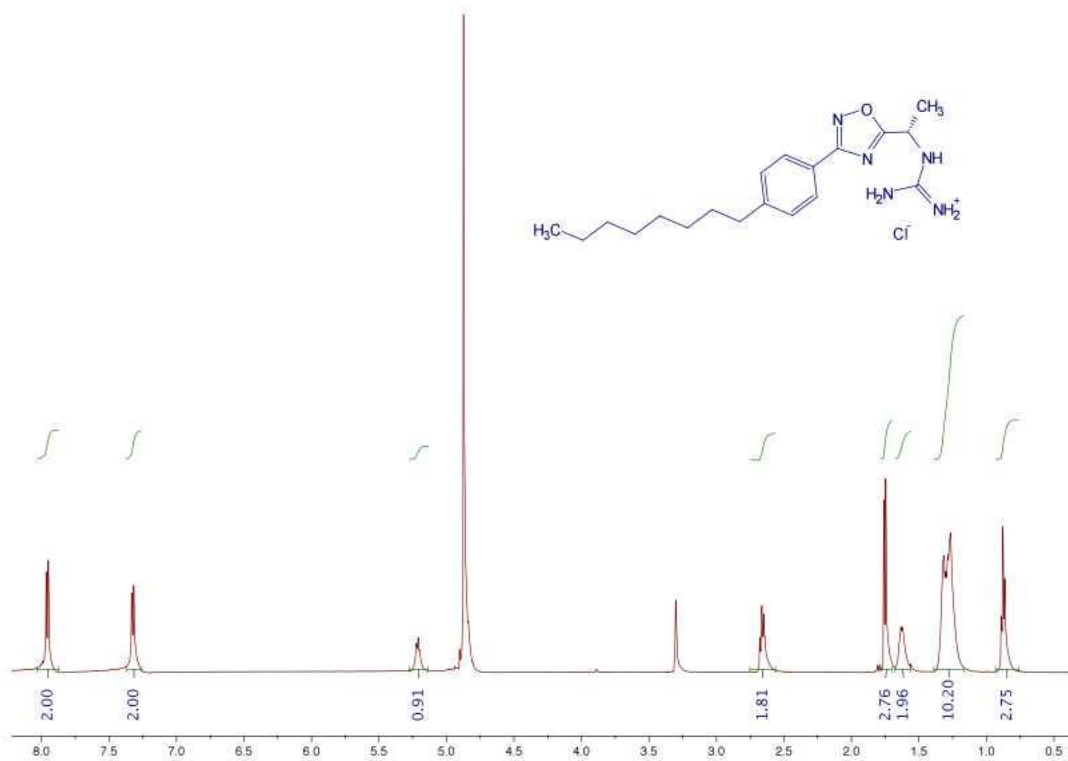
<sup>1</sup>H-NMR Spectrum for 1-methyl-1-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)guanidine hydrochloride **2.7b** –



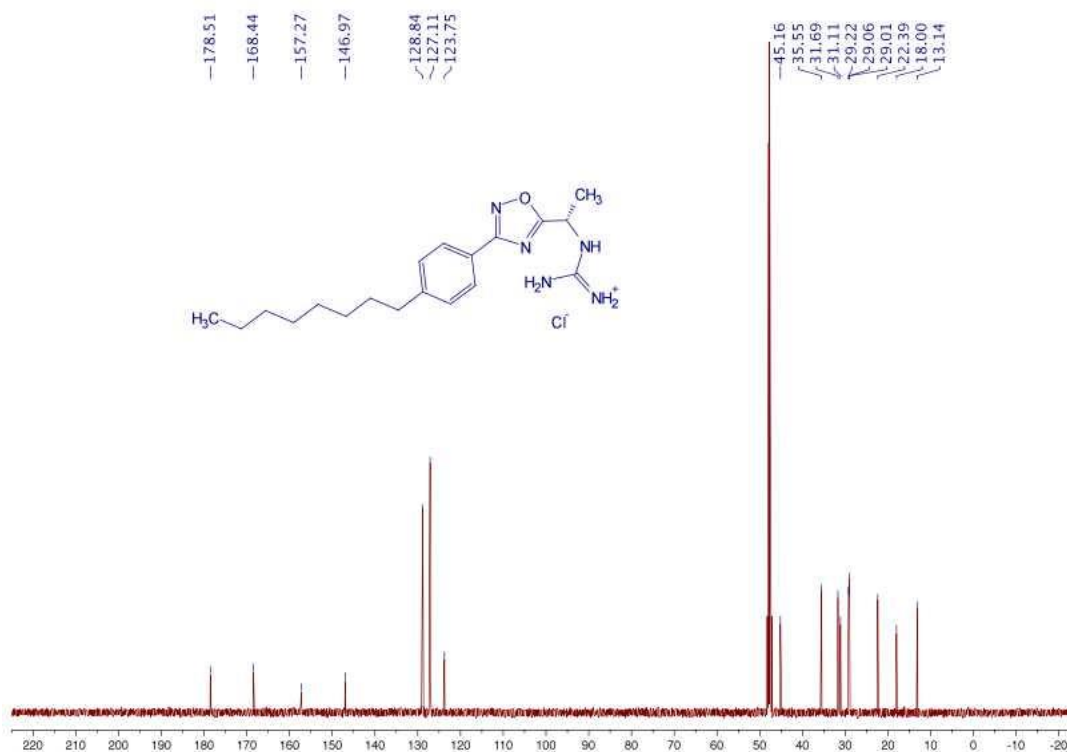
<sup>13</sup>C-NMR Spectrum for 1-methyl-1-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)guanidine hydrochloride **2.7b** –



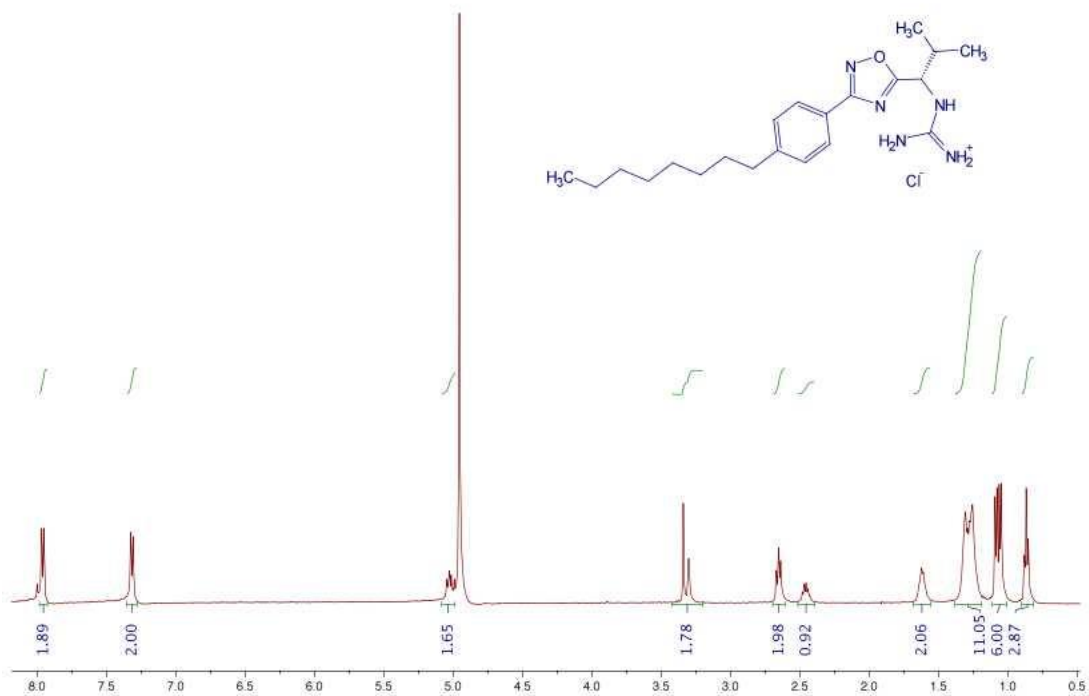
$^1\text{H-NMR}$  Spectrum for (*S*)-1-(1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)guanidine hydrochloride **2.7c** –



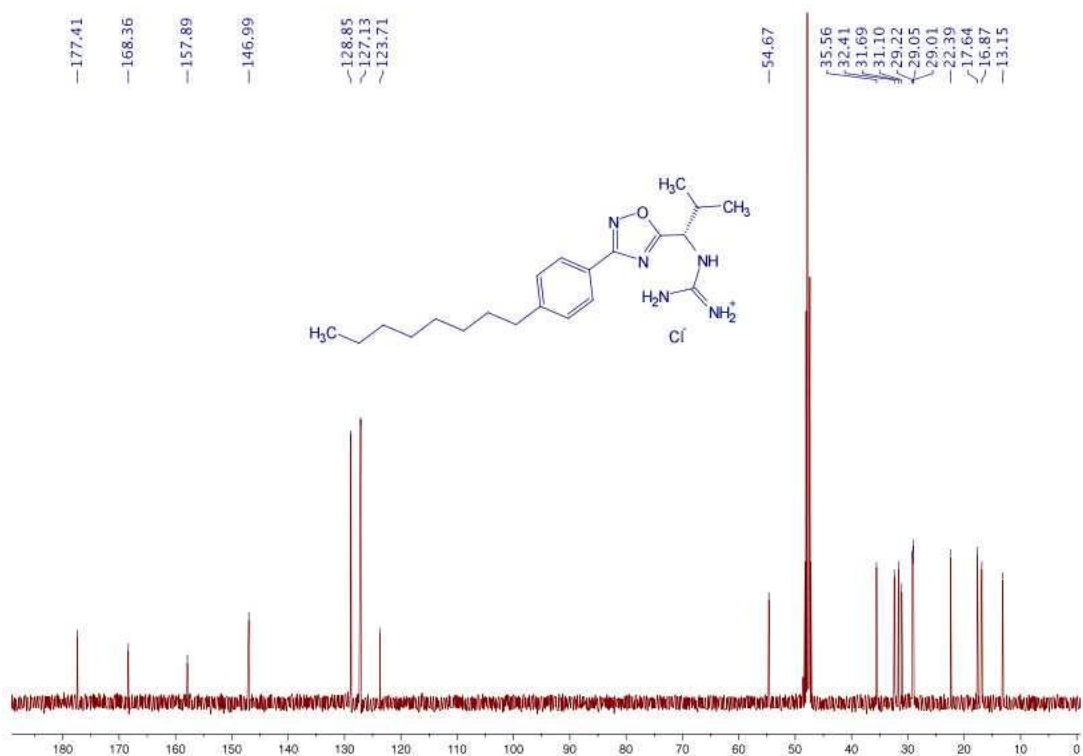
$^{13}\text{C-NMR}$  Spectrum for (*S*)-1-(1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)guanidine hydrochloride **2.7c** –



<sup>1</sup>H-NMR Spectrum for (S)-1-(2-methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)propyl)guanidine hydrochloride **2.7d** –

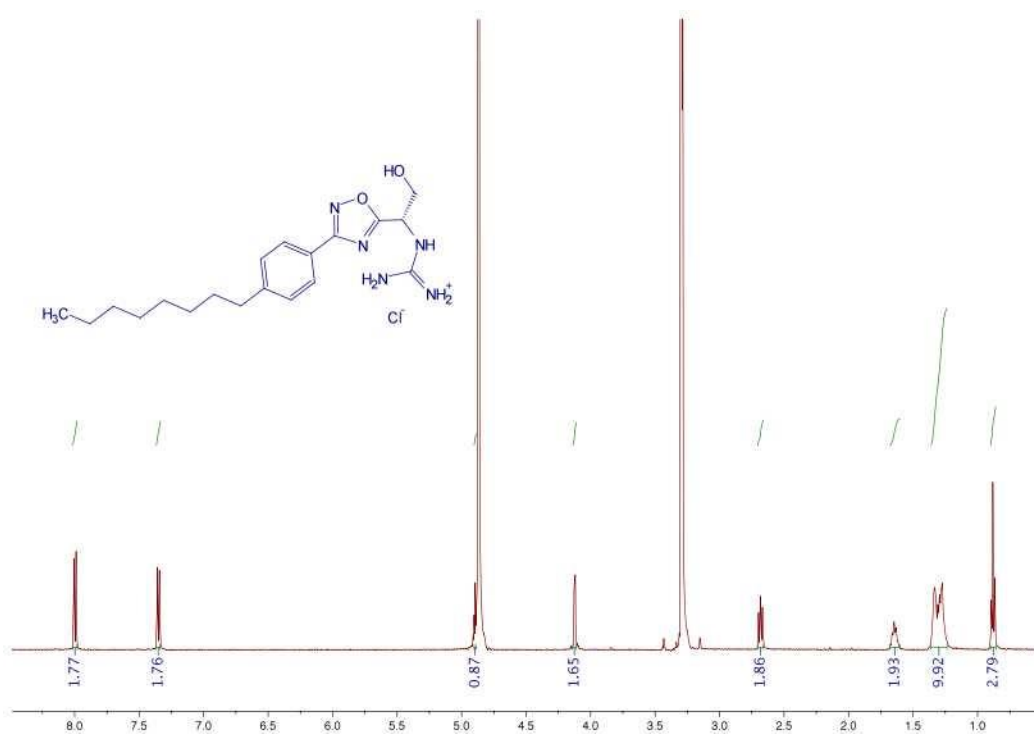


<sup>13</sup>C-NMR Spectrum for (S)-1-(2-methyl-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)propyl)guanidine hydrochloride **2.7d** –

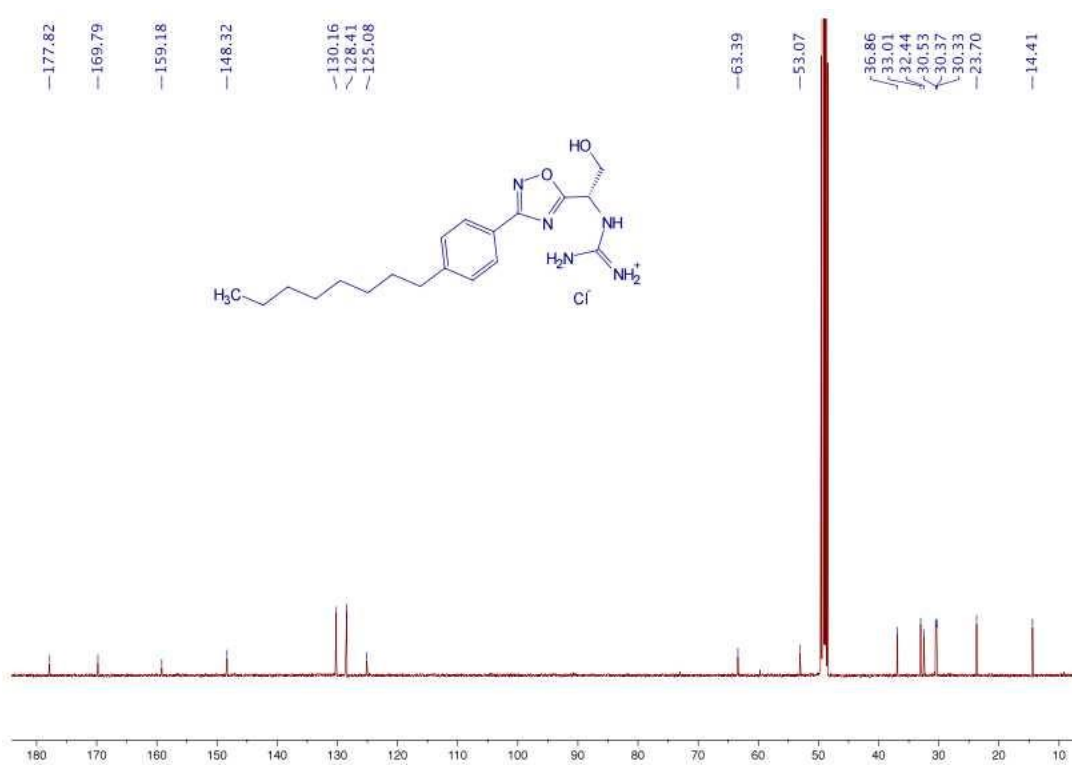




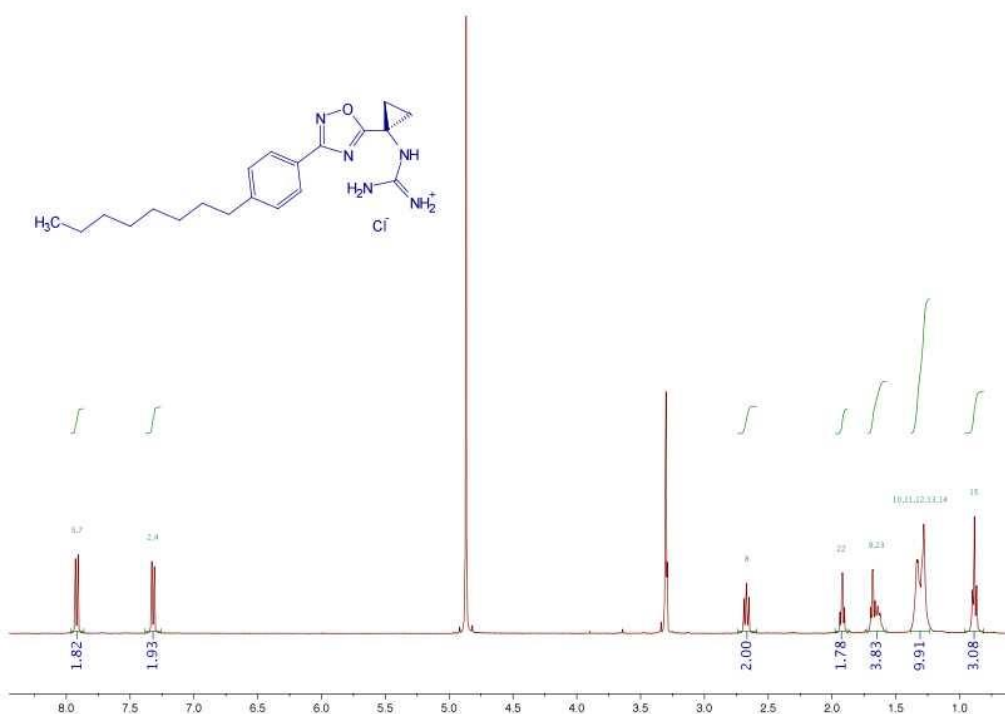
$^1\text{H-NMR}$  Spectrum for (*S*)-amino((2-hydroxy-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino) methaniminium chloride **2.7e** –



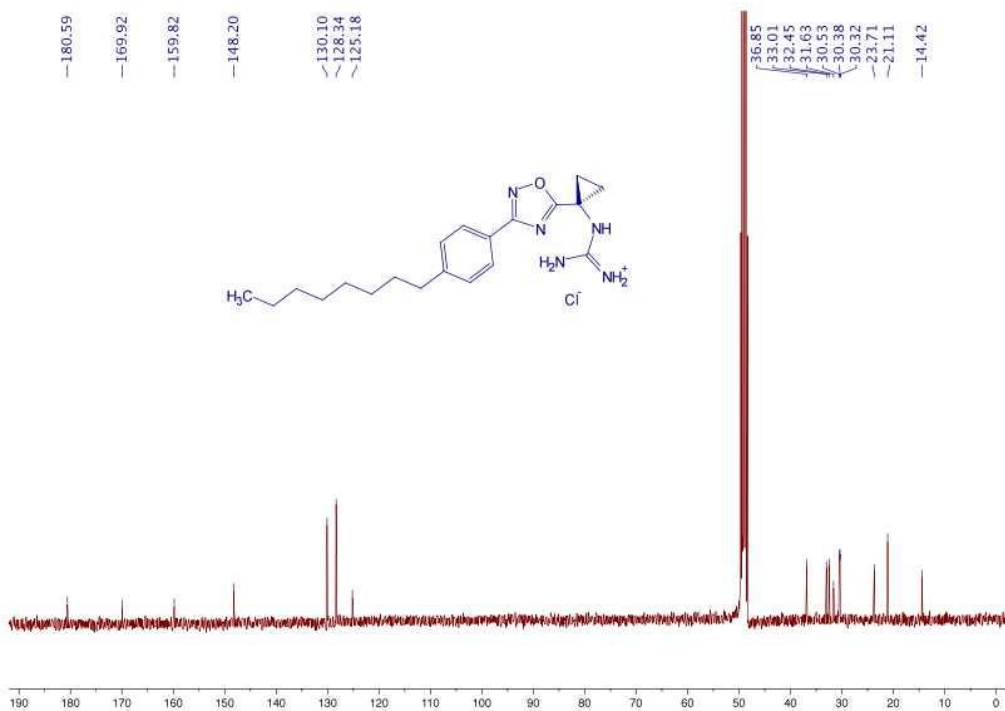
$^{13}\text{C-NMR}$  Spectrum for (*S*)-amino((2-hydroxy-1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino) methaniminium chloride **2.7e** –



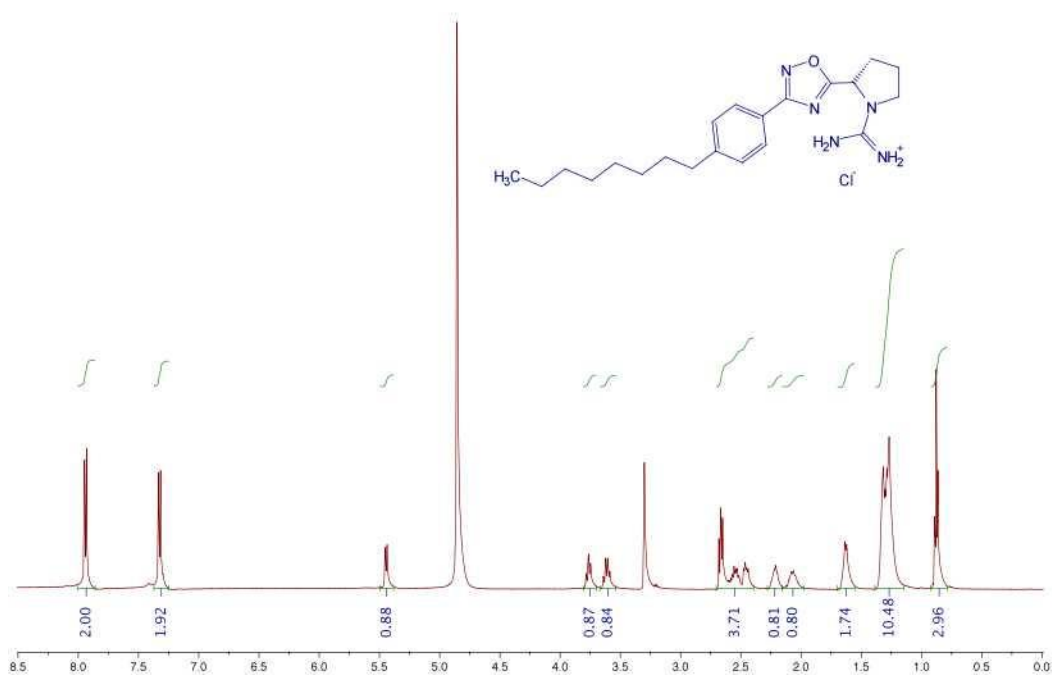
<sup>1</sup>H-NMR Spectrum for 1-(1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropyl)guanidine hydrochloride **2.7f** –



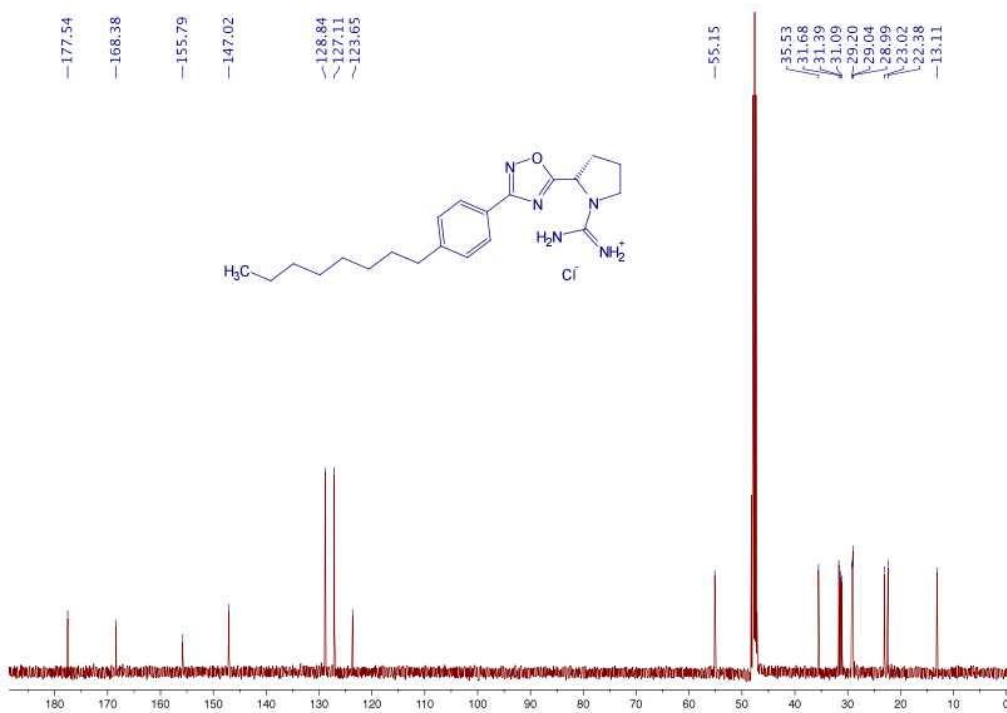
<sup>13</sup>C-NMR Spectrum for 1-(1-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropyl)guanidine hydrochloride **2.7f** –



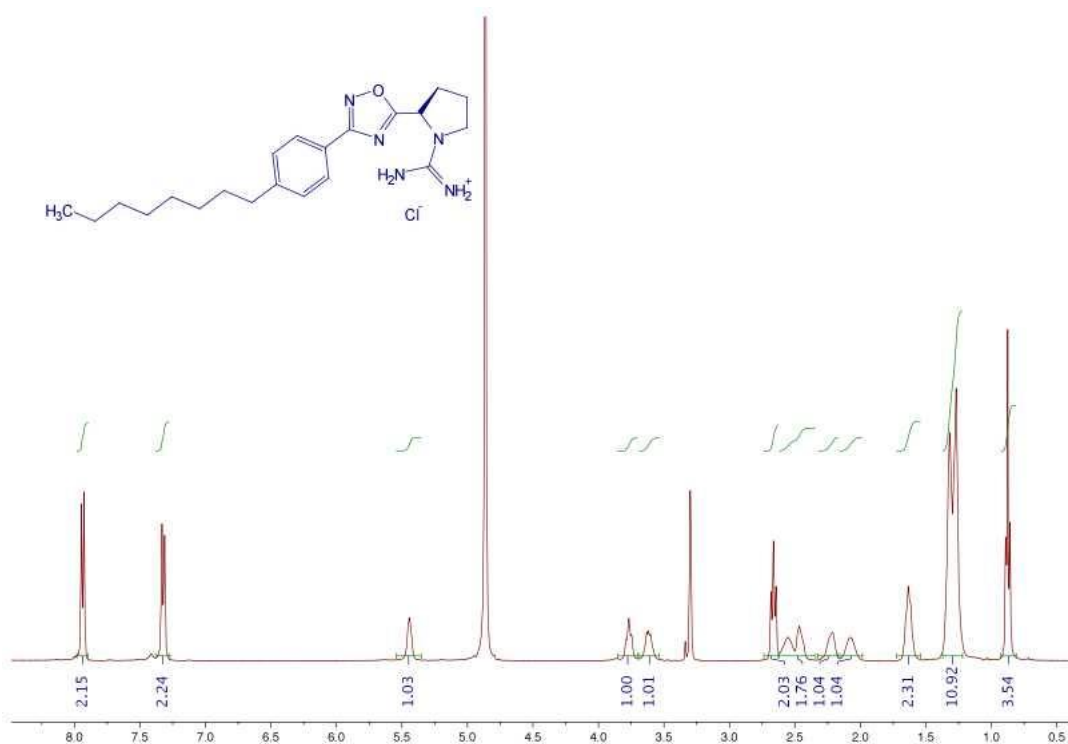
$^1\text{H-NMR}$  Spectrum for (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboximidamide hydrochloride **2.7g**–



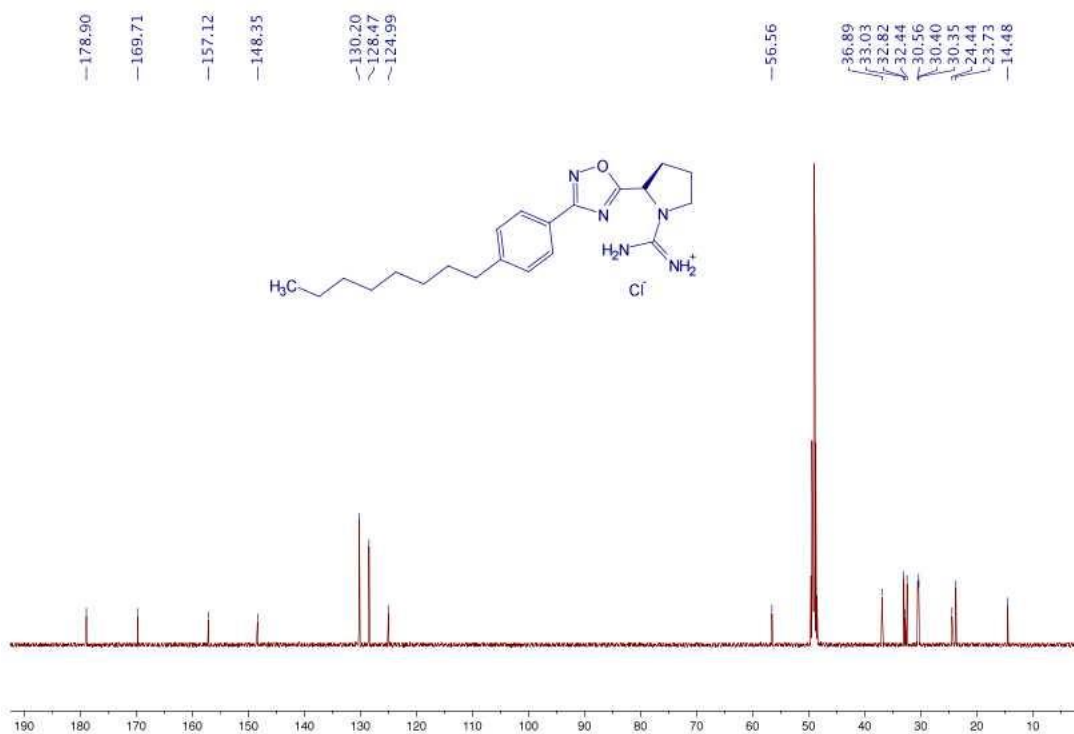
$^{13}\text{C-NMR}$  Spectrum for (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboximidamide hydrochloride **2.7g**–



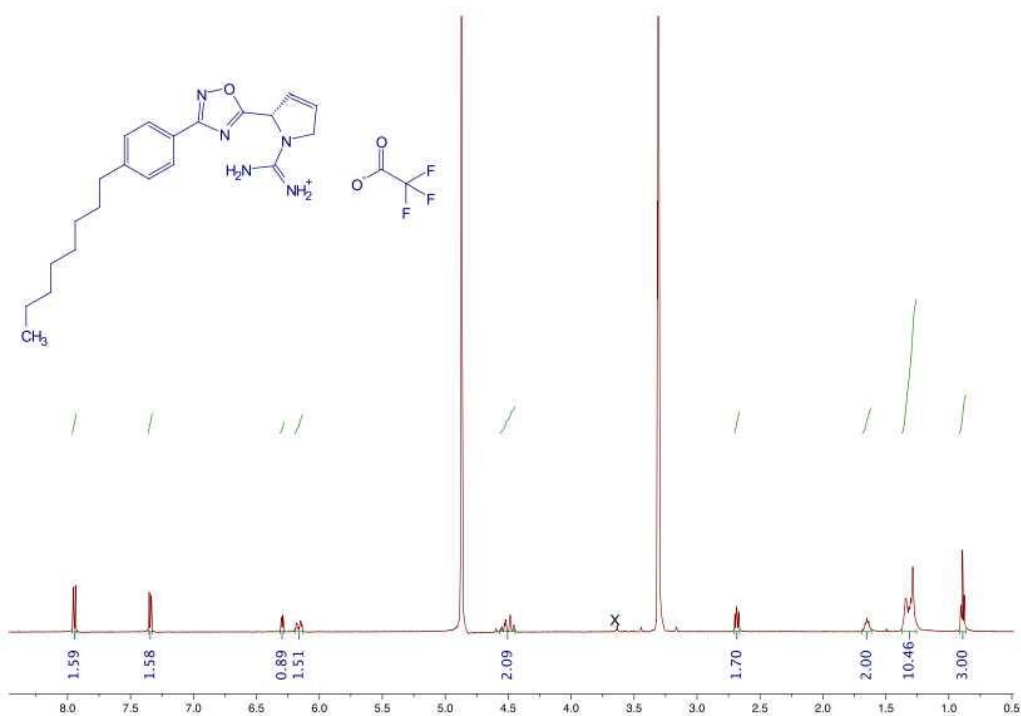
$^1\text{H-NMR}$  Spectrum for (*R*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboximidamide hydrochloride **2.7h** –



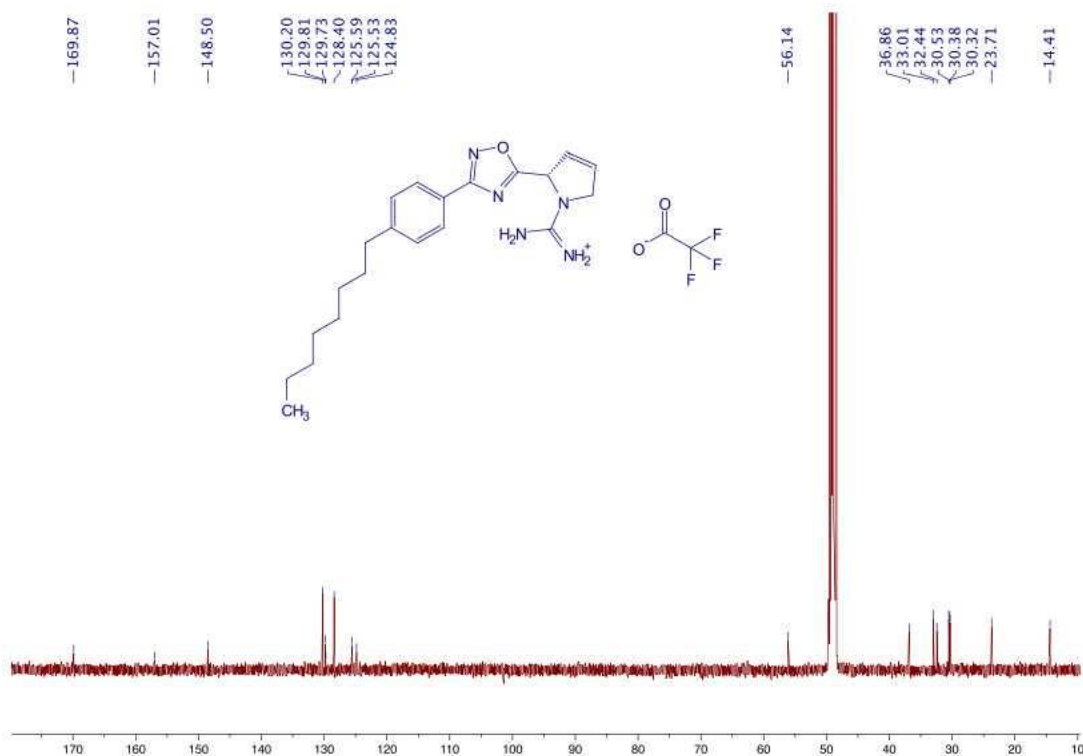
$^{13}\text{C-NMR}$  Spectrum for (*R*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboximidamide hydrochloride **2.7h** –



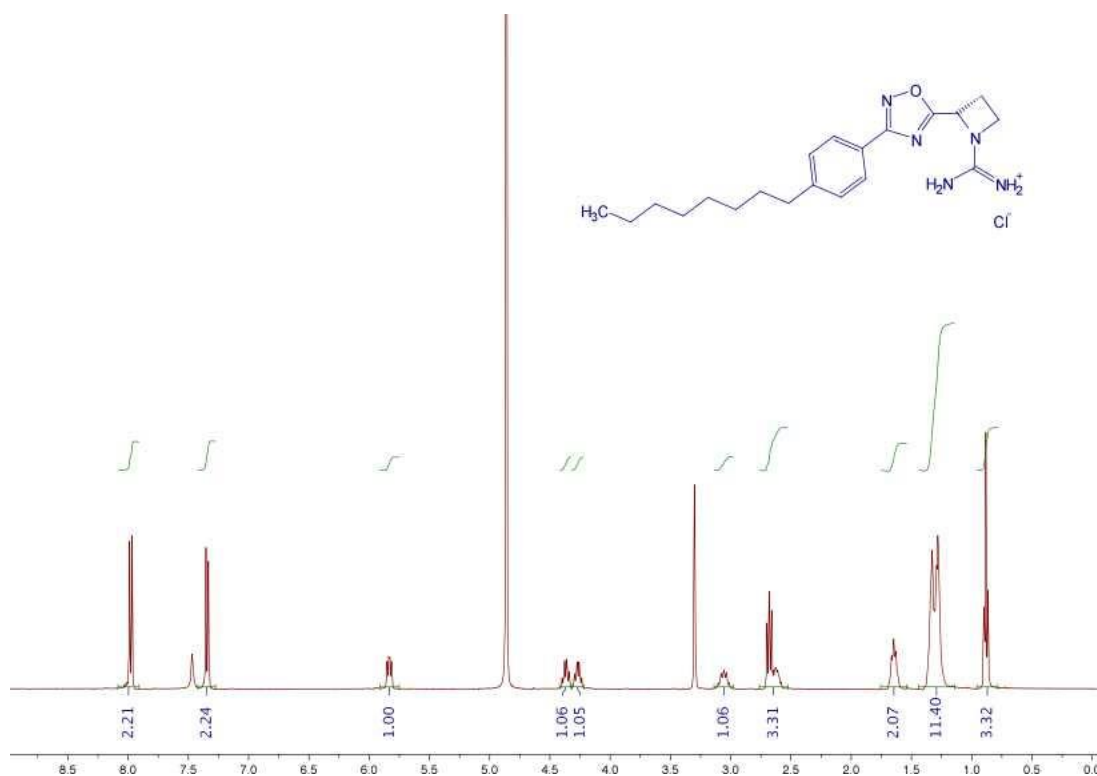
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)-2,5-dihydro-1H-pyrrol-1-yl)methaniminium chloride **2.7i** –



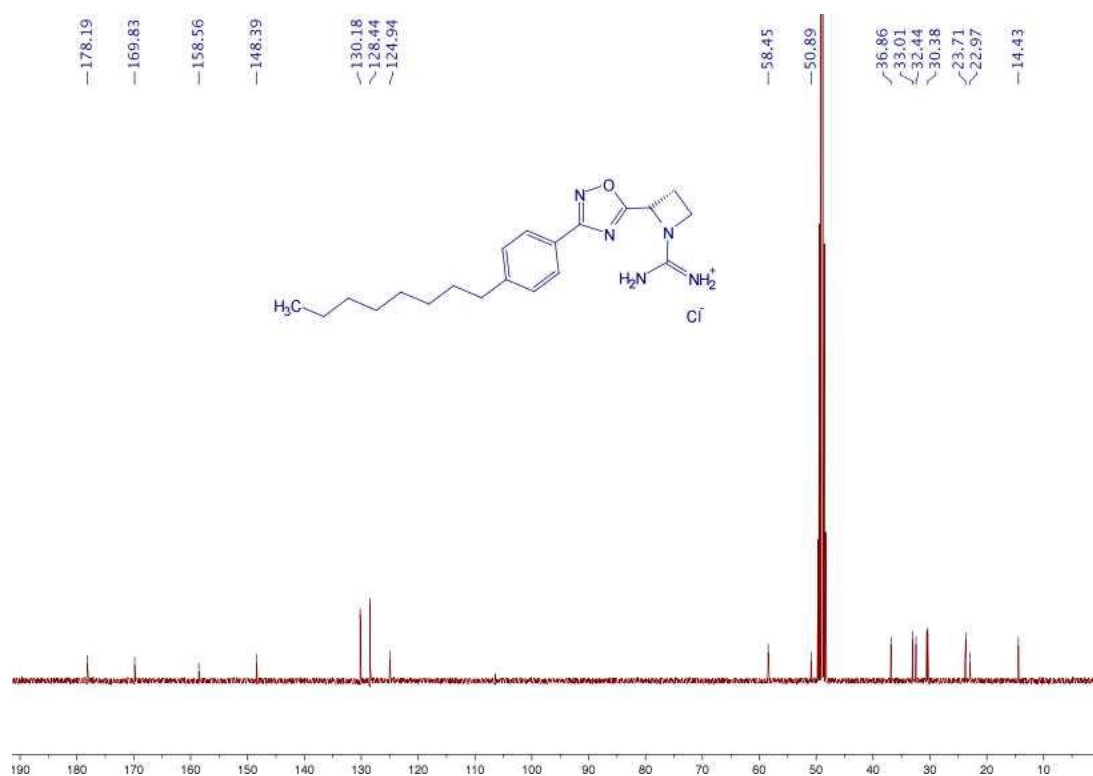
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)-2,5-dihydro-1H-pyrrol-1-yl)methaniminium chloride **2.7i** –



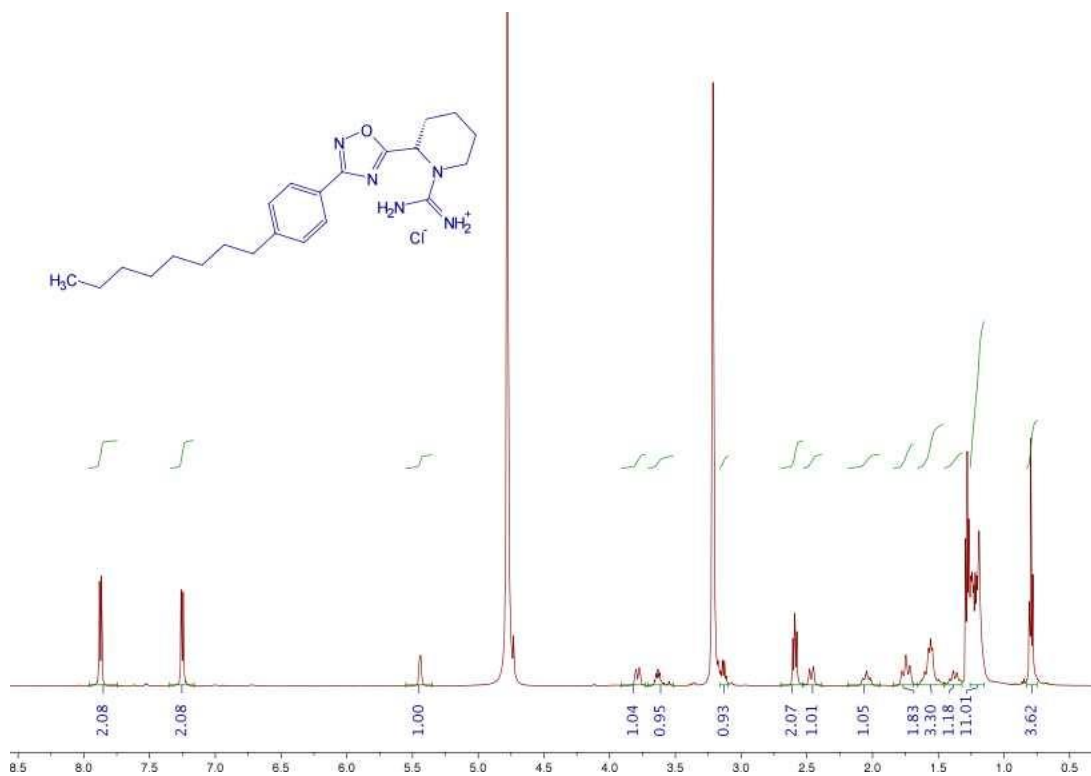
$^1\text{H-NMR}$  Spectrum for (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboximidamide hydrochloride **2.7j** –



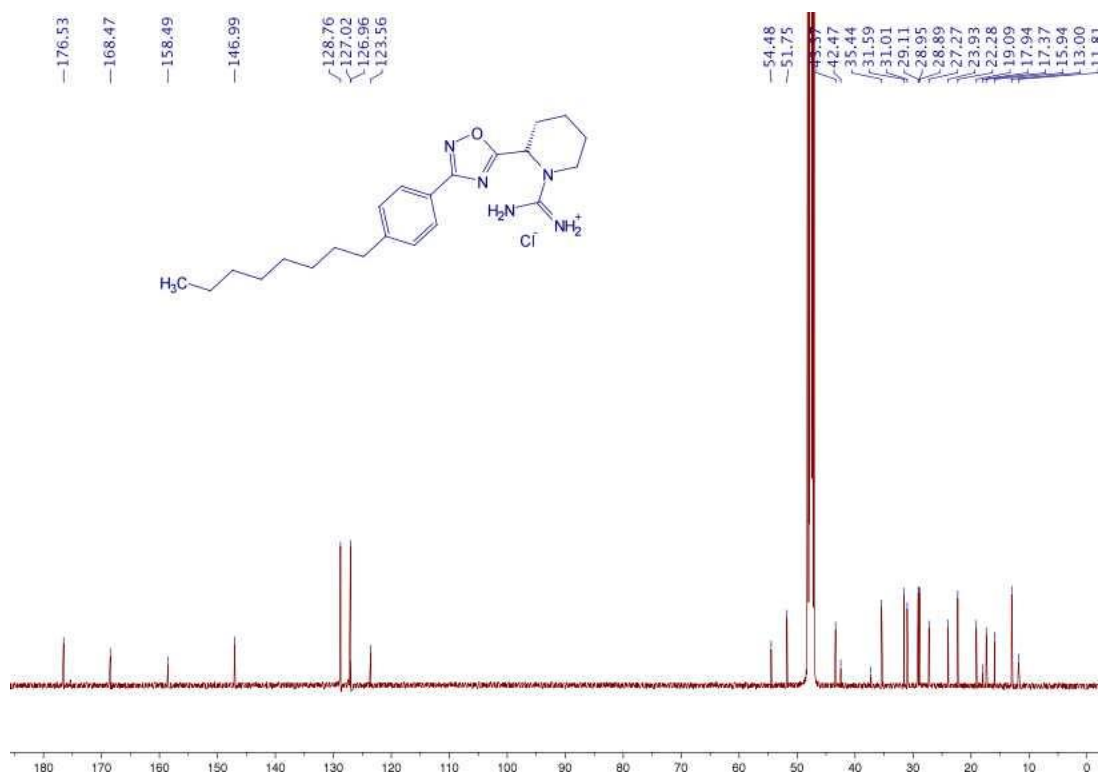
$^{13}\text{C-NMR}$  Spectrum for (*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboximidamide hydrochloride **2.7j** –



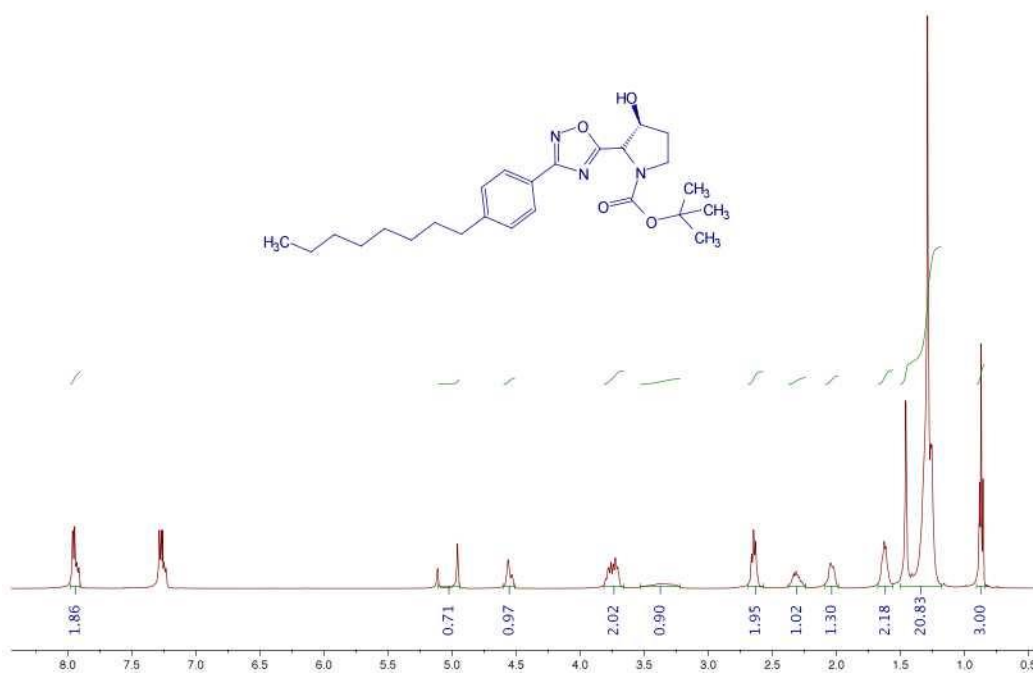
$^1\text{H-NMR}$  Spectrum for (*S*)-amino(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)methaniminium chloride **2.7k** –



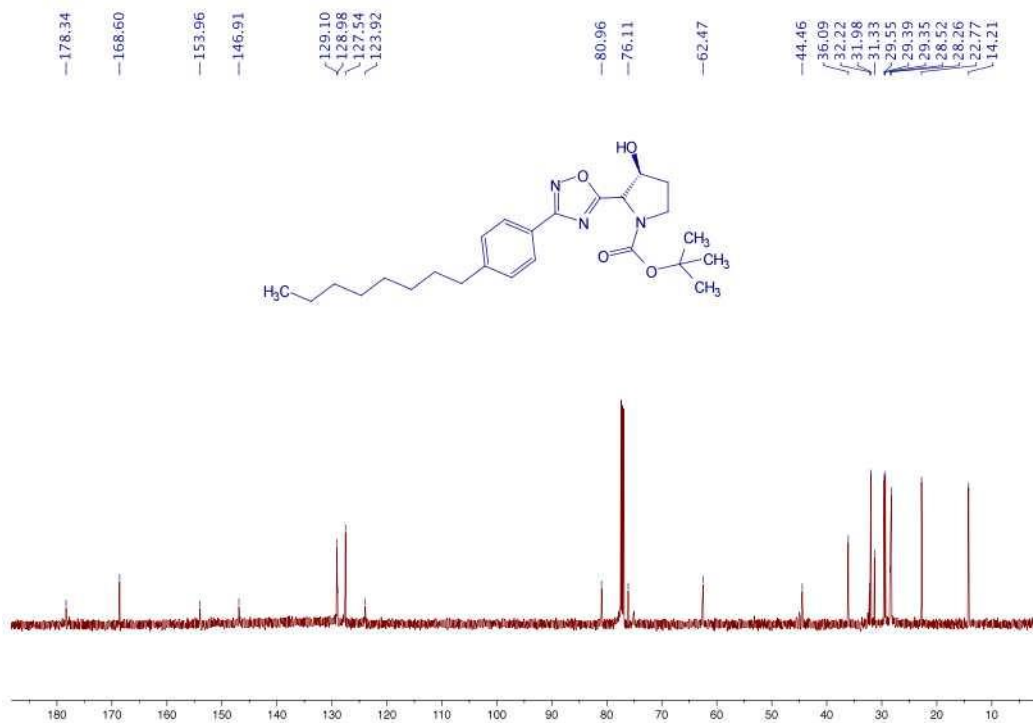
$^{13}\text{C-NMR}$  Spectrum for (*S*)-amino(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)methaniminium chloride **2.7k** –



$^1\text{H-NMR}$  Spectrum for (2*S*,3*S*)-*tert*-butyl-3-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.8** –

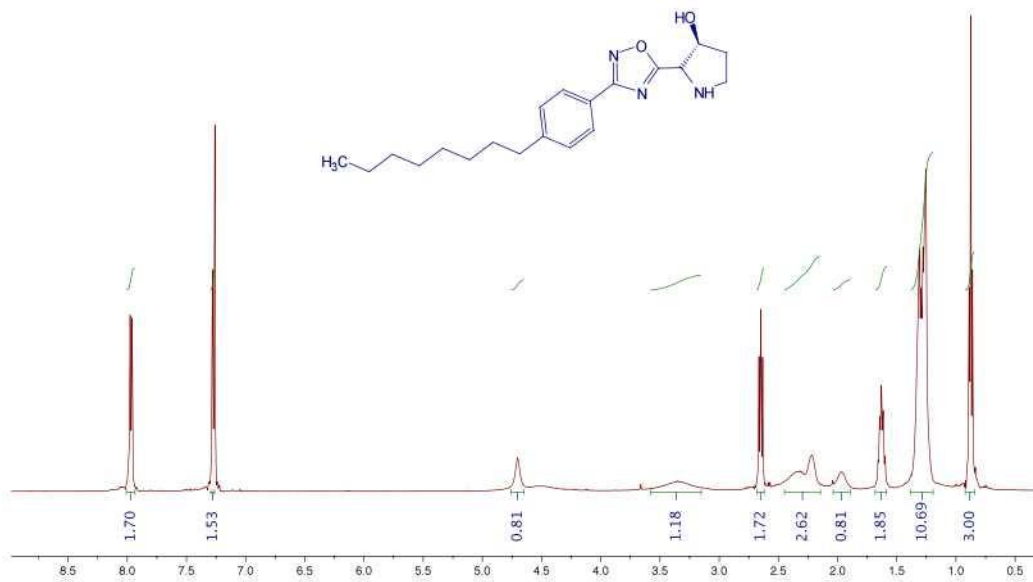


$^{13}\text{C-NMR}$  Spectrum for (2*S*,3*S*)-*tert*-butyl-3-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.8** –

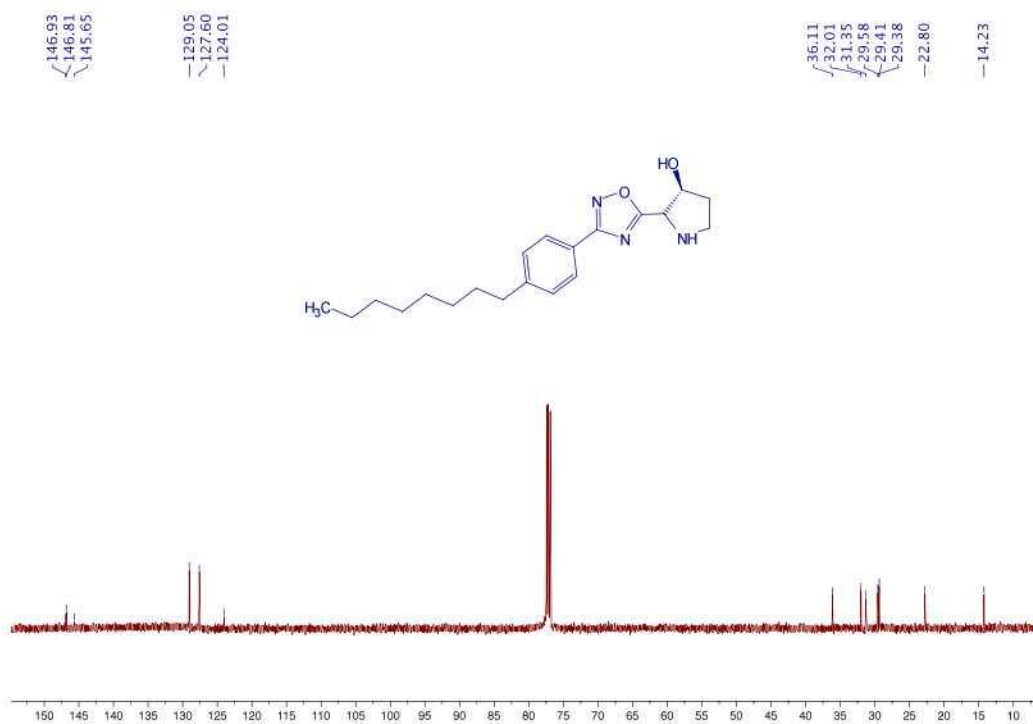




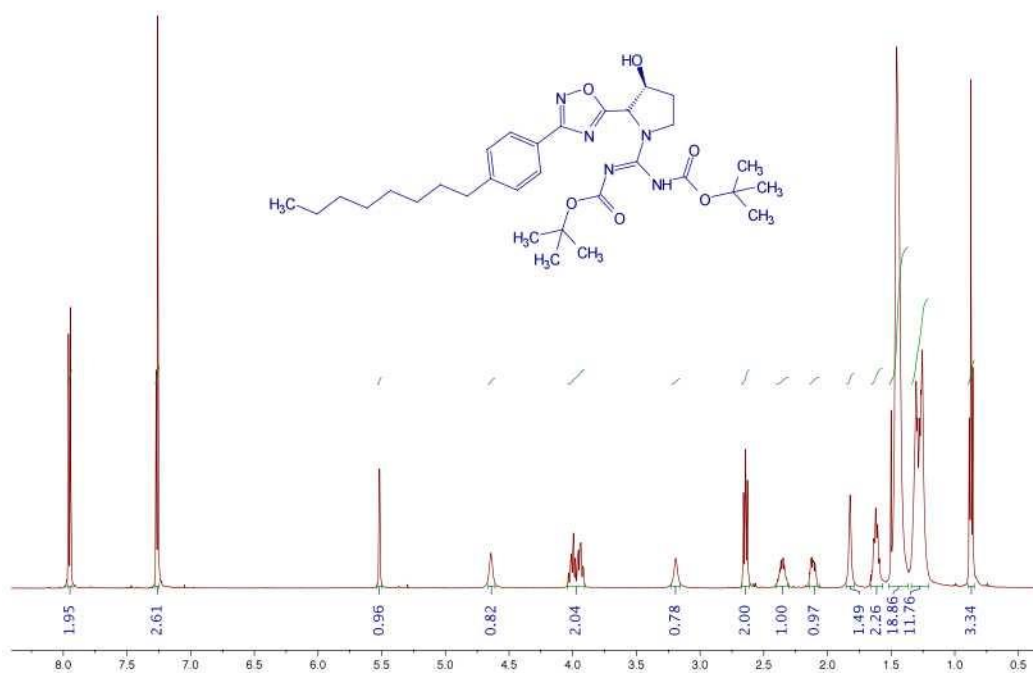
<sup>1</sup>H-NMR Spectrum for (2*S*,3*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-3-ol **2.9** –



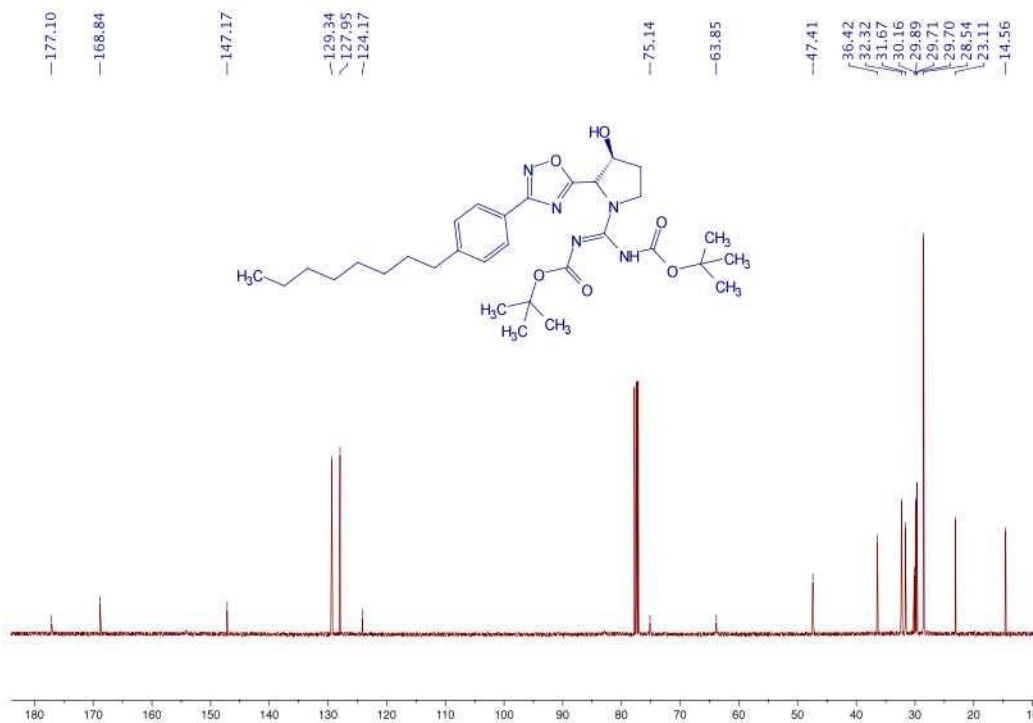
<sup>13</sup>C-NMR Spectrum for (2*S*,3*S*)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-3-ol **2.9** –



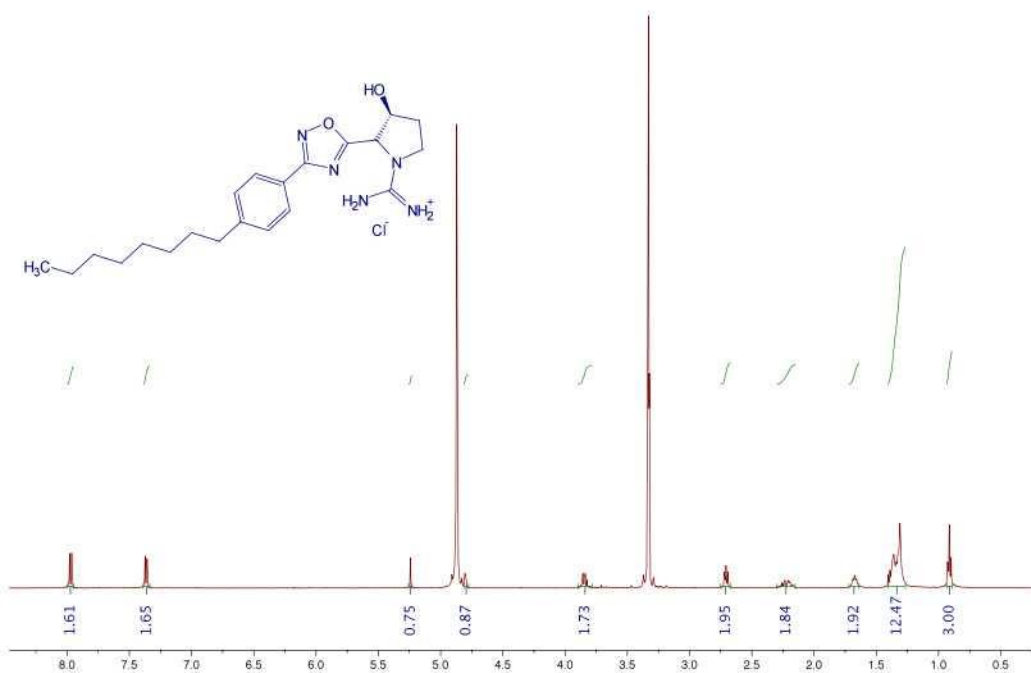
$^1\text{H-NMR}$  Spectrum for (*E*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)((2*S*,3*S*)-3-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **2.10** –



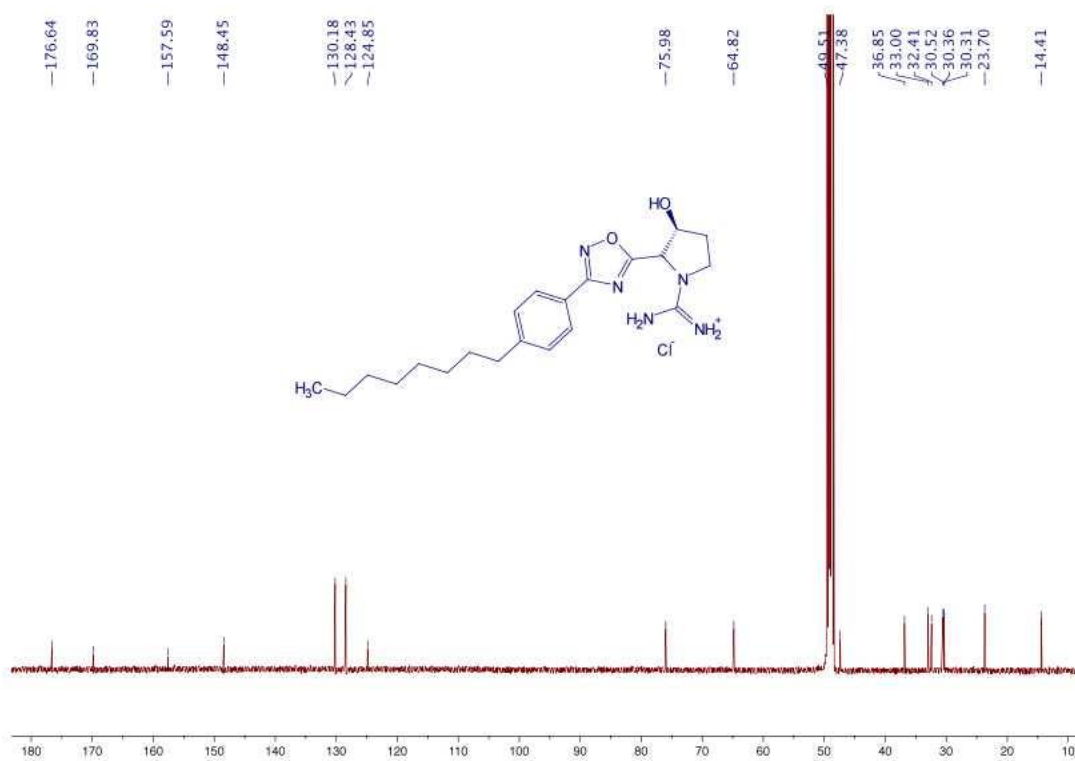
$^{13}\text{C-NMR}$  Spectrum for (*E*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)((2*S*,3*S*)-3-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **2.10** –



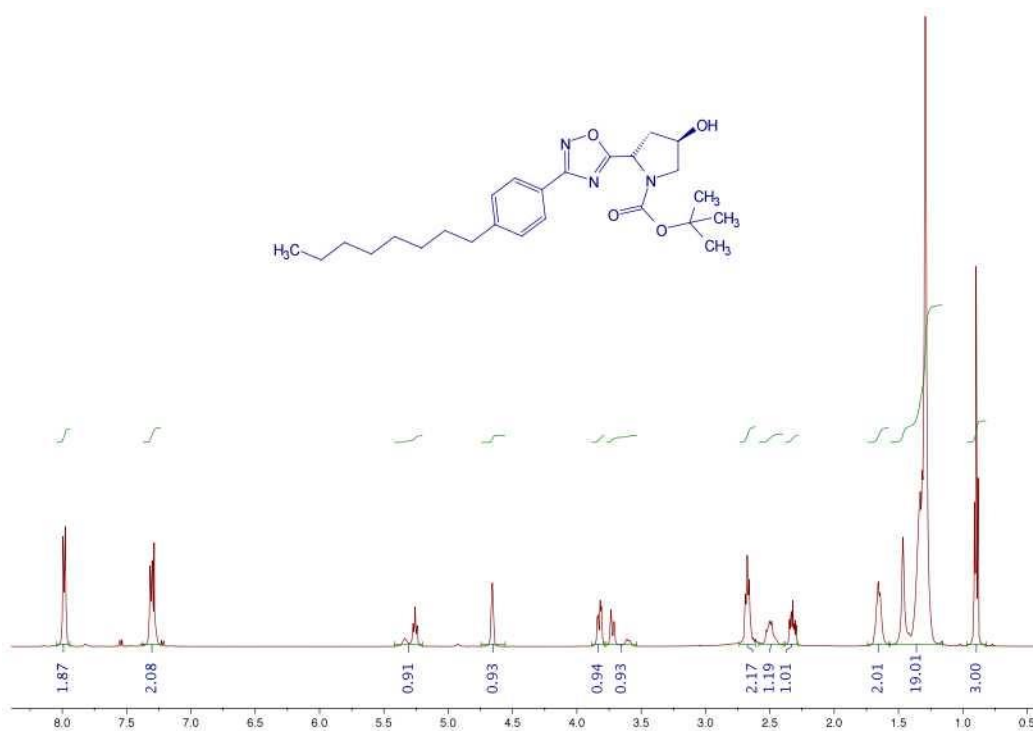
<sup>1</sup>H-NMR Spectrum for amino((1*S*,3*S*)-3-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **2.11** –



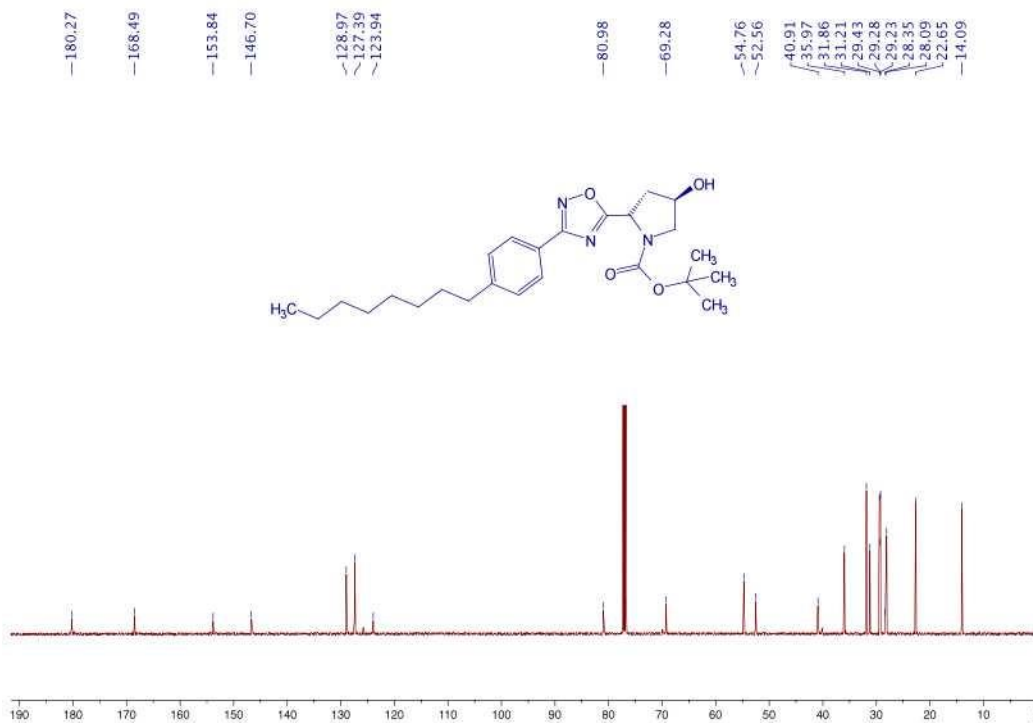
<sup>13</sup>C-NMR Spectrum for amino((1*S*,3*S*)-3-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **2.11** –



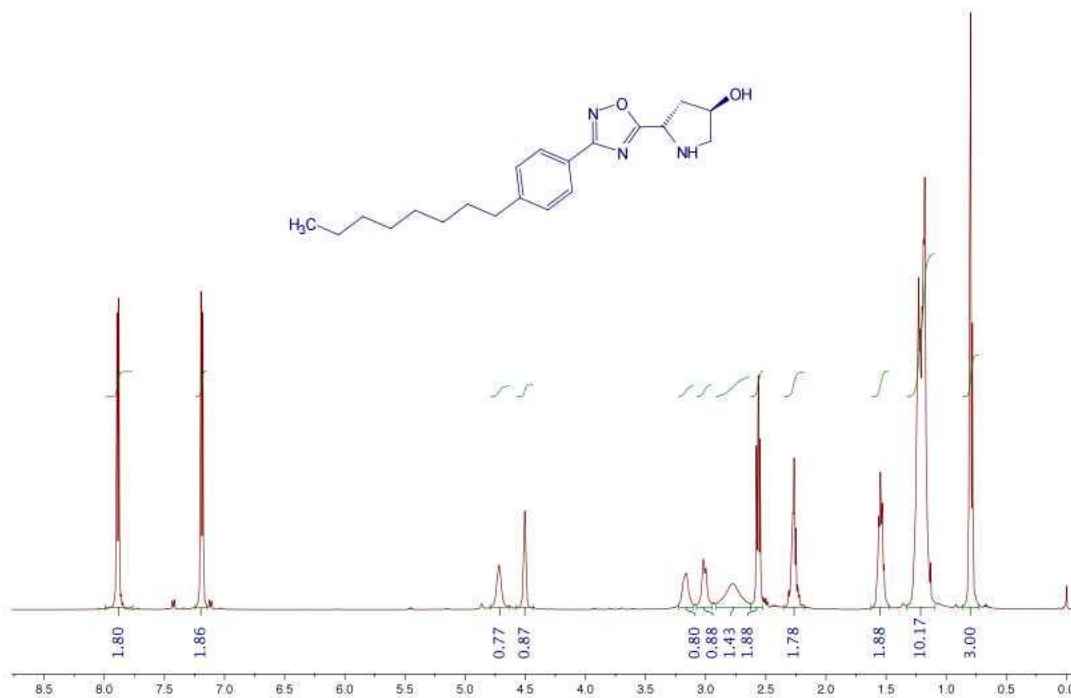
$^1\text{H-NMR}$  Spectrum for (2*S*,4*R*)-*tert*-butyl 4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.12** –



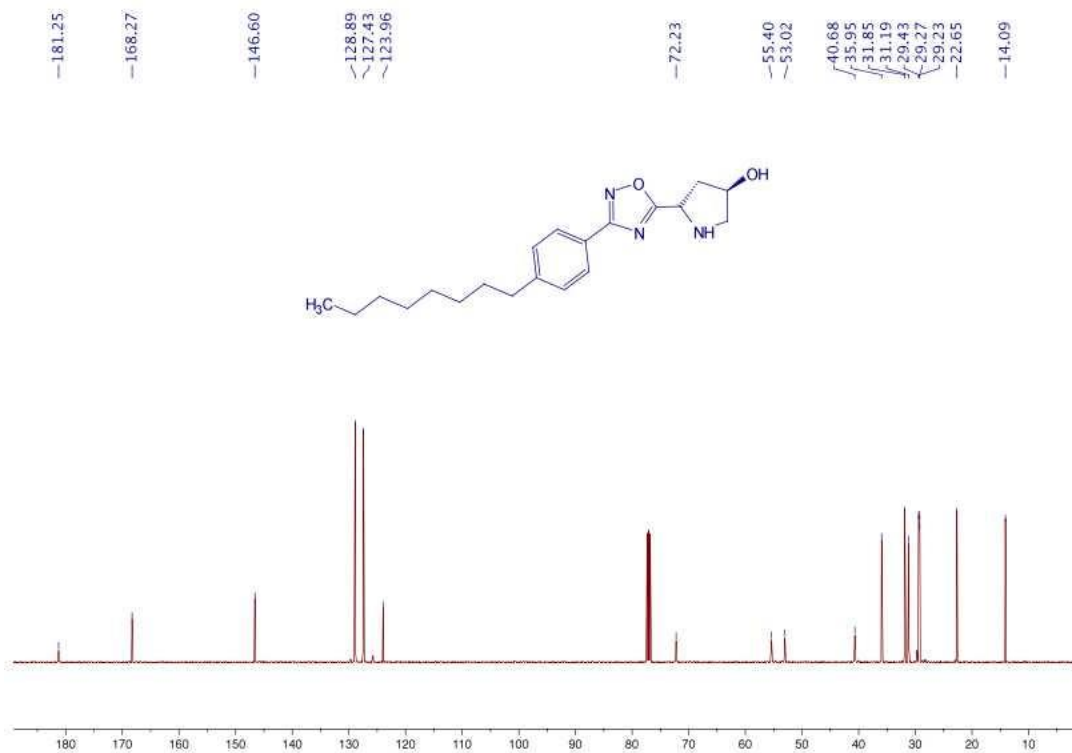
$^{13}\text{C-NMR}$  Spectrum for (2*S*,4*R*)-*tert*-butyl 4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.12** –



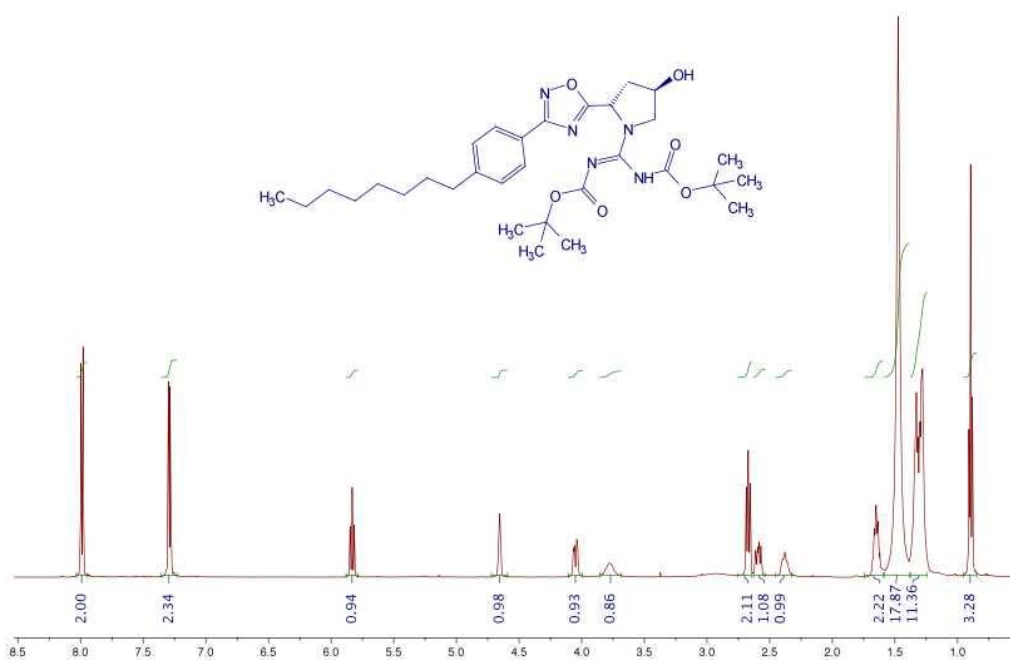
$^1\text{H-NMR}$  Spectrum for (3*R*,5*S*)-5-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-3-ol **2.13** –



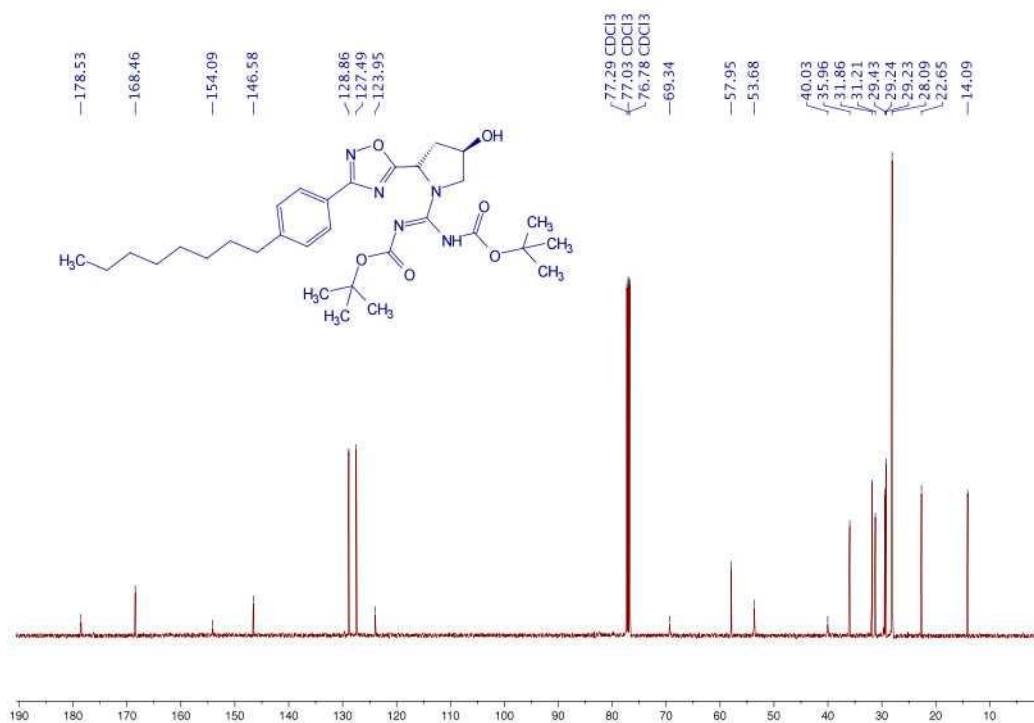
$^{13}\text{C-NMR}$  Spectrum for (3*R*,5*S*)-5-(3-(4-Octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-3-ol **2.13** –



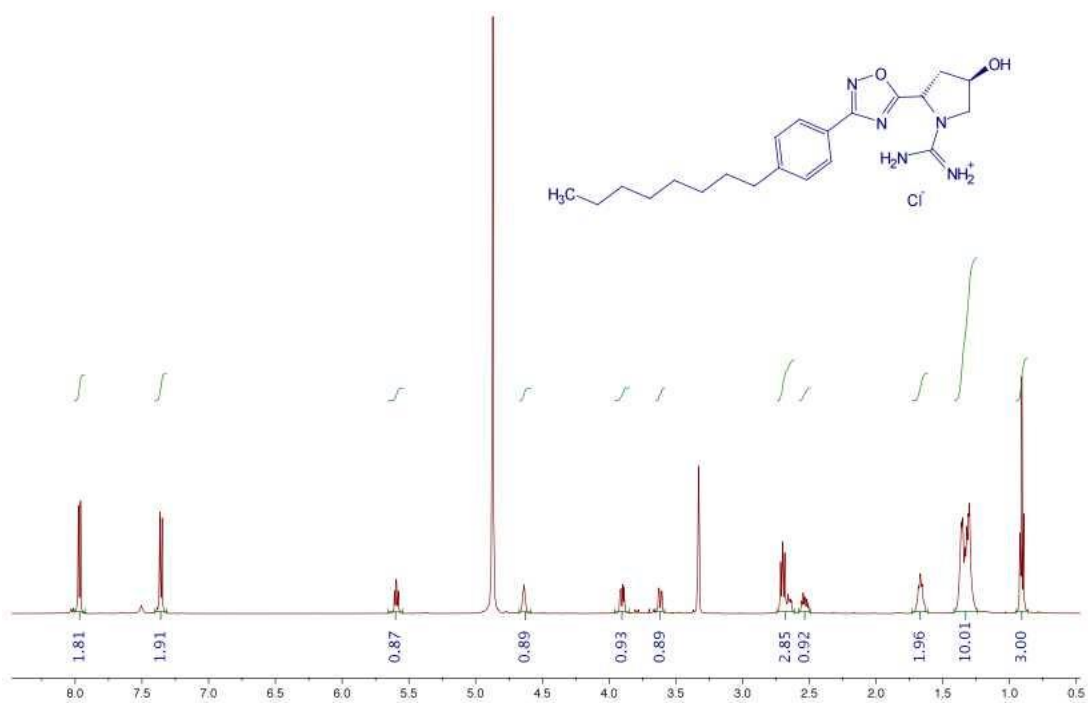
<sup>1</sup>H-NMR Spectrum for Tert-butyl (((tert-butoxycarbonyl)imino)((2*S*,4*R*)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methyl)carbamate **2.14** –



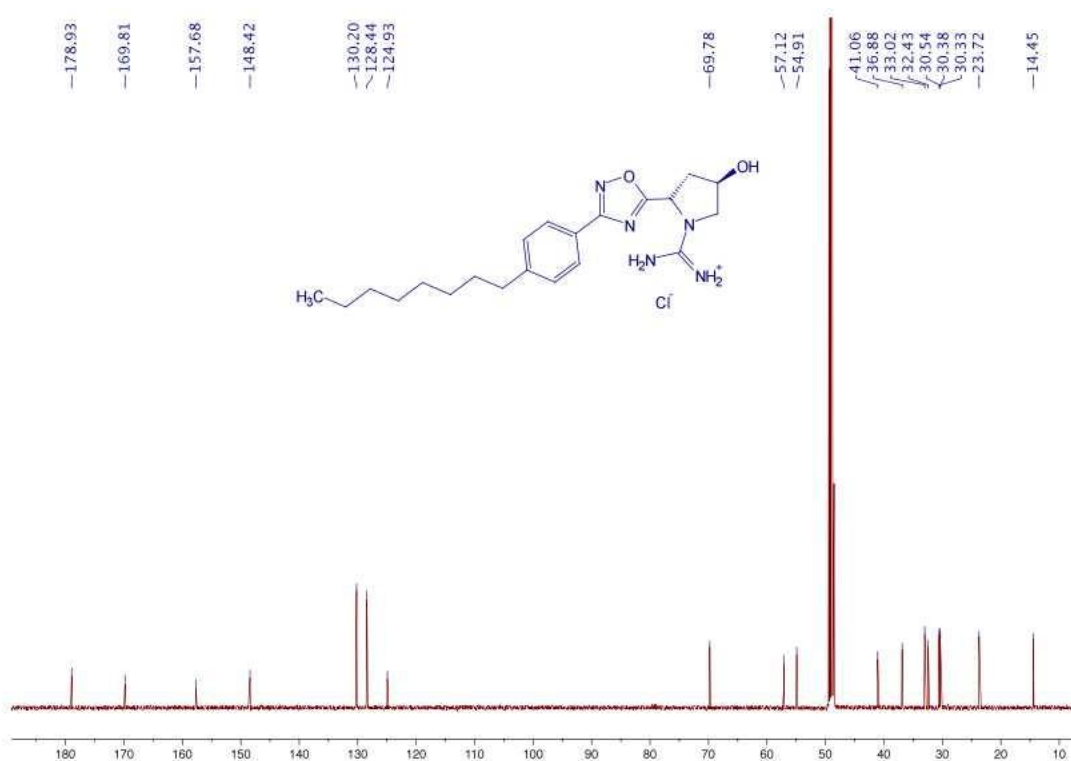
<sup>13</sup>C-NMR Spectrum for Tert-butyl (((tert-butoxycarbonyl)imino)((2*S*,4*R*)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methyl)carbamate **2.14** –



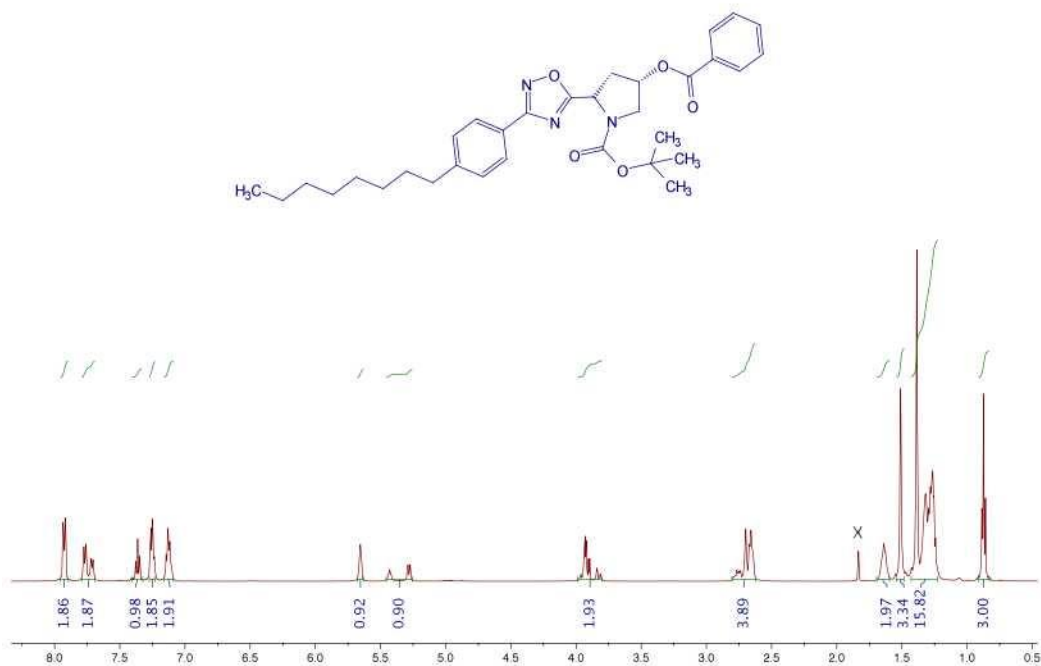
$^1\text{H-NMR}$  Spectrum for amino((2*S*,4*R*)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl) methaniminium chloride **2.15** –



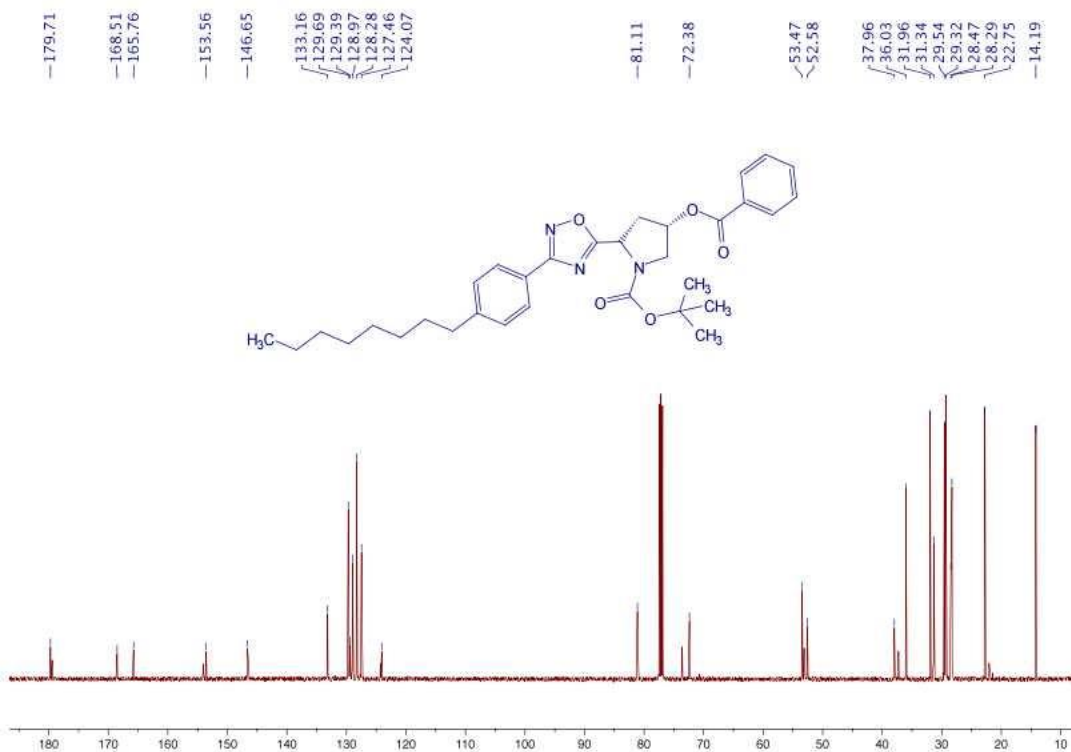
$^{13}\text{C-NMR}$  Spectrum for amino((2*S*,4*R*)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl) methaniminium chloride **2.15** –



$^1\text{H-NMR}$  Spectrum for (2*S*,4*S*)-*tert*-butyl 4-(benzoyloxy)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.16** –

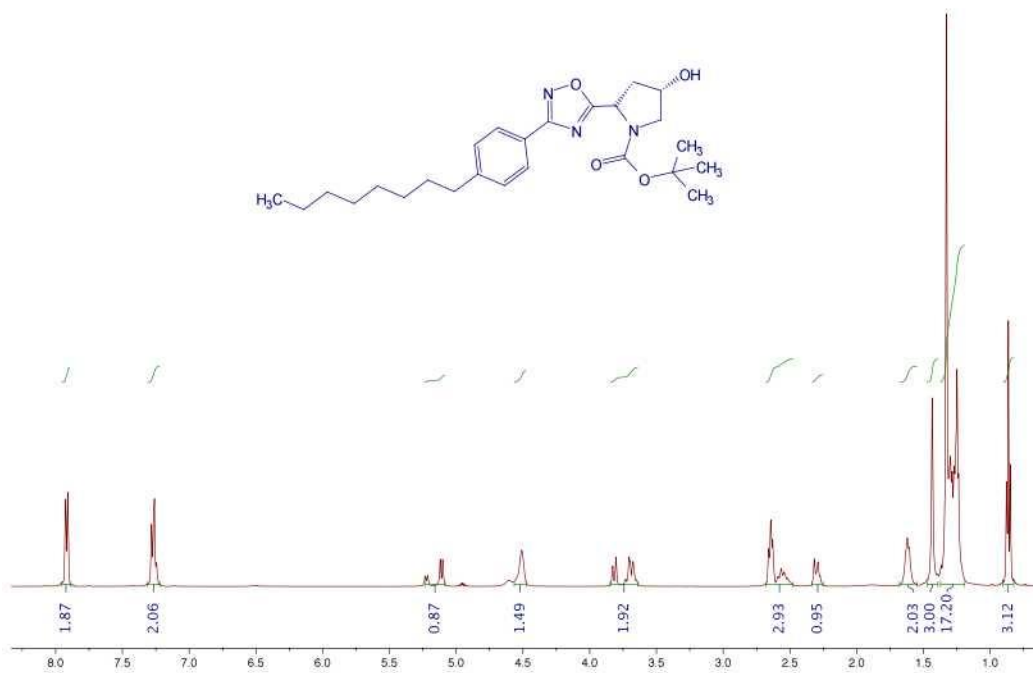


$^{13}\text{C-NMR}$  Spectrum for (2*S*,4*S*)-*tert*-butyl 4-(benzoyloxy)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.16** –

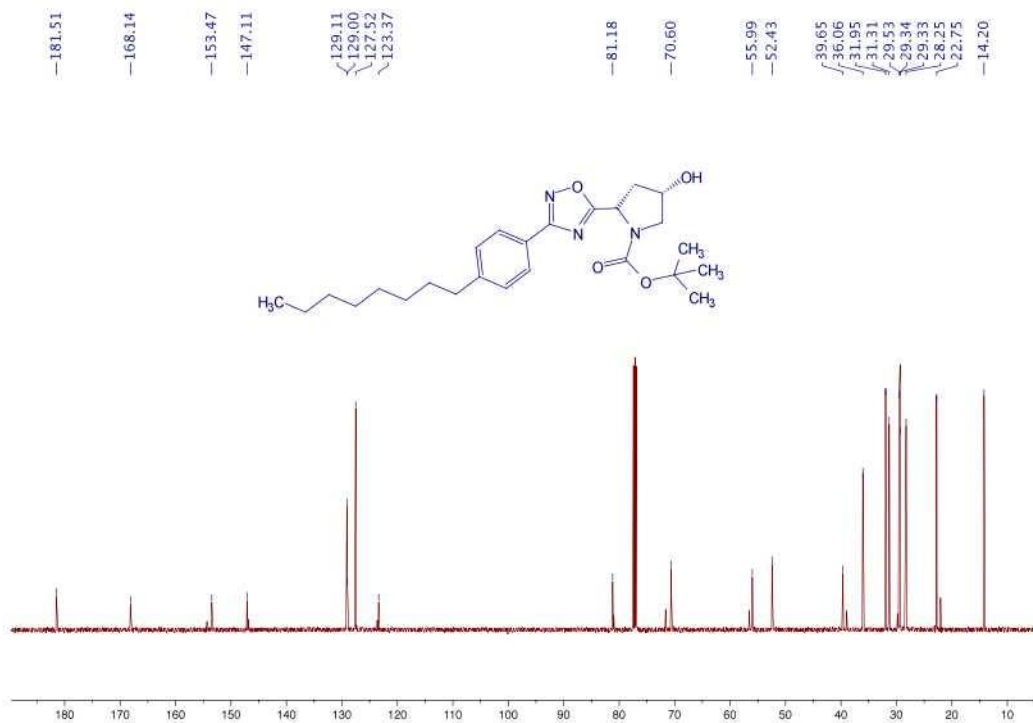




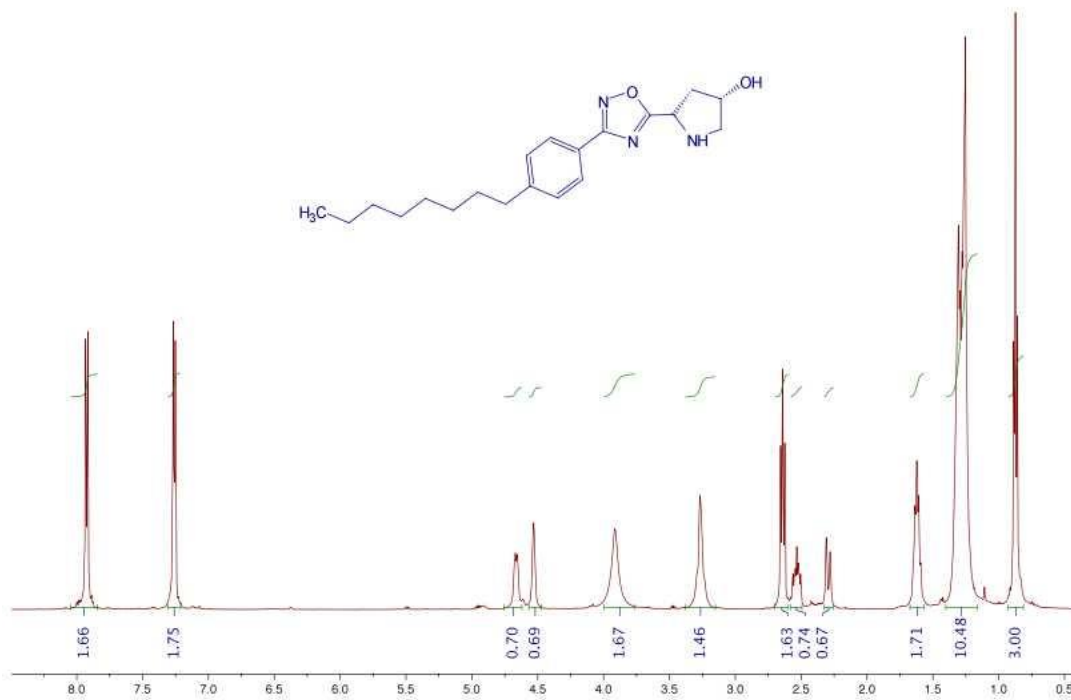
$^1\text{H-NMR}$  Spectrum for (2*S*,4*S*)-*tert*-butyl-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



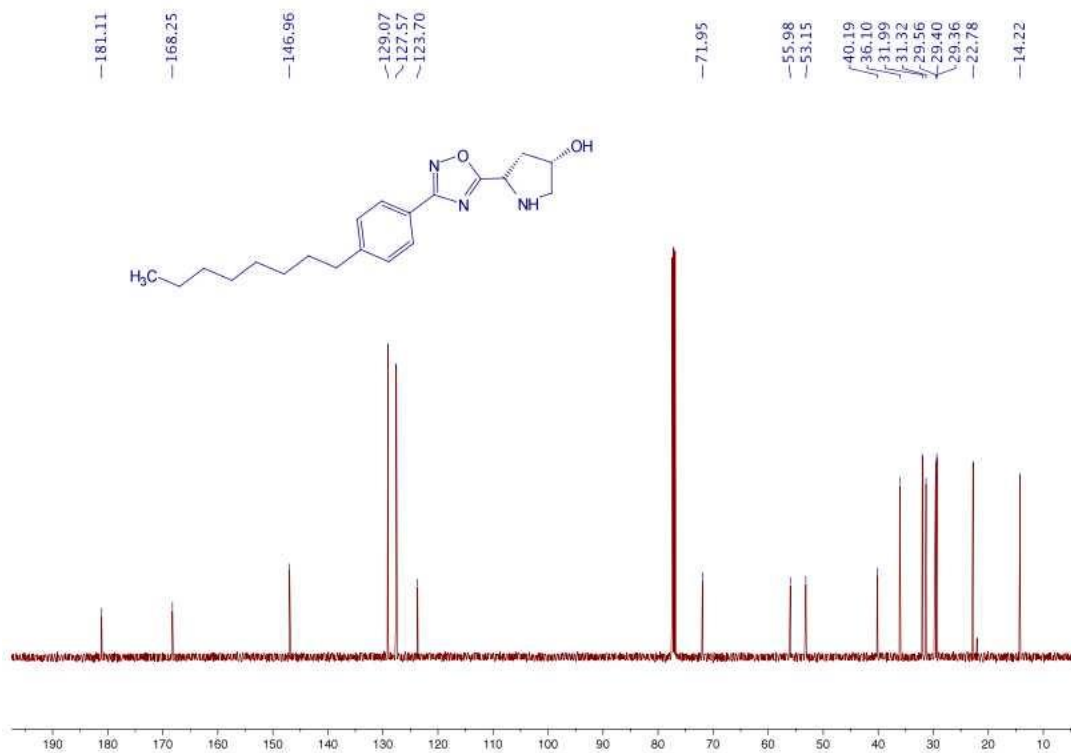
$^{13}\text{C-NMR}$  Spectrum for (2*S*,4*S*)-*tert*-butyl-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



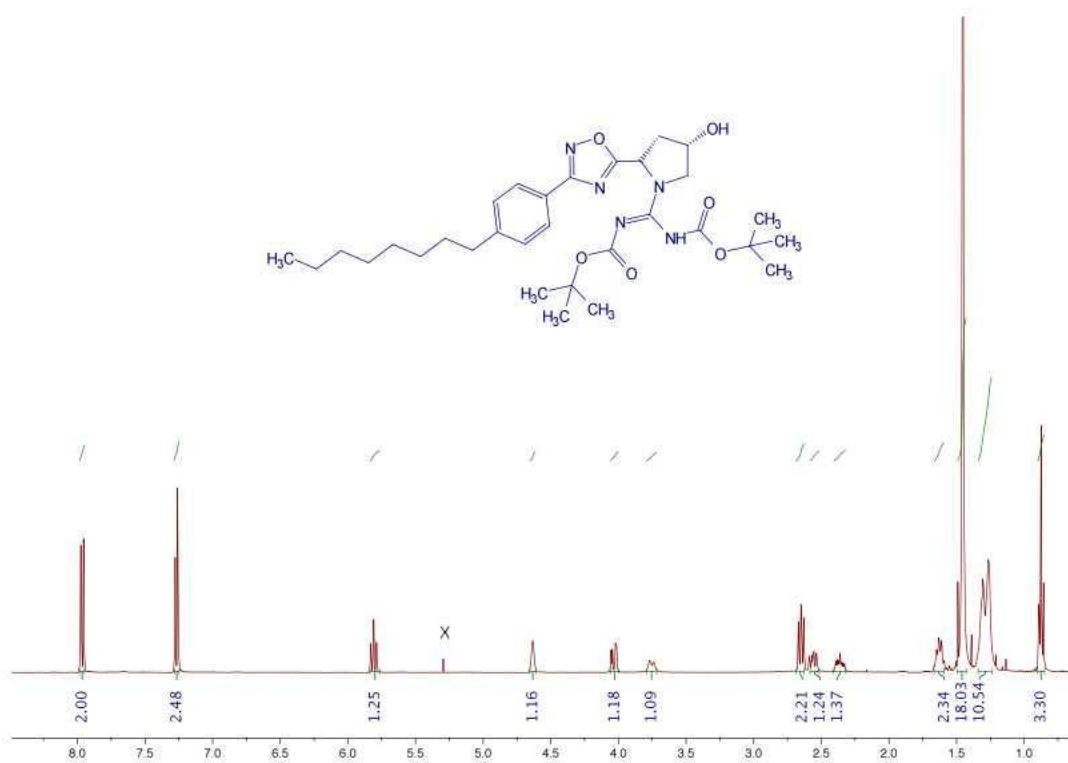
<sup>1</sup>H-NMR Spectrum for (2S,4S)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-4-ol-



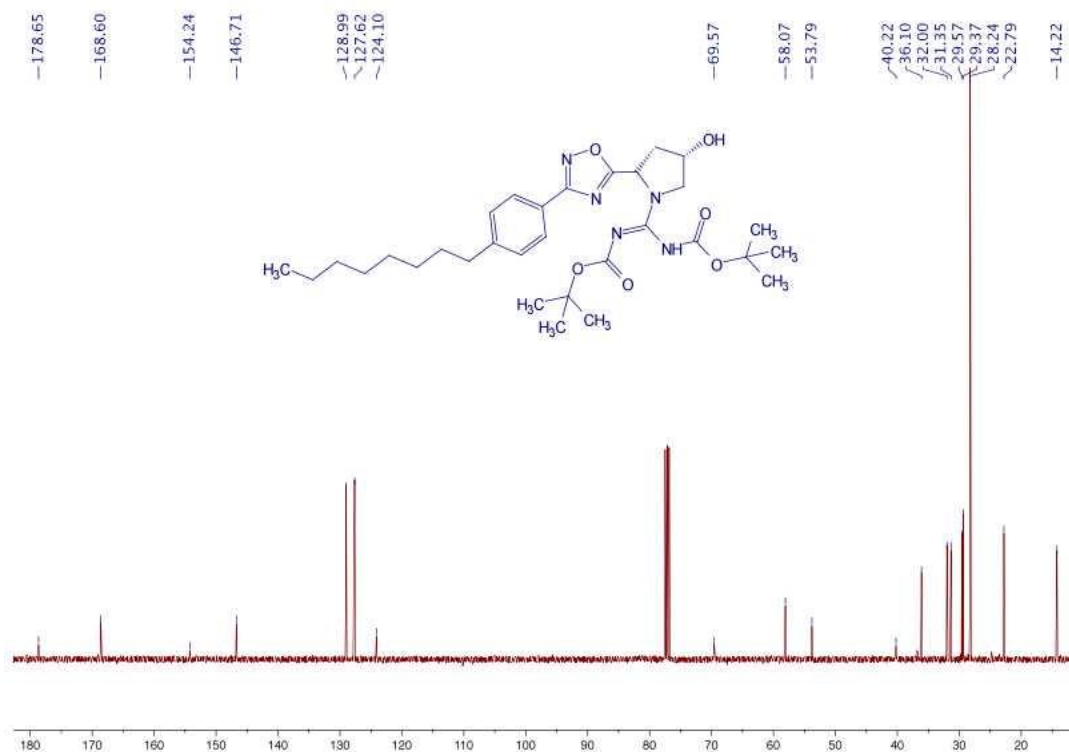
<sup>13</sup>C-NMR Spectrum for (2S,4S)-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-4-ol -



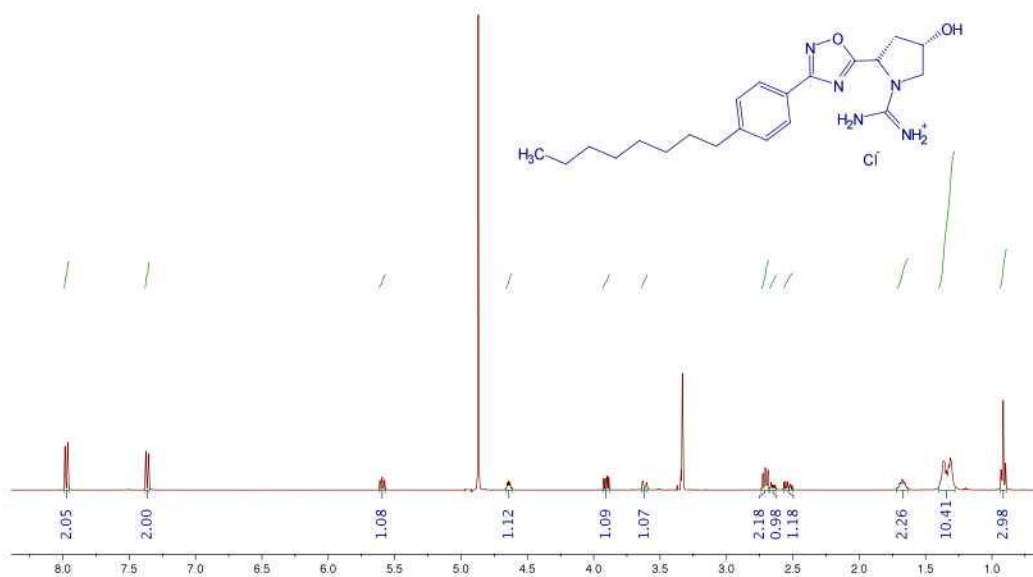
$^1\text{H-NMR}$  Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)((2*S*,4*S*)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



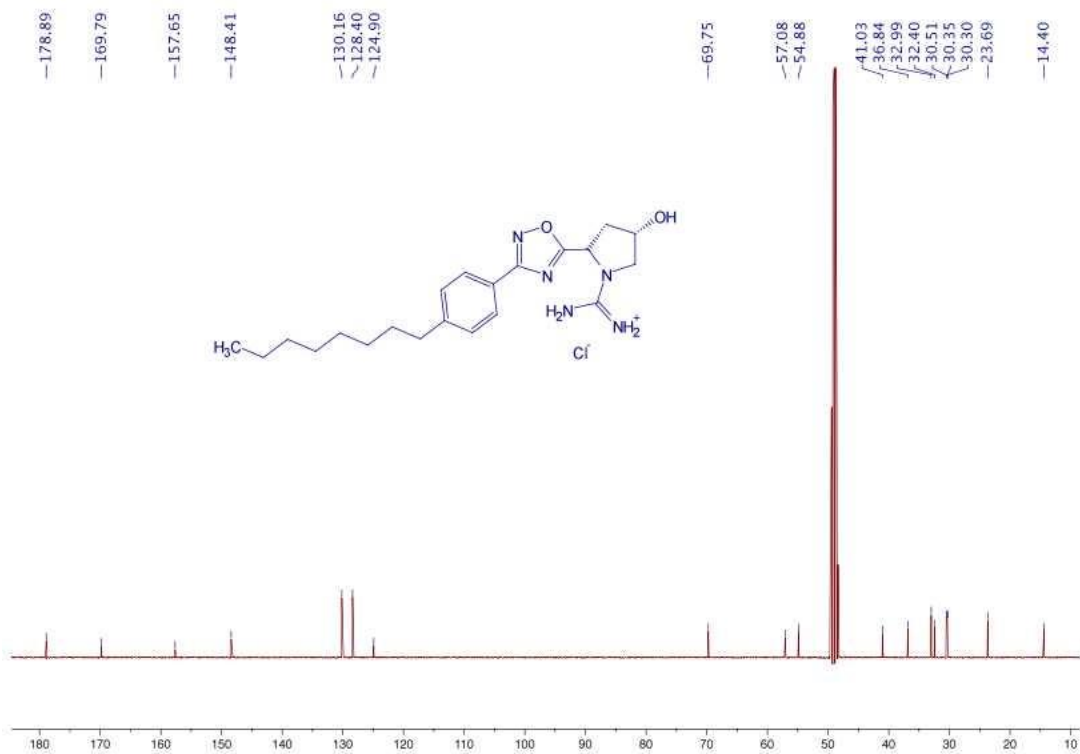
$^{13}\text{C-NMR}$  Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)((2*S*,4*S*)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



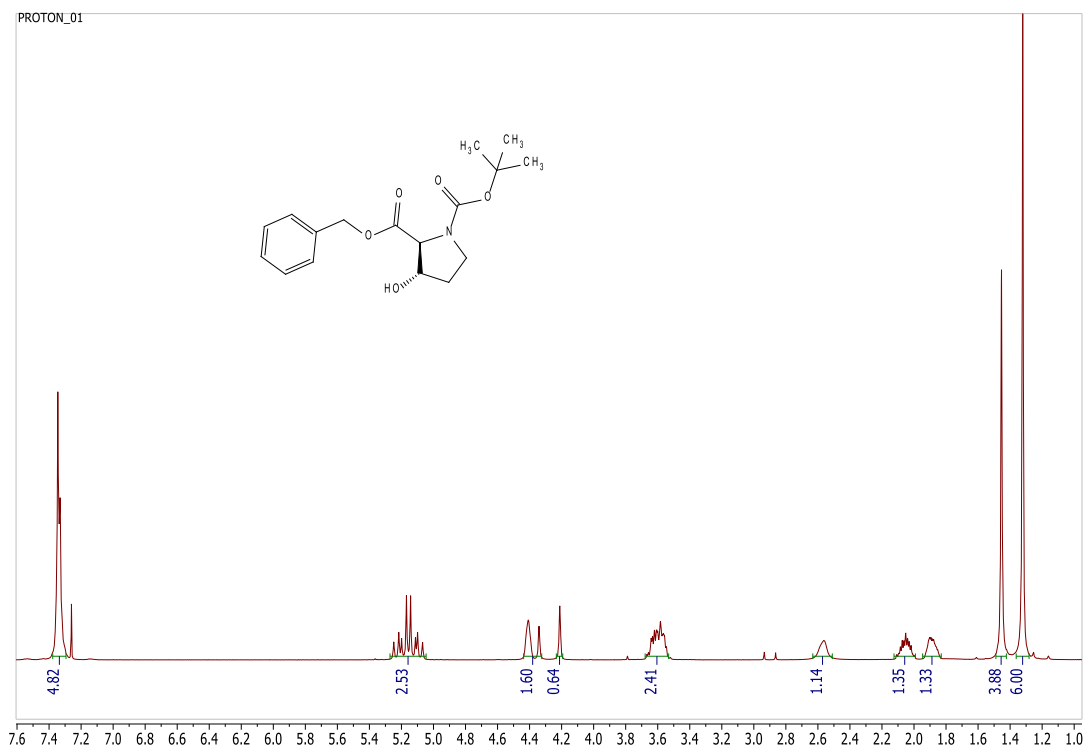
<sup>1</sup>H-NMR Spectrum for amino((1*S*,4*S*)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **2.17** –



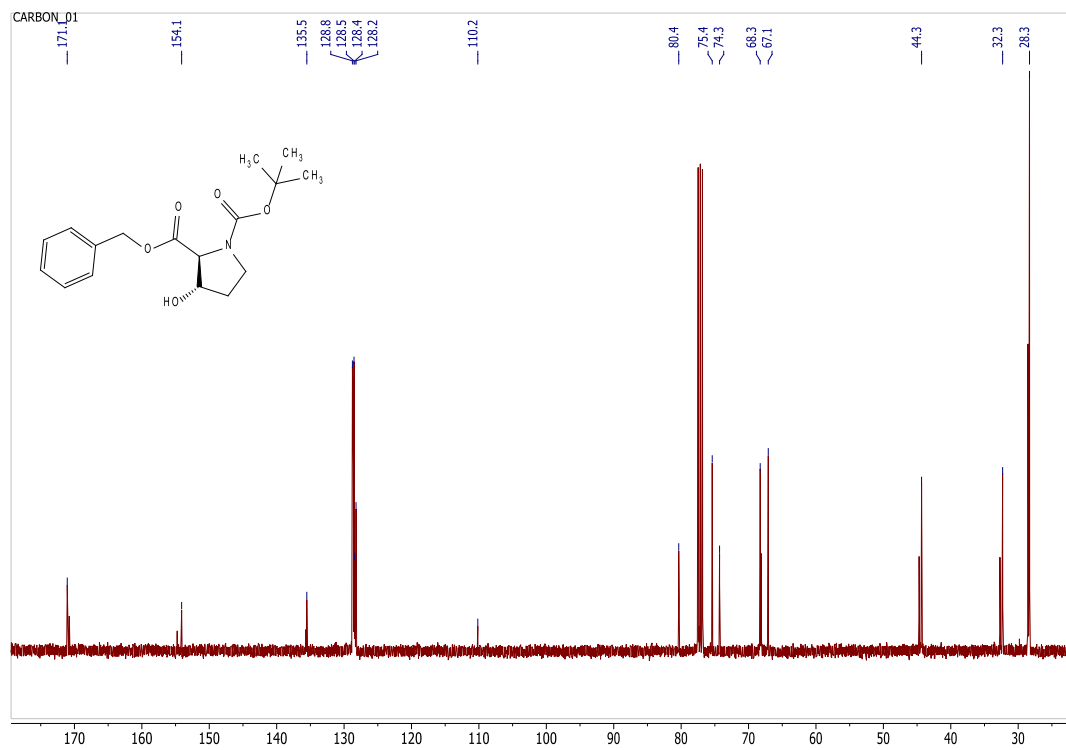
<sup>13</sup>C-NMR Spectrum for amino((1*S*,4*S*)-4-hydroxy-2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **2.17** –



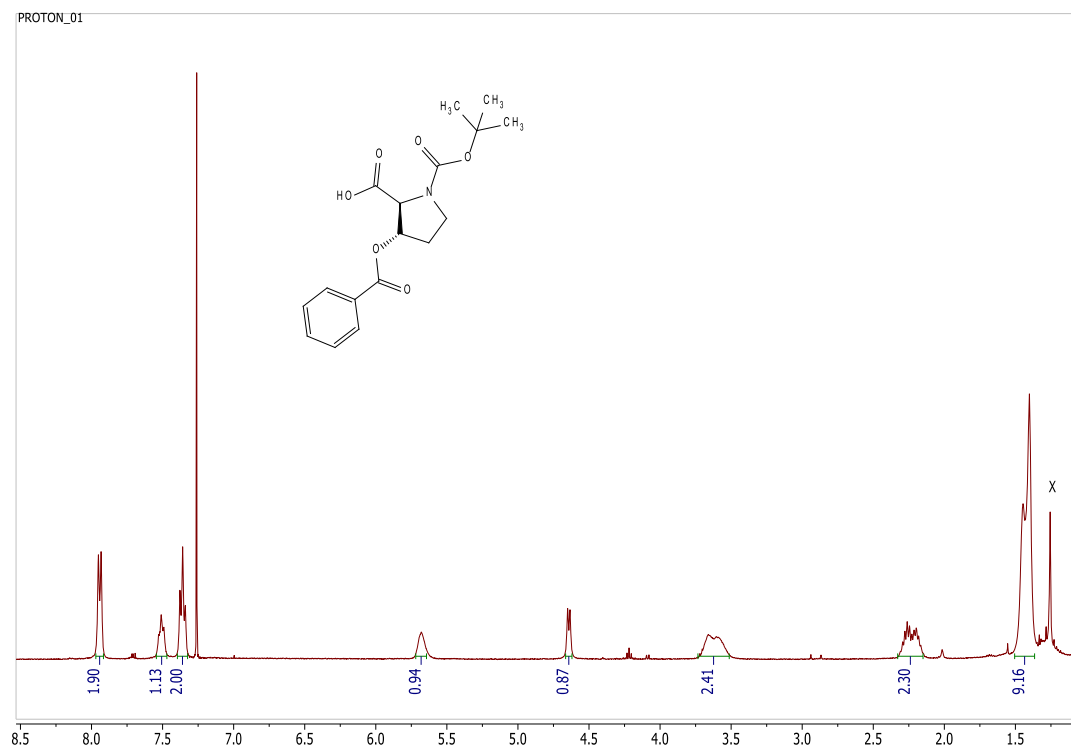
<sup>1</sup>H-NMR Spectrum for (2*S*,3*S*)-2-benzyl 1-*tert*-butyl 3-hydroxypyrrolidine-1,2-dicarboxylate **2.20**



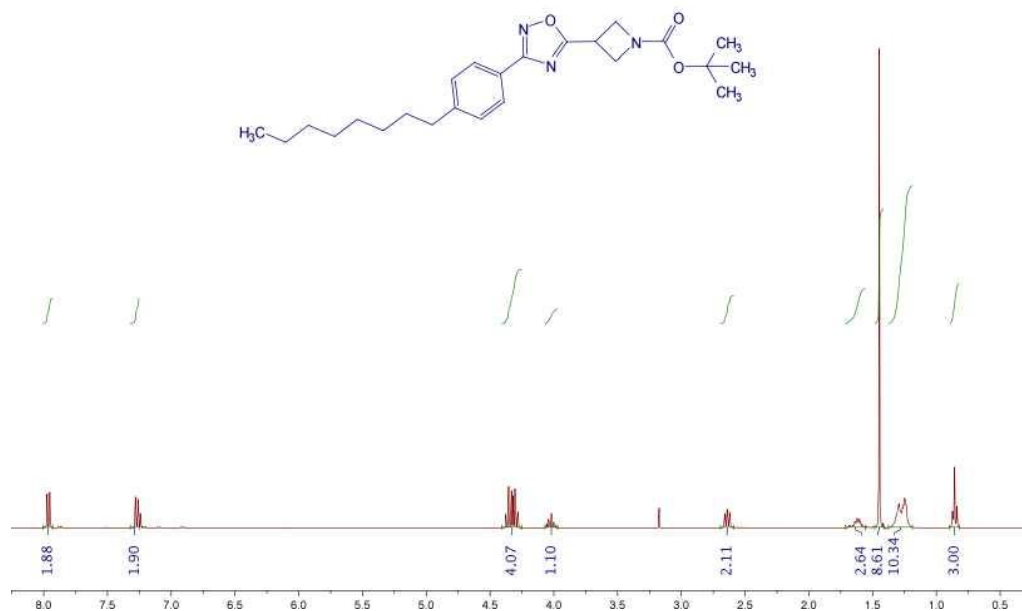
<sup>13</sup>C-NMR Spectrum for (2*S*,3*S*)-2-benzyl 1-*tert*-butyl 3-hydroxypyrrolidine-1,2-dicarboxylate **2.20**



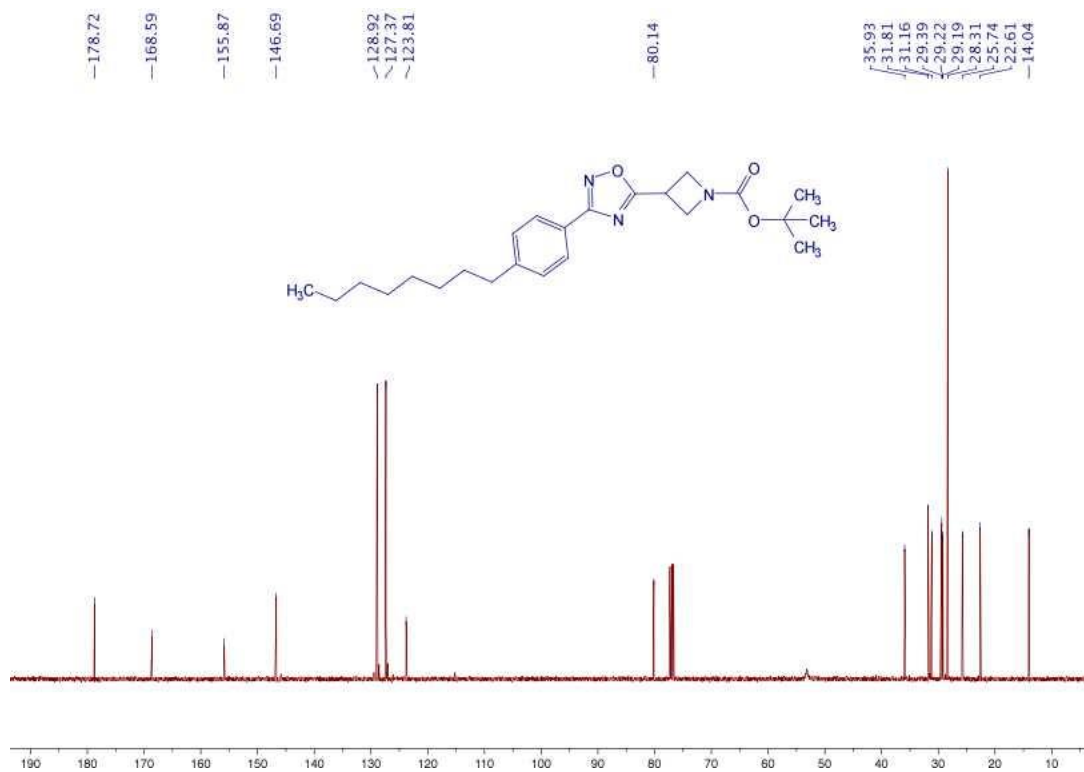
<sup>1</sup>H-NMR Spectrum for (2*S*,3*S*)-3-(benzyloxy)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid **2.21** –



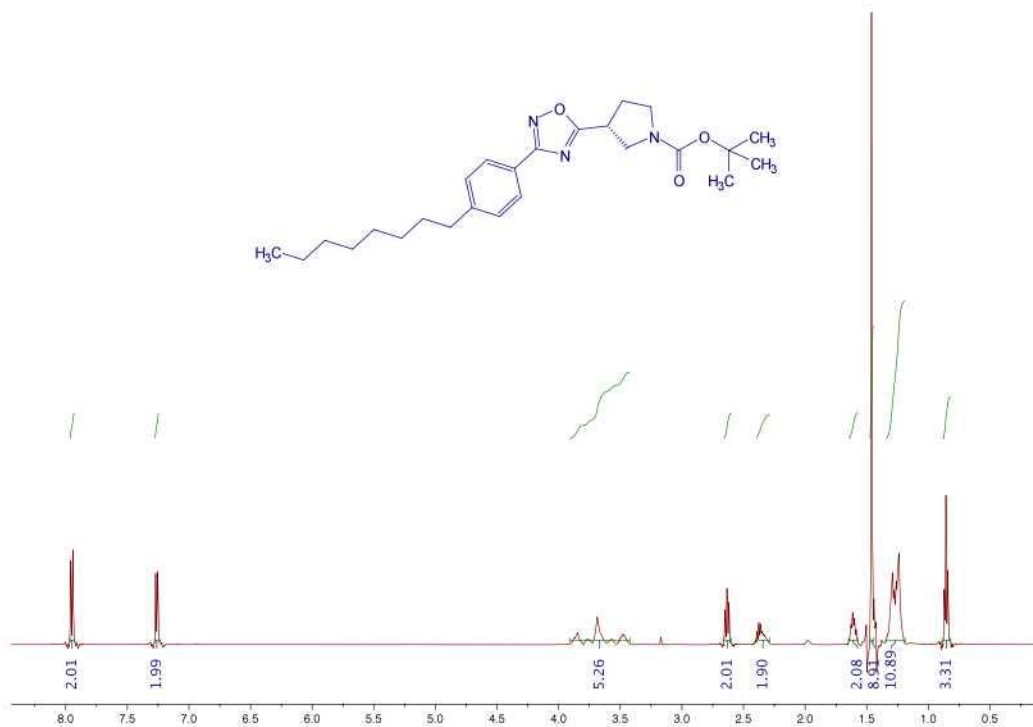
<sup>1</sup>H-NMR Spectrum for *tert*-butyl 3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate **2.24a** –



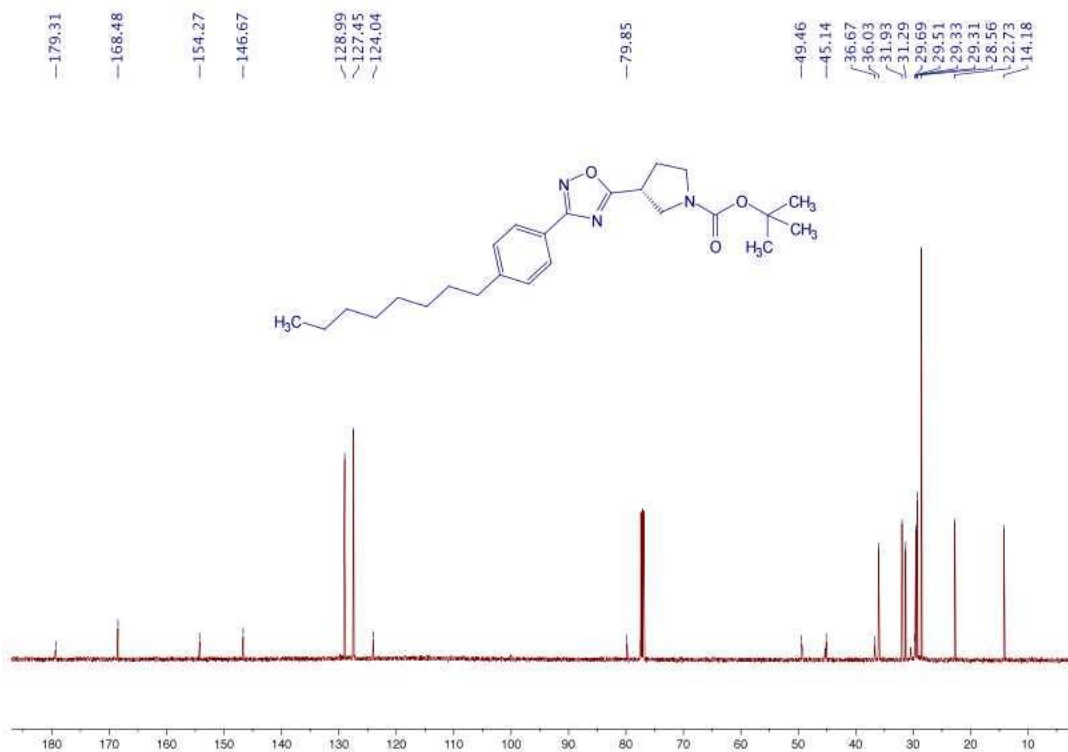
<sup>13</sup>C-NMR Spectrum for *tert*-butyl 3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate **2.24a** –



$^1\text{H-NMR}$  Spectrum for (*R*)-*tert*-butyl 3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.24b**–

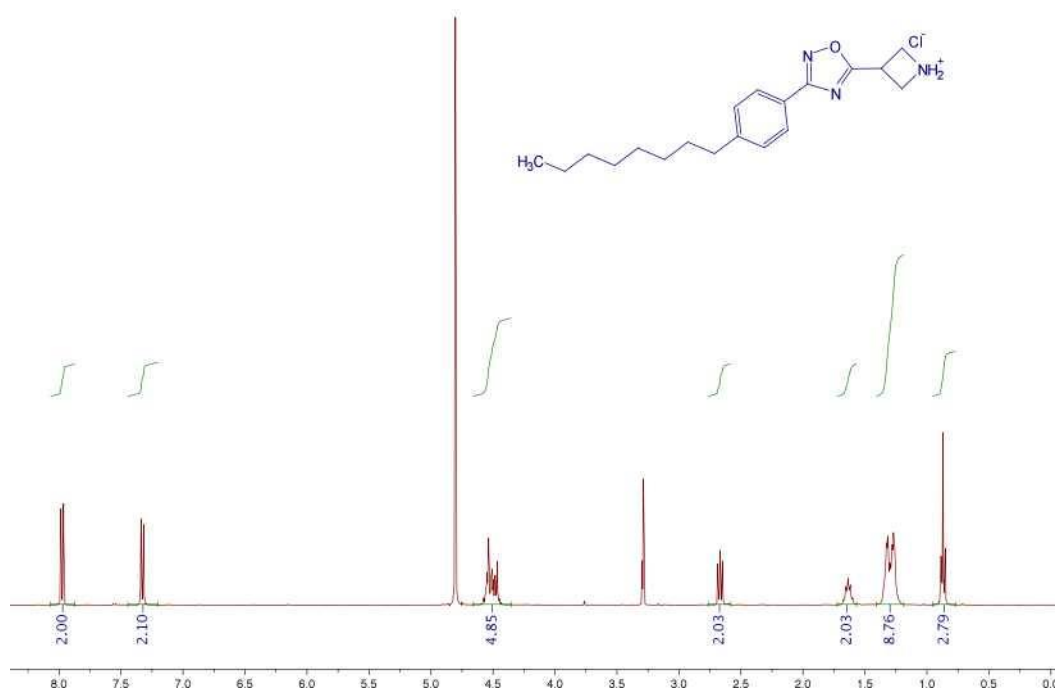


$^{13}\text{C-NMR}$  Spectrum for (*R*)-*tert*-butyl 3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.24b**– –

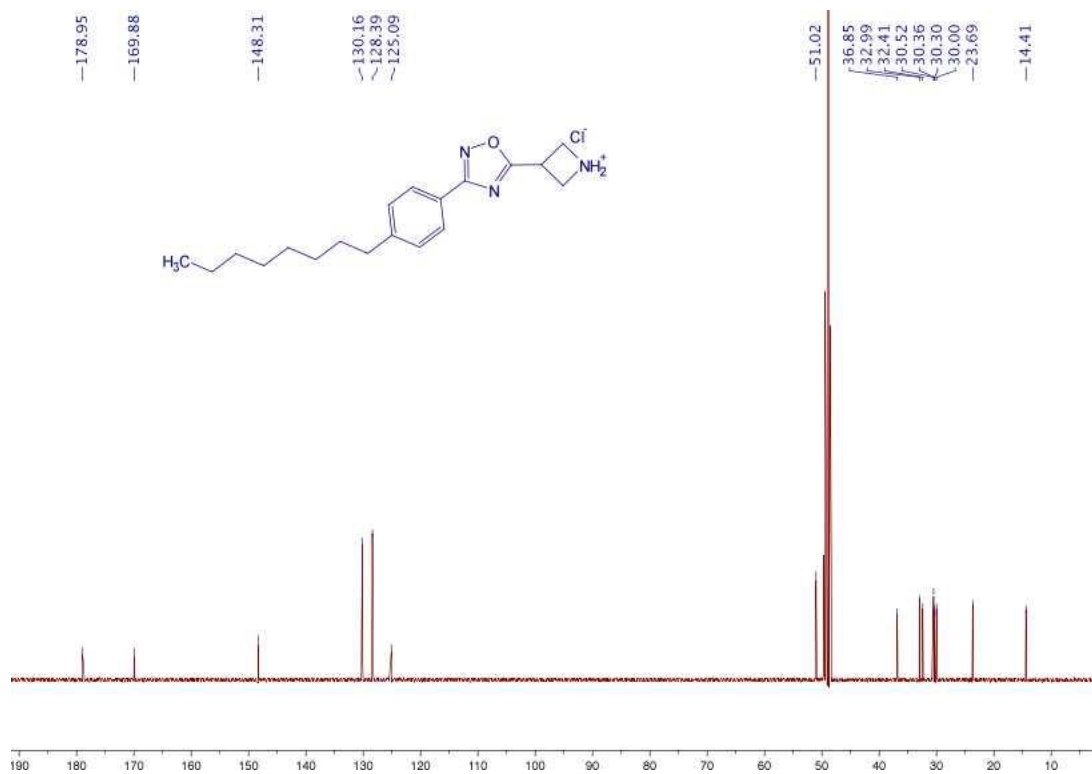




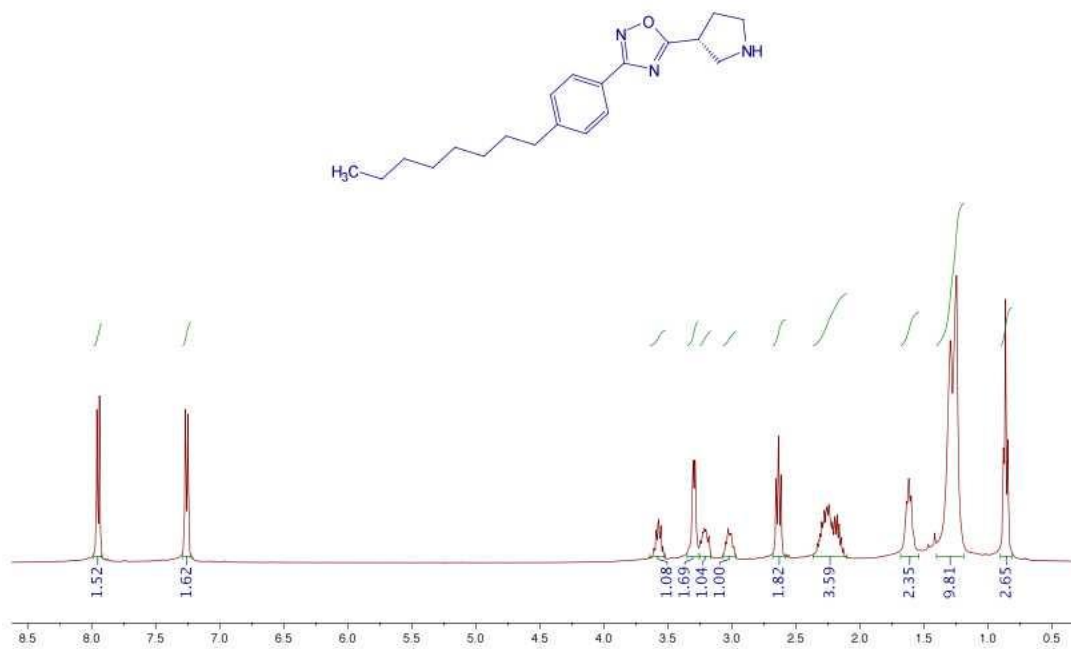
<sup>1</sup>H-NMR Spectrum for 3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-ium chloride **2.25a** –



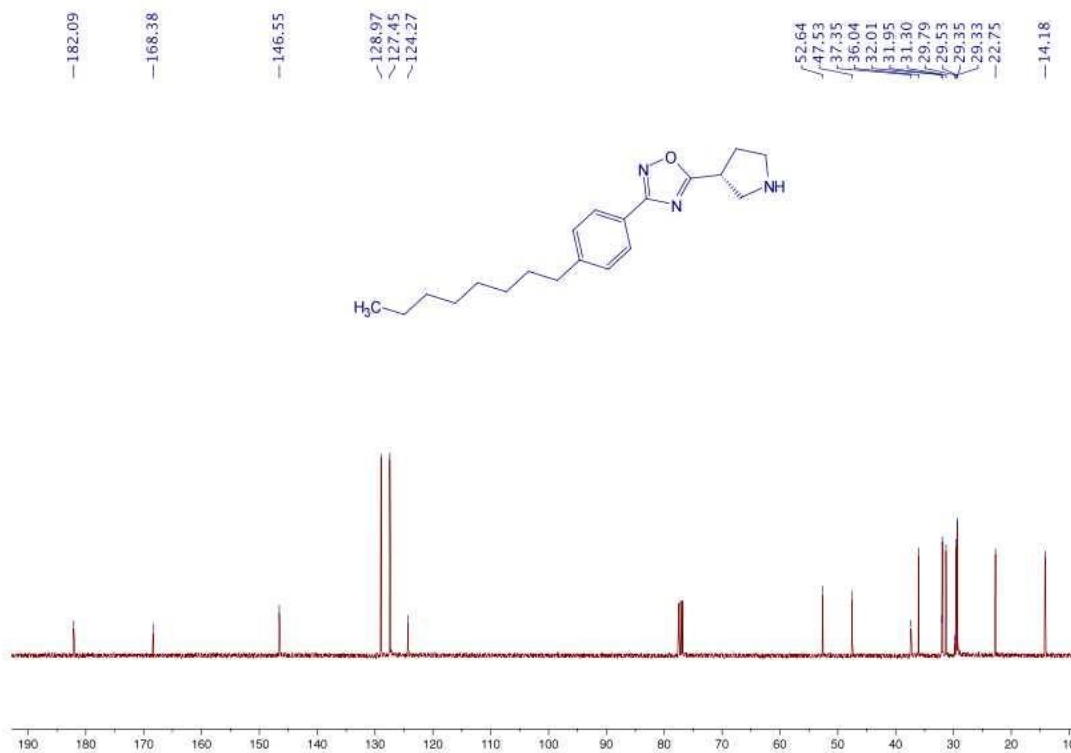
<sup>13</sup>C-NMR Spectrum for 3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-ium chloride **2.25a**



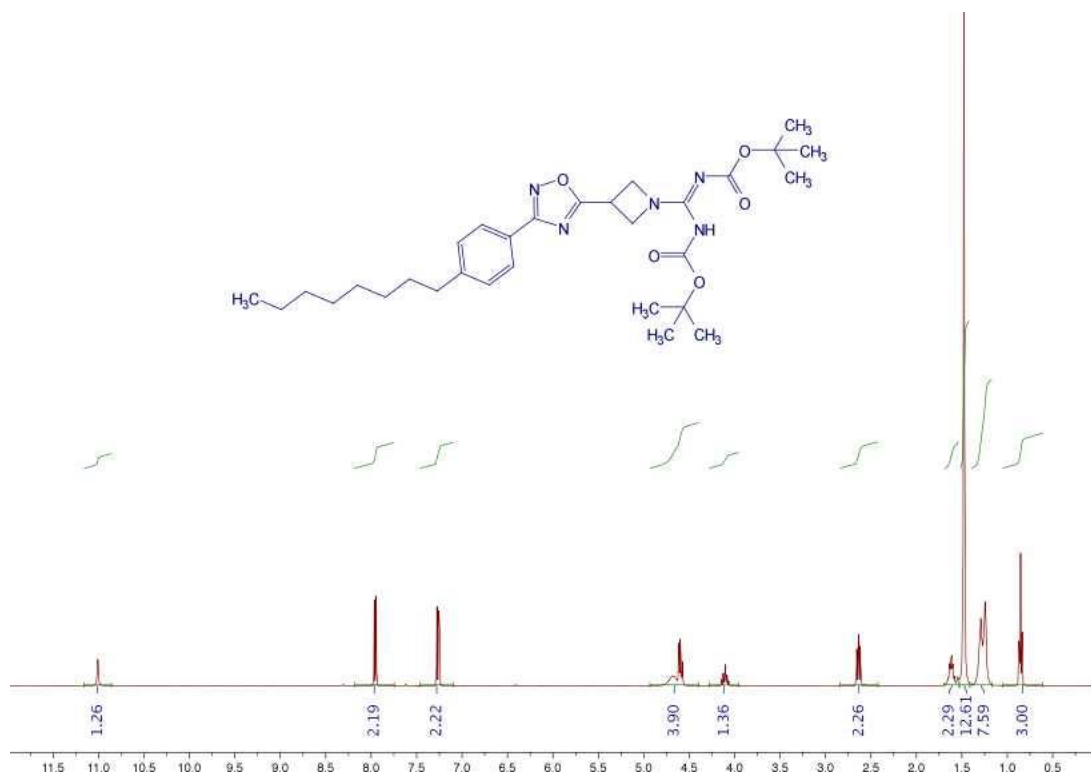
$^1\text{H-NMR}$  Spectrum for (*R*)-3-(4-octylphenyl)-5-(pyrrolidin-3-yl)-1,2,4-oxadiazole **2.25b** –



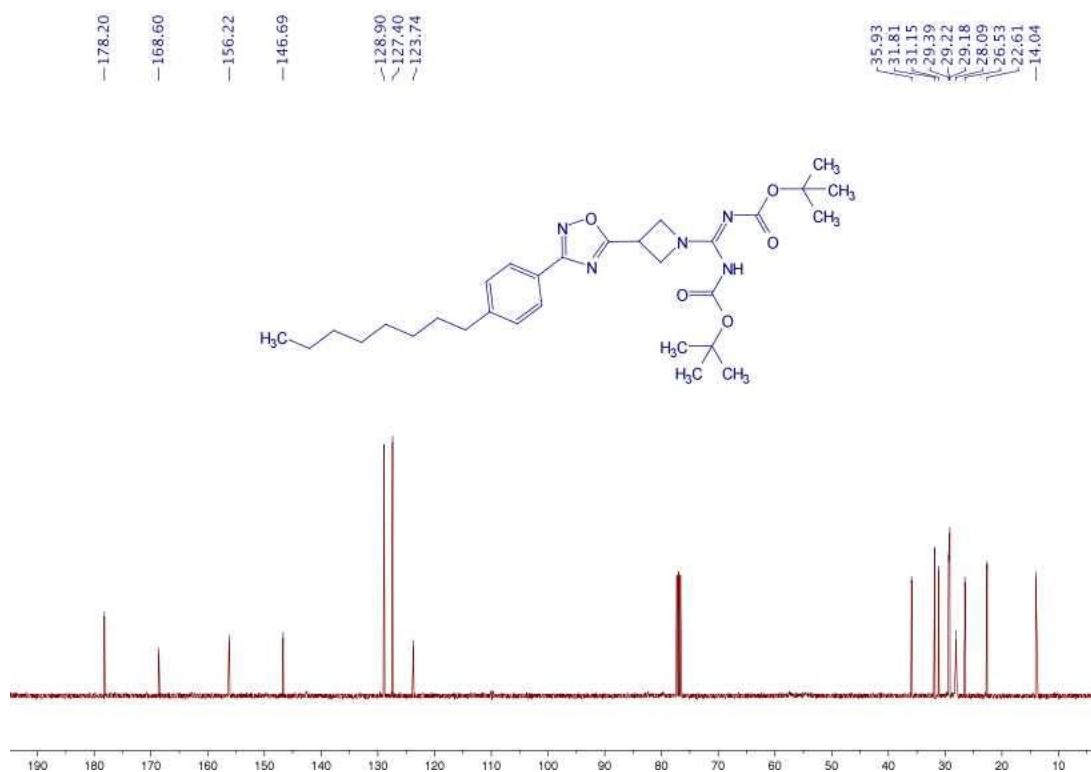
$^{13}\text{C-NMR}$  Spectrum for (*R*)-3-(4-octylphenyl)-5-(pyrrolidin-3-yl)-1,2,4-oxadiazole **2.25b** –



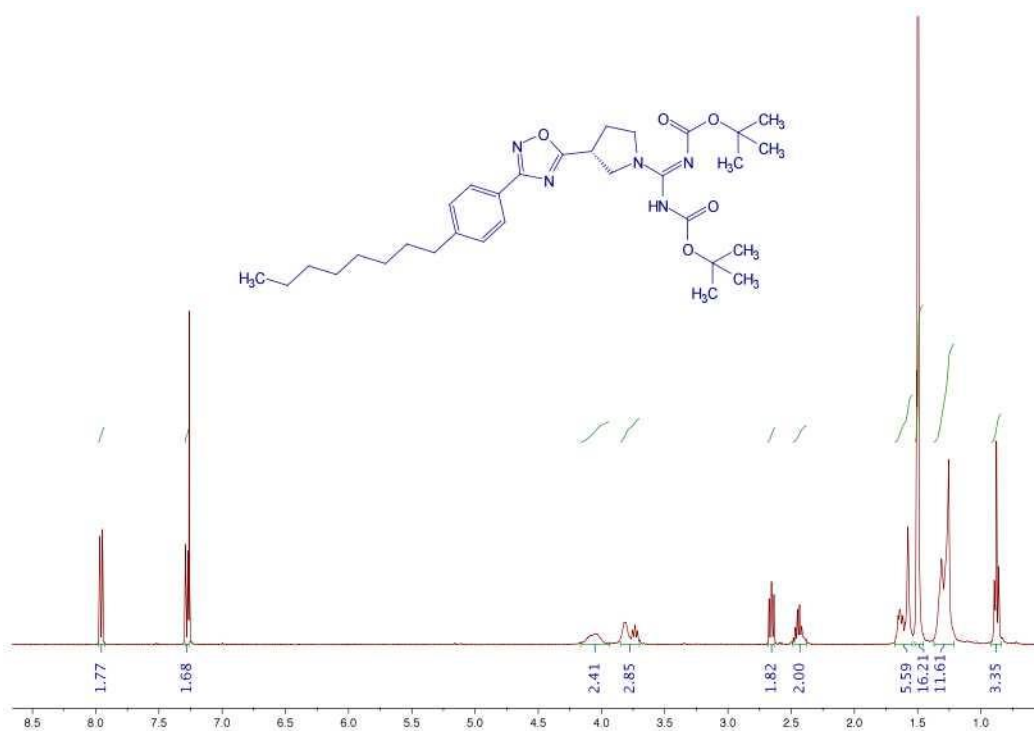
$^1\text{H-NMR}$  Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)(3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methylene)carbamate –



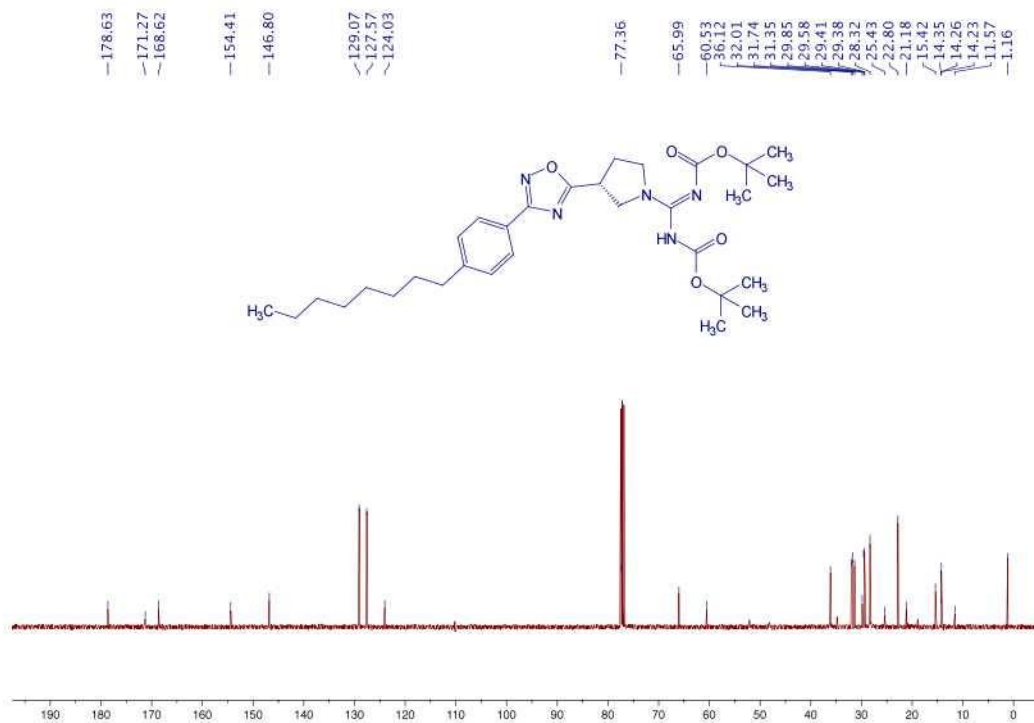
$^{13}\text{C-NMR}$  Spectrum *tert*-butyl (((*tert*-butoxycarbonyl)amino)(3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methylene)carbamate –



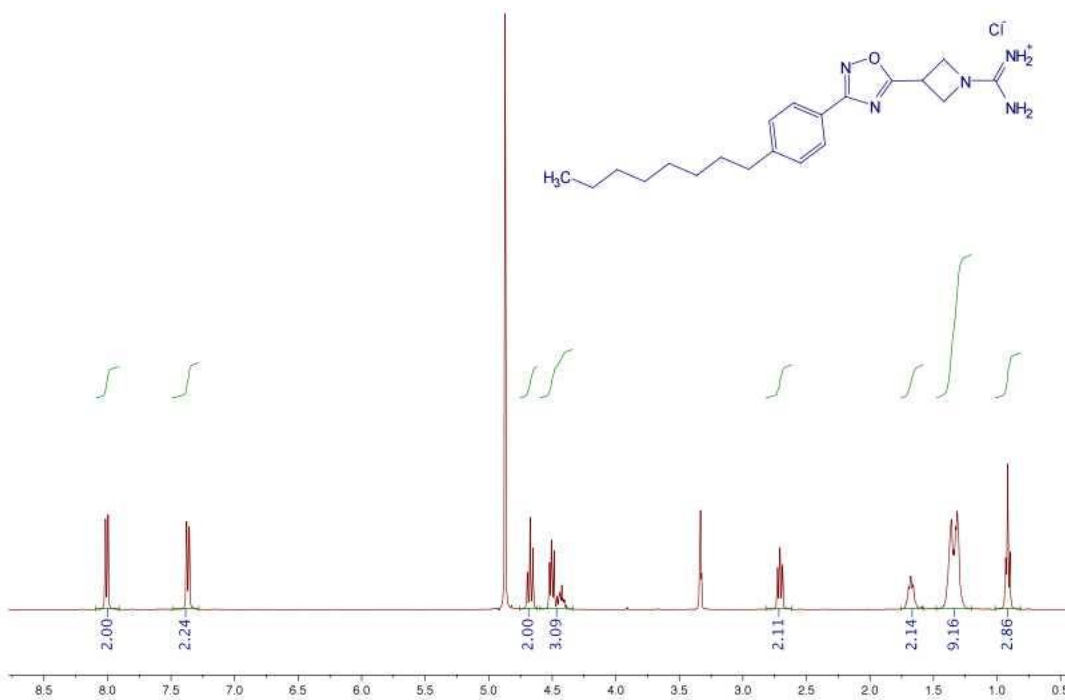
$^1\text{H-NMR}$  Spectrum for (*R,Z*)-*tert*-butyl (((*tert*-butoxycarbonyl)imino)(3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methyl)carbamate –



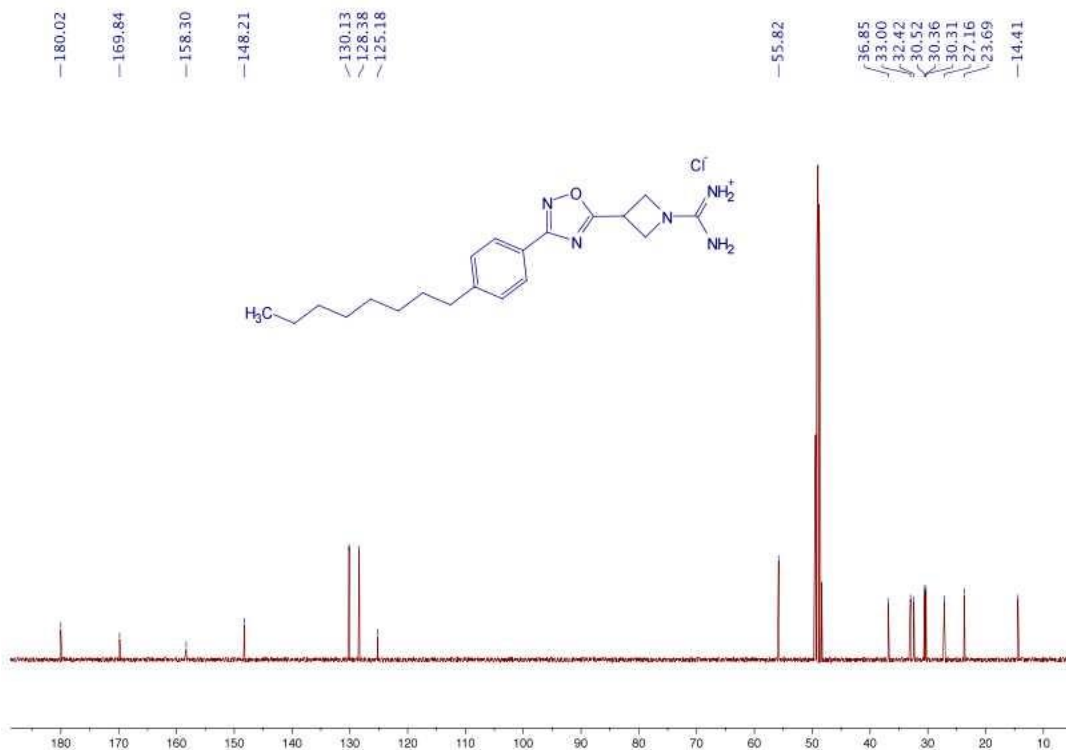
$^{13}\text{C-NMR}$  Spectrum for (*R,Z*)-*tert*-butyl (((*tert*-butoxycarbonyl)imino)(3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methyl)carbamate –



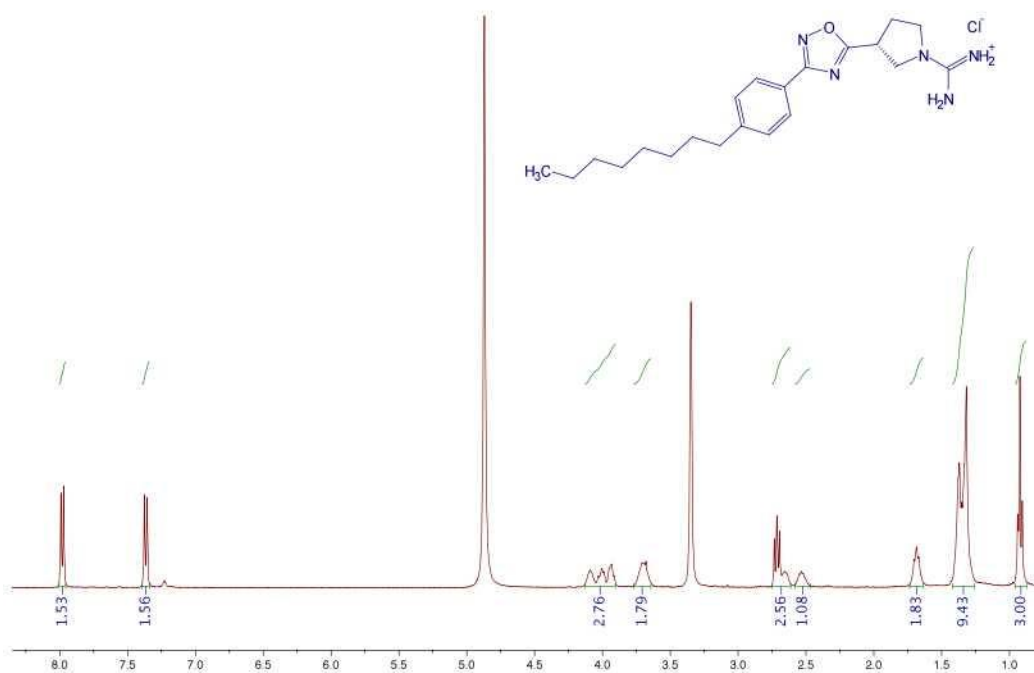
$^1\text{H-NMR}$  Spectrum for amino(3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methaniminium chloride **2.26a** –



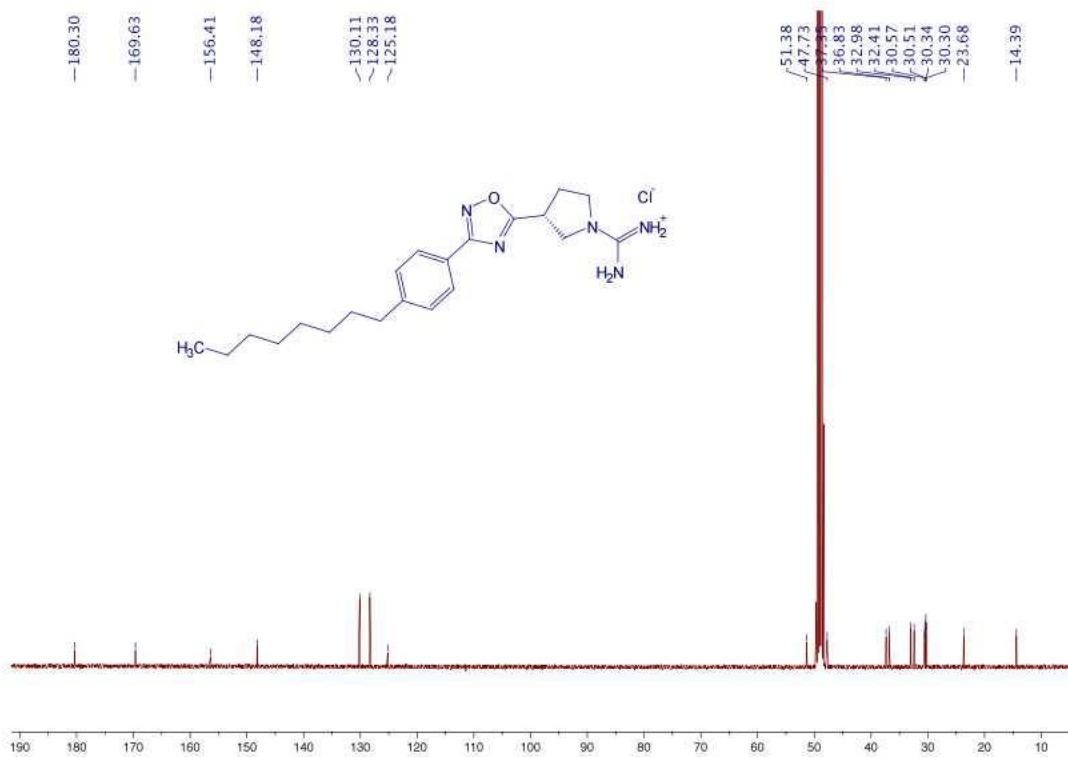
$^{13}\text{C-NMR}$  Spectrum for amino(3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methaniminium chloride **2.26a** –



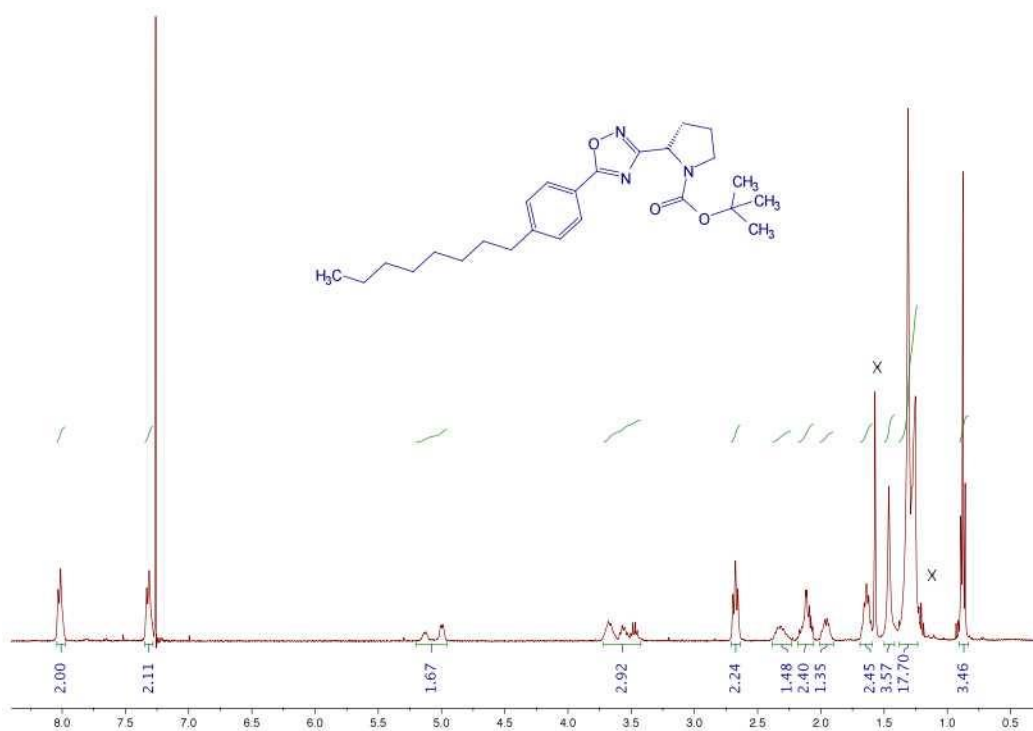
$^1\text{H-NMR}$  Spectrum for (*R*)-amino(3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **2.26b** –



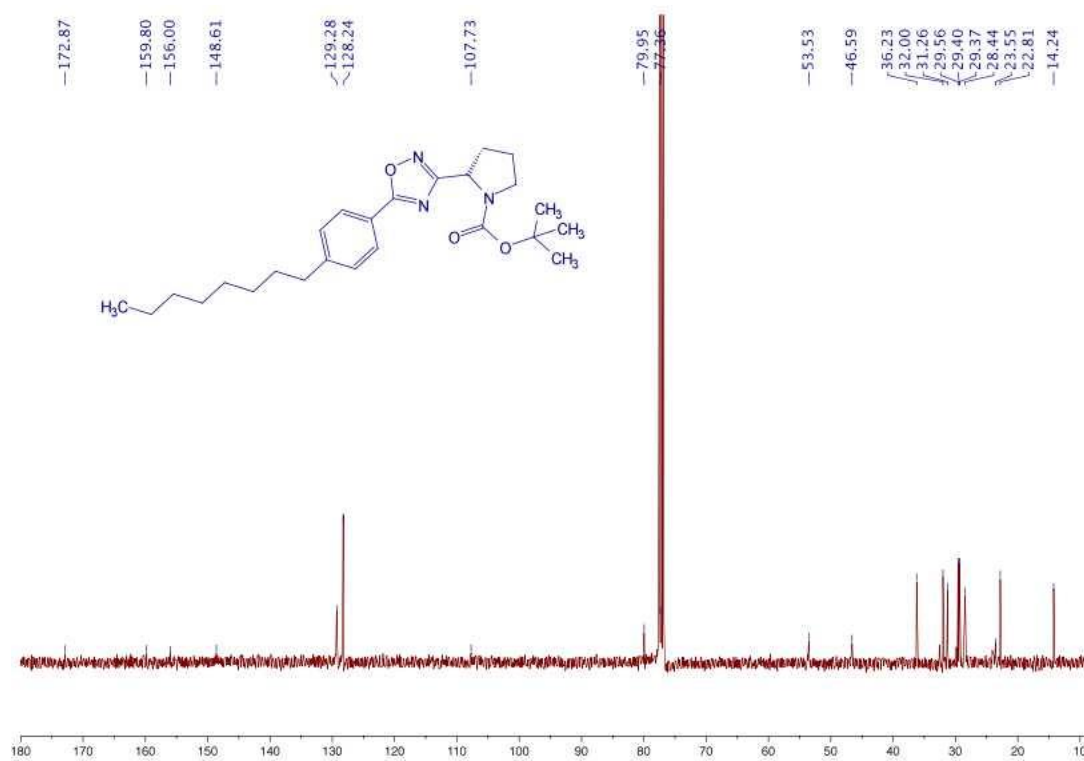
$^{13}\text{C-NMR}$  Spectrum for (*R*)-amino(3-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **2.26b** –



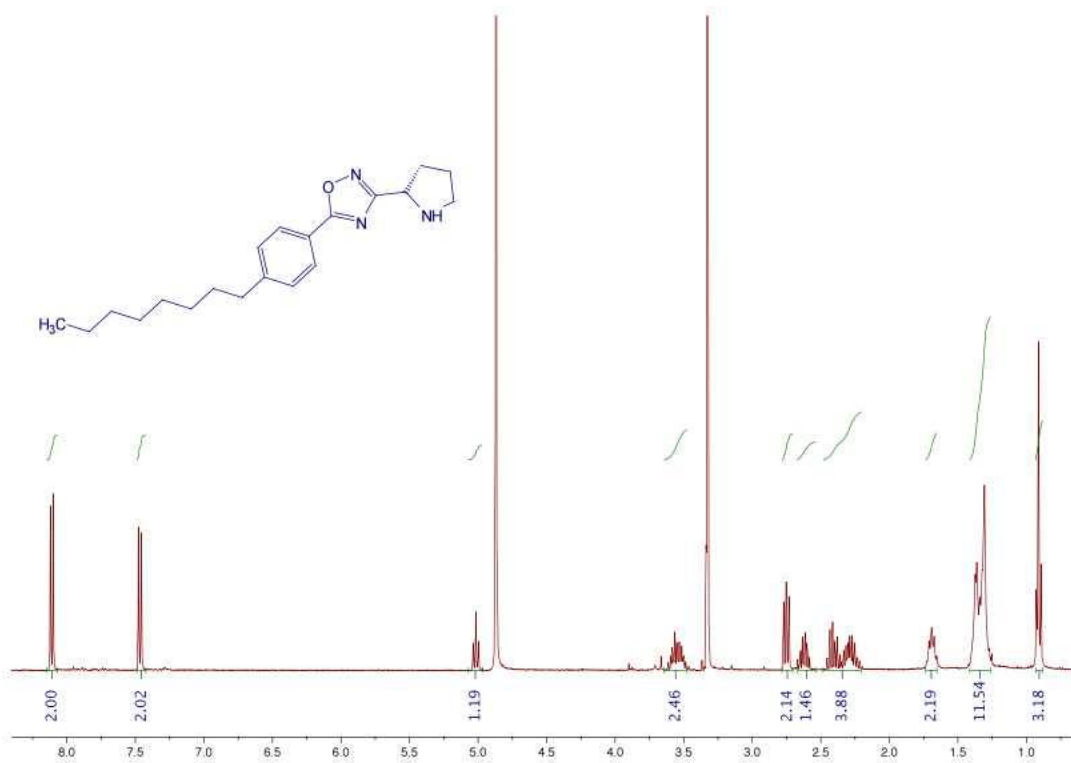
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(5-(4-octylphenyl)-1,2,4-oxadiazol-3-yl)pyrrolidine-1-carboxylate **2.28** –



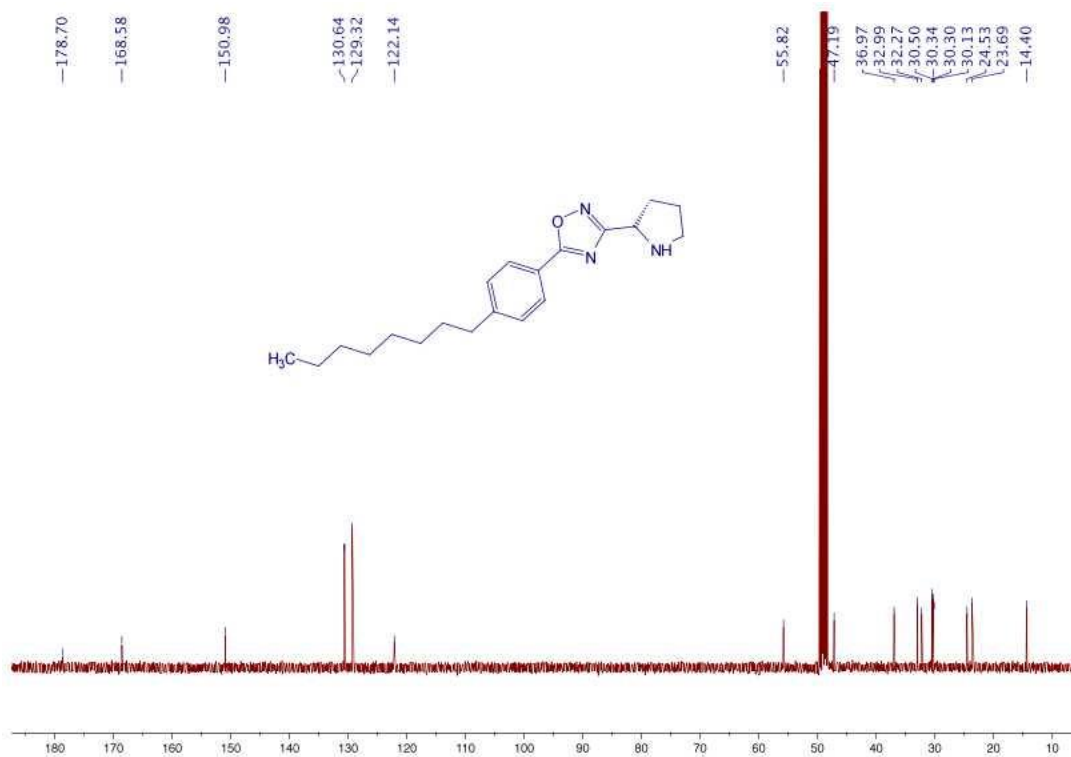
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(5-(4-octylphenyl)-1,2,4-oxadiazol-3-yl)pyrrolidine-1-carboxylate **2.28** –



<sup>1</sup>H-NMR Spectrum for (S)-5-(4-octylphenyl)-3-(pyrrolidin-2-yl)-1,2,4-oxadiazole -

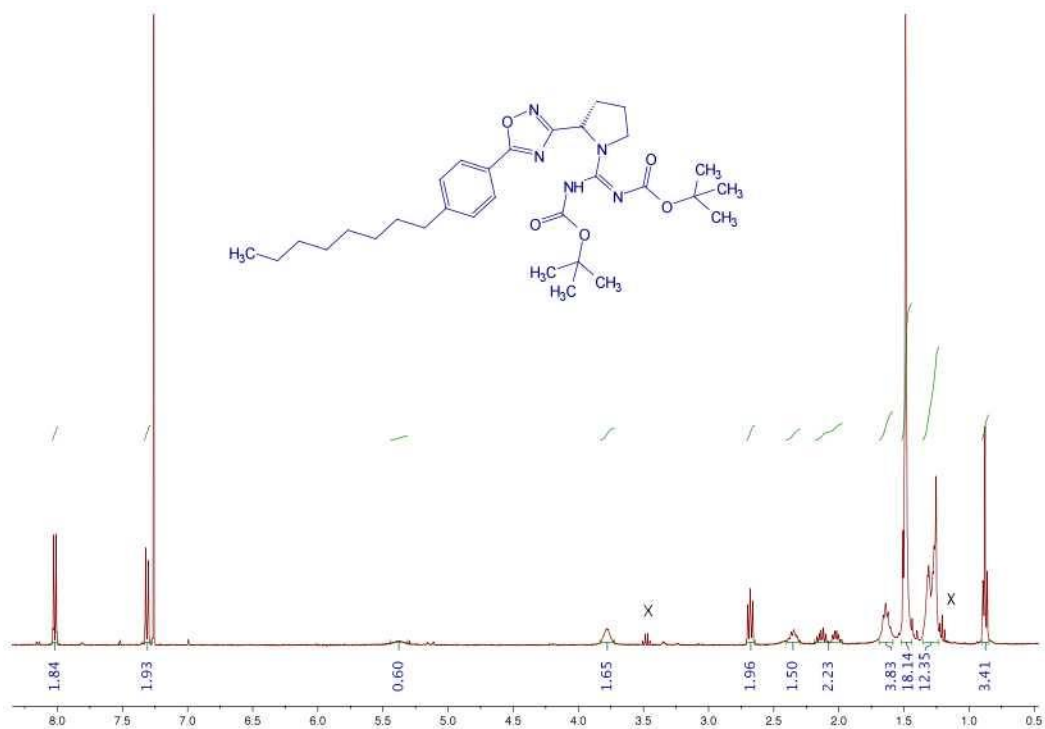


<sup>13</sup>C-NMR Spectrum for (S)-5-(4-octylphenyl)-3-(pyrrolidin-2-yl)-1,2,4-oxadiazole -

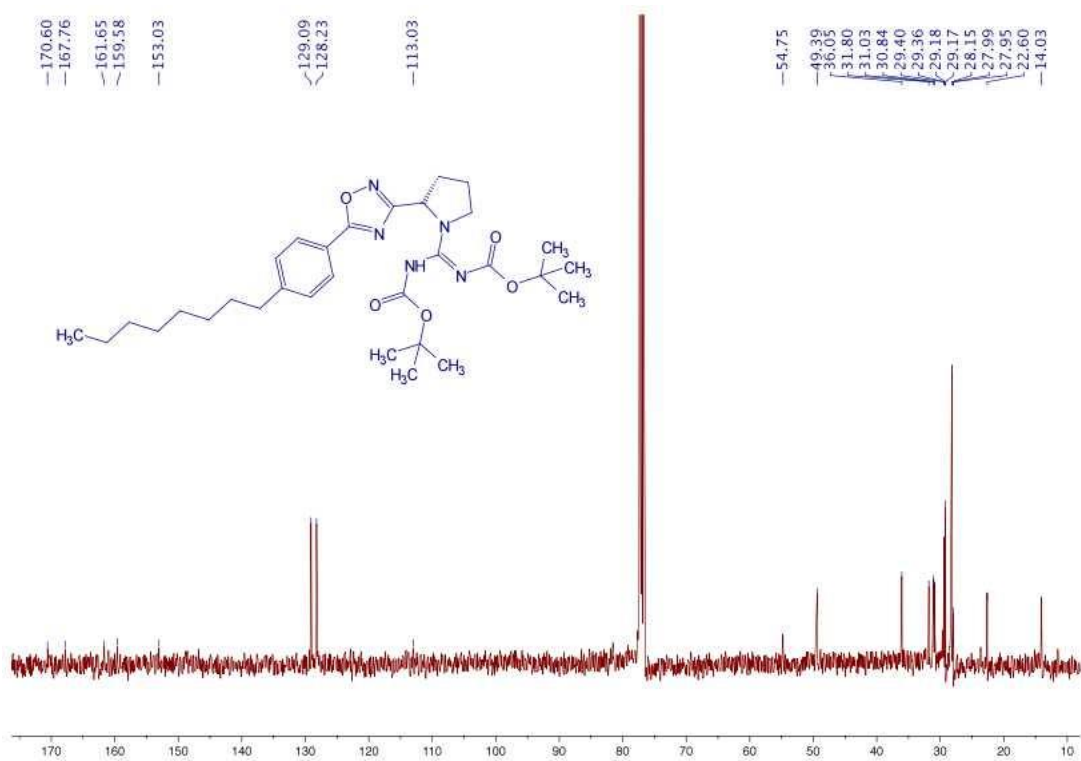




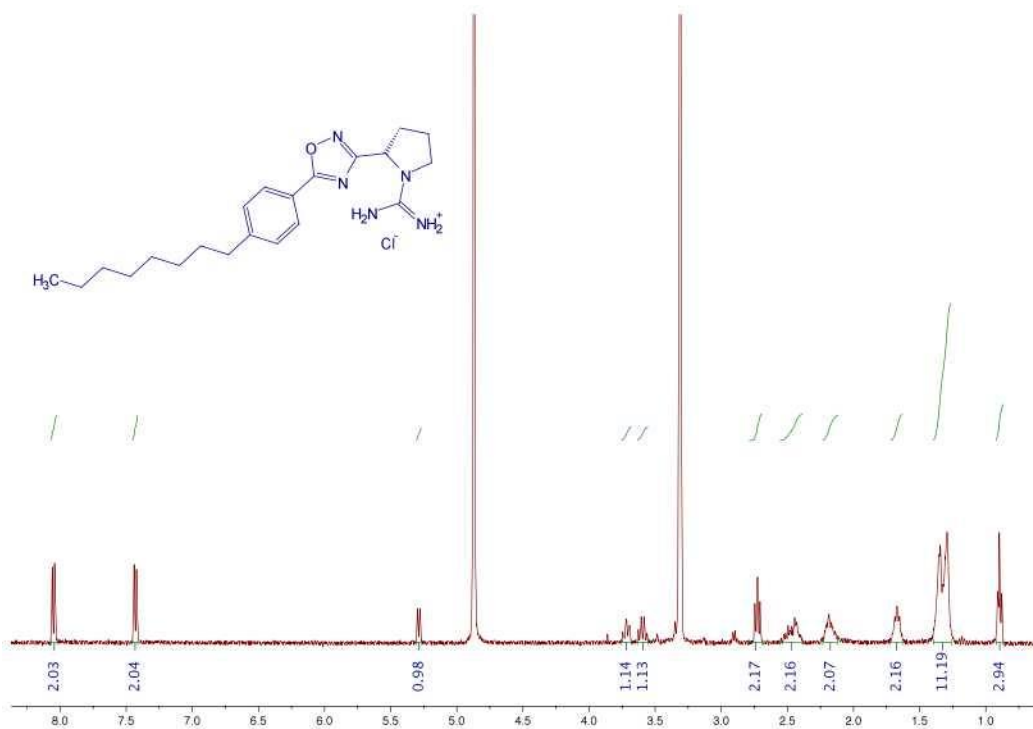
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(5-(4-octylphenyl)-1,2,4-oxadiazol-3-yl)pyrrolidin-1-yl)methylene)carbamate –



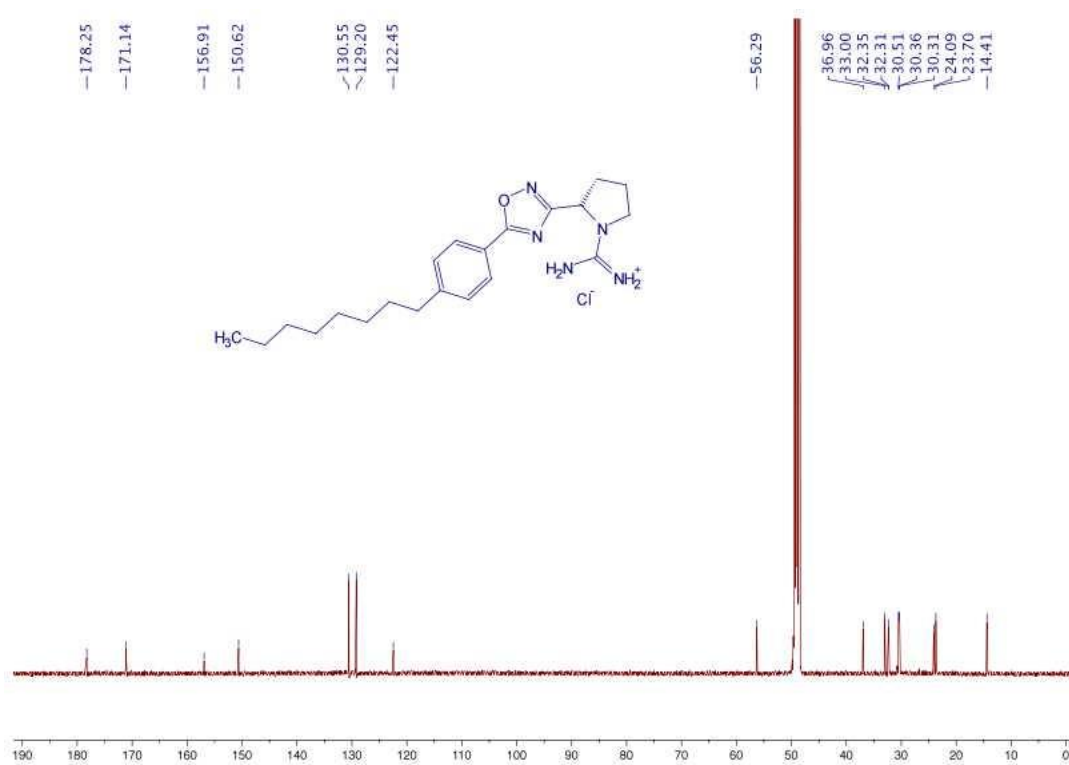
<sup>13</sup>C-NMR Spectrum for for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(5-(4-octylphenyl)-1,2,4-oxadiazol-3-yl)pyrrolidin-1-yl)methylene)carbamate –



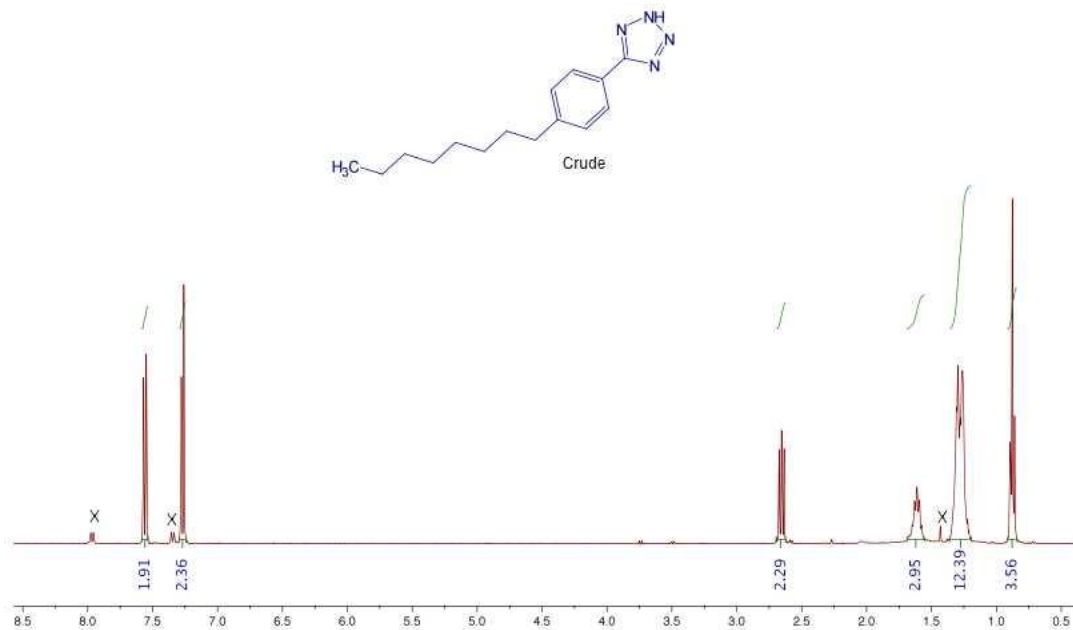
$^1\text{H-NMR}$  Spectrum for (*S*)-amino(2-(5-(4-octylphenyl)-1,2,4-oxadiazol-3-yl)pyrrolidin-1-yl)methaniminium chloride **2.29** –



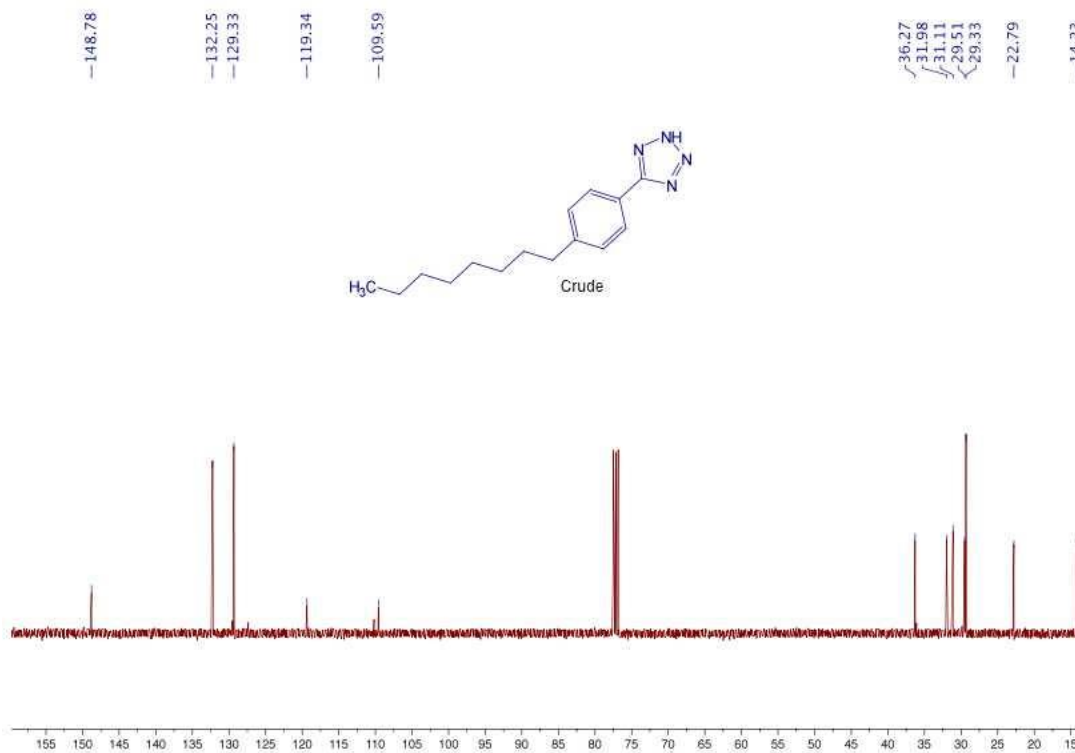
$^{13}\text{C-NMR}$  Spectrum for (*S*)-amino(2-(5-(4-octylphenyl)-1,2,4-oxadiazol-3-yl)pyrrolidin-1-yl)methaniminium chloride **2.29** –



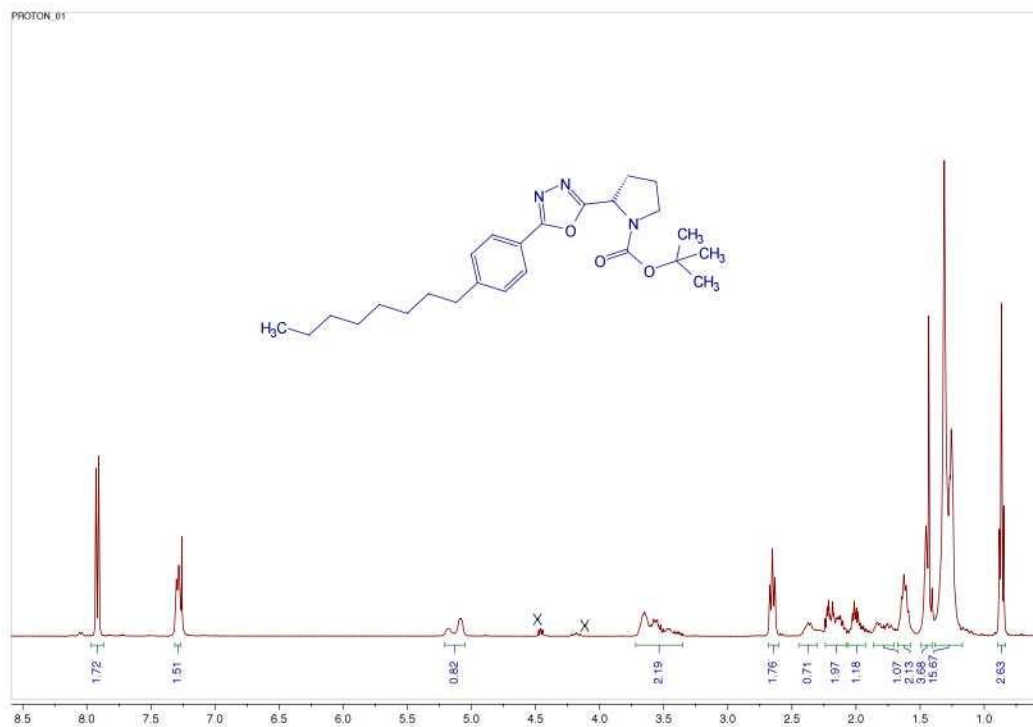
<sup>1</sup>H-NMR Spectrum for 5-(4-octylphenyl)-2H-tetrazole **2.30** –



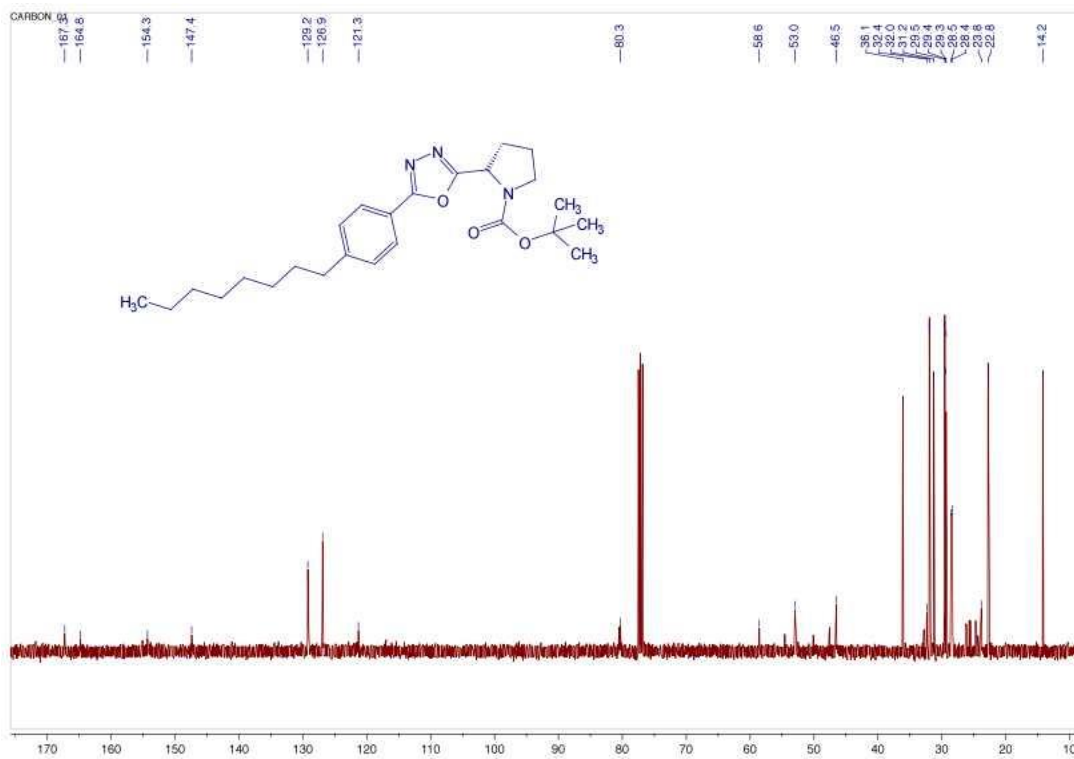
<sup>13</sup>C-NMR Spectrum for 5-(4-octylphenyl)-2H-tetrazole **2.30** –



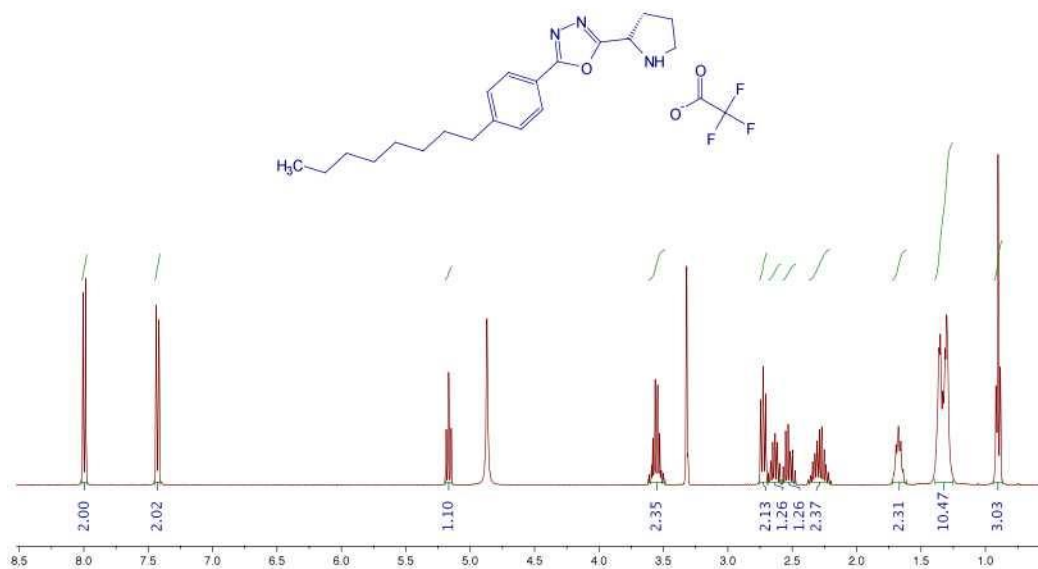
$^1\text{H-NMR}$  Spectrum for (*S*)-*tert*-butyl 2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate **2.31** –



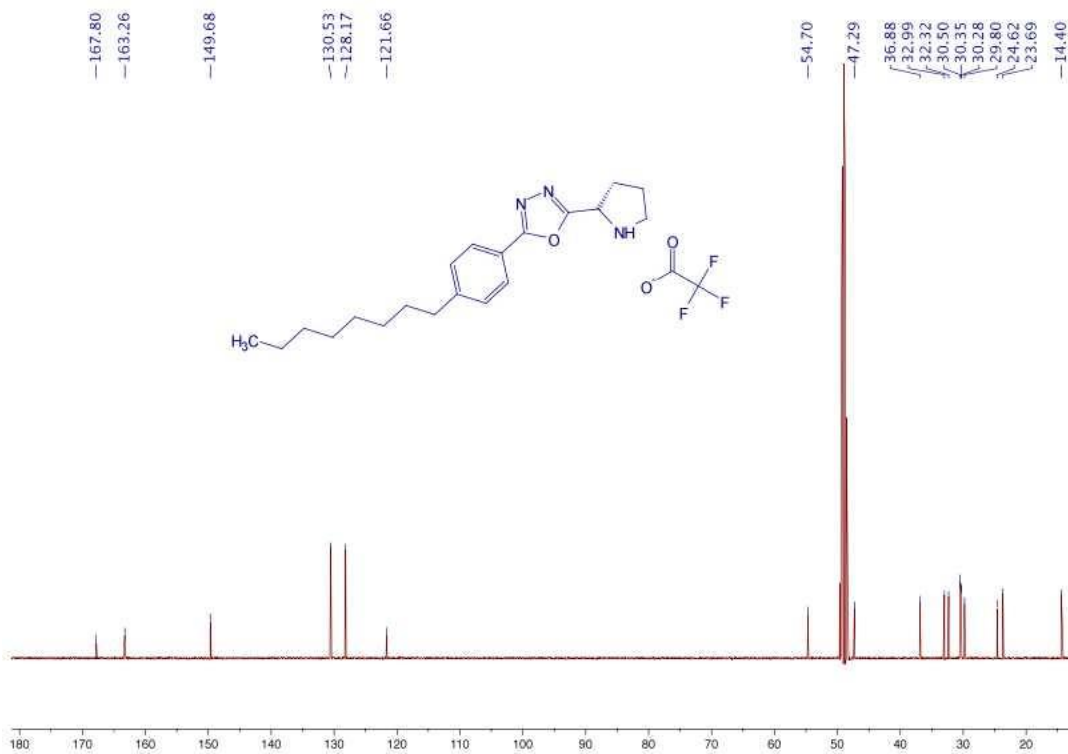
$^{13}\text{C-NMR}$  Spectrum for (*S*)-*tert*-butyl 2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidine-1-carboxylate **2.31** –



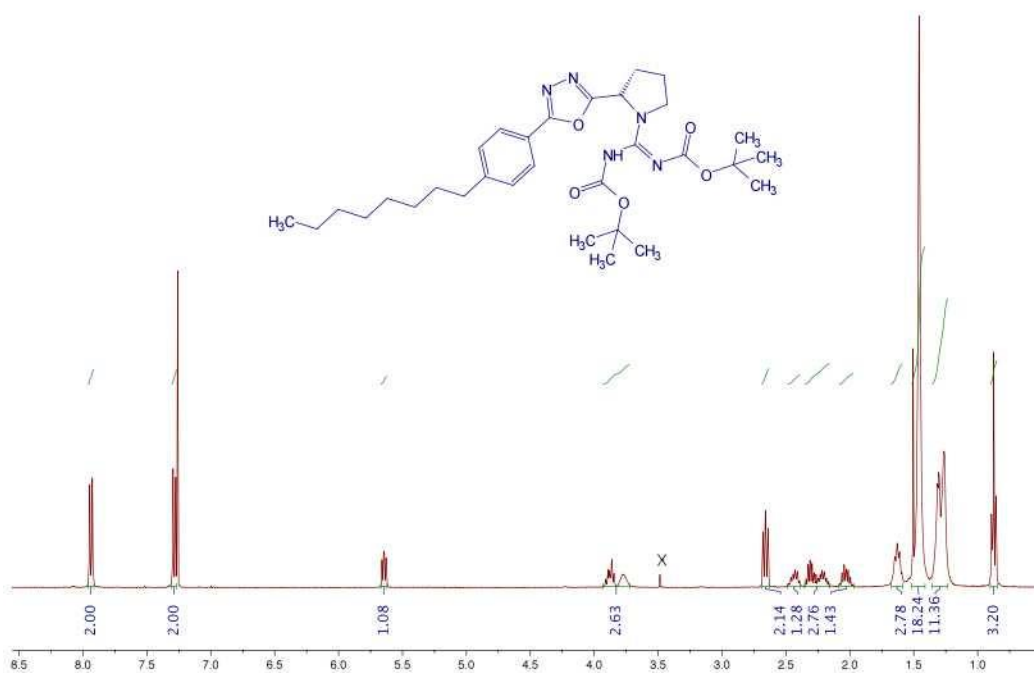
<sup>1</sup>H-NMR Spectrum for (S)-2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



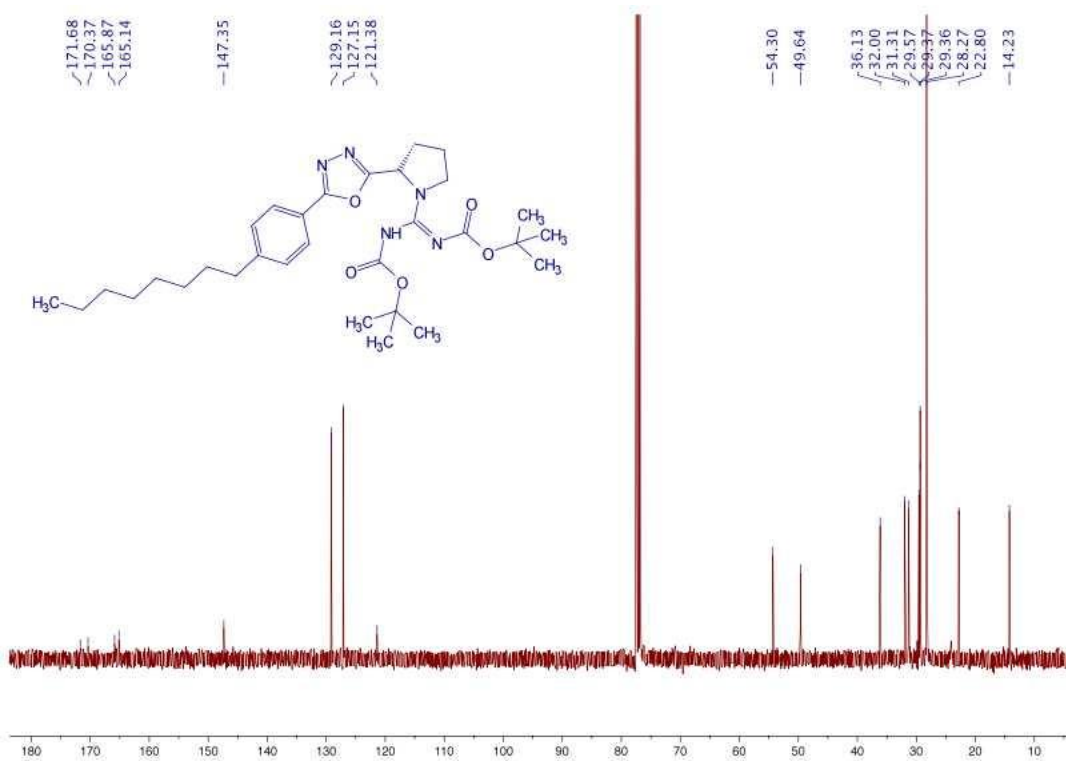
<sup>13</sup>C-NMR Spectrum for (S)-2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



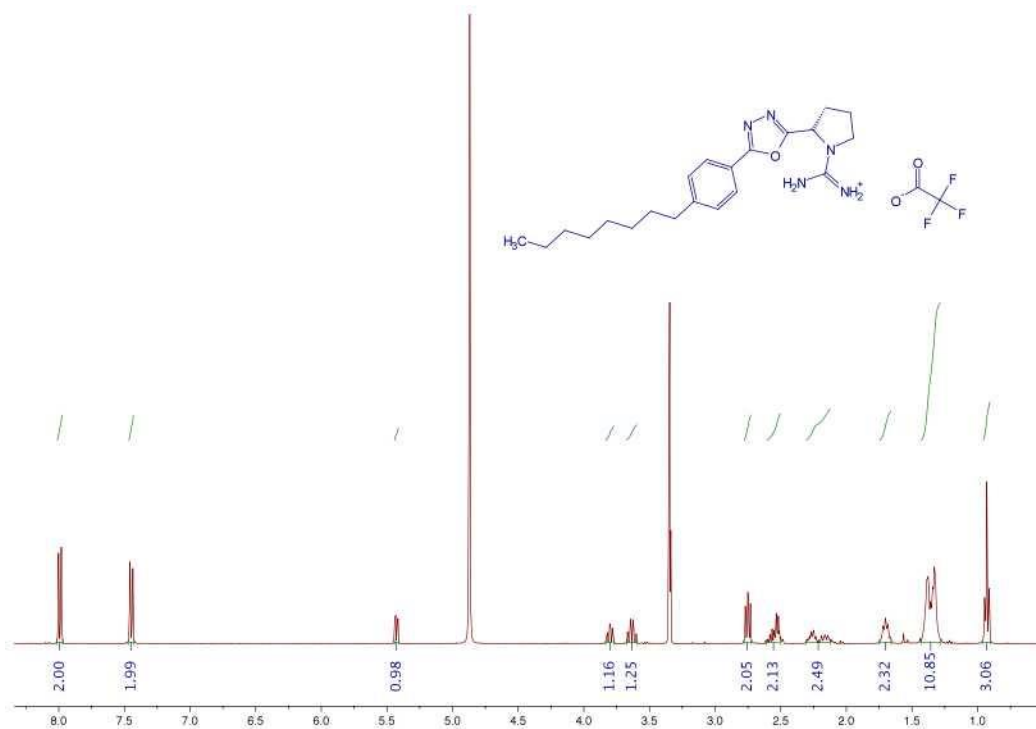
$^1\text{H-NMR}$  Spectrum for (*S,E*)-*tert*-butyl (((*tert*-butoxycarbonyl)imino)(2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl)methyl)carbamate –



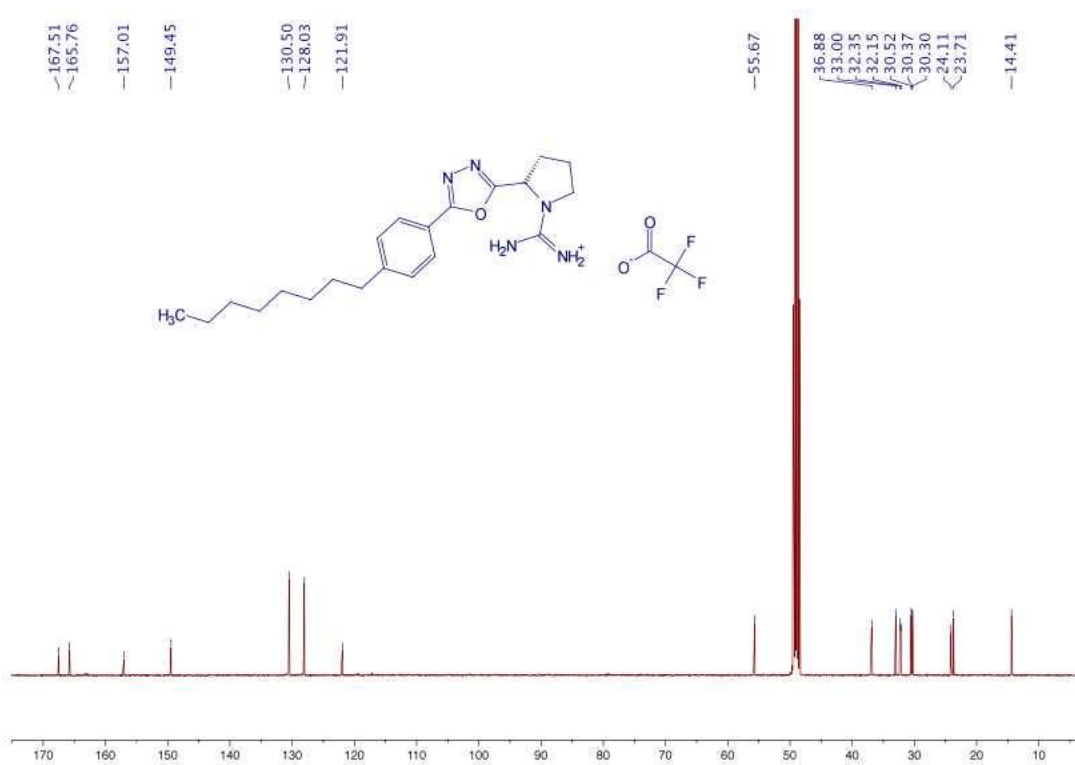
$^{13}\text{C-NMR}$  Spectrum for (*S,E*)-*tert*-butyl (((*tert*-butoxycarbonyl)imino)(2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl)methyl)carbamate –



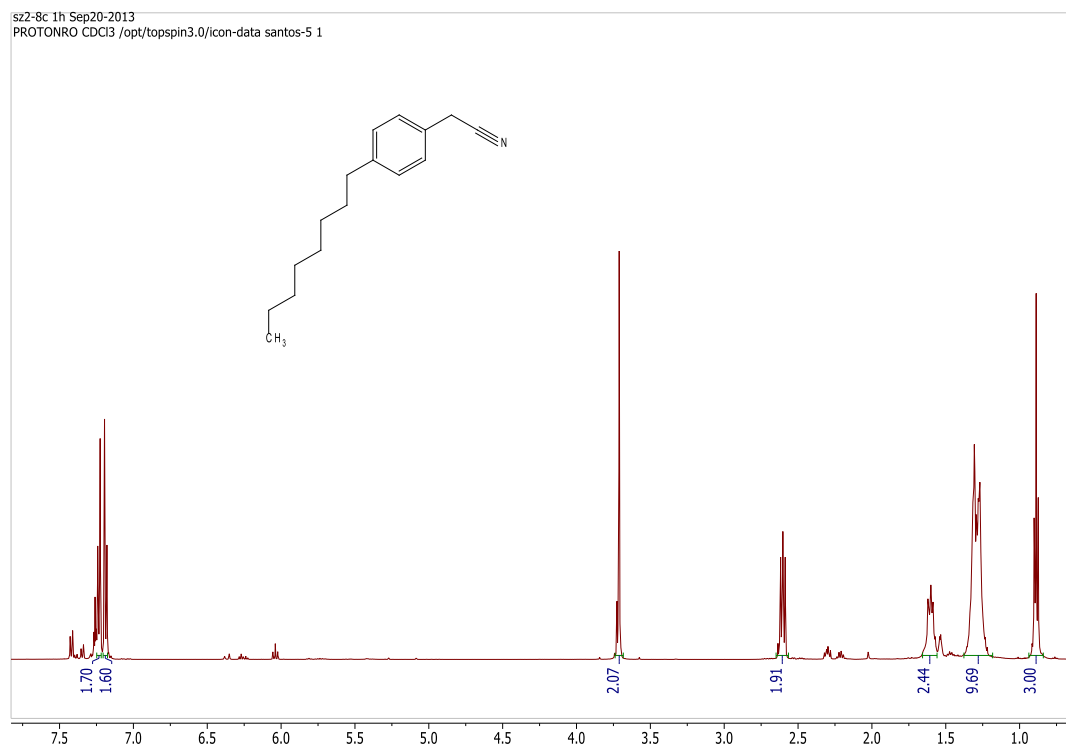
$^1\text{H-NMR}$  Spectrum for (*S*)-amino(2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.32**–



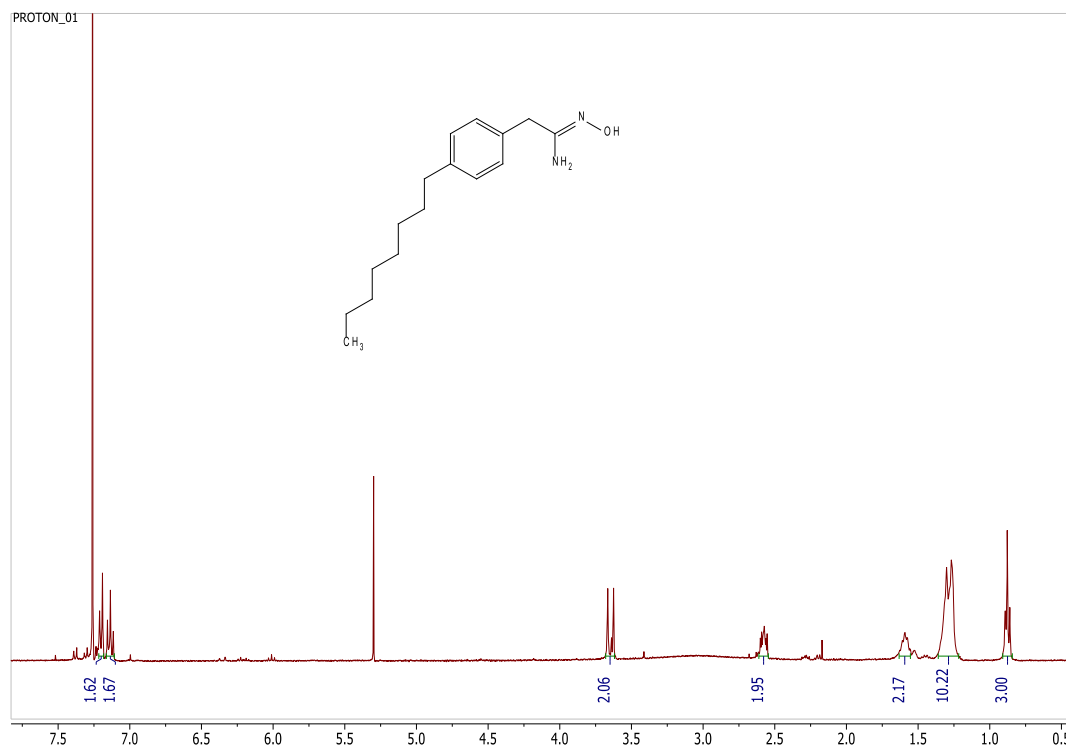
$^{13}\text{C-NMR}$  Spectrum for (*S*)-amino(2-(5-(4-octylphenyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.32**–



### <sup>1</sup>H-NMR Spectrum for 2-(4-octylphenyl)acetonitrile **2.33** –

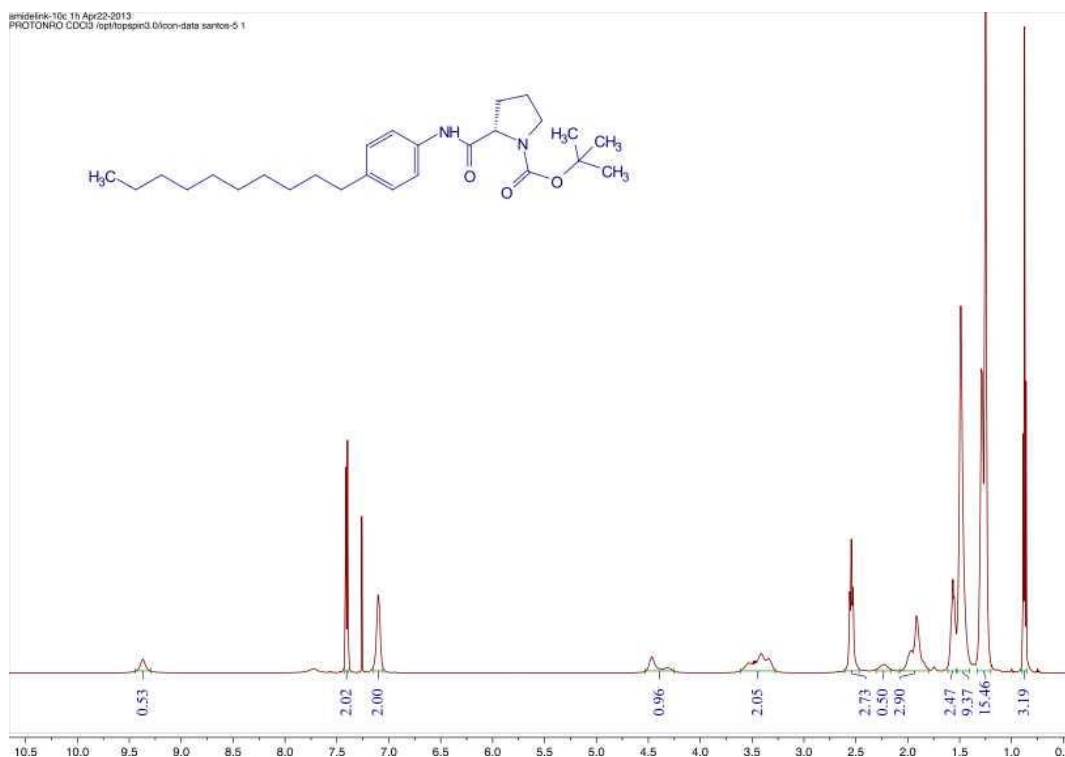


### <sup>1</sup>H-NMR Spectrum for (Z)-N'-hydroxy-2-(4-octylphenyl)acetimidamide **2.34** –

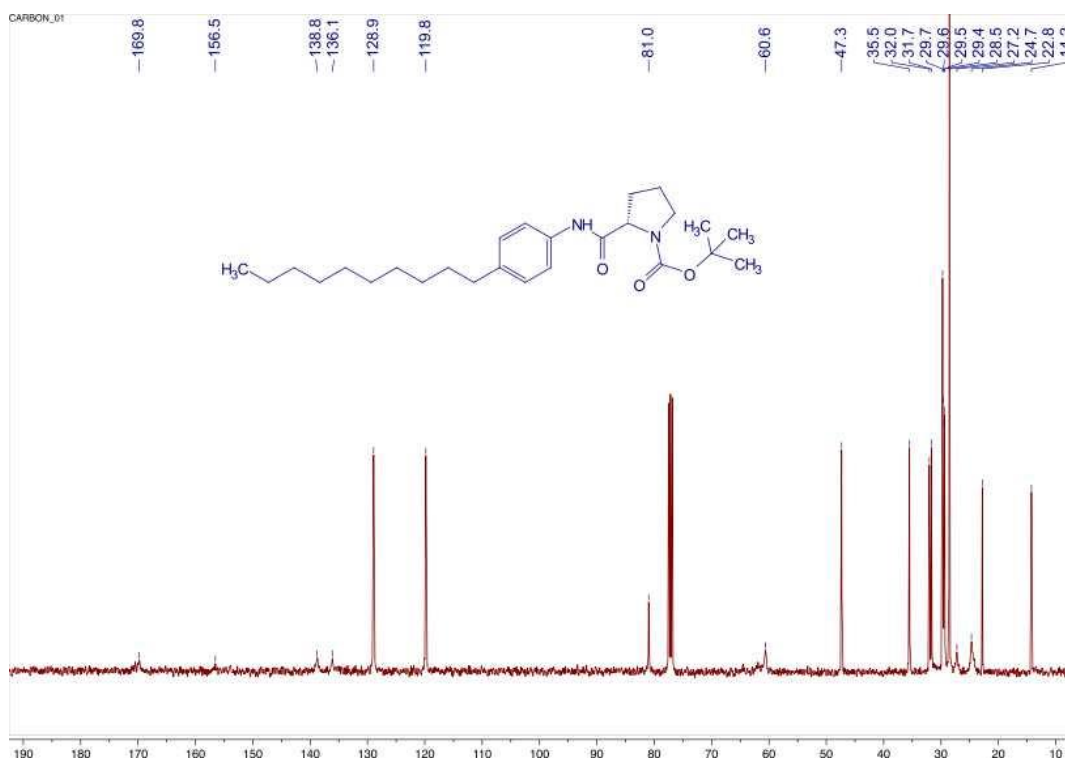




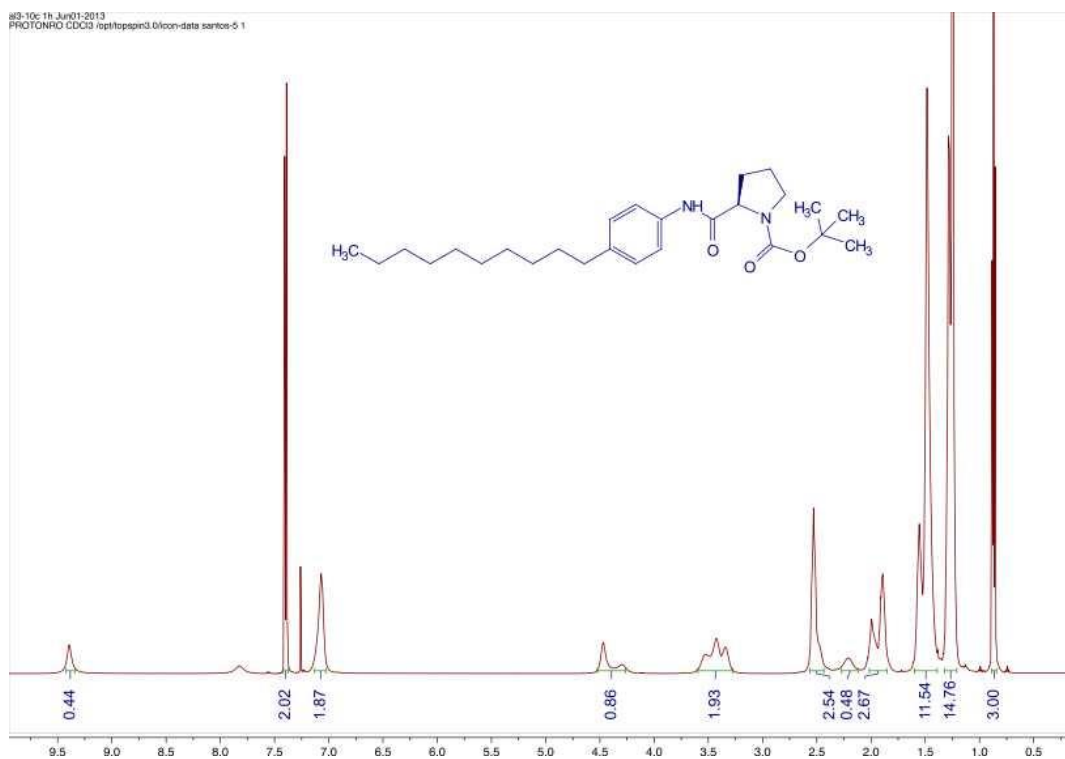
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-((4-decylphenyl)carbamoyl)pyrrolidine-1-carboxylate **2.36a** -



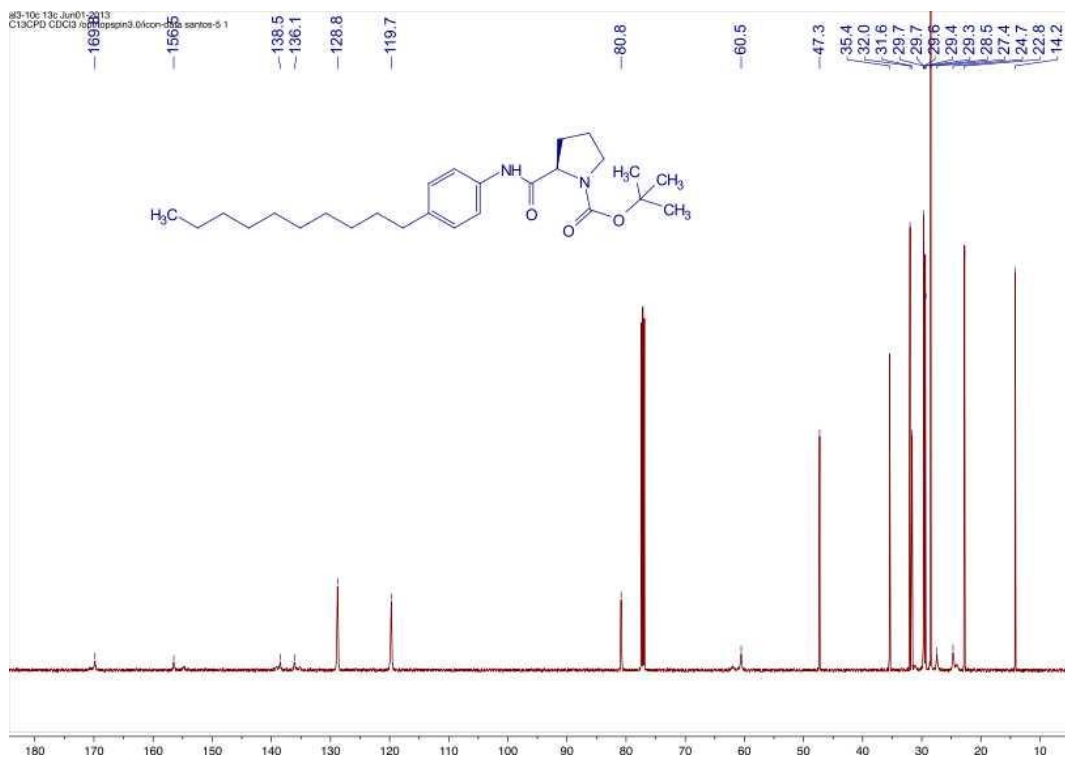
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-((4-decylphenyl)carbamoyl)pyrrolidine-1-carboxylate **2.36a** -



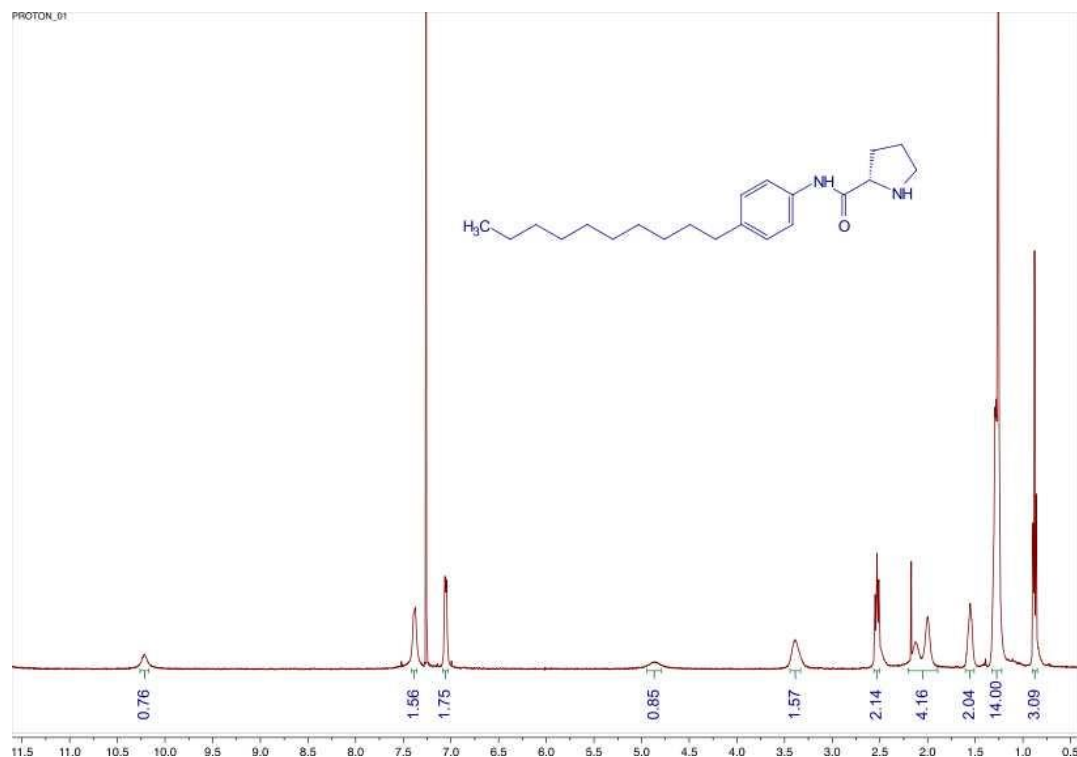
<sup>1</sup>H-NMR Spectrum for (*R*)-*tert*-butyl 2-((4-decylphenyl)carbamoyl)pyrrolidine-1-carboxylate **2.36b** –



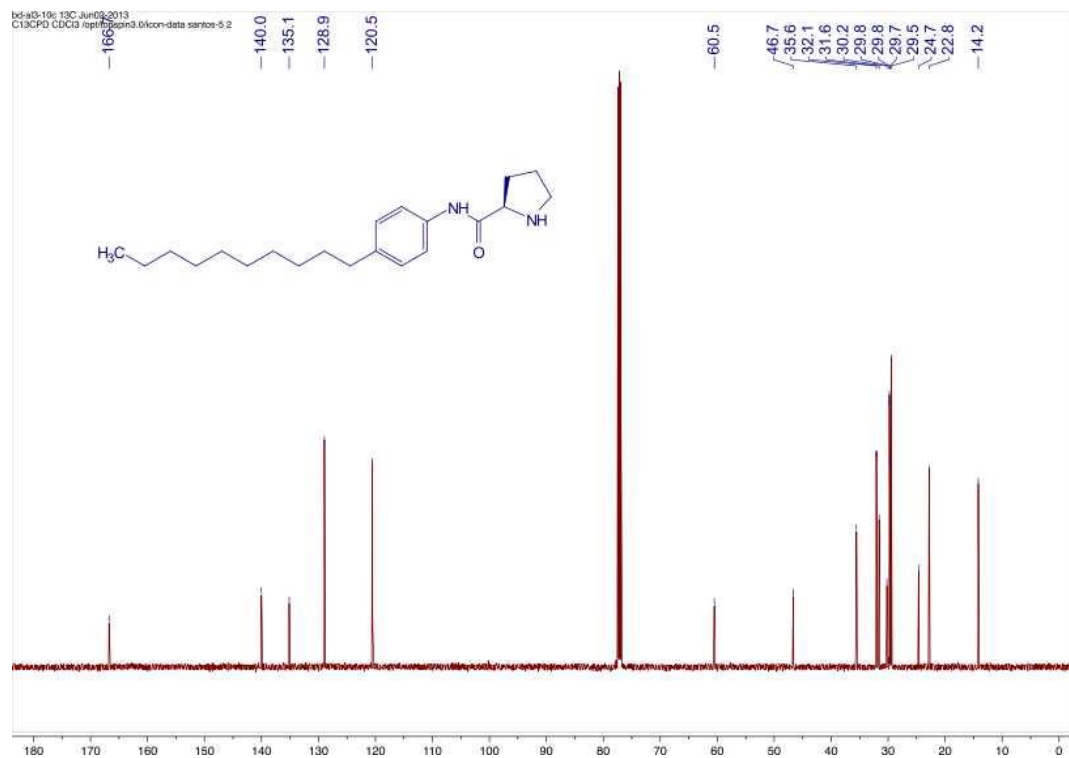
<sup>13</sup>C-NMR Spectrum for (*R*)-*tert*-butyl 2-((4-decylphenyl)carbamoyl)pyrrolidine-1-carboxylate **2.36b** –



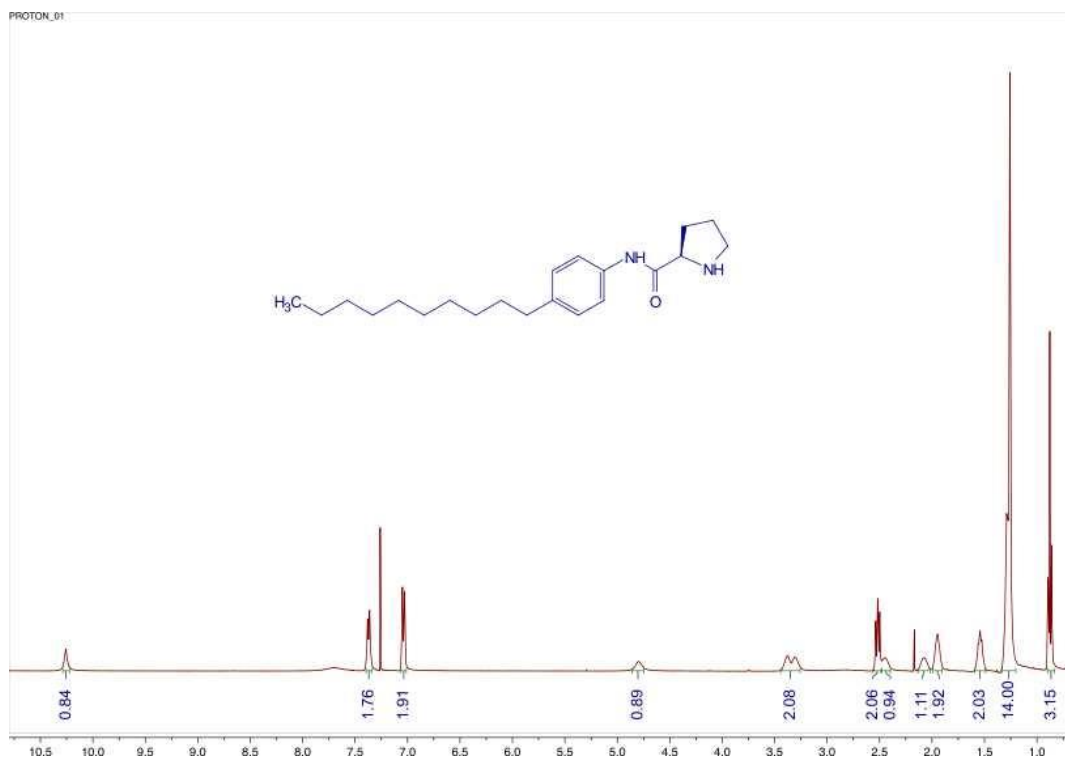
<sup>1</sup>H-NMR Spectrum for (*S*)-2-((4-decylphenyl)carbamoyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **2.37a**-



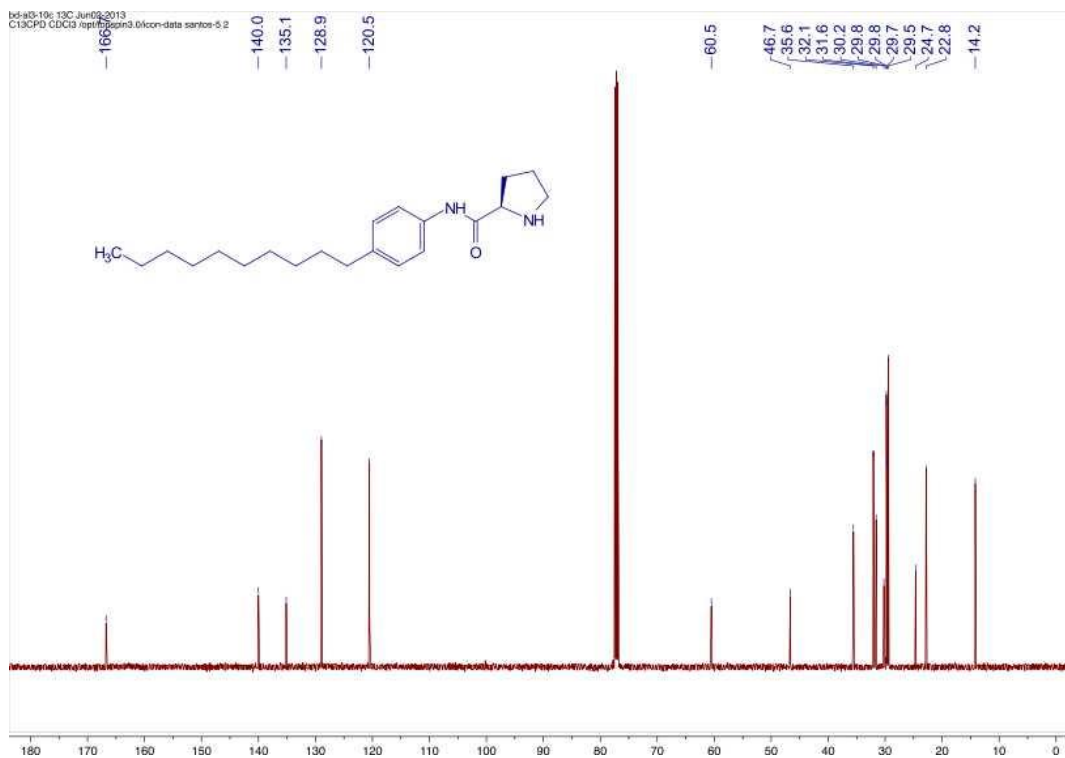
<sup>13</sup>C-NMR Spectrum for (*S*)-2-((4-decylphenyl)carbamoyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **2.37a**-



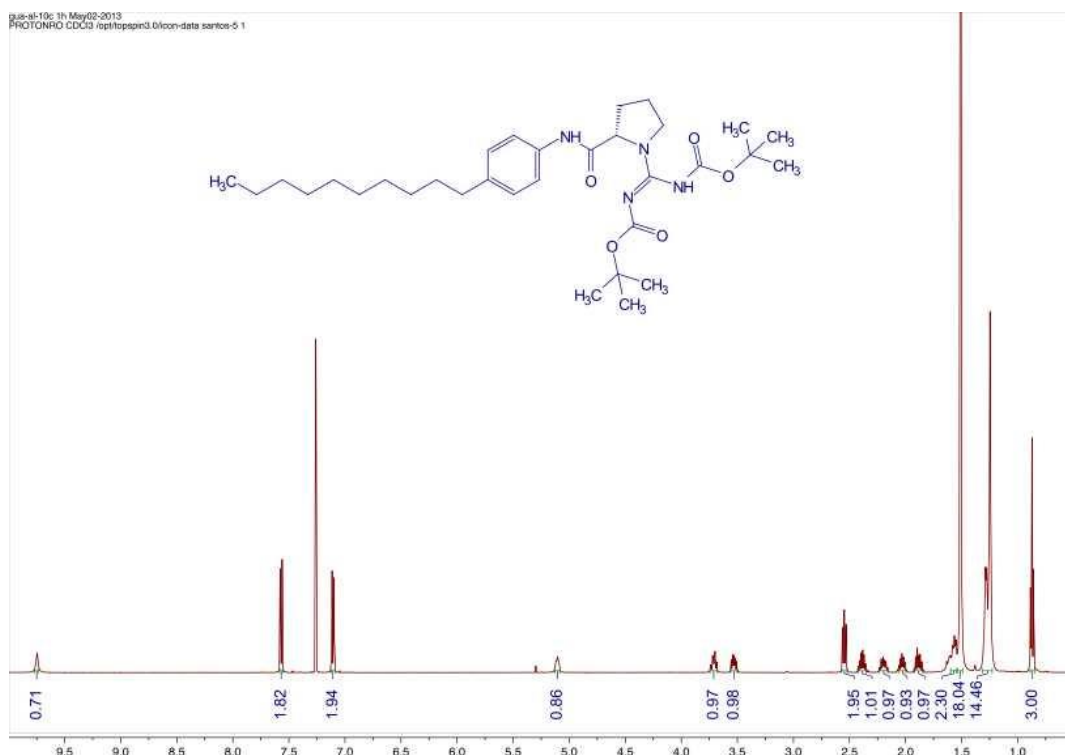
<sup>1</sup>H-NMR Spectrum for (*R*)-2-((4-decylphenyl)carbamoyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **2.37b**-



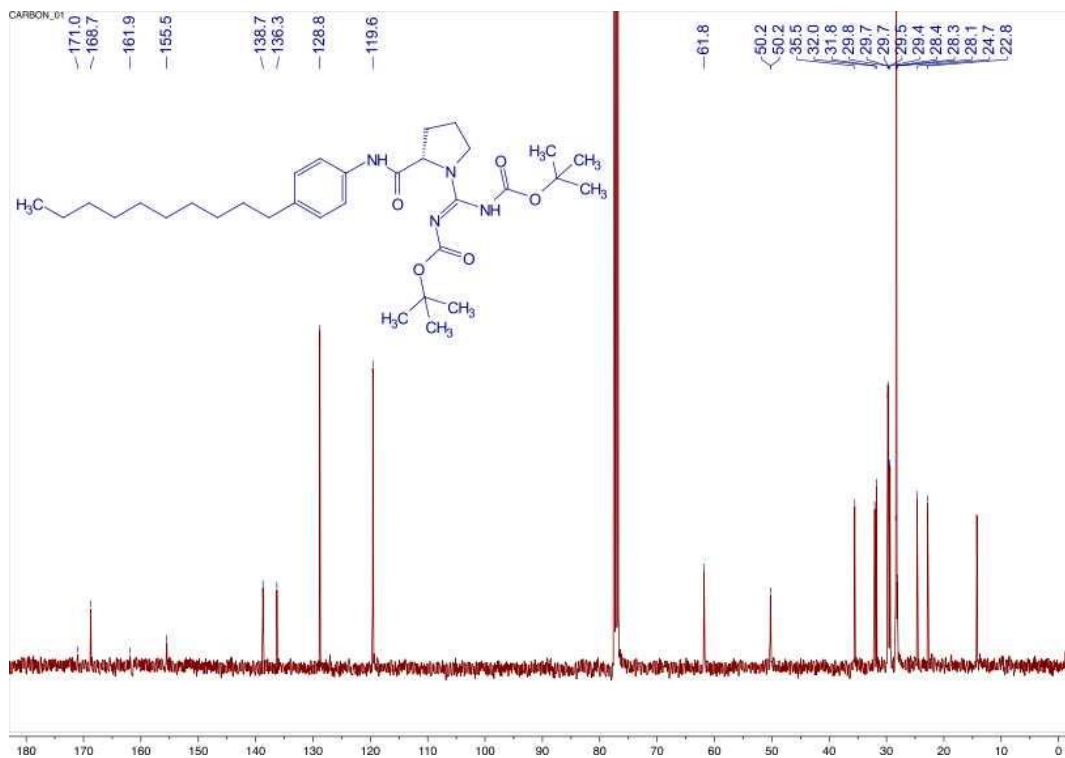
<sup>13</sup>C-NMR Spectrum for (*R*)-2-((4-decylphenyl)carbamoyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **2.37b**-



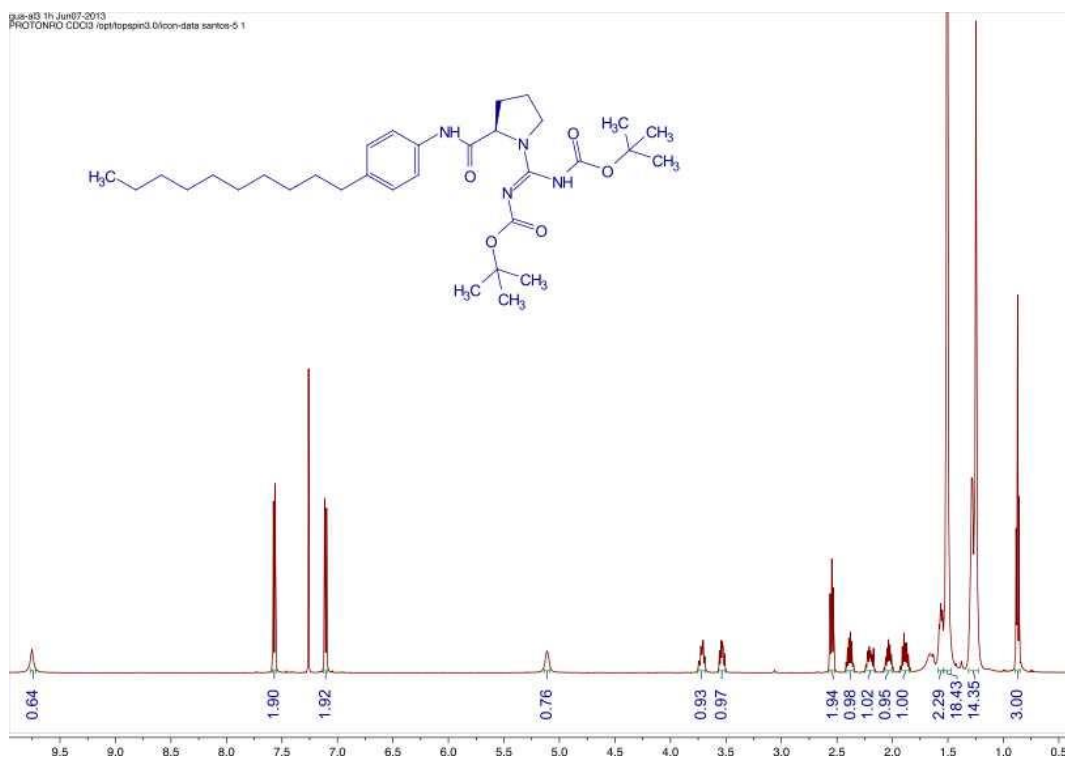
<sup>1</sup>H-NMR Spectrum for (S)-tert-butyl (((tert-butoxycarbonyl)imino)(2-((4-decylphenyl)carbamoyl)pyrrolidin-1-yl)methyl)carbamate-



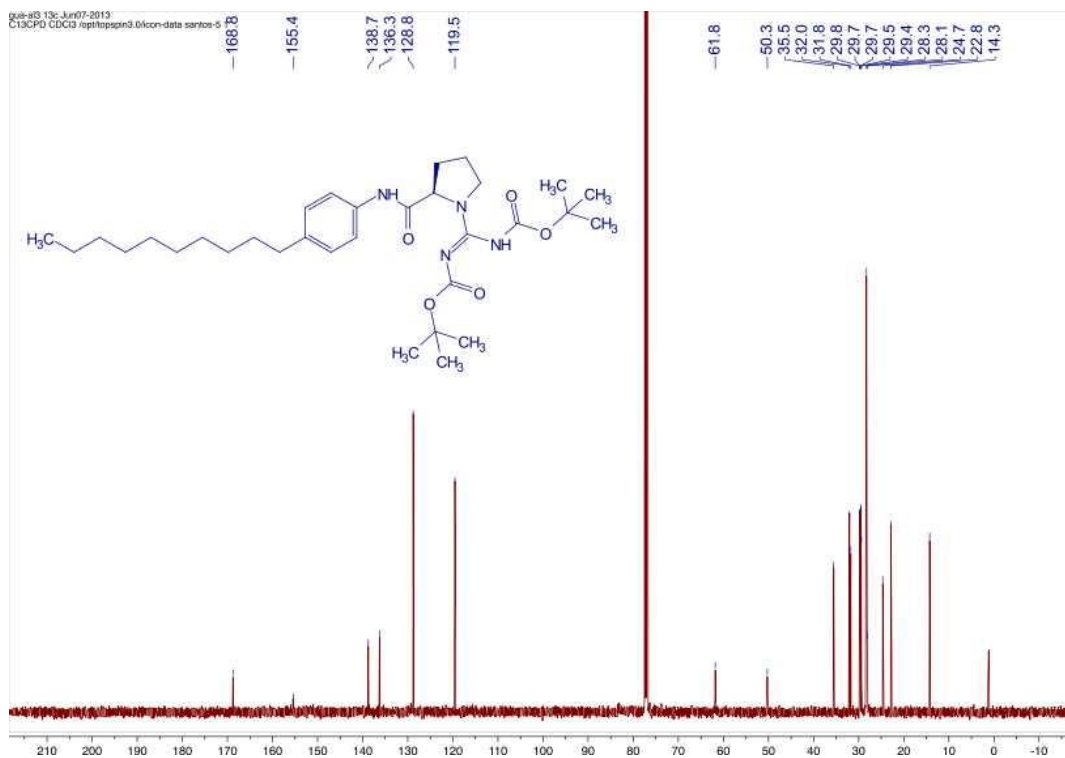
<sup>13</sup>C-NMR Spectrum for (S)-tert-butyl (((tert-butoxycarbonyl)imino)(2-((4-decylphenyl)carbamoyl)pyrrolidin-1-yl)methyl)carbamate-



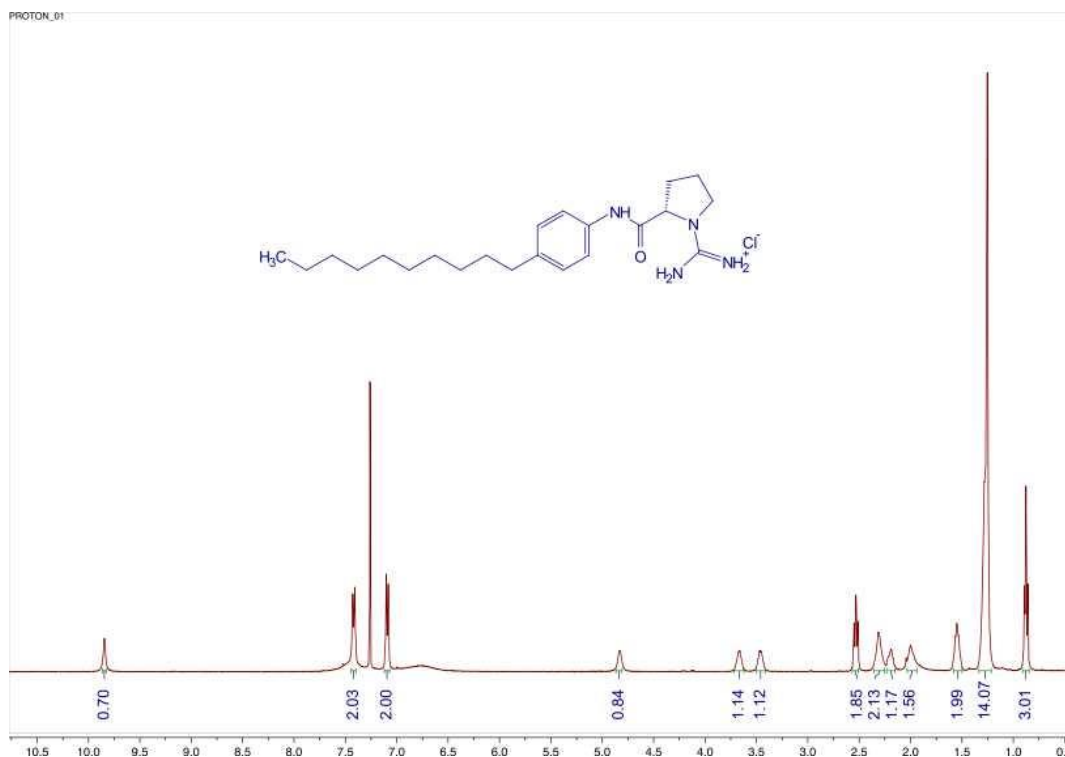
<sup>1</sup>H-NMR Spectrum for (R)-tert-butyl (((tert-butoxycarbonyl)imino)(2-((4-decylphenyl)carbamoyl)pyrrolidin-1-yl)methyl)carbamate-



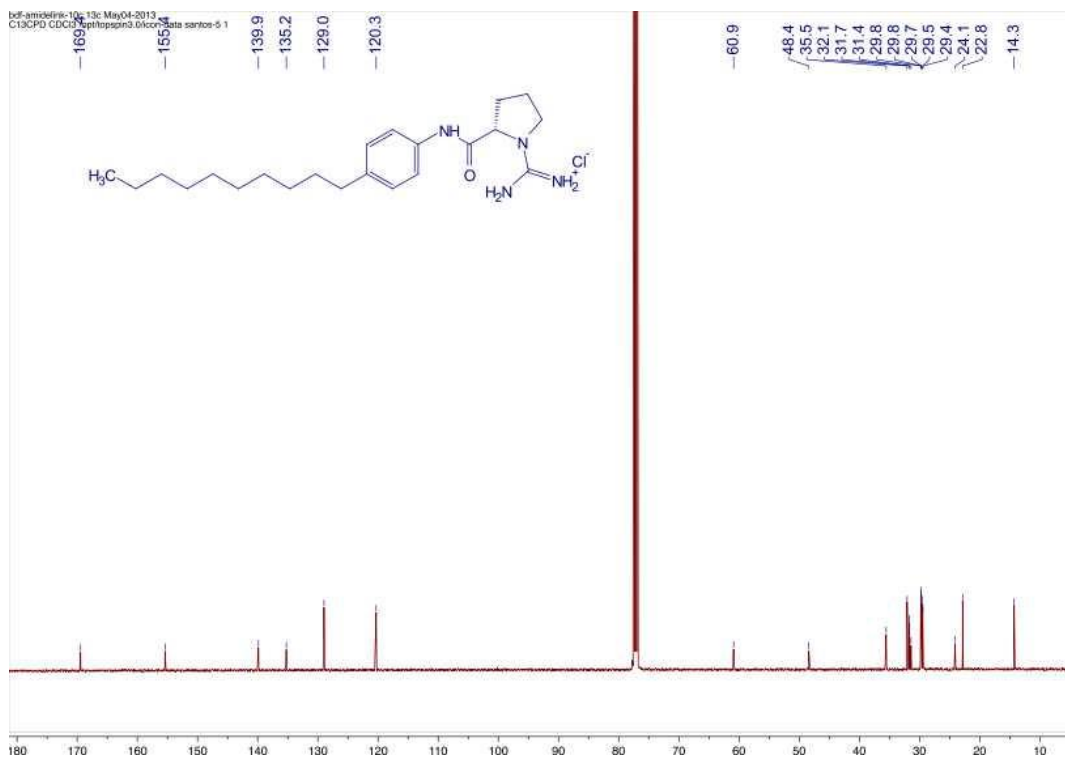
<sup>13</sup>C-NMR Spectrum for (R)-tert-butyl (((tert-butoxycarbonyl)imino)(2-((4-decylphenyl)carbamoyl)pyrrolidin-1-yl)methyl)carbamate-



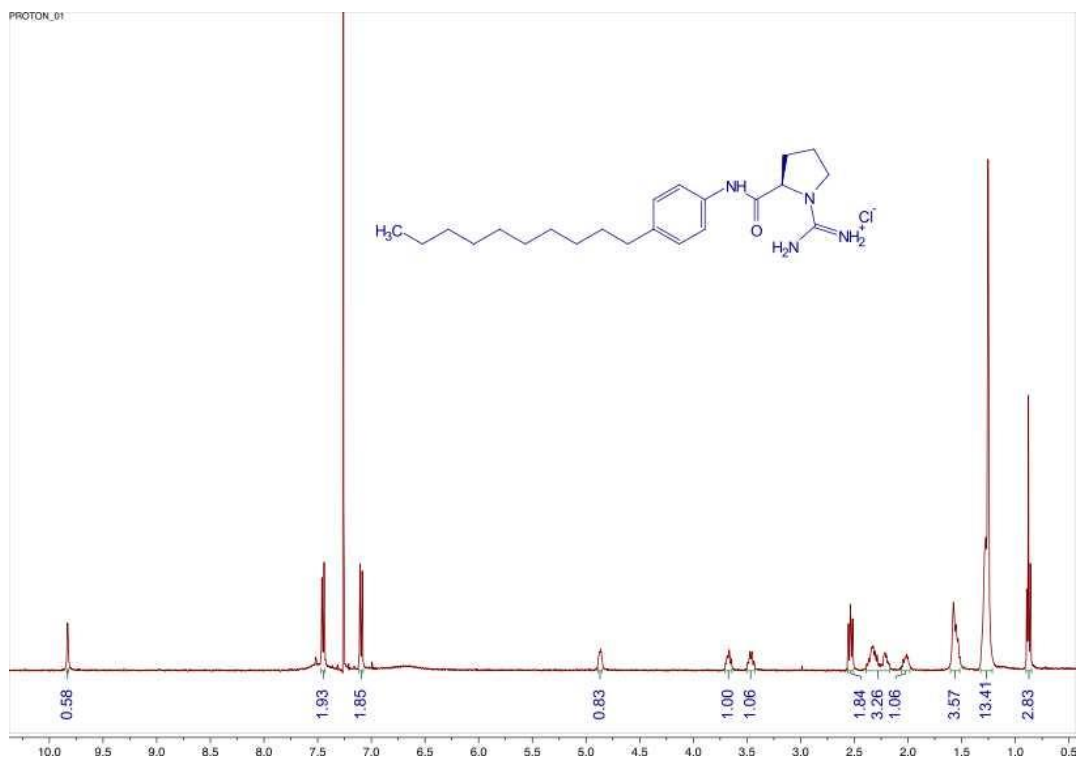
<sup>1</sup>H-NMR Spectrum for (*S*)-amino (2-((4-decylphenyl)carbamoyl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.38a**-



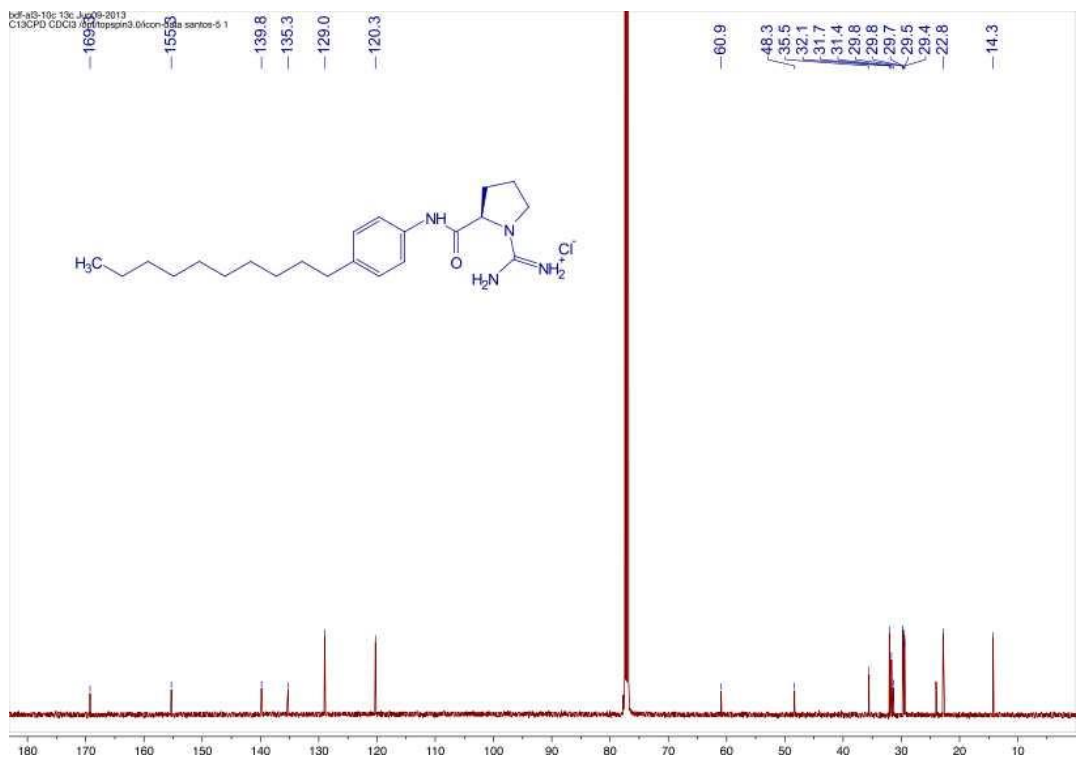
<sup>13</sup>C-NMR Spectrum for (*S*)-amino (2-((4-decylphenyl)carbamoyl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.38a**-



<sup>1</sup>H-NMR Spectrum for (*R*)-amino(2-((4-decylphenyl)carbamoyl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.38b**-

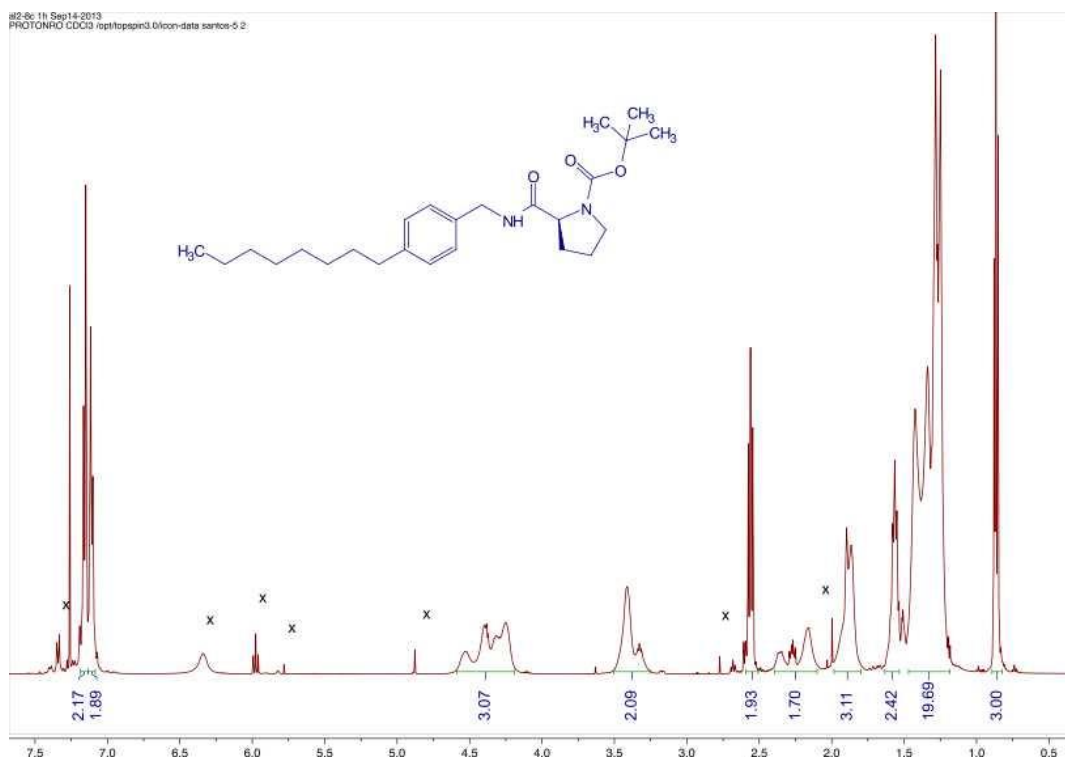


<sup>13</sup>C-NMR Spectrum for (*R*)-amino(2-((4-decylphenyl)carbamoyl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.38b**-

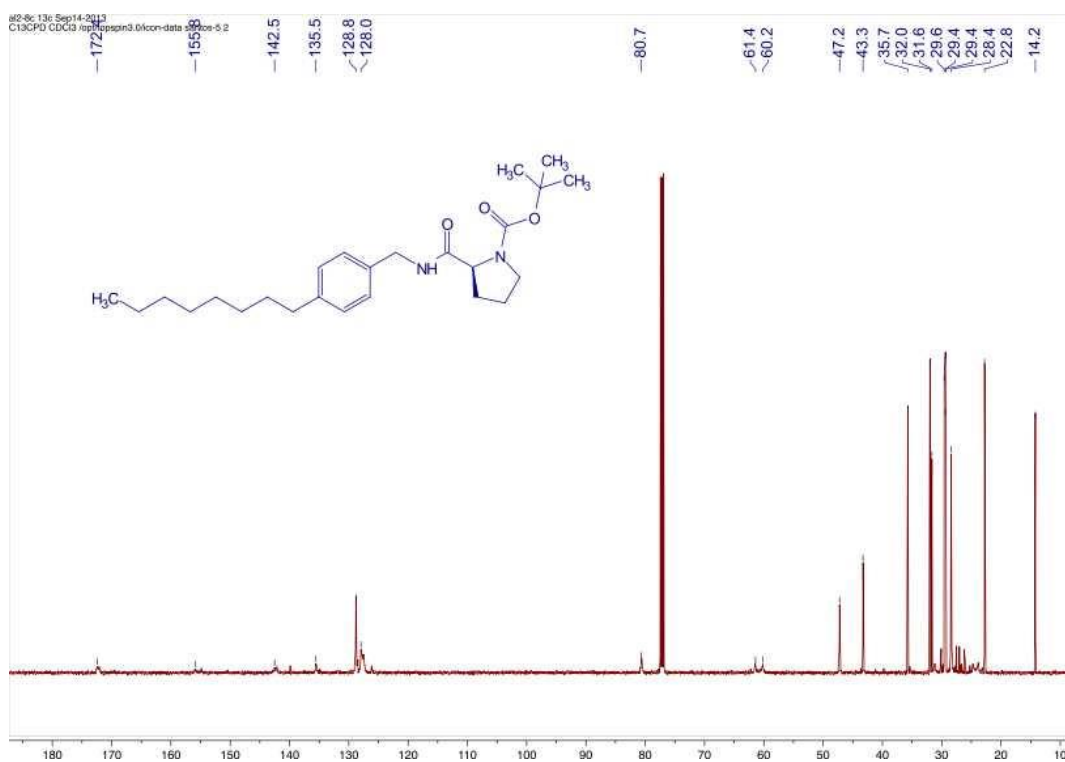




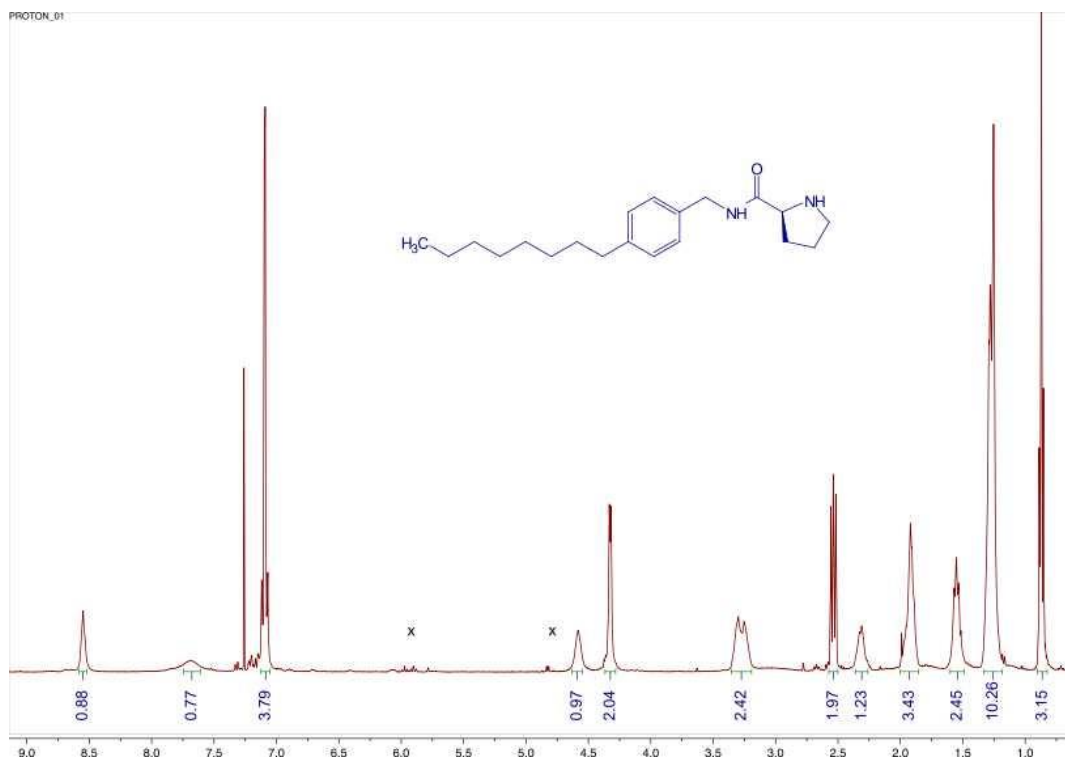
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-((4-octylbenzyl)carbamoyl)pyrrolidine-1-carboxylate-



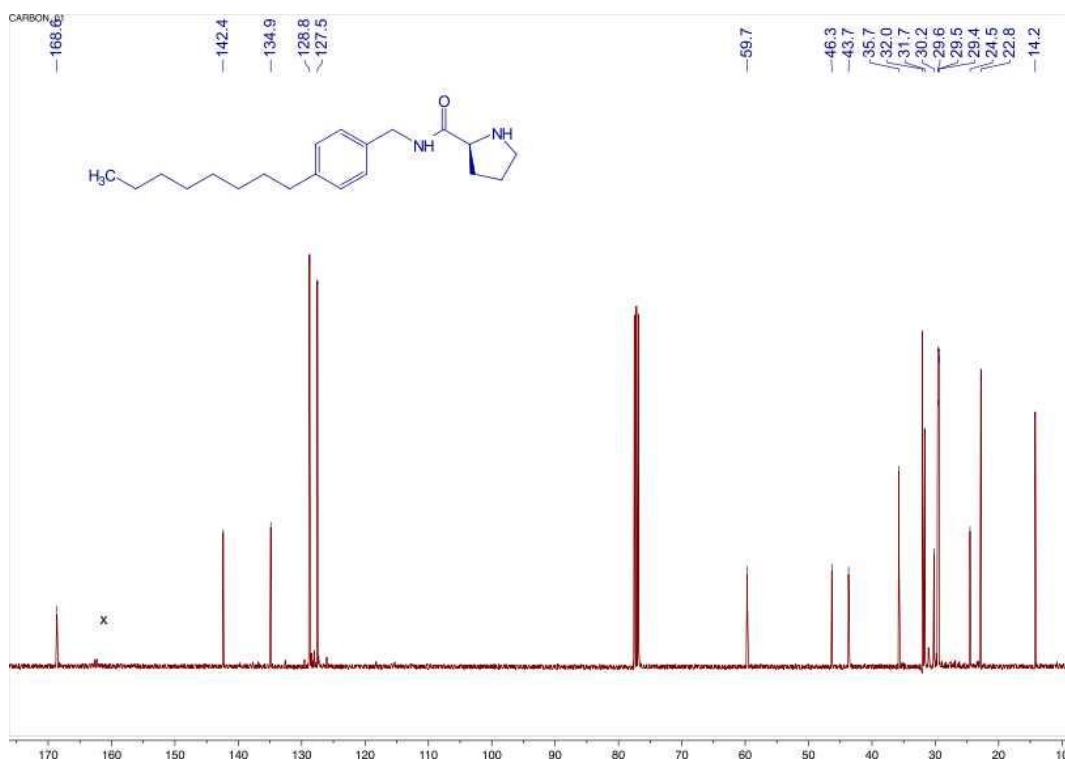
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-((4-octylbenzyl)carbamoyl)pyrrolidine-1-carboxylate-



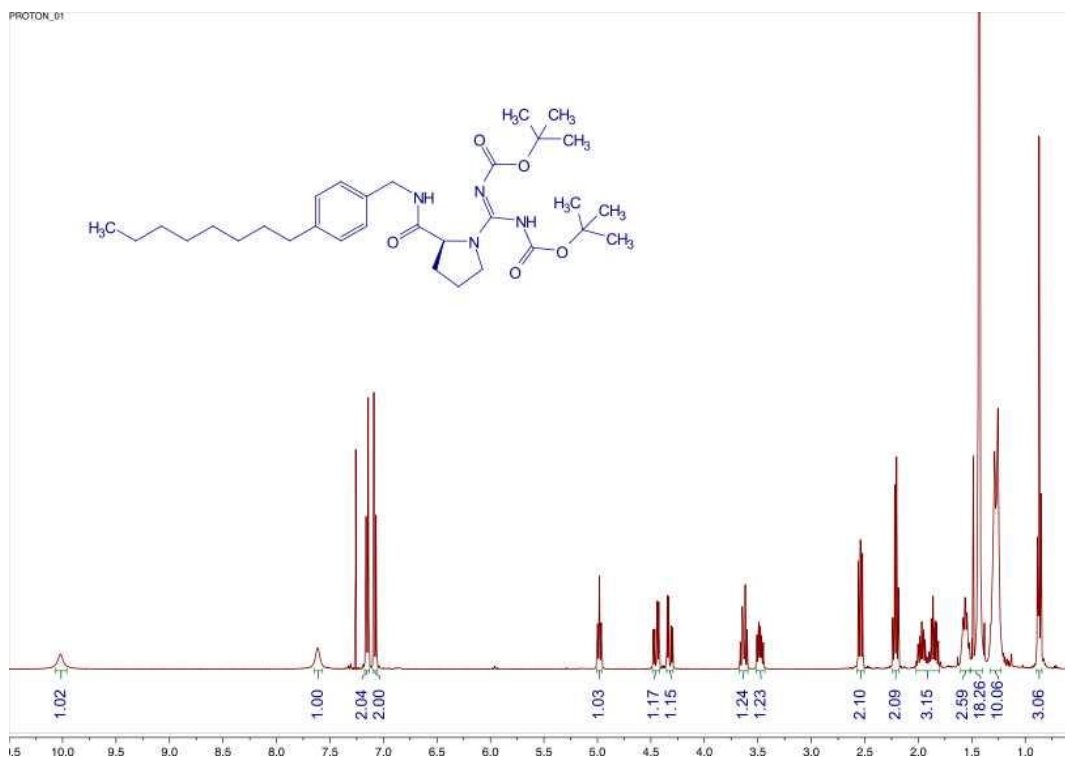
<sup>1</sup>H-NMR Spectrum for (S)-2-((4-octylbenzyl)carbamoyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate-



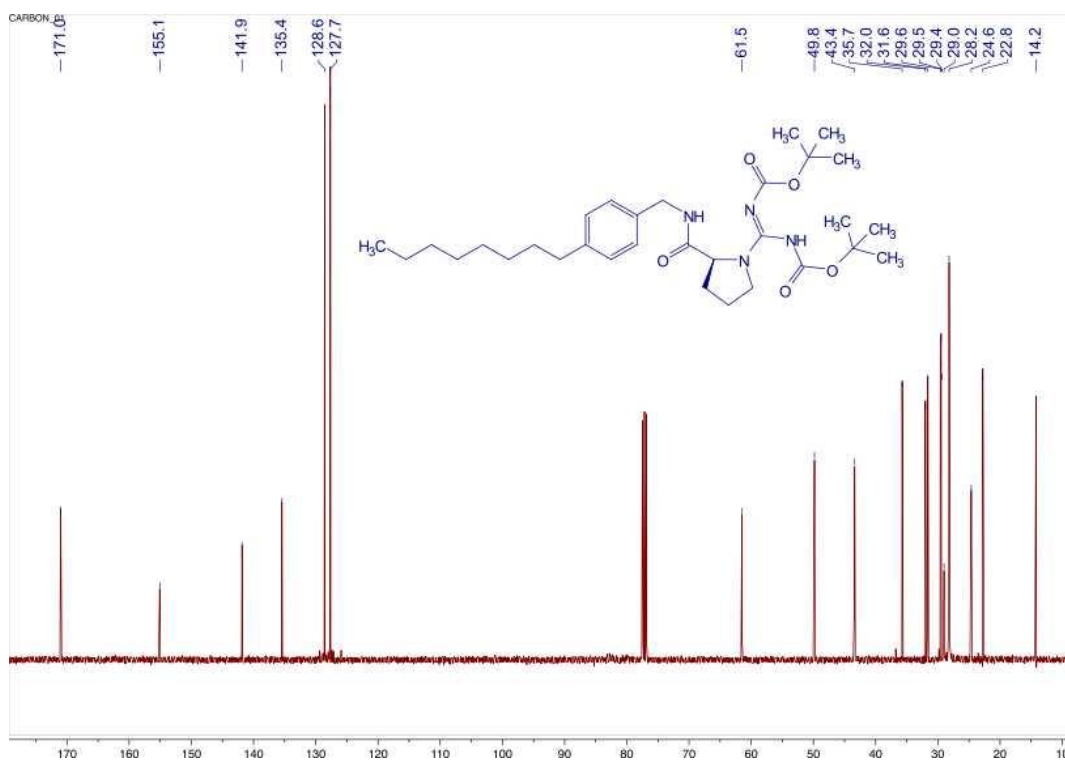
<sup>13</sup>C-NMR Spectrum for (S)-2-((4-octylbenzyl)carbamoyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate-



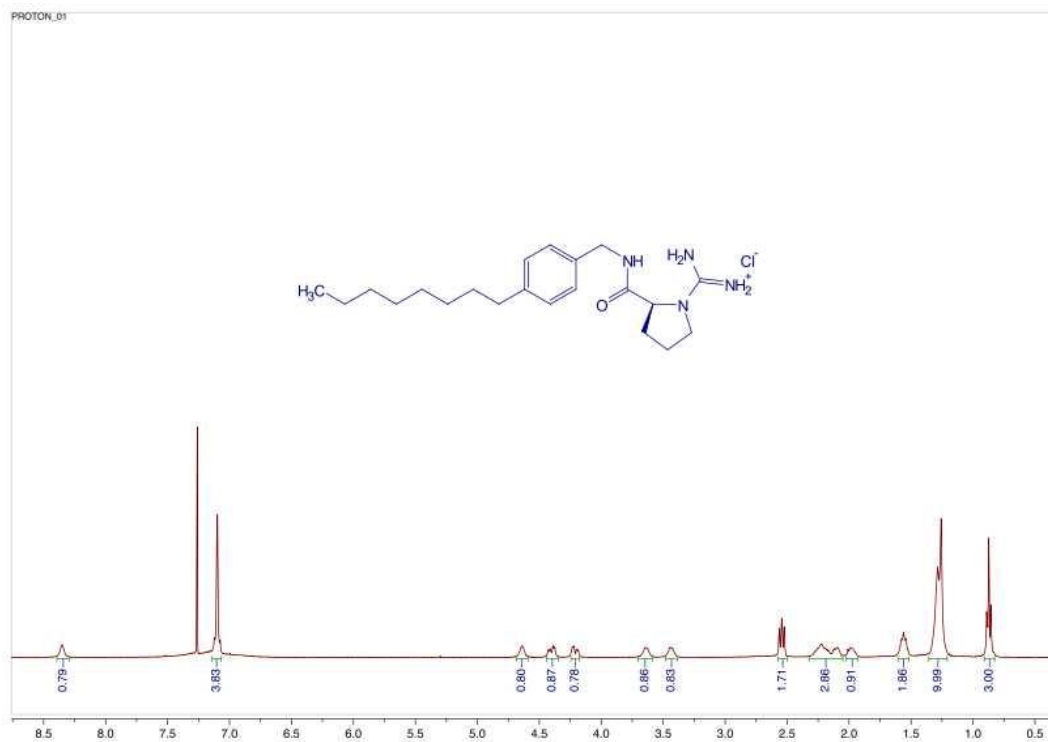
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-((4-octylbenzyl)carbamoyl)pyrrolidin-1-yl)methylene)carbamate **2.39**-



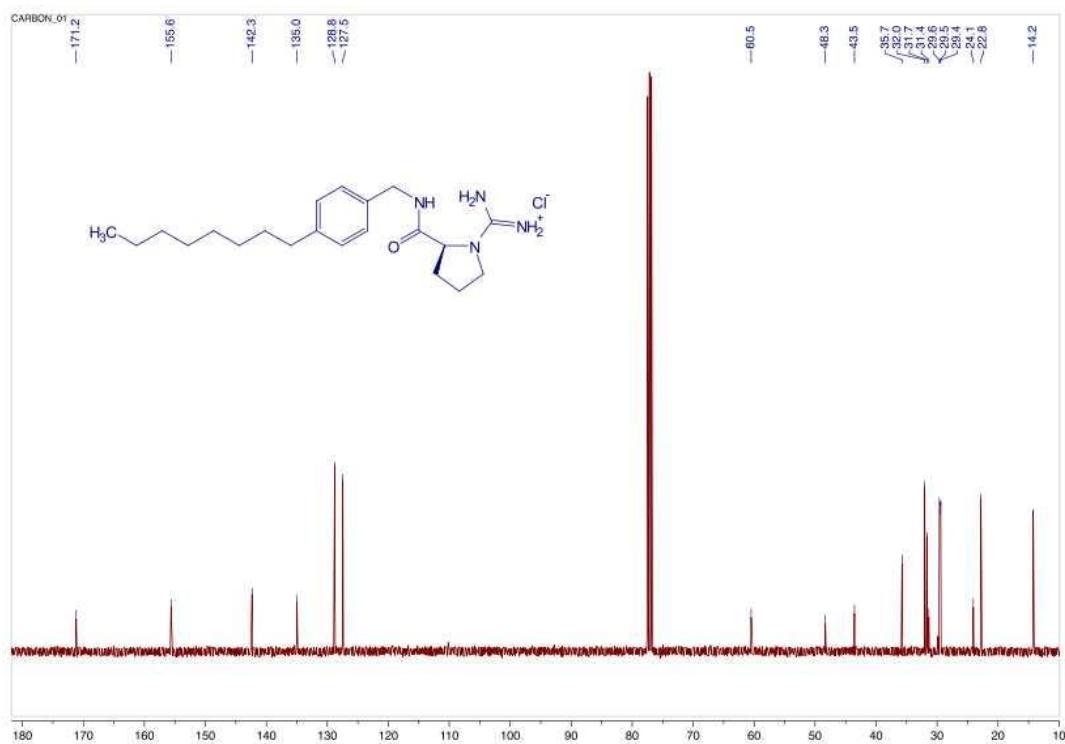
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-((4-octylbenzyl)carbamoyl)pyrrolidin-1-yl)methylene)carbamate **2.39**-



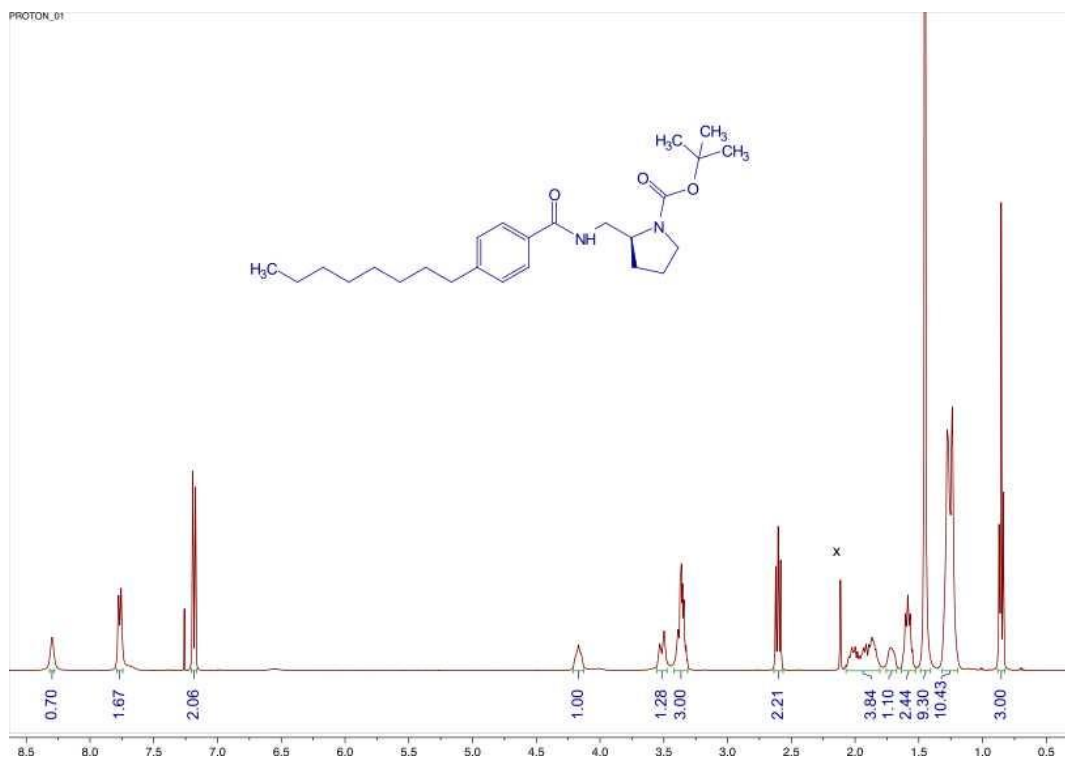
<sup>1</sup>H-NMR Spectrum for (*S*)-amino (2-((4-octylbenzyl)carbamoyl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.40**-



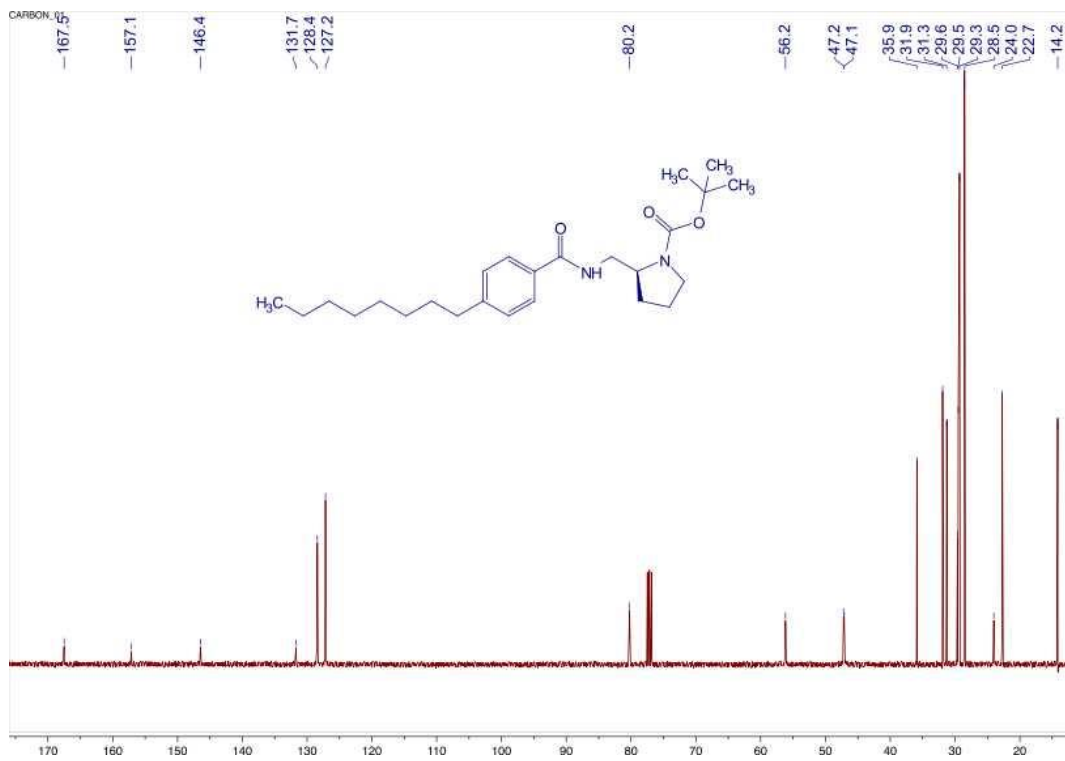
<sup>13</sup>C-NMR Spectrum for (*S*)-amino (2-((4-octylbenzyl)carbamoyl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.40**-



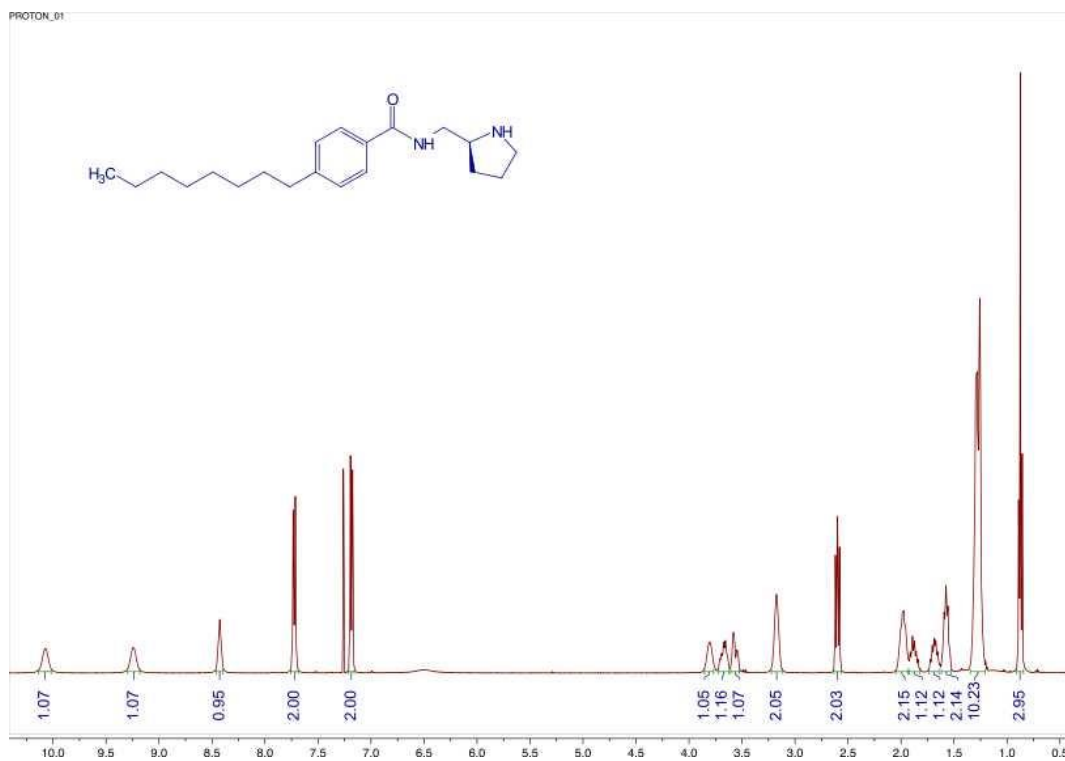
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-((4-octylbenzamido)methyl)pyrrolidine-1-carboxylate  
2.41-



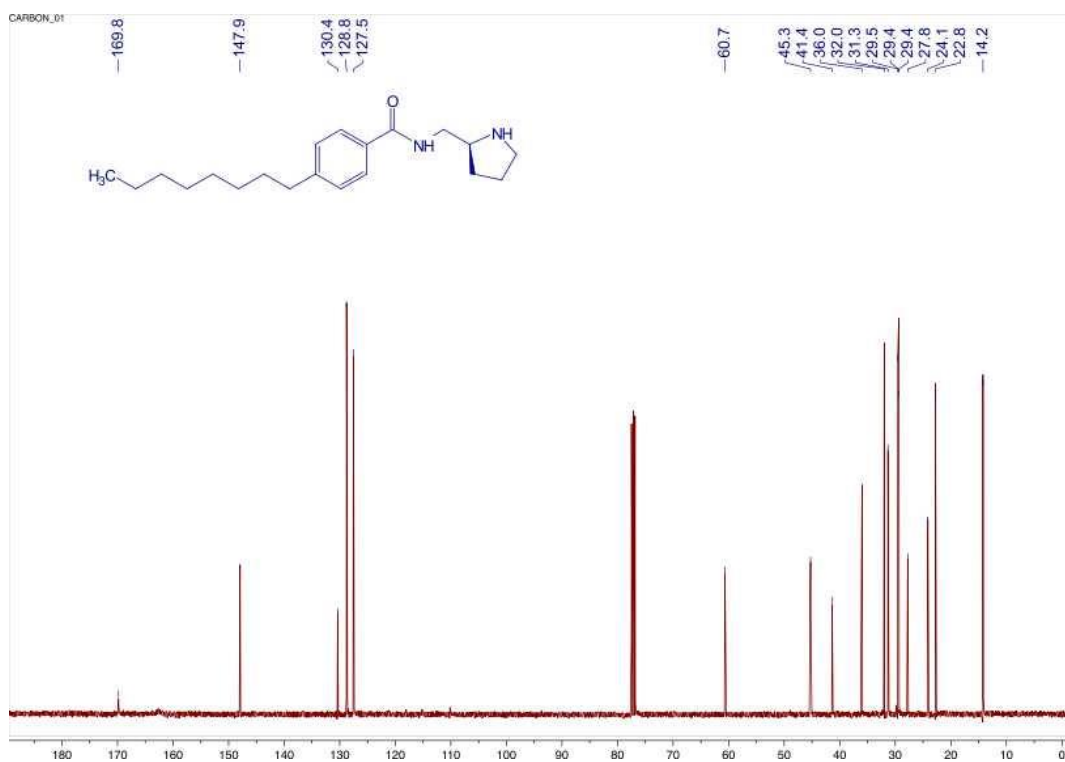
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-((4-octylbenzamido)methyl)pyrrolidine-1-carboxylate  
2.41-



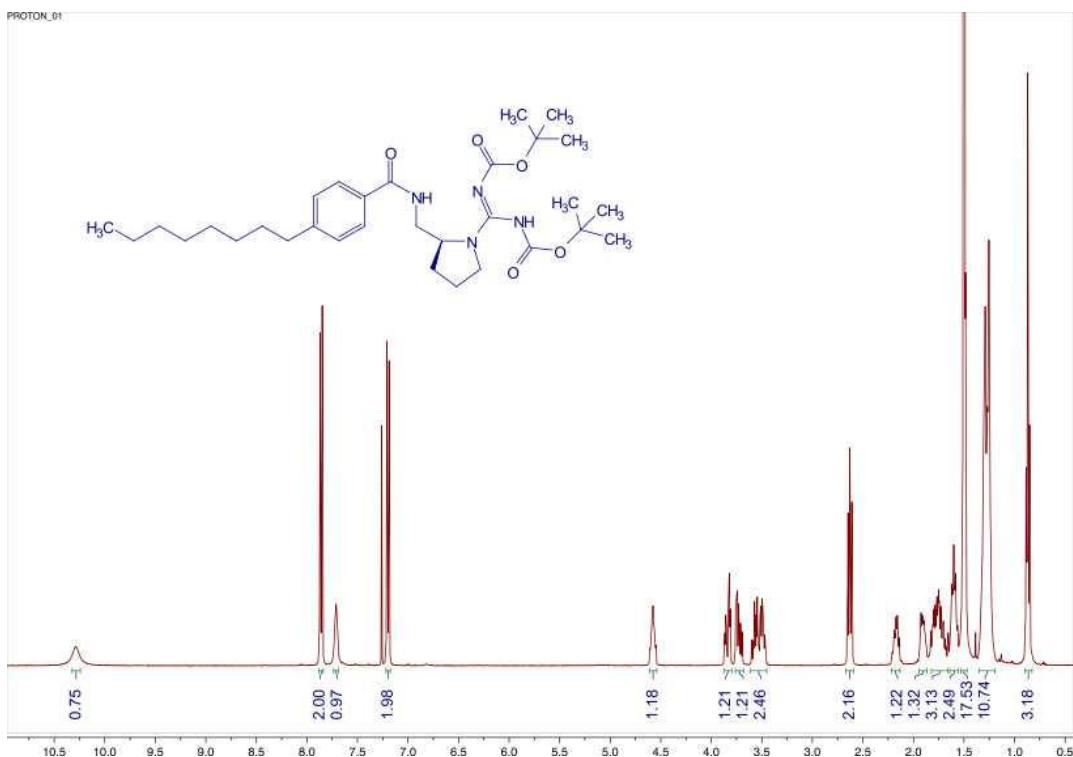
$^1\text{H-NMR}$  Spectrum for (*S*)-2-((4-octylbenzamido)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate-



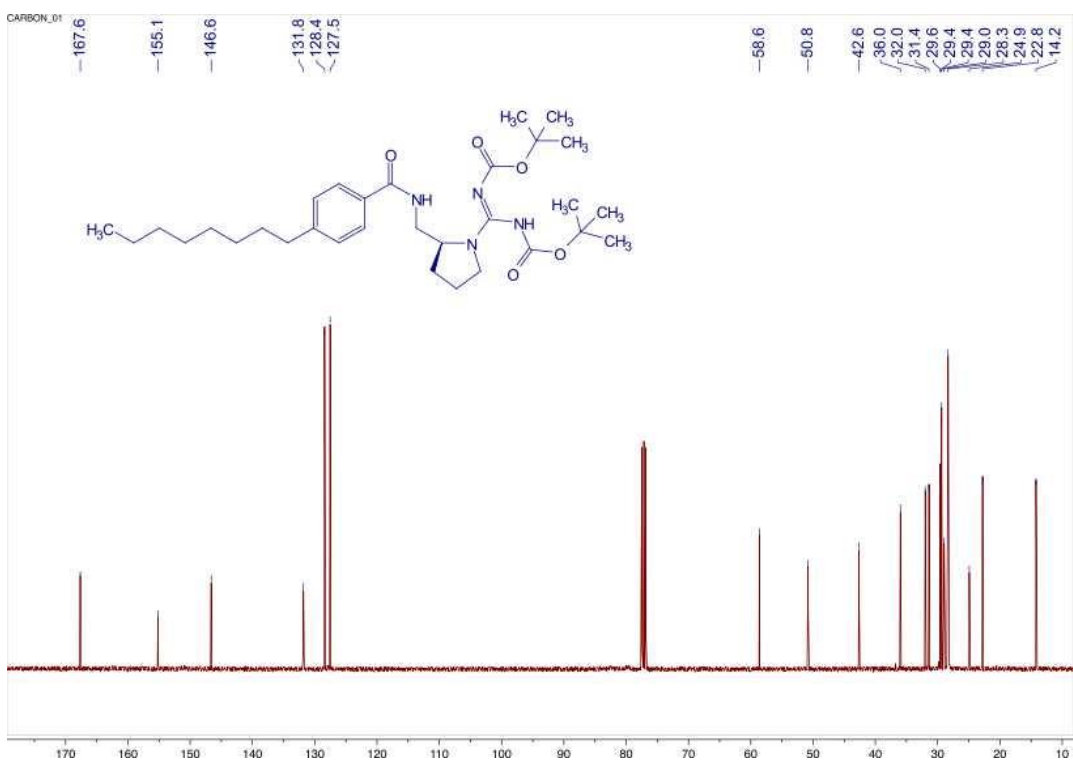
$^{13}\text{C-NMR}$  Spectrum for (*S*)-2-((4-octylbenzamido)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate-



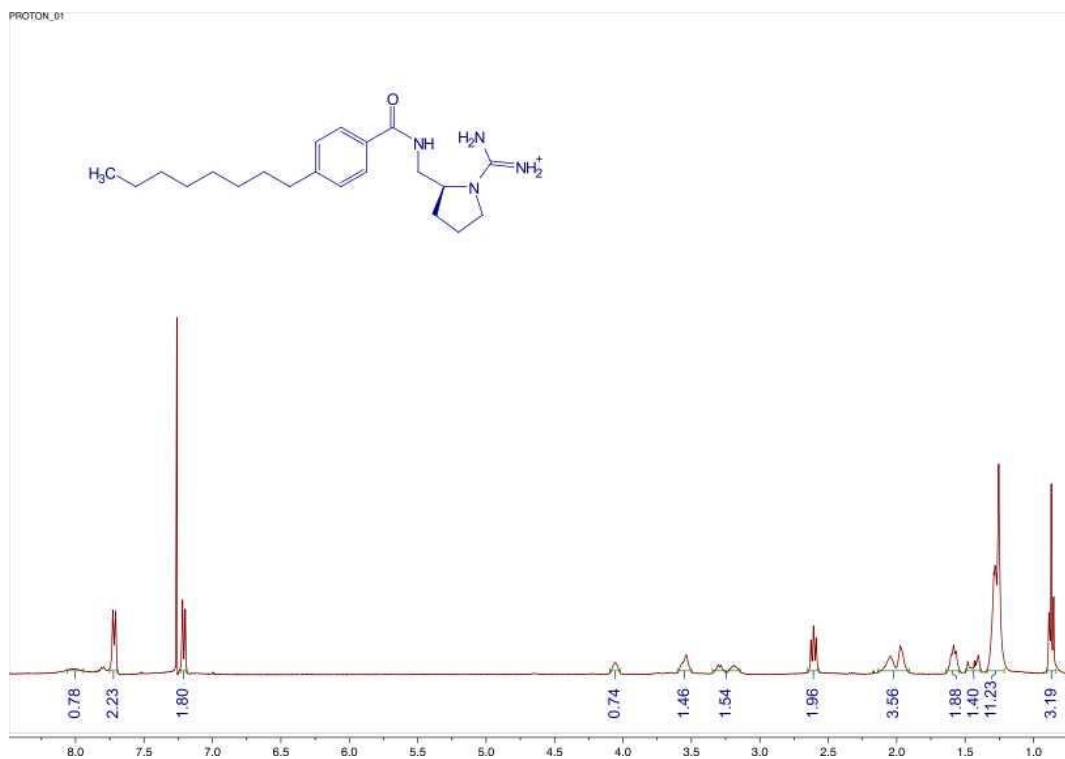
<sup>1</sup>H-NMR Spectrum for (S)-tert-butyl (((tert-butoxycarbonyl)amino)(2-((4-octylbenzamido)methyl)pyrrolidin-1-yl)methylene)carbamate-



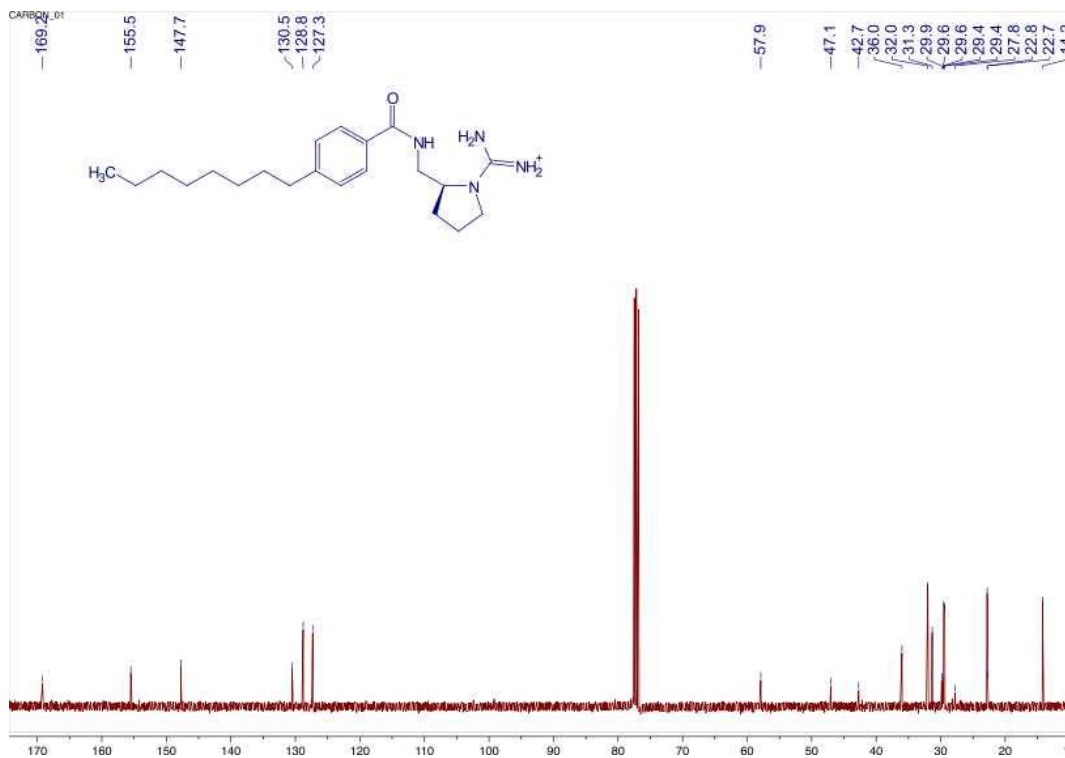
<sup>13</sup>C-NMR Spectrum for (S)-tert-butyl (((tert-butoxycarbonyl)amino)(2-((4-octylbenzamido)methyl)pyrrolidin-1-yl)methylene)carbamate-



<sup>1</sup>H-NMR Spectrum for (*S*)-amino (2-((4-octylbenzamido)methyl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.42**-

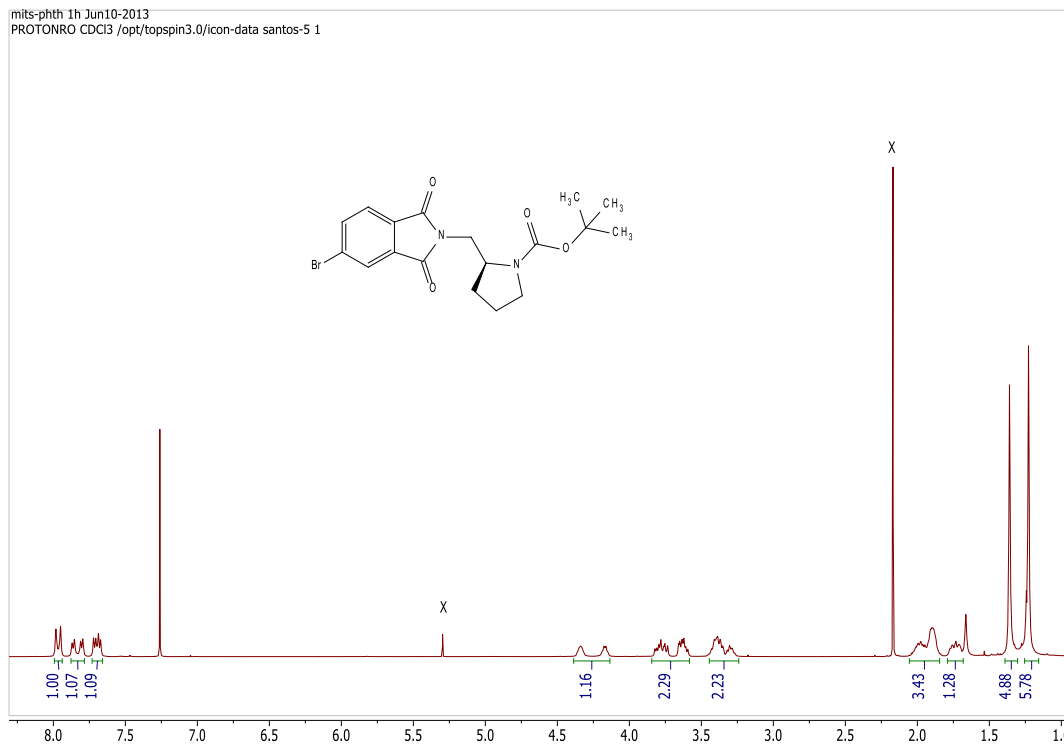


<sup>13</sup>C-NMR Spectrum for (*S*)-amino (2-((4-octylbenzamido)methyl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.42**-

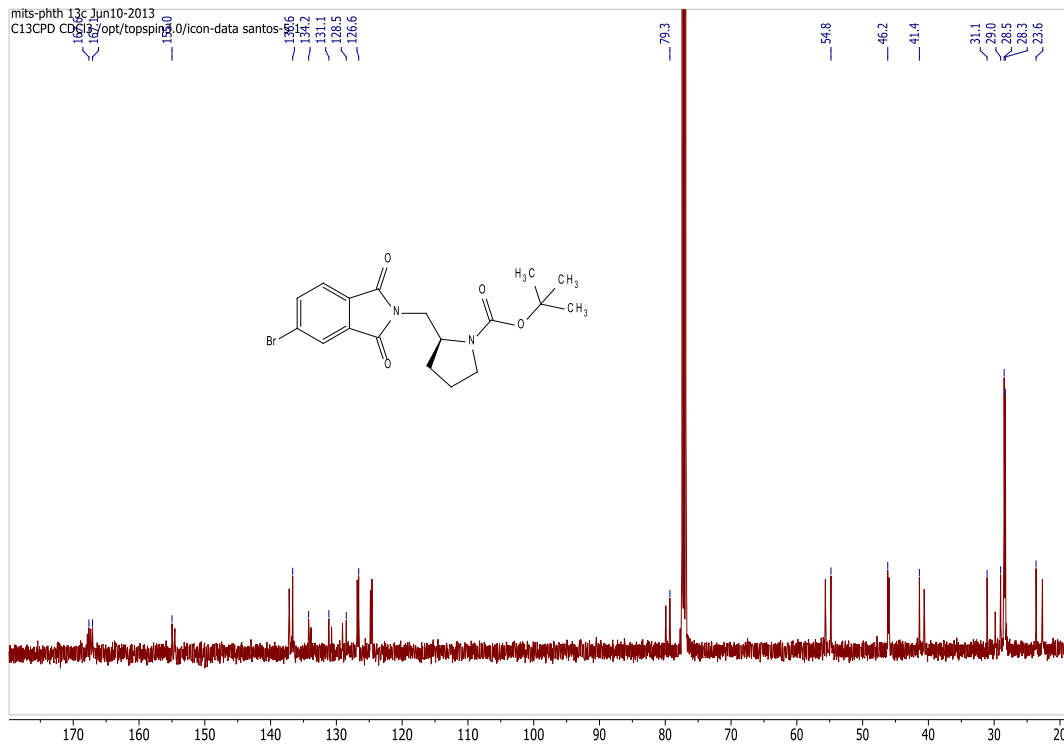




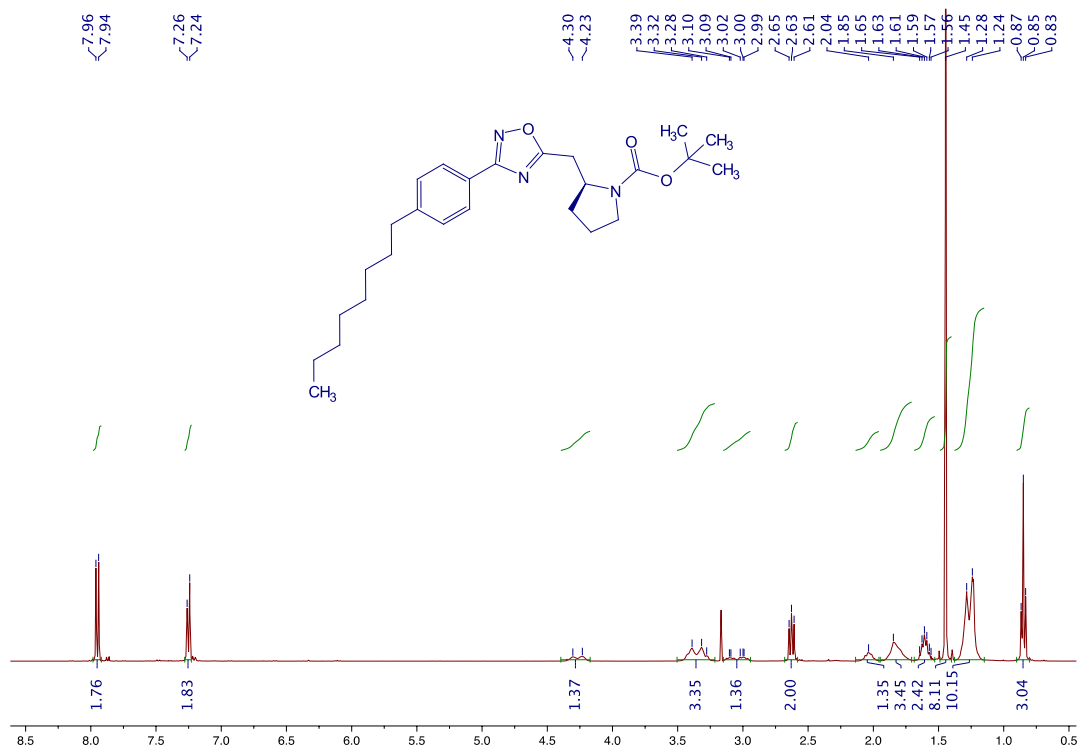
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-((5-bromo-1,3-dioxisoindolin-2-yl)methyl)pyrrolidine-1-carboxylate **2.44** –



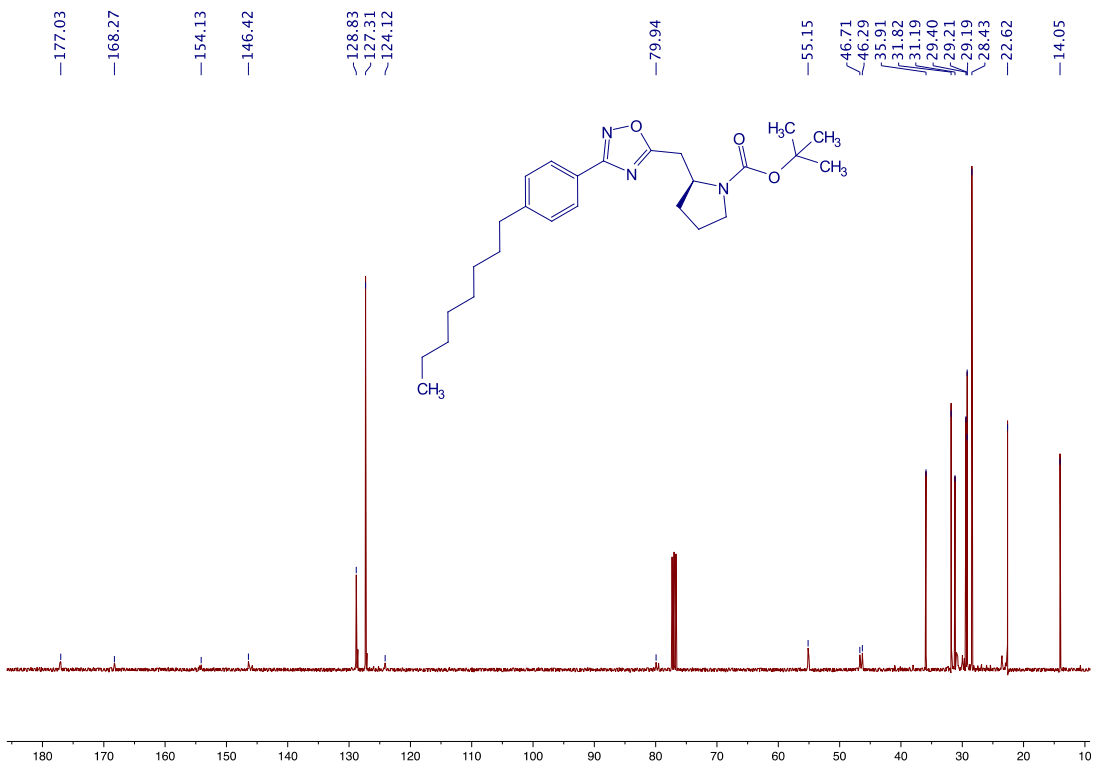
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-((5-bromo-1,3-dioxisoindolin-2-yl)methyl)pyrrolidine-1-carboxylate **2.44** –



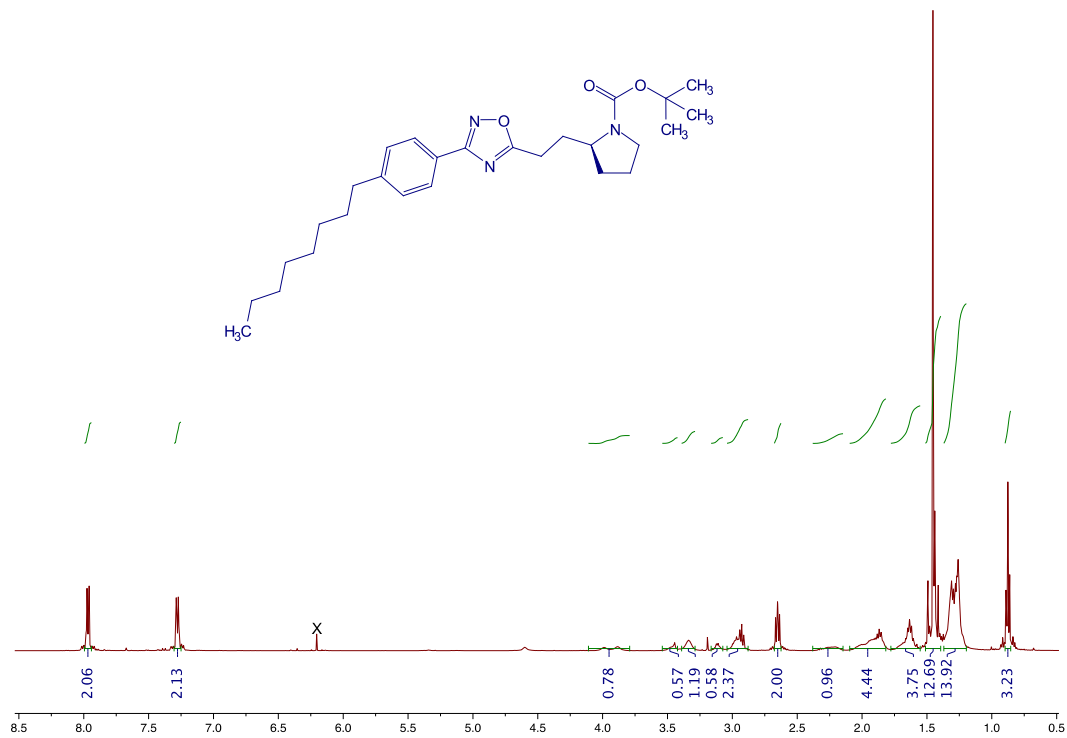
<sup>1</sup>H-NMR Spectrum for *tert*-butyl (S)-2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate **2.47a** -



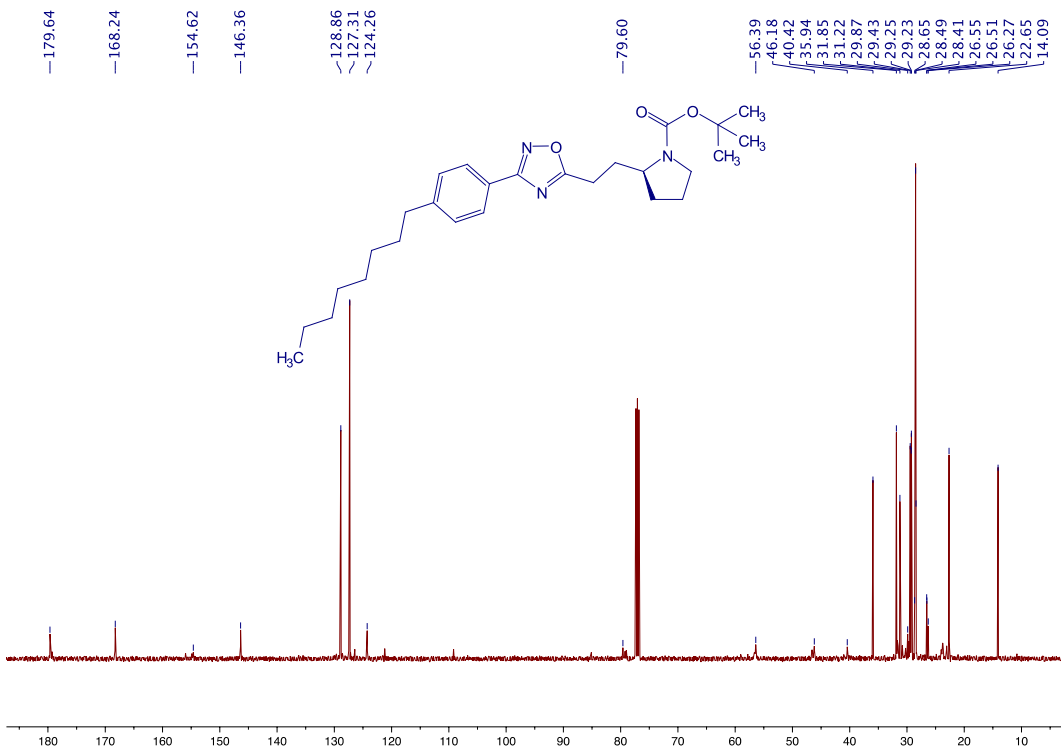
<sup>13</sup>C-NMR Spectrum for *tert*-butyl (*S*)-2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidine-1-carboxylate **2.47a** -



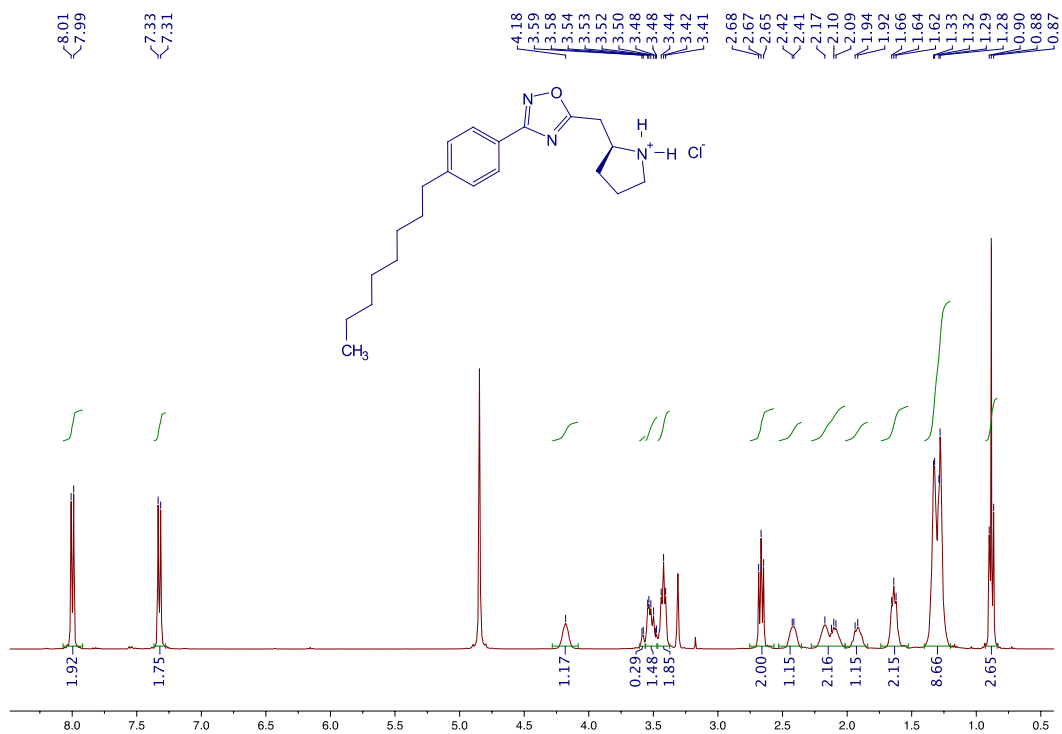
<sup>1</sup>H-NMR Spectrum for *tert*-butyl (*S*)-2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)pyrrolidine-1-carboxylate **2.47b**-



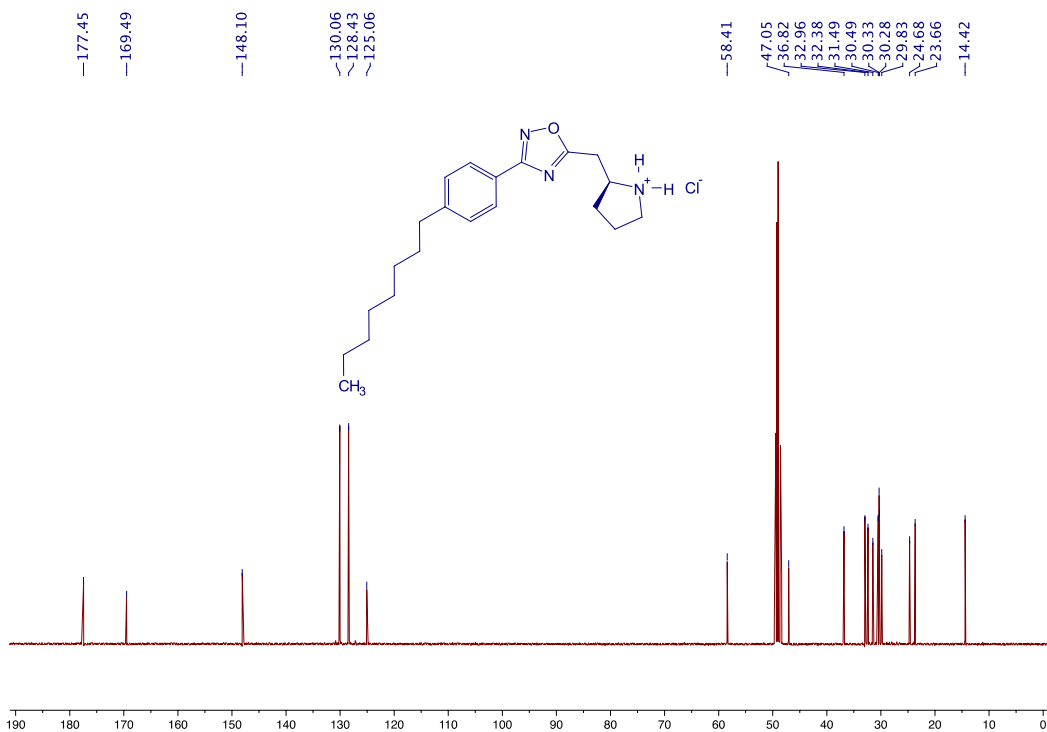
<sup>13</sup>C-NMR Spectrum for *tert*-butyl (*S*)-2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)pyrrolidine-1-carboxylate **2.47b**-



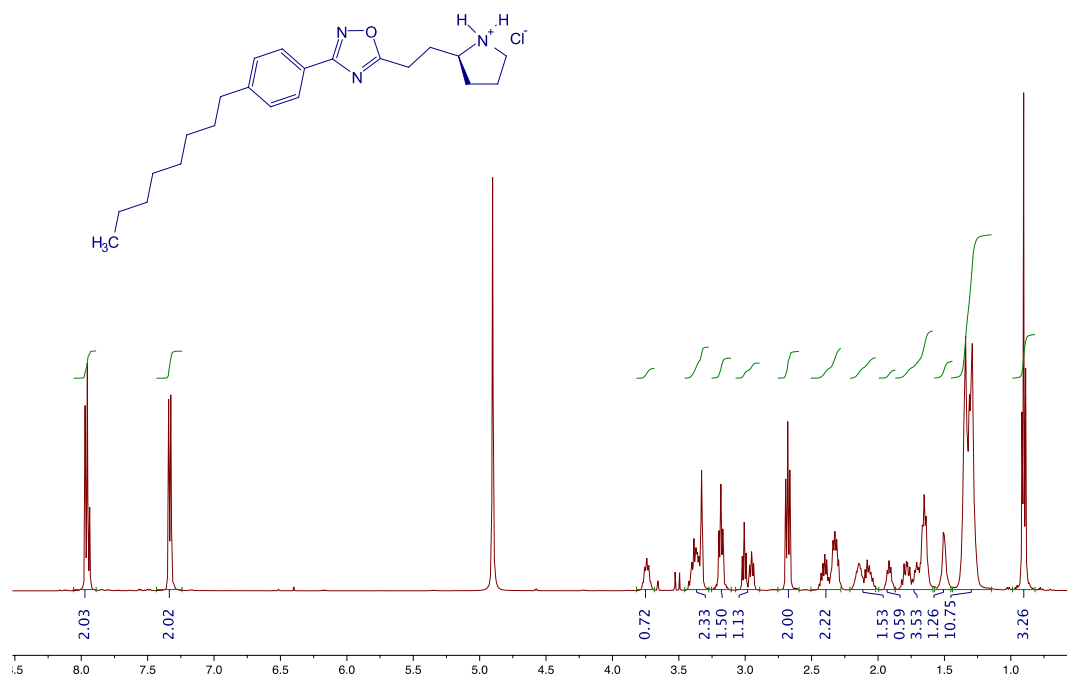
<sup>1</sup>H-NMR Spectrum for (S)-2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-ium chloride-



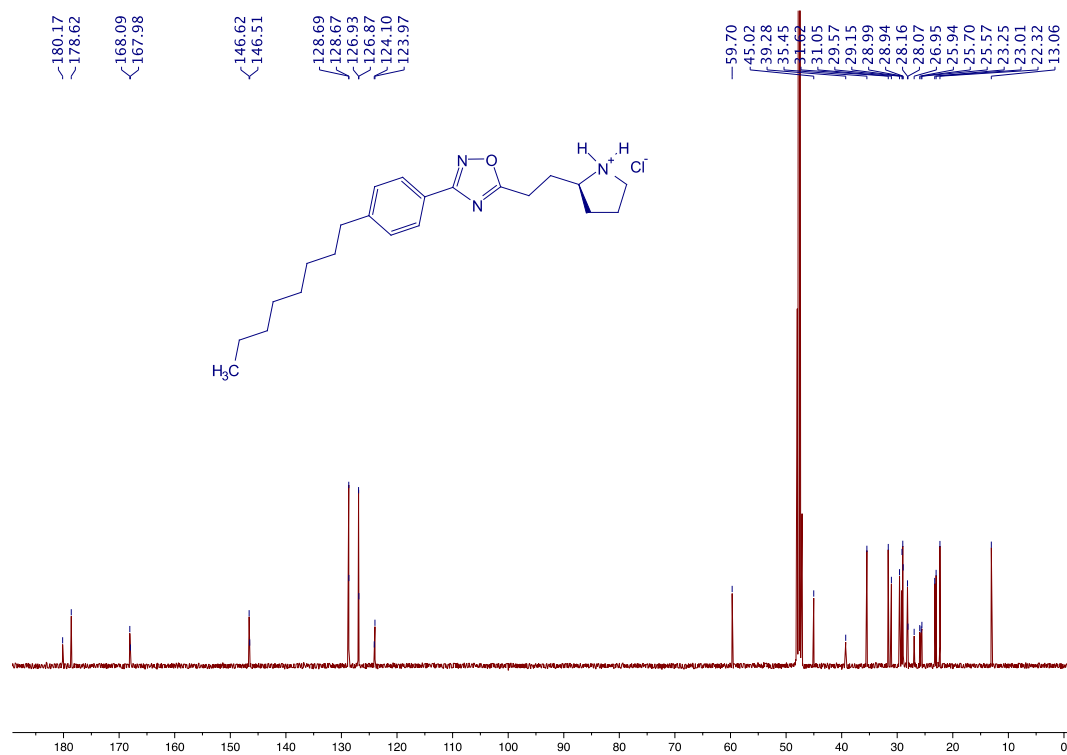
<sup>13</sup>C-NMR Spectrum for (S)-2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-ium chloride-



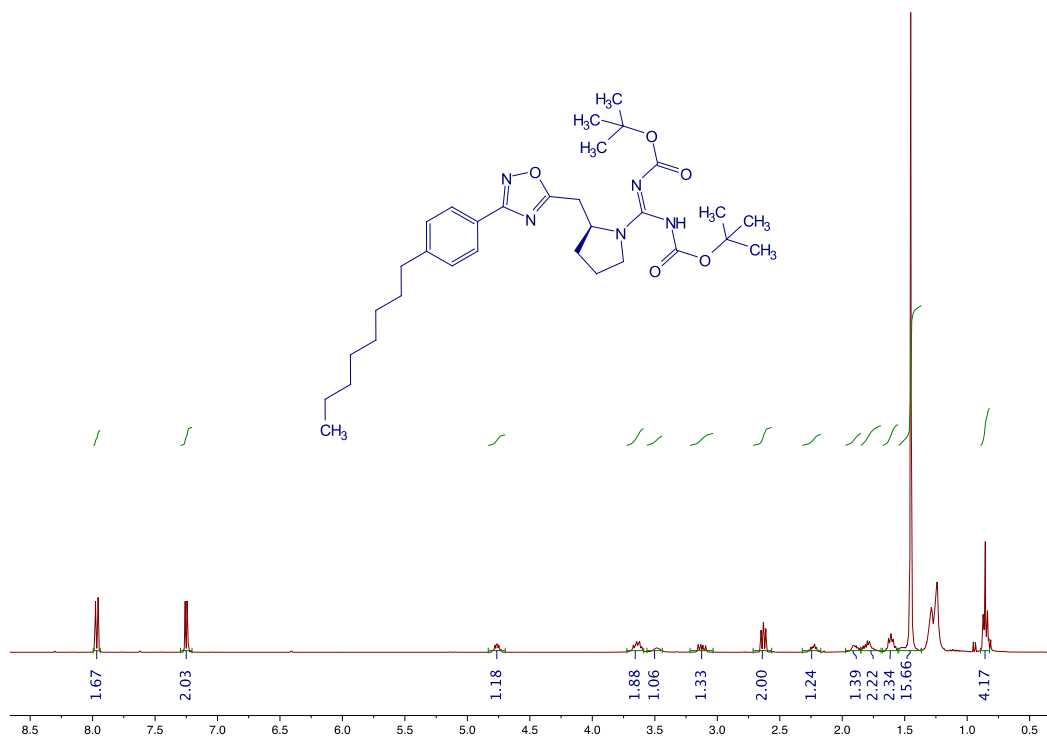
<sup>1</sup>H-NMR Spectrum for (*S*)-2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)pyrrolidin-1-ium chloride-



<sup>13</sup>C-NMR Spectrum for (*S*)-2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)pyrrolidin-1-ium chloride-

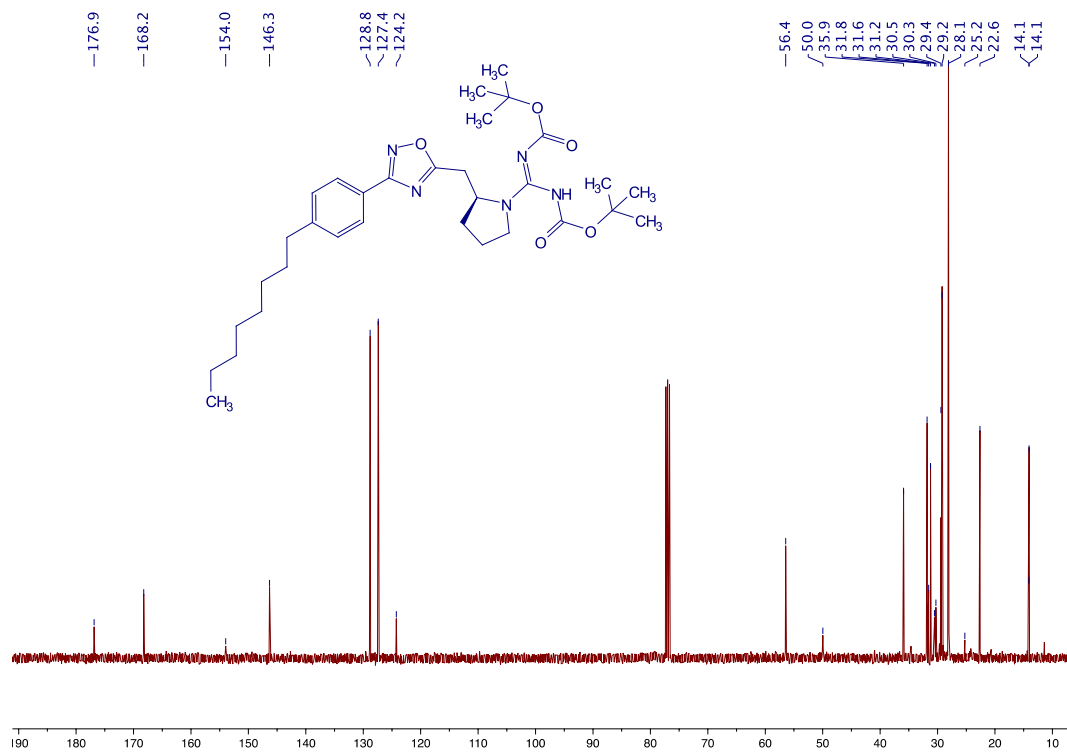


<sup>1</sup>H-NMR Spectrum for *tert*-butyl (*S*)-(((*tert*-butoxycarbonyl)amino)(2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methylene)carbamate-

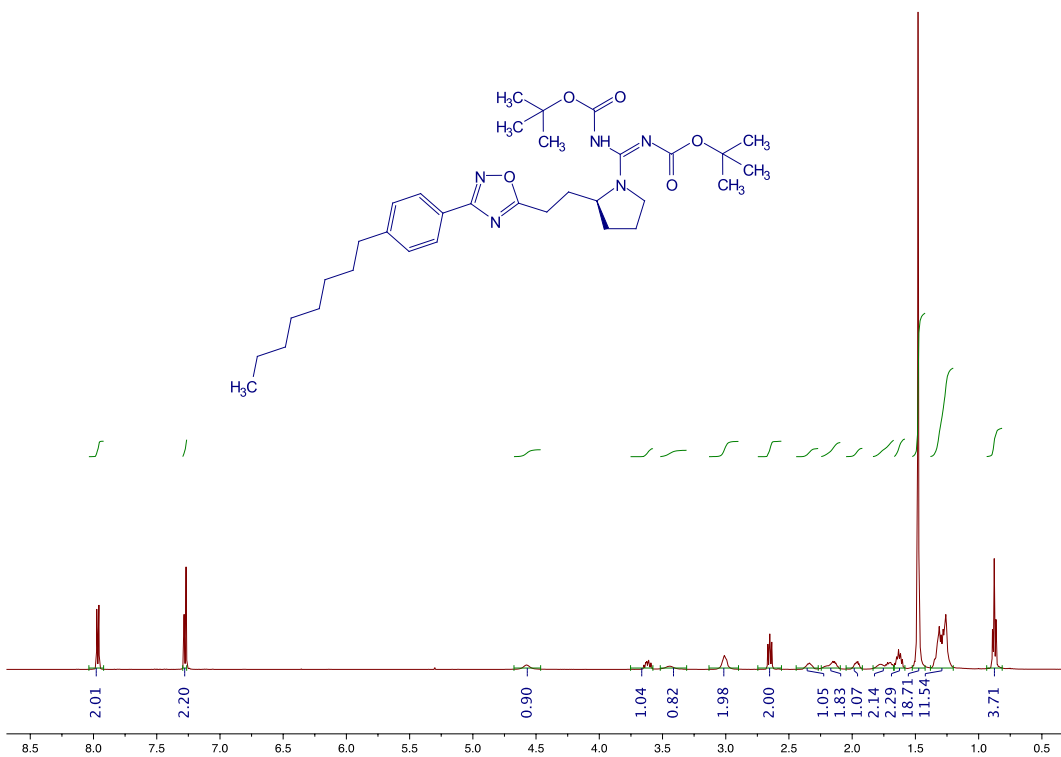




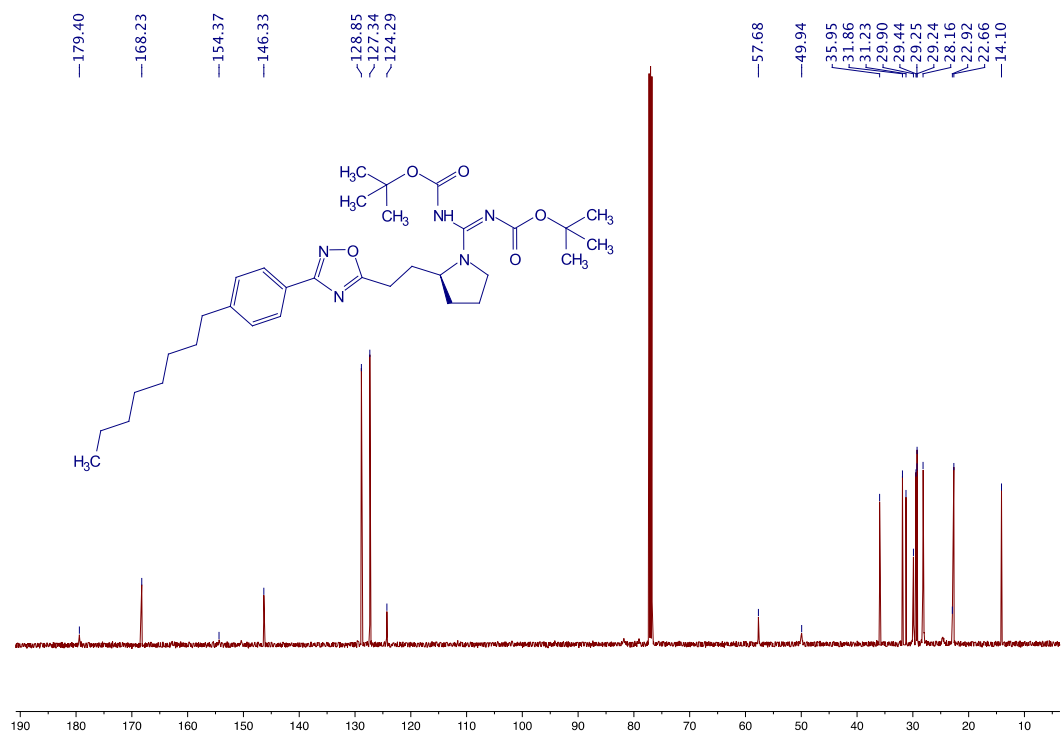
$^{13}\text{C}$ -NMR Spectrum for *tert*-butyl (*S*)-(((*tert*-butoxycarbonyl)amino)(2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methylene)carbamate-



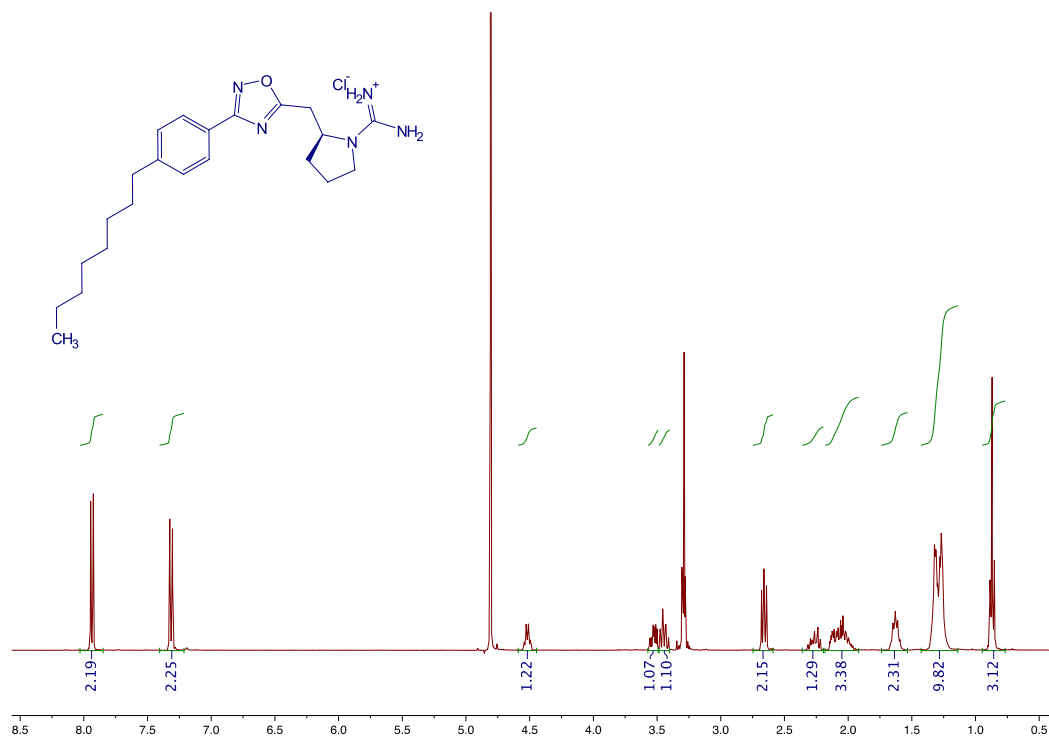
$^1\text{H-NMR}$  Spectrum for *tert*-butyl (*S*)-(((*tert*-butoxycarbonyl)imino)(2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)pyrrolidin-1-yl)methyl)carbamate-



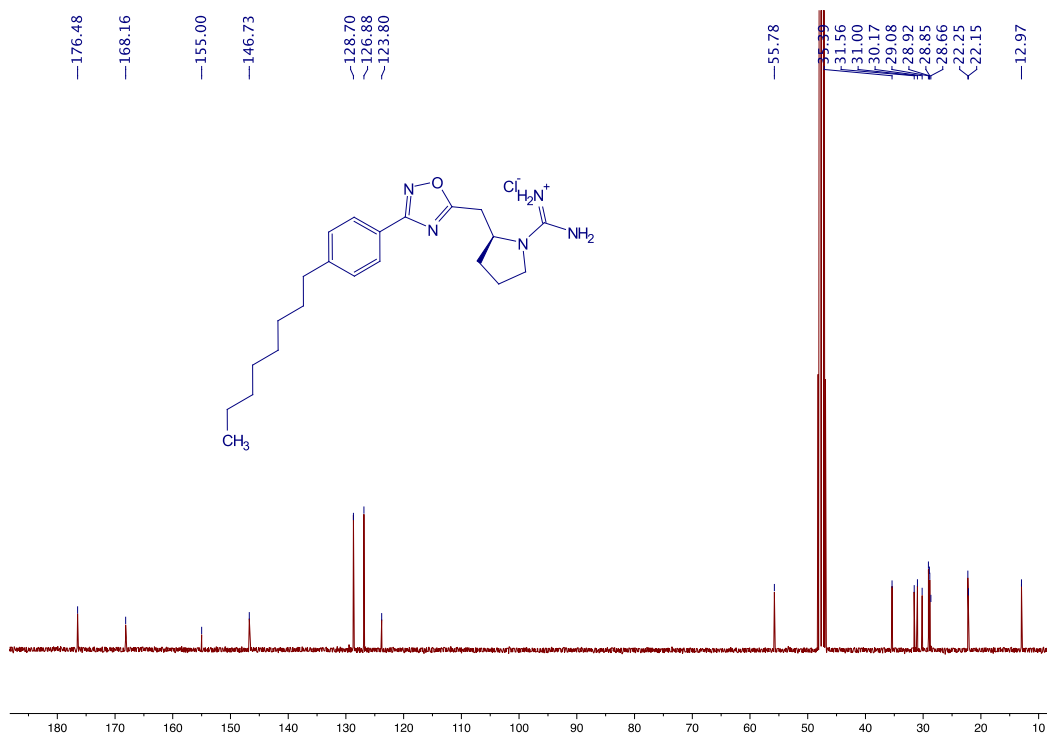
<sup>13</sup>C-NMR Spectrum for *tert*-butyl (*S*)-(((*tert*-butoxycarbonyl)imino)(2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)pyrrolidin-1-yl)methyl)carbamate-



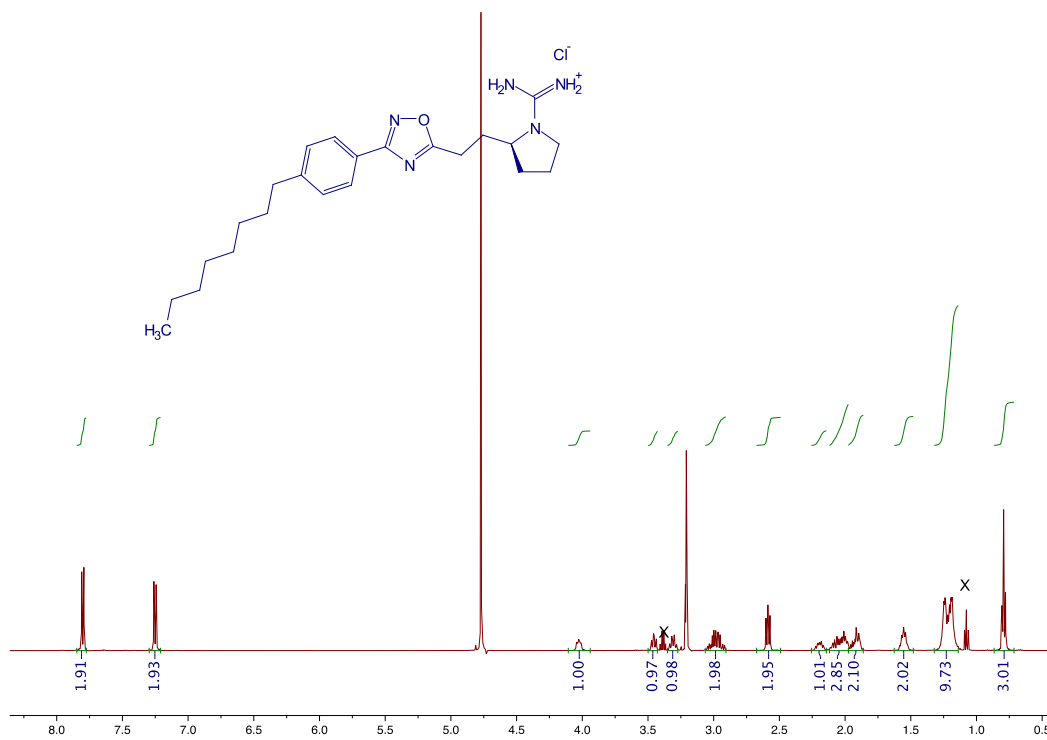
$^1\text{H-NMR}$  Spectrum for (*S*)-amino(2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride **2.48a**-



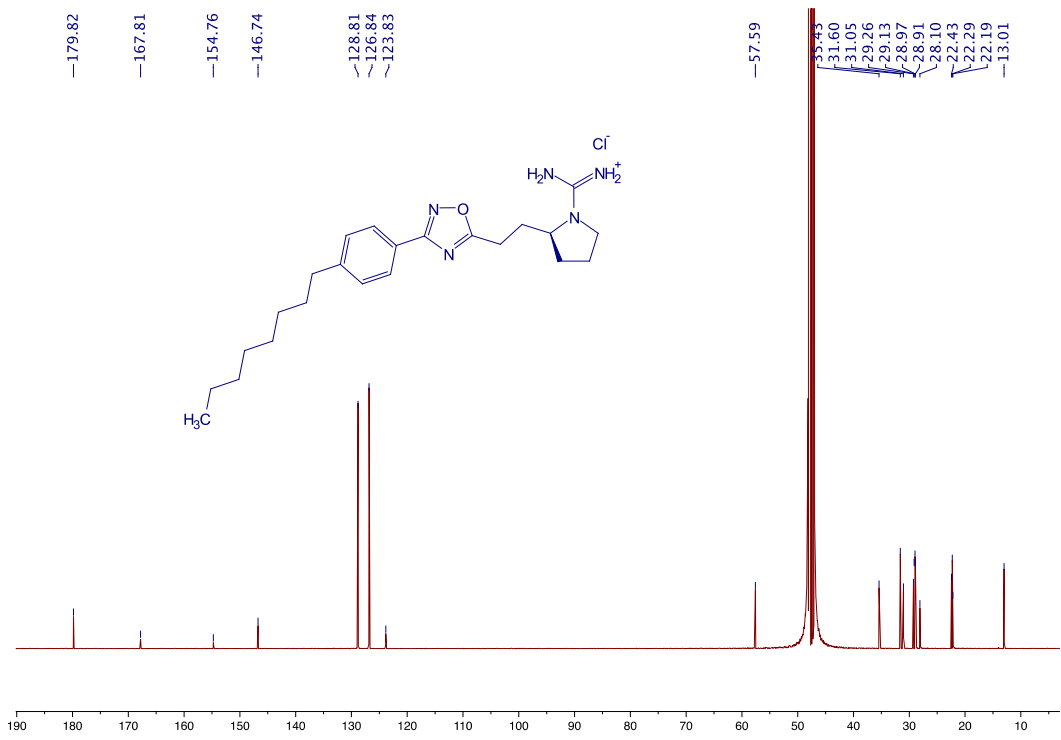
<sup>13</sup>C-NMR Spectrum for (S)-amino(2-((3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrrolidin-1-yl)methaniminium chloride **2.48a**-



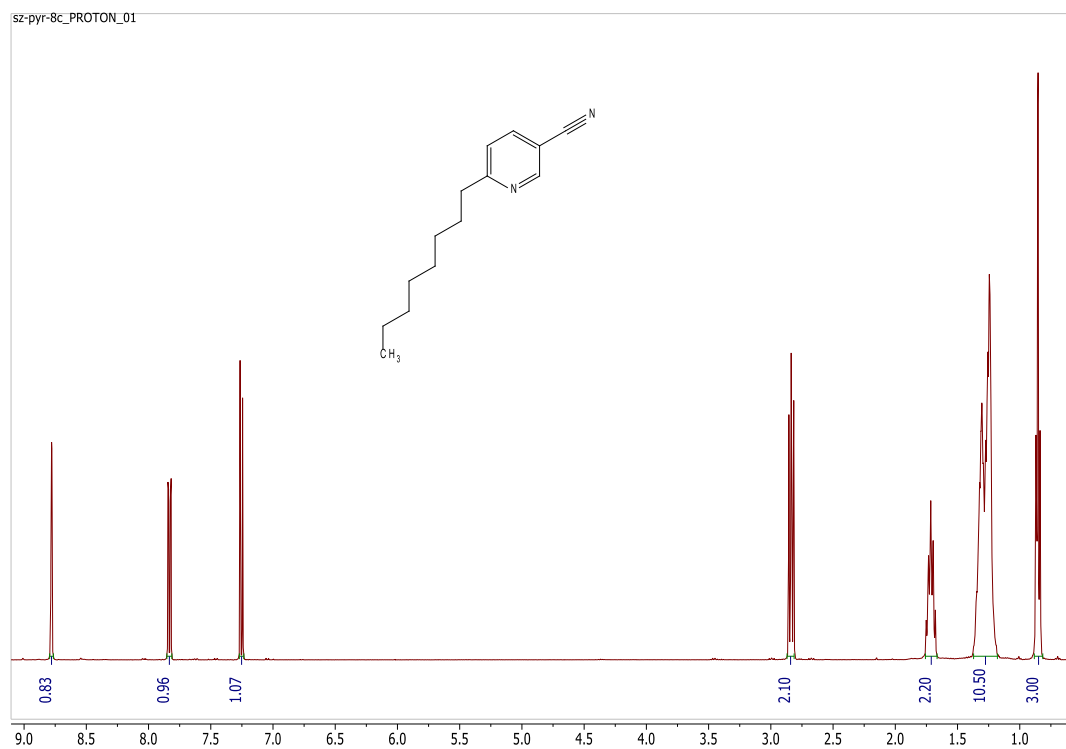
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)pyrrolidin-1-yl)methaniminium chloride **2.48b**-



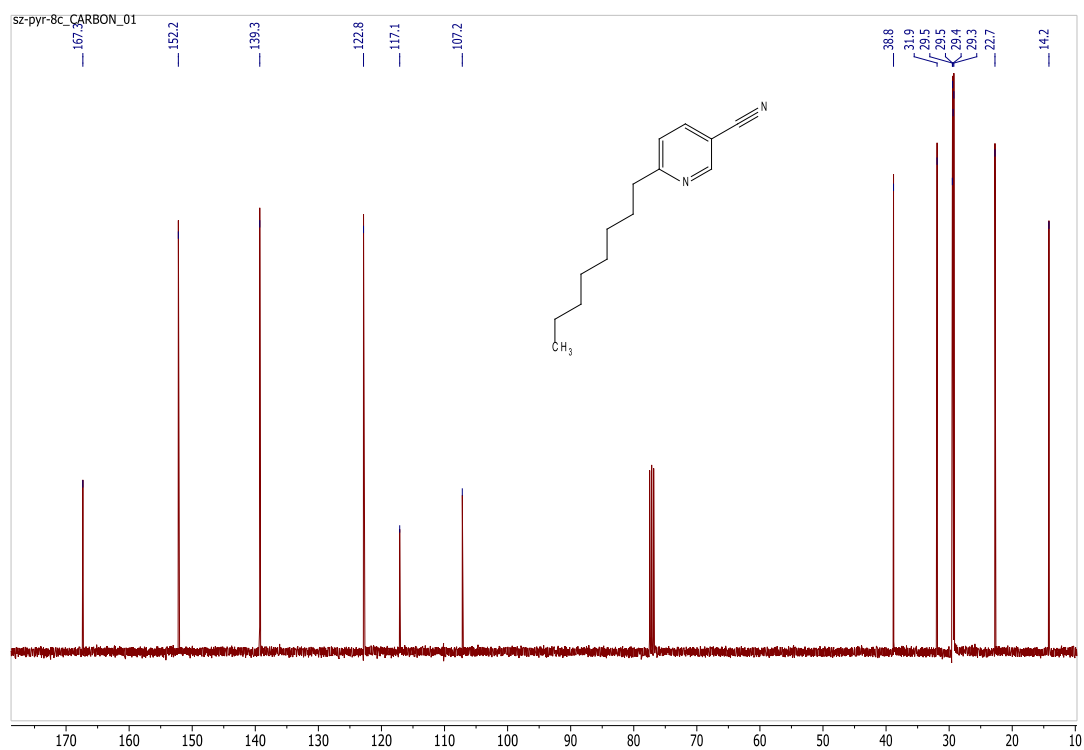
<sup>13</sup>C-NMR Spectrum for (S)-amino(2-(2-(3-(4-octylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)pyrrolidin-1-yl)methaniminium chloride **2.48b**-



### <sup>1</sup>H-NMR Spectrum for 6-octylnicotinonitrile **2.49**-

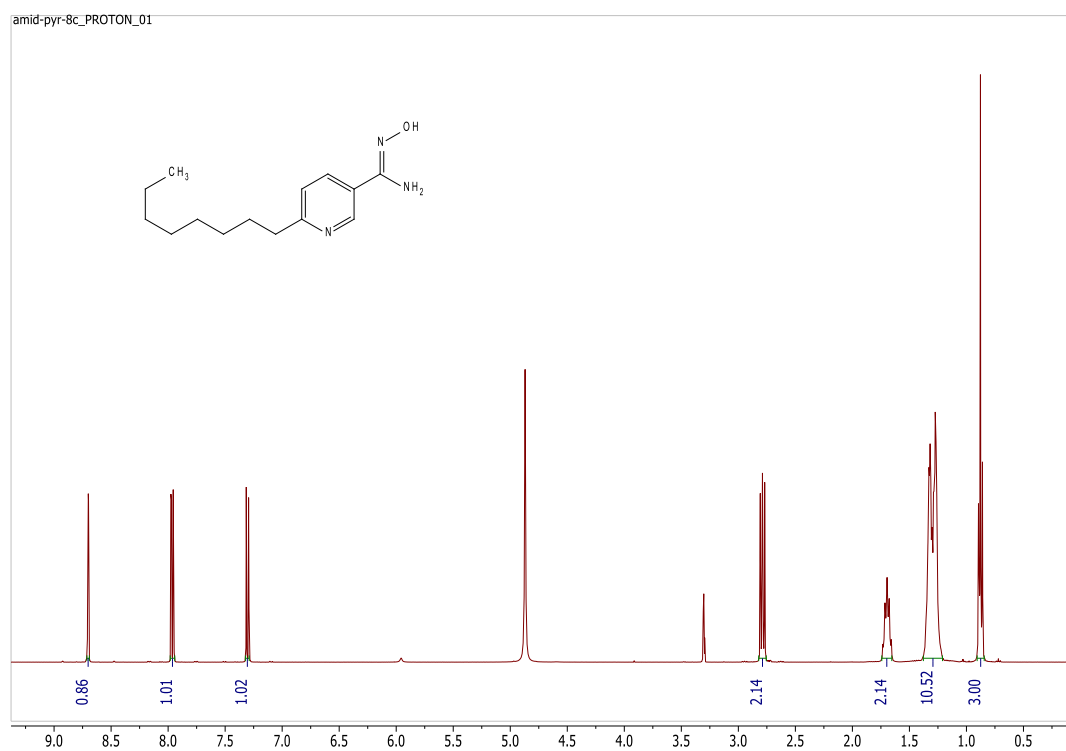


### <sup>13</sup>C-NMR Spectrum for 6-octylnicotinonitrile **2.49**-

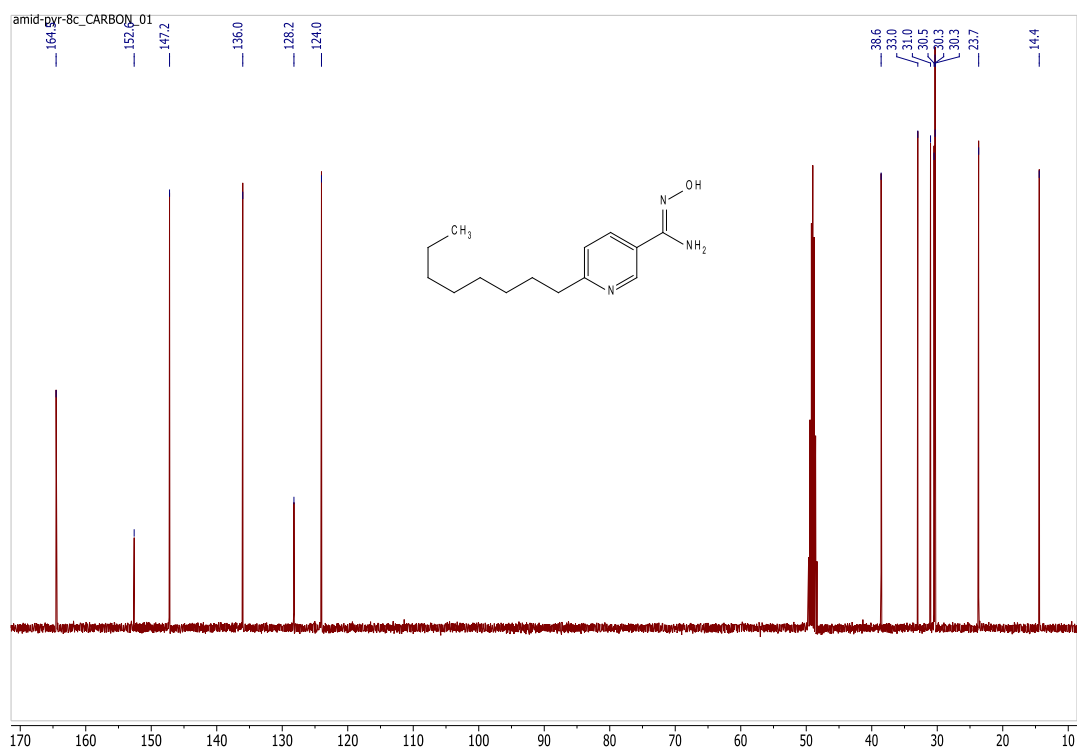




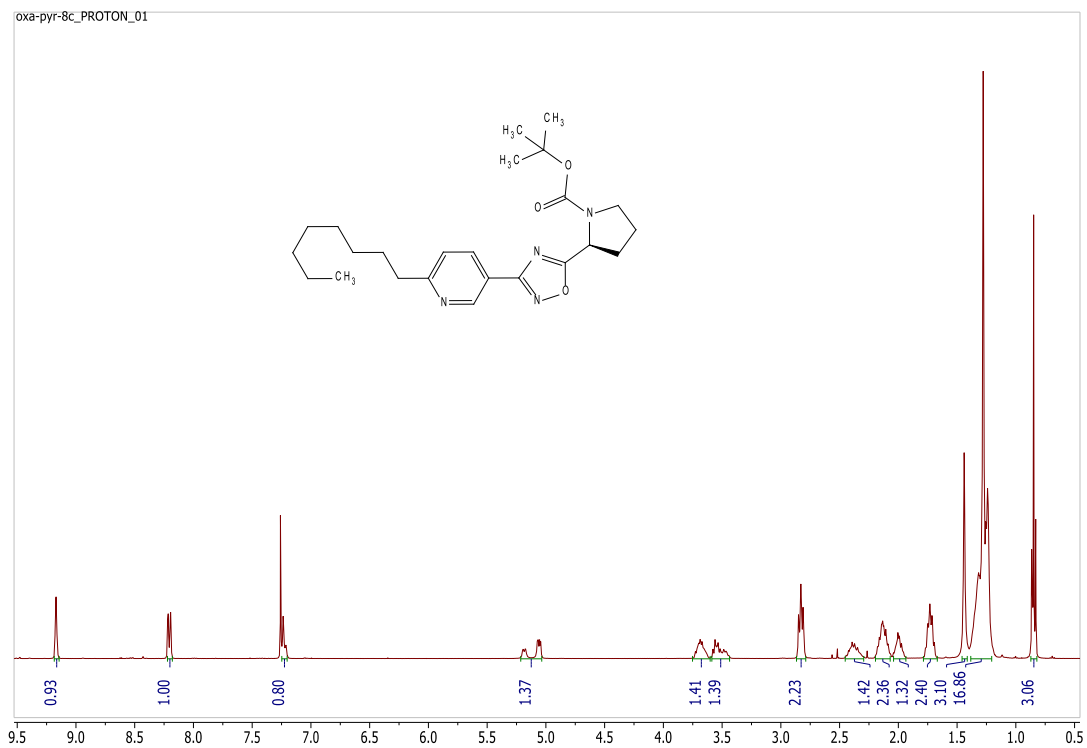
<sup>1</sup>H-NMR Spectrum for (Z)-N'-hydroxy-6-octylnicotinimidamide –



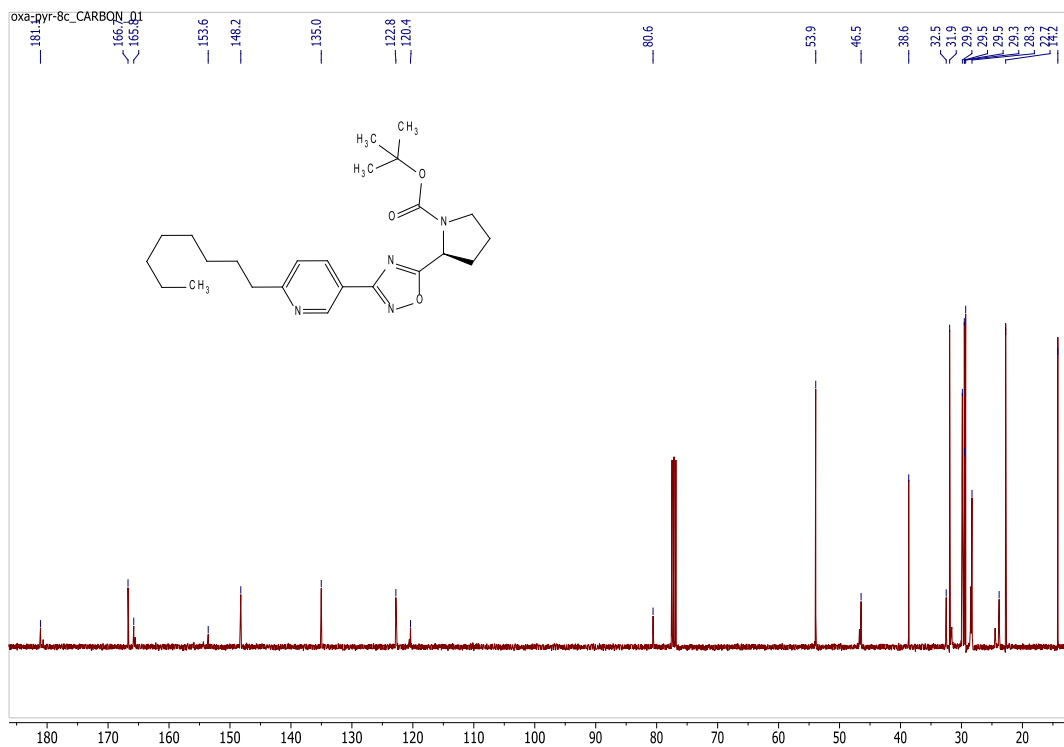
<sup>13</sup>C-NMR Spectrum for (Z)-N'-hydroxy-6-octylnicotinimidamide –



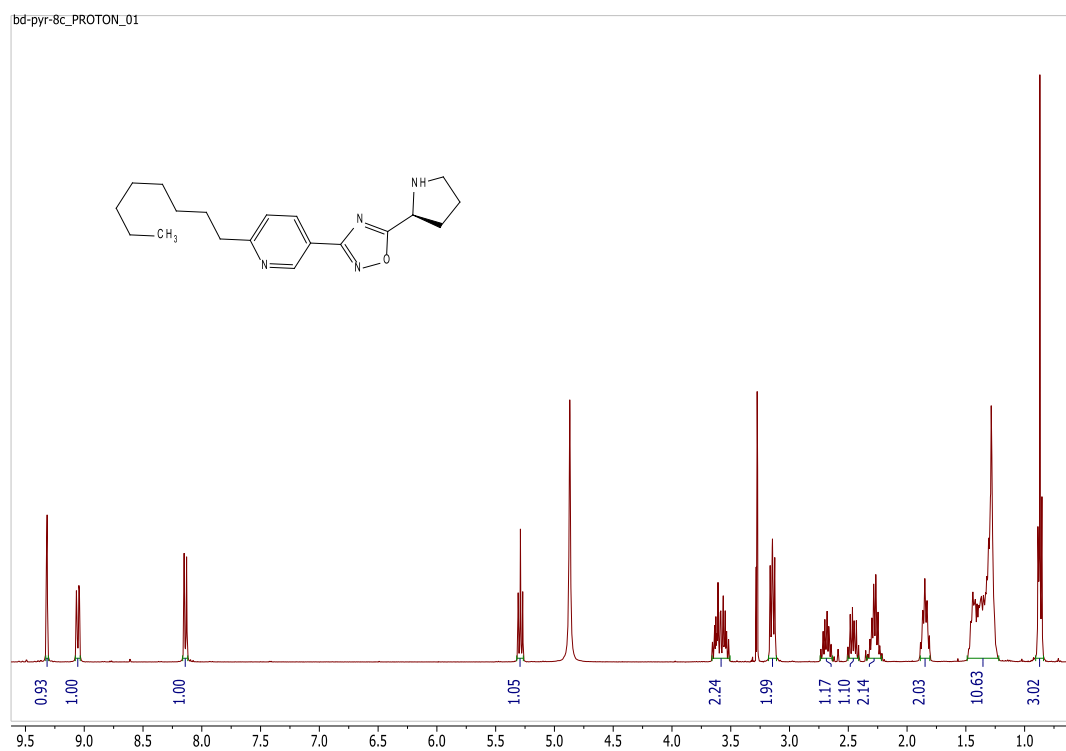
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate -



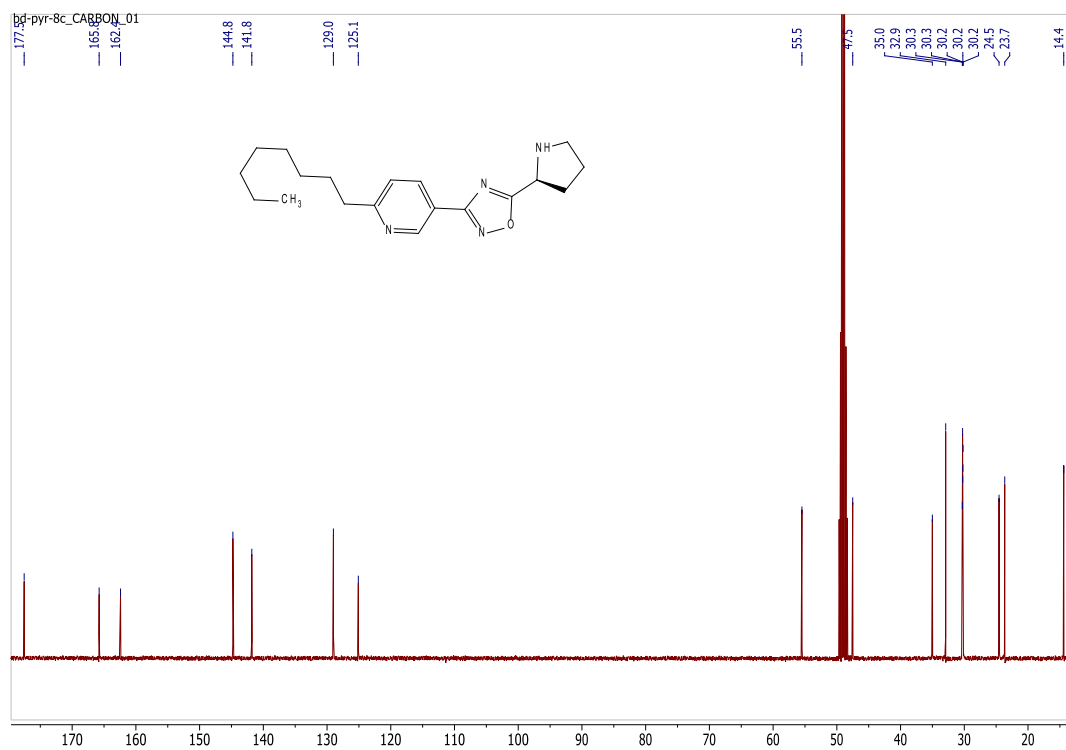
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate -



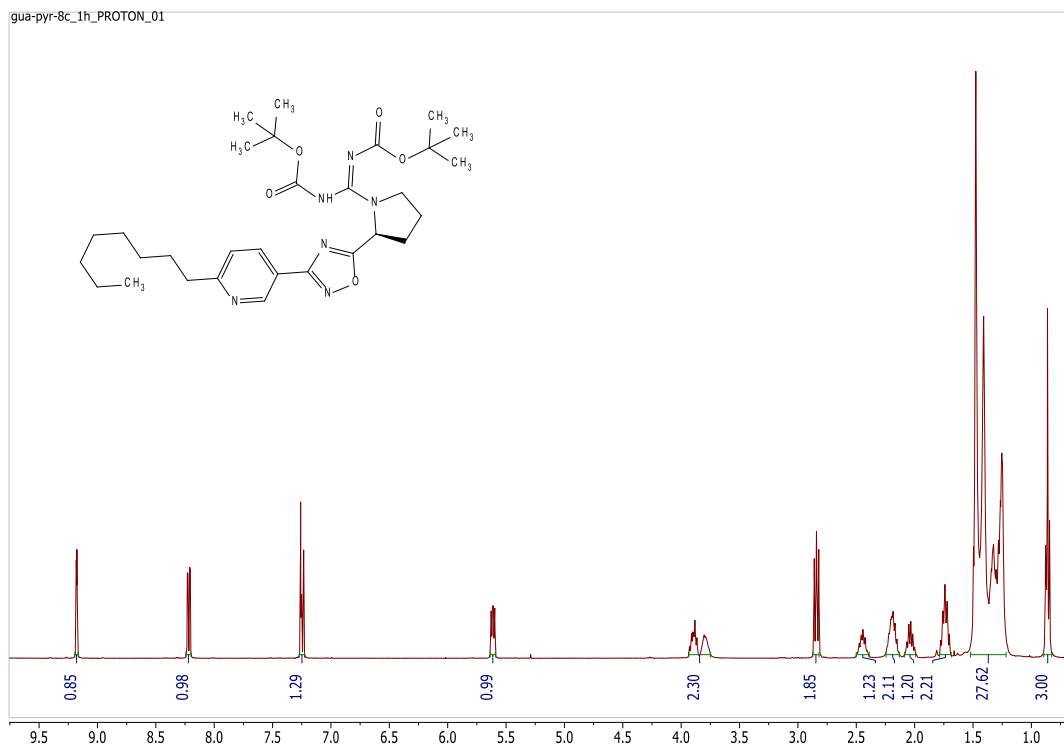
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium chloride –



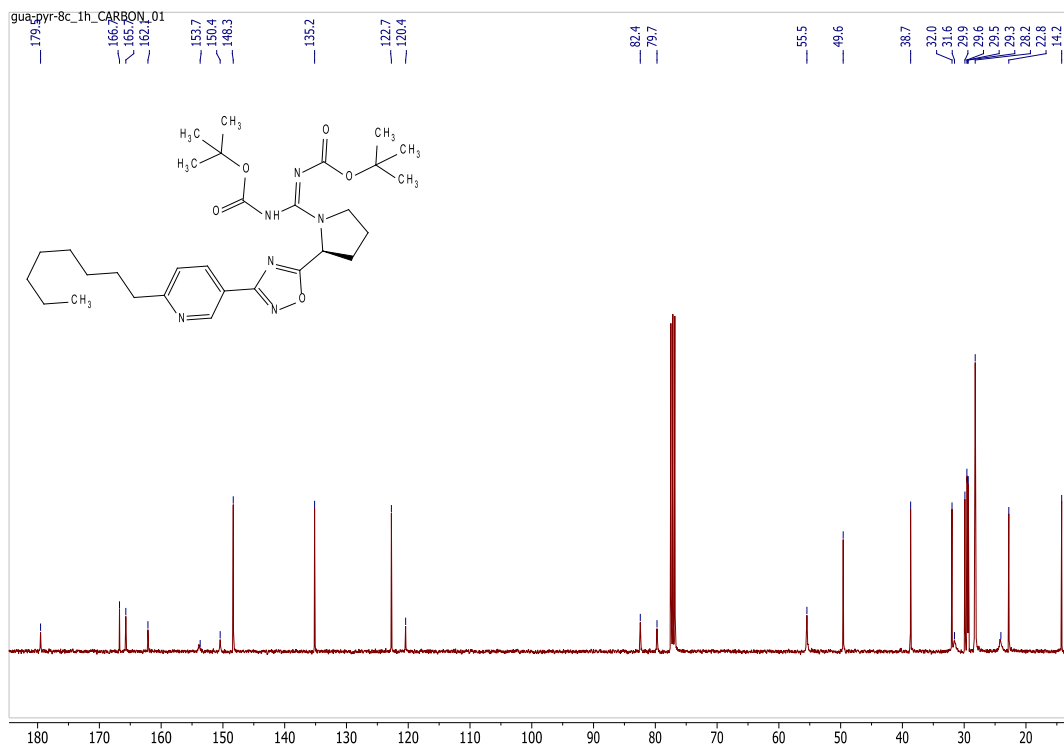
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium chloride –



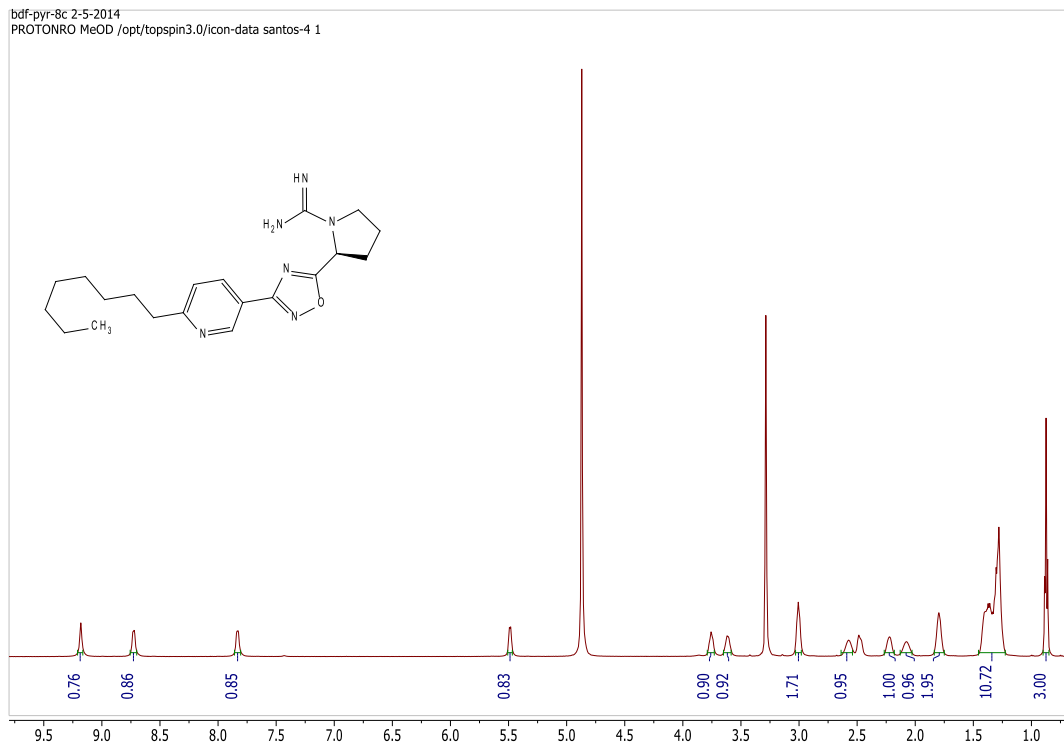
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



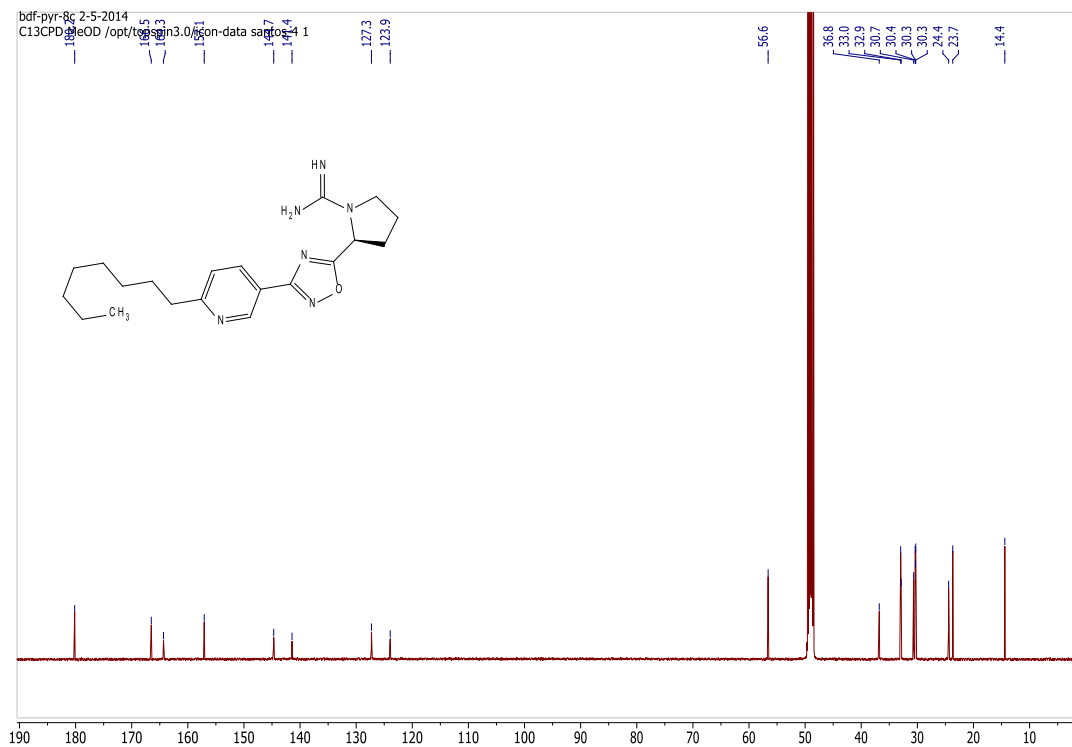
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



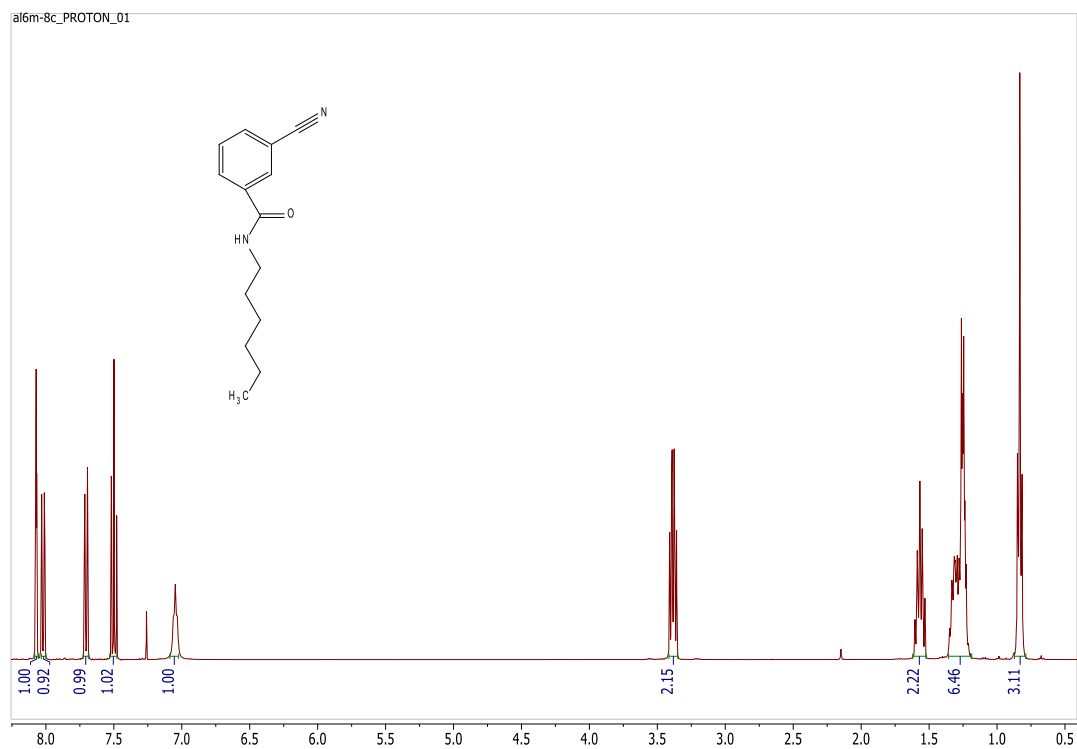
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **2.50**-



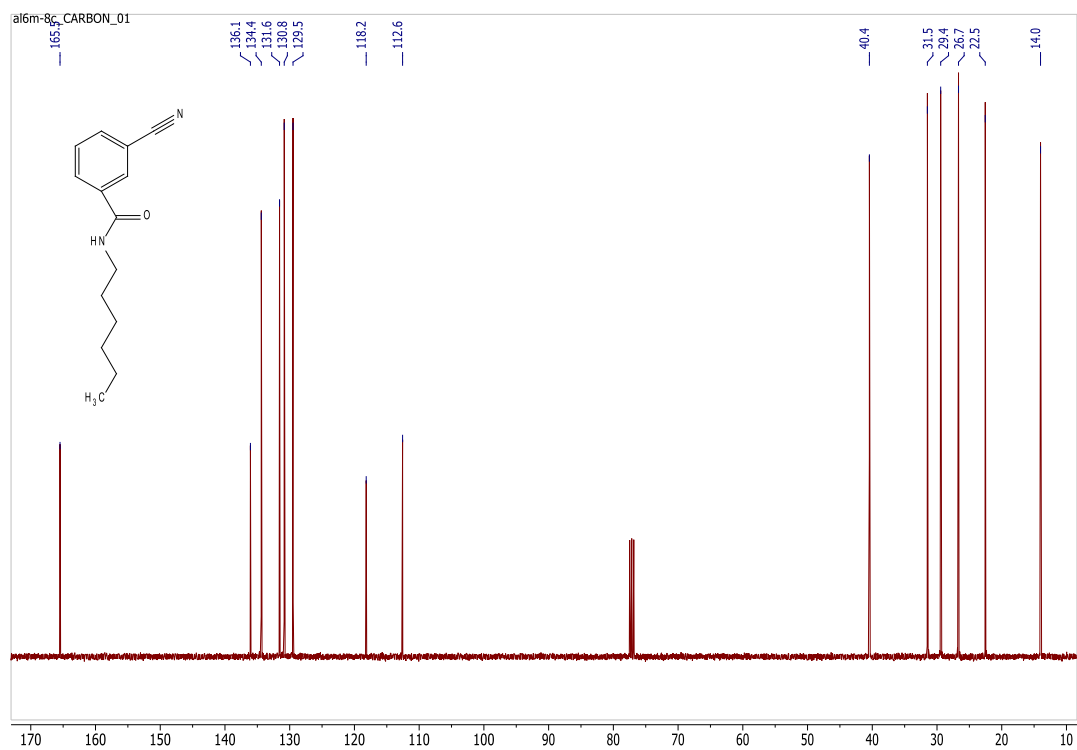
<sup>13</sup>C-NMR Spectrum for (S)-amino(2-(3-(6-octylpyridin-3-yl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **2.50**-



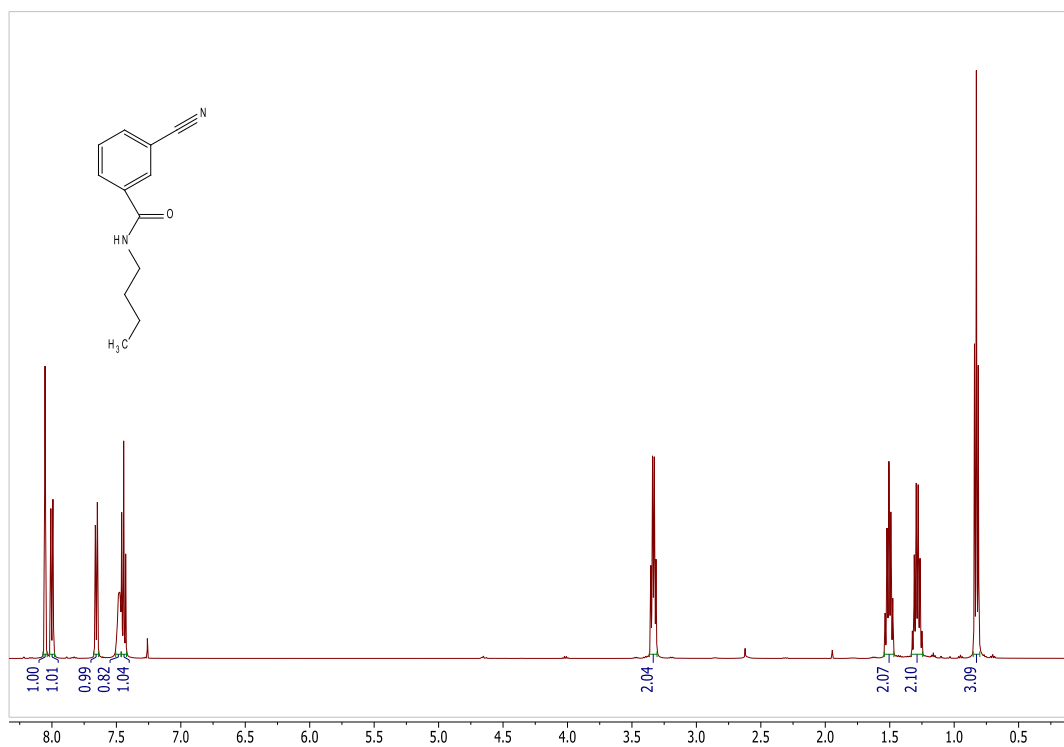
<sup>1</sup>H-NMR Spectrum for 3-cyano-N-hexylbenzamide **2.52a**-



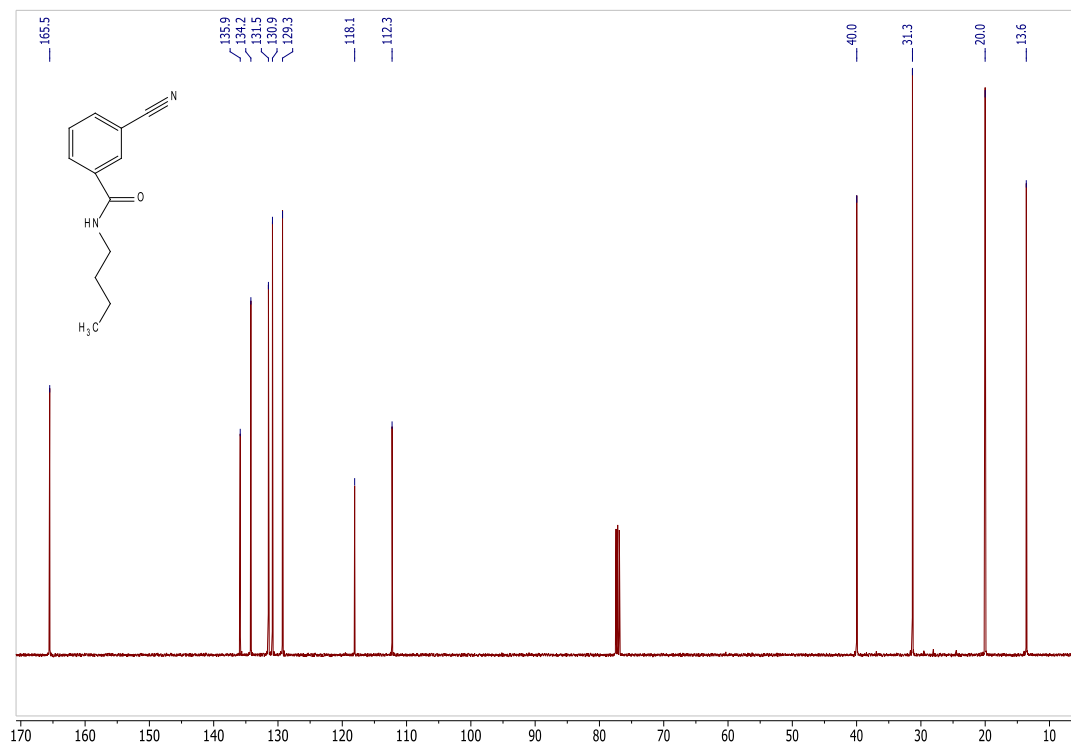
<sup>13</sup>C-NMR Spectrum for 3-cyano-N-hexylbenzamide **2.52a**-



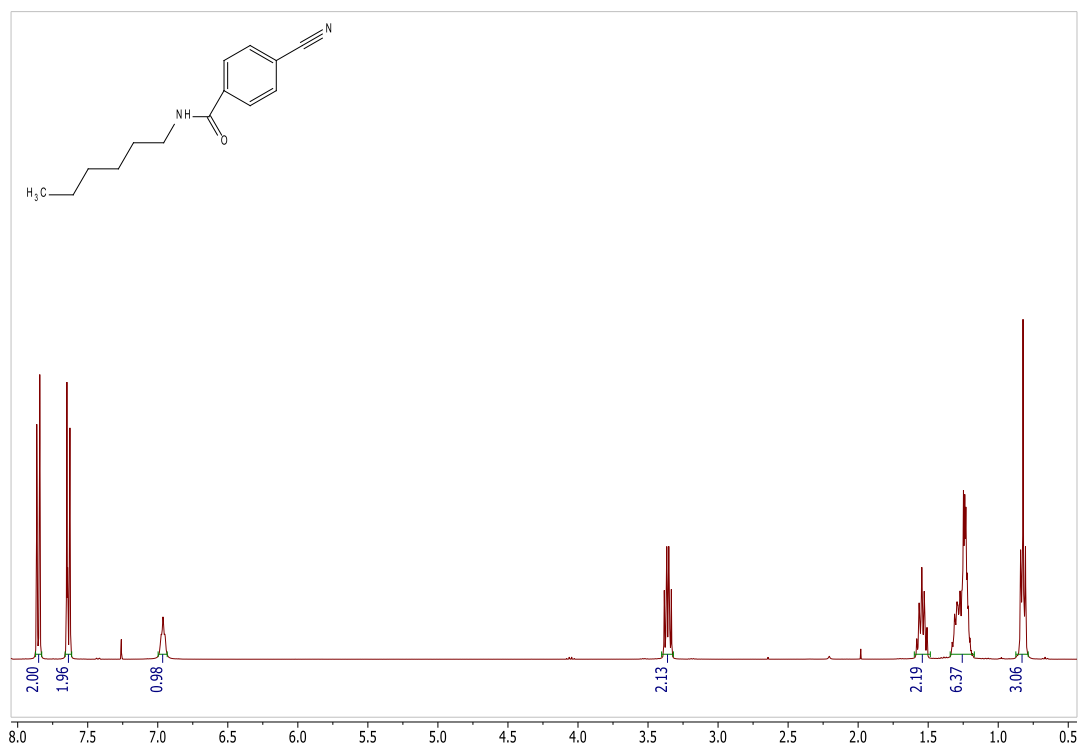
<sup>1</sup>H-NMR Spectrum for N-butyl-3-cyanobenzamide **2.52b**-



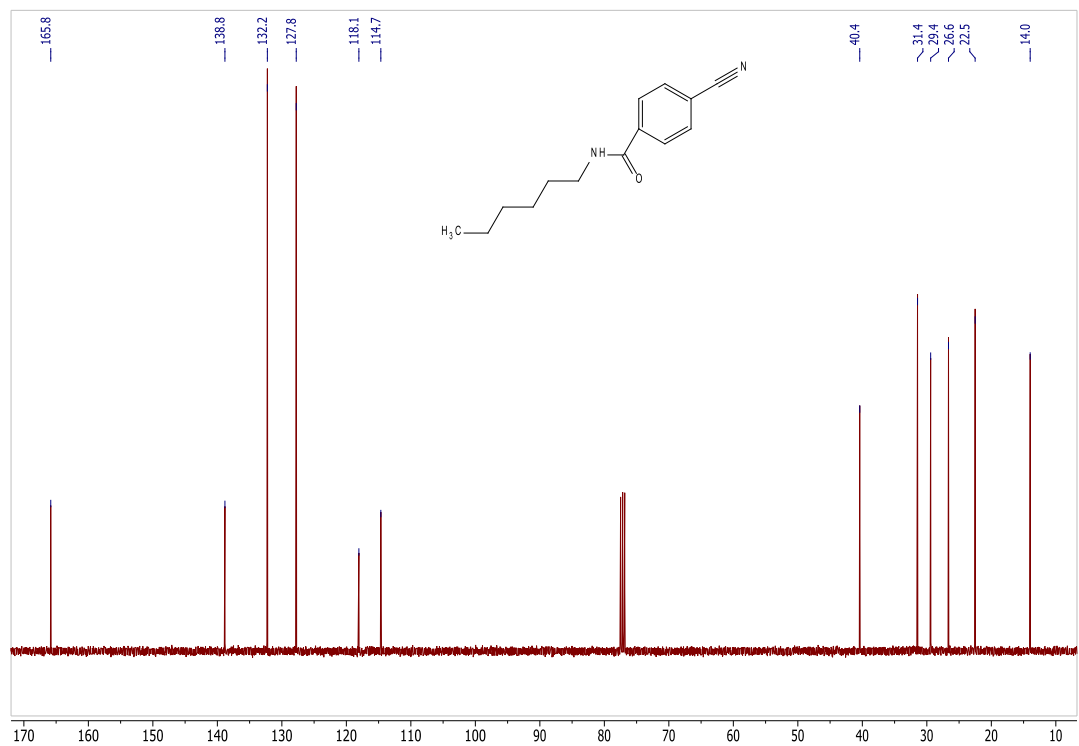
<sup>13</sup>C-NMR Spectrum for N-butyl-3-cyanobenzamide **2.52b**-



<sup>1</sup>H-NMR Spectrum for 4-cyano-N-hexylbenzamide **2.52c**-

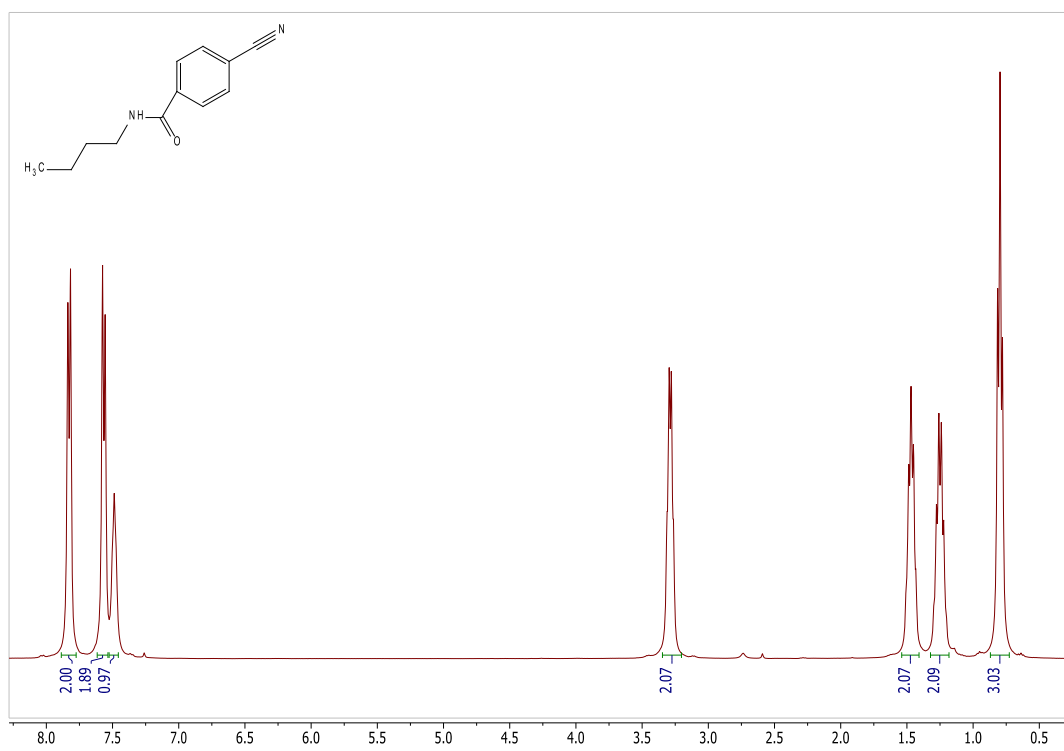


<sup>13</sup>C-NMR Spectrum for 4-cyano-N-hexylbenzamide **2.52c**-

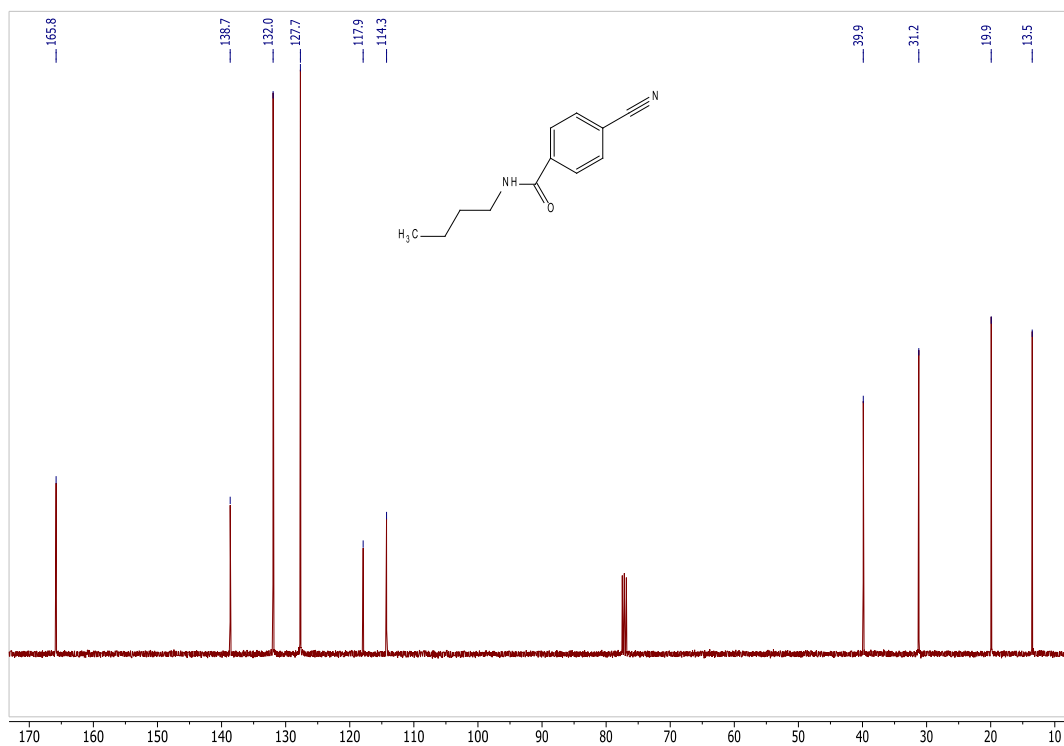




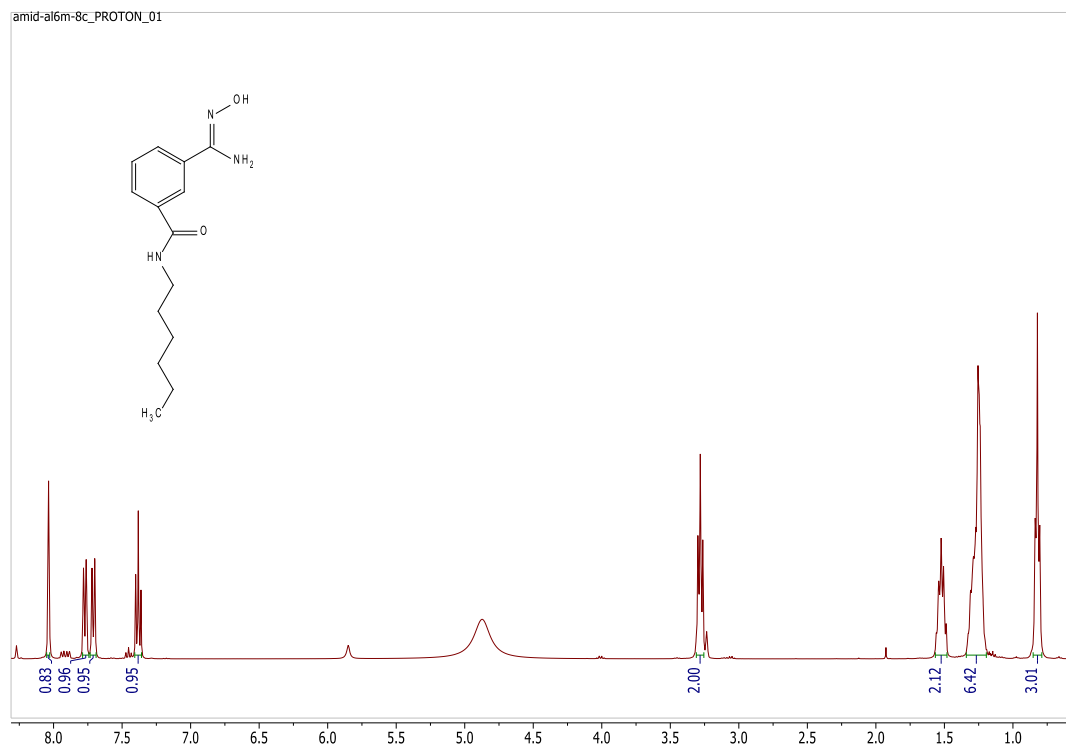
<sup>1</sup>H-NMR Spectrum for N-butyl-4-cyanobenzamide **2.52d**-



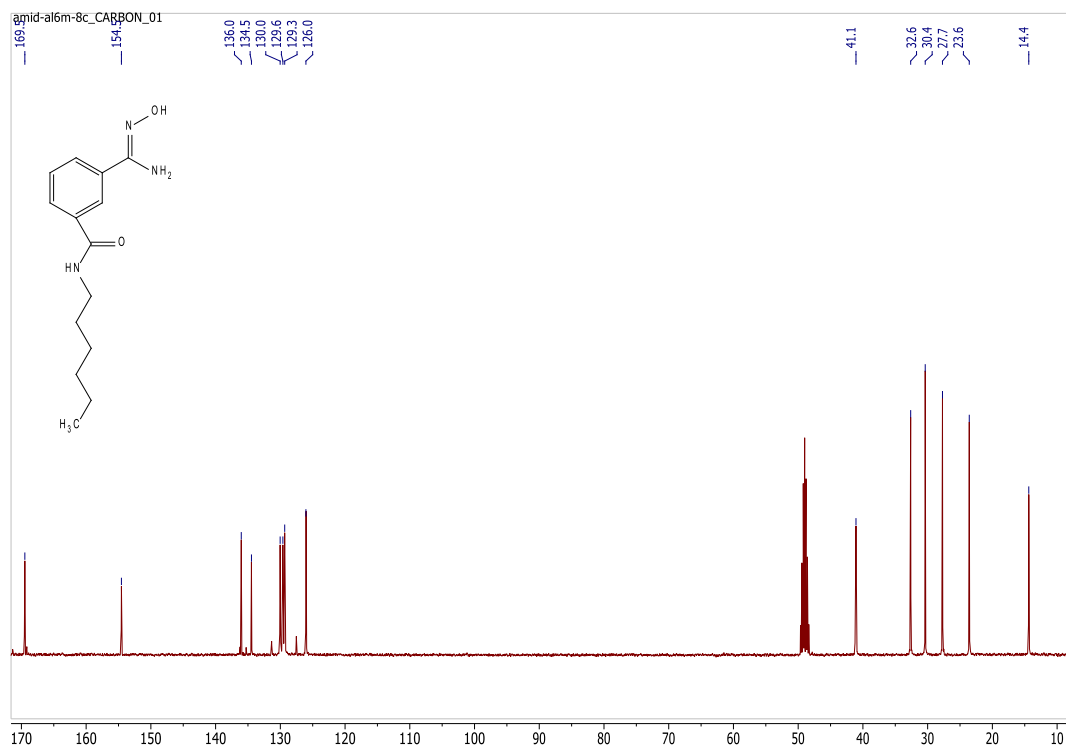
<sup>13</sup>C-NMR Spectrum for N-butyl-4-cyanobenzamide **2.52d**-



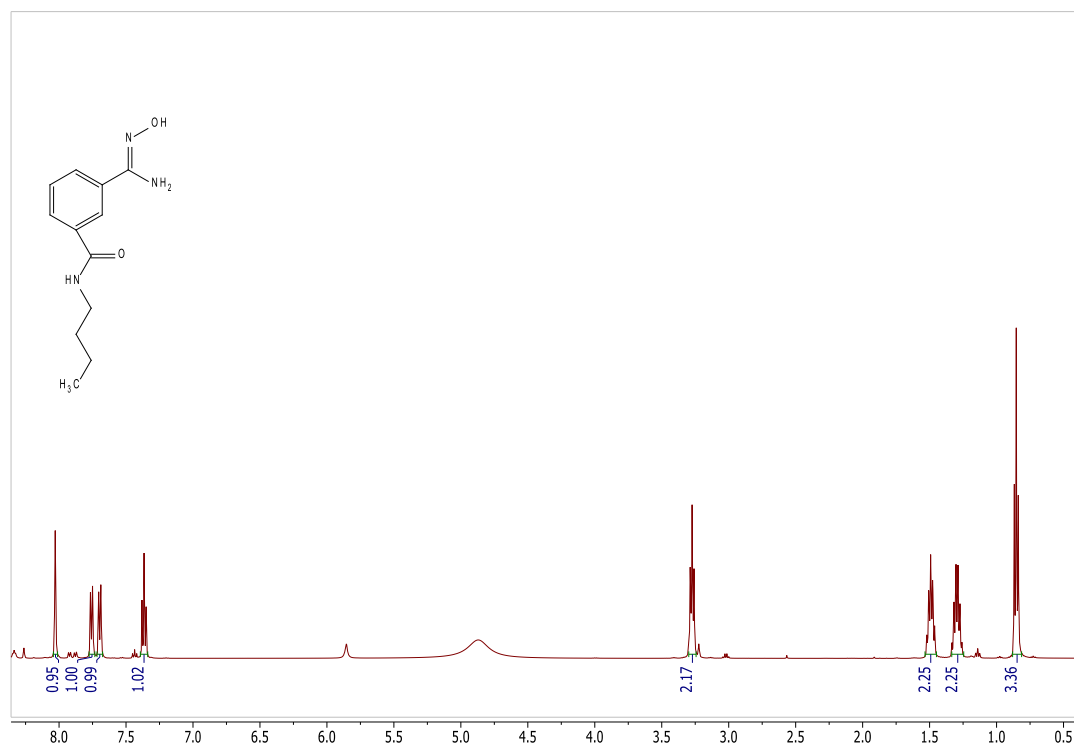
<sup>1</sup>H-NMR Spectrum for (Z)-N-hexyl-3-(N'-hydroxycarbamimidoyl)benzamide –



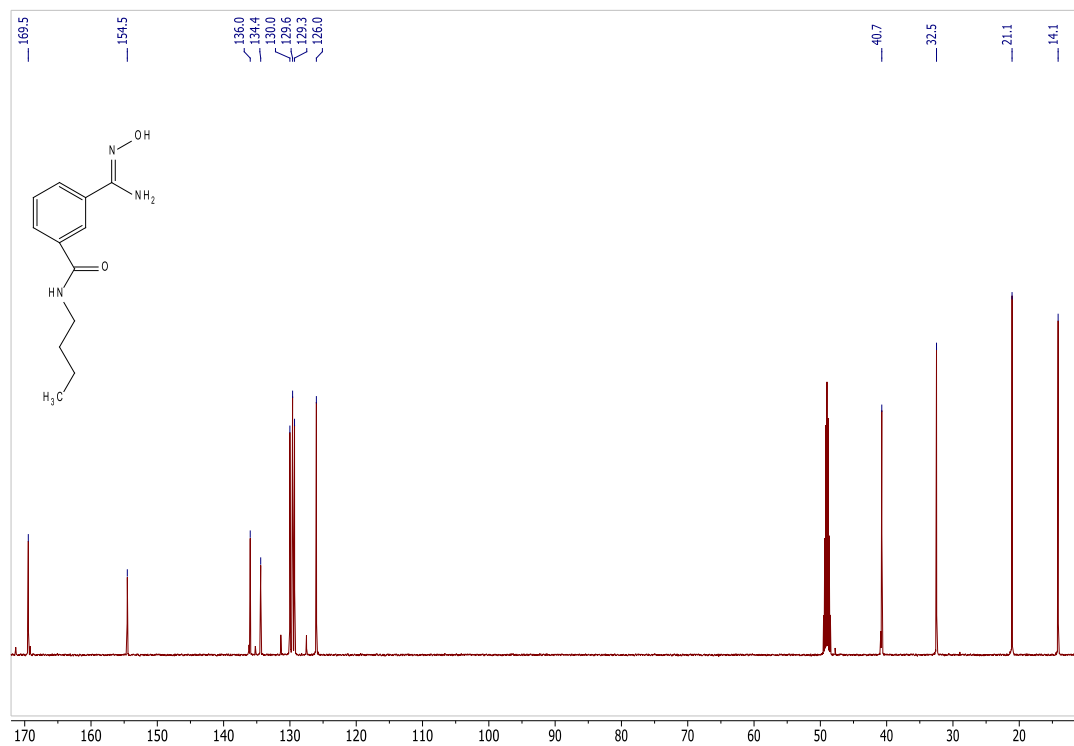
<sup>13</sup>C-NMR Spectrum for (Z)-N-hexyl-3-(N'-hydroxycarbamimidoyl)benzamide –



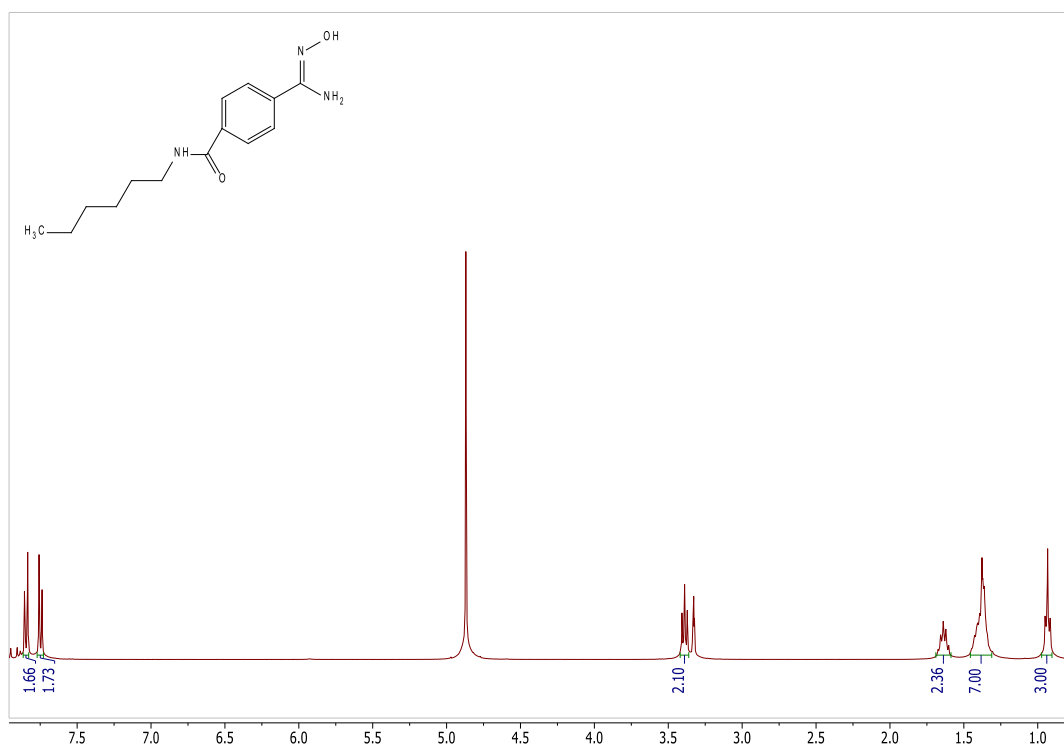
<sup>1</sup>H-NMR Spectrum for (Z)-N-butyl-3-(N'-hydroxycarbamimidoyl)benzamide-



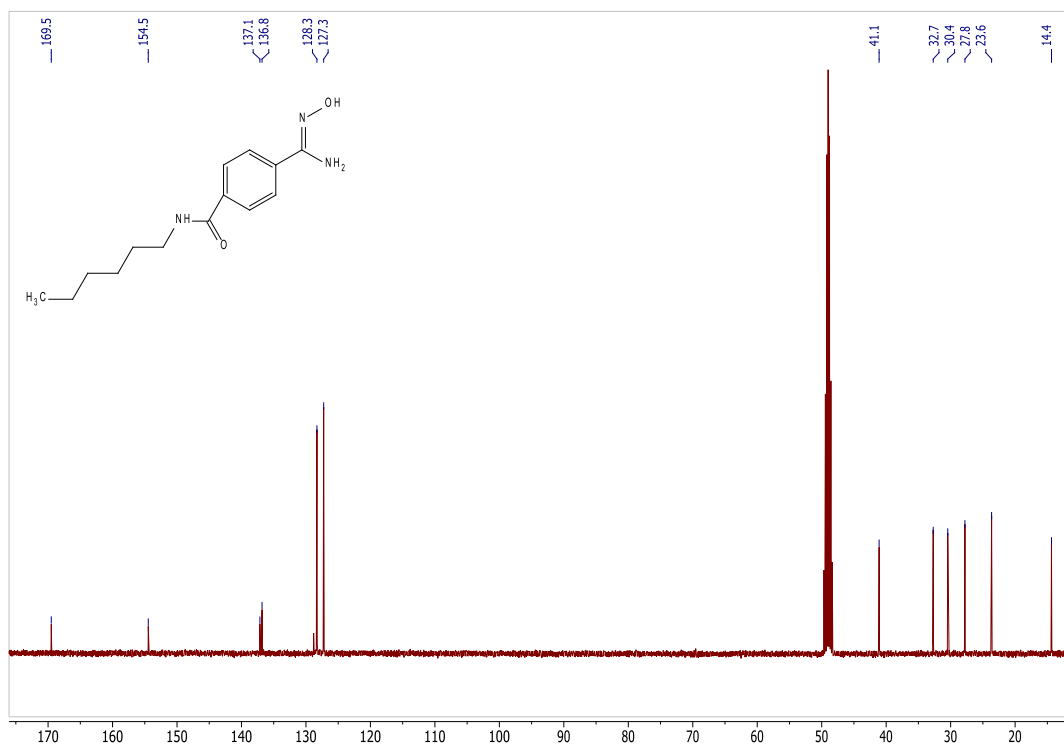
<sup>13</sup>C-NMR Spectrum for (Z)-N-butyl-3-(N'-hydroxycarbamimidoyl)benzamide-



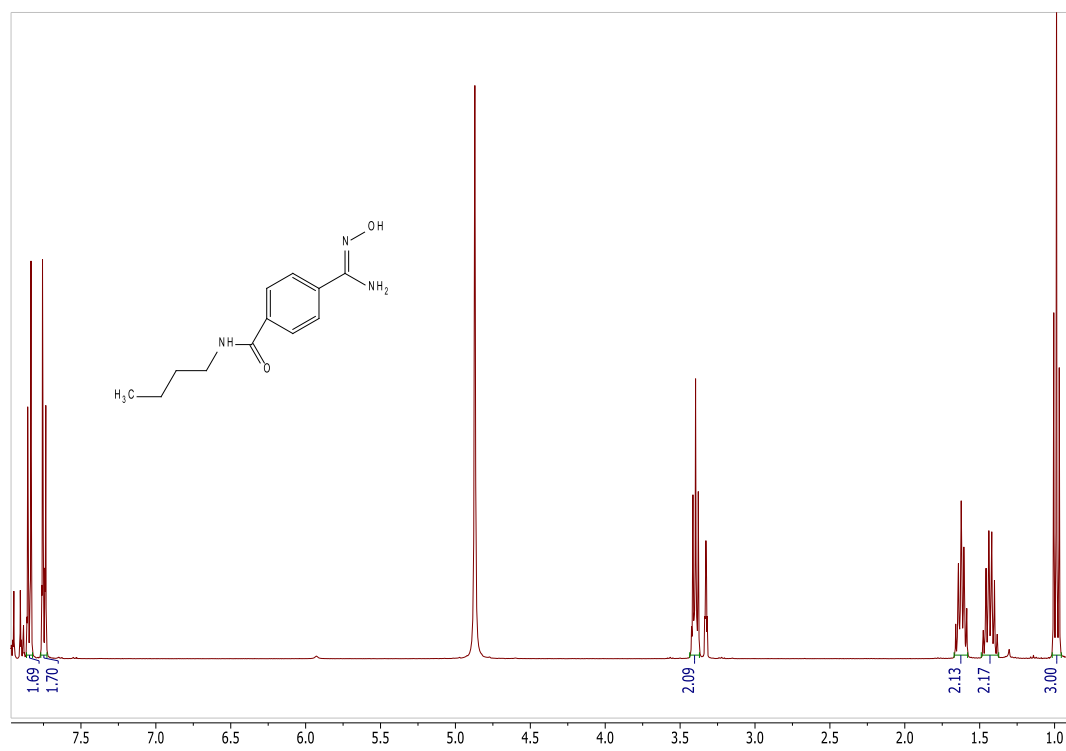
<sup>1</sup>H-NMR Spectrum for (Z)-N-hexyl-4-(N'-hydroxycarbamimidoyl)benzamide –



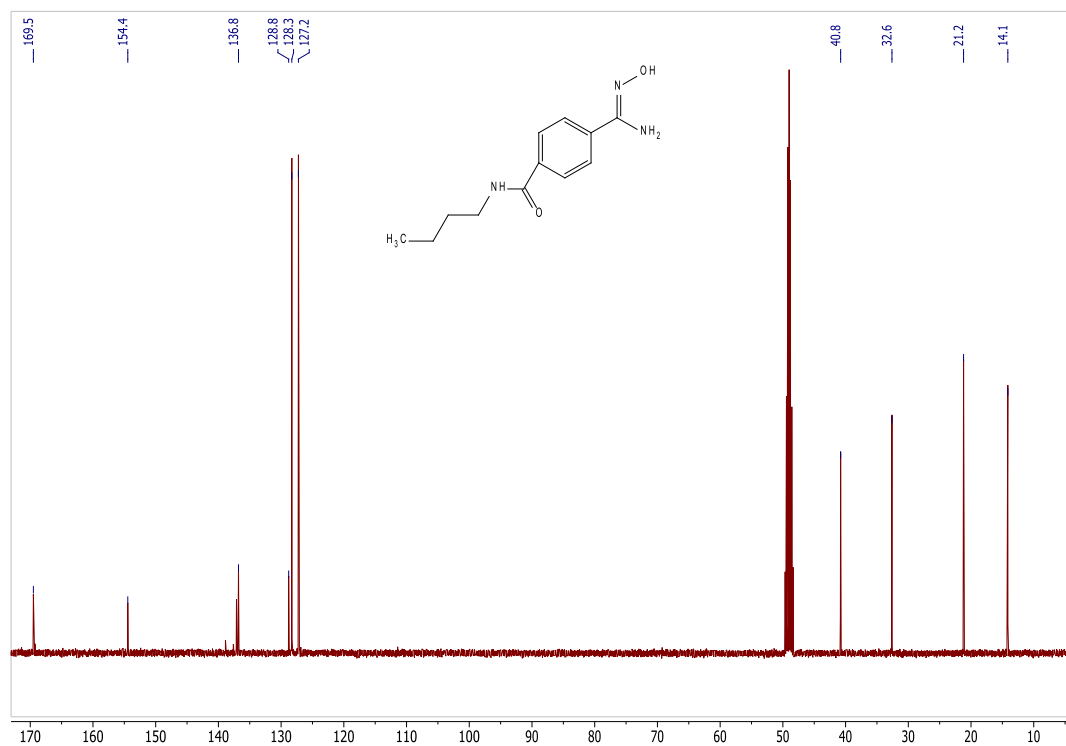
<sup>13</sup>C-NMR Spectrum for (Z)-N-hexyl-4-(N'-hydroxycarbamimidoyl)benzamide –



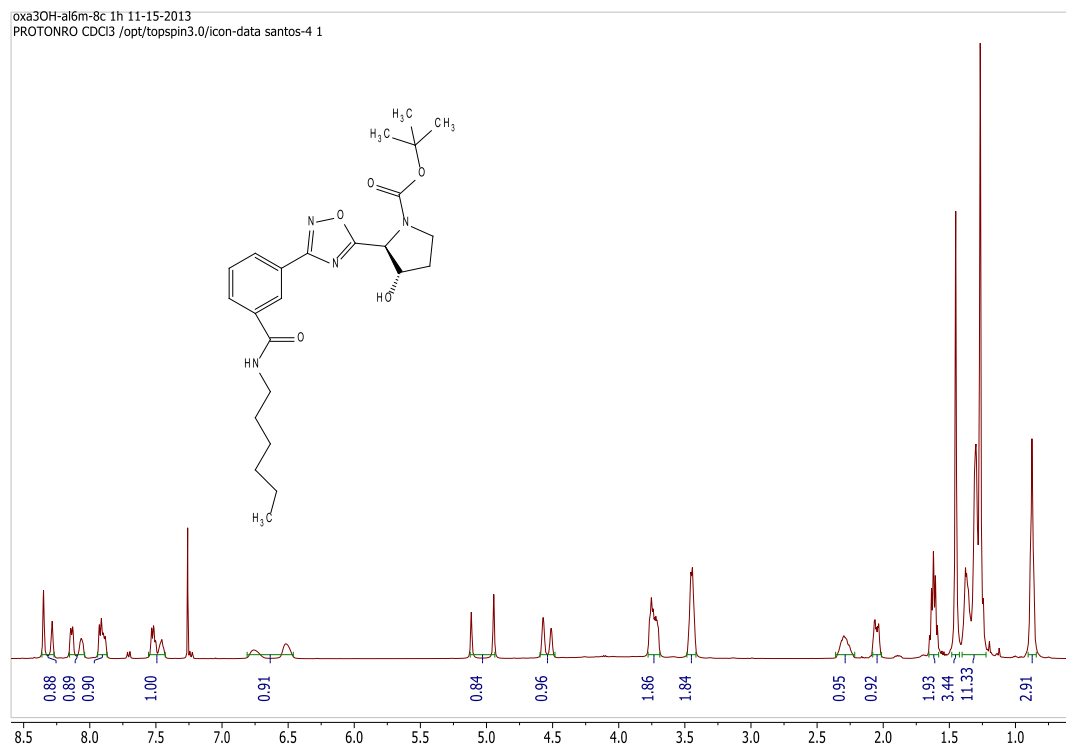
<sup>1</sup>H-NMR Spectrum for (Z)-N-butyl-4-(N'-hydroxycarbamimidoyl)benzamide –



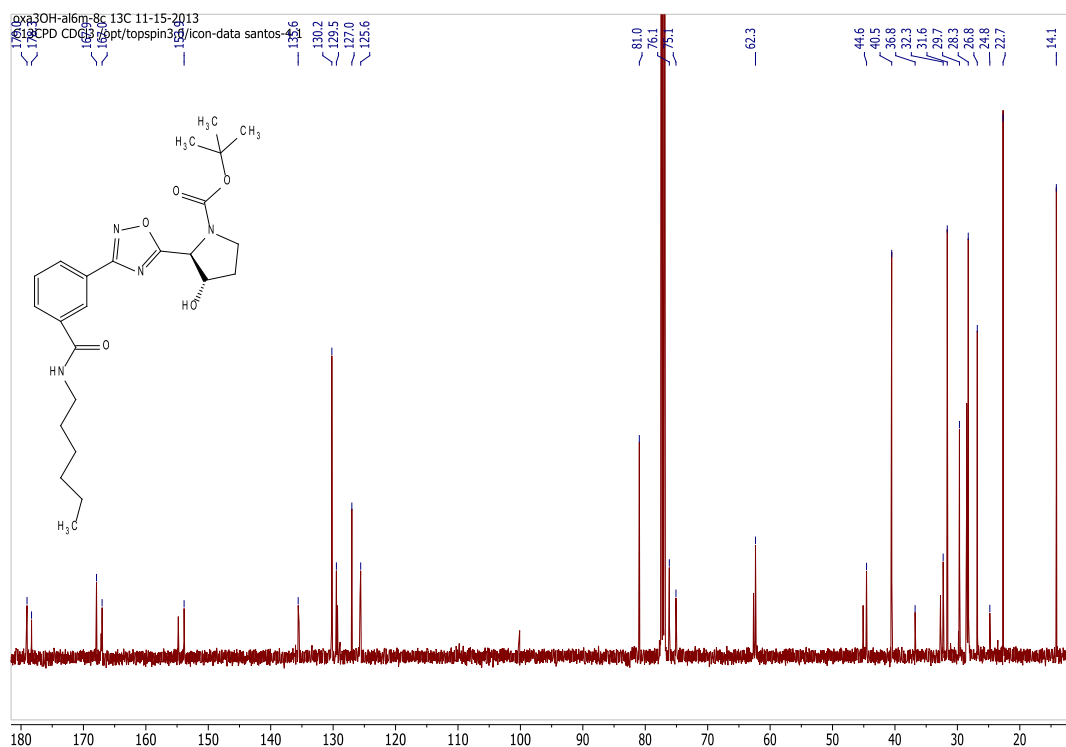
<sup>13</sup>C-NMR Spectrum for (Z)-N-butyl-4-(N'-hydroxycarbamimidoyl)benzamide –



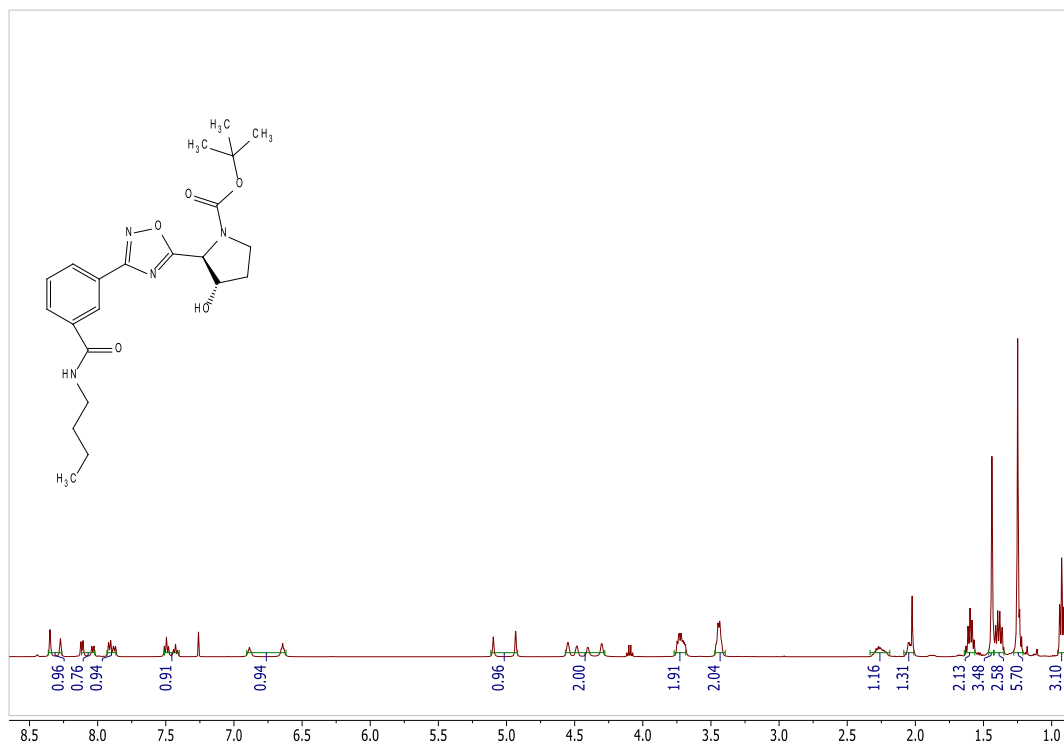
<sup>1</sup>H-NMR Spectrum for (2*S*,3*S*)-*tert*-butyl 2-(3-(3-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidine-1-carboxylate **2.53a**-



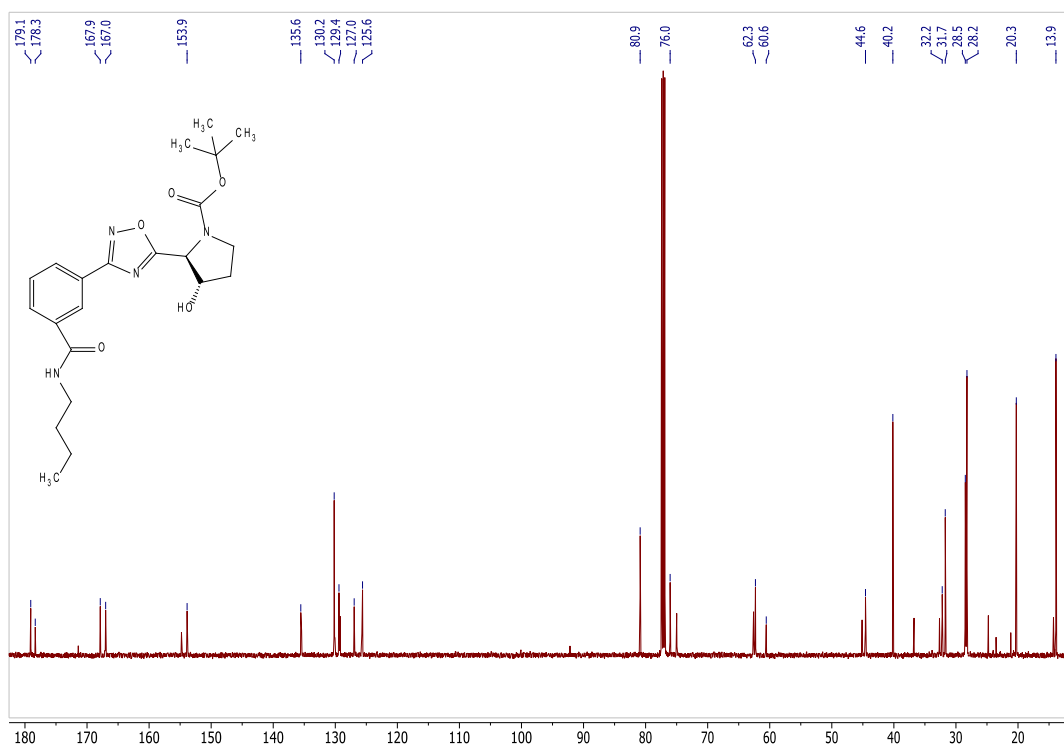
<sup>13</sup>C-NMR Spectrum for (2*S*,3*S*)-*tert*-butyl 2-(3-(3-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidine-1-carboxylate **2.53a**-



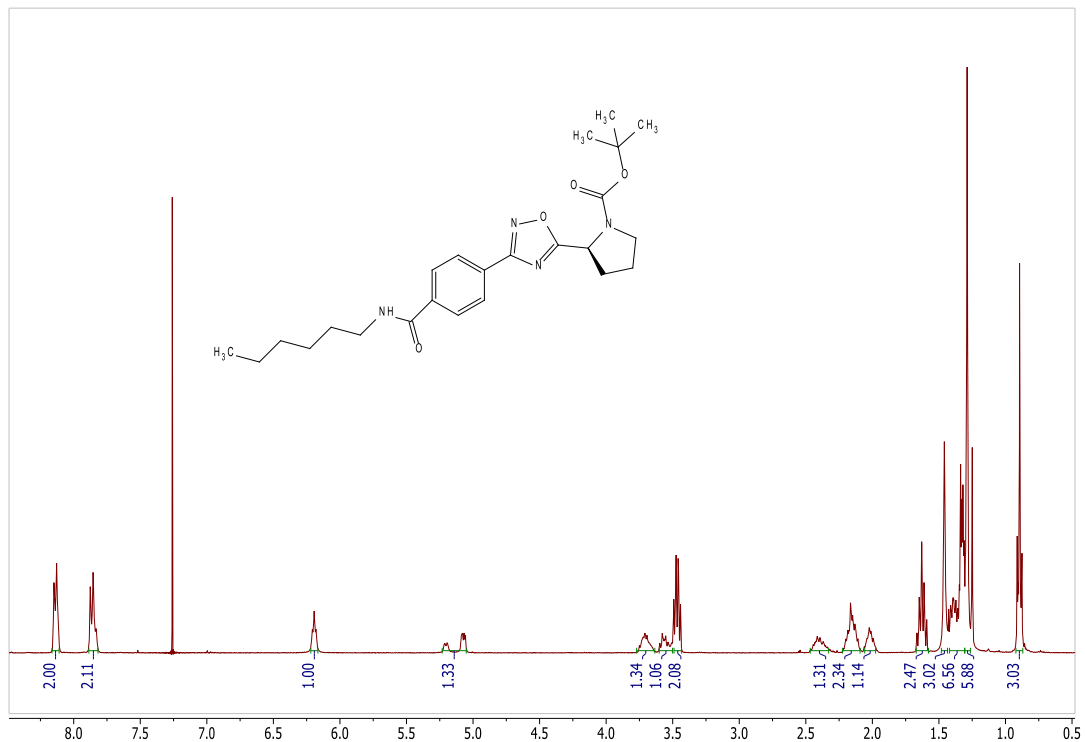
<sup>1</sup>H-NMR Spectrum for (2*S*,3*S*)-*tert*-butyl 2-(3-(3-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidine-1-carboxylate **2.53b**-



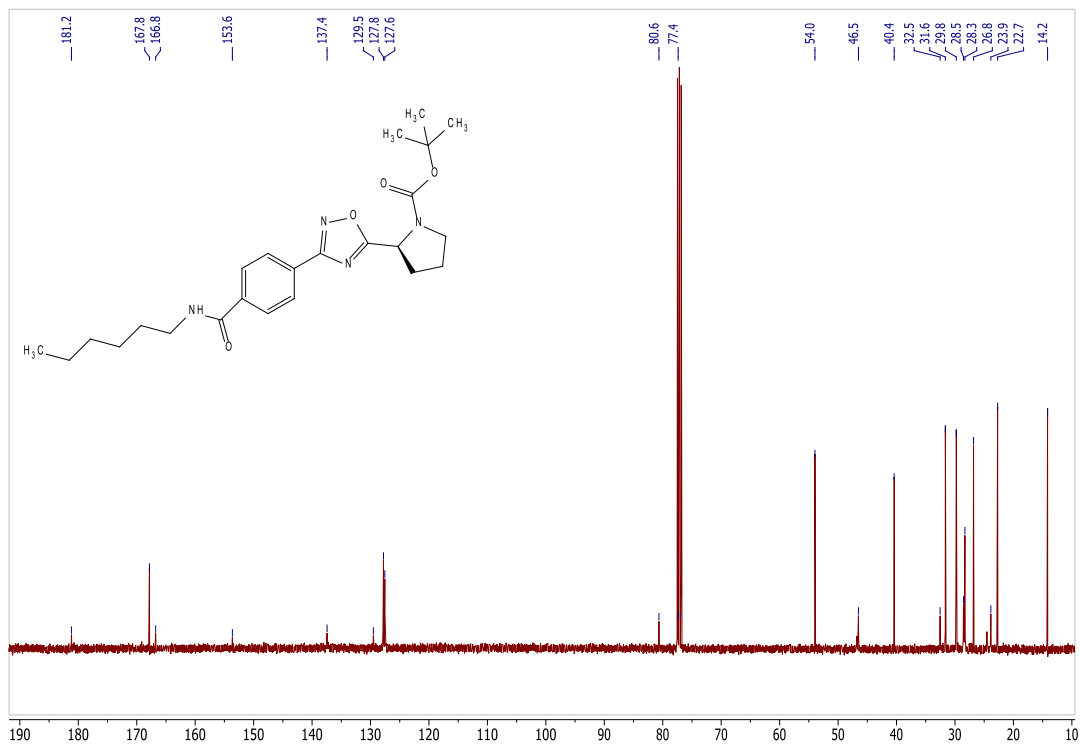
<sup>13</sup>C-NMR Spectrum for (2*S*,3*S*)-*tert*-butyl 2-(3-(3-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidine-1-carboxylate **2.53b** -



<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.53c**-

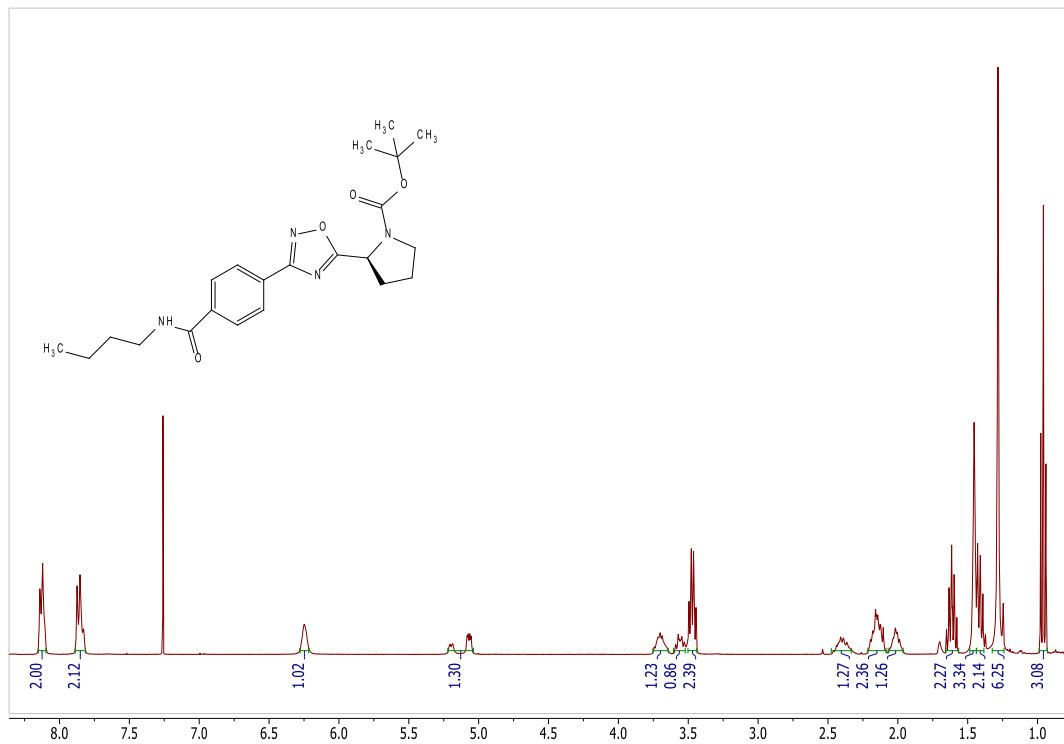


<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.53c**-

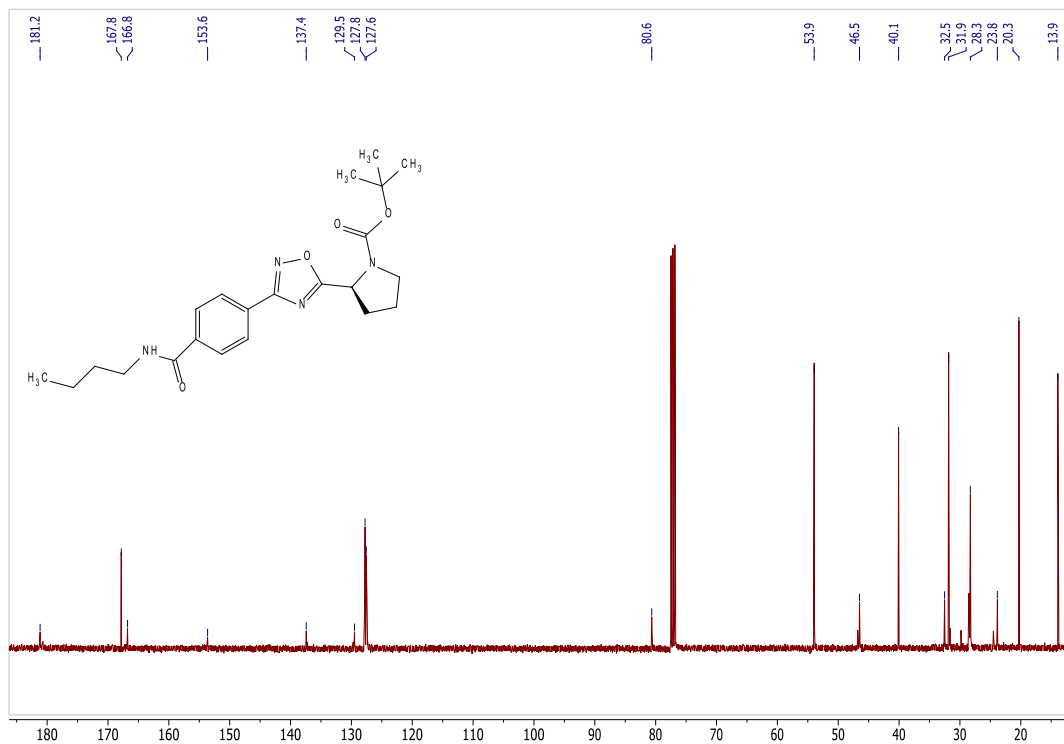




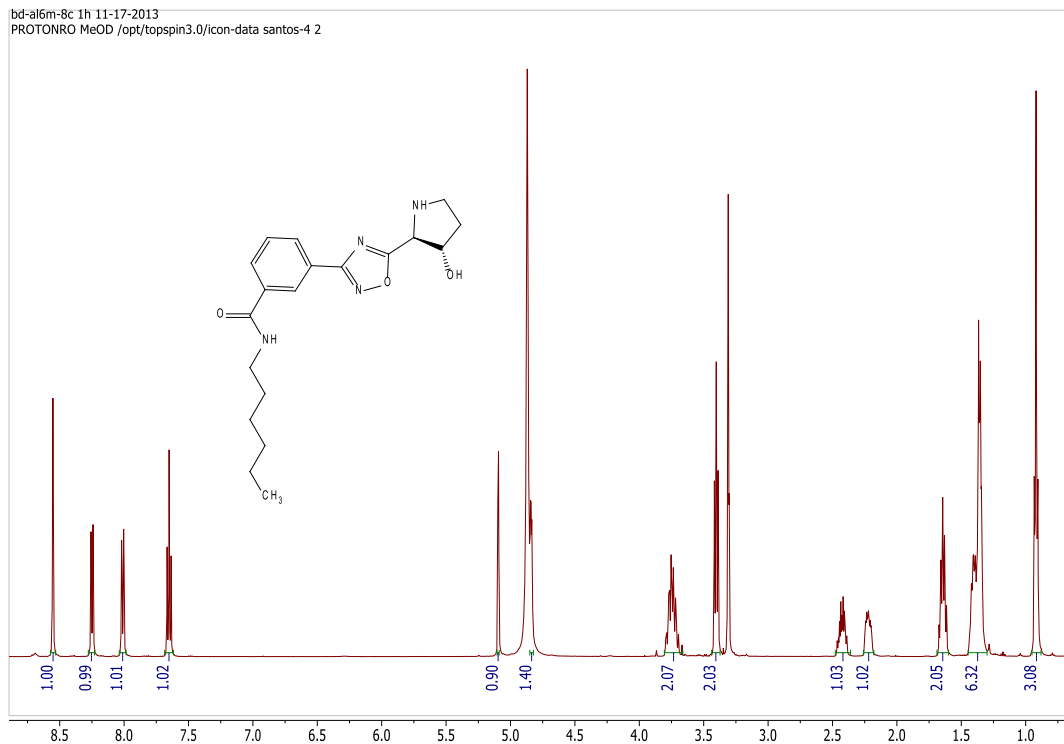
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.53d**-



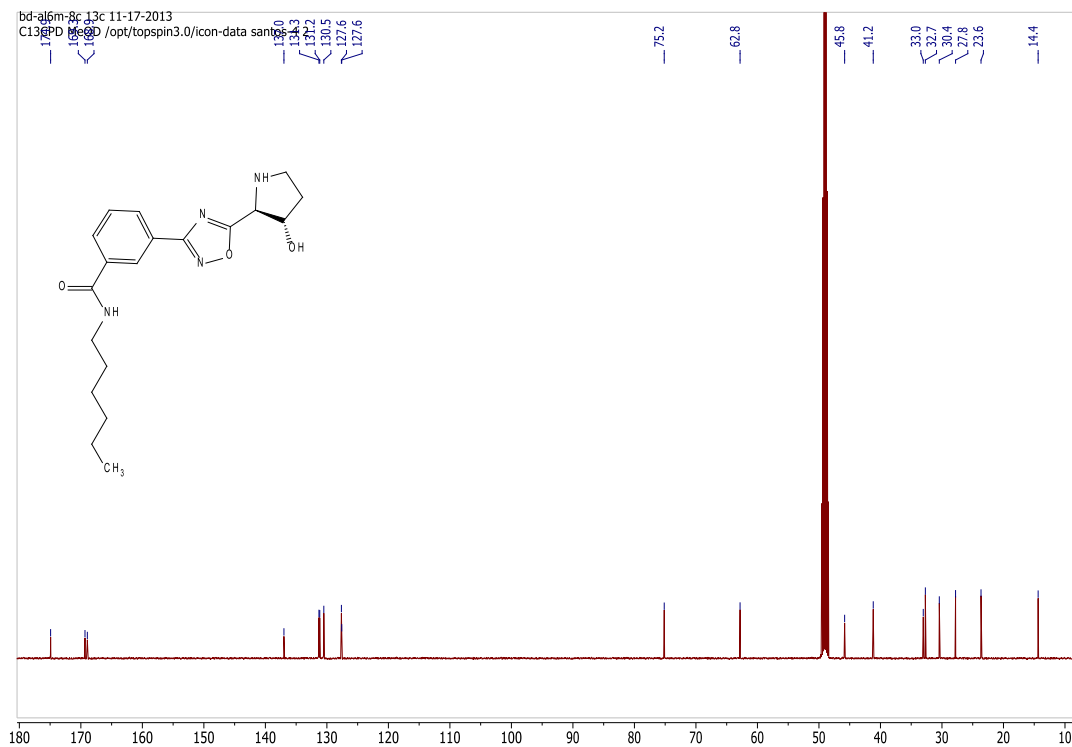
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **2.53d**-



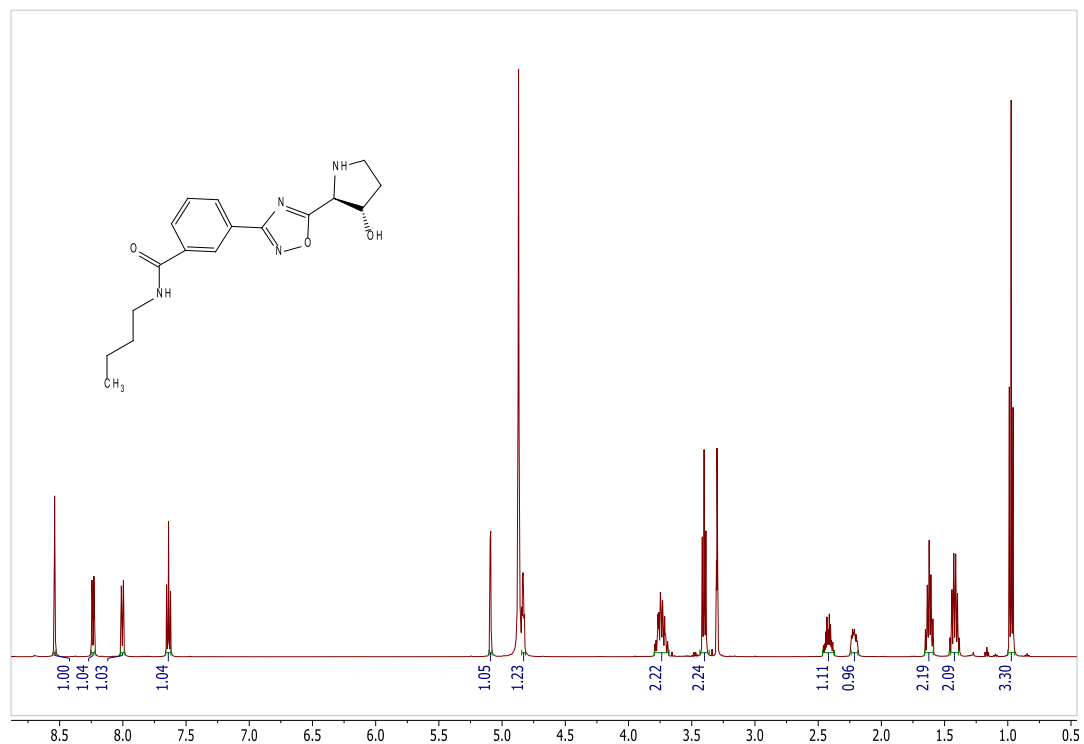
<sup>1</sup>H-NMR Spectrum for (2*S*,3*S*)-2-(3-(3-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-ium 2,2,2-trifluoroacetate –



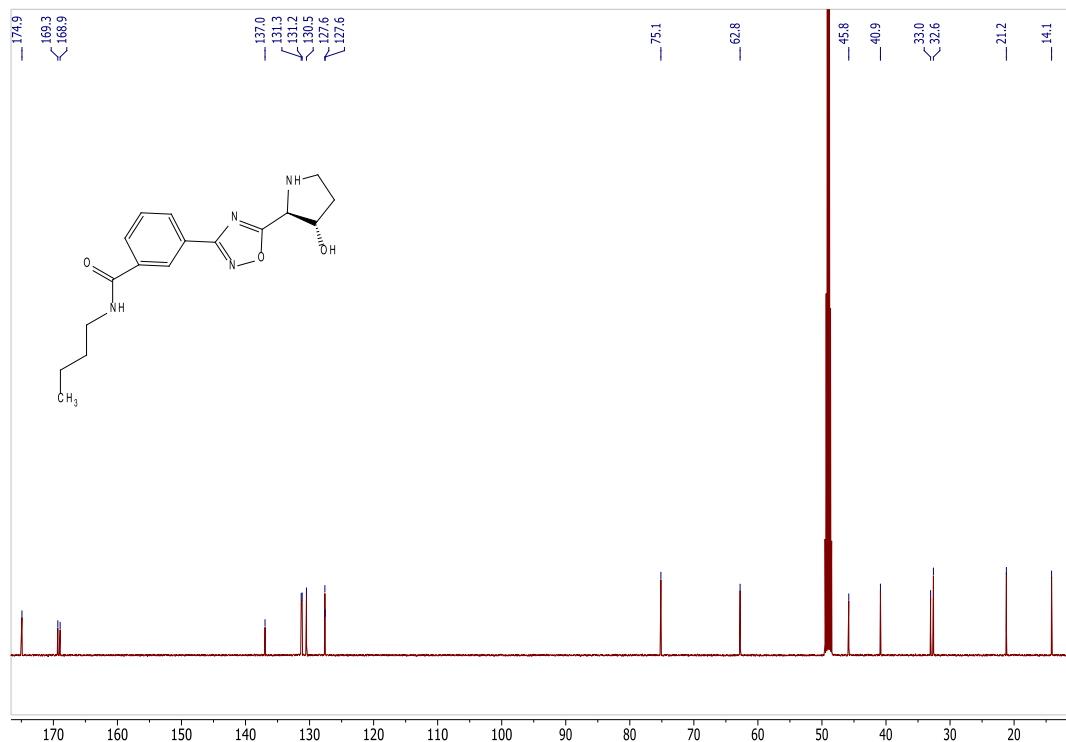
<sup>13</sup>C-NMR Spectrum for (2*S*,3*S*)-2-(3-(3-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-ium 2,2,2-trifluoroacetate –



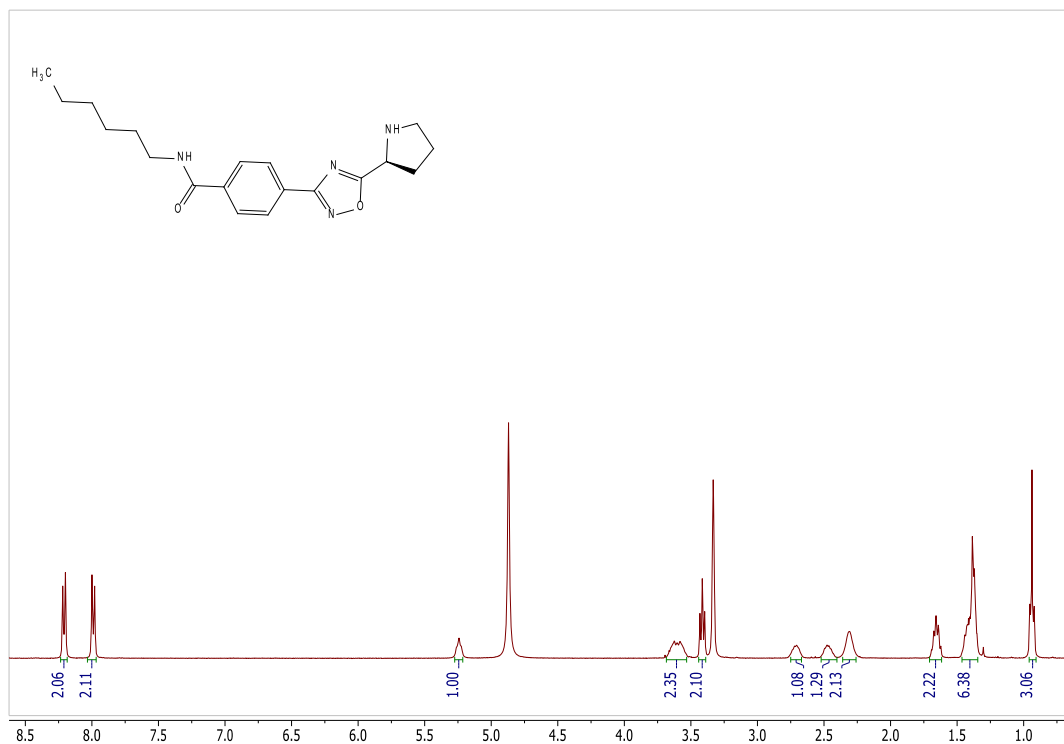
<sup>1</sup>H-NMR Spectrum for (2*S*,3*S*)-2-(3-(3-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-ium 2,2,2-trifluoroacetate –



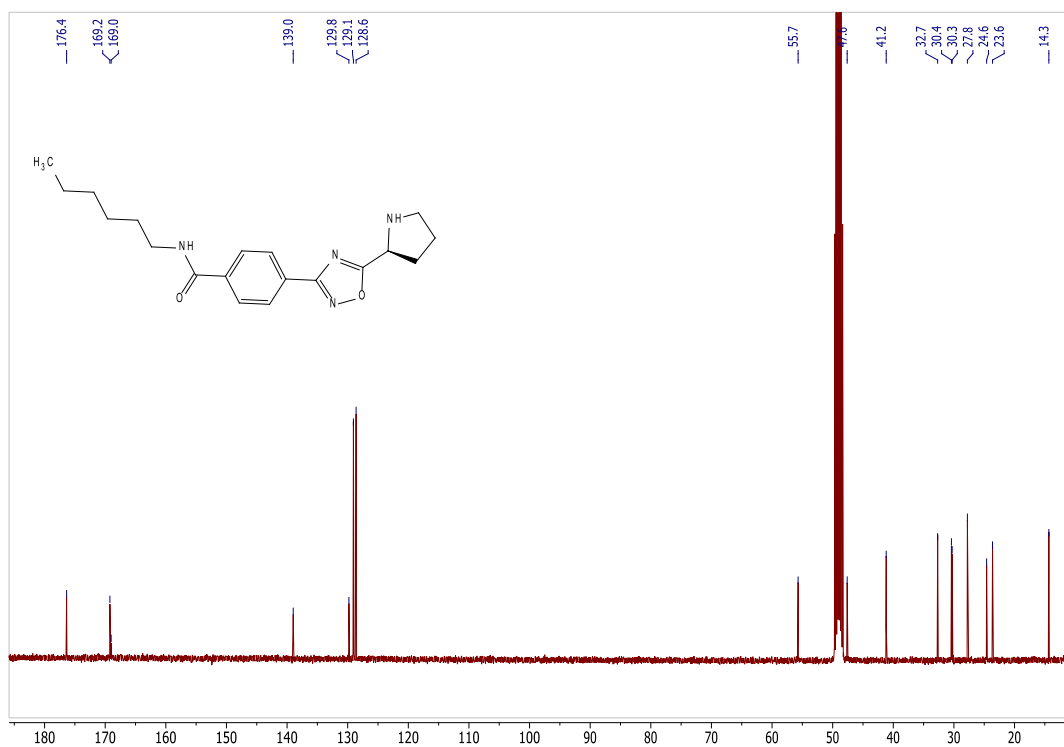
<sup>13</sup>C-NMR Spectrum for (2*S*,3*S*)-2-(3-(3-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-ium 2,2,2-trifluoroacetate –



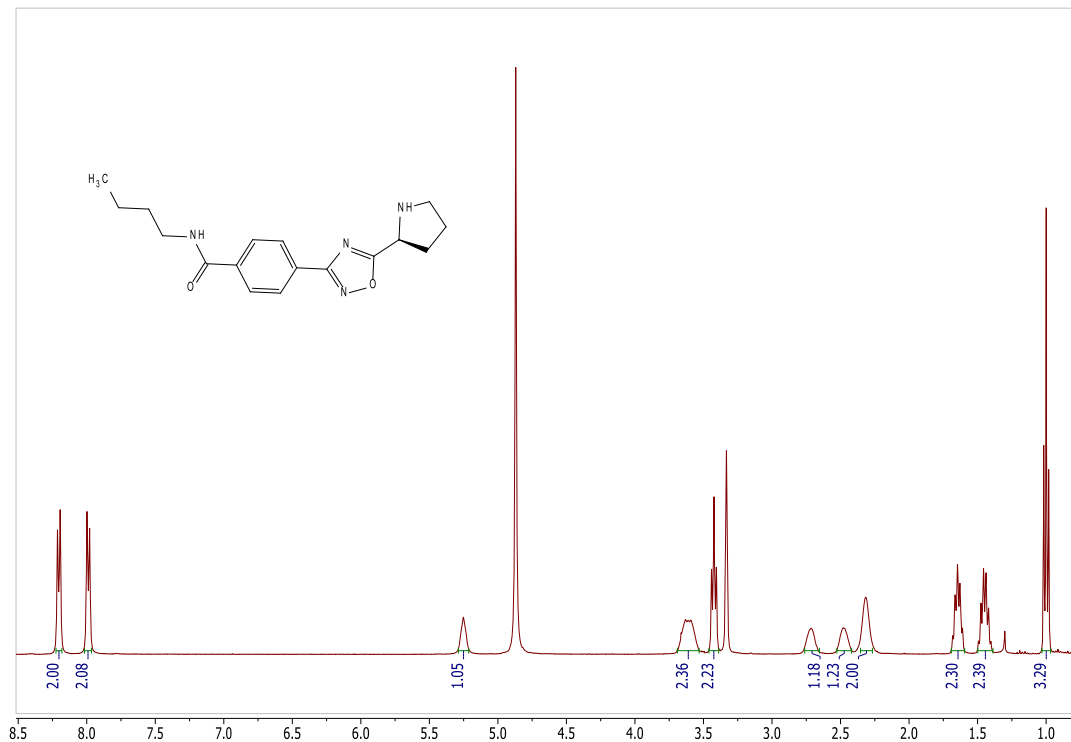
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



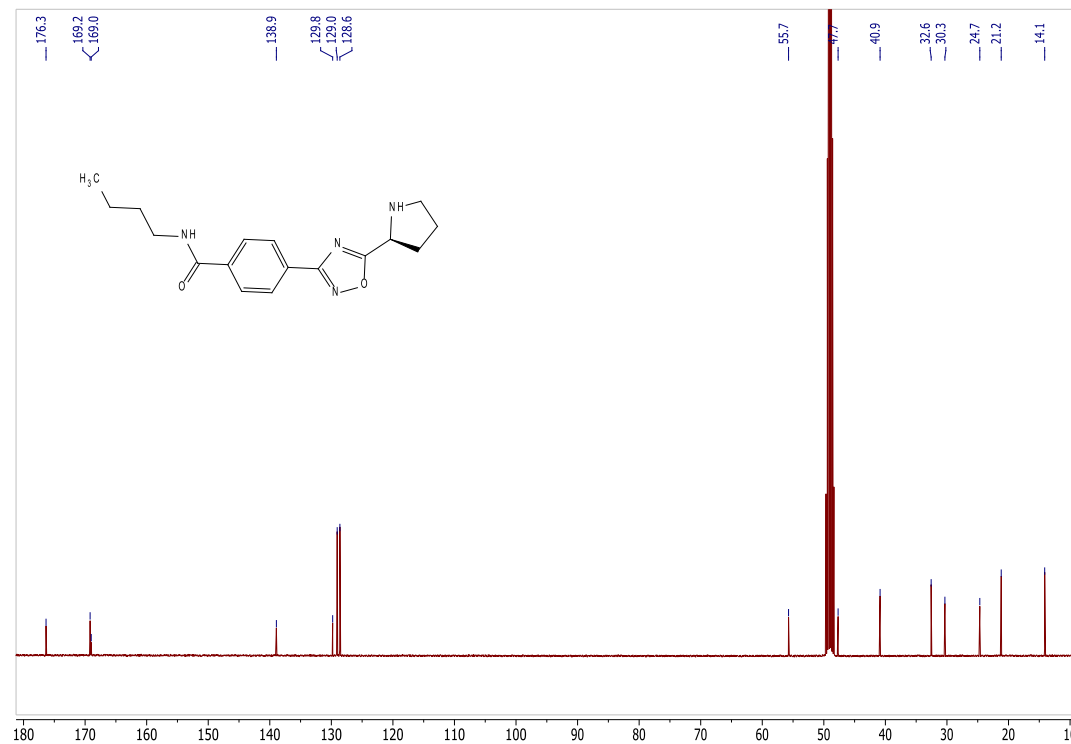
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



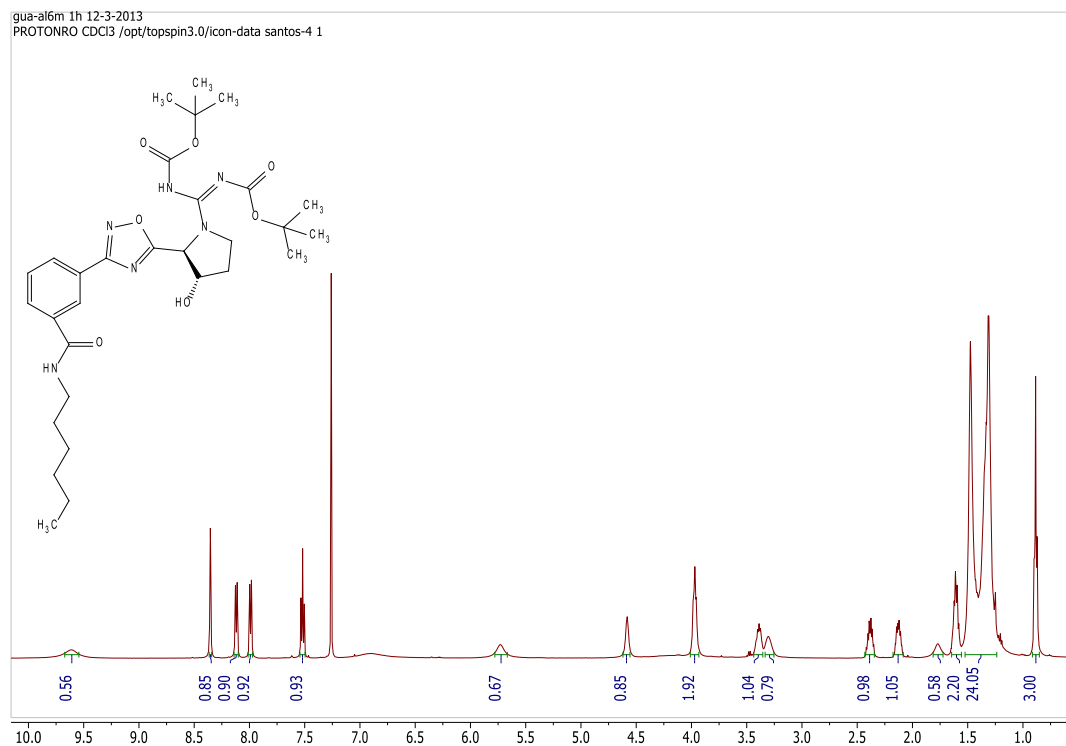
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



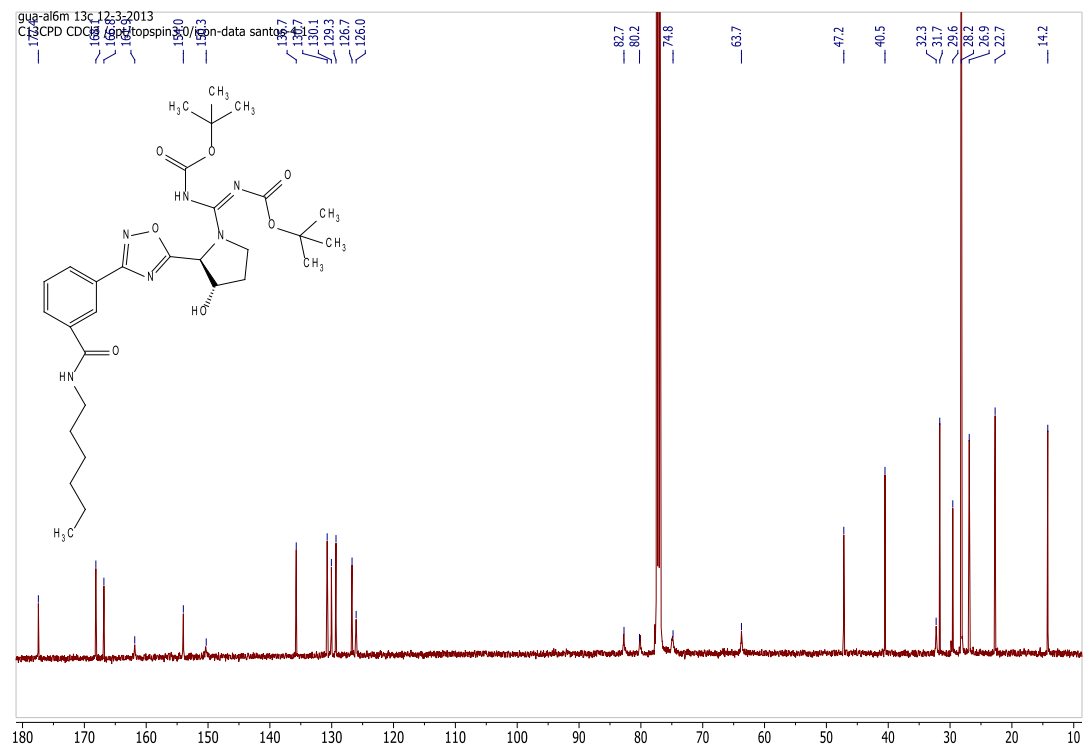
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



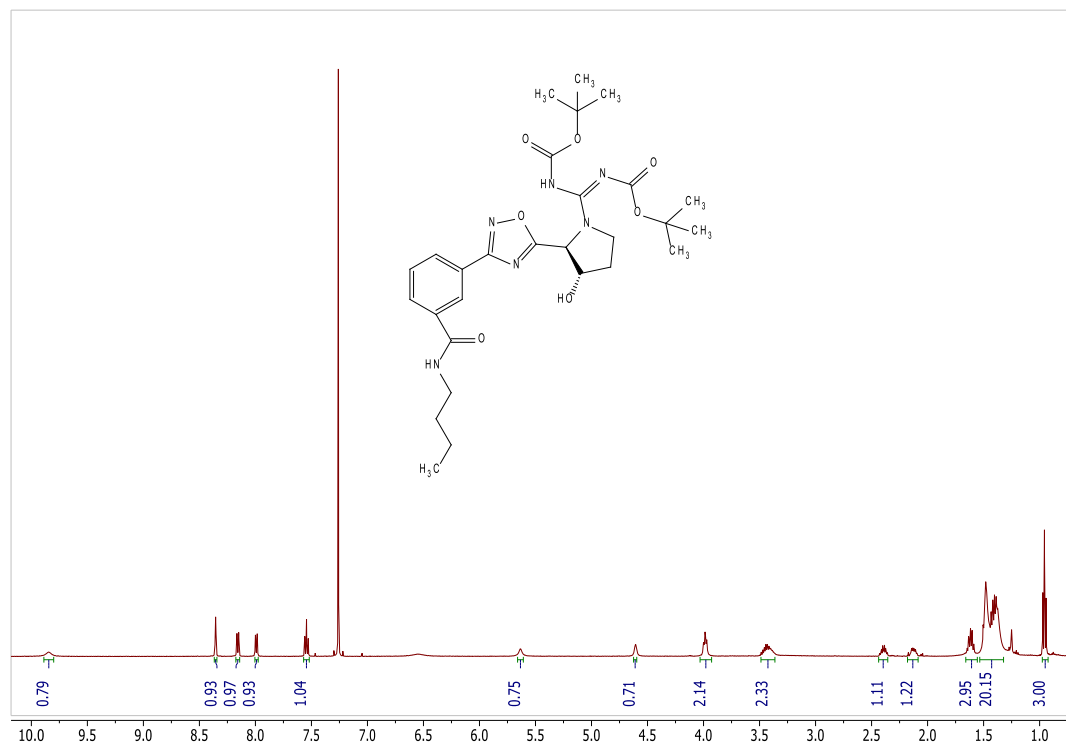
$^1\text{H-NMR}$  Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)((2*S*,3*S*)-2-(3-(3-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl)methylene)carbamate **2.54a**



<sup>13</sup>C-NMR Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)((2*S*,3*S*)-2-(3-(3-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl)methylene)carbamate **2.54a**

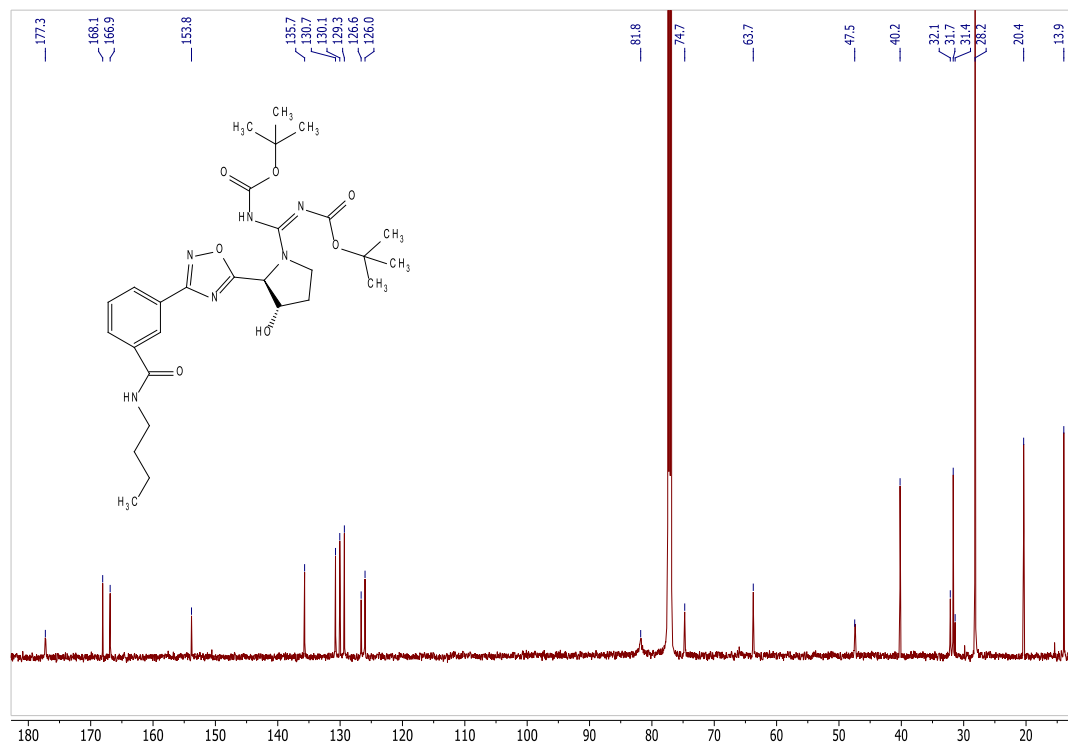


<sup>1</sup>H-NMR Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)((2*S*,3*S*)-2-(3-(3-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl)methylene)carbamate **2.54b**-

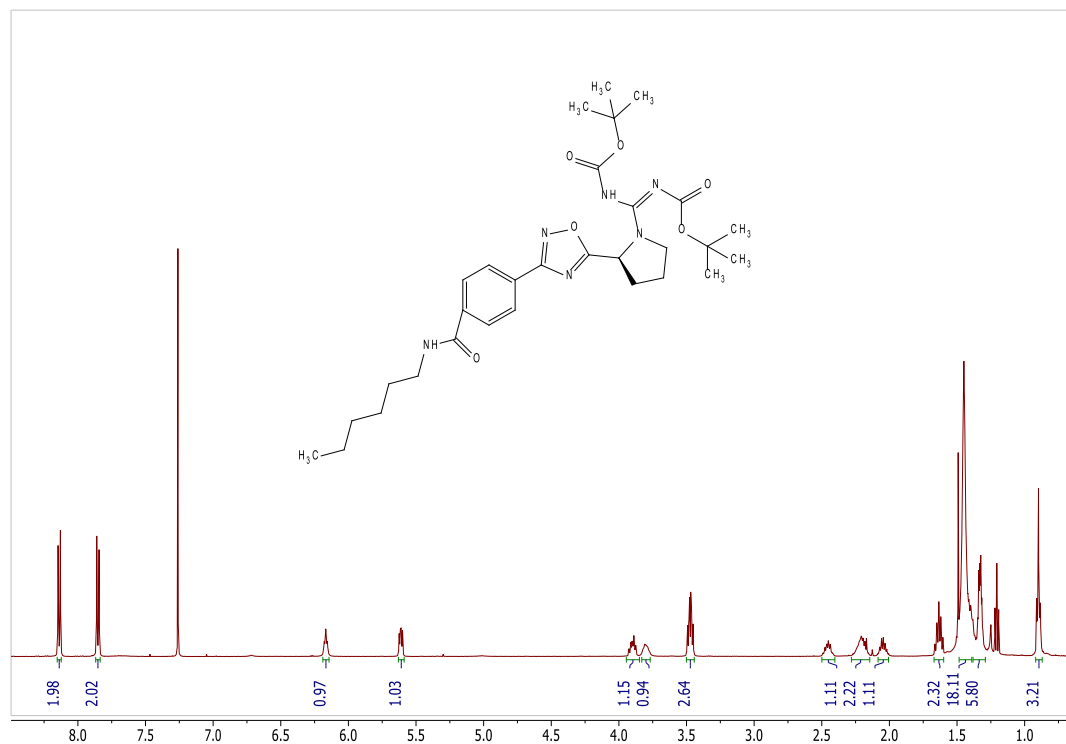




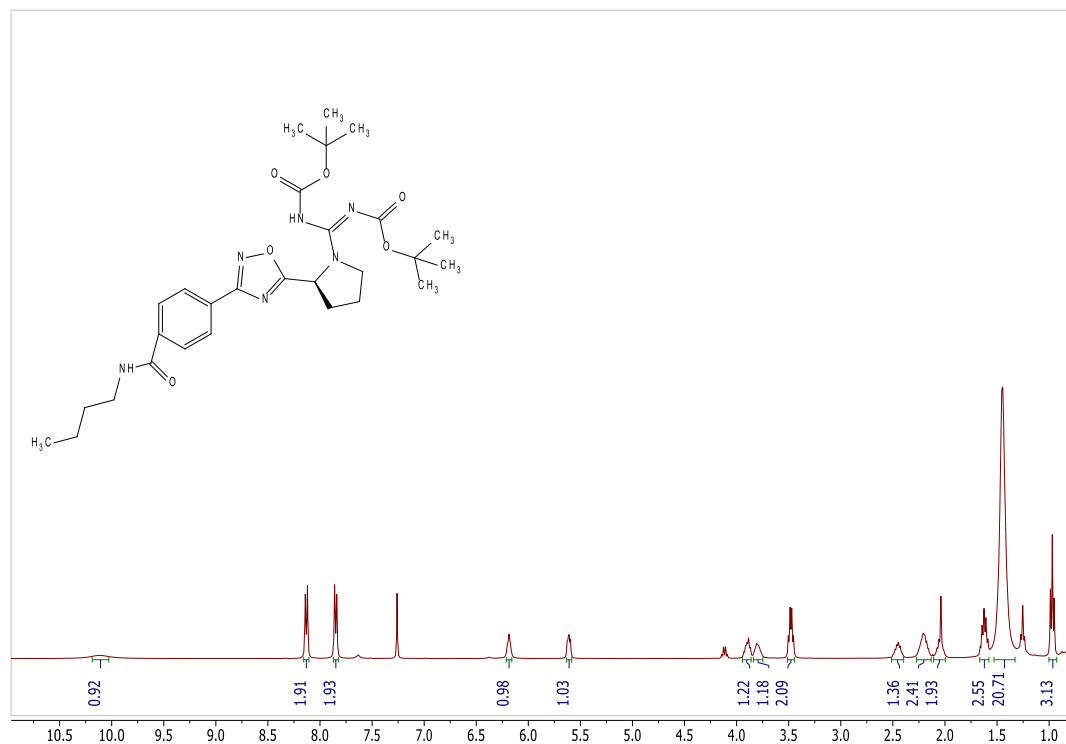
<sup>13</sup>C-NMR Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)((2*S*,3*S*)-2-(3-(3-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl)methylene)carbamate **2.54b**



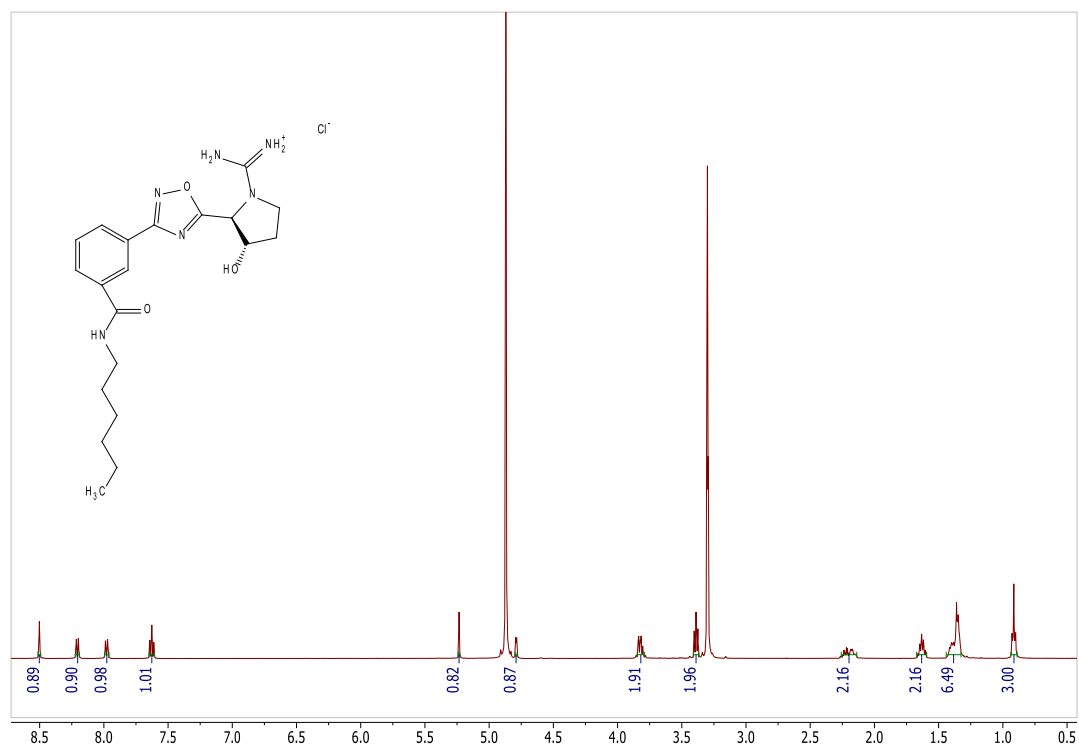
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **2.54c**-



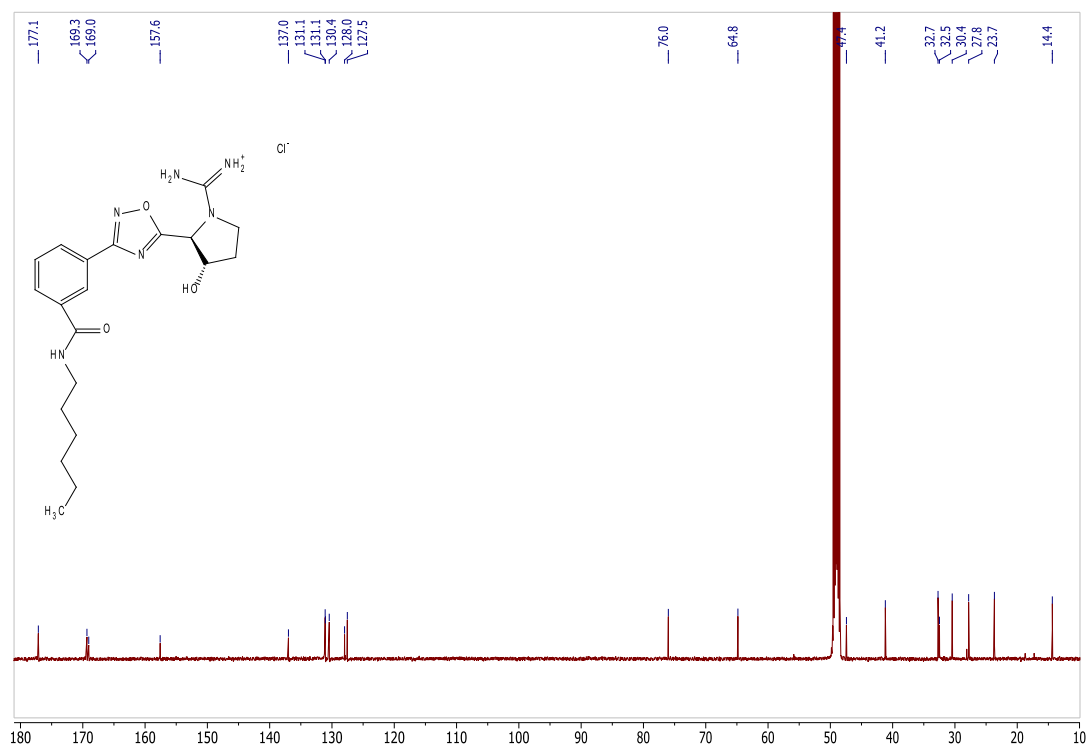
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **2.54d**-



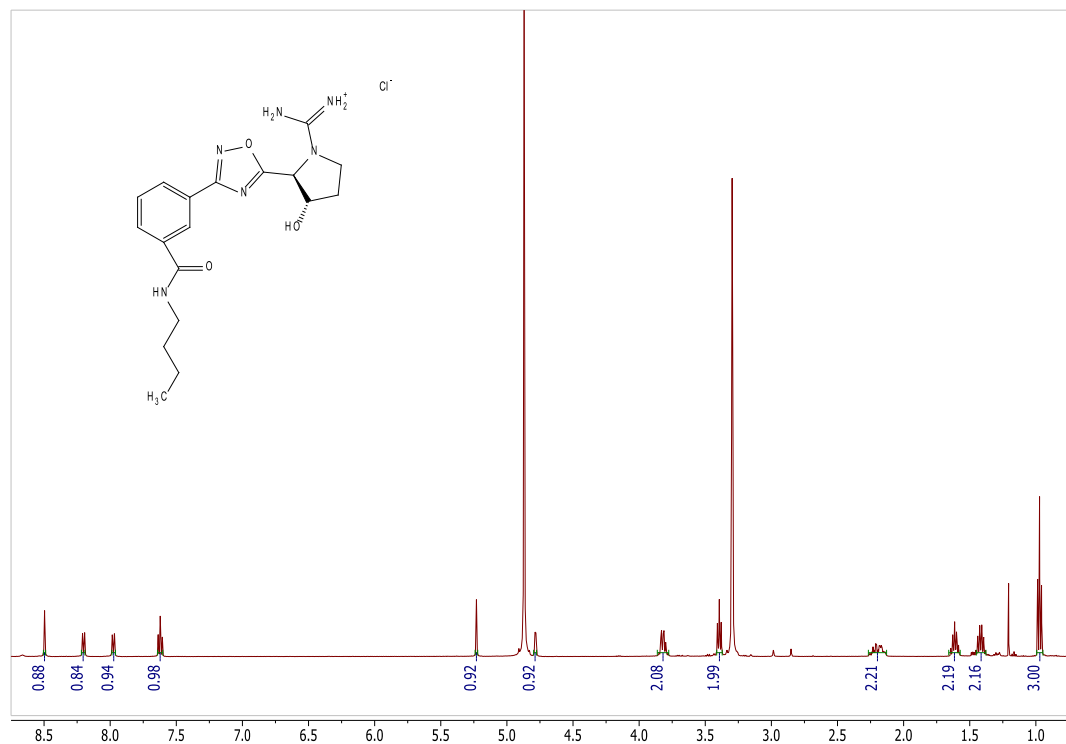
$^1\text{H-NMR}$  Spectrum for amino((2*S*,3*S*)-2-(3-(3-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl)methaniminium chloride **2.55a**-



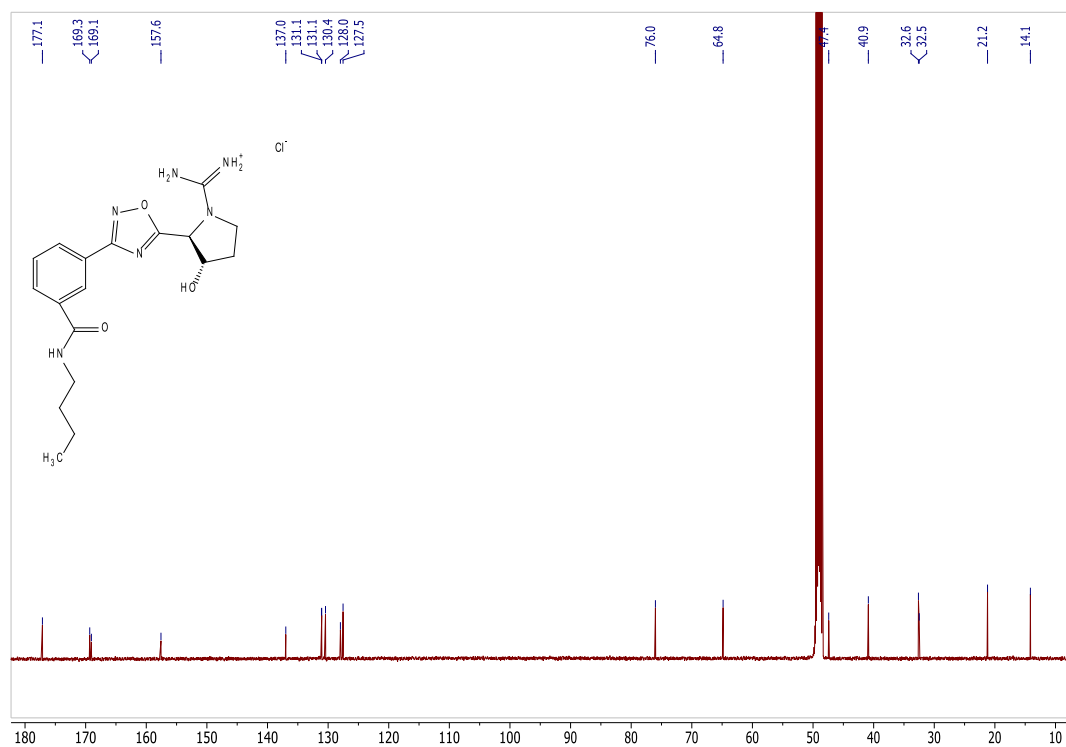
$^{13}\text{C-NMR}$  Spectrum for amino((2*S*,3*S*)-2-(3-(3-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl)methaniminium chloride **2.55a**-



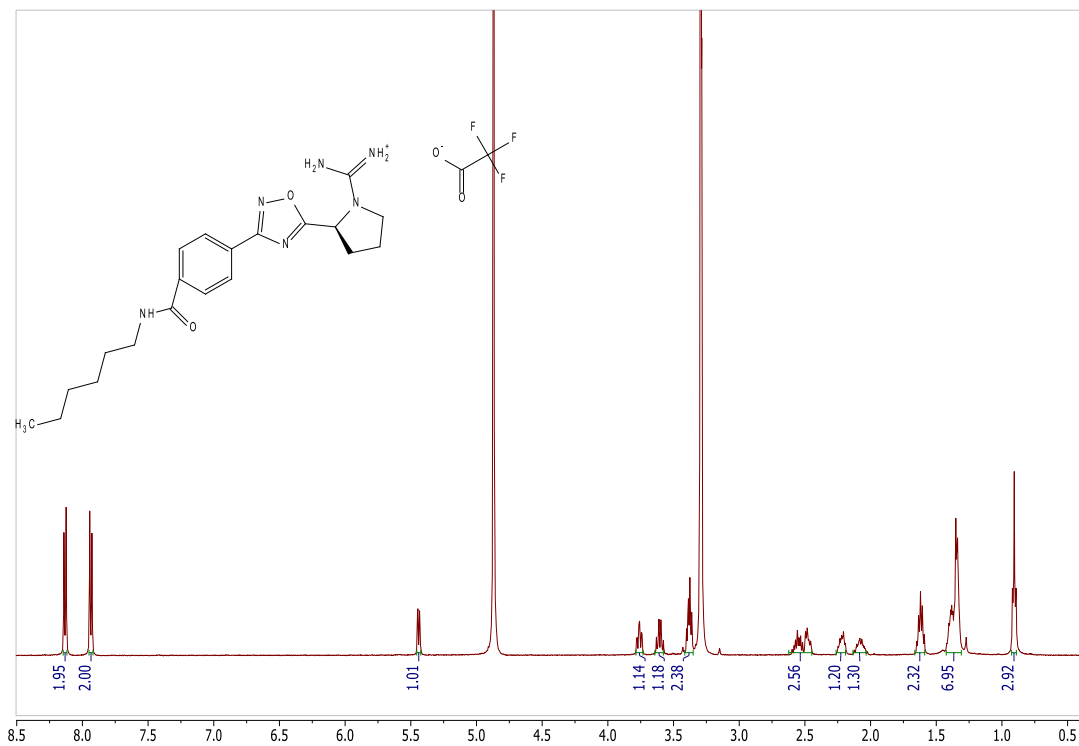
$^1\text{H-NMR}$  Spectrum for *amino((2S,3S)-2-(3-(3-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl)methaniminium chloride 2.55b-*



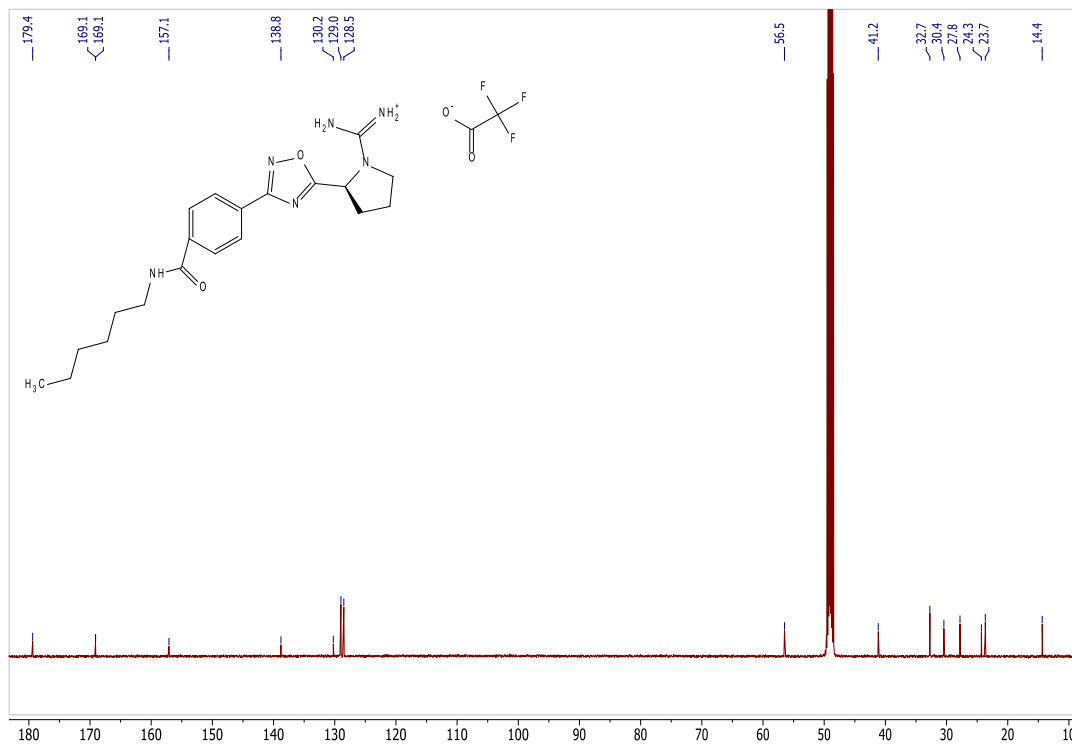
$^{13}\text{C-NMR}$  Spectrum for *amino((2S,3S)-2-(3-(3-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)-3-hydroxypyrrolidin-1-yl)methaniminium chloride 2.55b-*



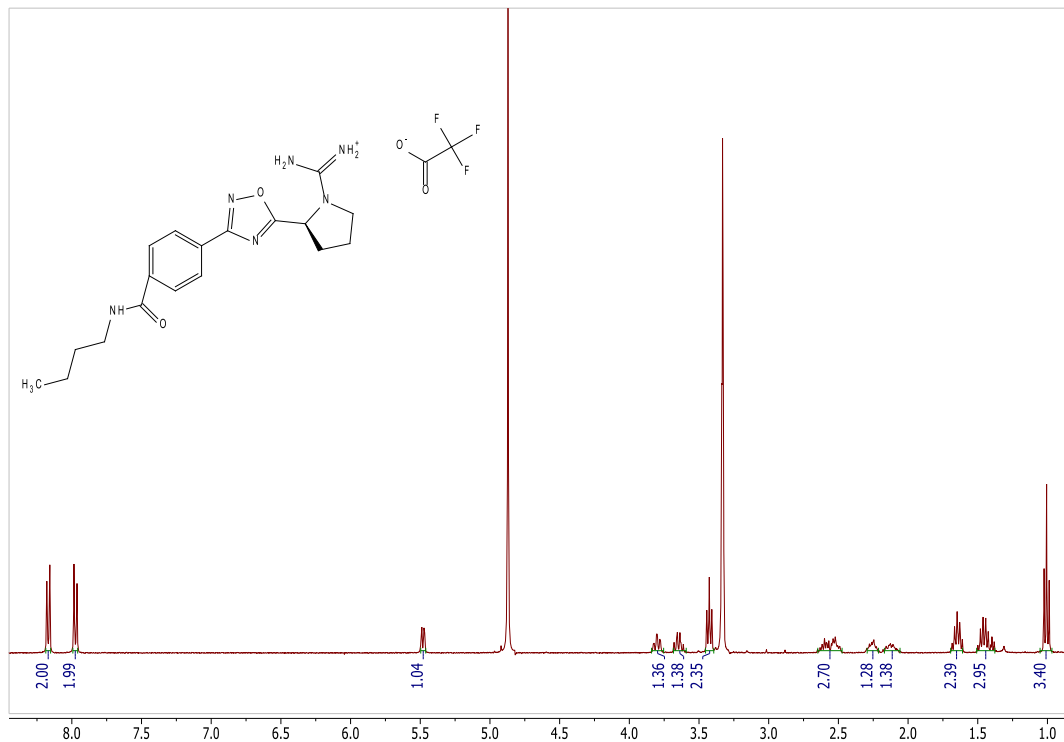
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.55c**-



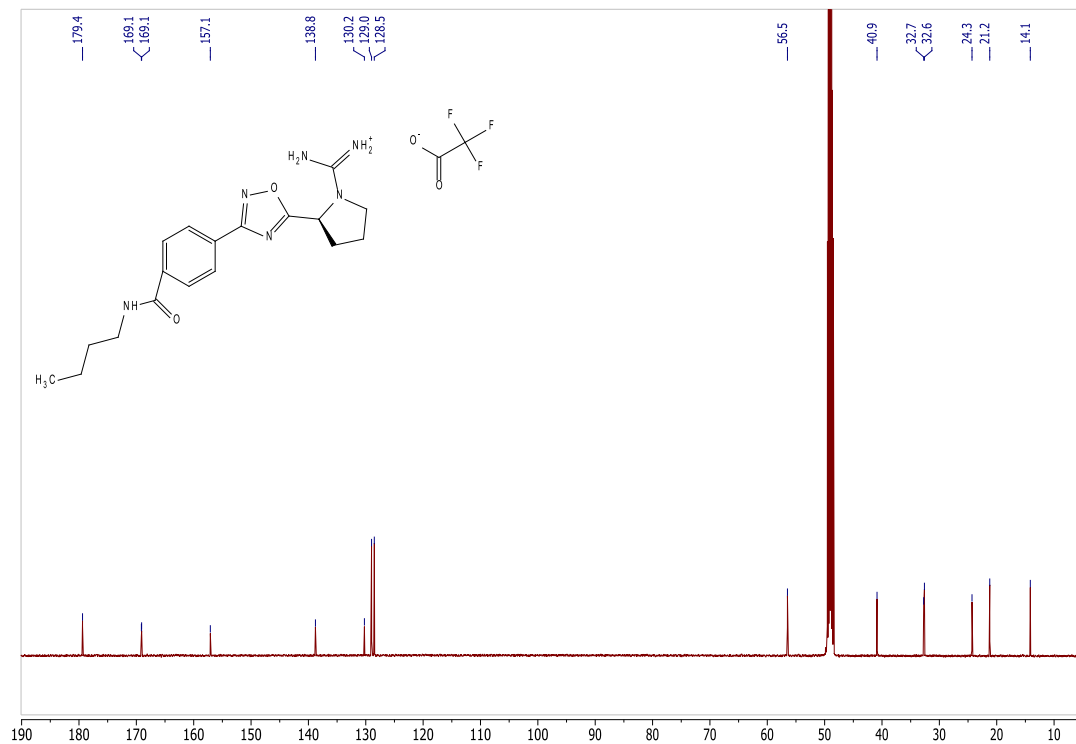
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-(hexylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.55c**-



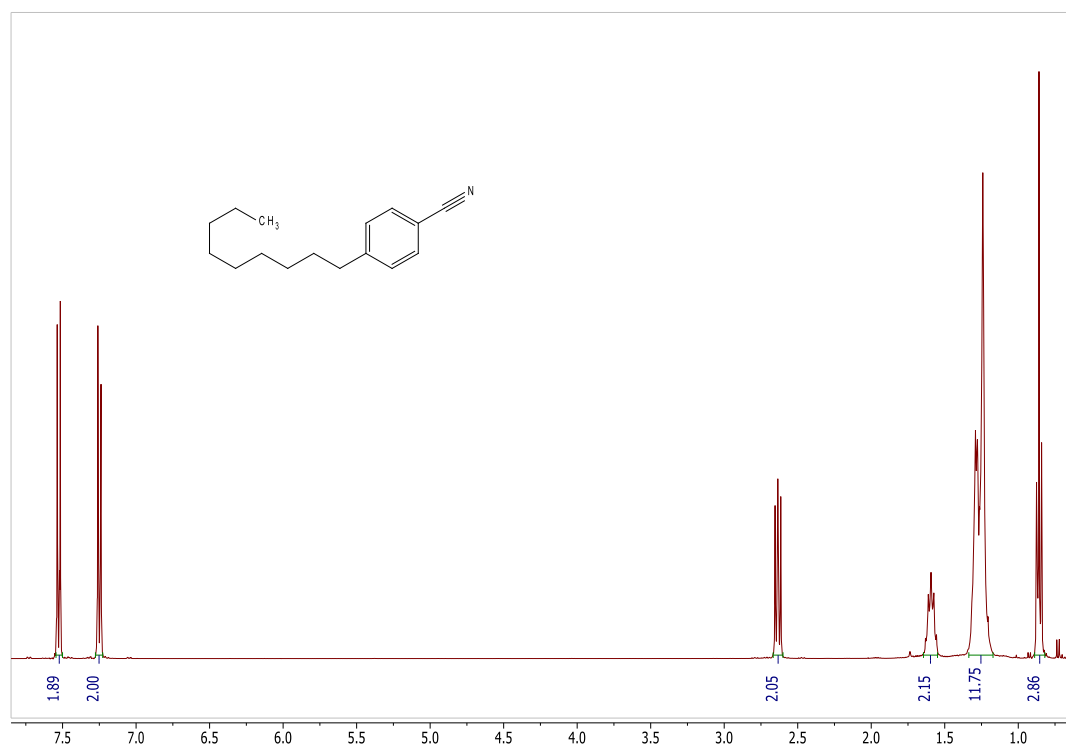
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.55d**-



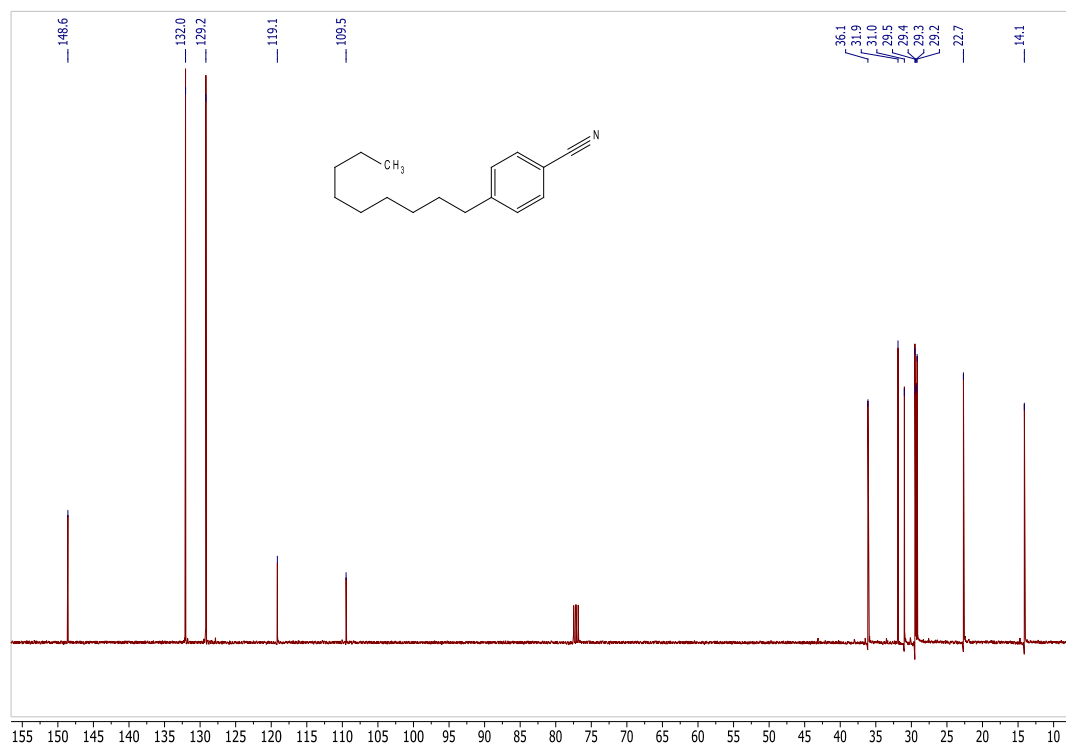
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-(butylcarbamoyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **2.55d**-



<sup>1</sup>H-NMR Spectrum for 4-nonylbenzonitrile **2.57**-

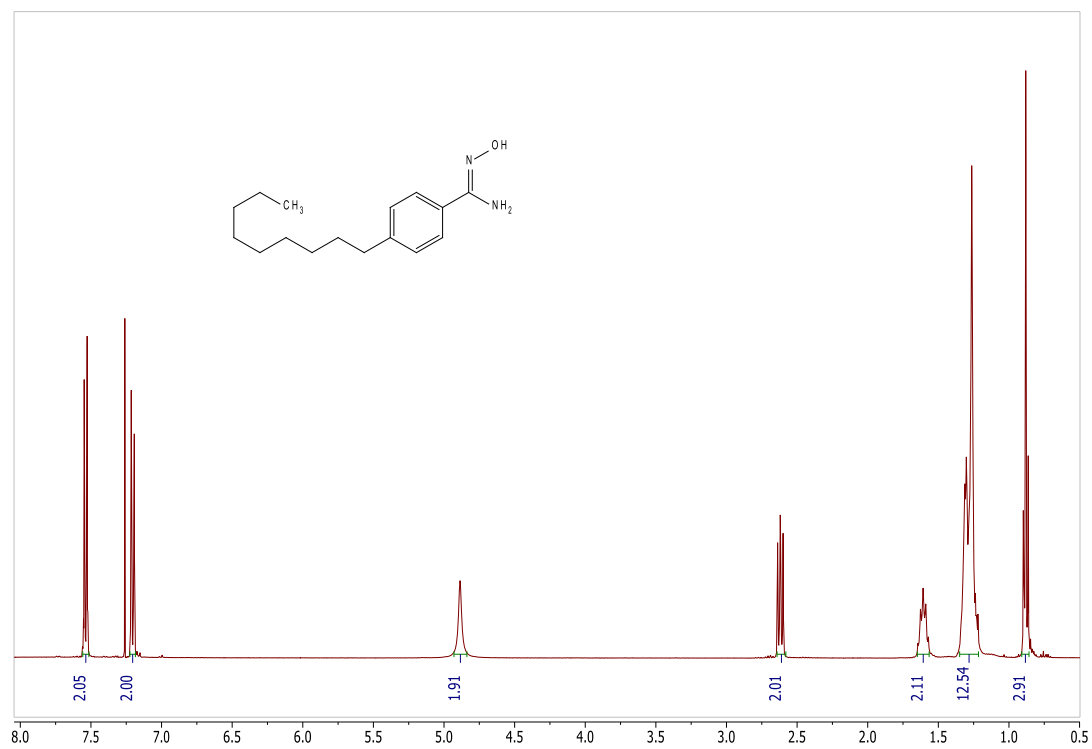


<sup>13</sup>C-NMR Spectrum for 4-nonylbenzonitrile **2.57**-





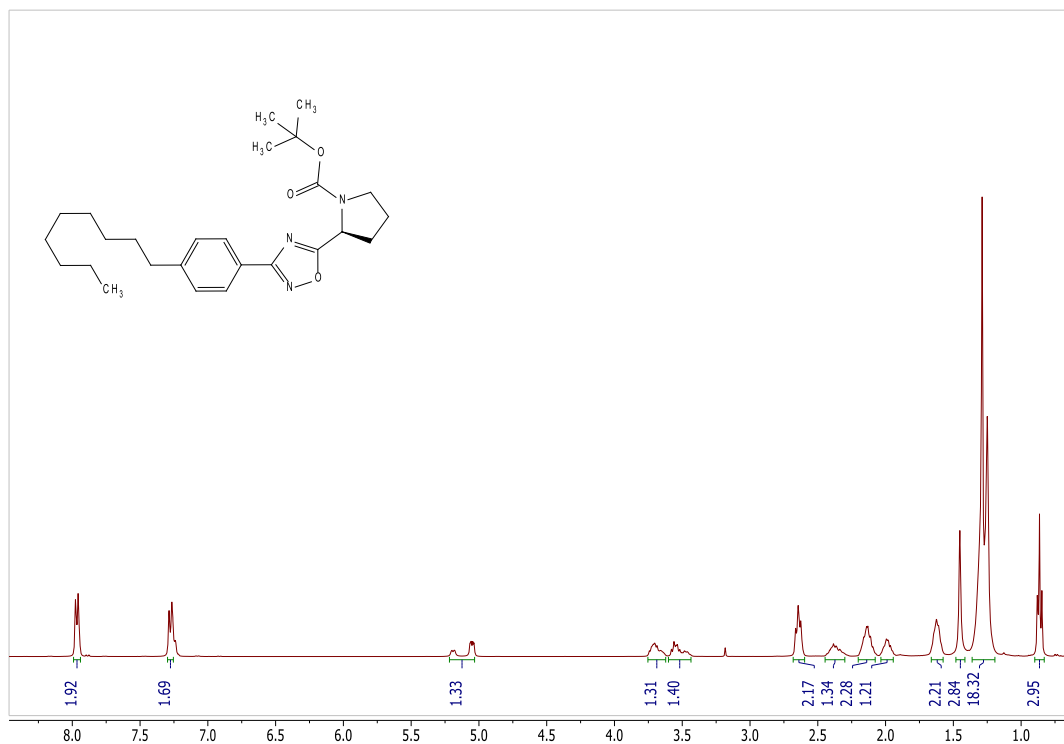
<sup>1</sup>H-NMR Spectrum for (Z)-N'-hydroxy-4-nonylbenzimidamide –



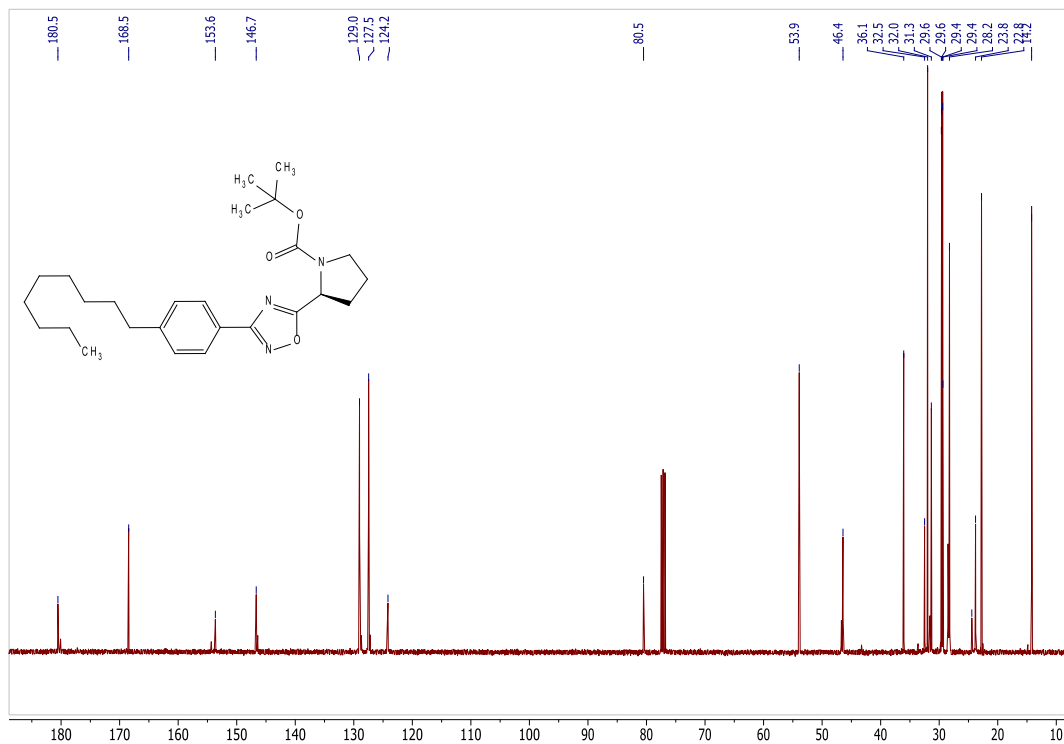
<sup>13</sup>C-NMR Spectrum for (Z)-N'-hydroxy-4-nonylbenzimidamide –



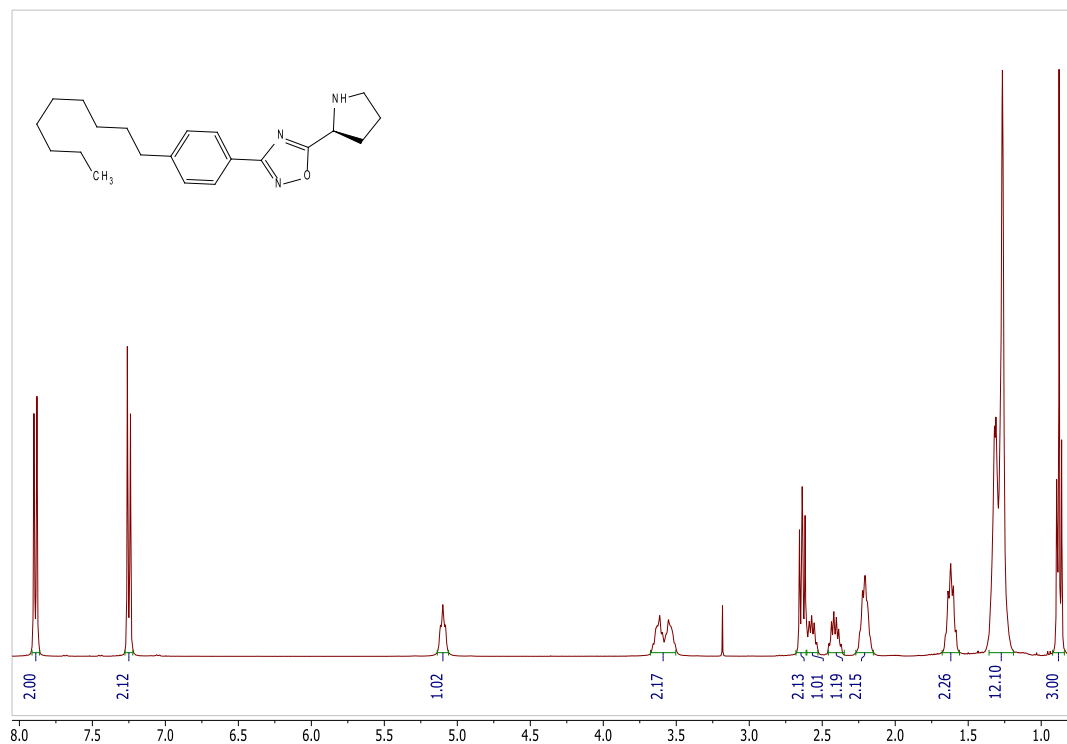
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate



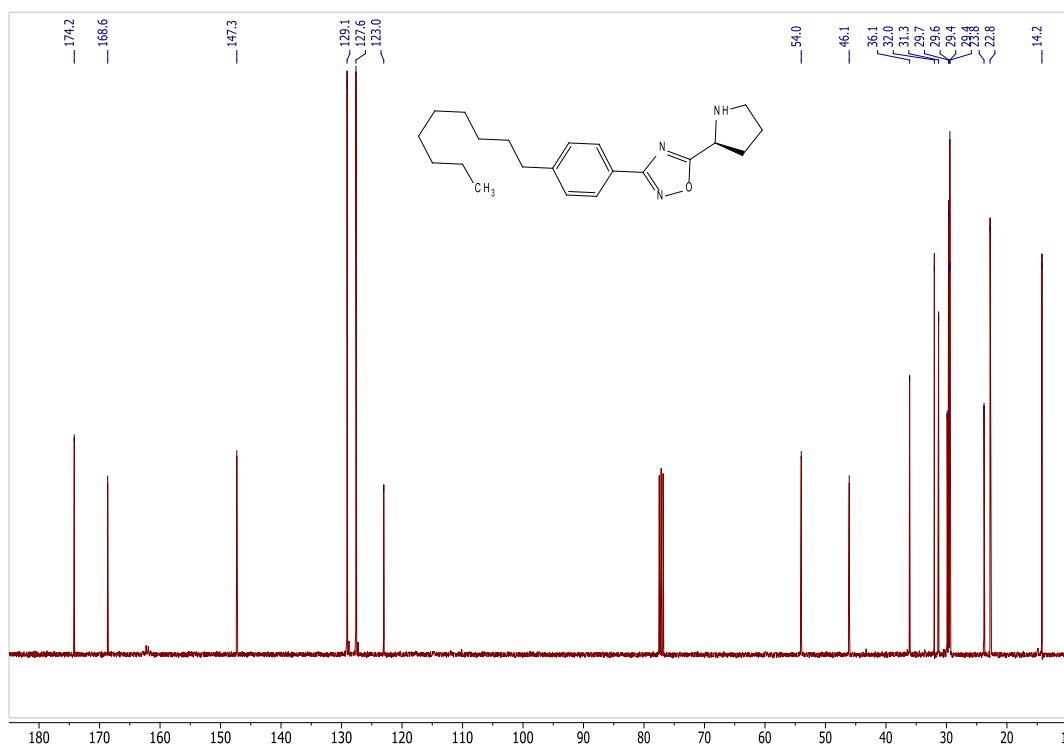
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate



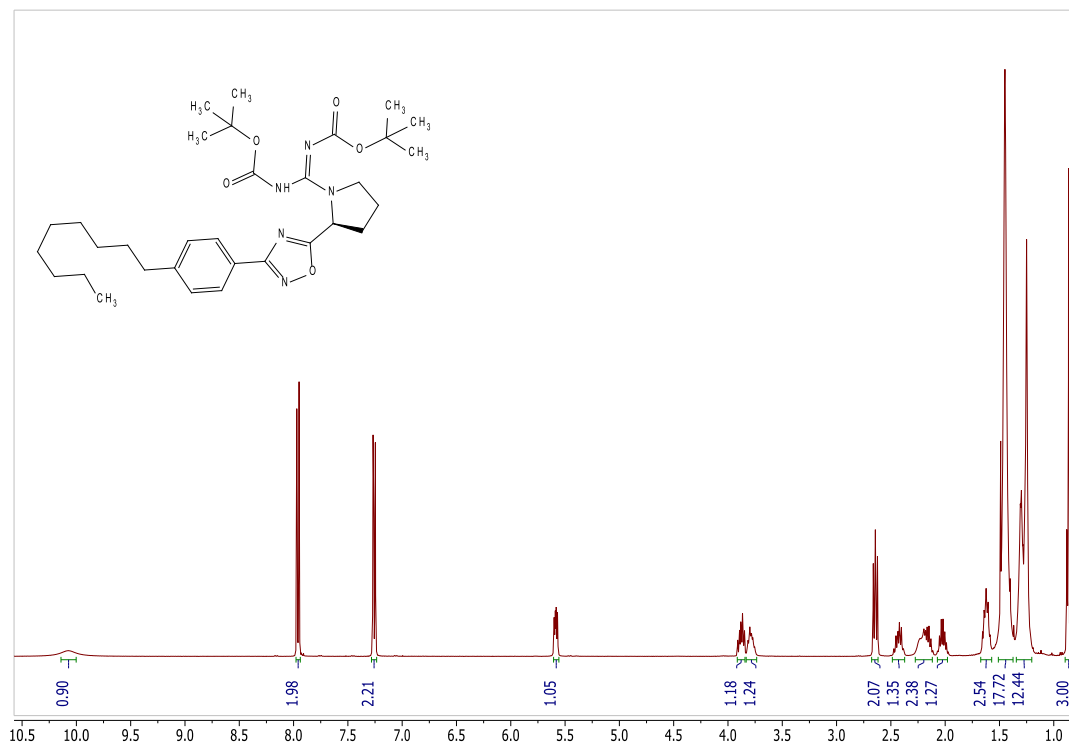
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



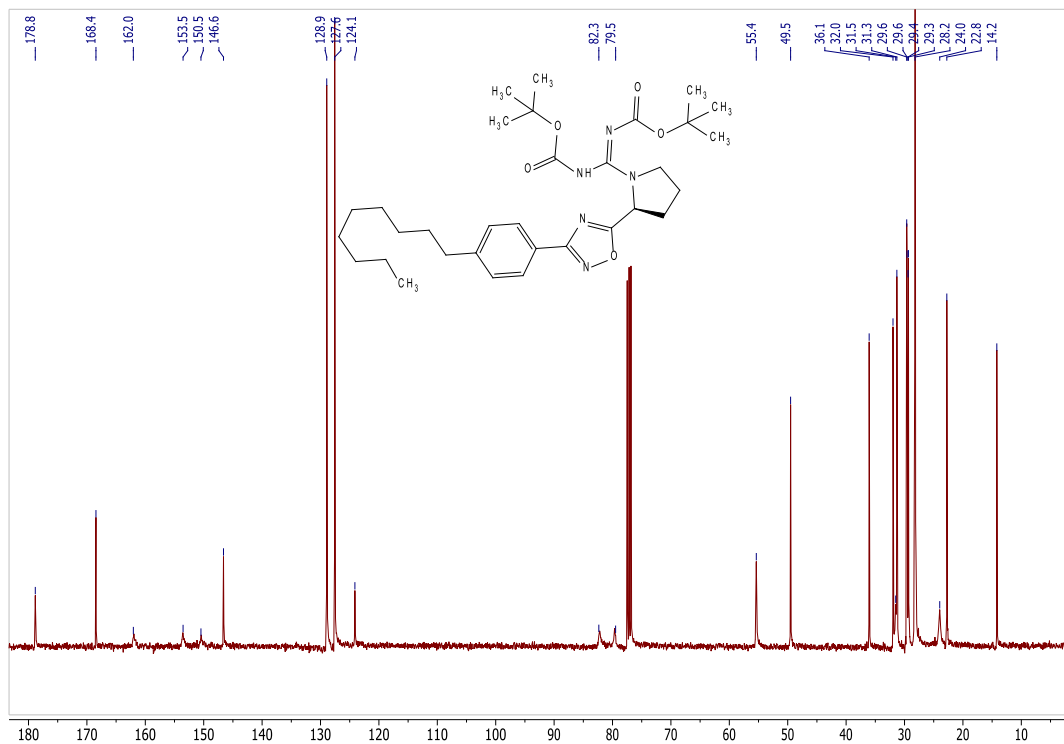
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



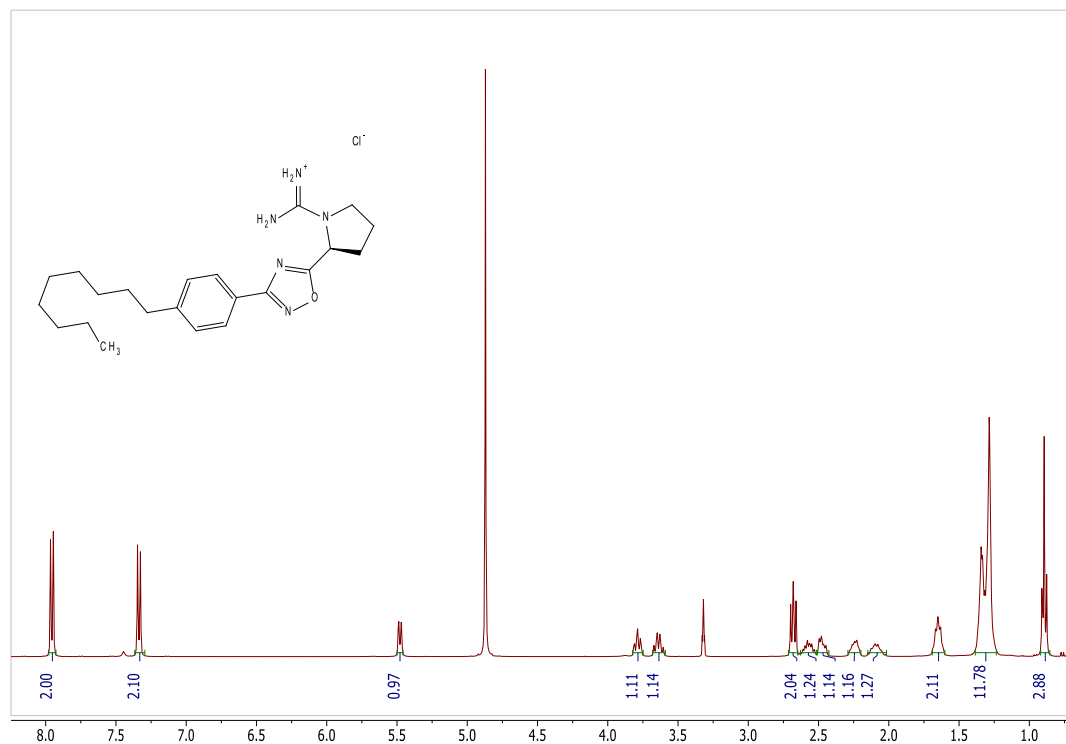
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



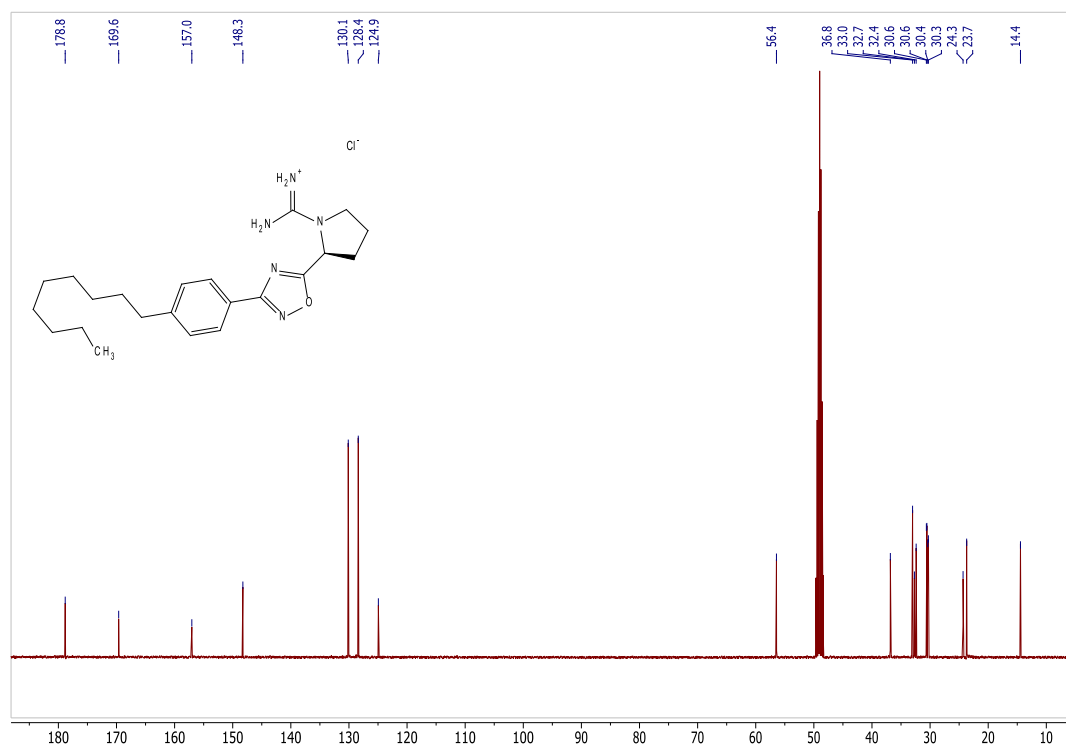
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



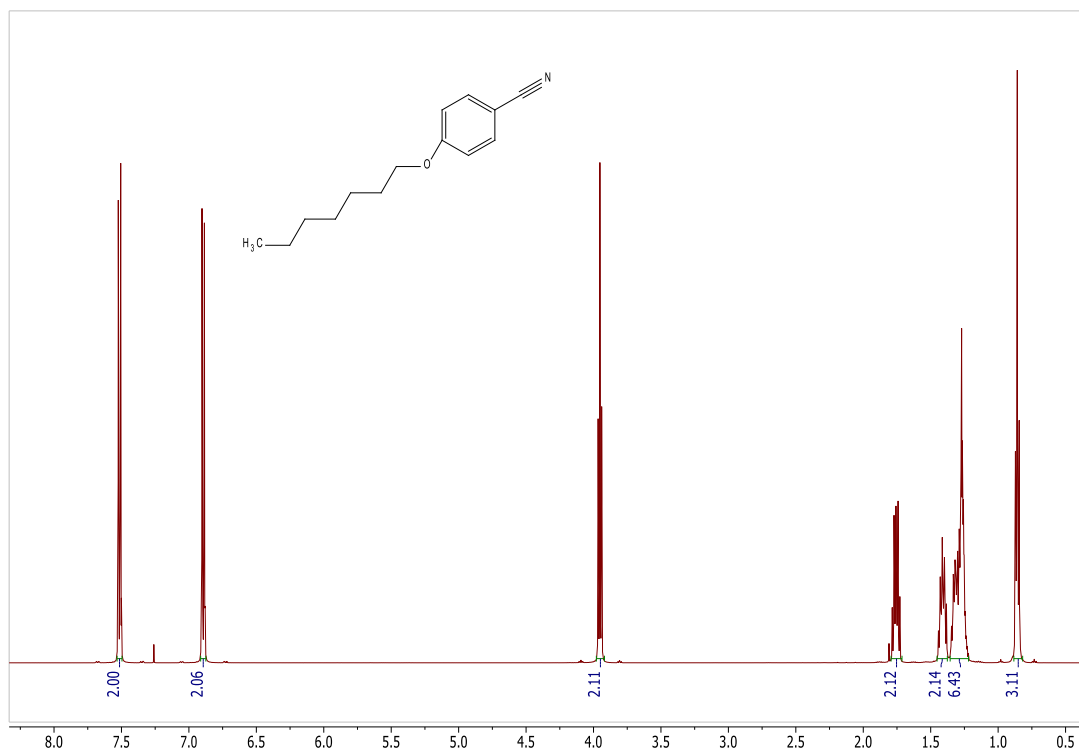
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **2.58**-



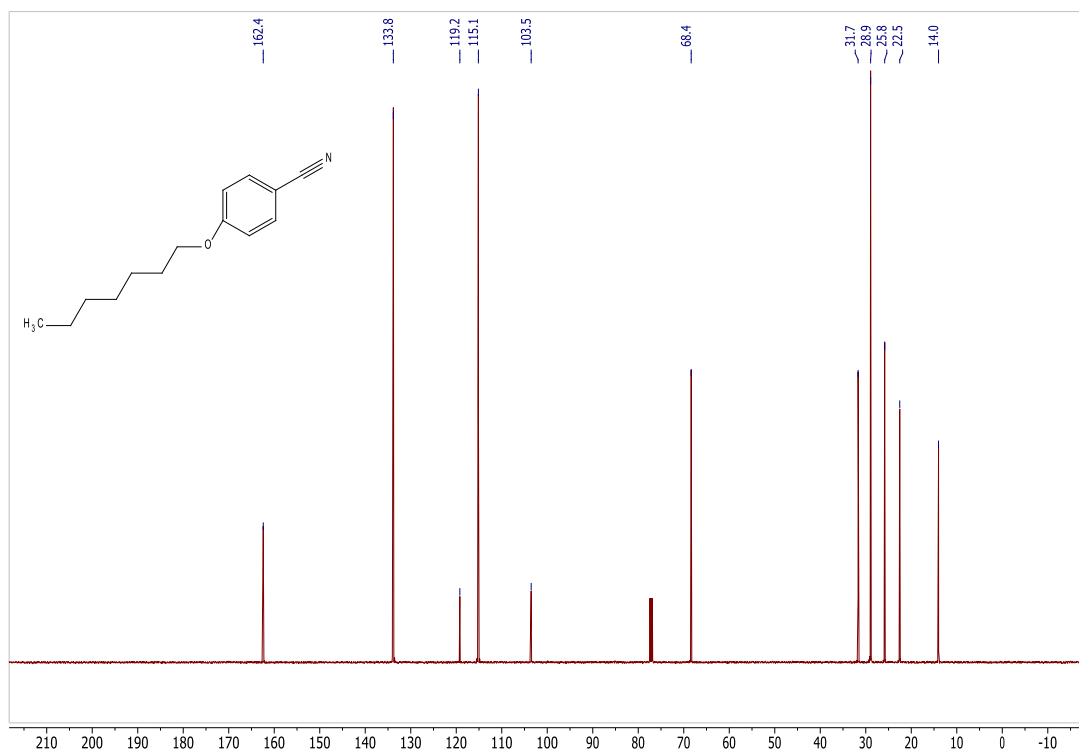
<sup>13</sup>C-NMR Spectrum for (S)-amino(2-(3-(4-nonylphenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **2.58**-



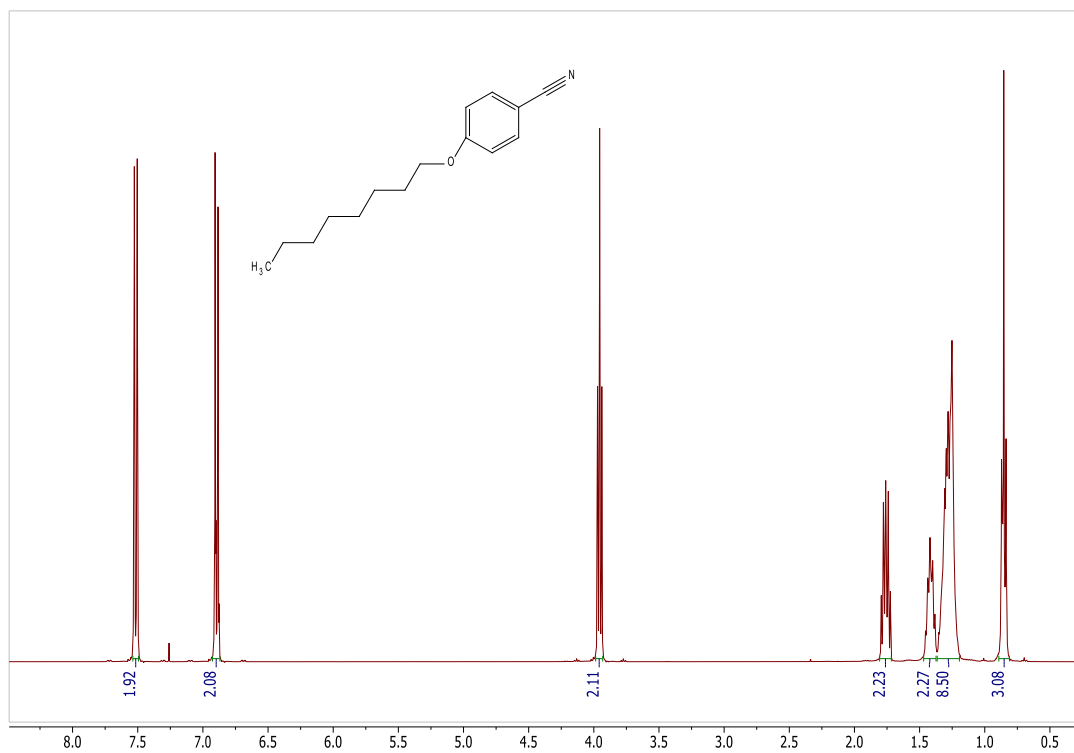
<sup>1</sup>H-NMR Spectrum for 4-(heptyloxy)benzonitrile **3.2a** –



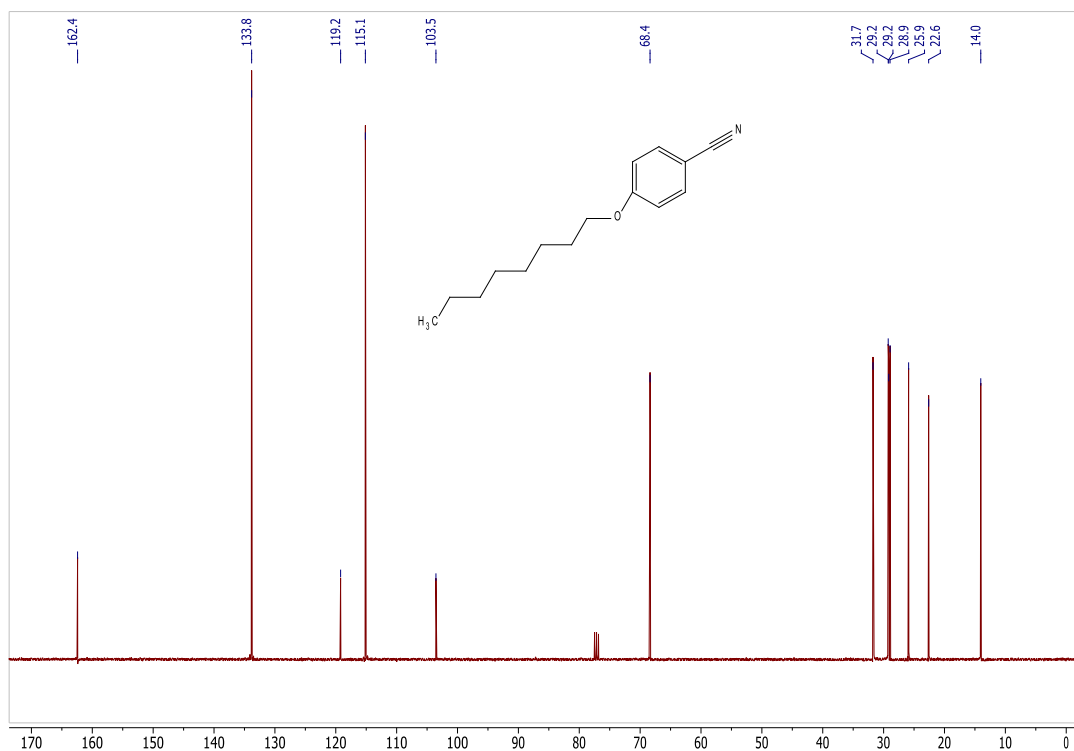
<sup>13</sup>C-NMR Spectrum for 4-(heptyloxy)benzonitrile **3.2a**–



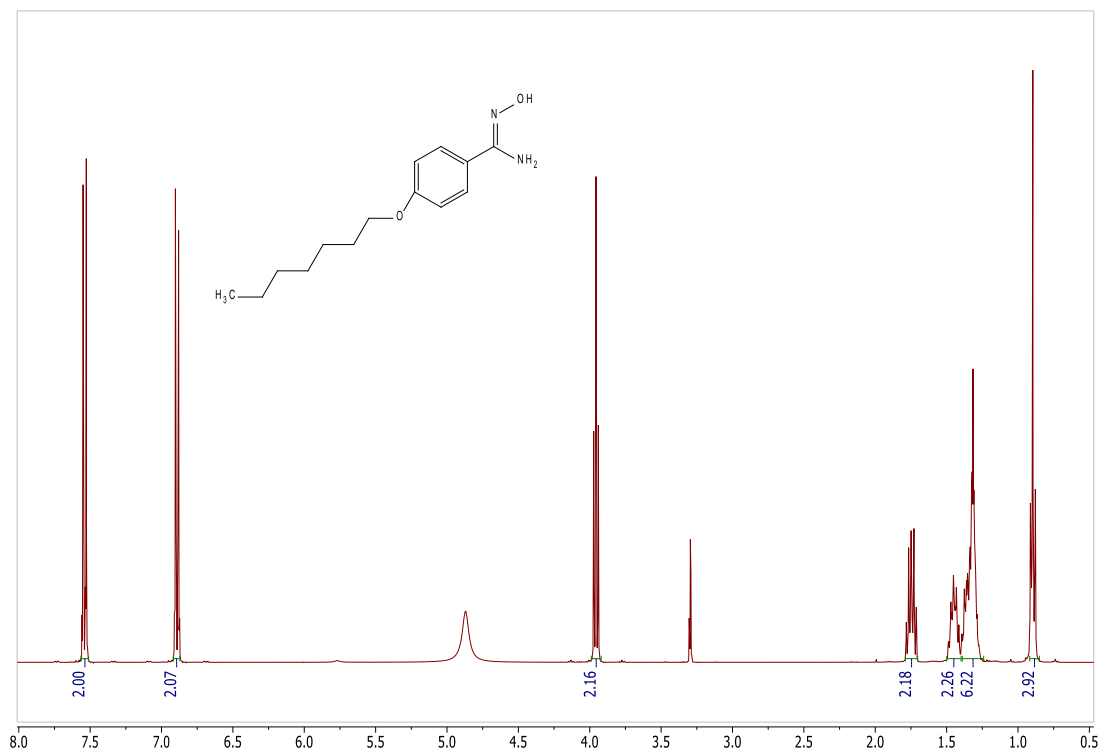
<sup>1</sup>H-NMR Spectrum for 4-(octyloxy)benzonitrile **3.2b** –



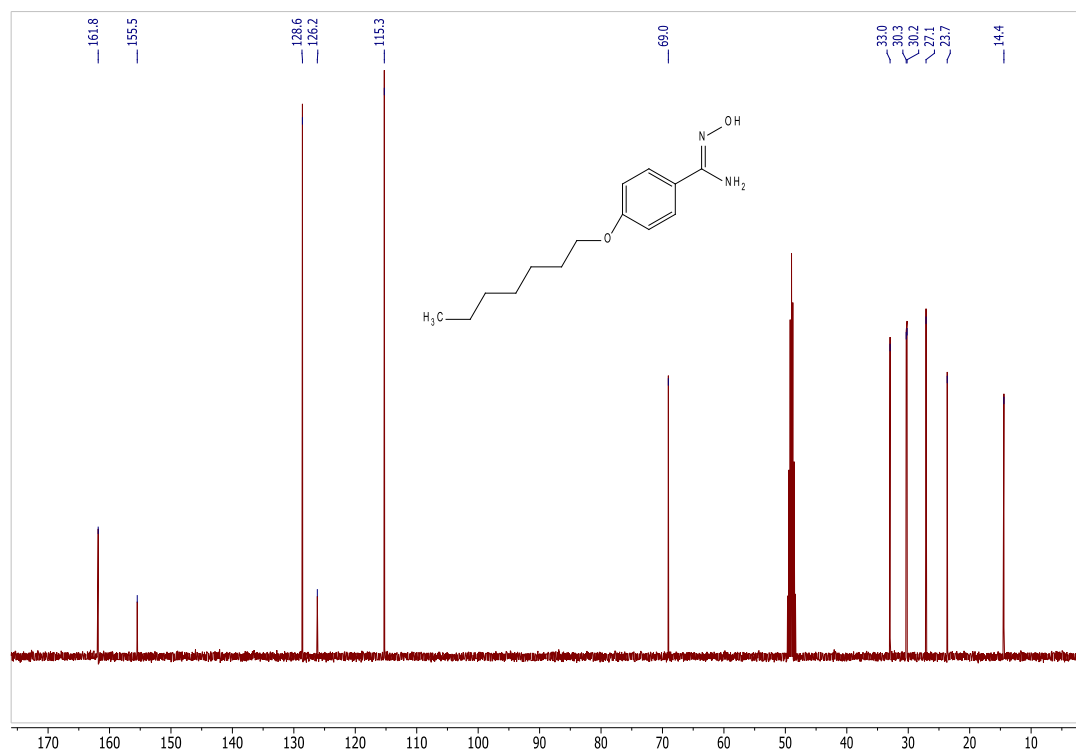
<sup>13</sup>C-NMR Spectrum for 4-(octyloxy)benzonitrile **3.2b**–



<sup>1</sup>H-NMR Spectrum for (Z)-4-(heptyloxy)-N'-hydroxybenzimidamide **3.3a** –

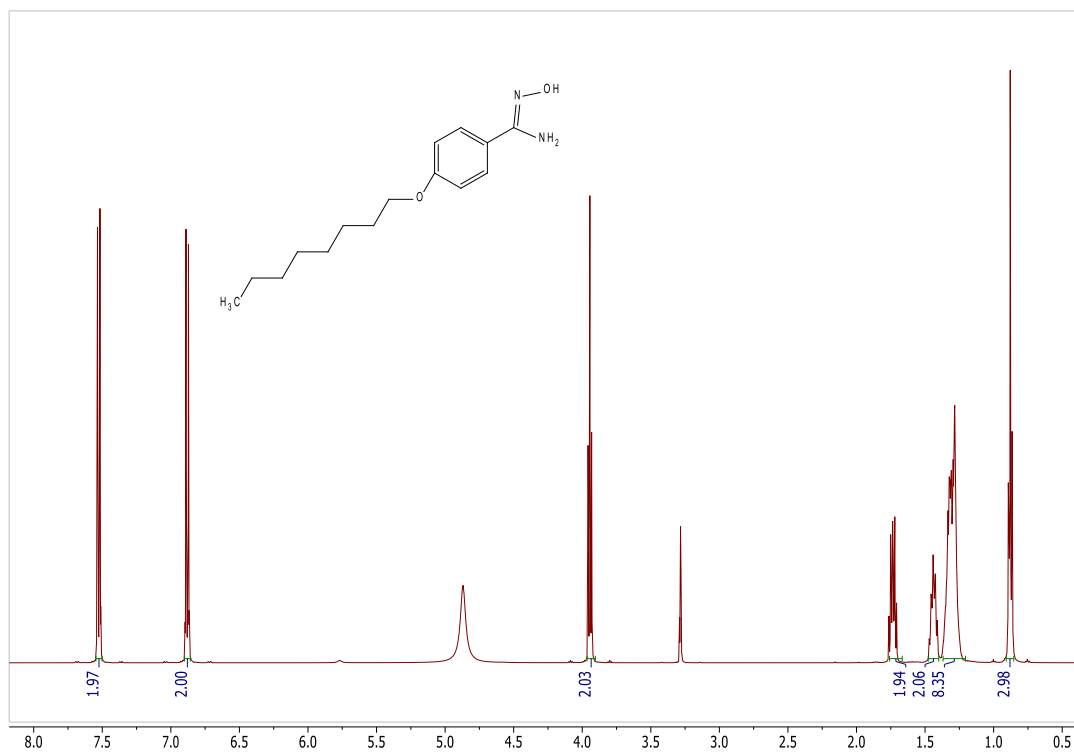


<sup>13</sup>C-NMR Spectrum for (Z)-4-(heptyloxy)-N'-hydroxybenzimidamide **3.3a**–

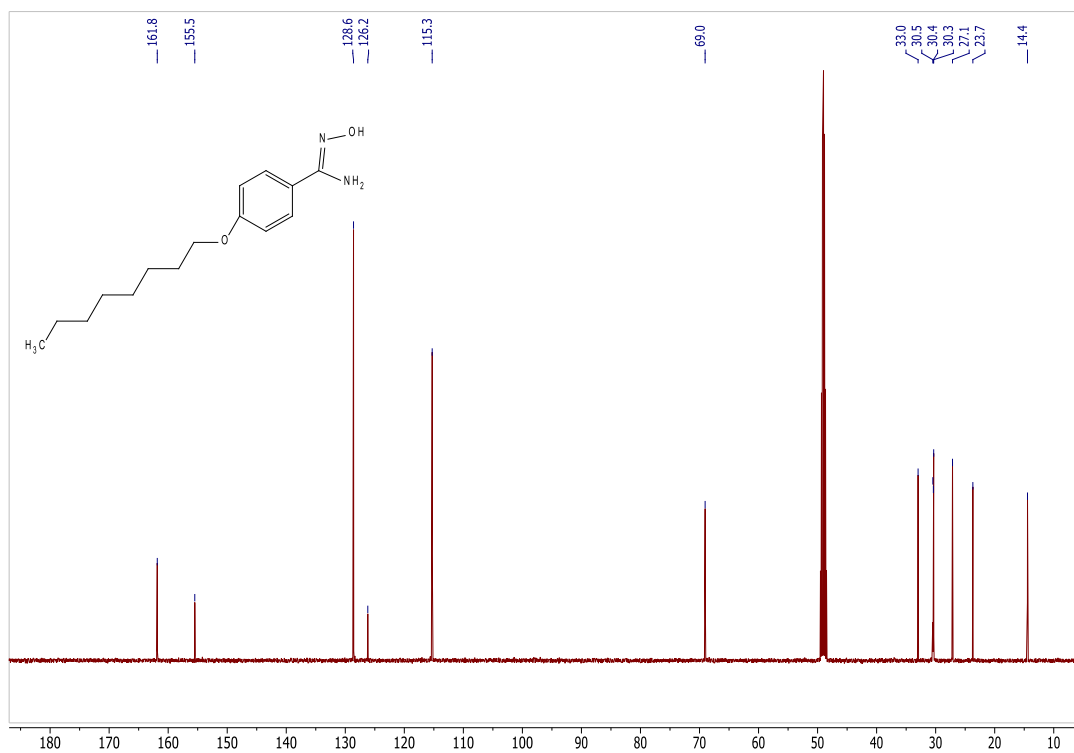




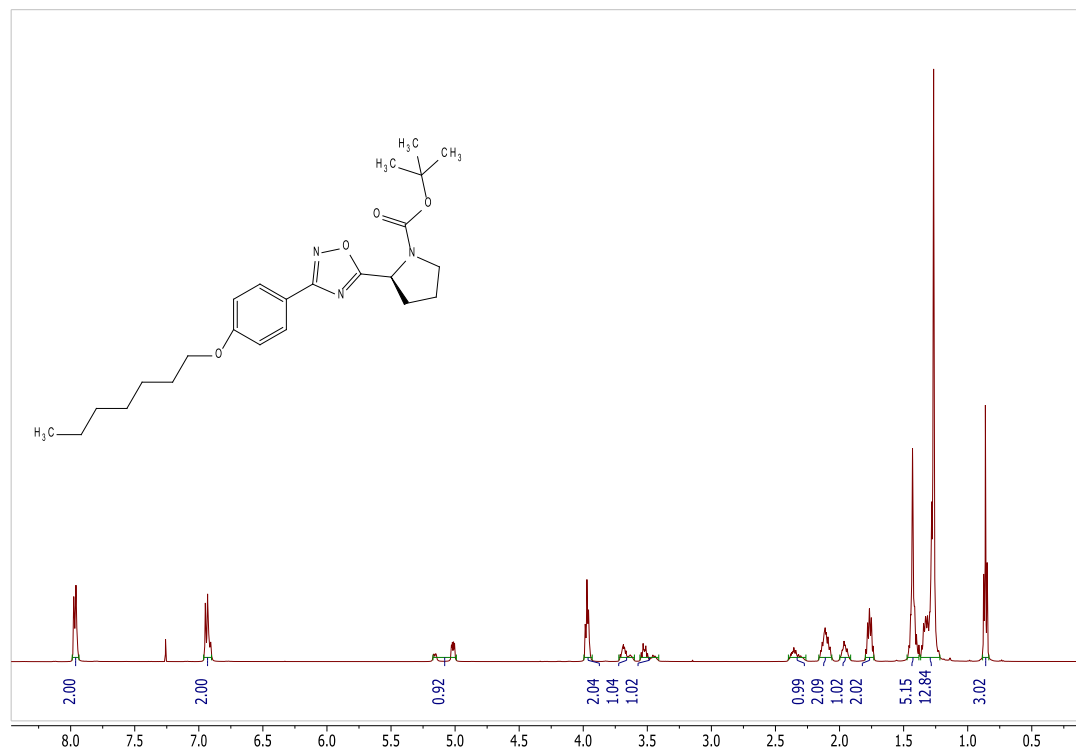
<sup>1</sup>H-NMR Spectrum for (Z)-4-(octyloxy)-N'-hydroxybenzimidamide **3.3b** –



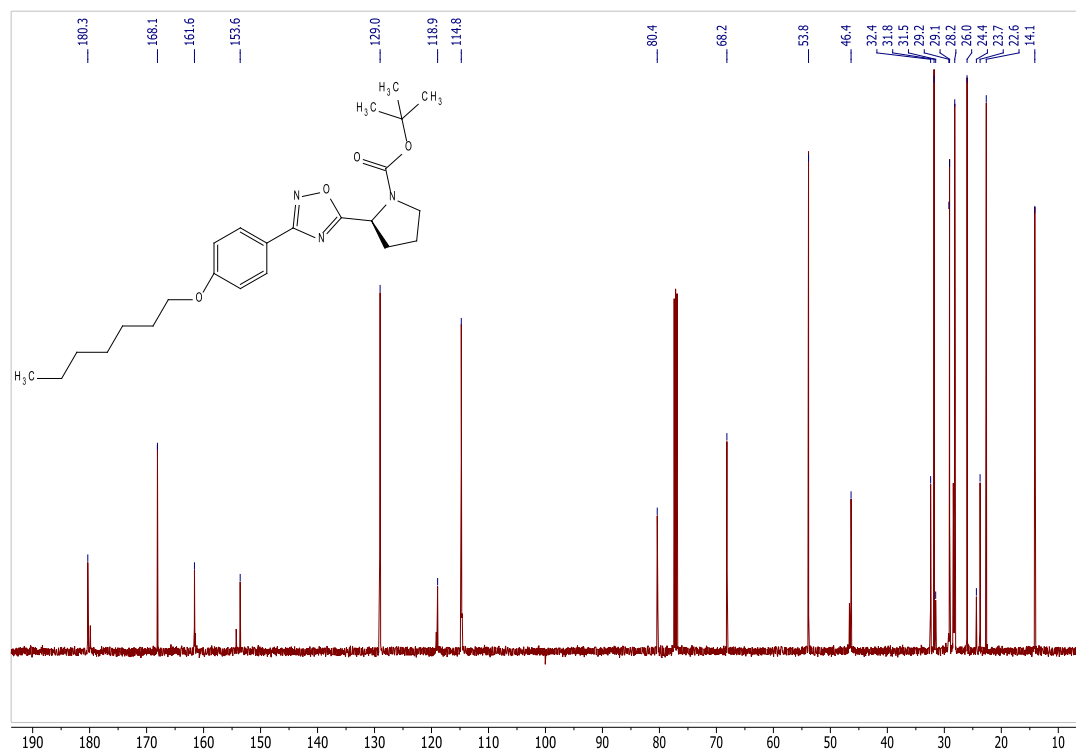
<sup>13</sup>C-NMR Spectrum for (Z)-4-(octyloxy)-N'-hydroxybenzimidamide **3.3b**–



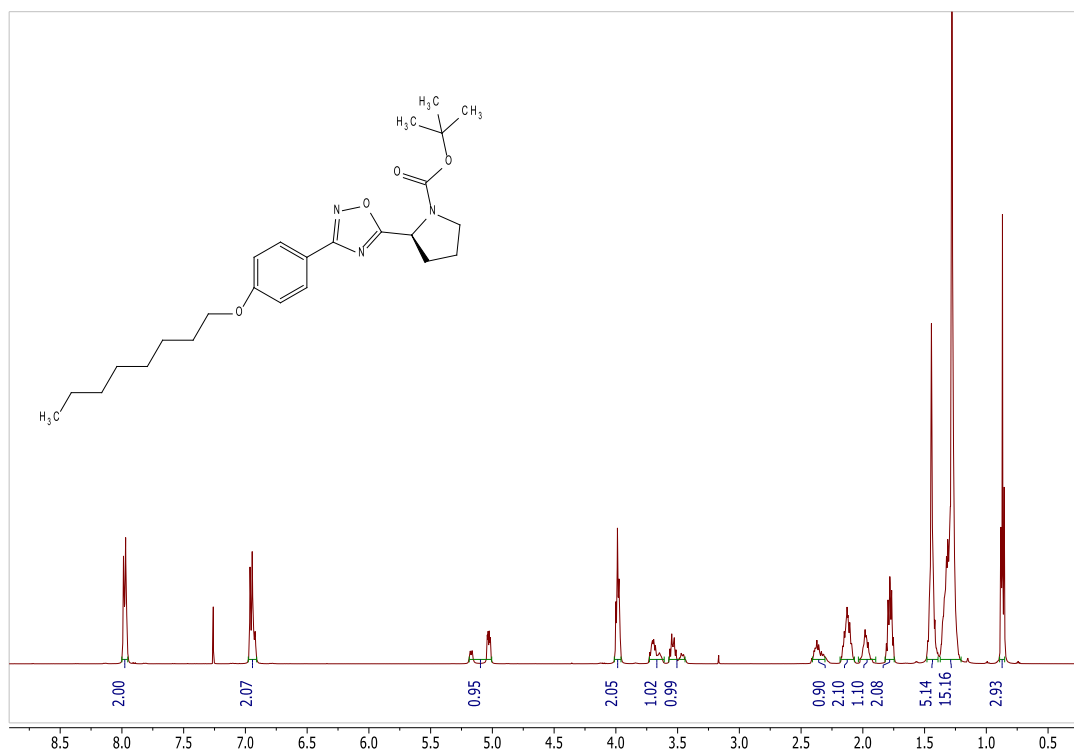
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.4a** –



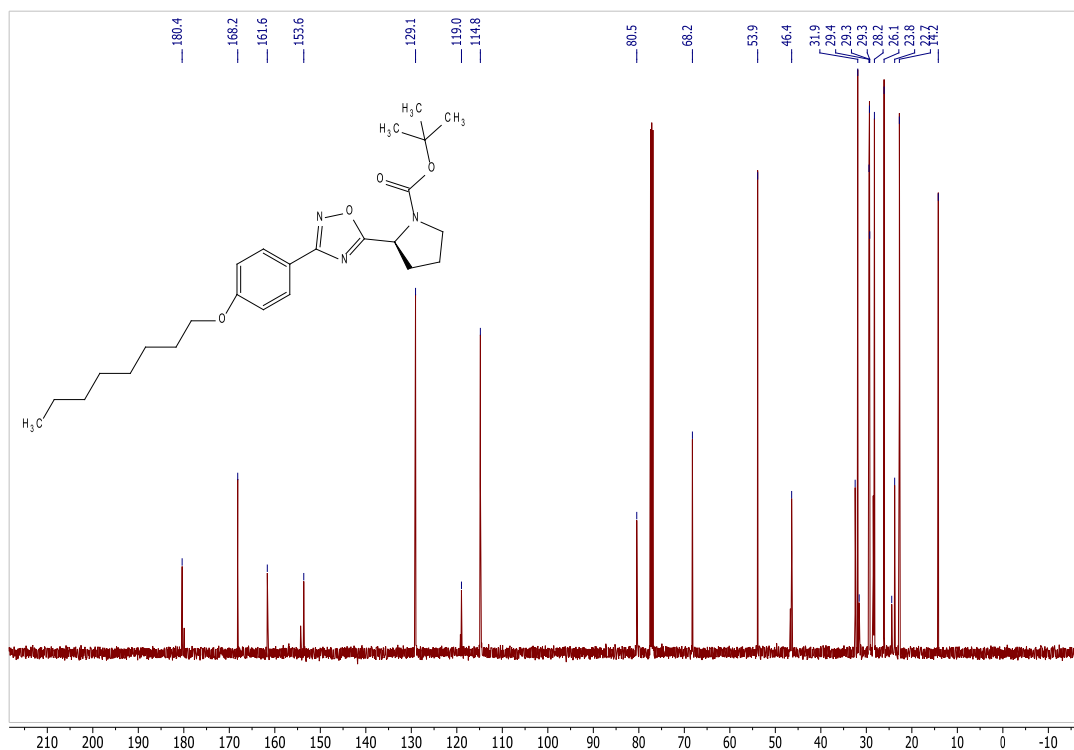
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.4a**–



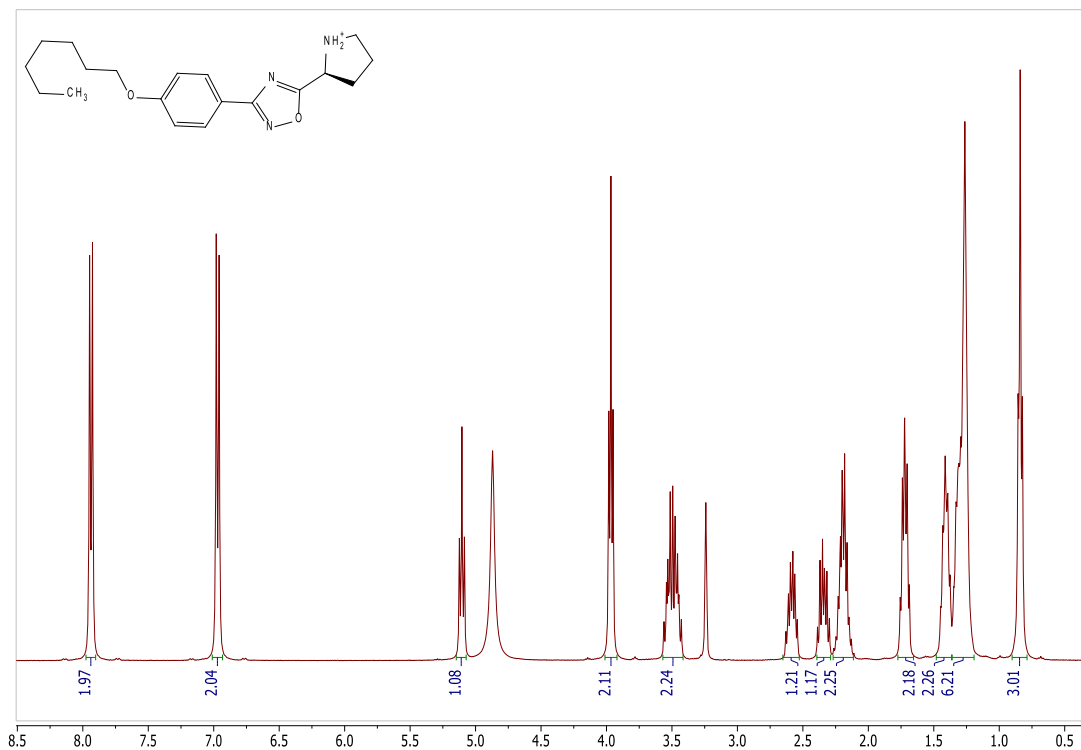
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.4b**—



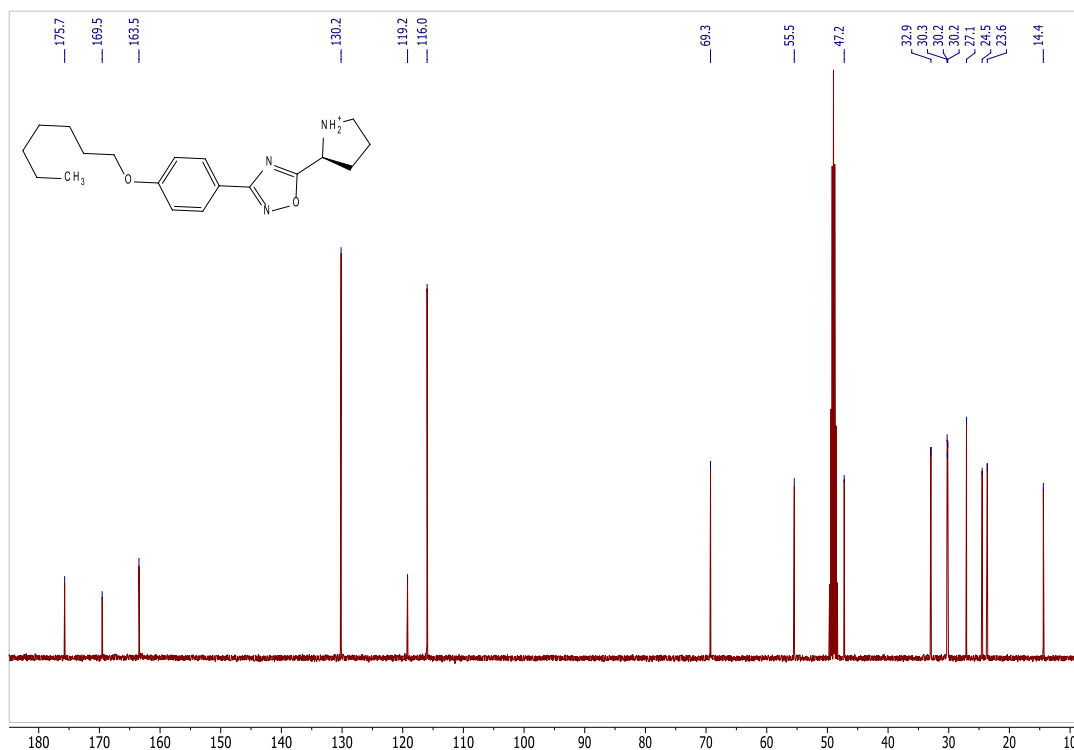
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.4b**—



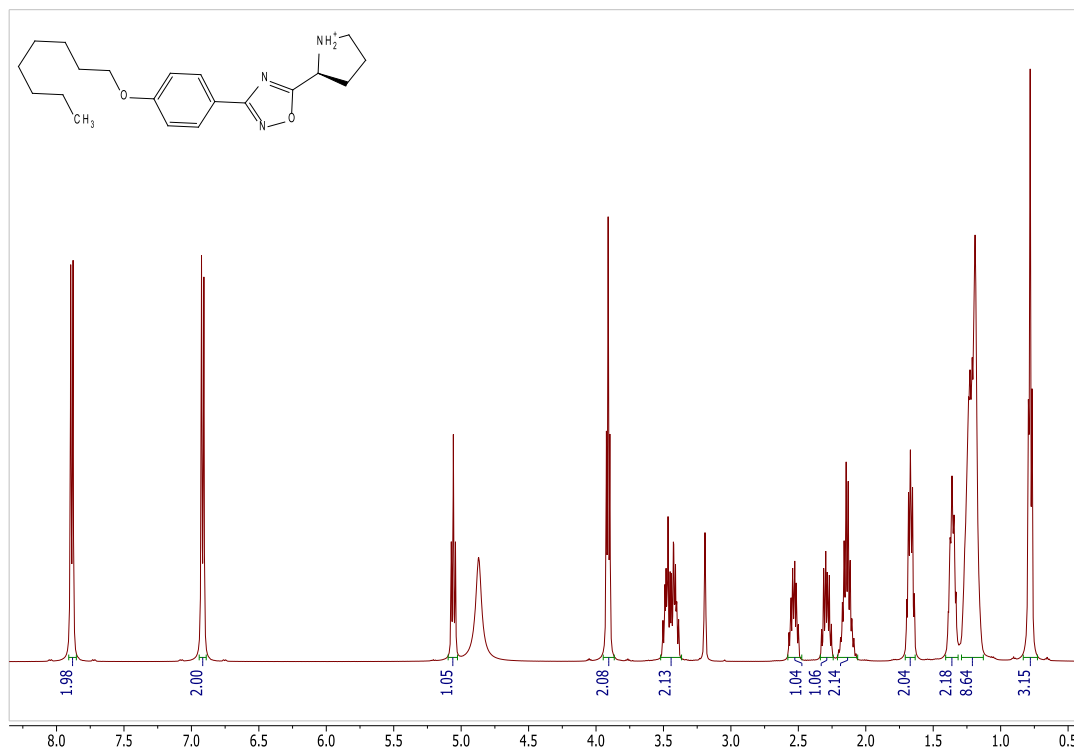
<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.5a** –



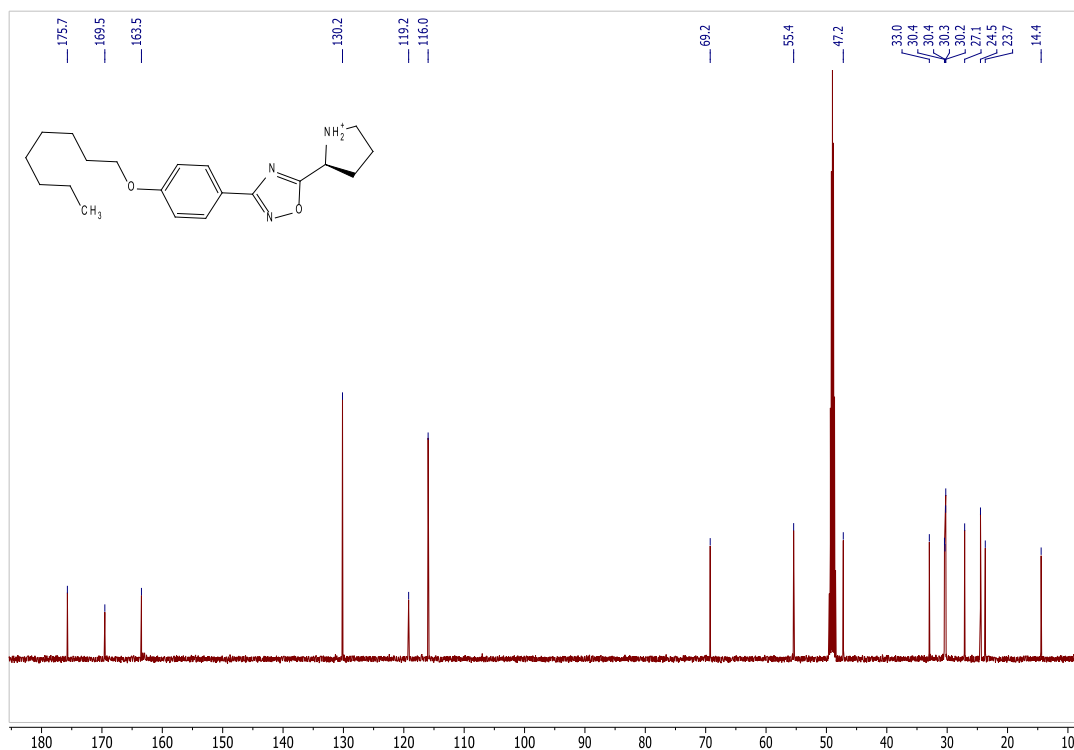
<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.5a** –



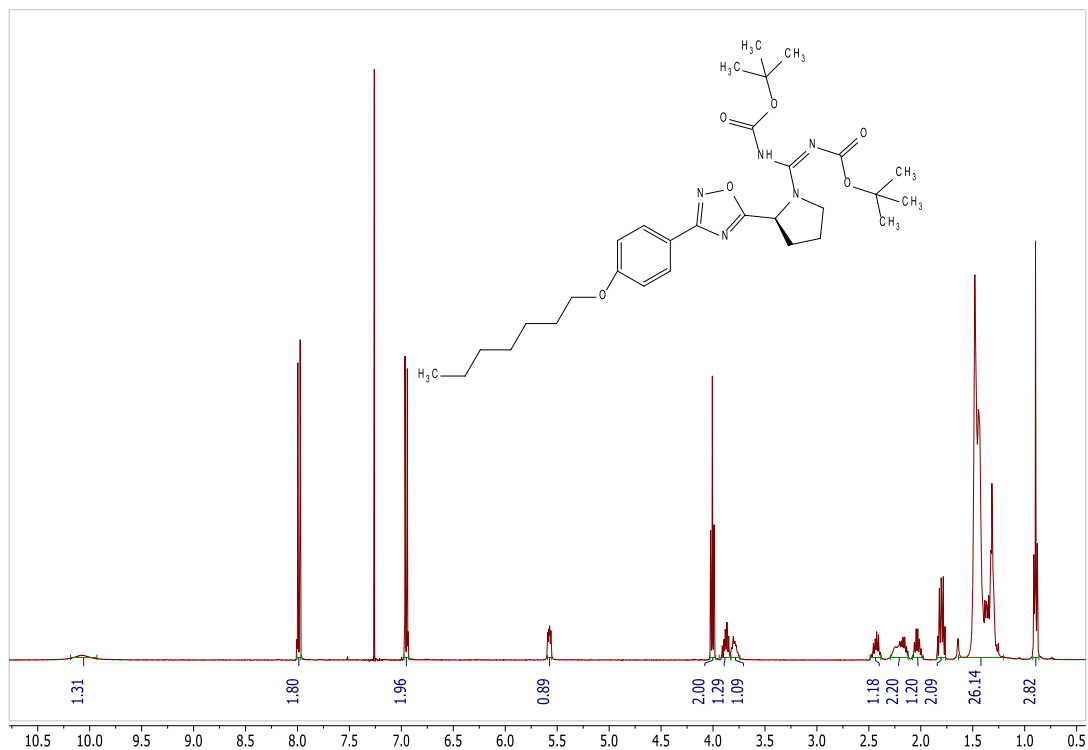
<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.5b** –



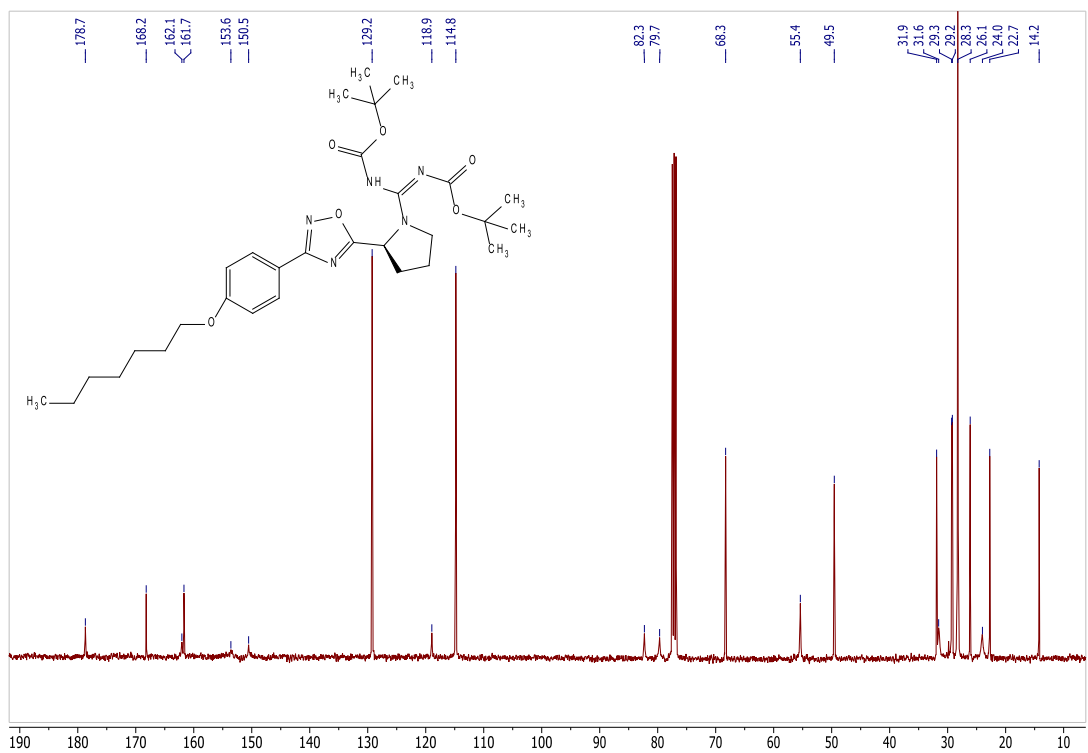
<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.5b** –



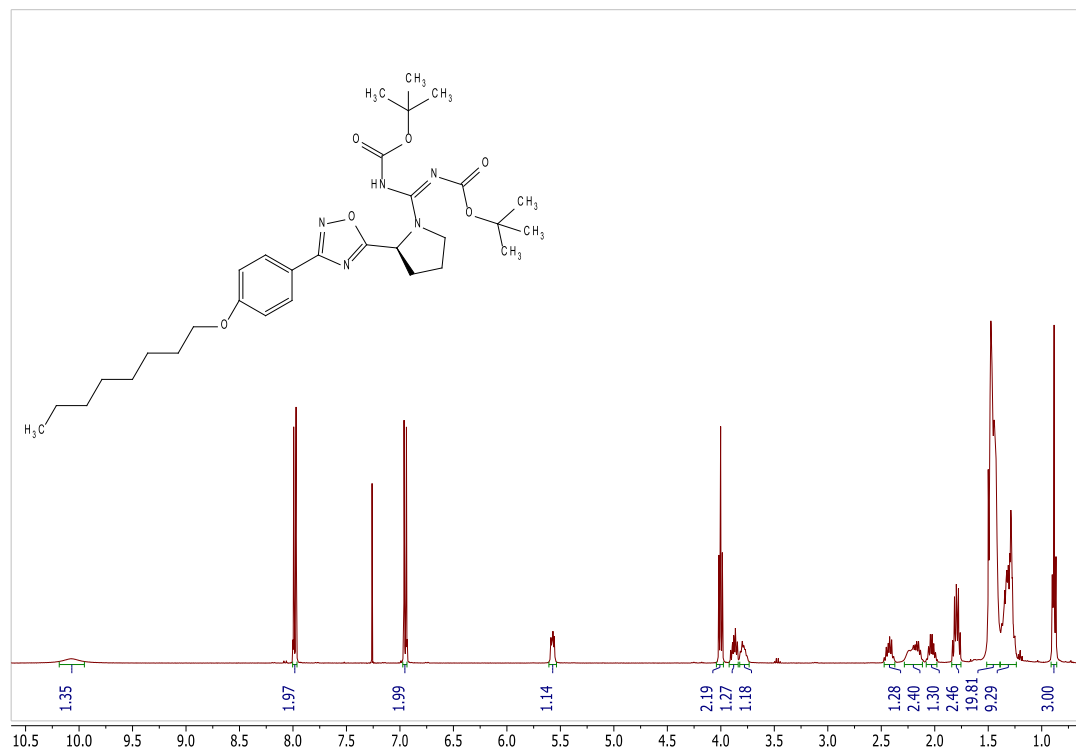
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.6a** –



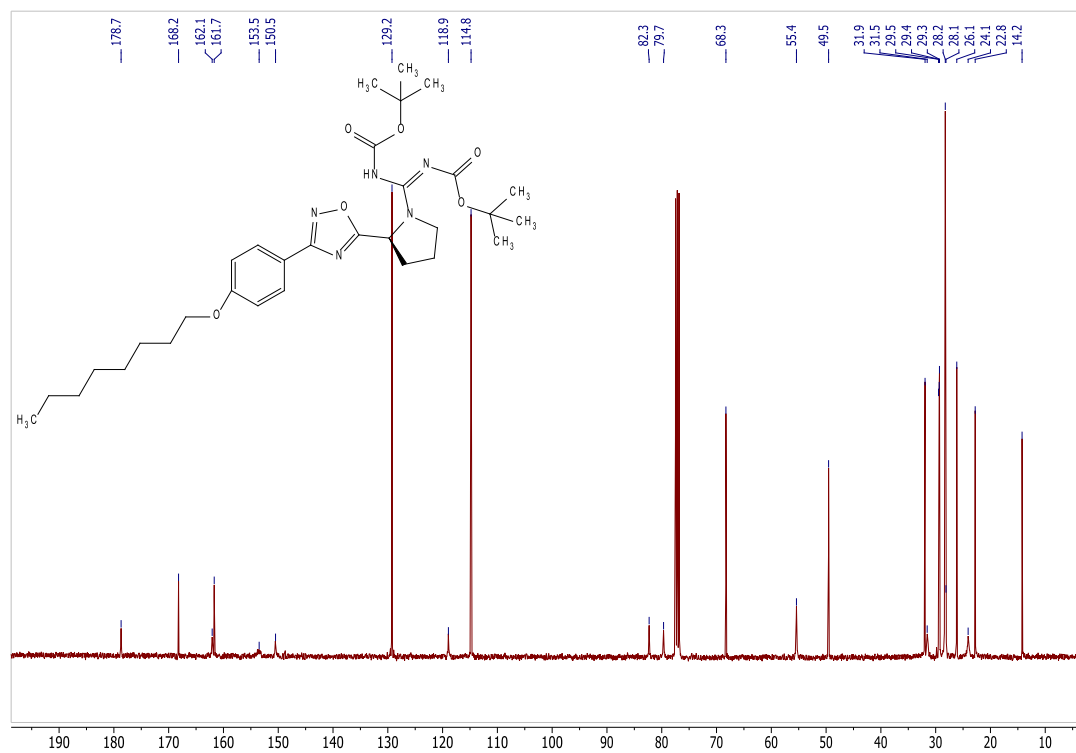
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.6a** –



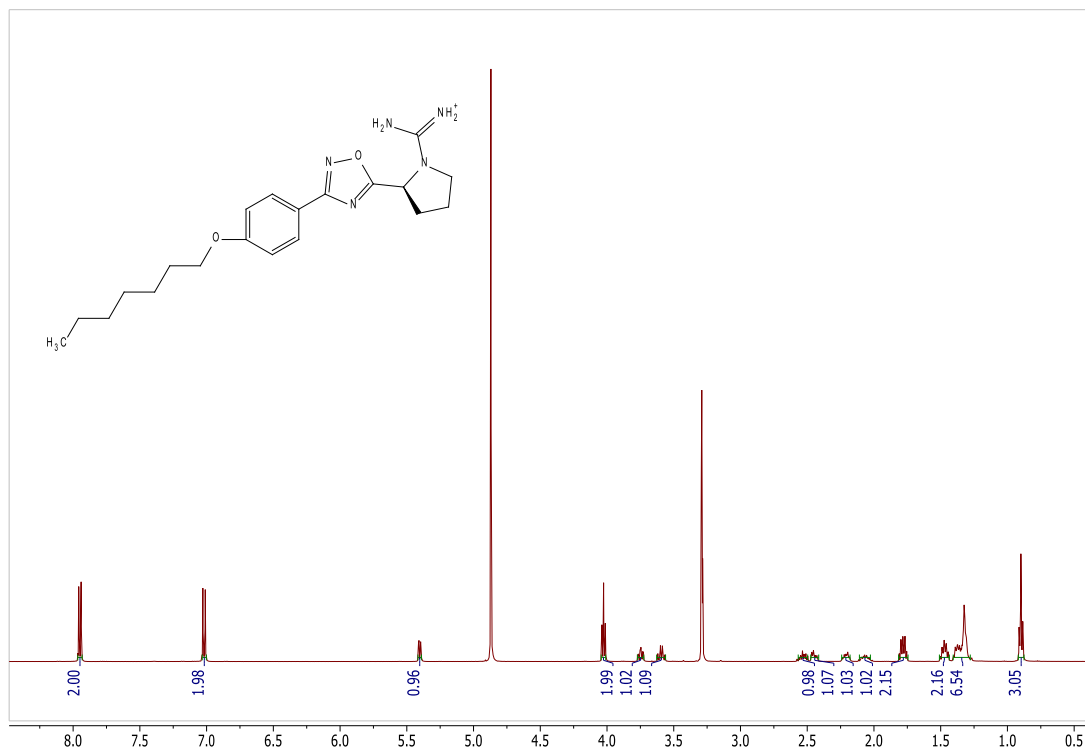
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.6b** –



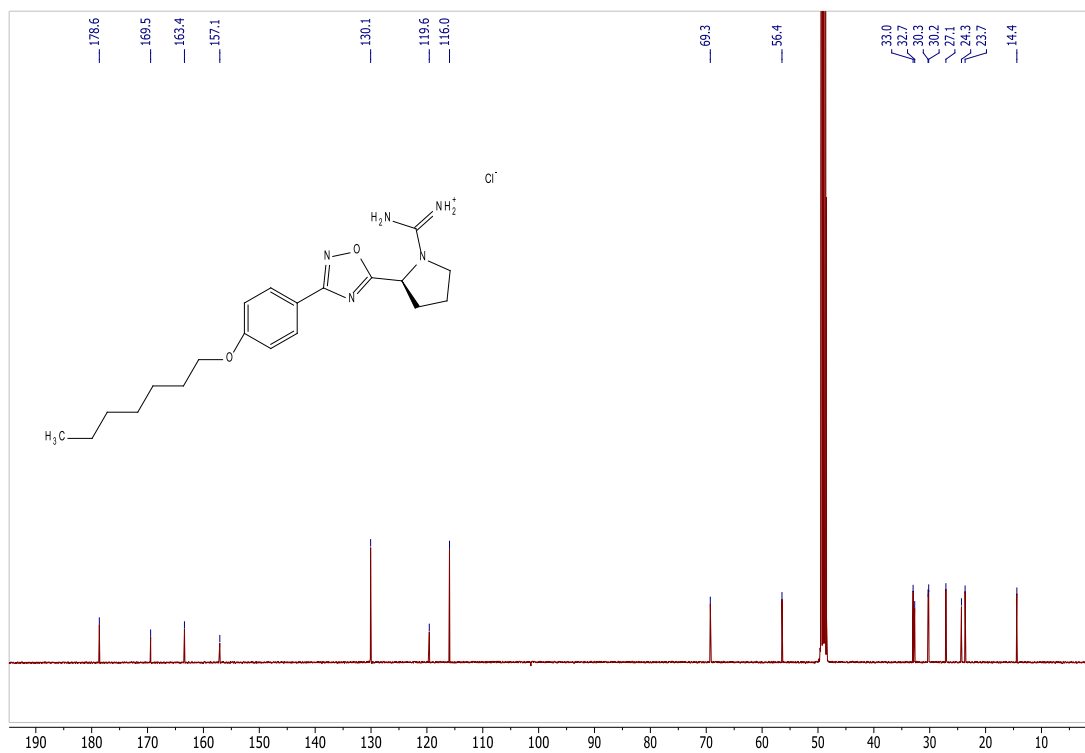
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.6b**–



<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.7a** –

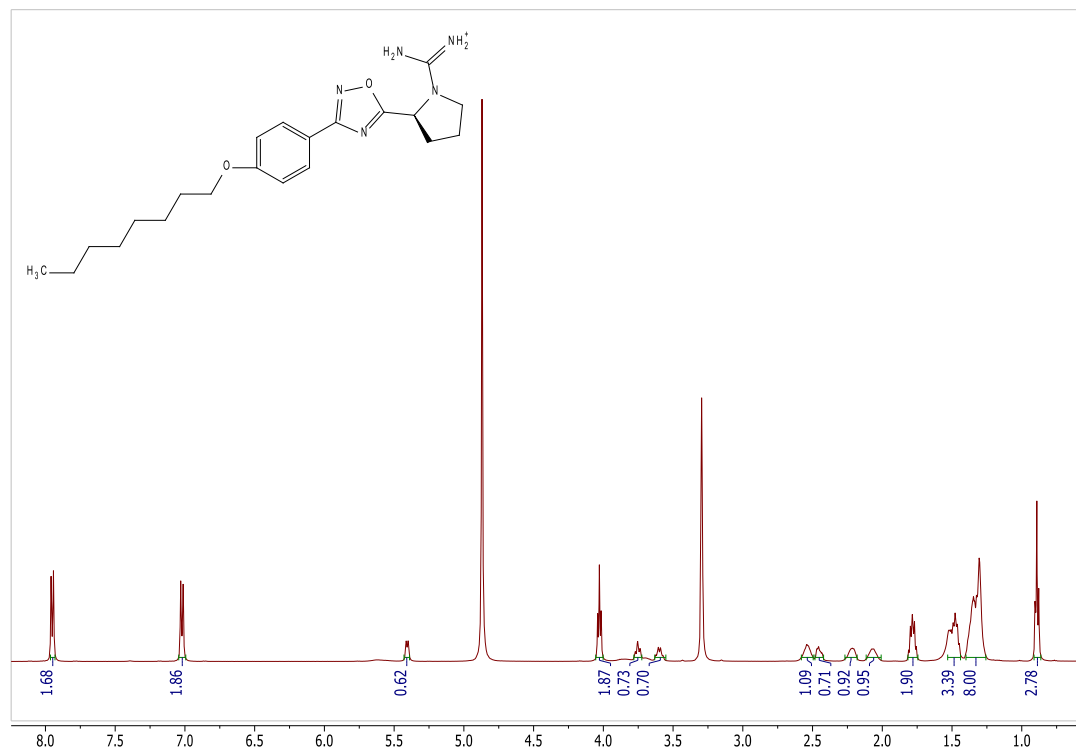


<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-(heptyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.7a** –

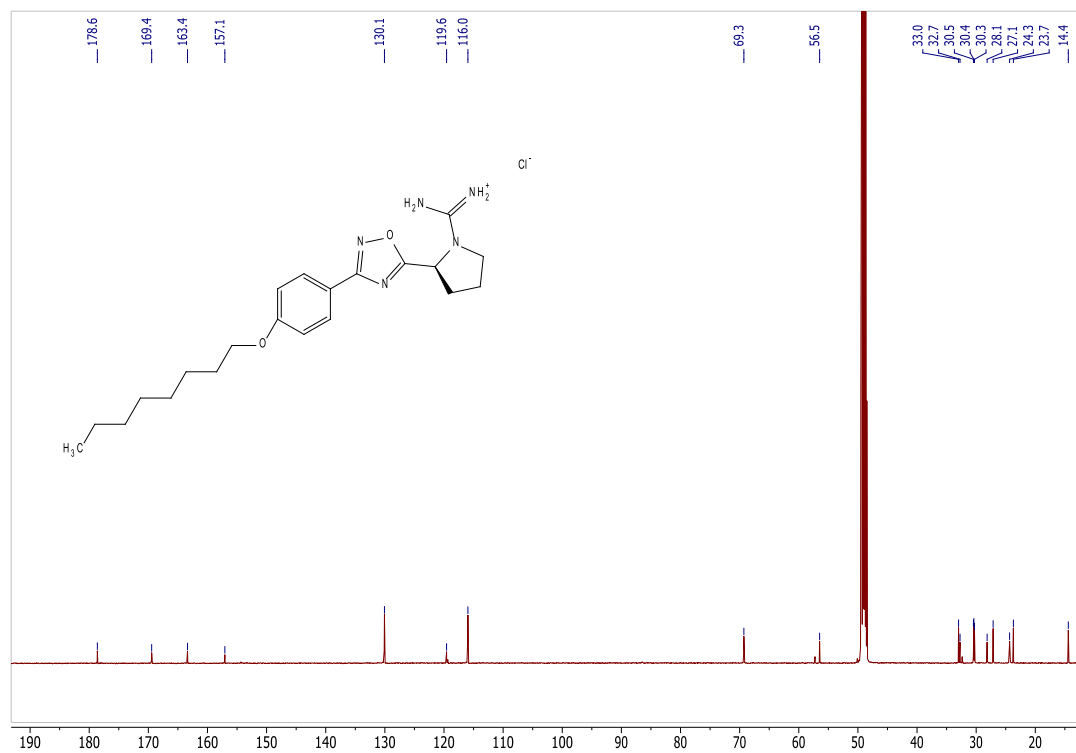




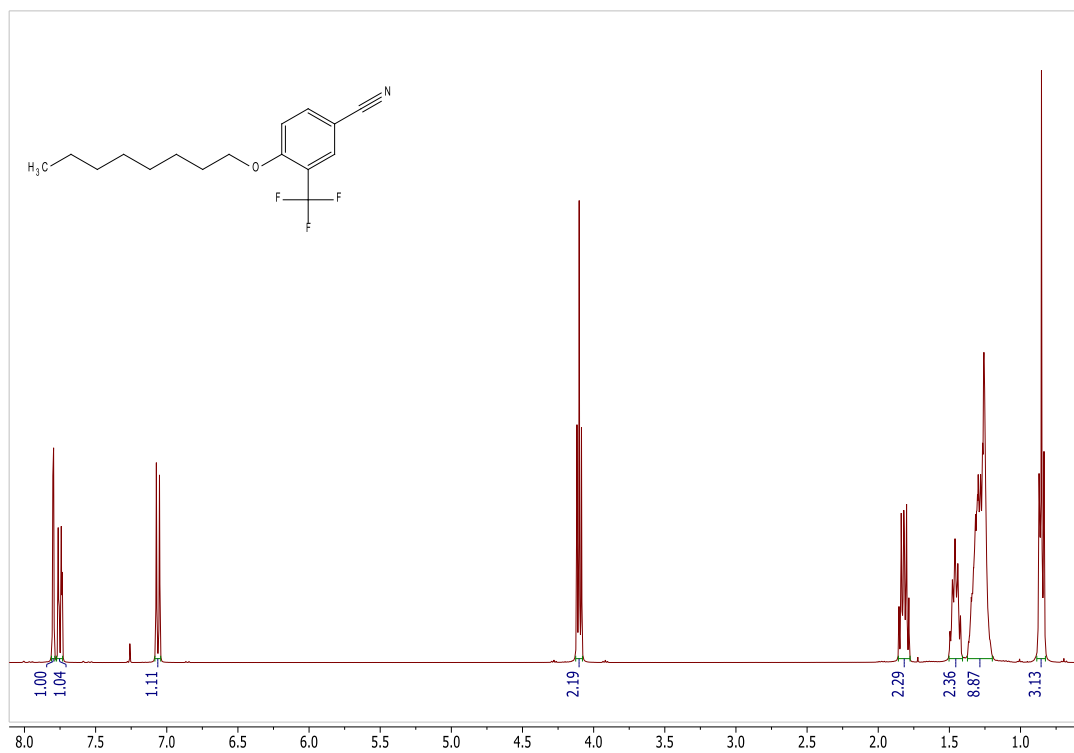
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.7b** –



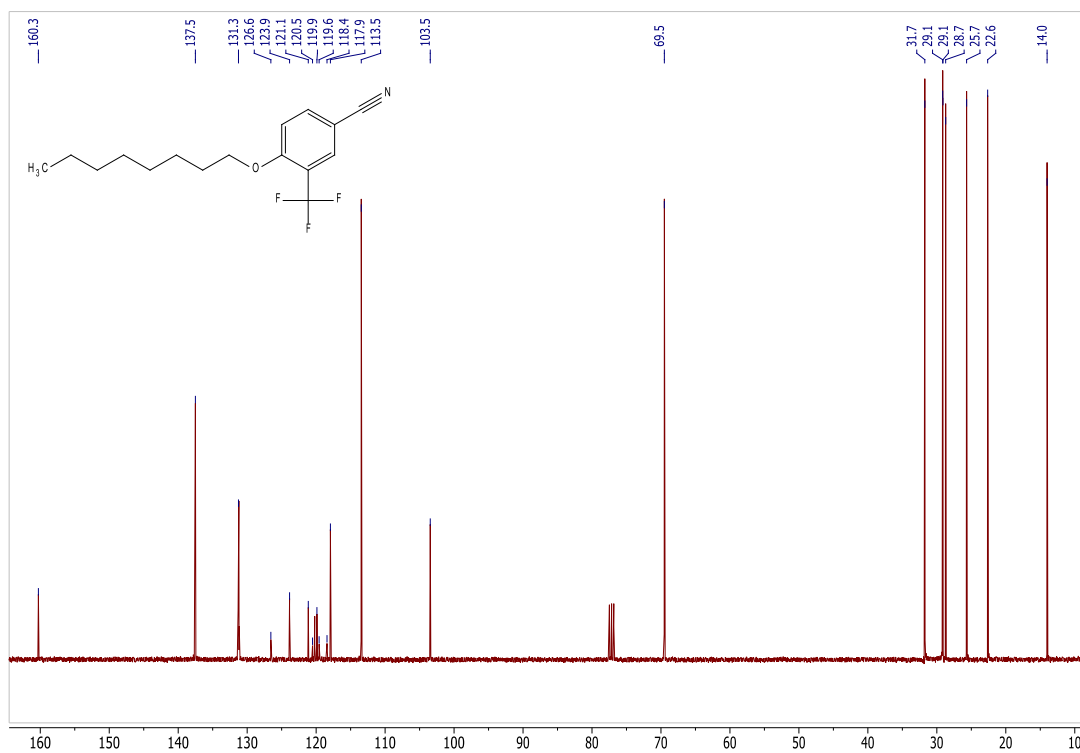
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.7b**–



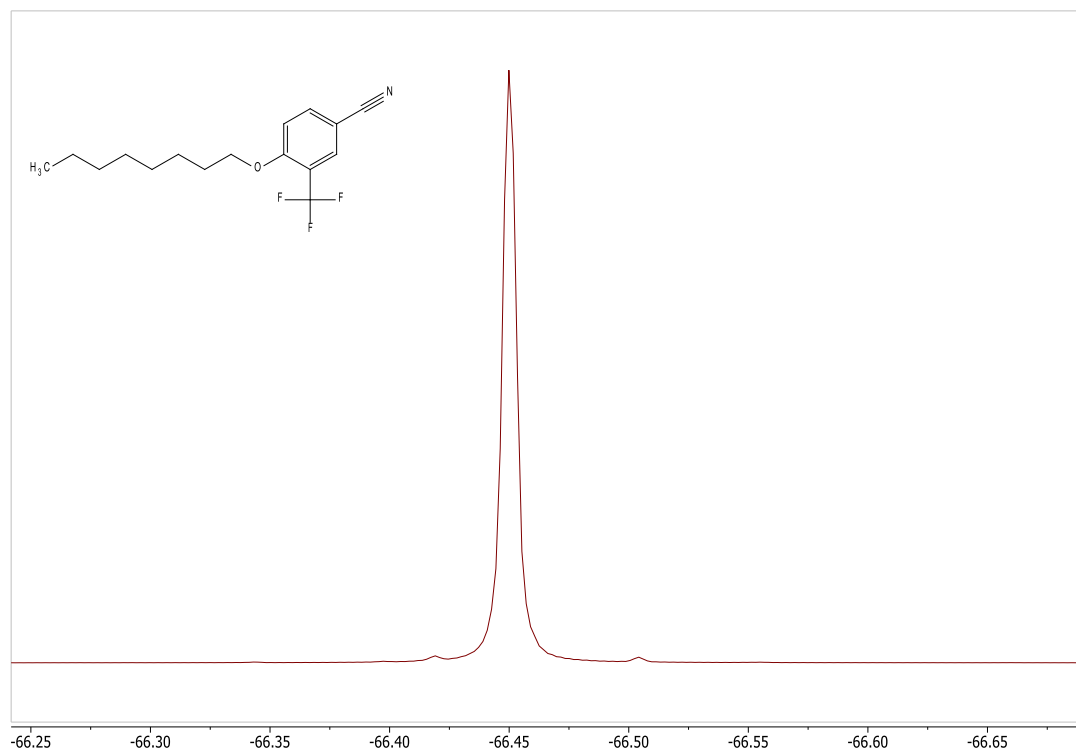
<sup>1</sup>H-NMR Spectrum for 4-(octyloxy)-3-(trifluoromethyl)benzonitrile **3.9a** –



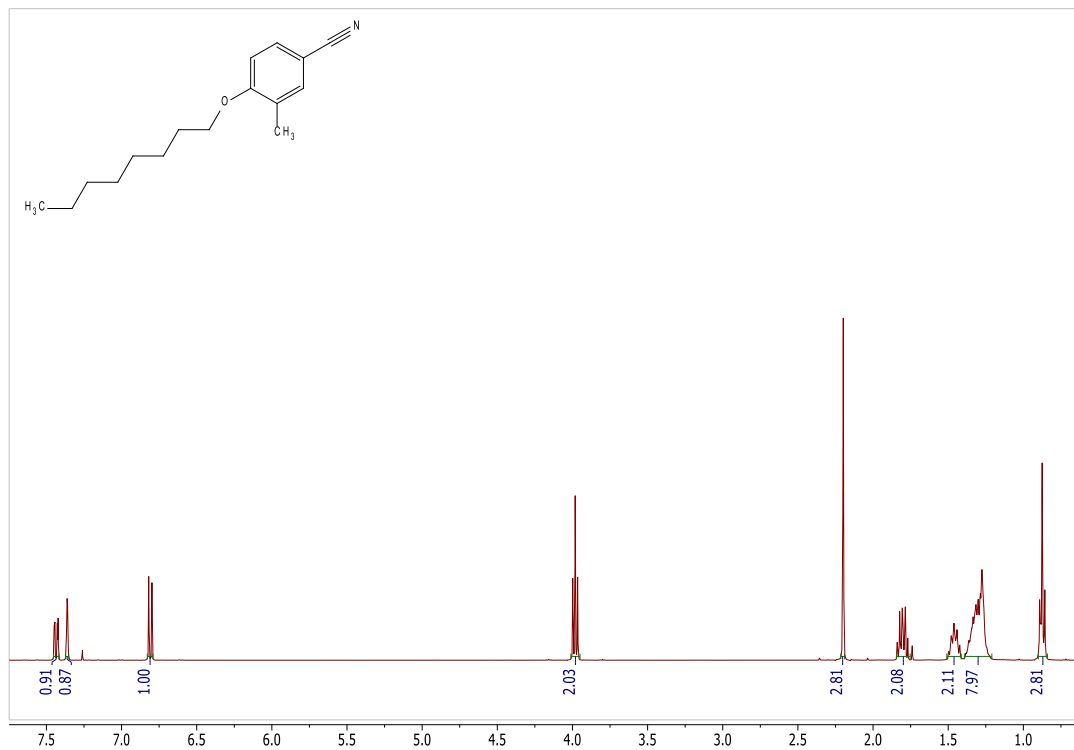
<sup>13</sup>C-NMR Spectrum for 4-(octyloxy)-3-(trifluoromethyl)benzonitrile **3.9a** –



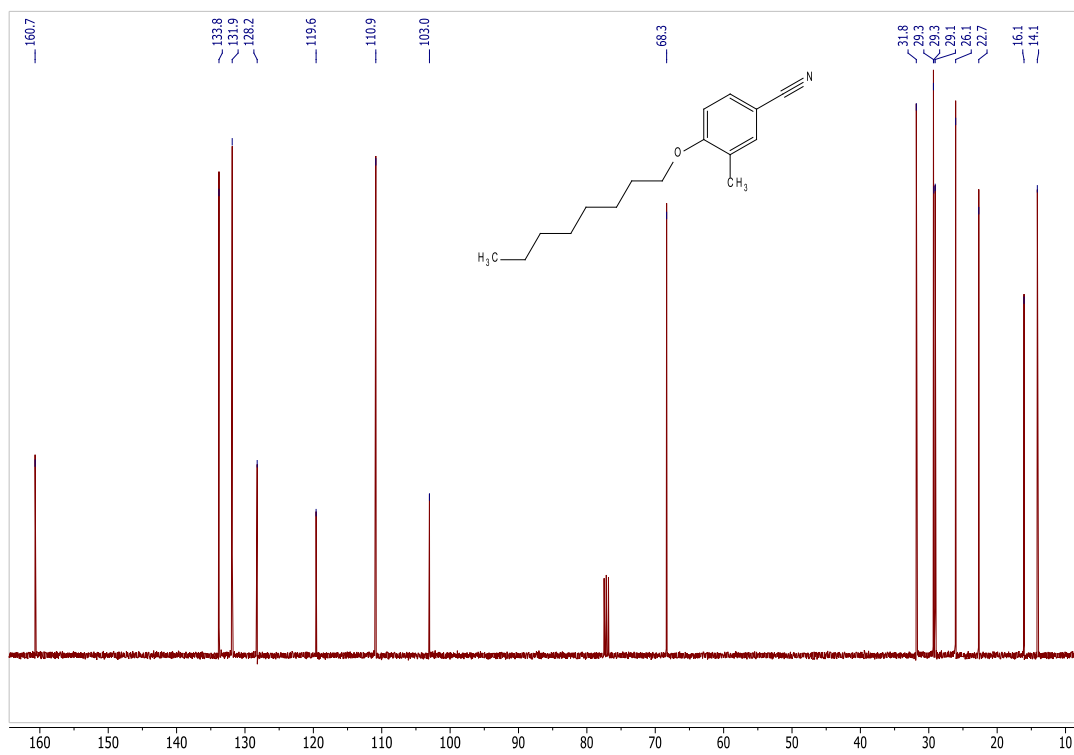
<sup>19</sup>F-NMR Spectrum for 4-(octyloxy)-3-(trifluoromethyl)benzonitrile **3.9a**



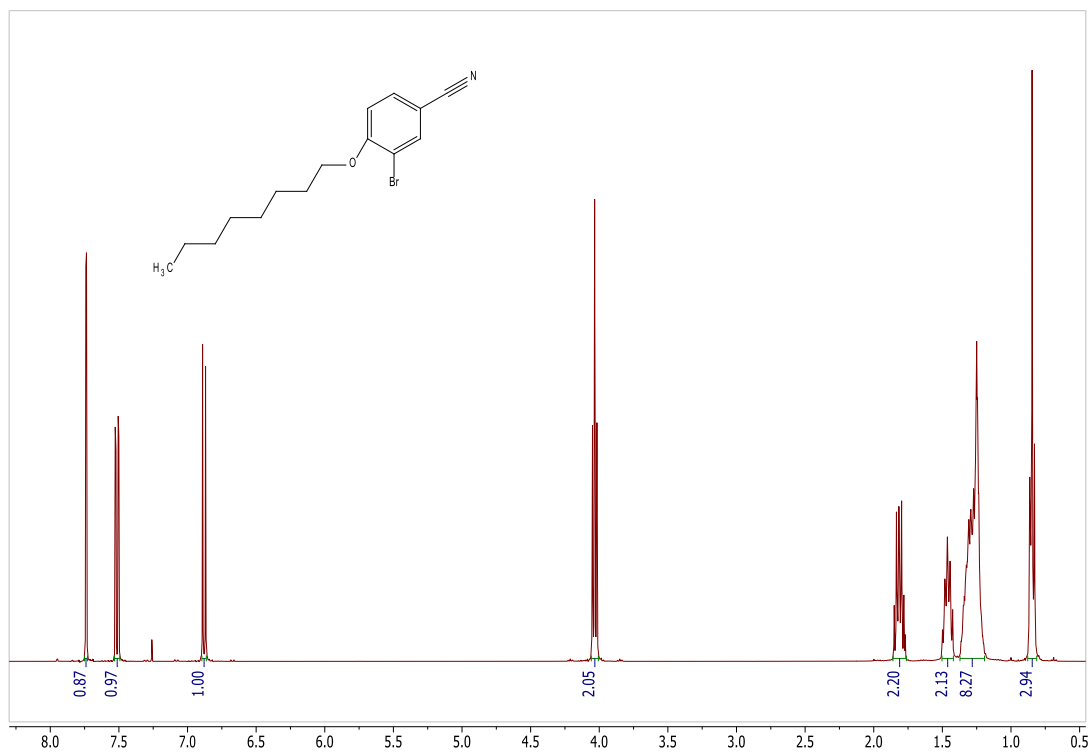
<sup>1</sup>H-NMR Spectrum for 3-methyl-4-(octyloxy)benzonitrile **3.9b** –



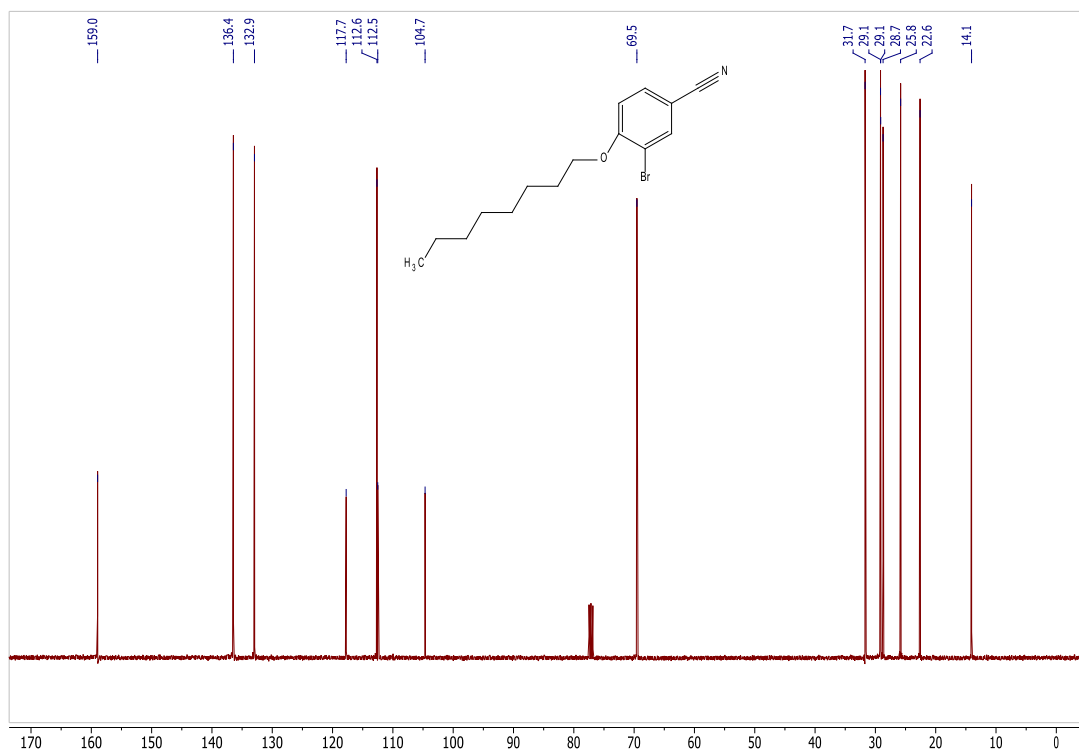
<sup>13</sup>C-NMR Spectrum for 3-methyl-4-(octyloxy)benzonitrile **3.9b** –



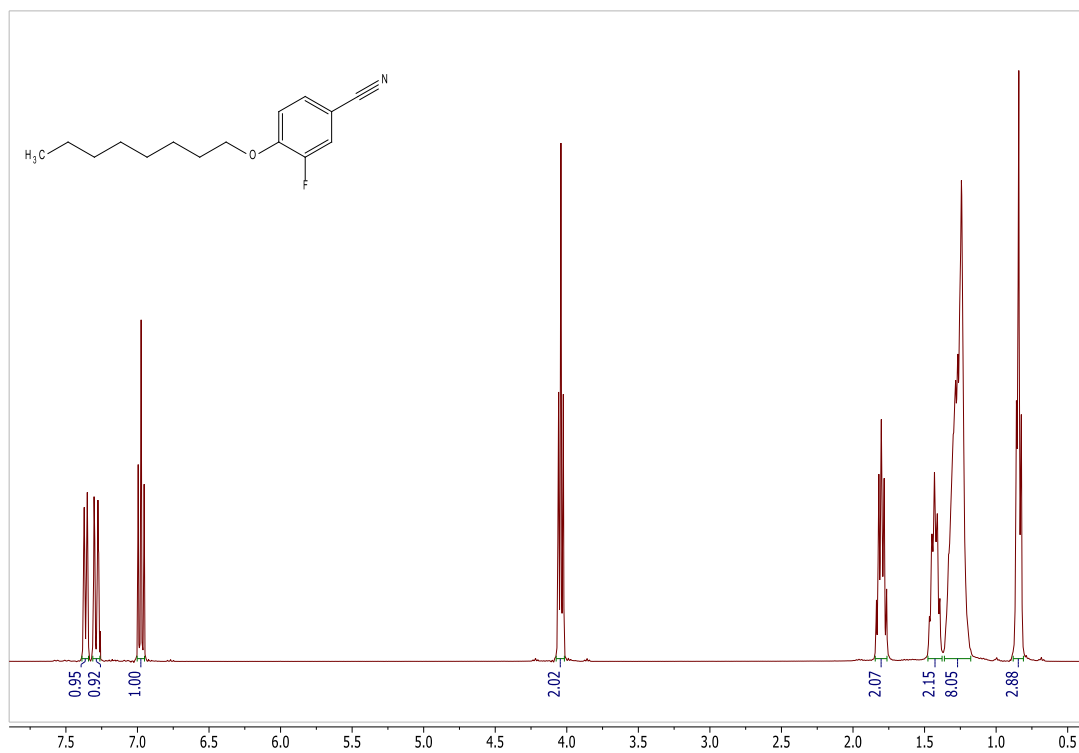
<sup>1</sup>H-NMR Spectrum for 3-bromo-4-(octyloxy)benzonitrile **3.9c** –



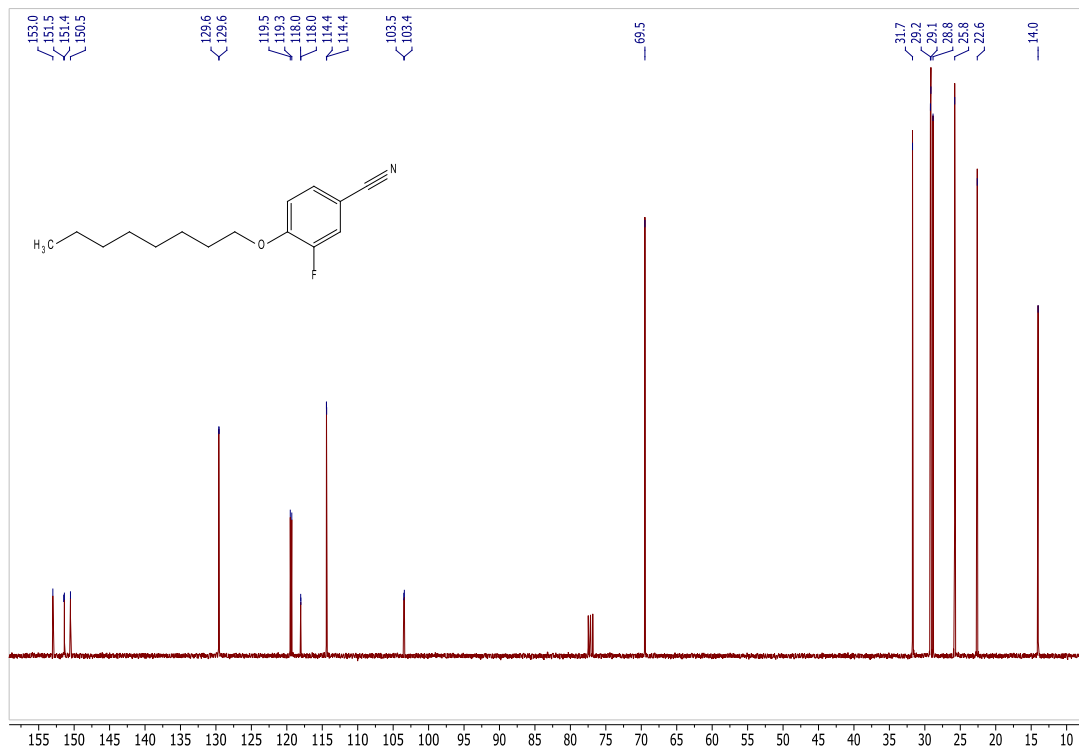
<sup>13</sup>C-NMR Spectrum for 3-bromo-4-(octyloxy)benzonitrile **3.9c** –



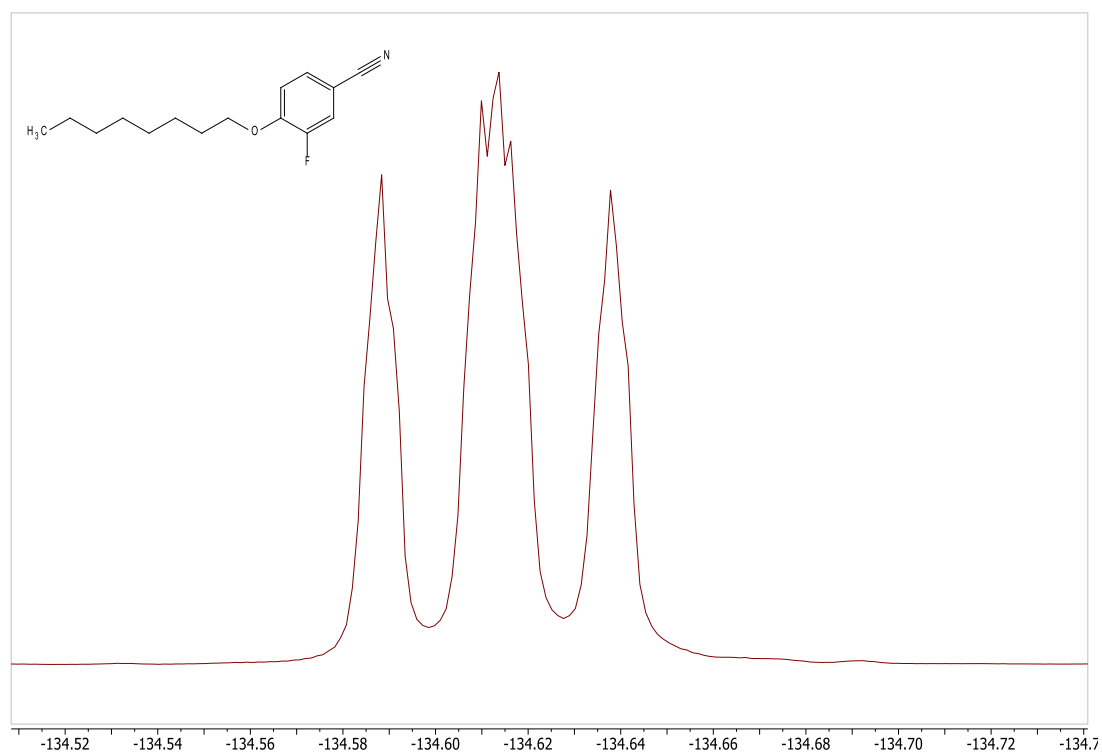
<sup>1</sup>H-NMR Spectrum for 3-fluoro-4-(octyloxy)benzonitrile **3.9d** –



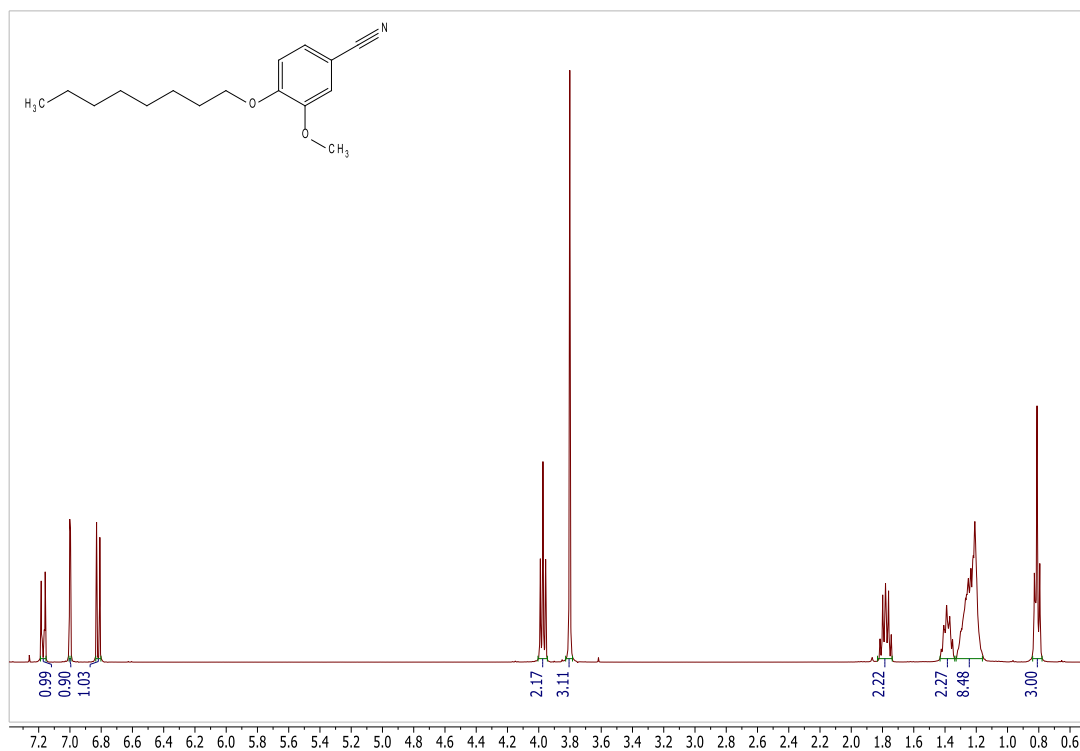
<sup>13</sup>C-NMR Spectrum for 3-fluoro-4-(octyloxy)benzonitrile **3.9d** –



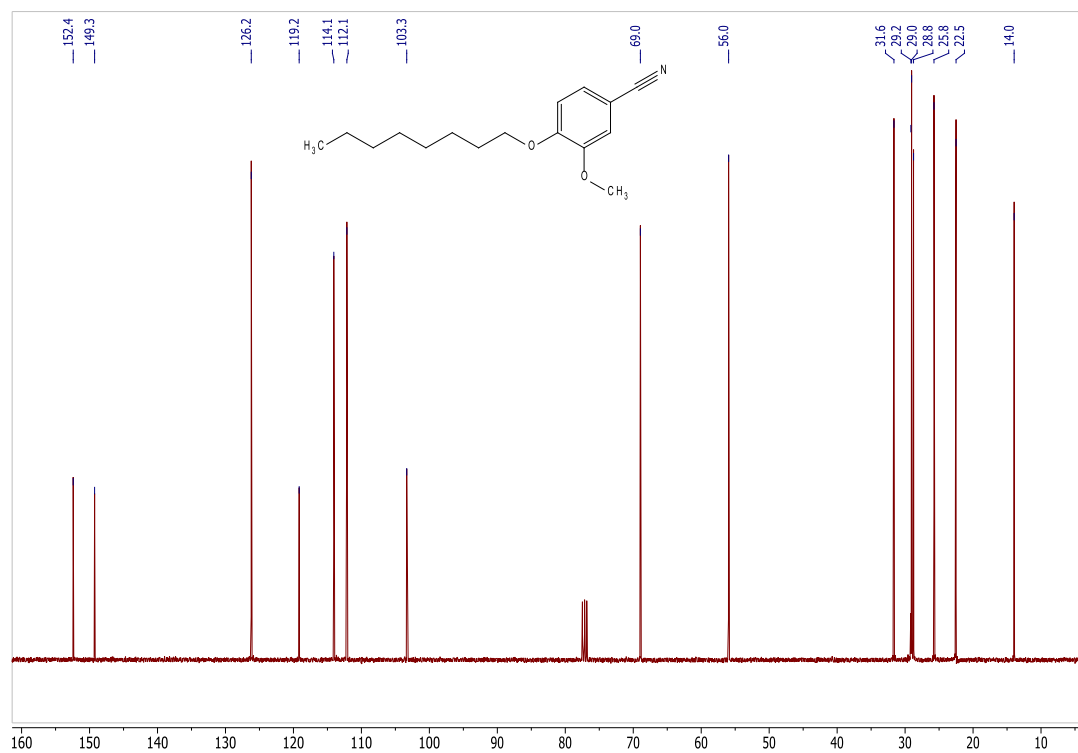
<sup>19</sup>F-NMR Spectrum for 3-fluoro-4-(octyloxy)benzonitrile **3.9d**-



<sup>1</sup>H-NMR Spectrum for 3-methoxy-4-(octyloxy)benzonitrile **3.9e** –

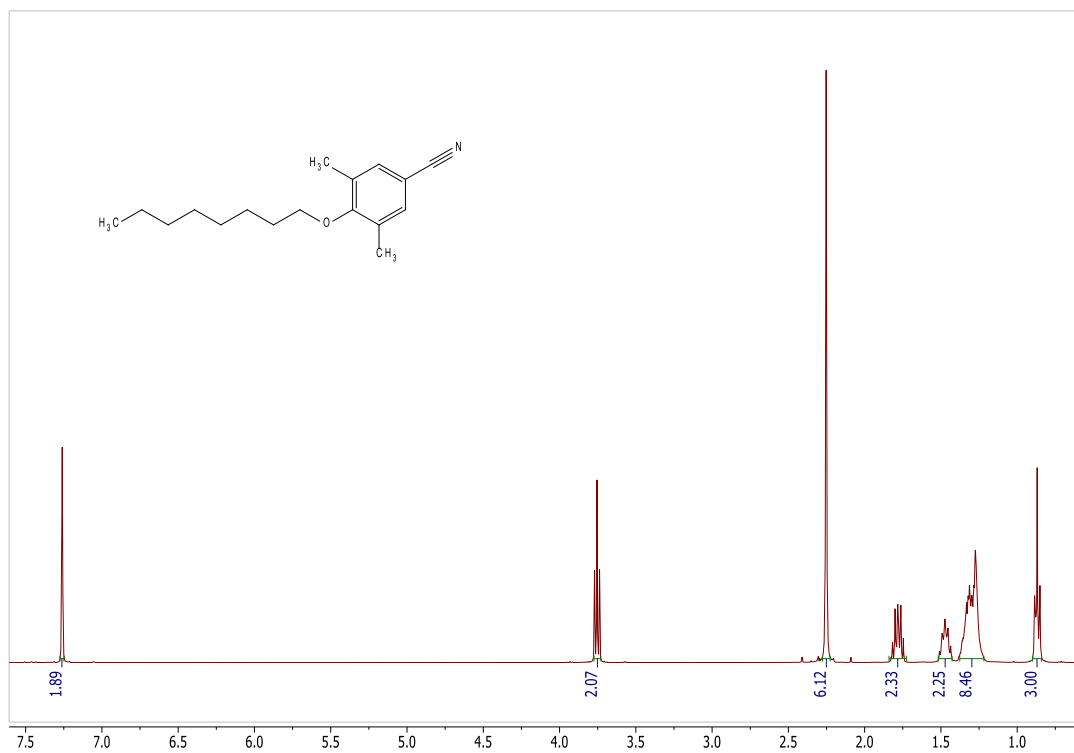


<sup>13</sup>C-NMR Spectrum for 3-methoxy-4-(octyloxy)benzonitrile **3.9e** –

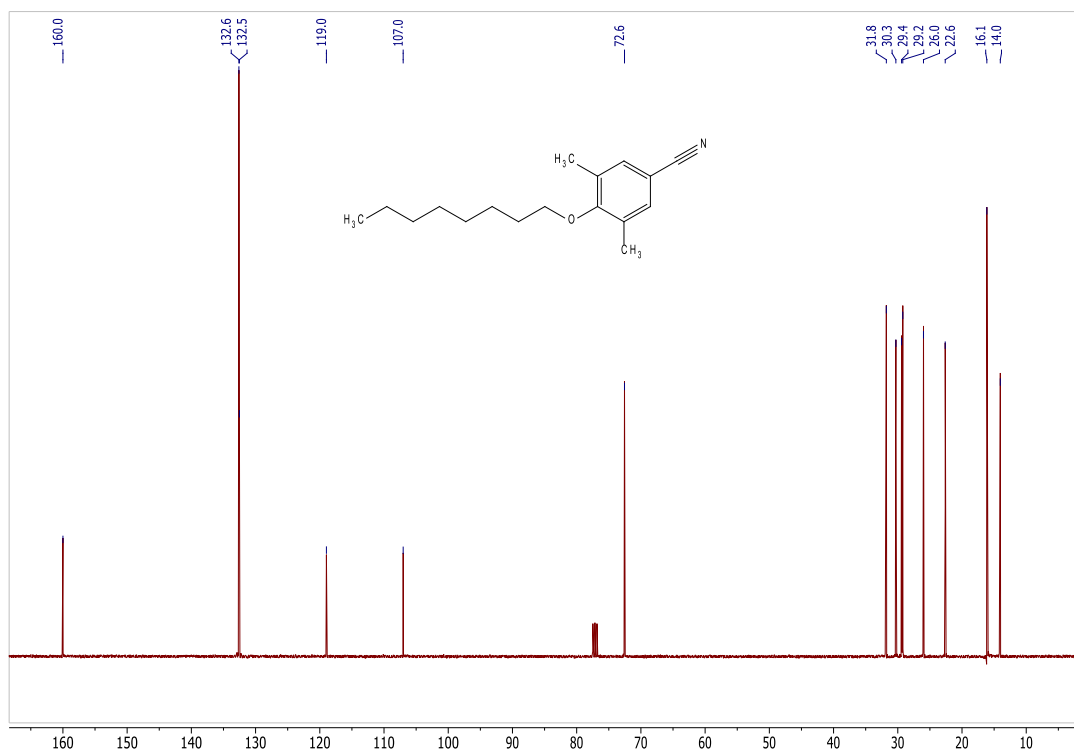




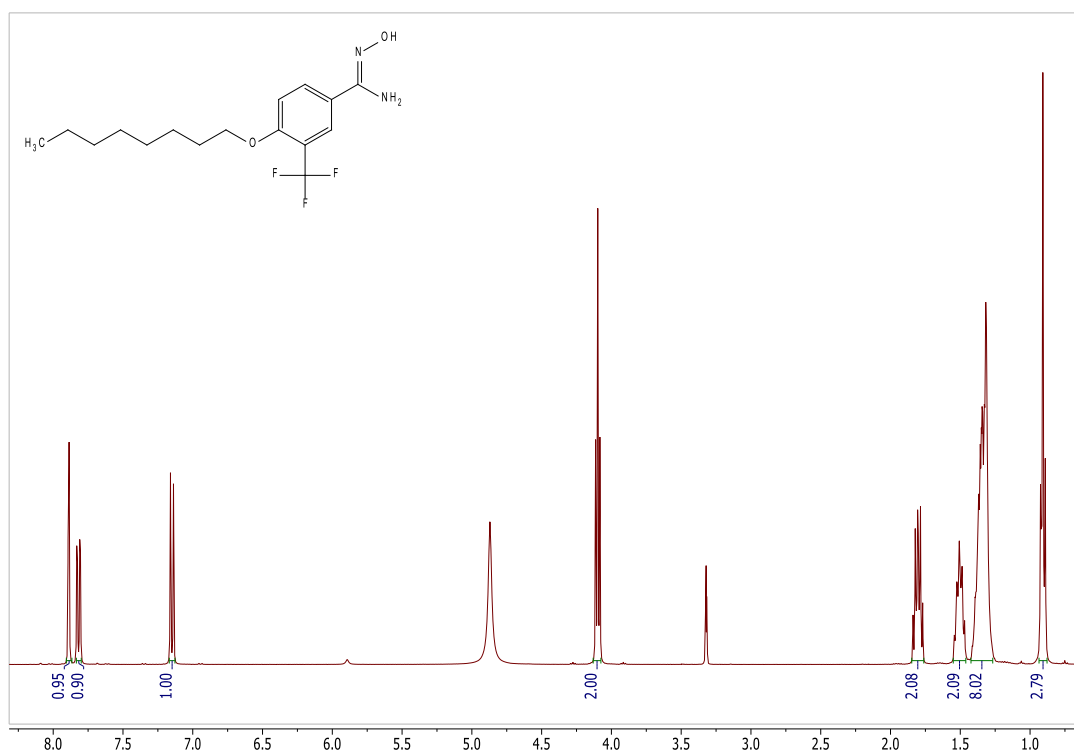
<sup>1</sup>H-NMR Spectrum for 3,5-dimethyl-4-(octyloxy)benzonitrile **3.9f** –



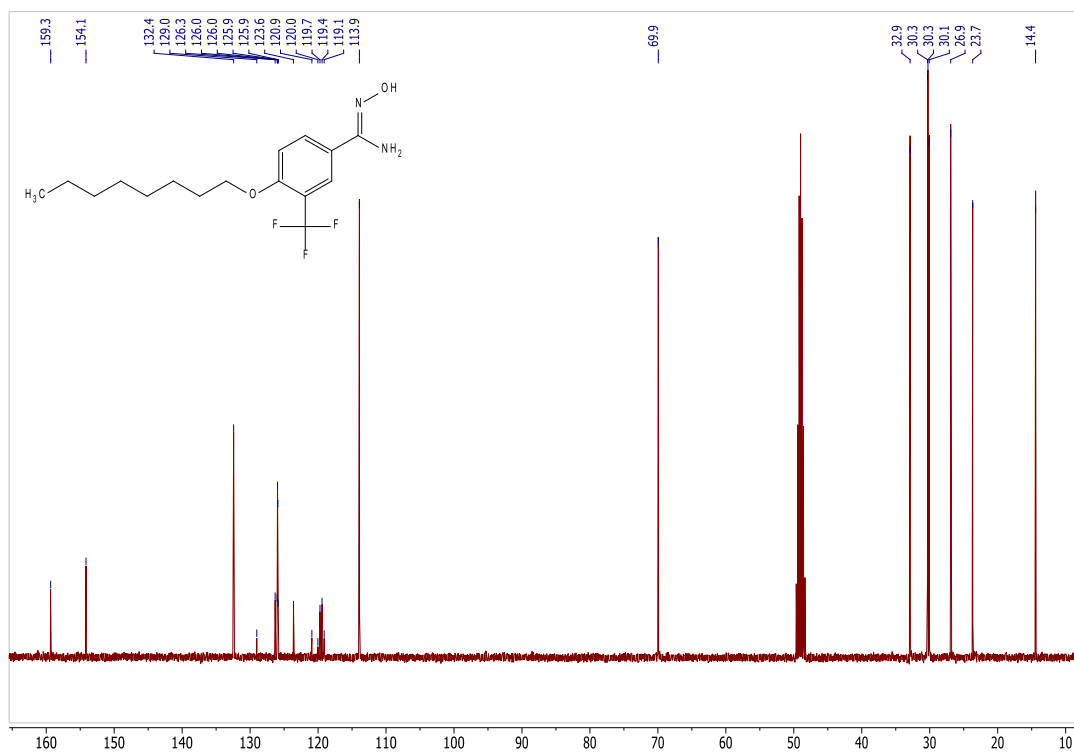
<sup>13</sup>C-NMR Spectrum for 3,5-dimethyl-4-(octyloxy)benzonitrile **3.9f** –



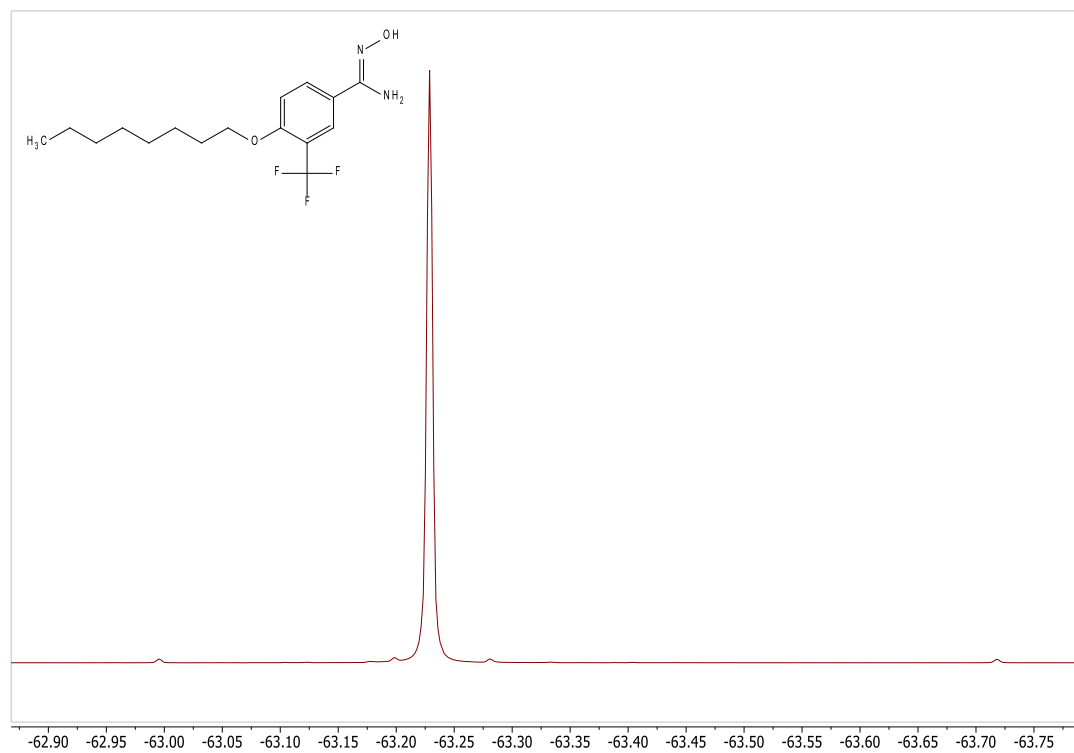
<sup>1</sup>H-NMR Spectrum for (Z)-N'-hydroxy-4-(octyloxy)-3-(trifluoromethyl)benzimidamide **3.10a** –



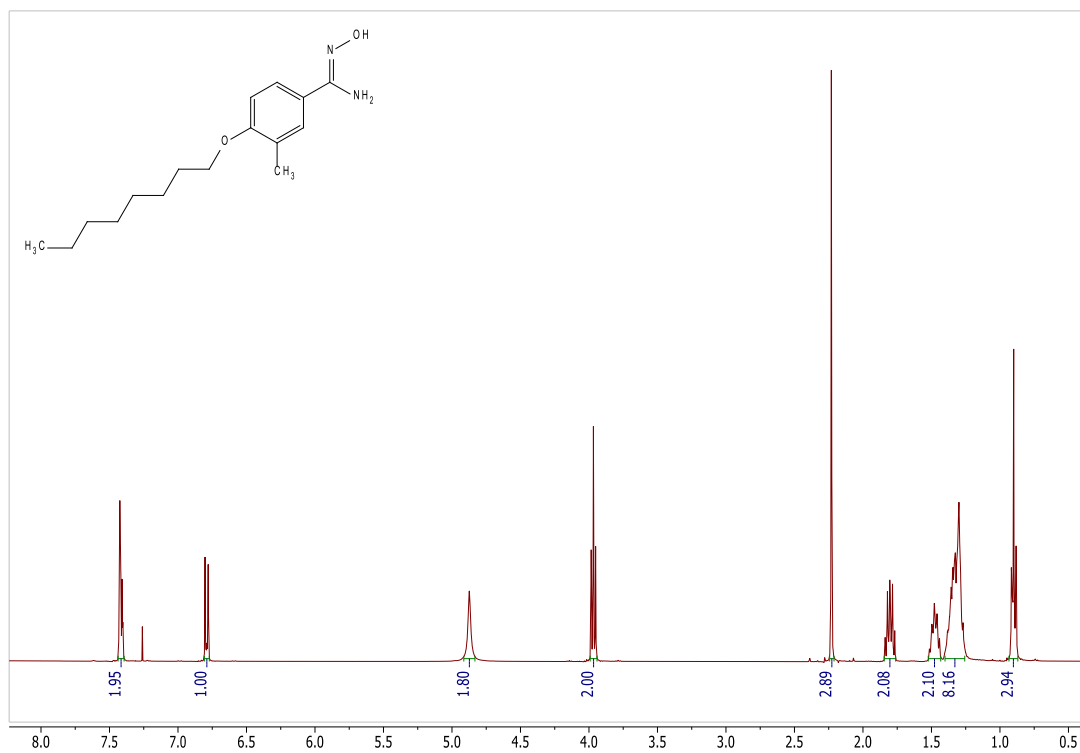
<sup>13</sup>C-NMR Spectrum for (Z)-N'-hydroxy-4-(octyloxy)-3-(trifluoromethyl)benzimidamide **3.10a** –



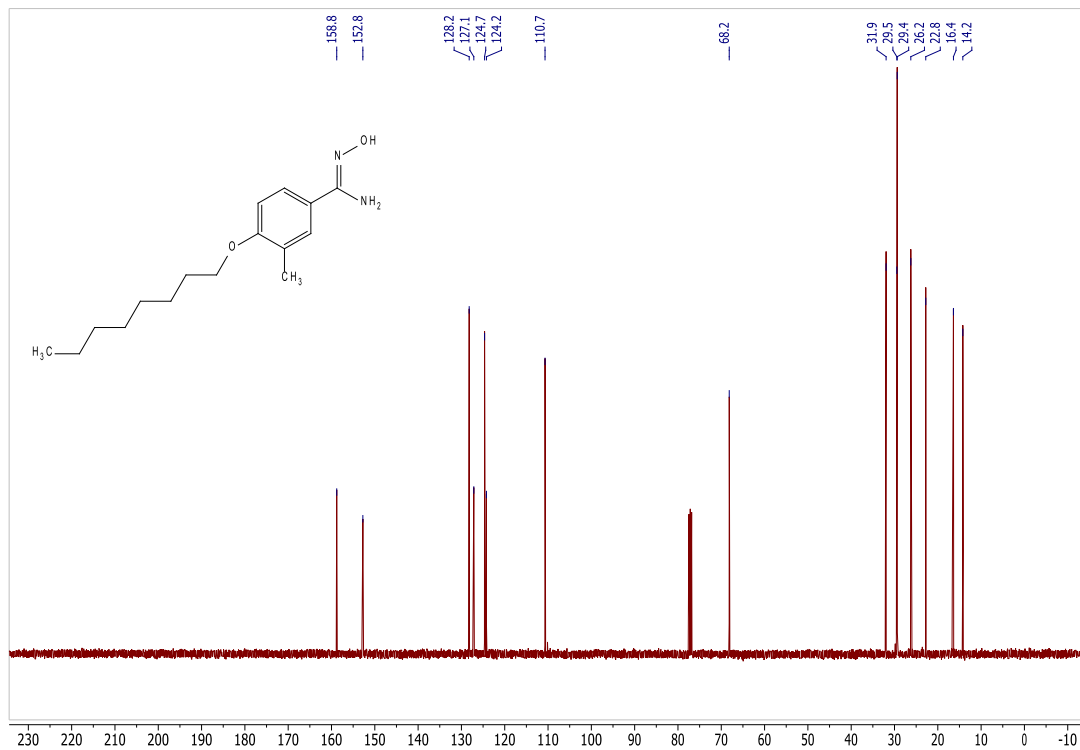
<sup>19</sup>F-NMR Spectrum for (Z)-N'-hydroxy-4-(octyloxy)-3-(trifluoromethyl)benzimidamide **3.10a**



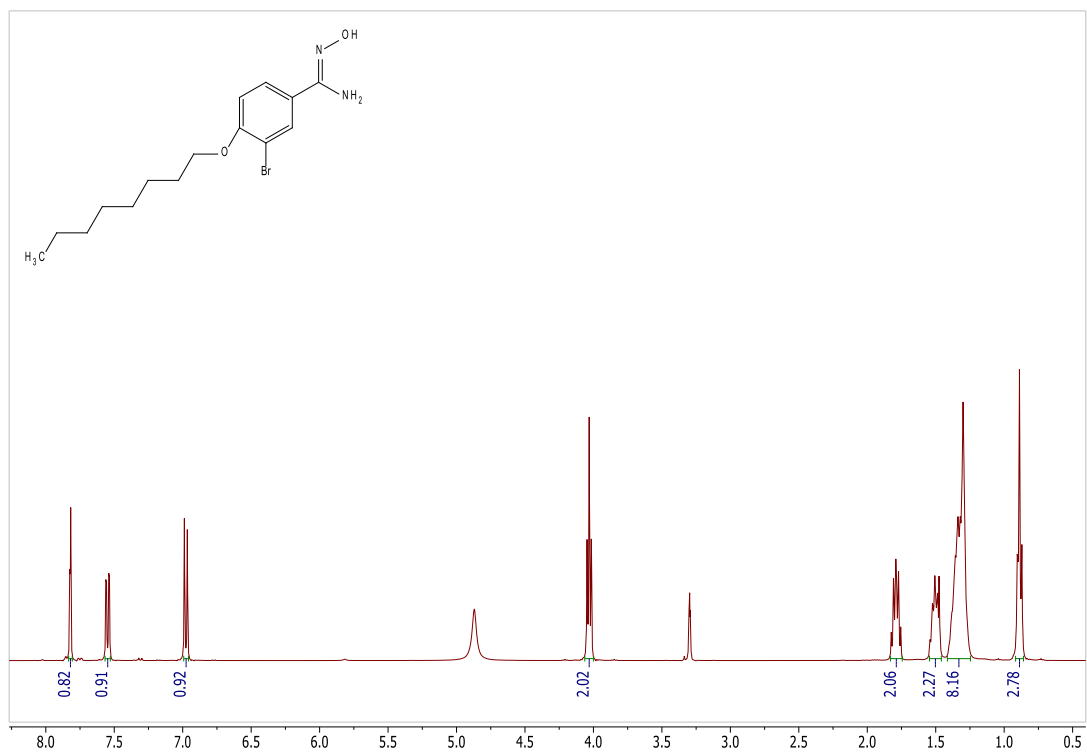
<sup>1</sup>H-NMR Spectrum for (Z)-N'-hydroxy-3-methyl-4-(octyloxy)benzimidamide **3.10b** –



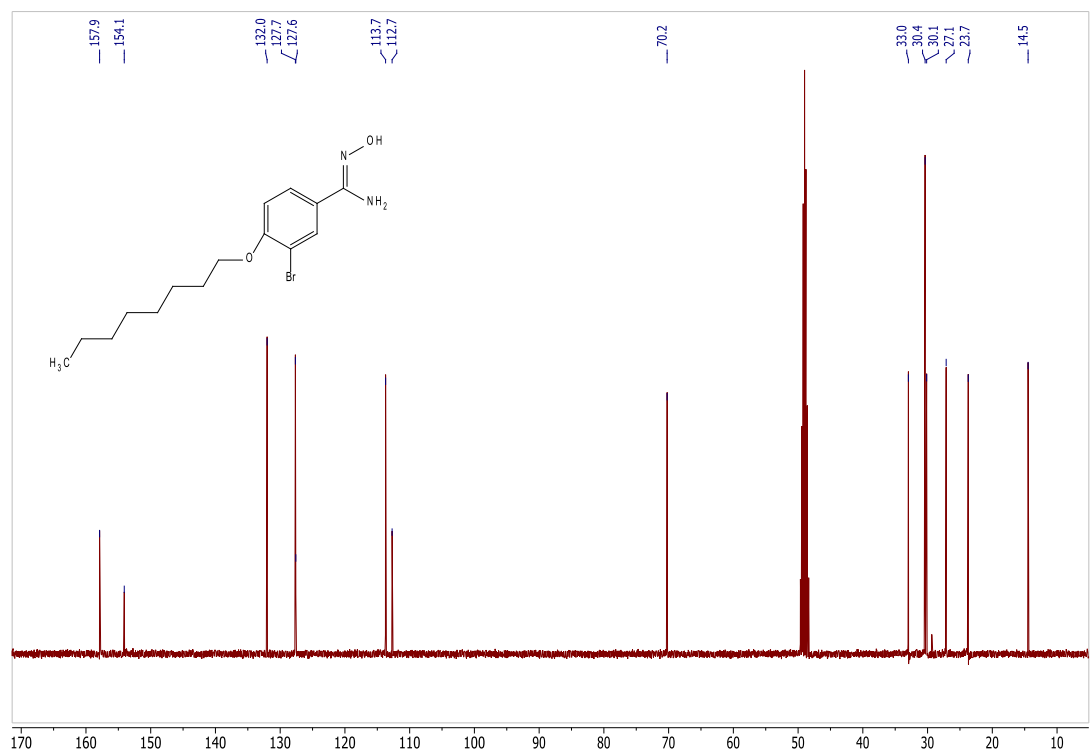
<sup>13</sup>C-NMR Spectrum for (Z)-N'-hydroxy-3-methyl-4-(octyloxy)benzimidamide **3.10b** –



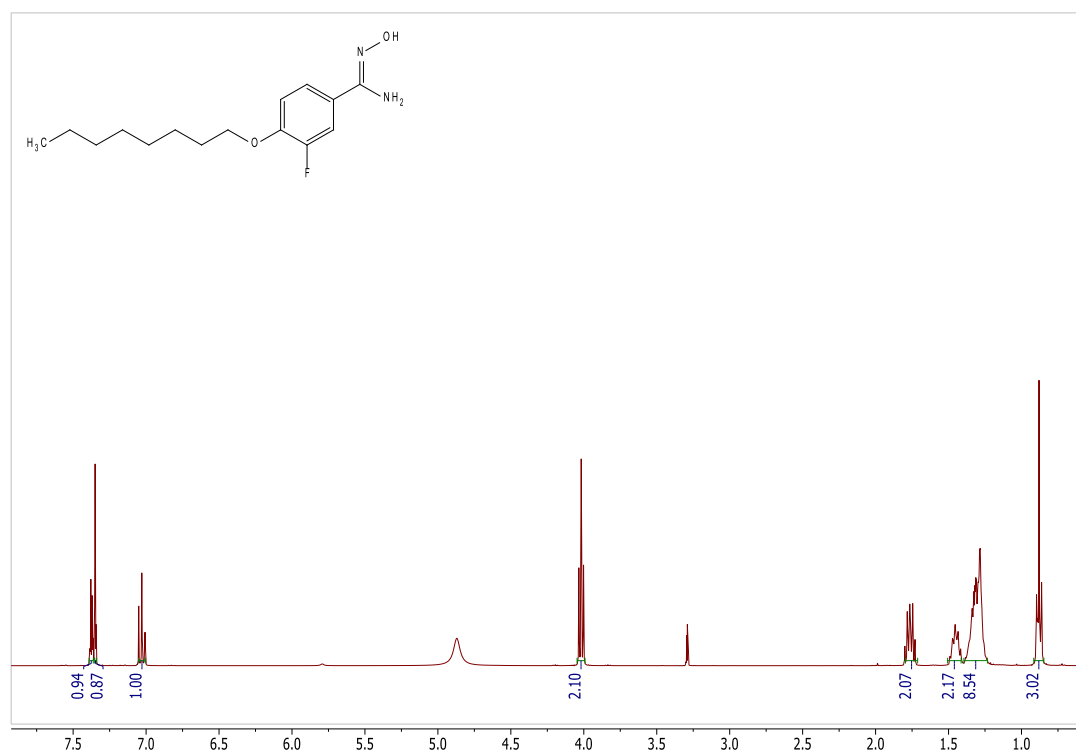
<sup>1</sup>H-NMR Spectrum for (Z)-3-bromo-N'-hydroxy-4-(octyloxy)benzimidamide **3.10c** –



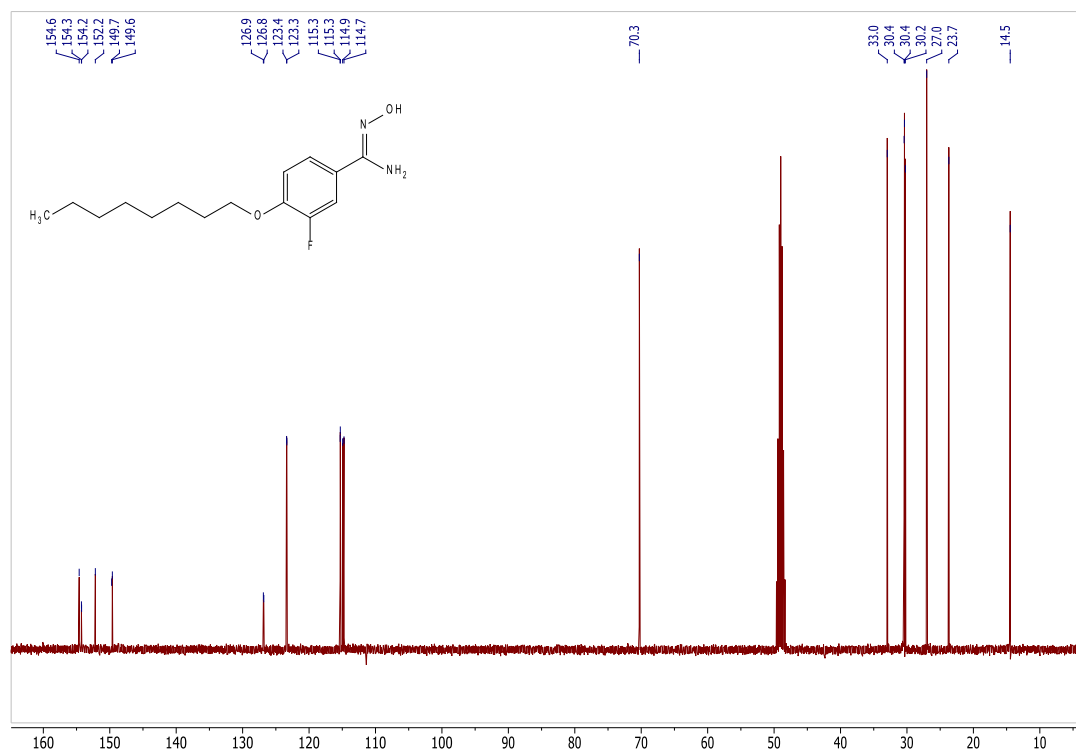
<sup>13</sup>C-NMR Spectrum for (Z)-3-bromo-N'-hydroxy-4-(octyloxy)benzimidamide **3.10c** –



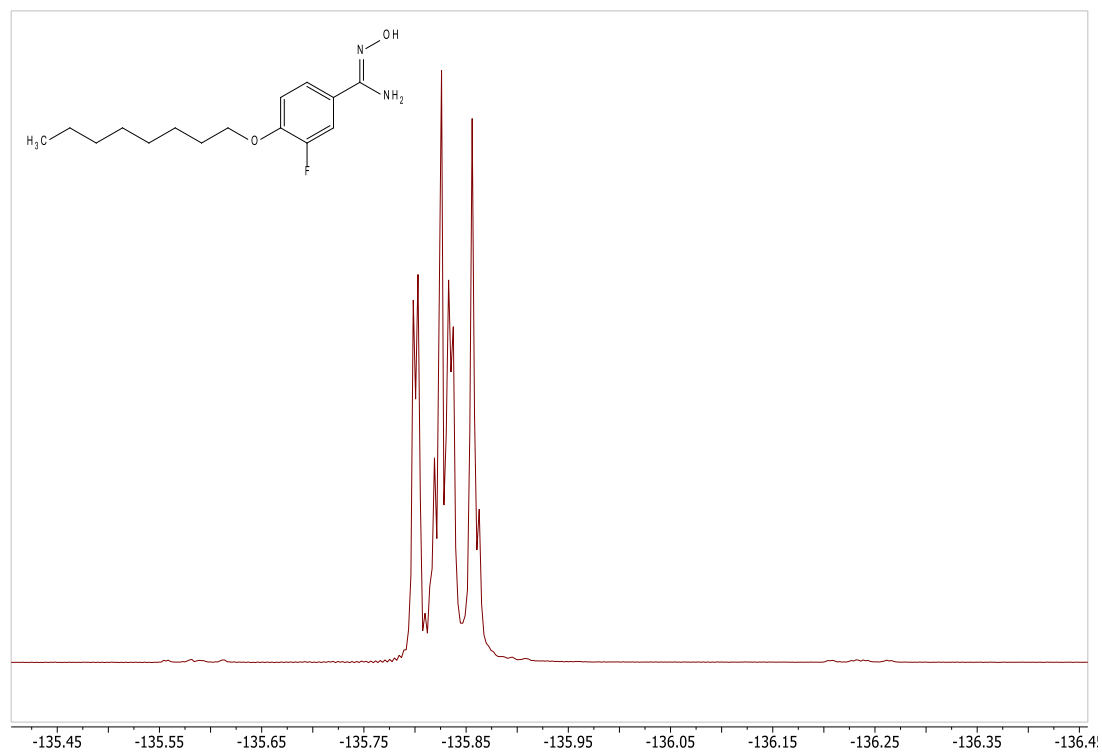
<sup>1</sup>H-NMR Spectrum for (Z)-3-fluoro-N'-hydroxy-4-(octyloxy)benzimidamide **3.10d** –



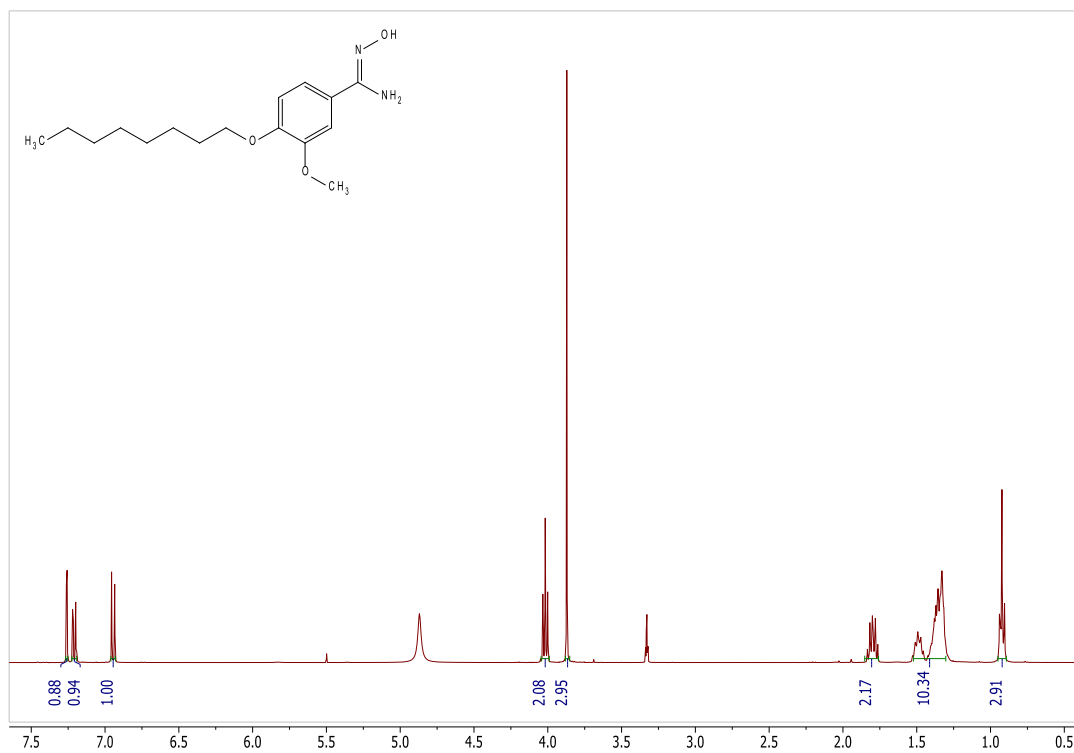
<sup>13</sup>C-NMR Spectrum for (Z)-3-fluoro-N'-hydroxy-4-(octyloxy)benzimidamide **3.10d** –



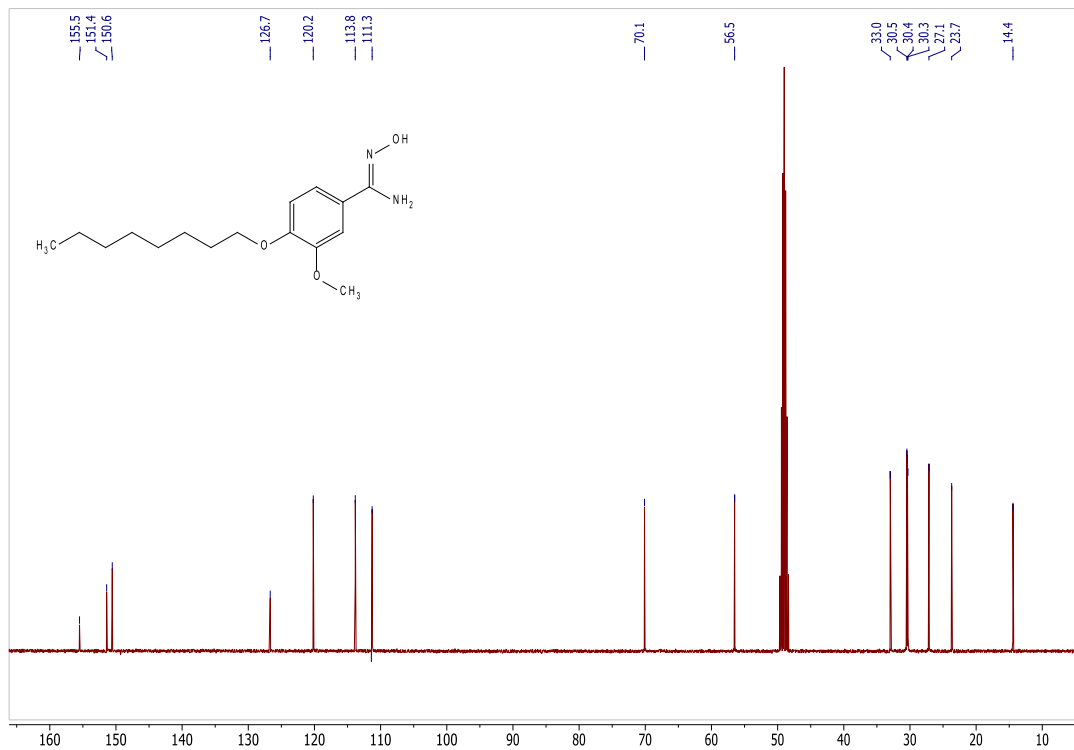
<sup>19</sup>F-NMR Spectrum for (Z)-3-fluoro-N'-hydroxy-4-(octyloxy)benzimidamide **3.10d**



<sup>1</sup>H-NMR Spectrum for (Z)-N'-hydroxy-3-methoxy-4-(octyloxy)benzimidamide **3.10e** –

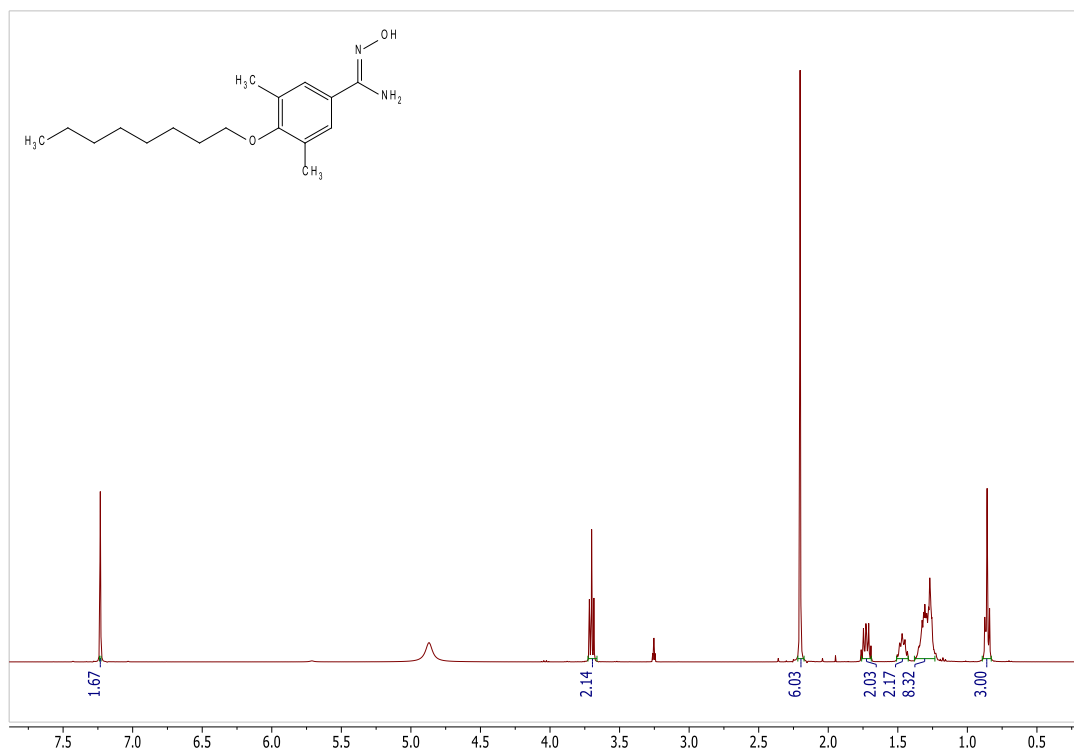


<sup>13</sup>C-NMR Spectrum for (Z)-N'-hydroxy-3-methoxy-4-(octyloxy)benzimidamide **3.10e** –

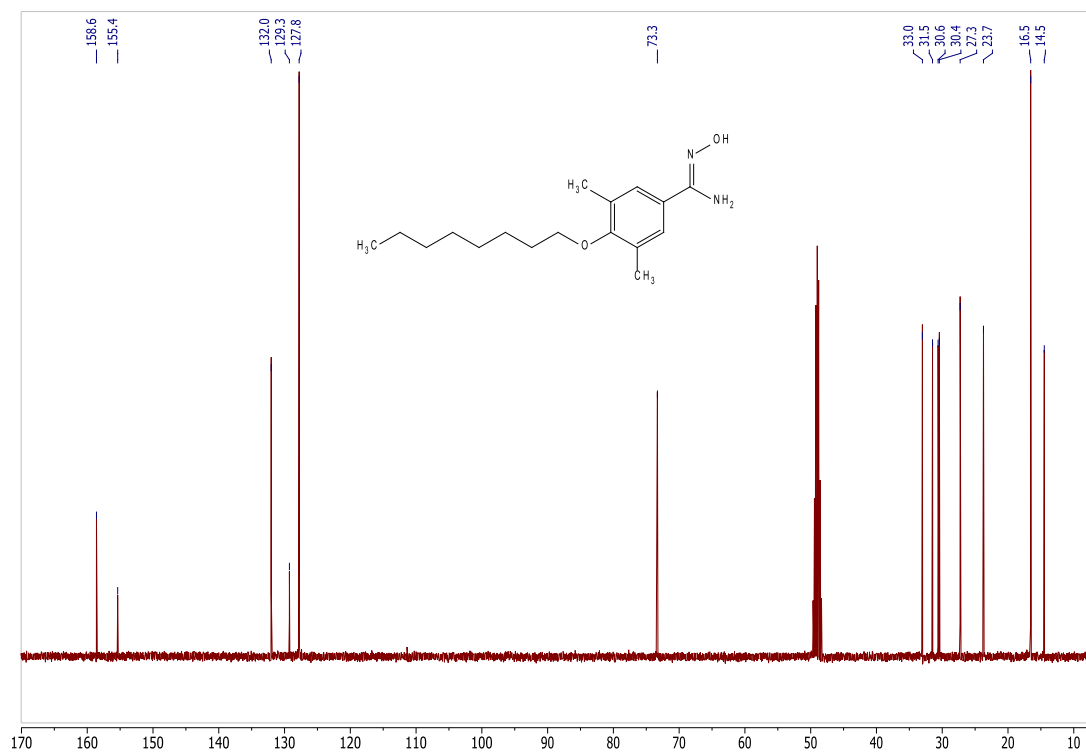




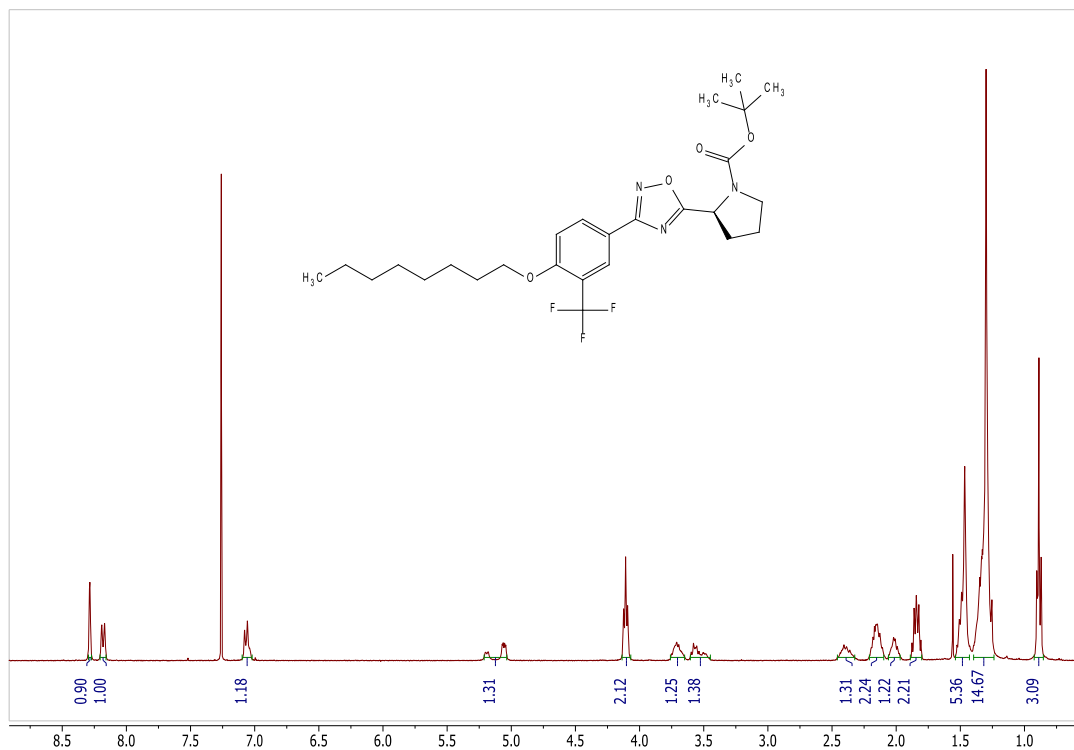
<sup>1</sup>H-NMR Spectrum for (Z)-N'-hydroxy-3,5-dimethyl-4-(octyloxy)benzimidamide **3.10f** –



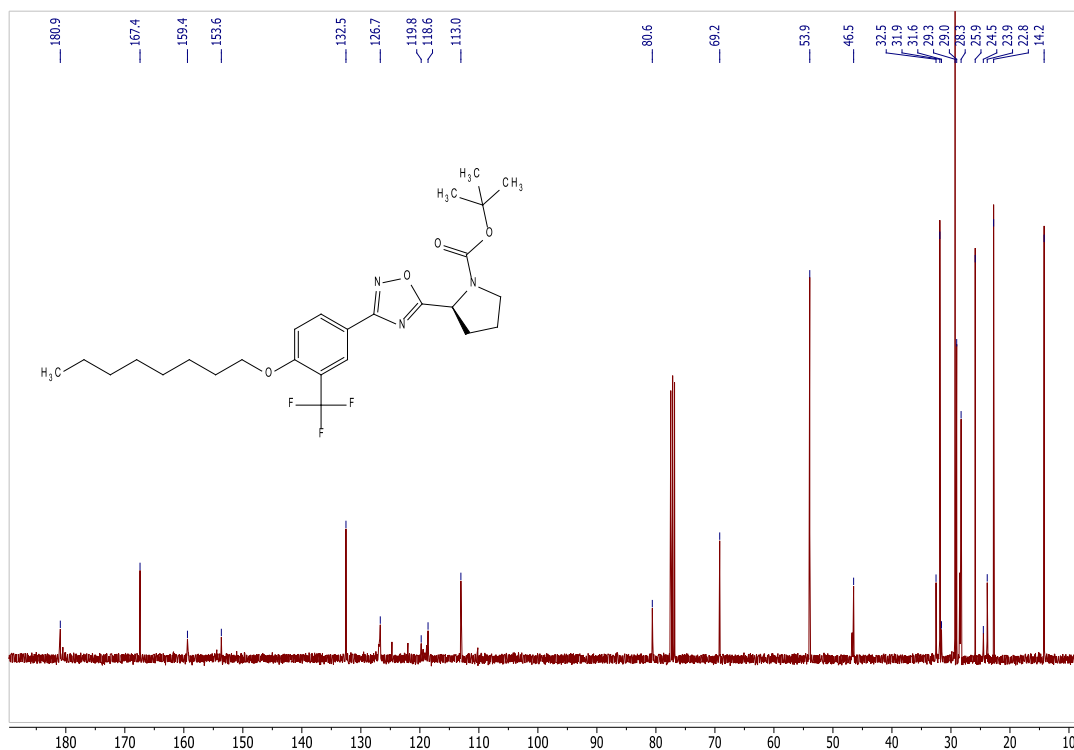
<sup>13</sup>C-NMR Spectrum for (Z)-N'-hydroxy-3,5-dimethyl-4-(octyloxy)benzimidamide **3.10f** –



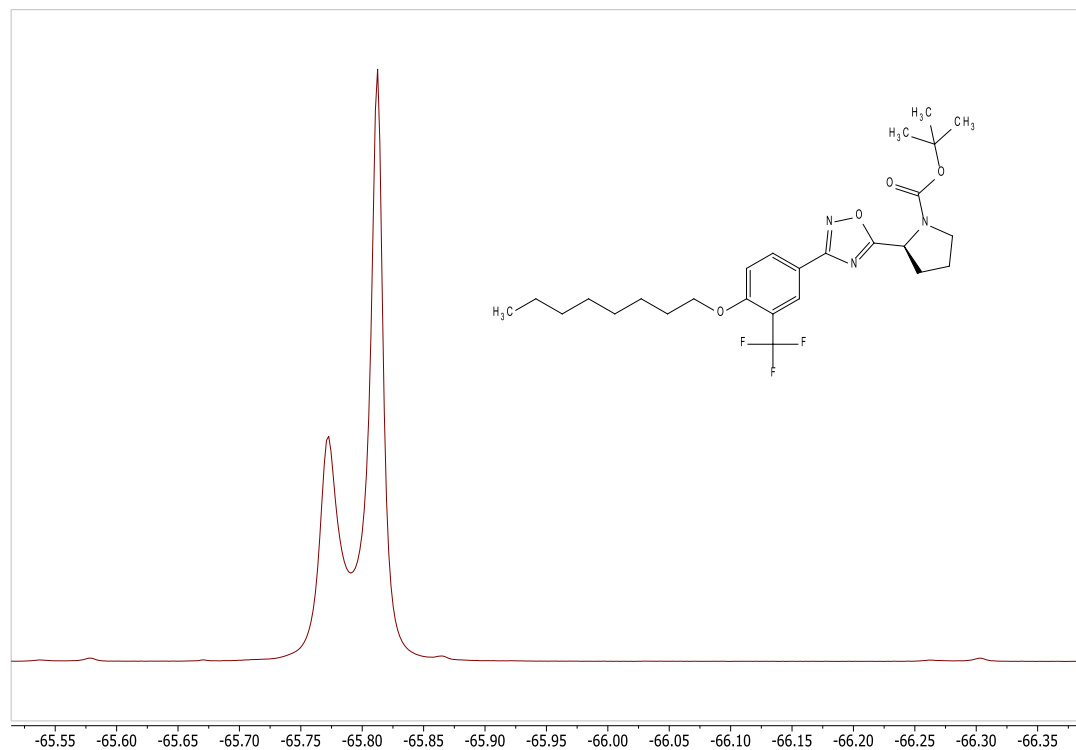
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11a** –



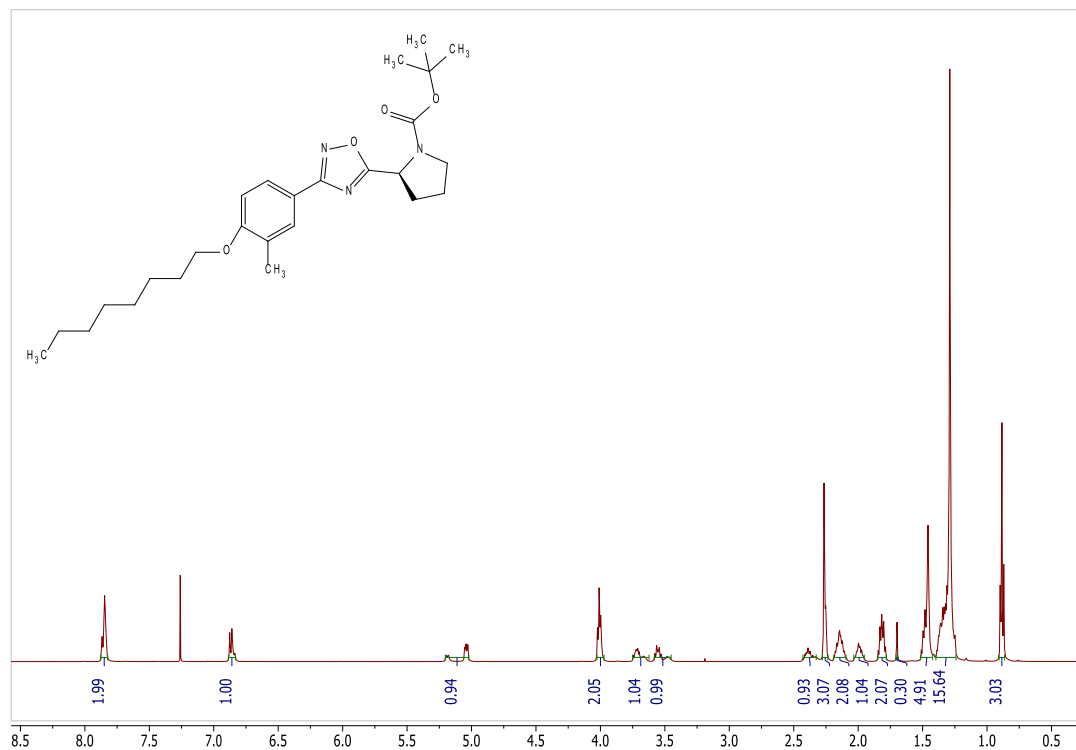
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11a** –



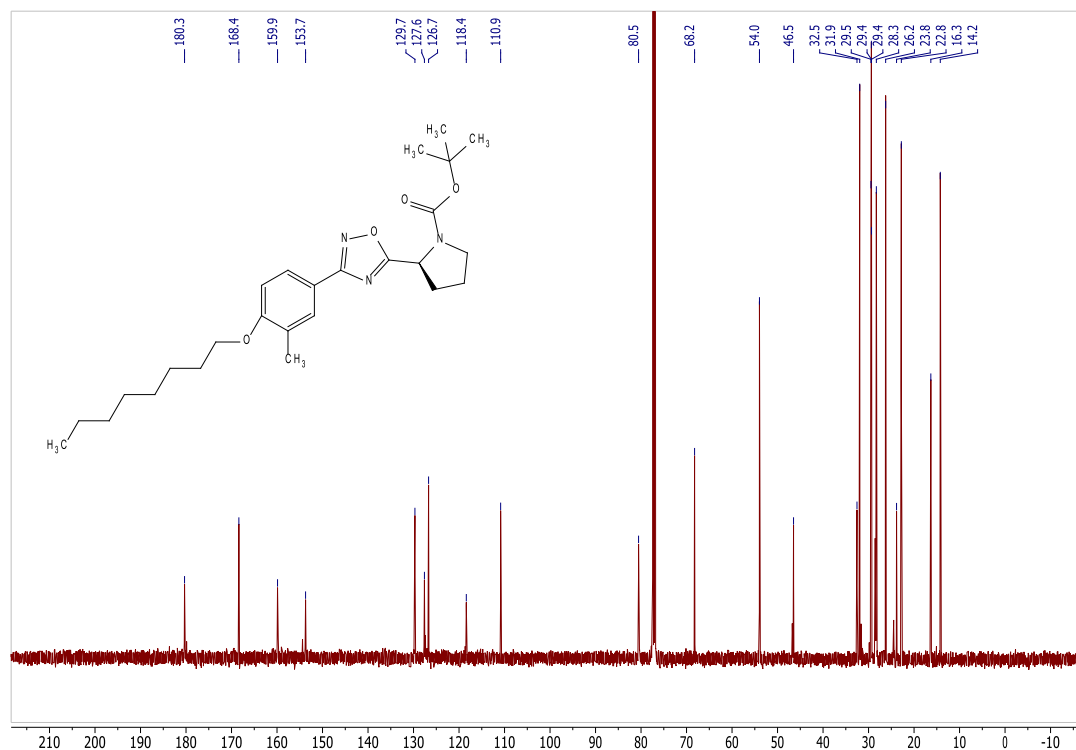
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11a**



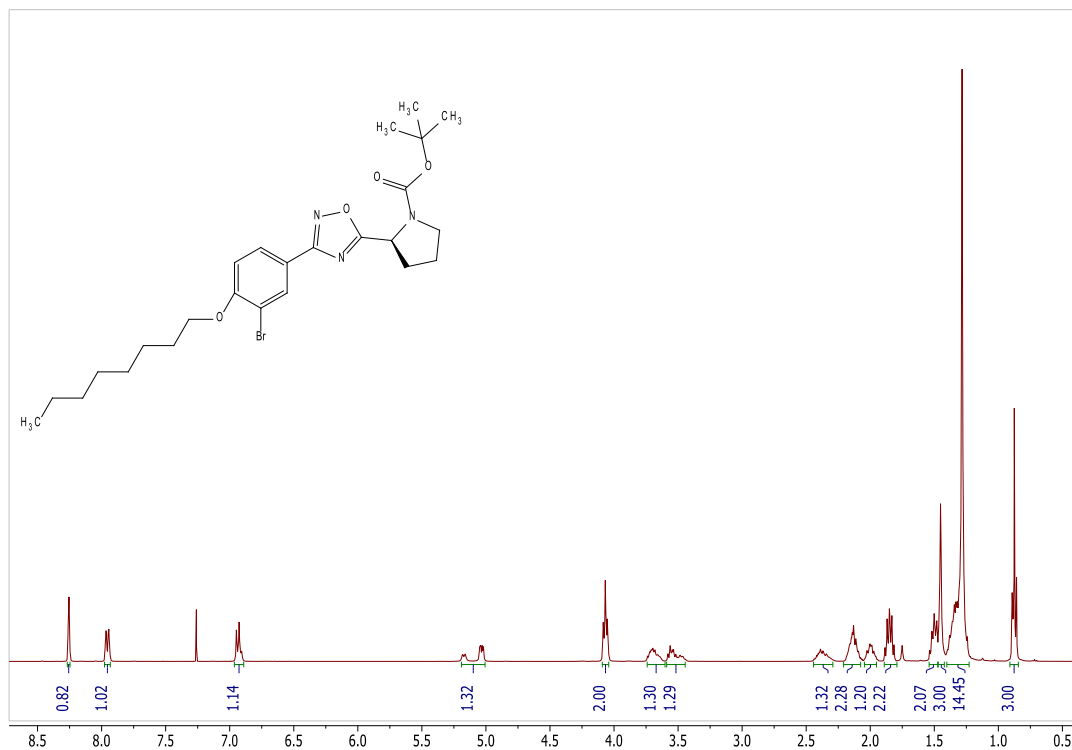
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11b** –



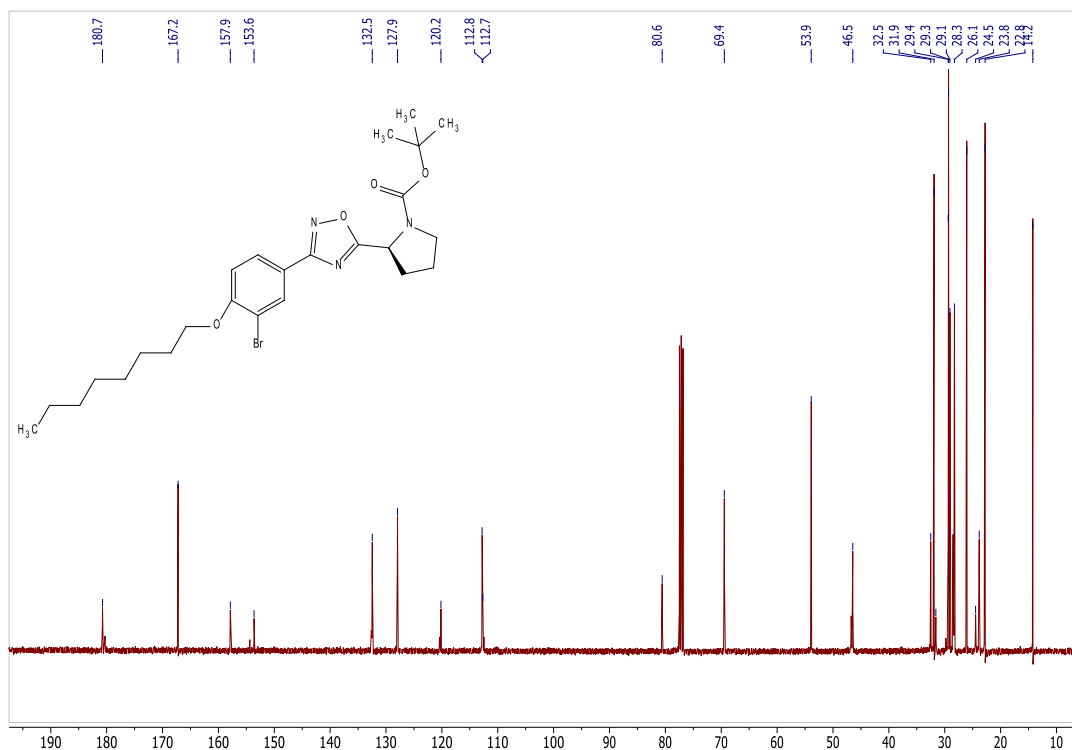
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11b** –



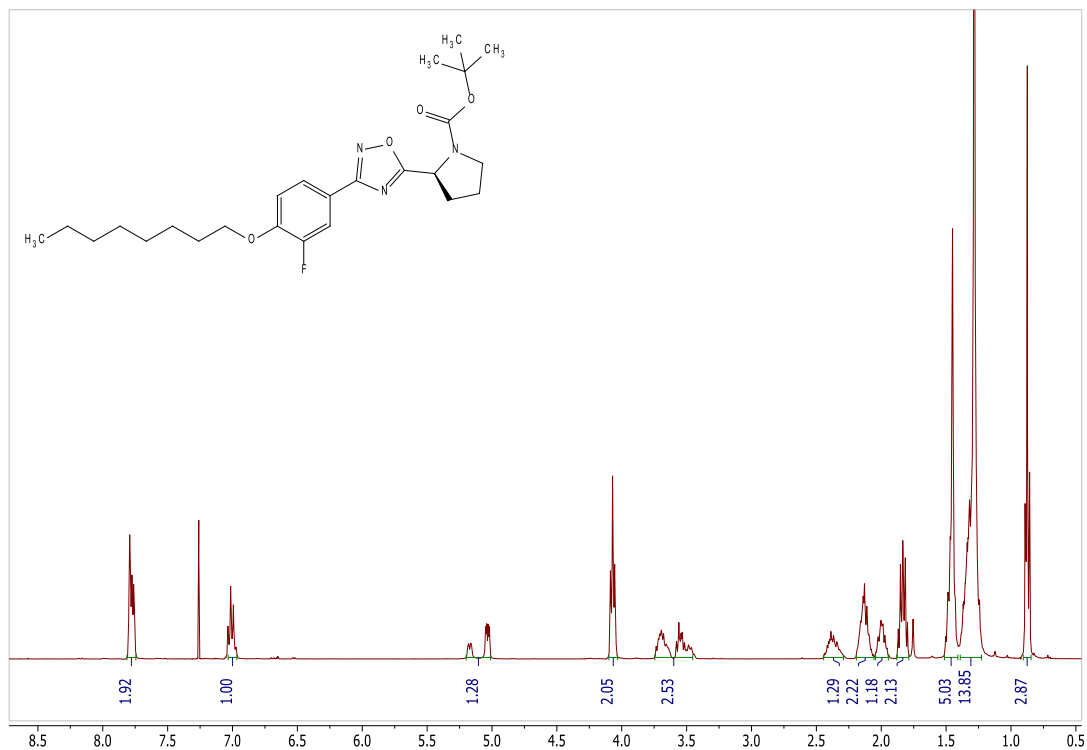
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11c** –



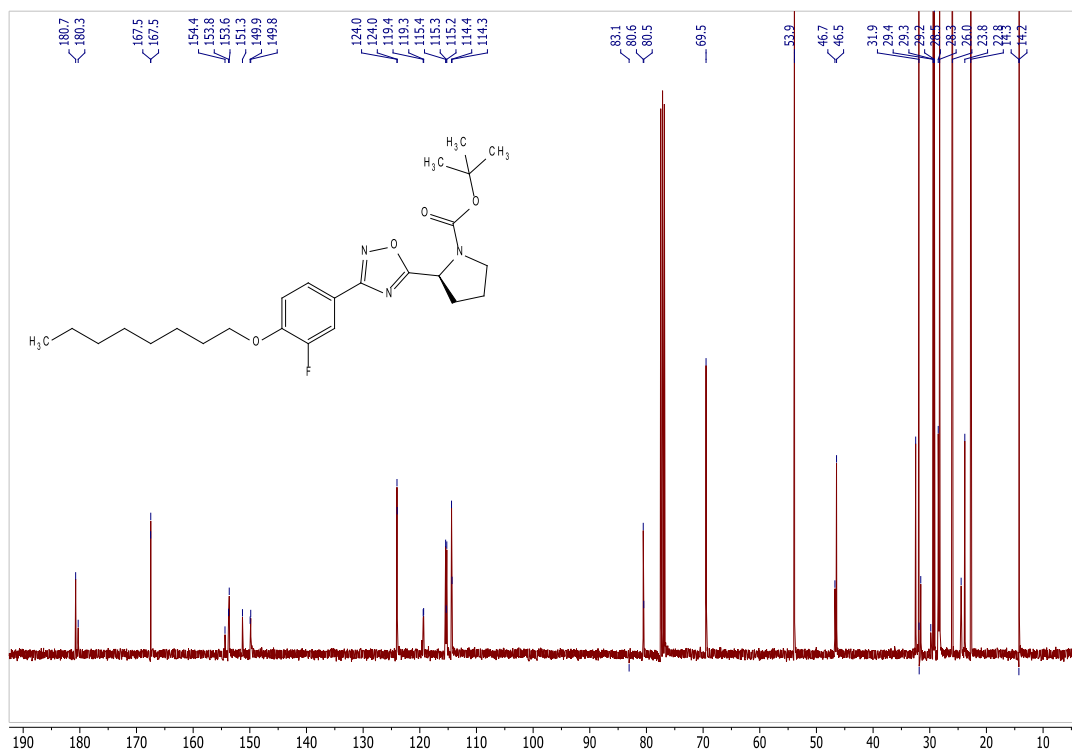
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11c** –



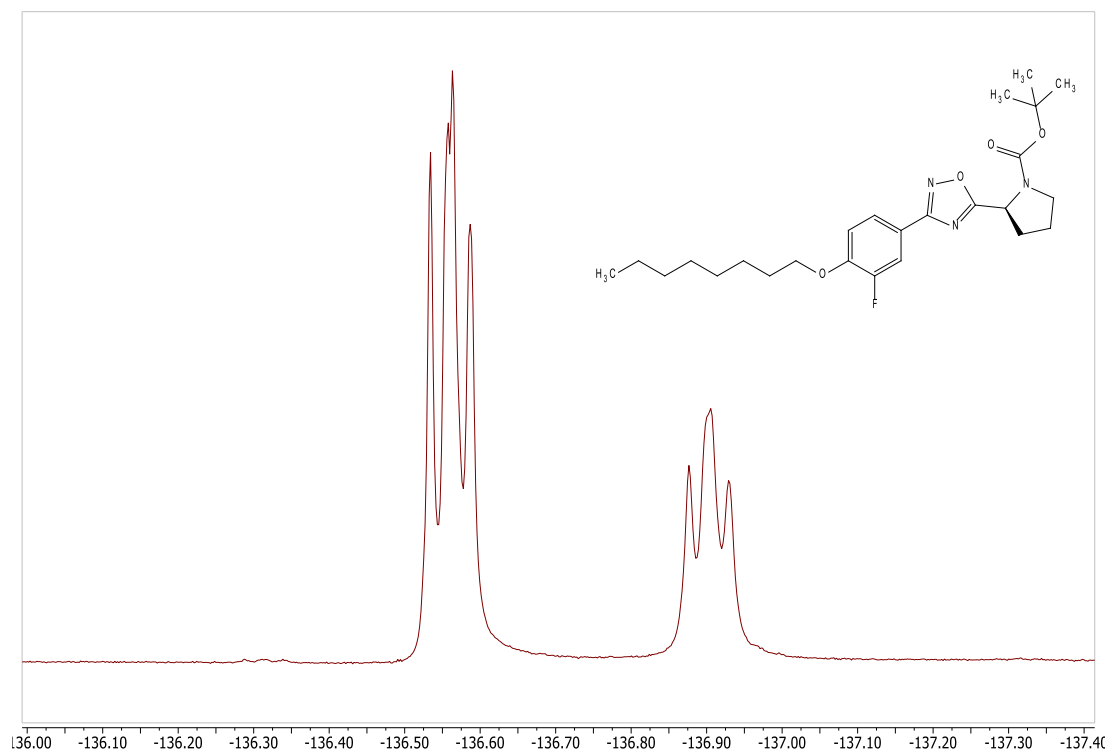
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11d** –



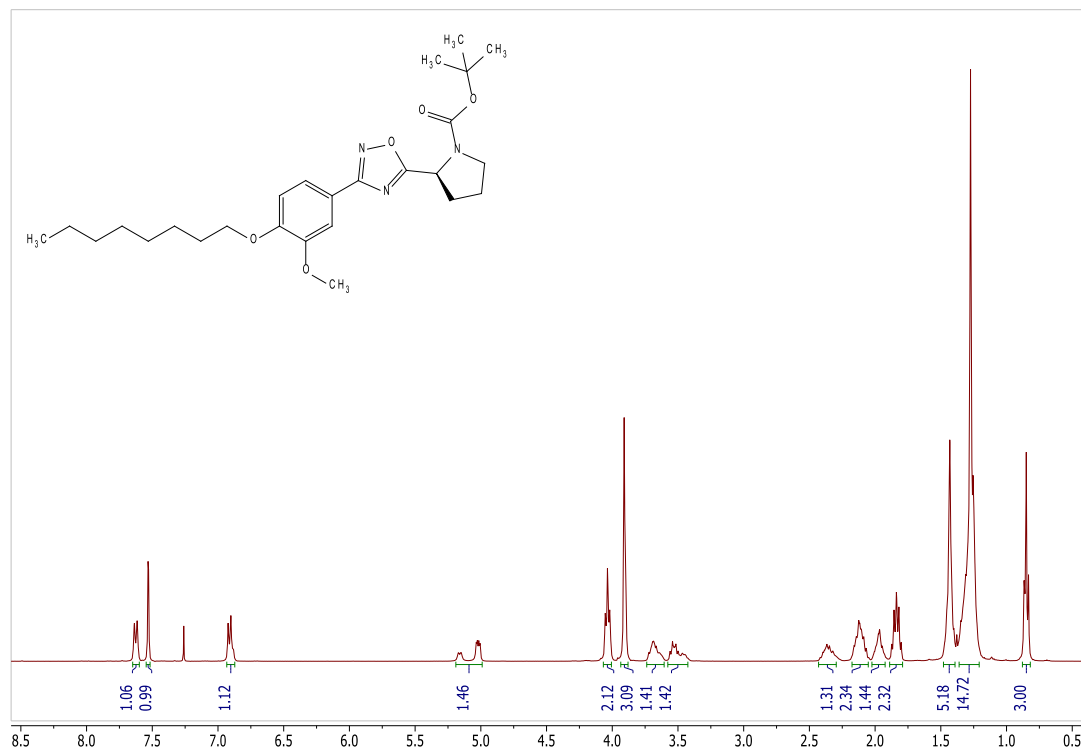
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11d** –



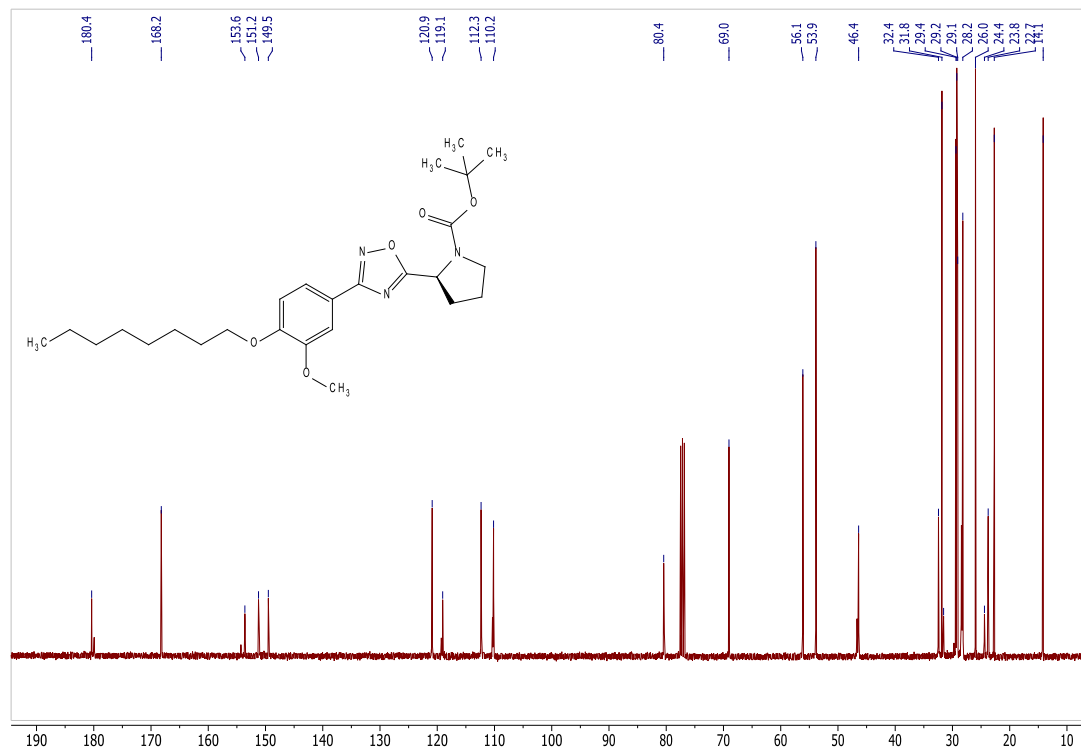
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11d** –



<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11e**–

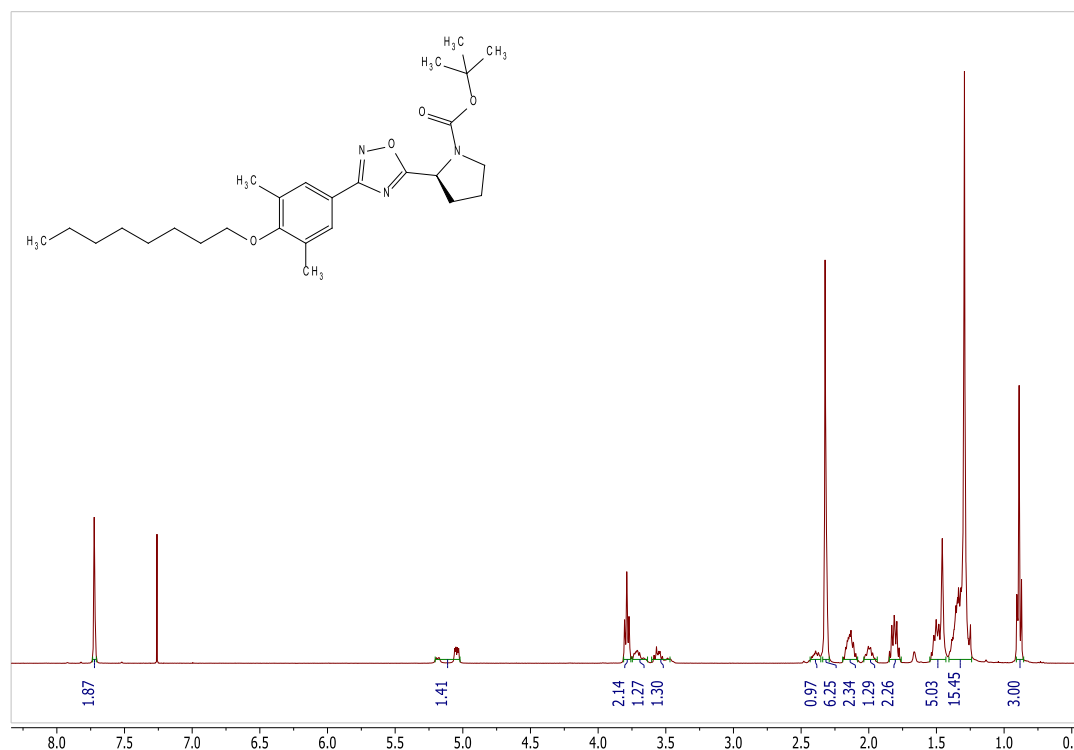


<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11e**–

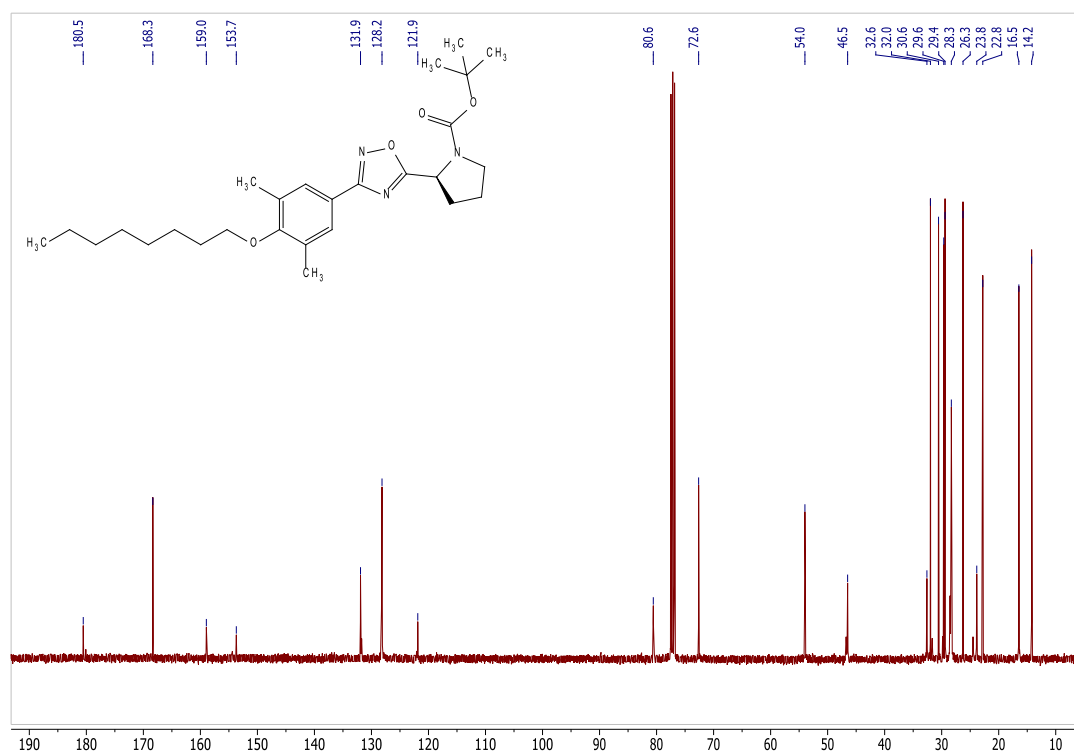




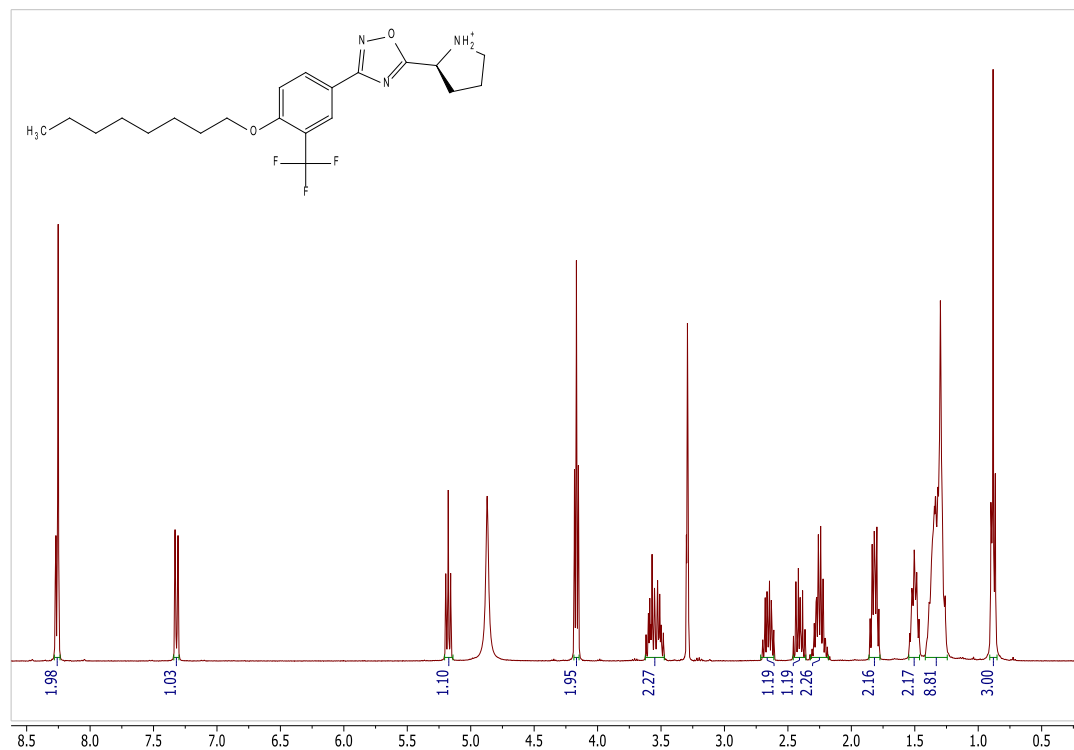
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11f**–



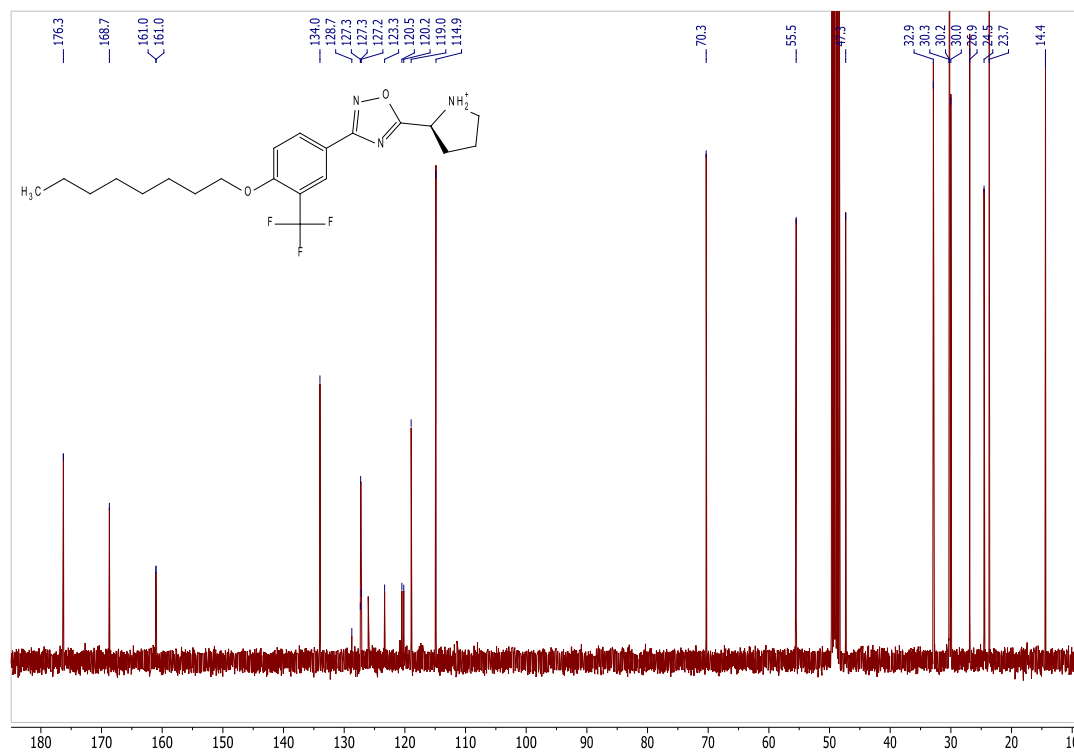
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.11f**–



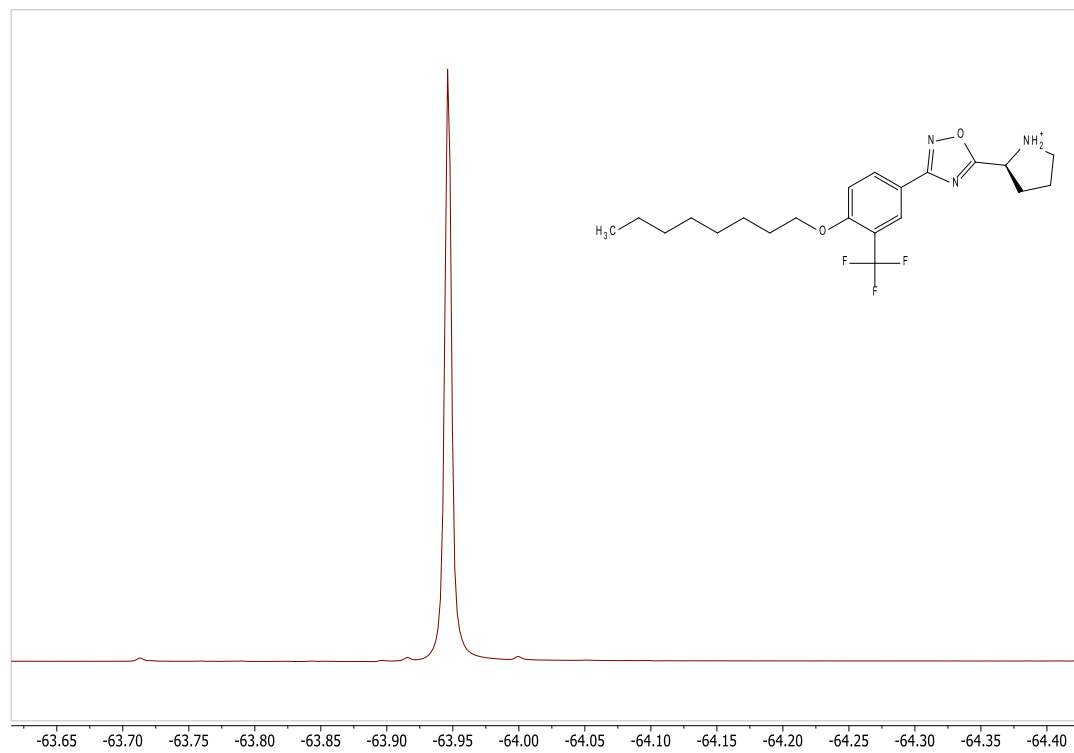
<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12a**—



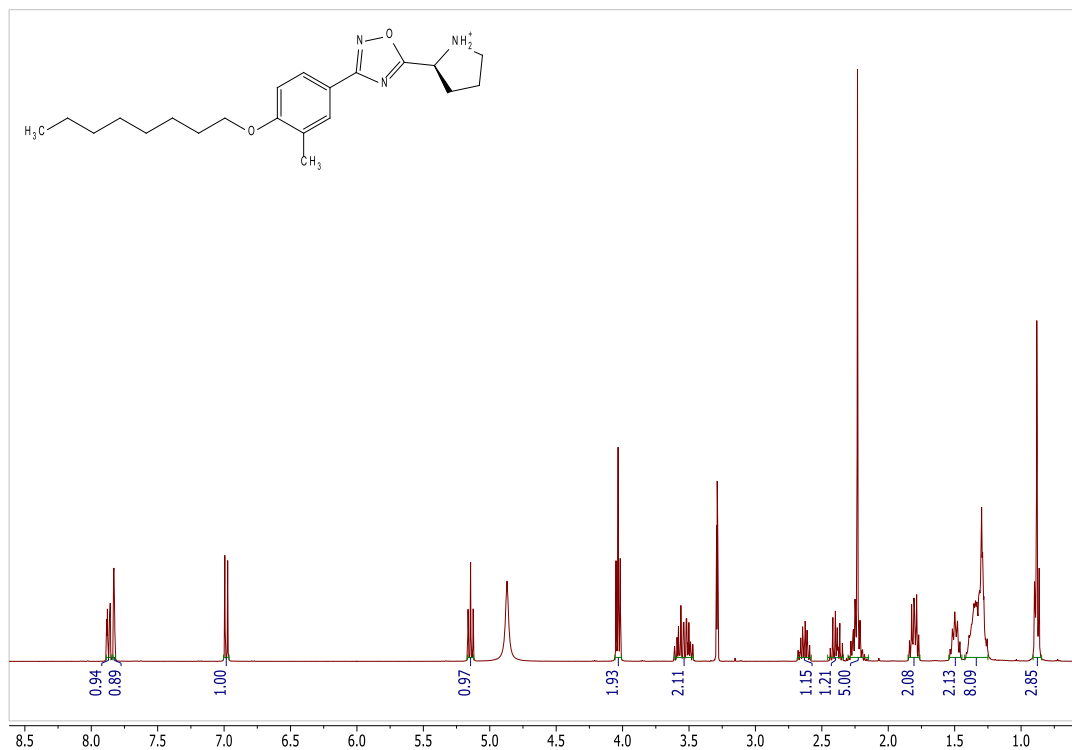
<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12a**—



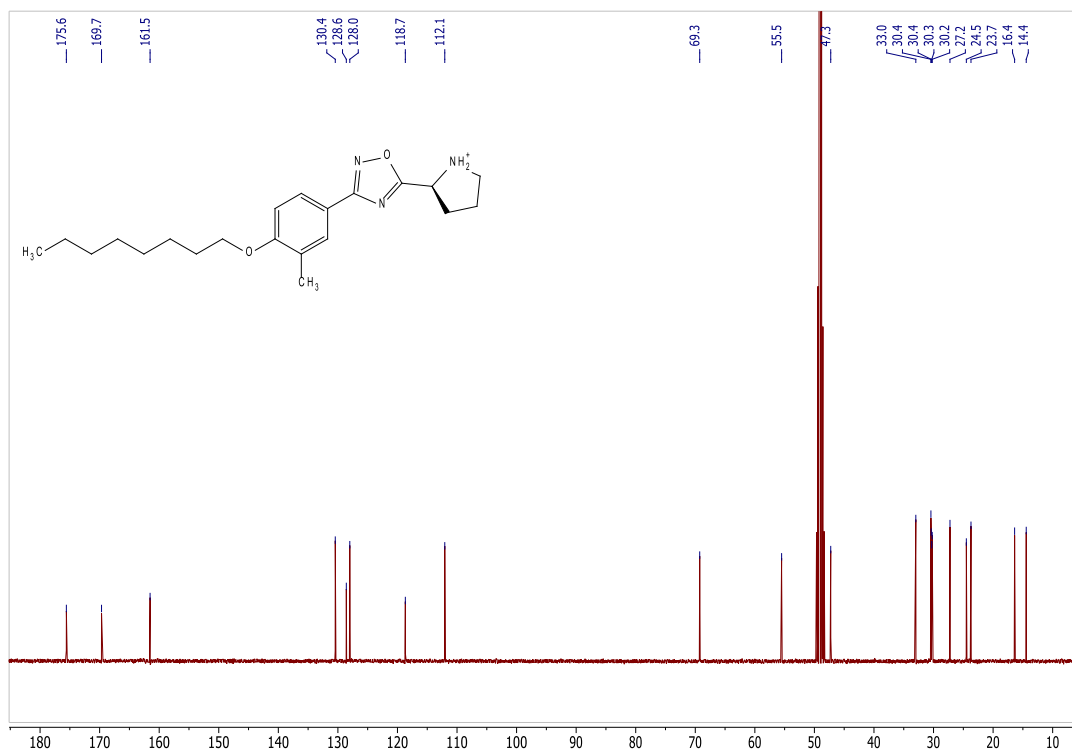
$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12a**—



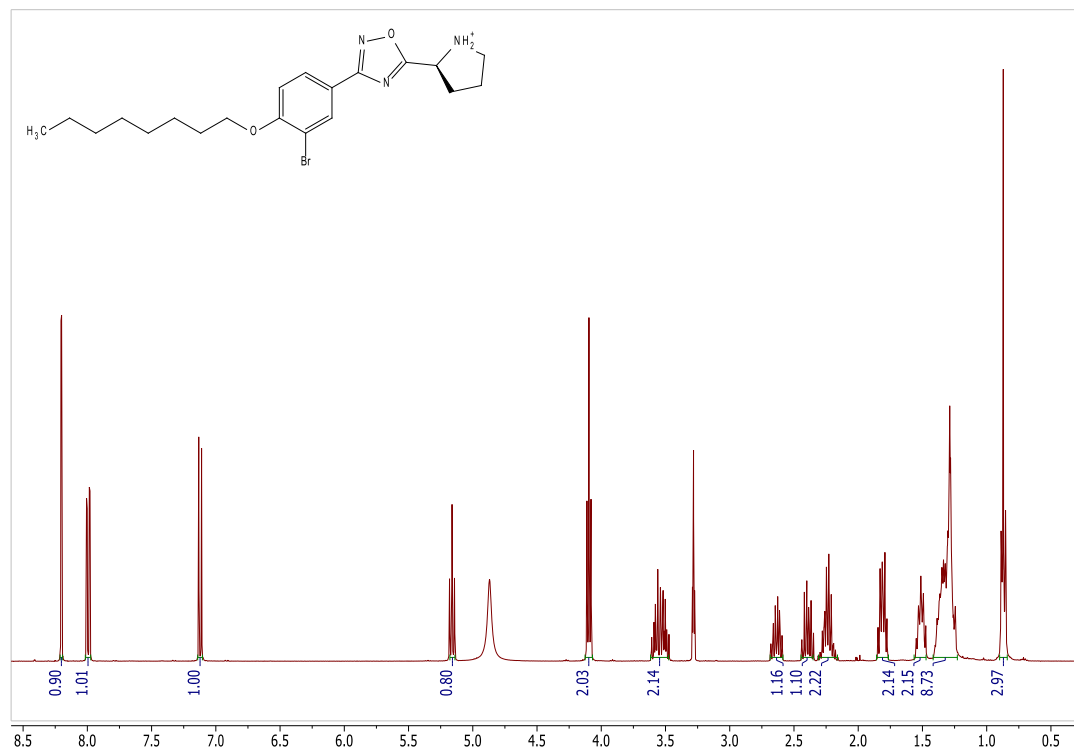
<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12b**



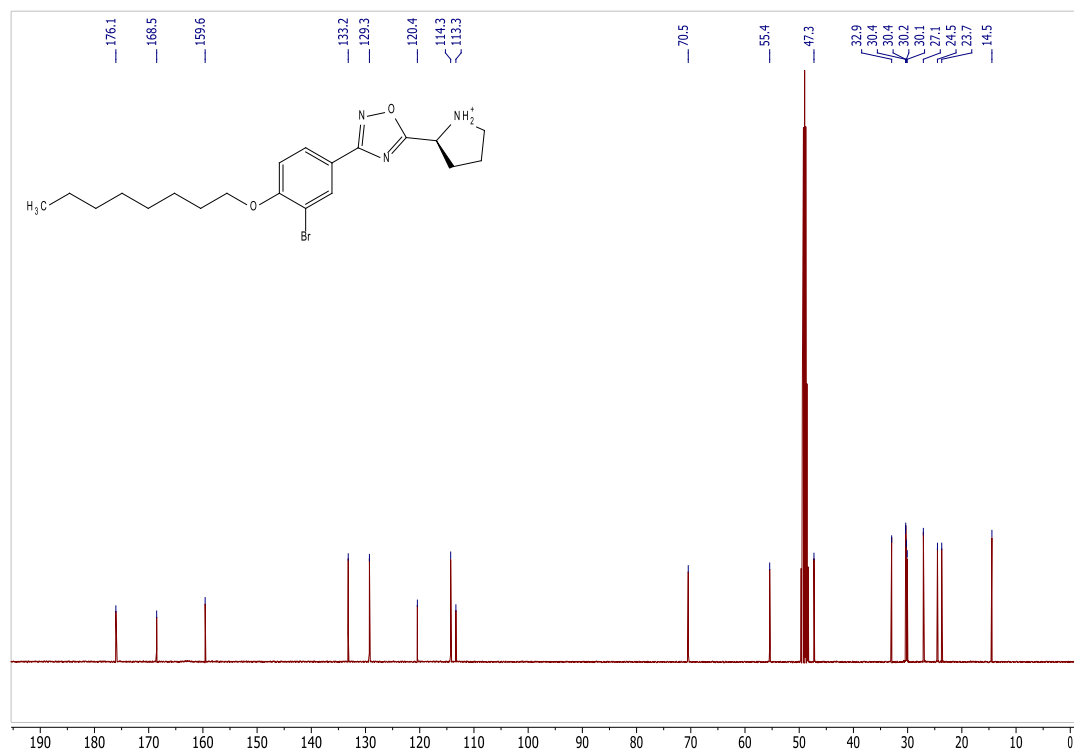
<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12b**



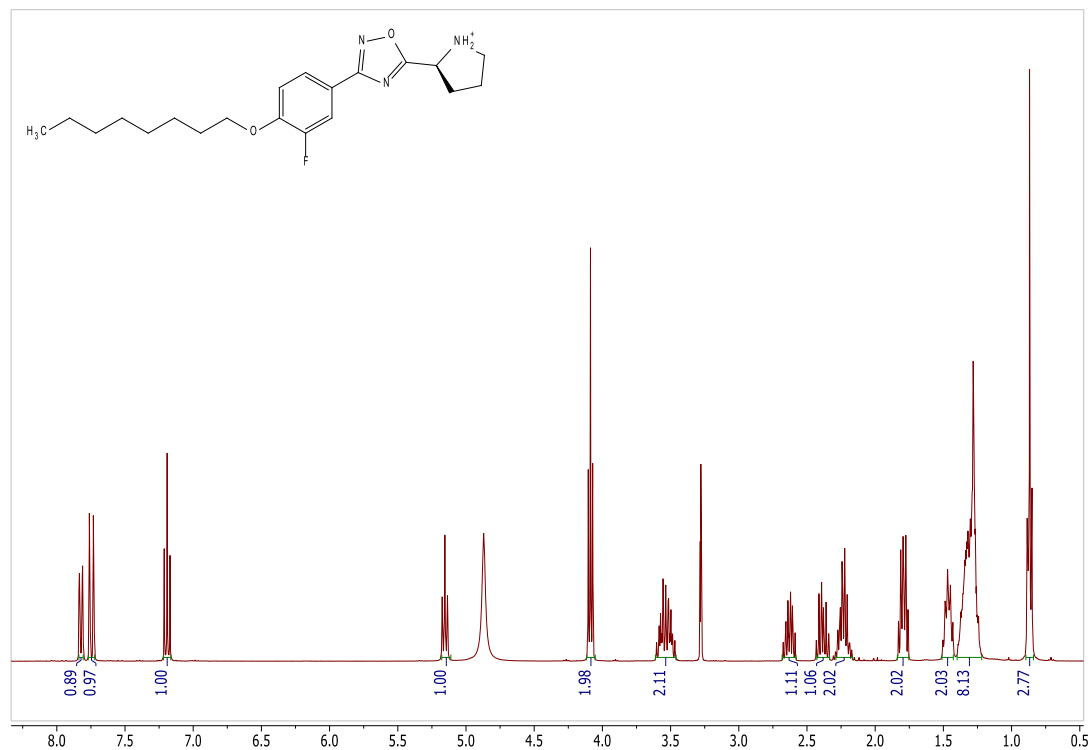
<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12c**–



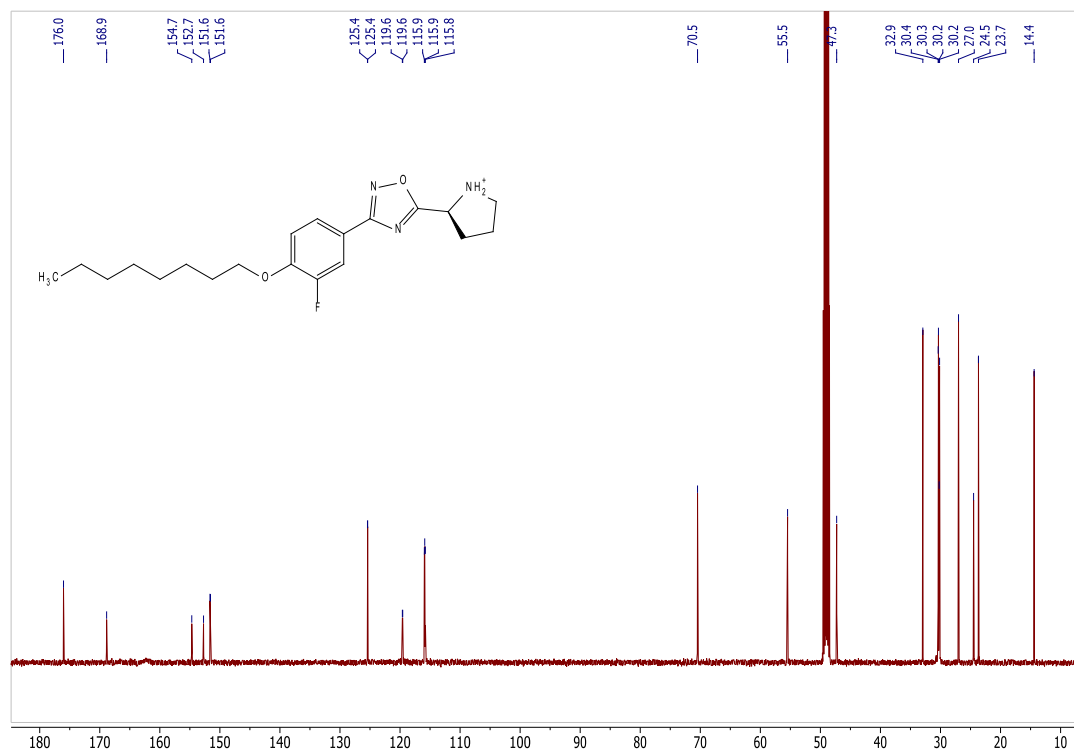
<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12c**–



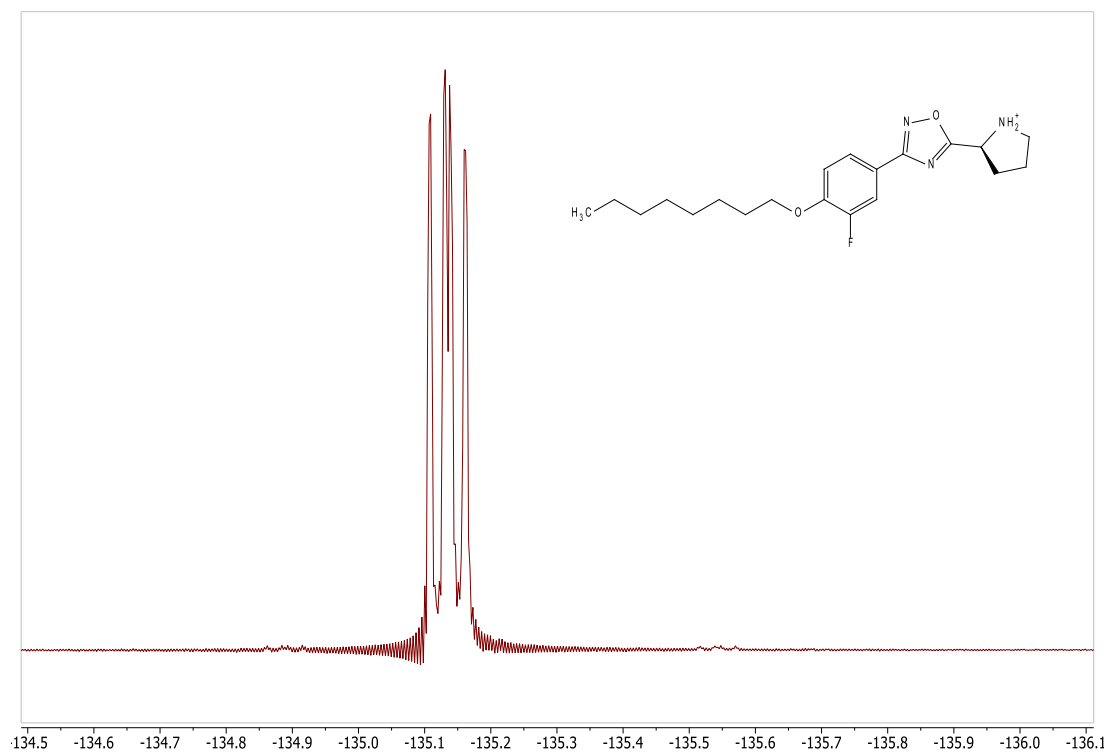
<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12d**–



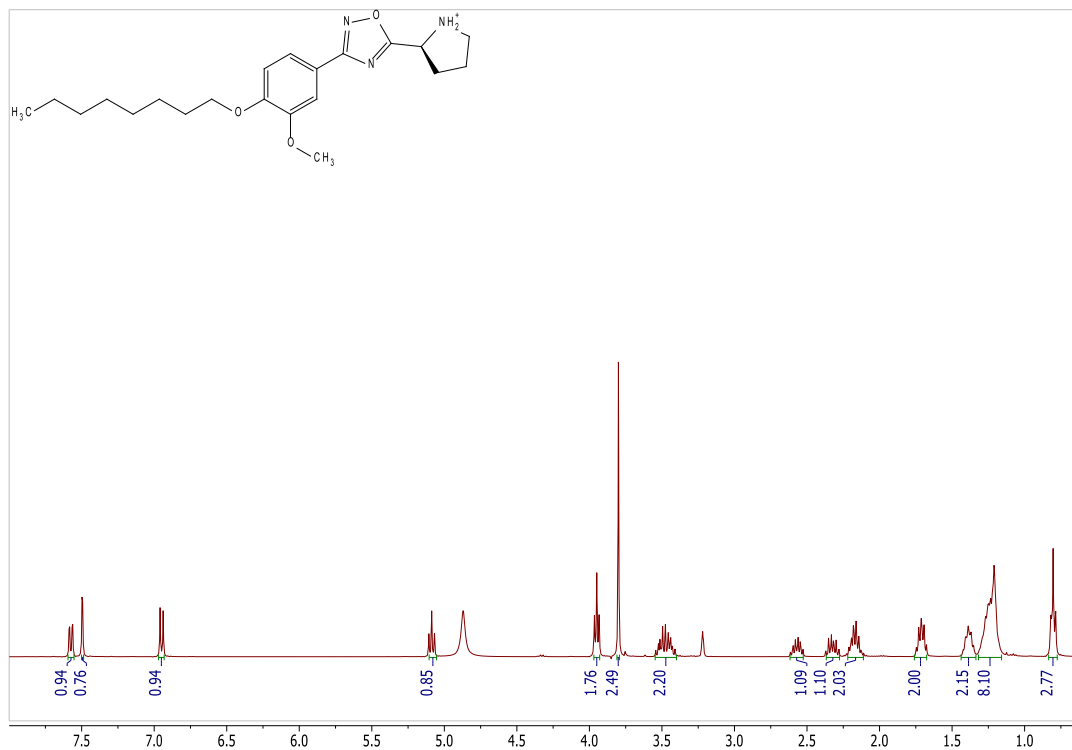
<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12d**–



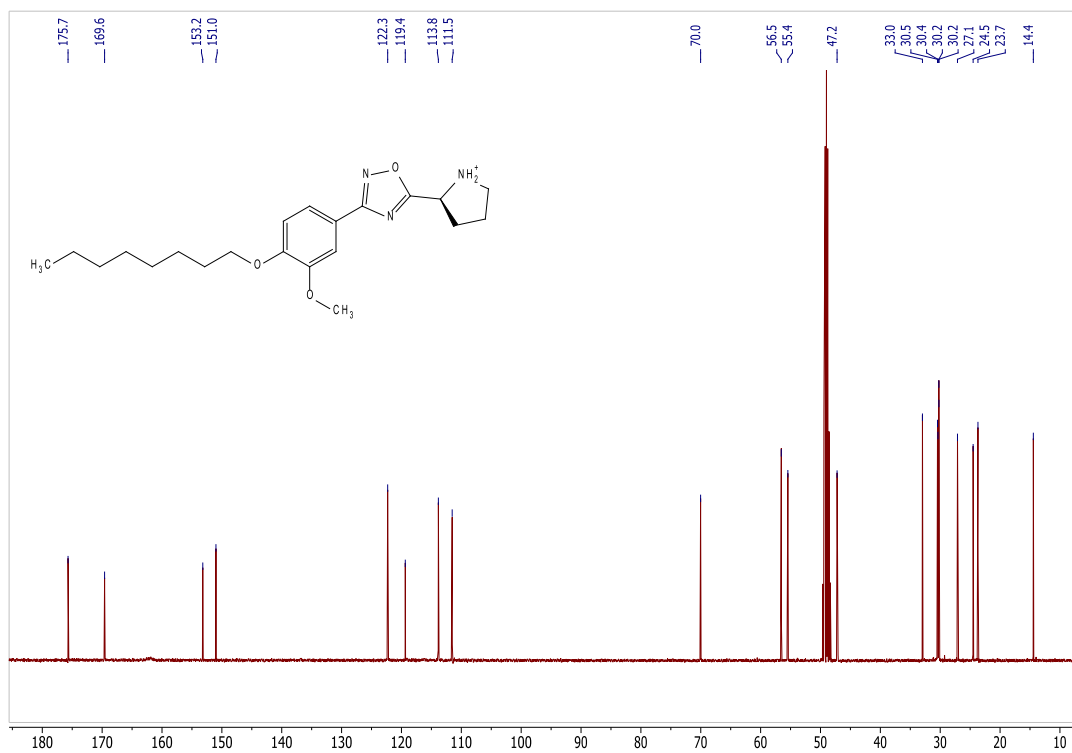
<sup>19</sup>F-NMR Spectrum for (*S*)-2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12d**–



<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12e**—

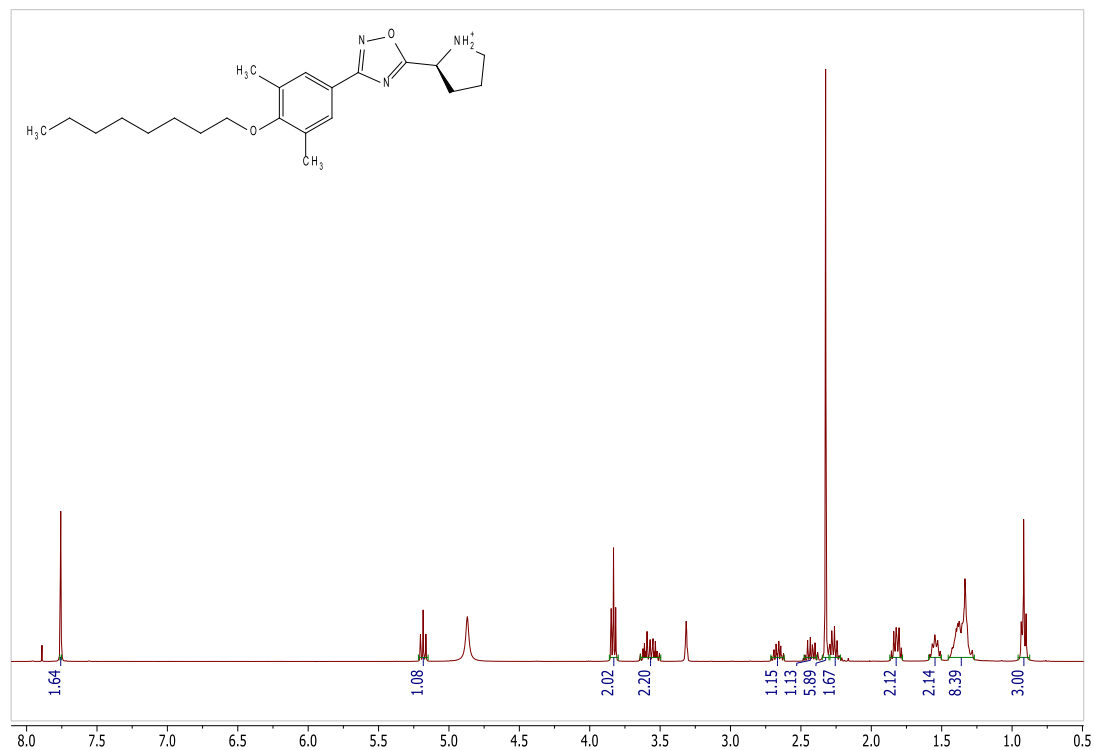


<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12e**—

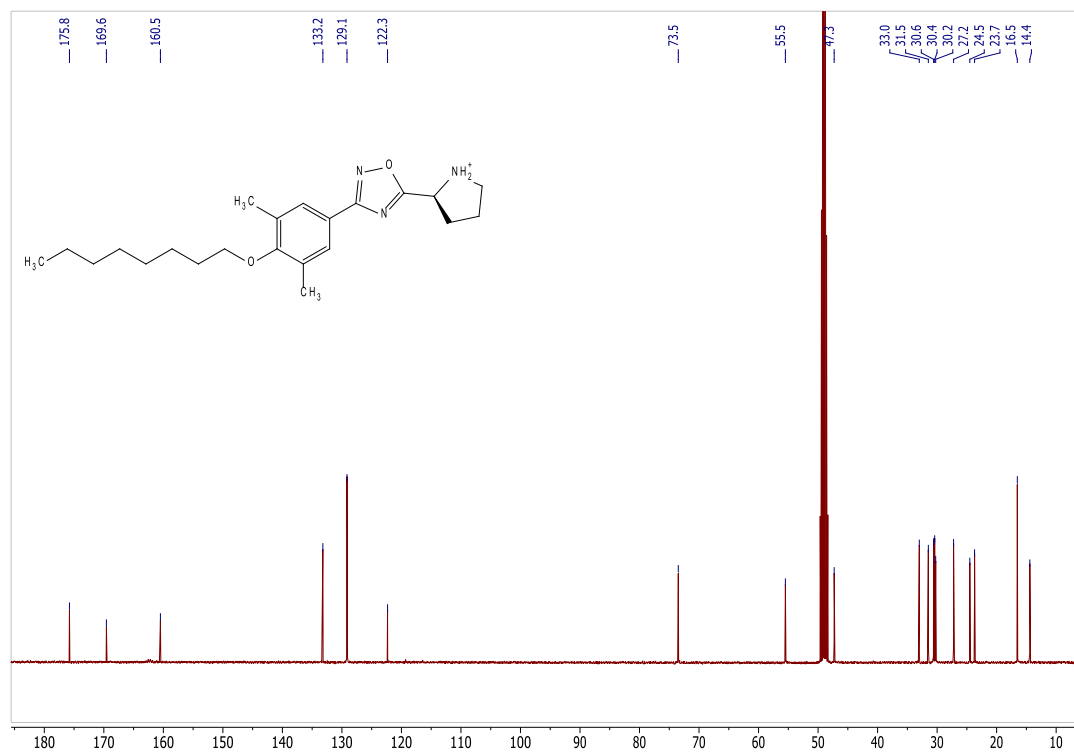




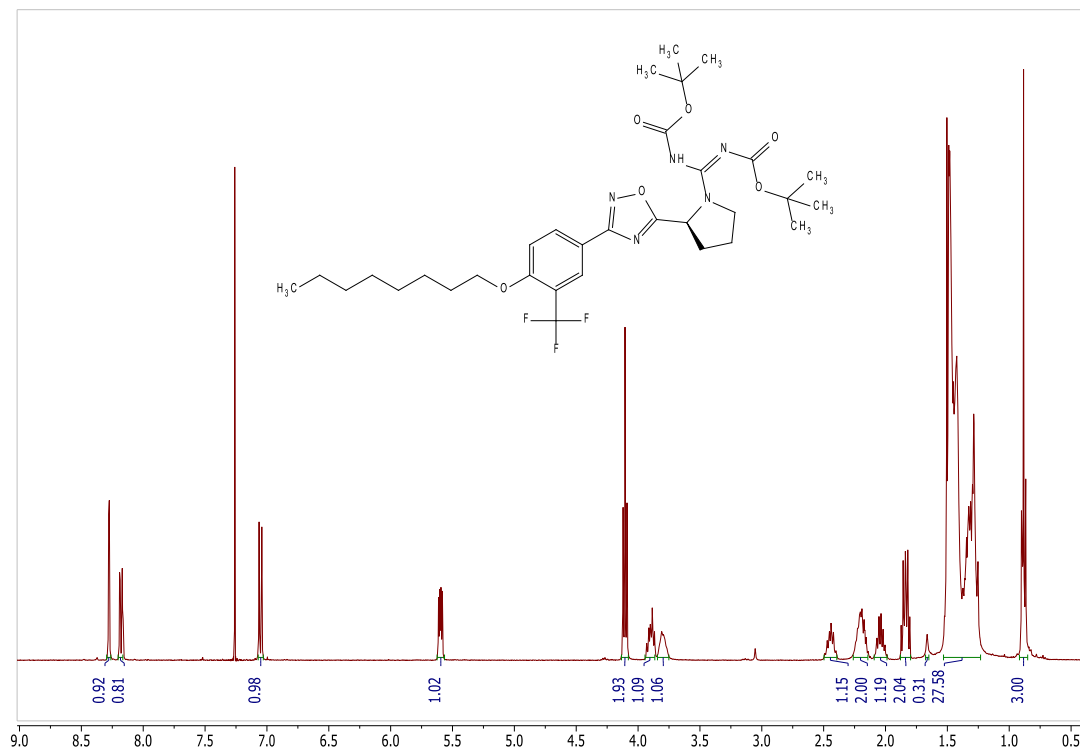
$^1\text{H-NMR}$  Spectrum for (*S*)-2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12f**–



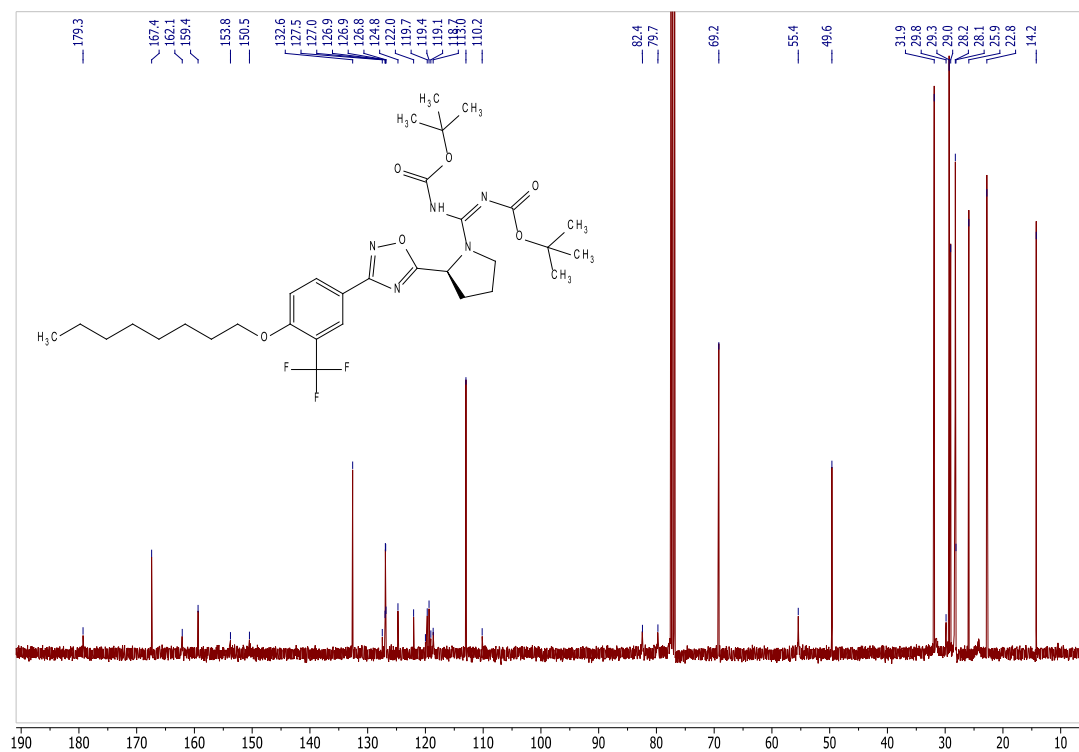
$^{13}\text{C-NMR}$  Spectrum for (*S*)-2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.12f**–



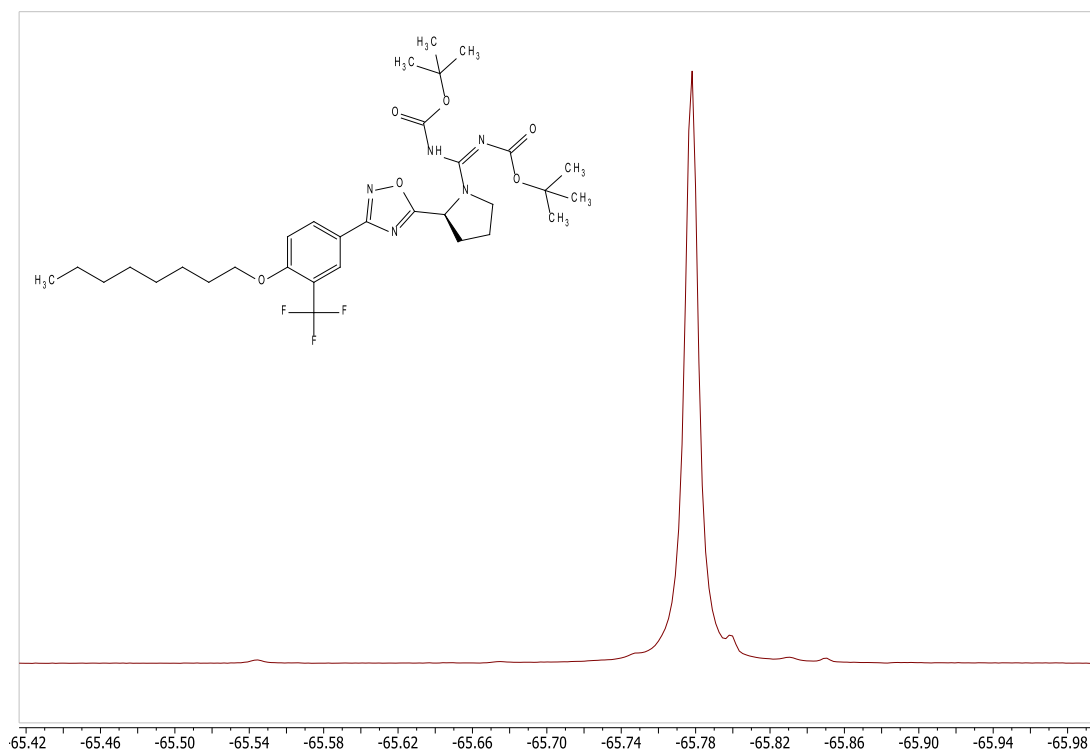
$^1\text{H-NMR}$  Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13a**—



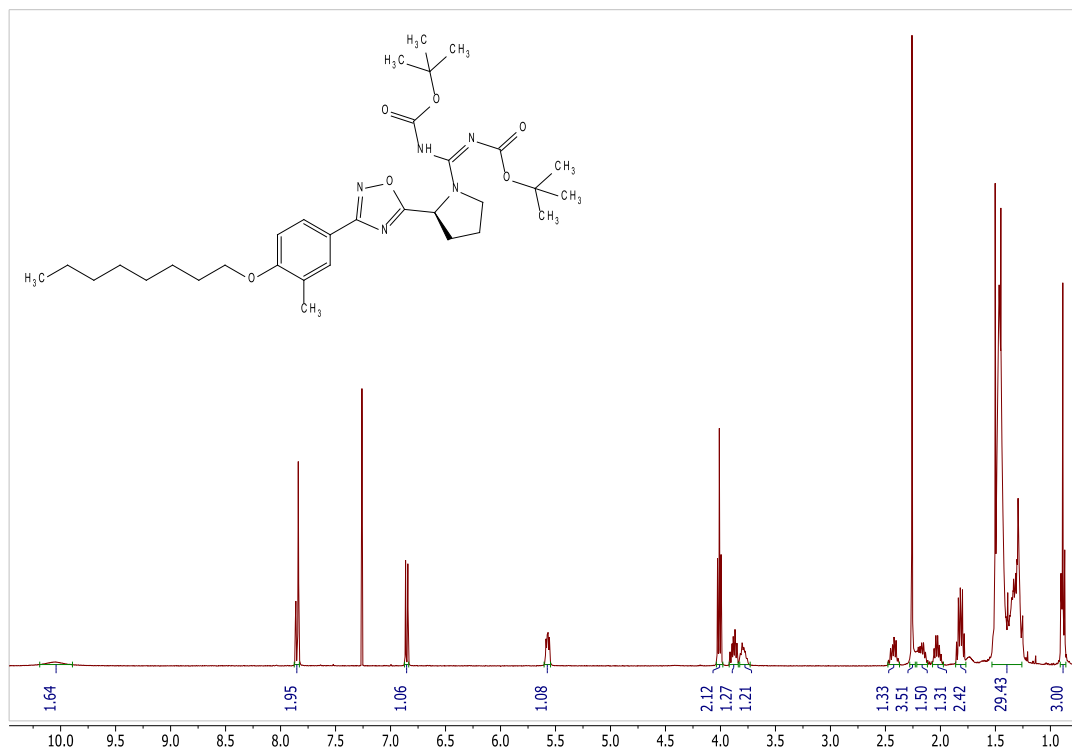
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13a**—



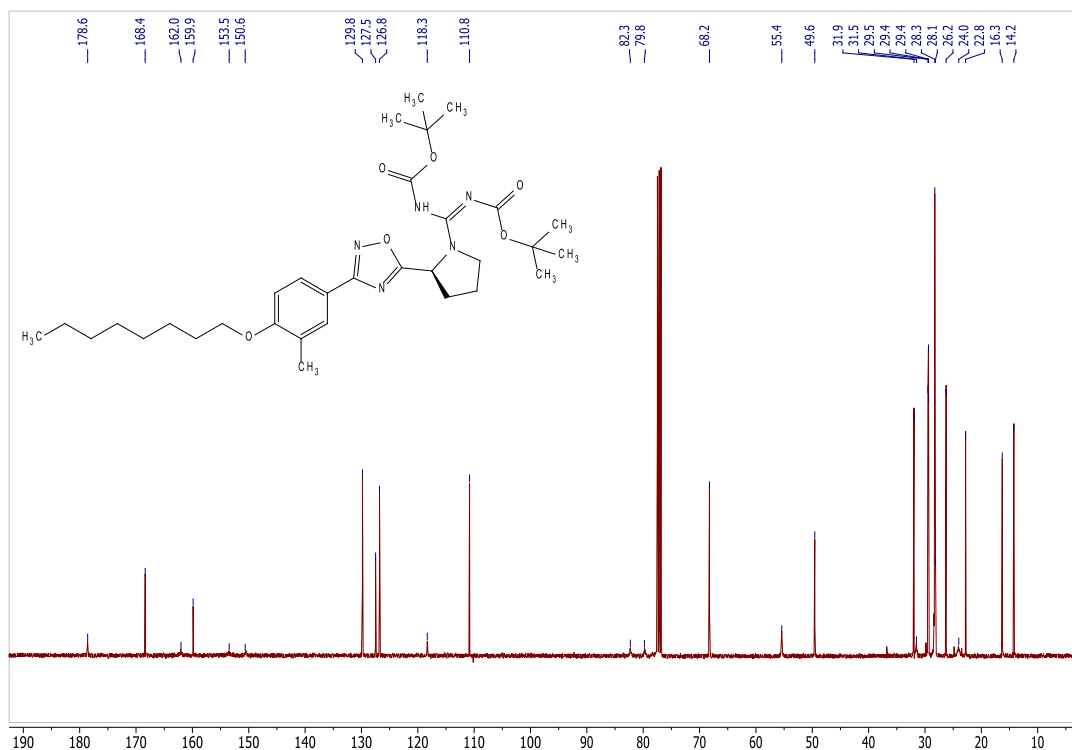
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13a**—



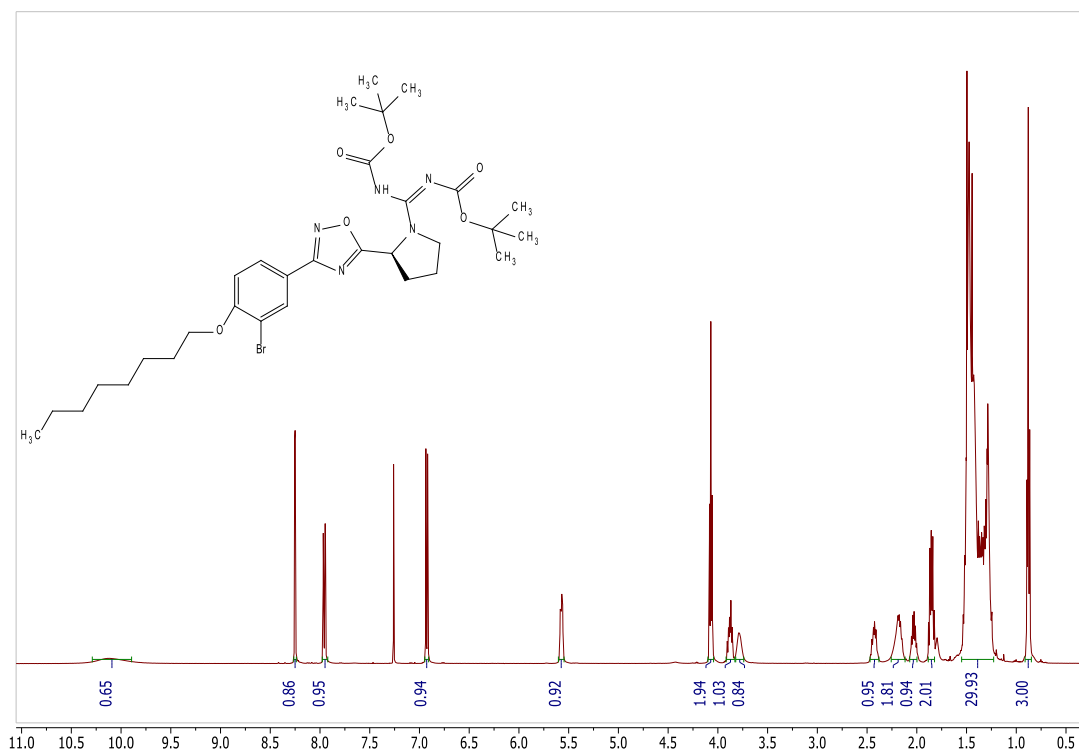
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13b**—



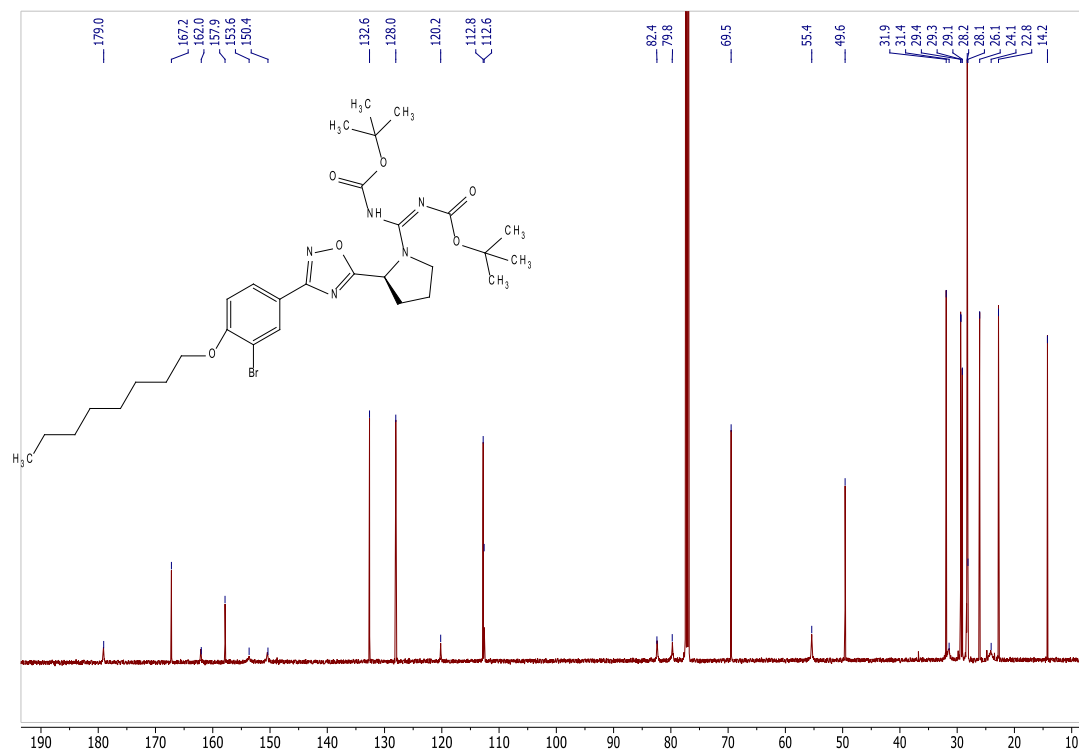
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13b**—



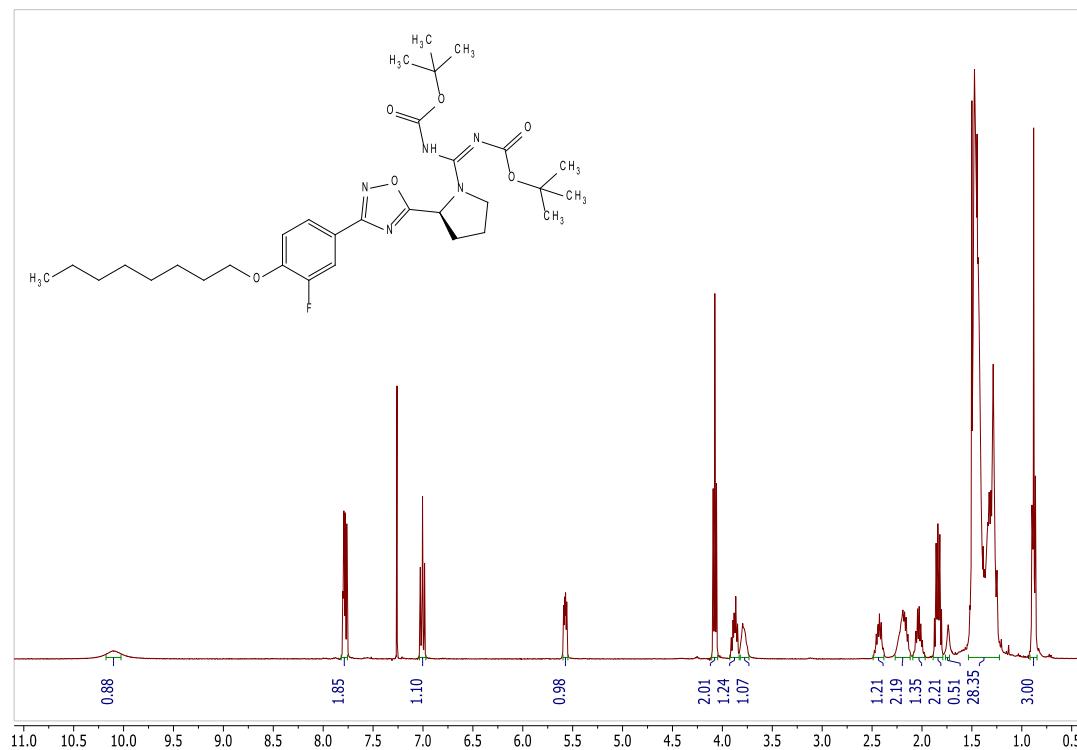
<sup>1</sup>H-NMR Spectrum for (*S*-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13c**–



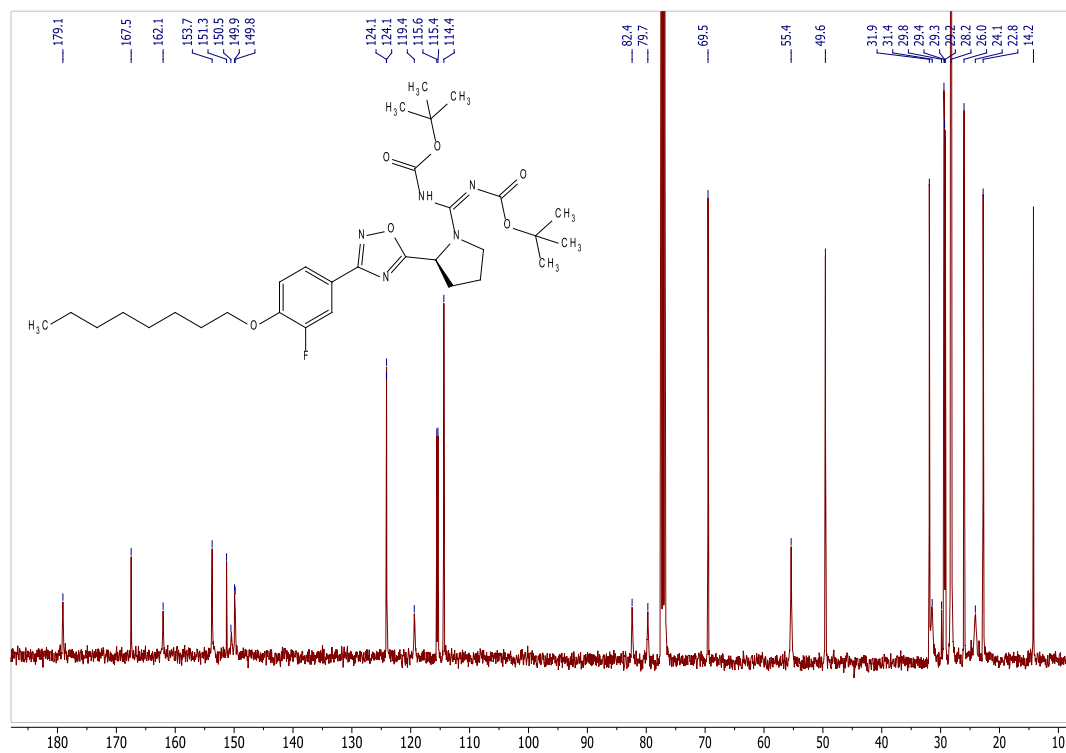
<sup>13</sup>C-NMR Spectrum for (*S*-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13c**–



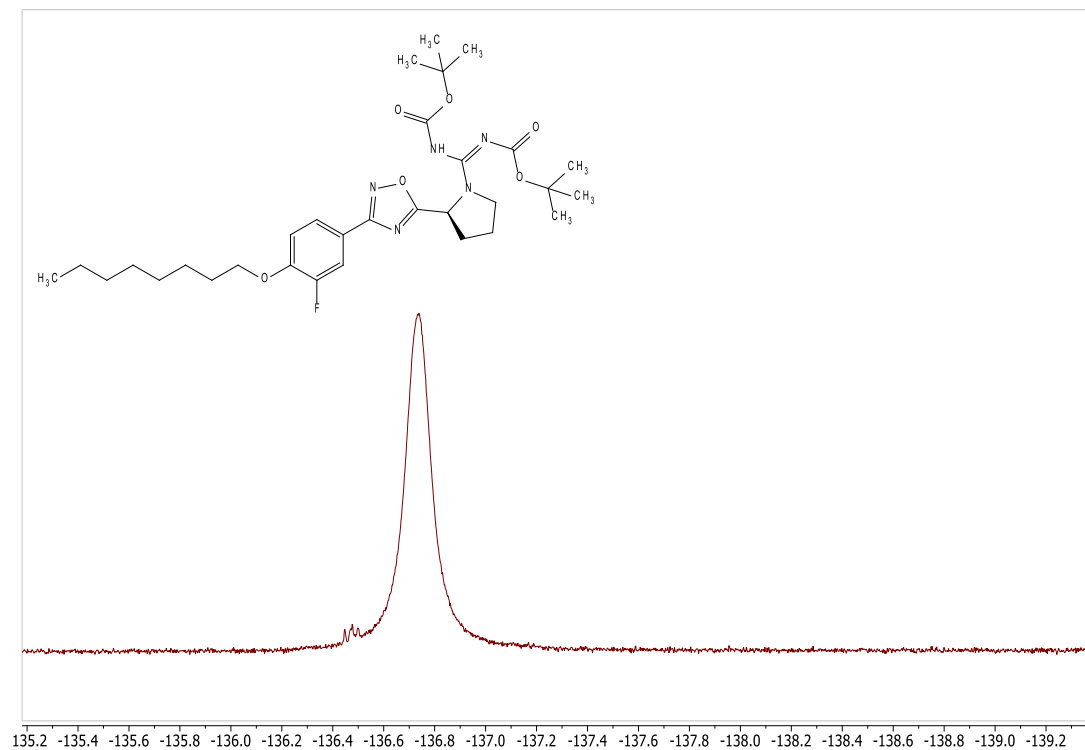
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13d**—



<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13d**—

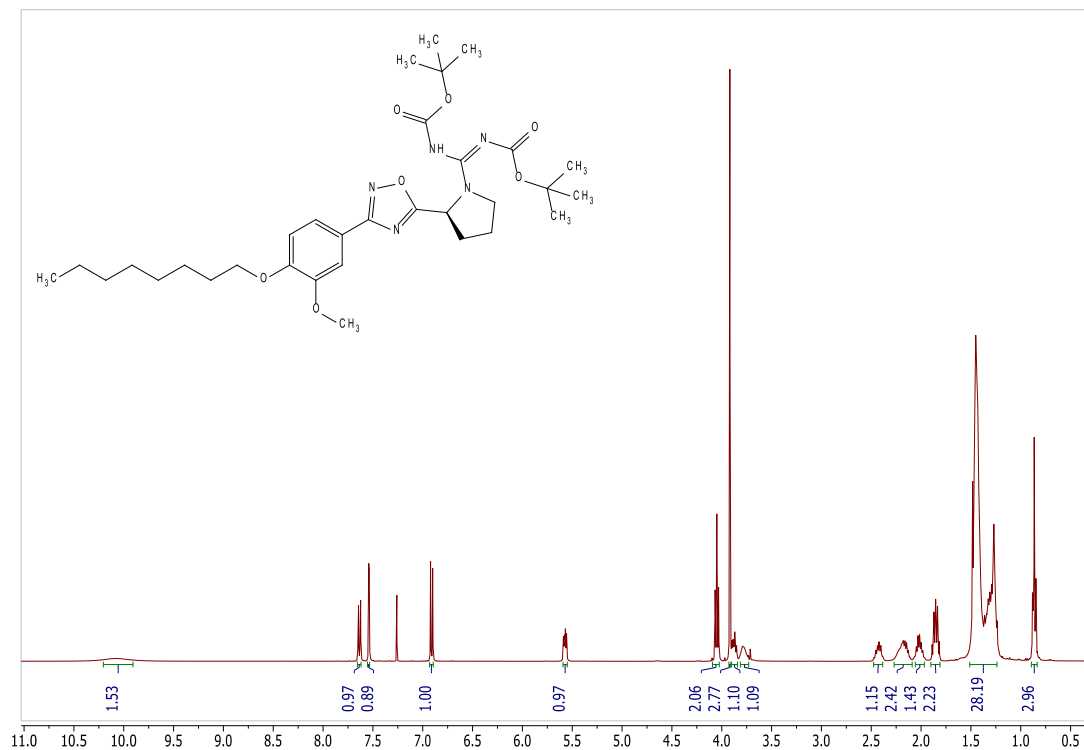


<sup>19</sup>F-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13d**

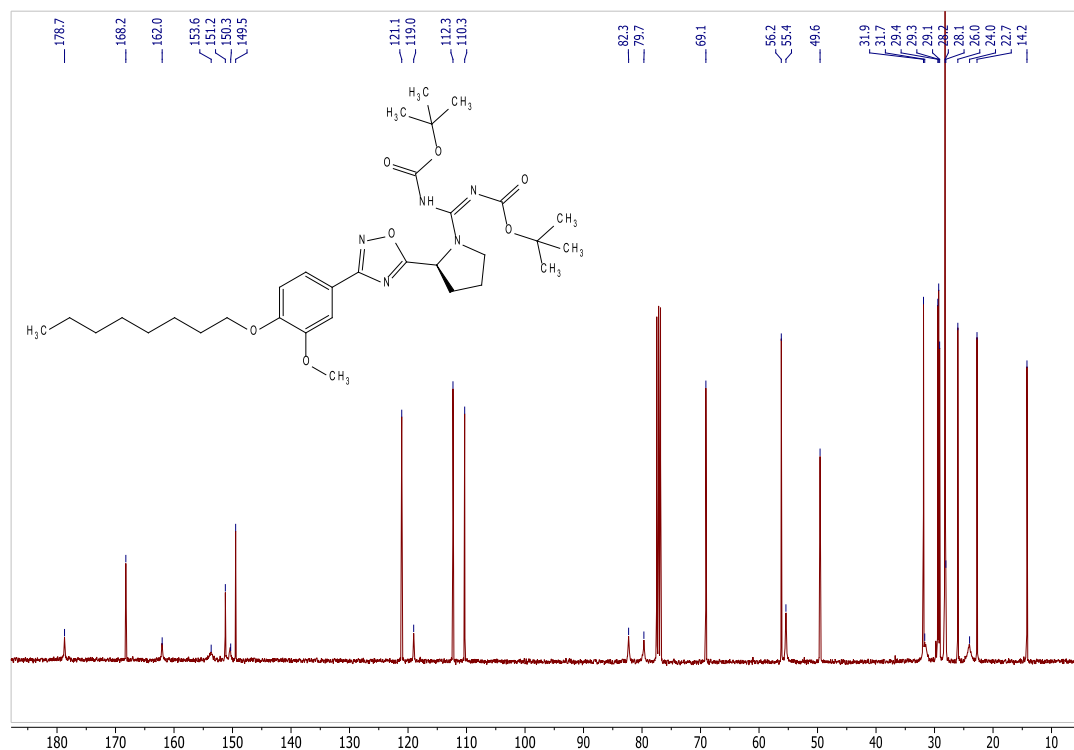




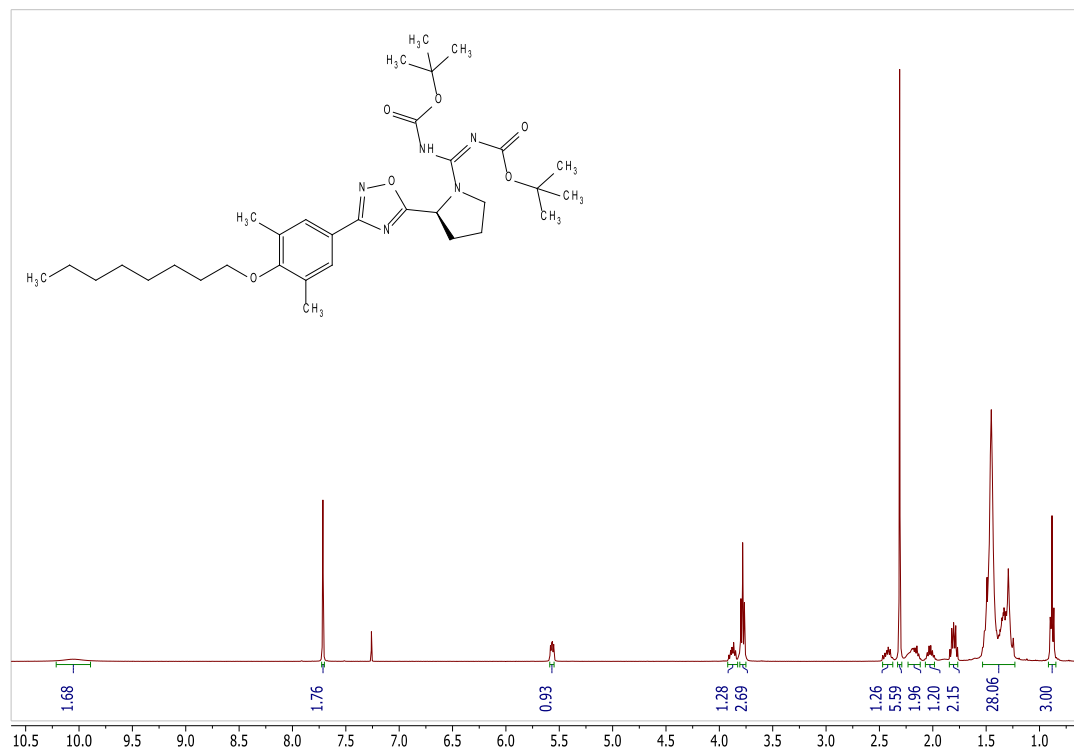
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13e**–



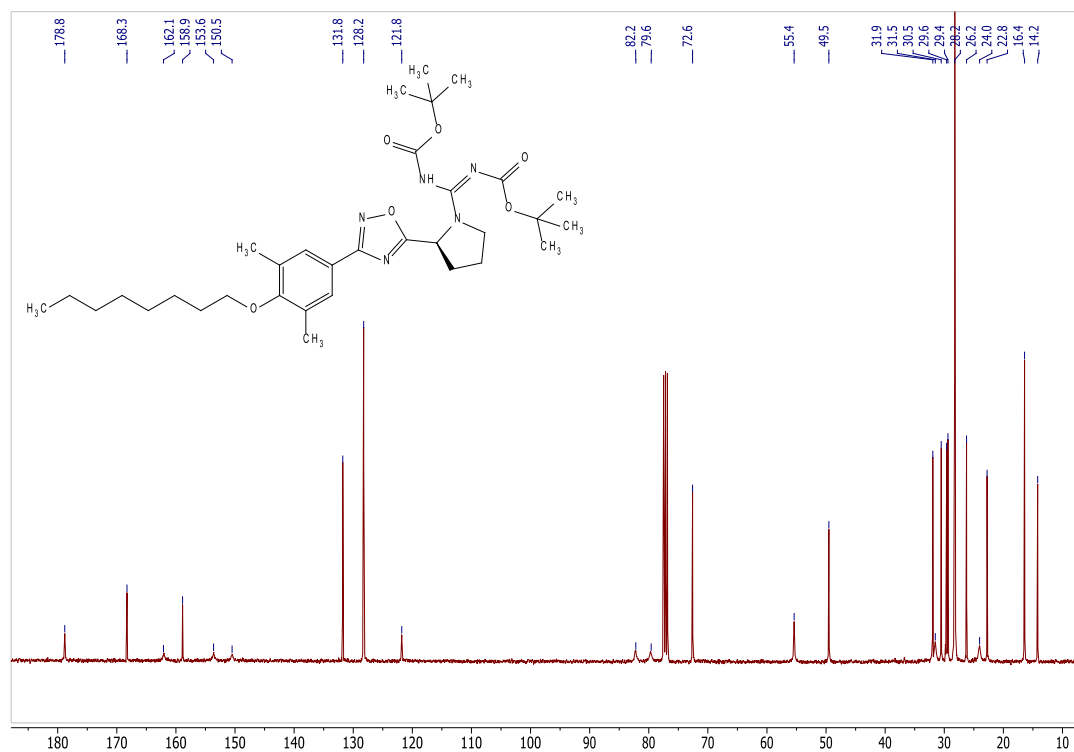
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13e**–



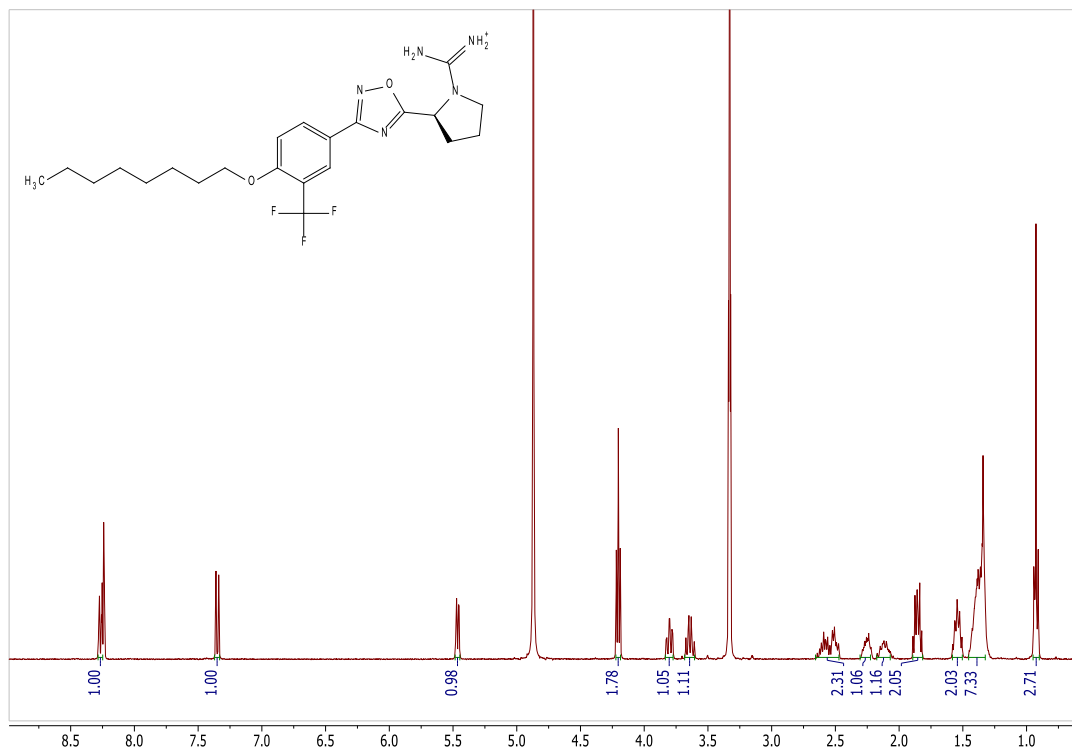
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13f**–



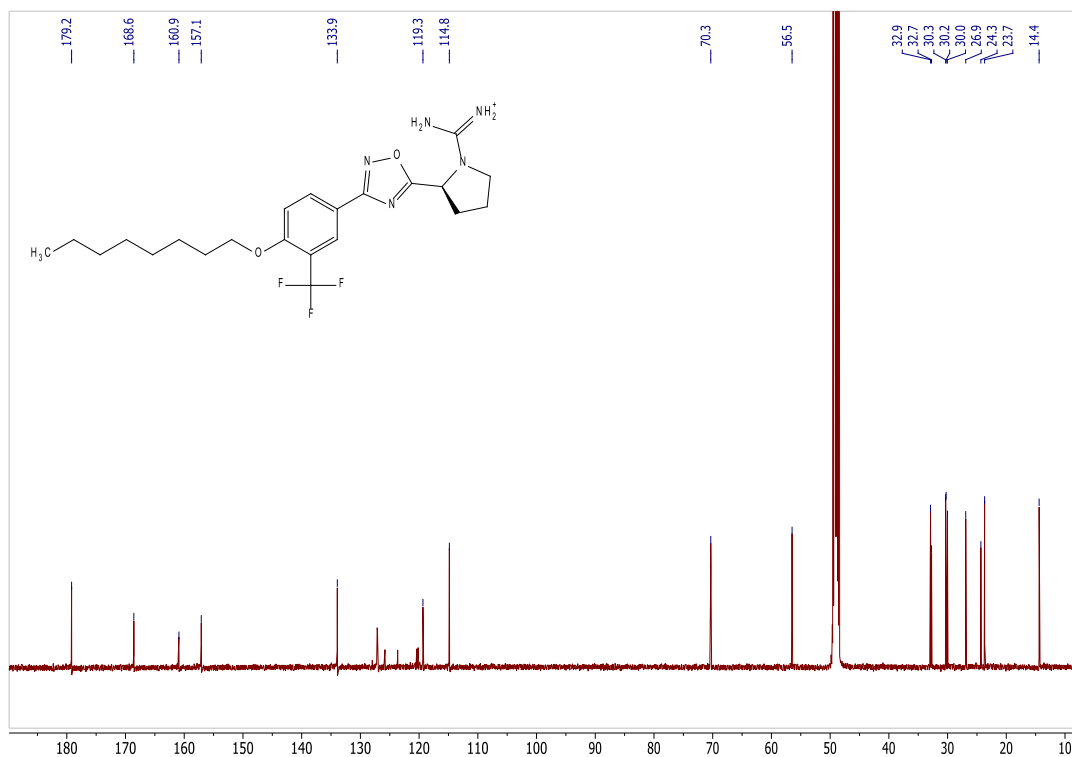
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.13f**–



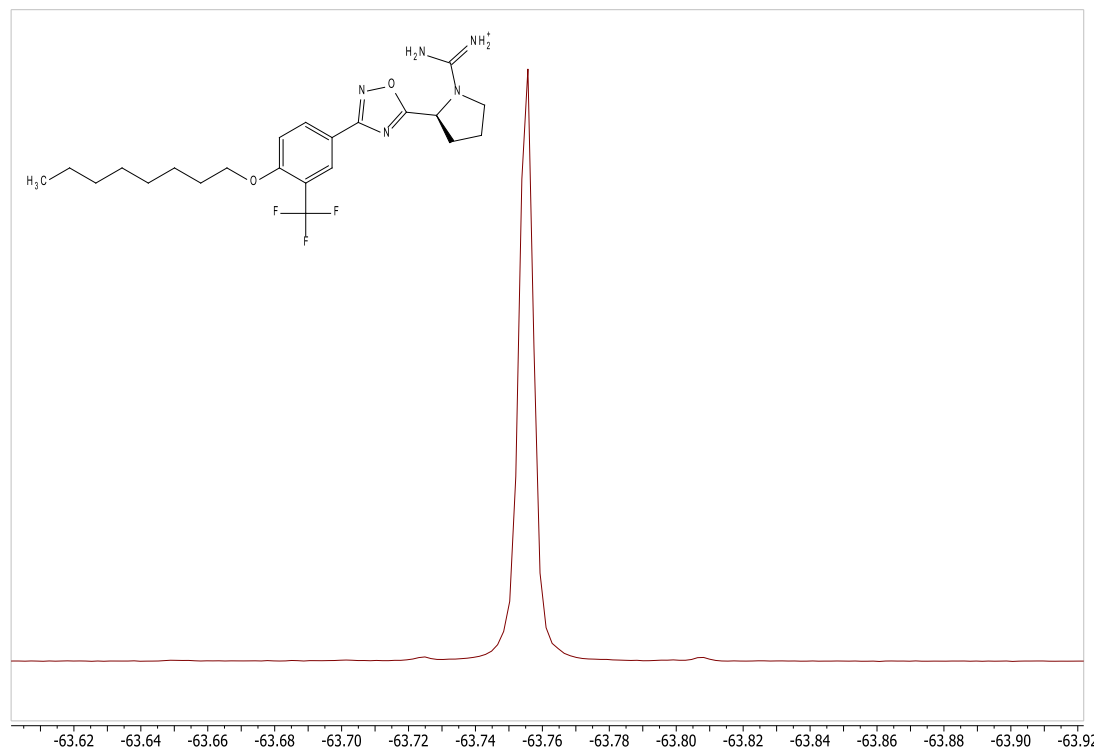
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14a**–



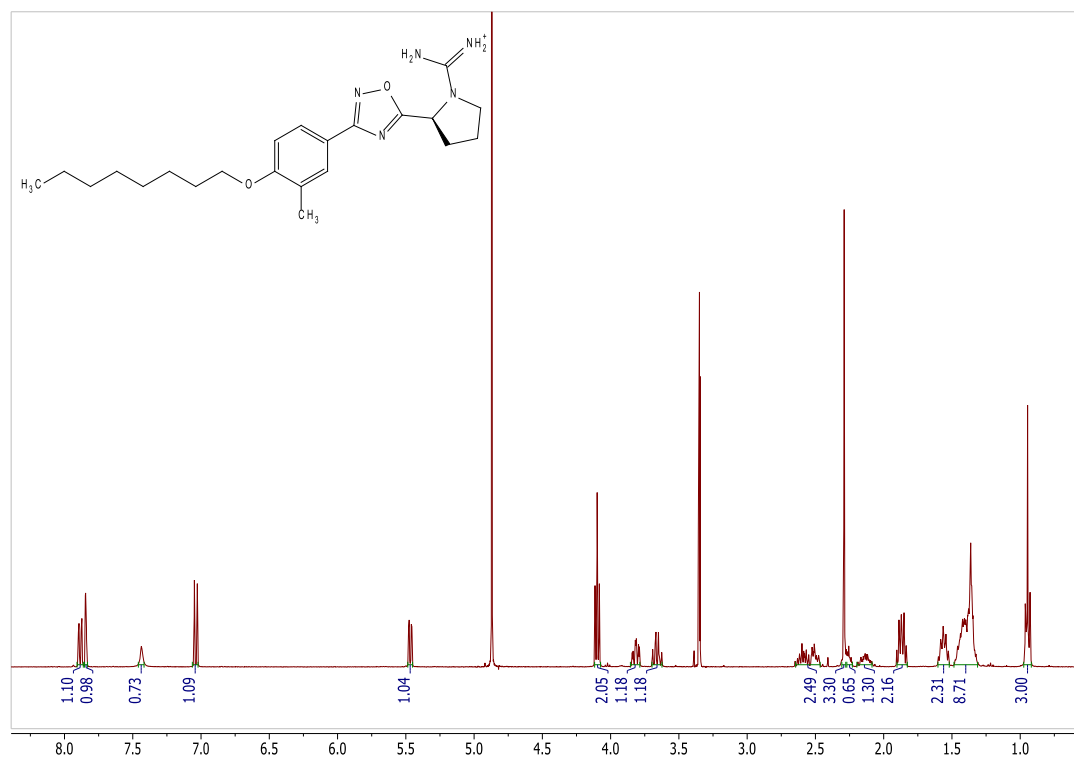
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14a**–



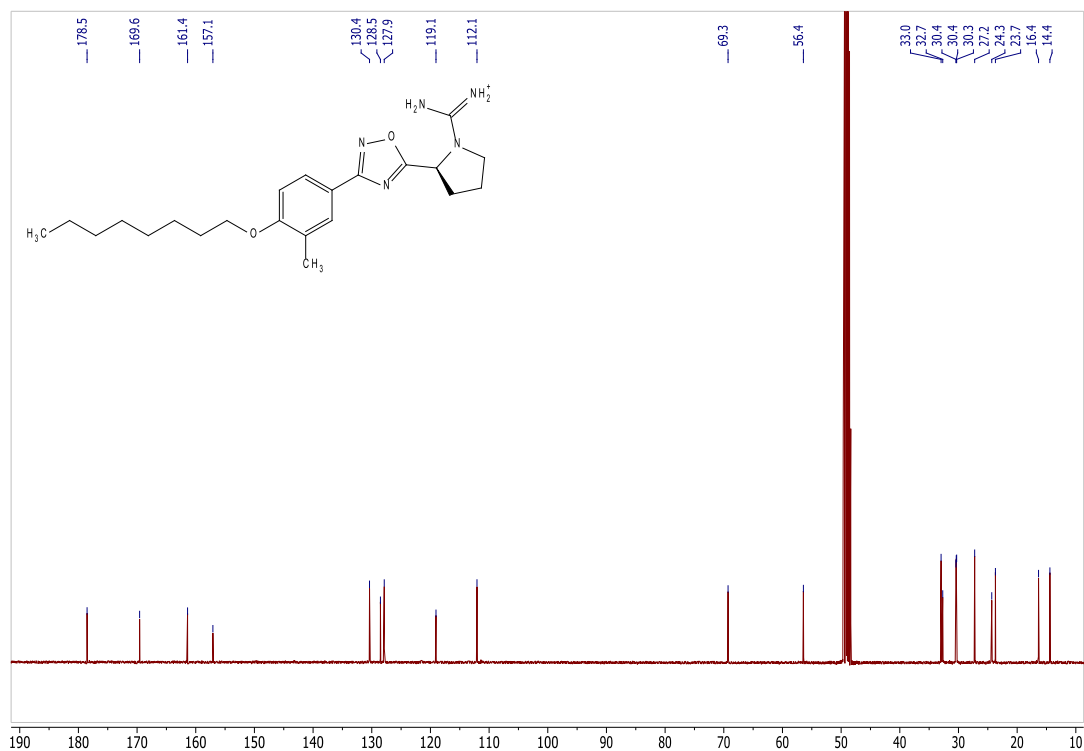
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14a**—



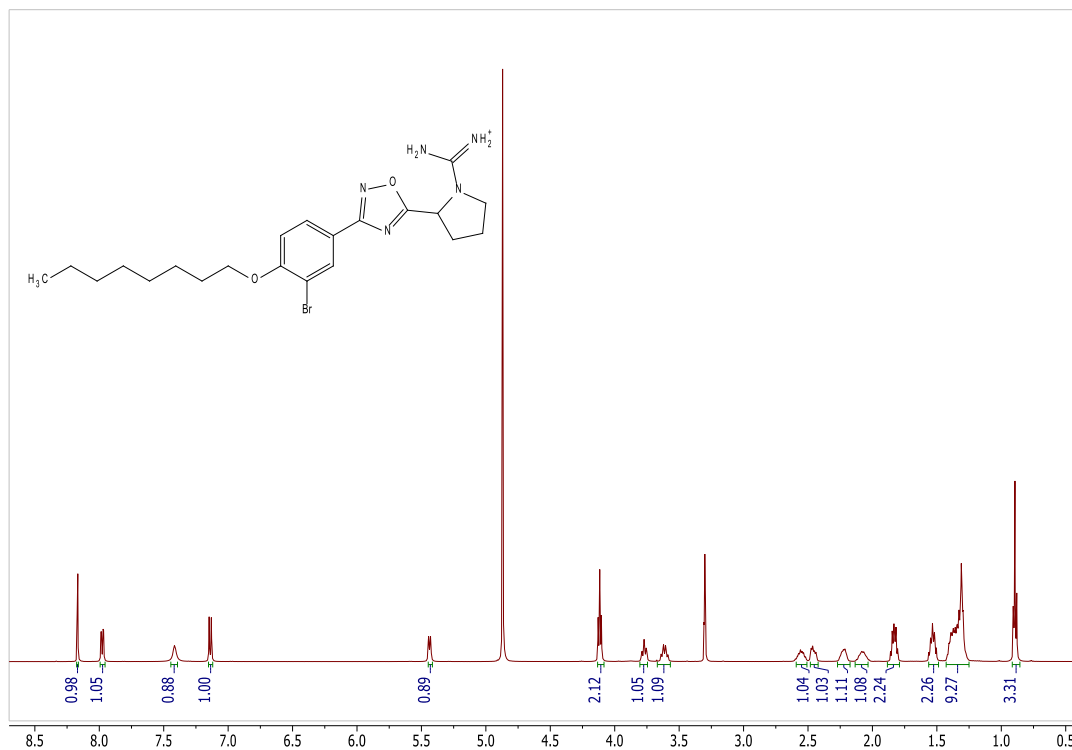
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14b**–



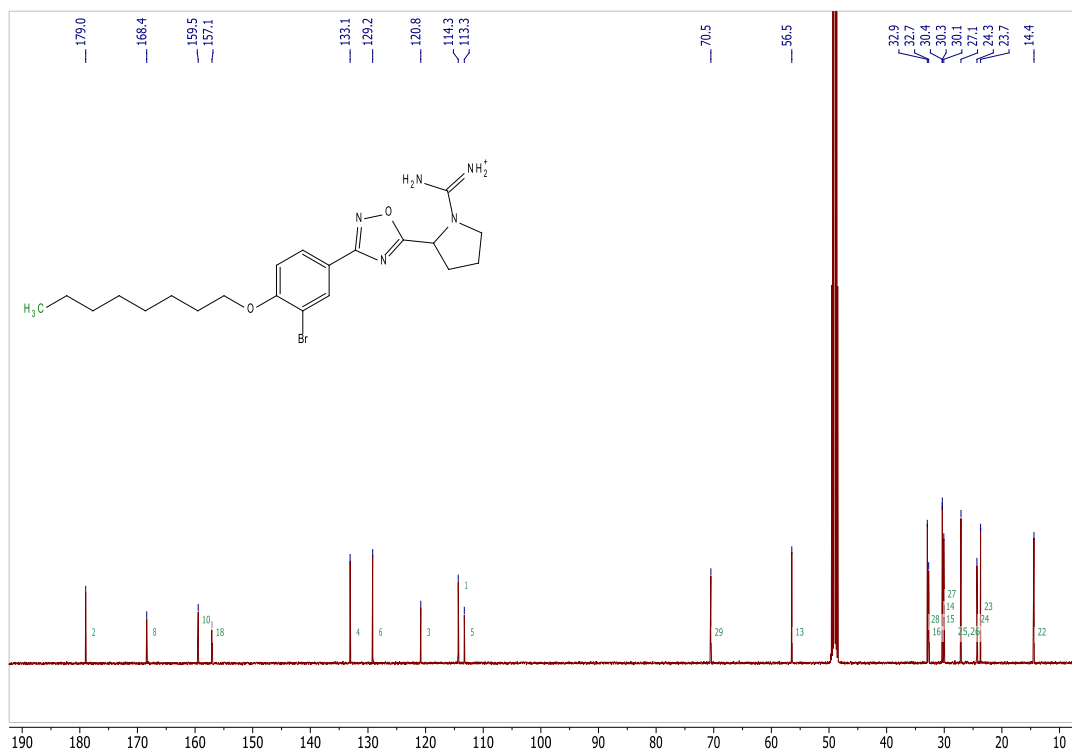
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(3-methyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14b**–



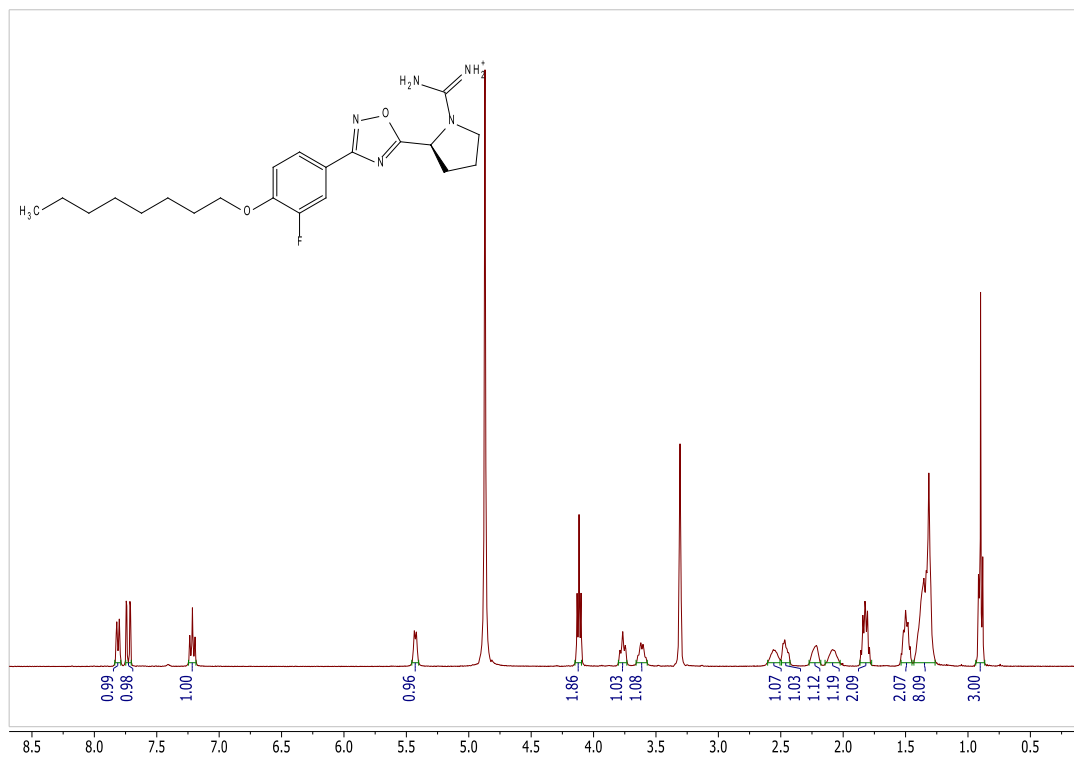
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14c**–



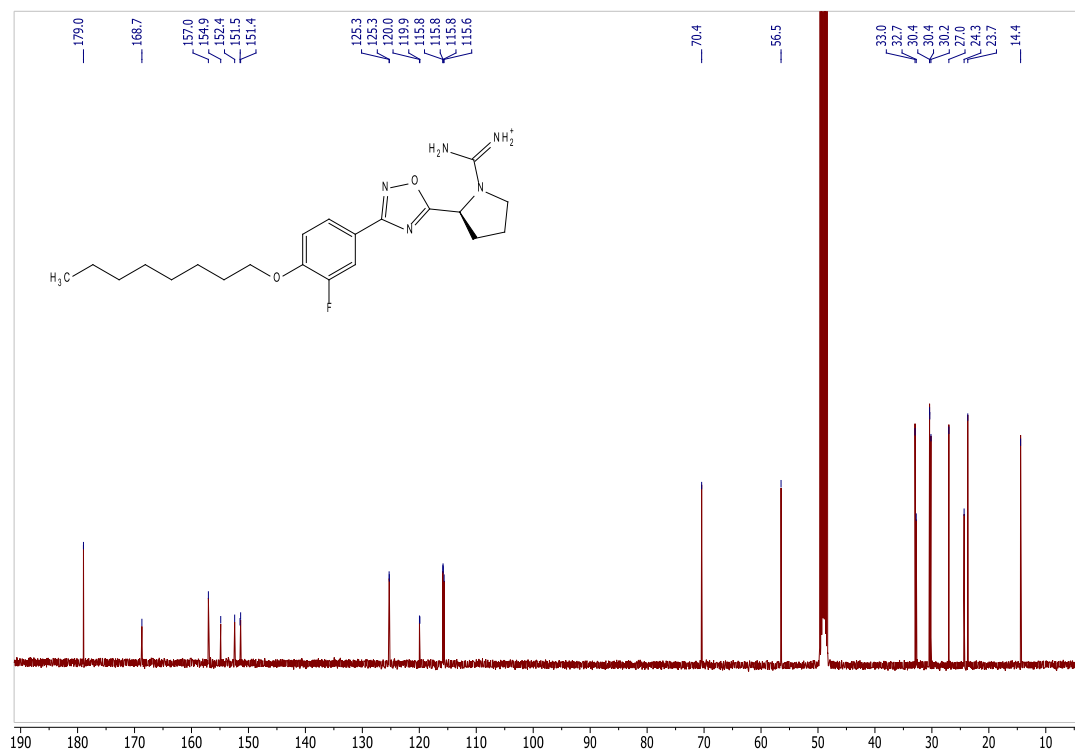
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(3-bromo-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14c**–



<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14d**–

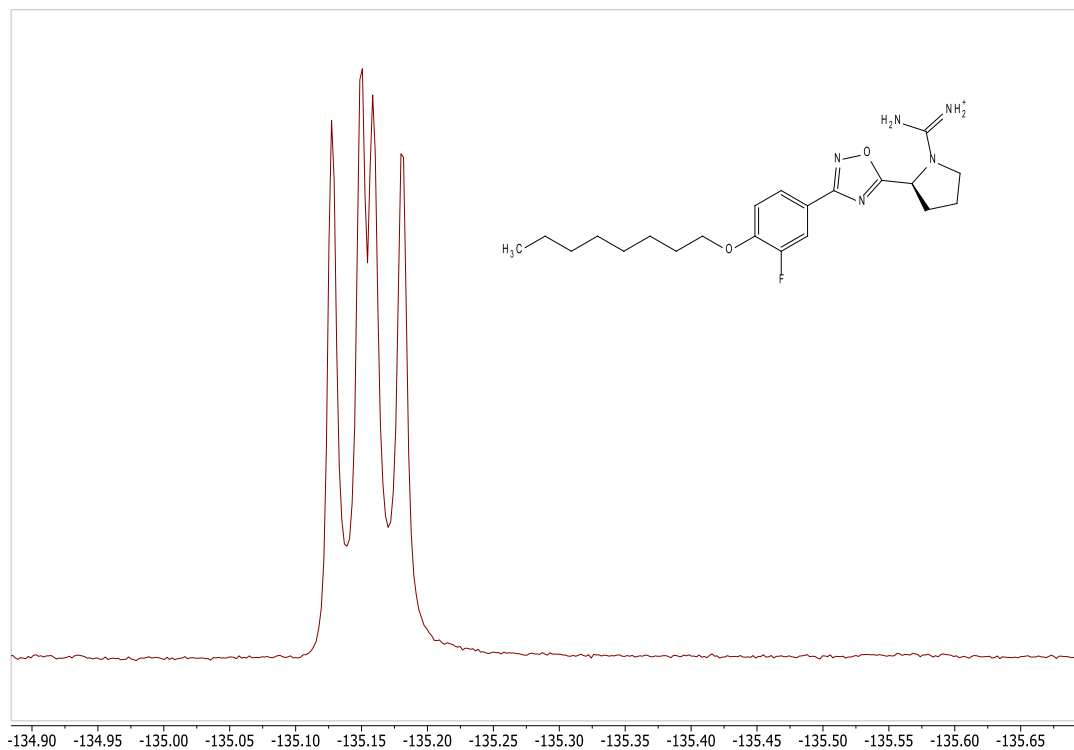


<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14d**–

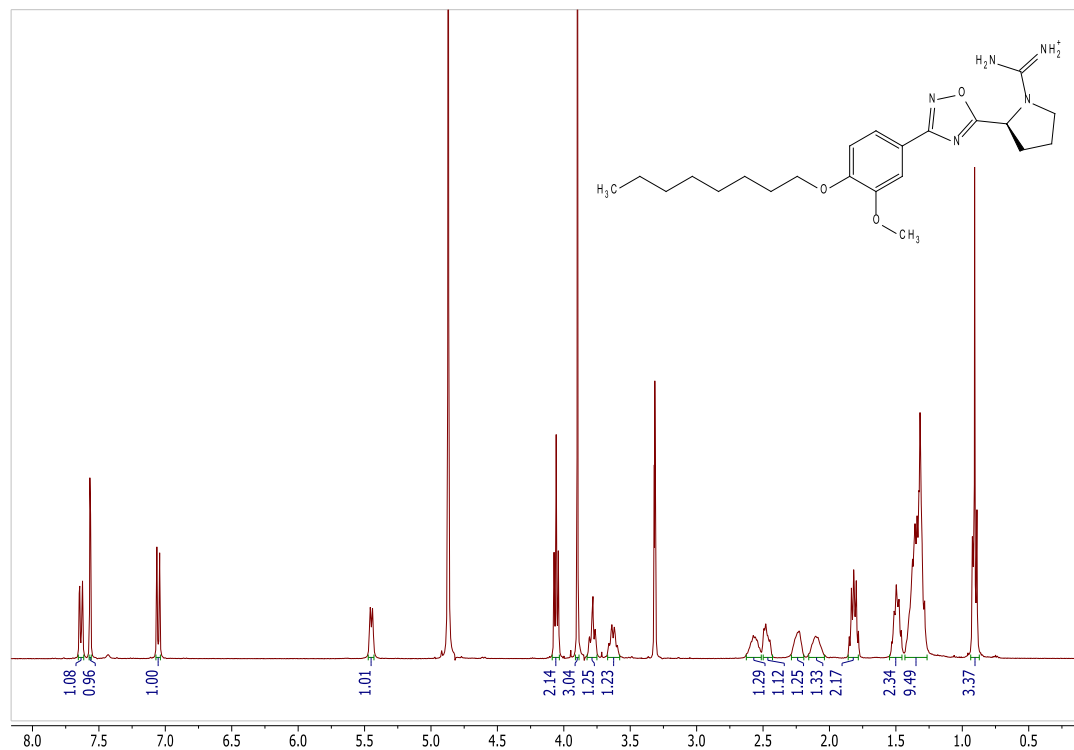




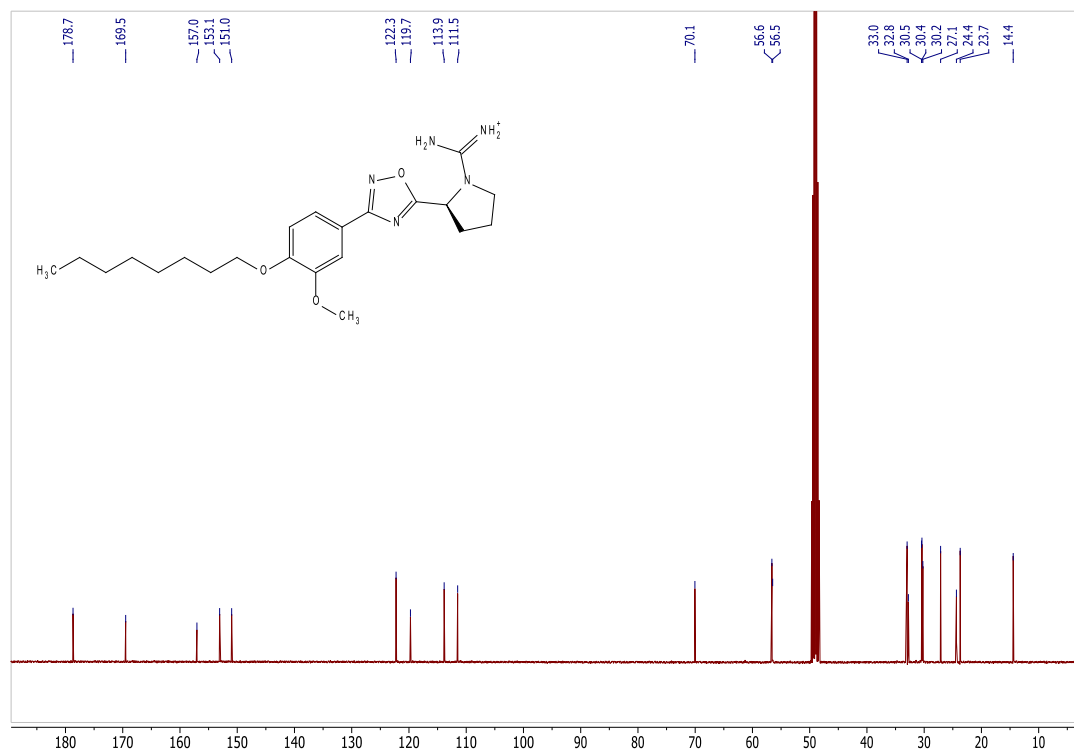
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(3-fluoro-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14d**–



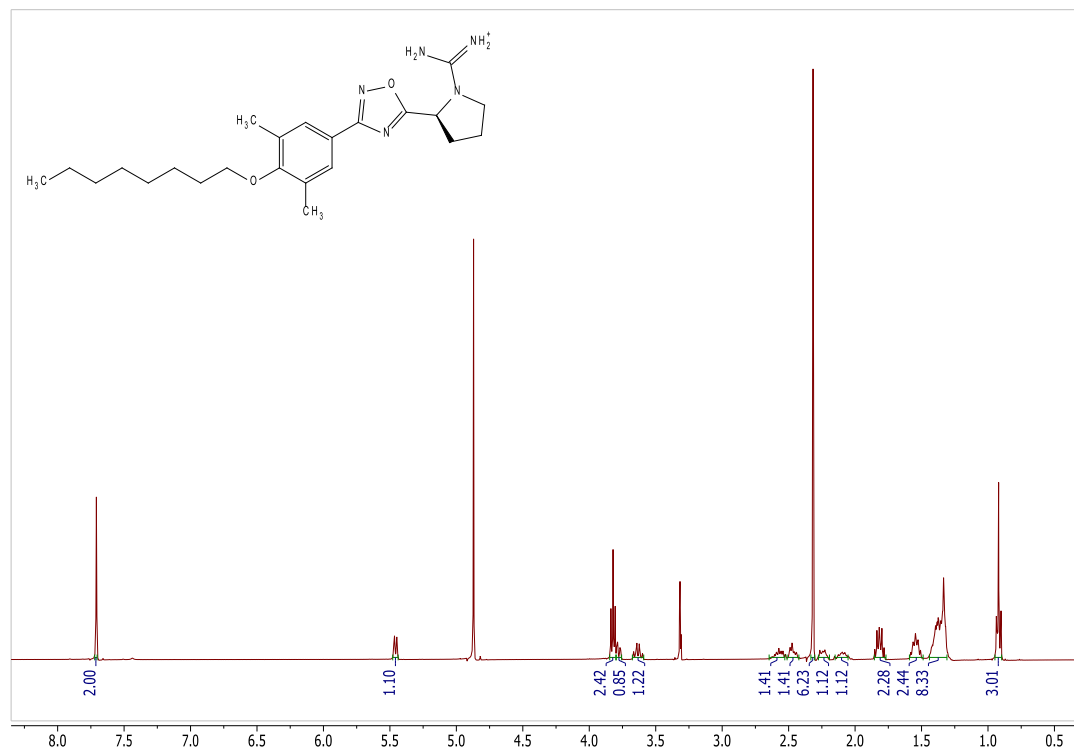
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14e**–



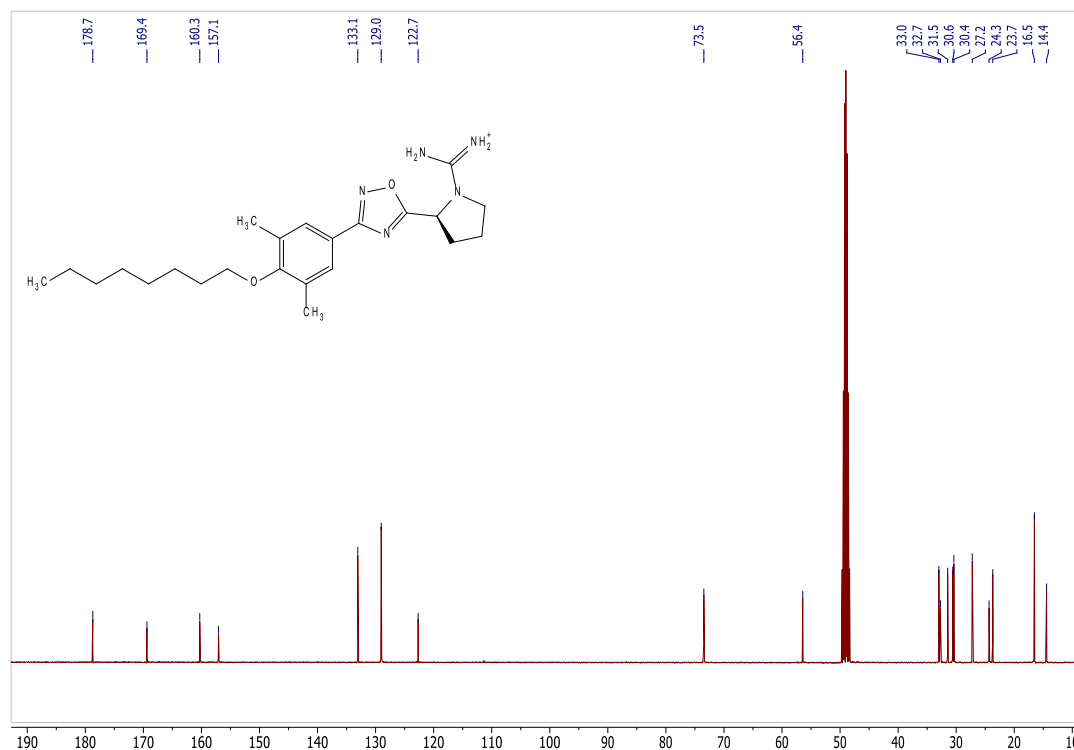
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(3-methoxy-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14e**–



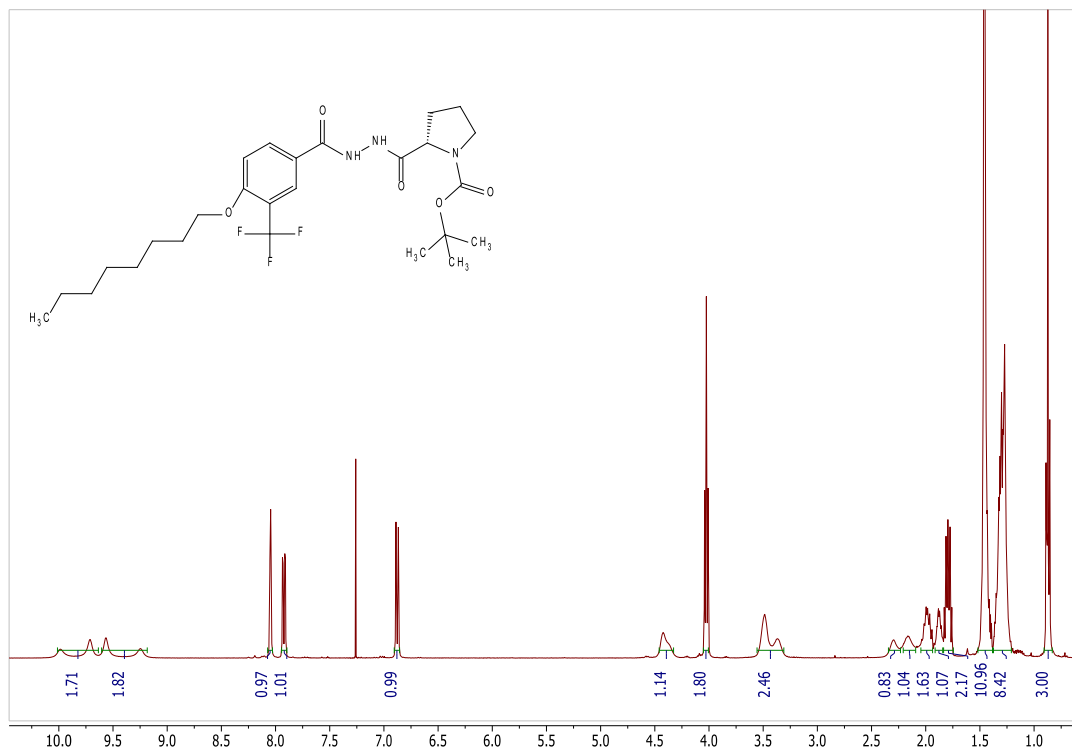
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14f**–



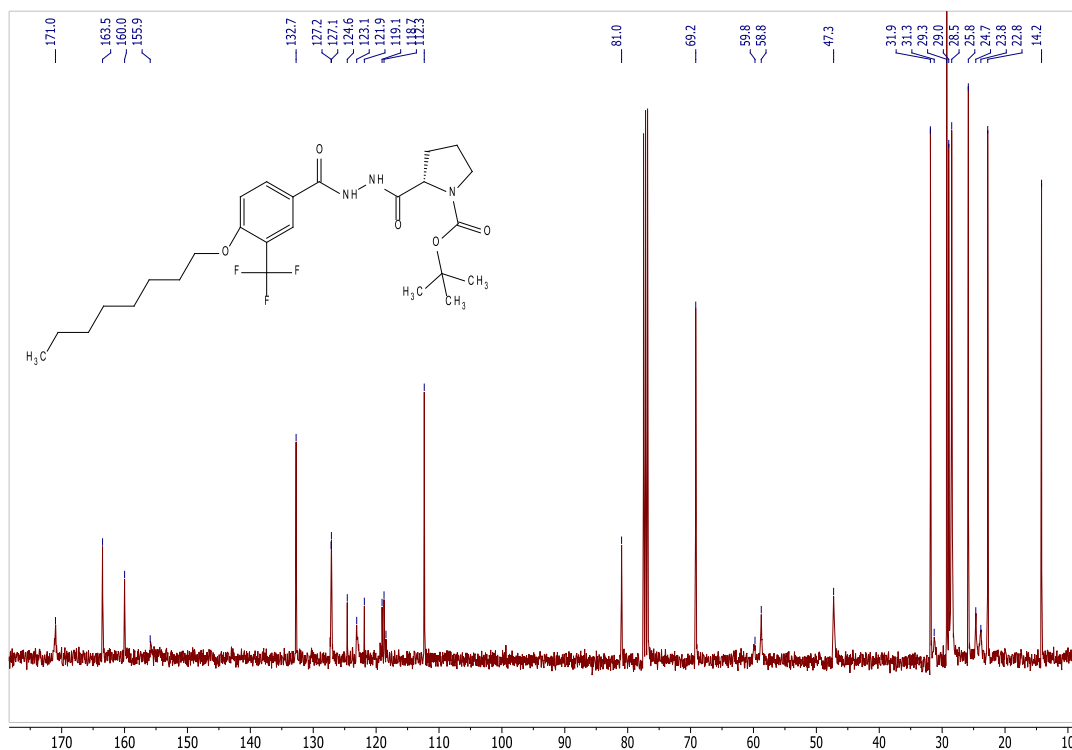
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(3,5-dimethyl-4-(octyloxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.14f**–



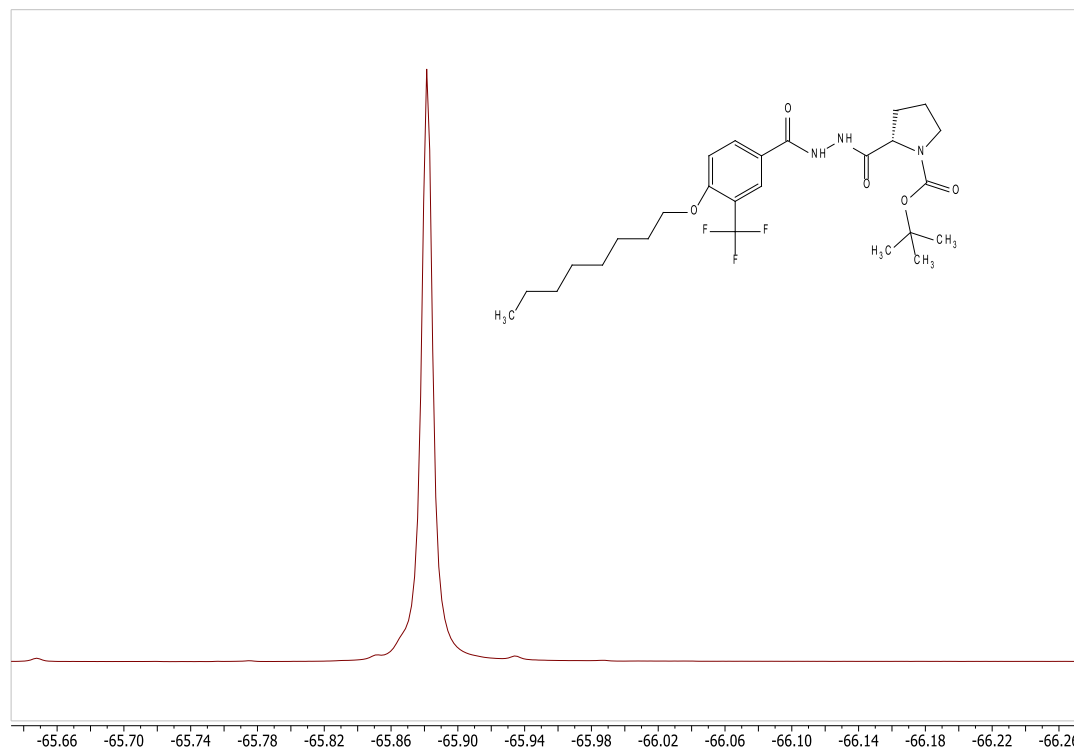
<sup>1</sup>H-NMR Spectrum for (S)-tert-butyl 2-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)pyrrolidine-1-carboxylate **3.16**–



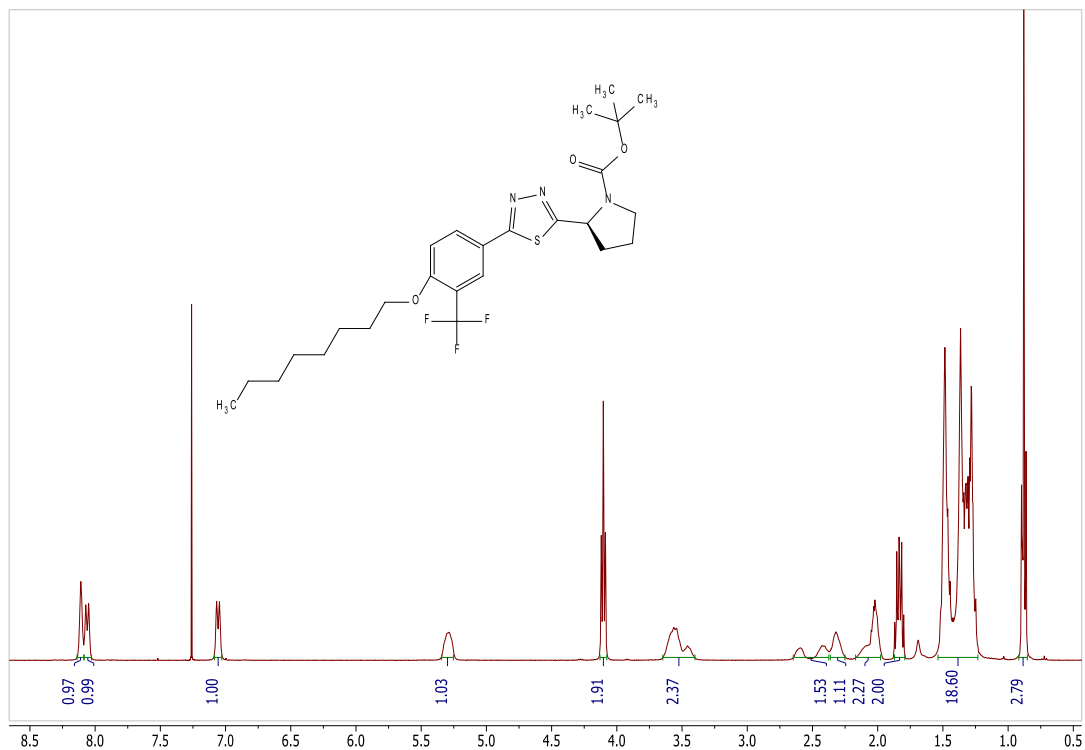
<sup>13</sup>C-NMR Spectrum for (S)-tert-butyl 2-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)pyrrolidine-1-carboxylate **3.16**–



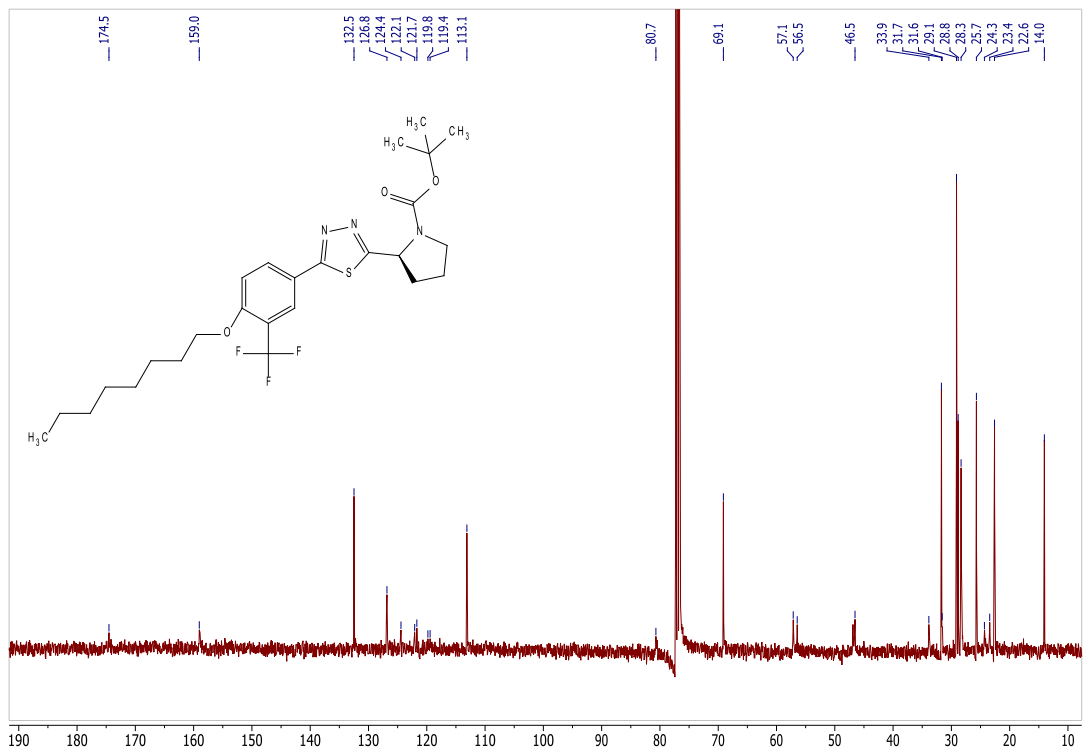
<sup>19</sup>F-NMR Spectrum for (S)-tert-butyl 2-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)pyrrolidine-1-carboxylate **3.16**



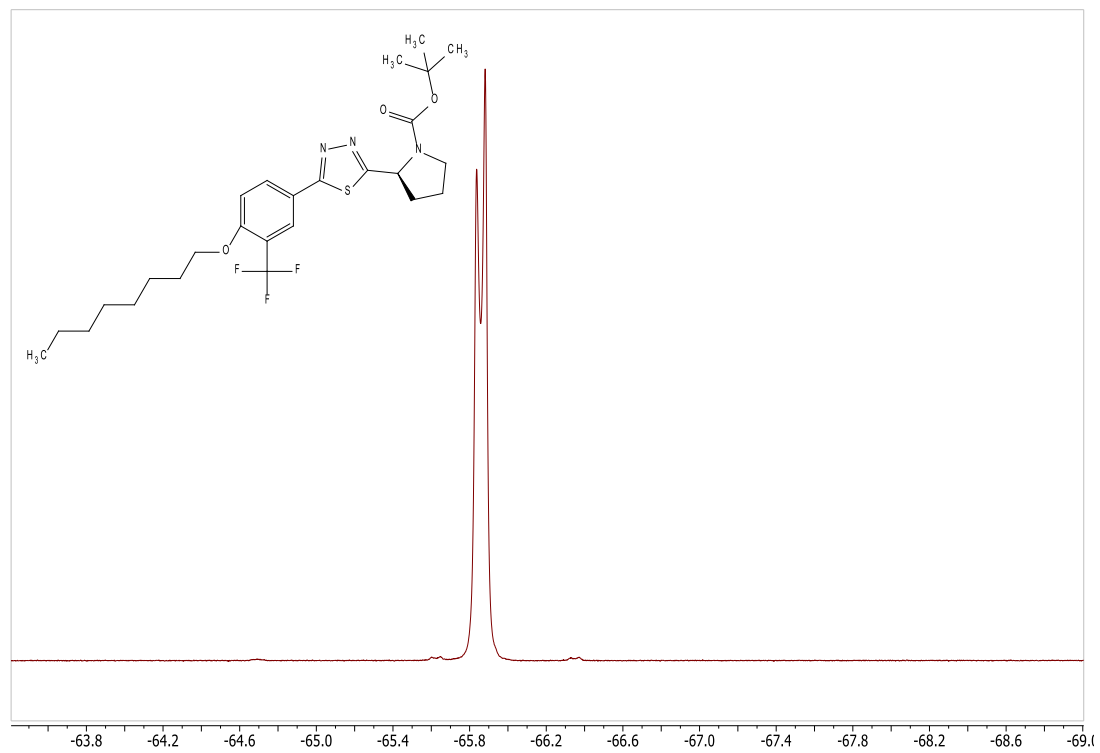
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidine-1-carboxylate **3.17**–



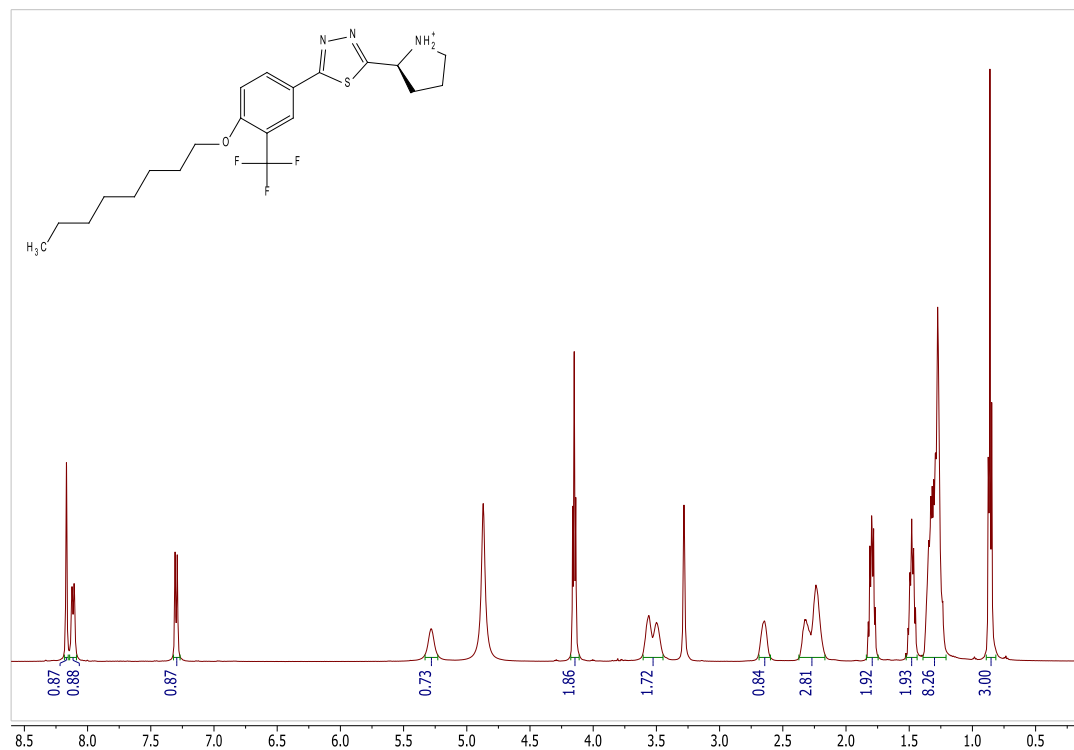
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidine-1-carboxylate **3.17**–



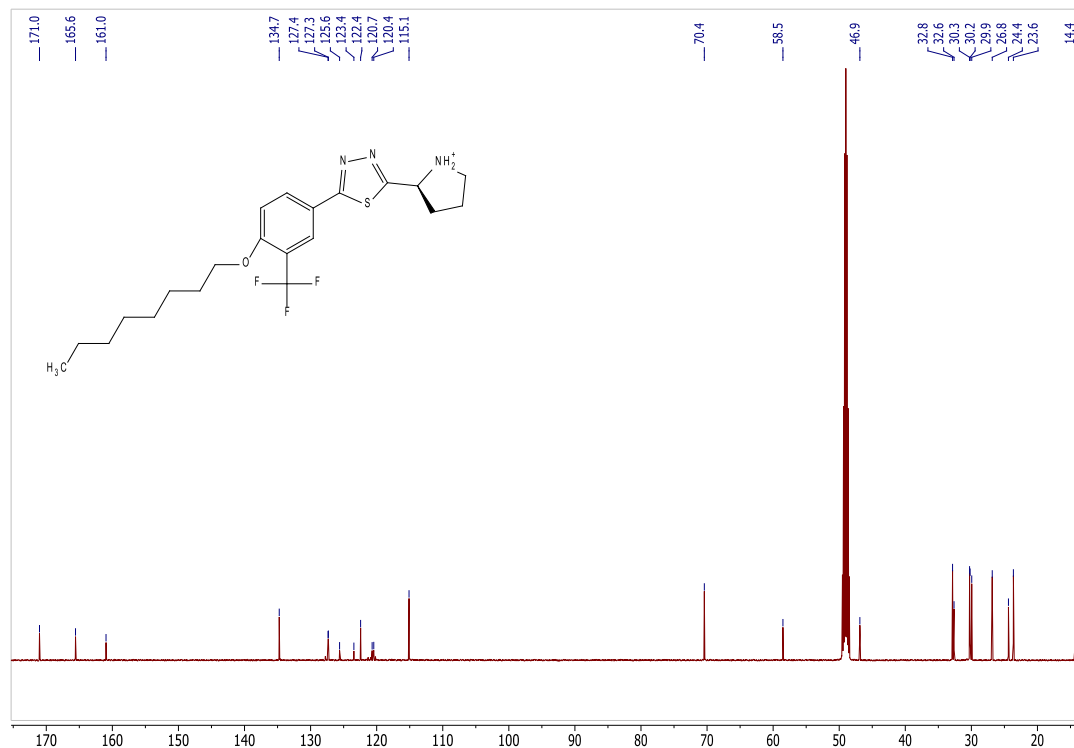
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidine-1-carboxylate **3.17**–



<sup>1</sup>H-NMR Spectrum for (S)-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –

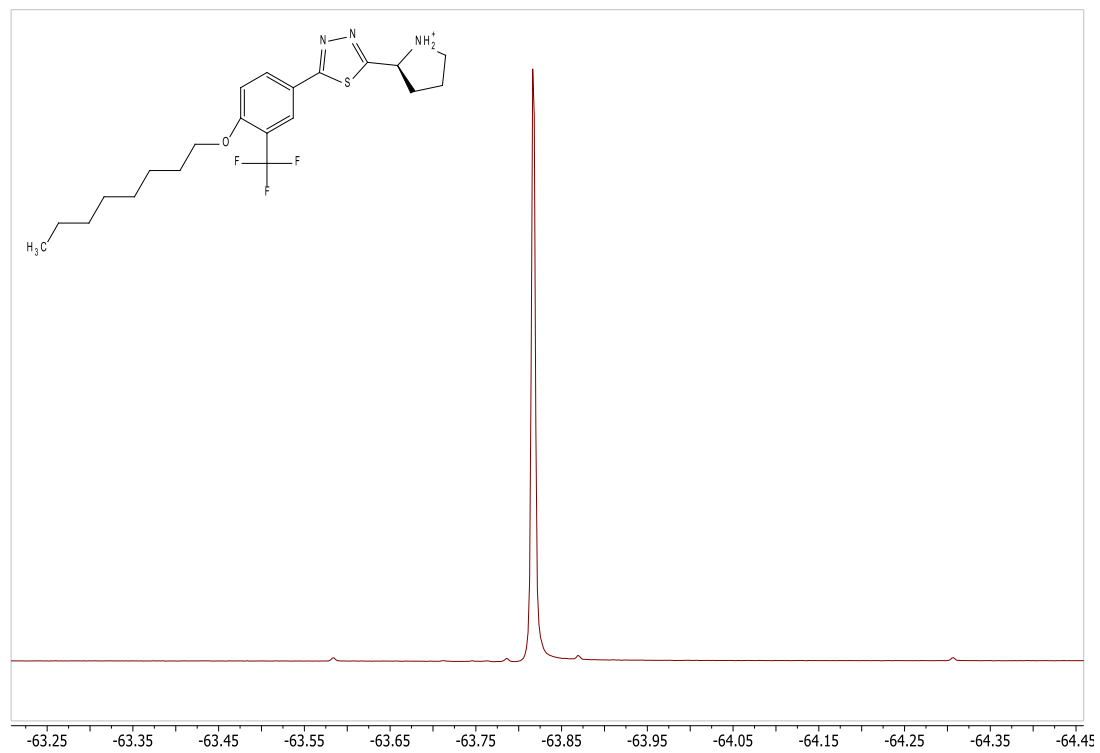


<sup>13</sup>C-NMR Spectrum for (S)-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –

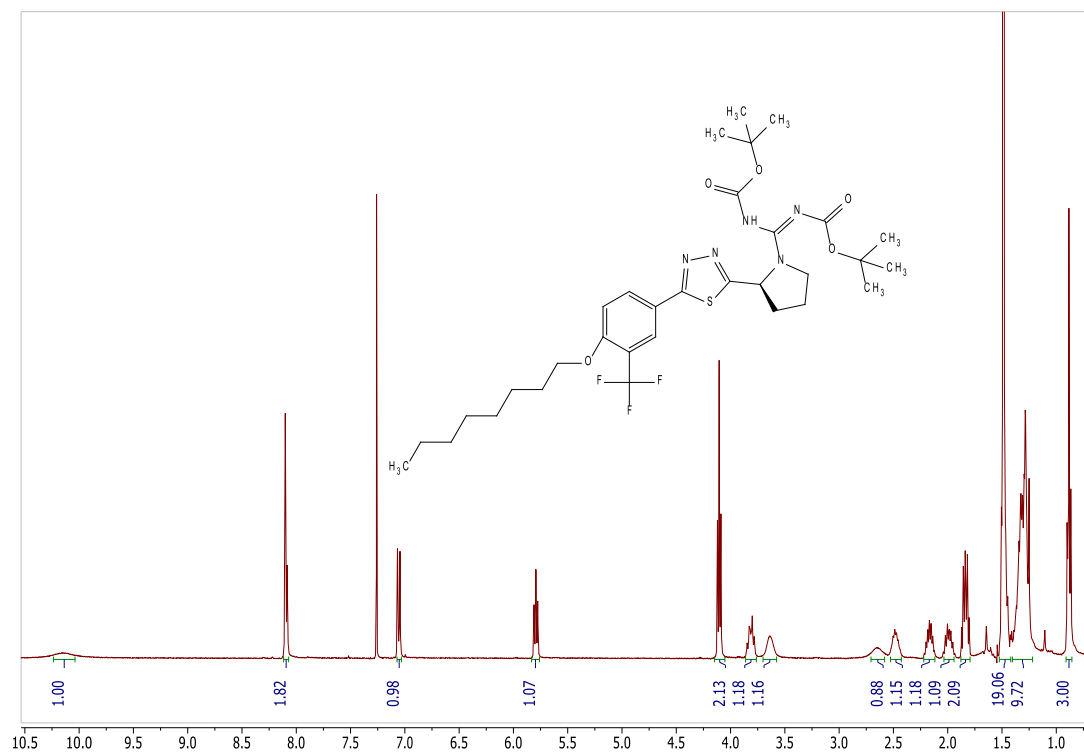




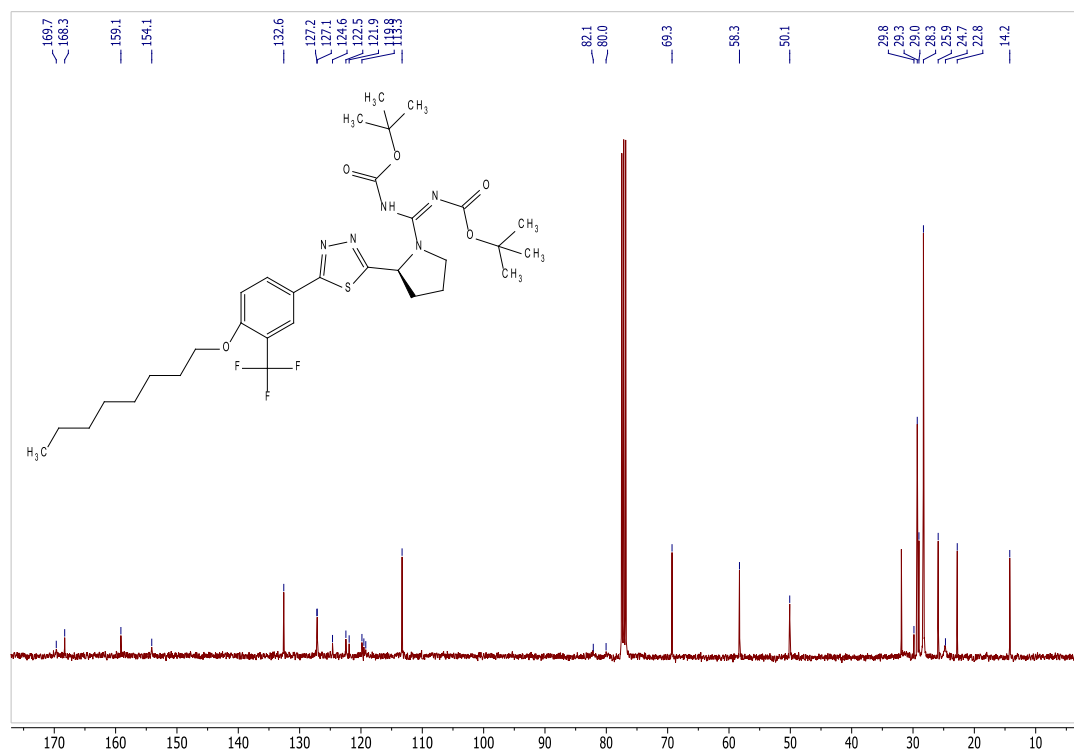
$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



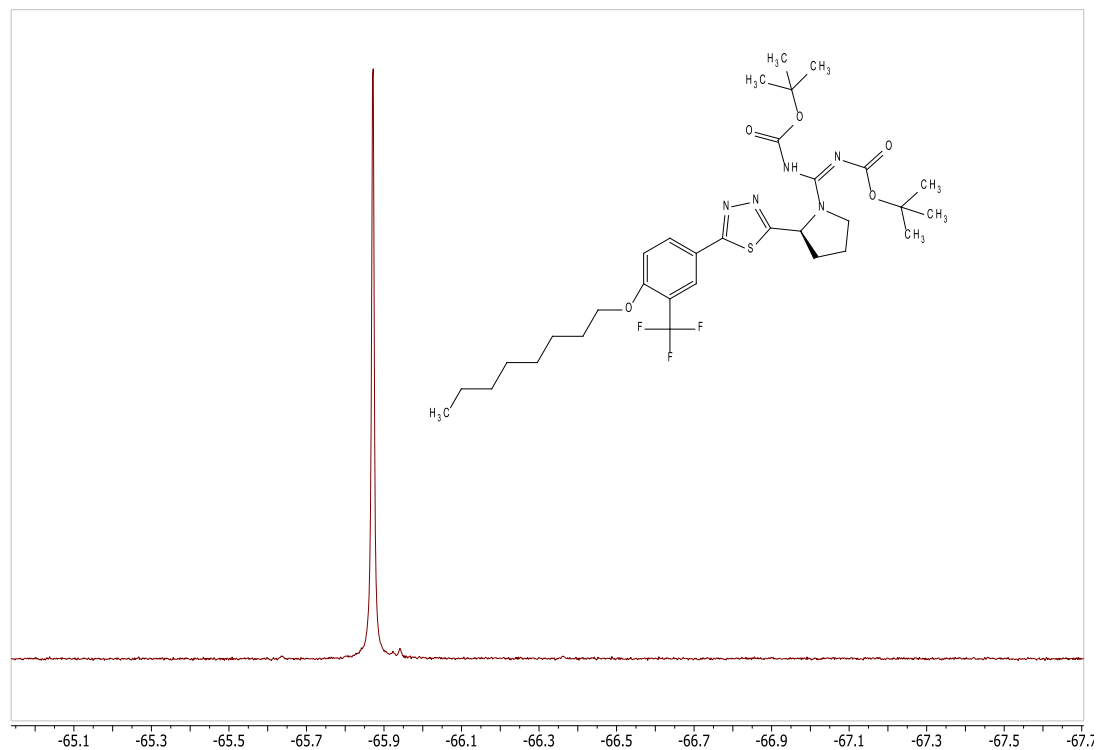
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-yl)methylene)carbamate –



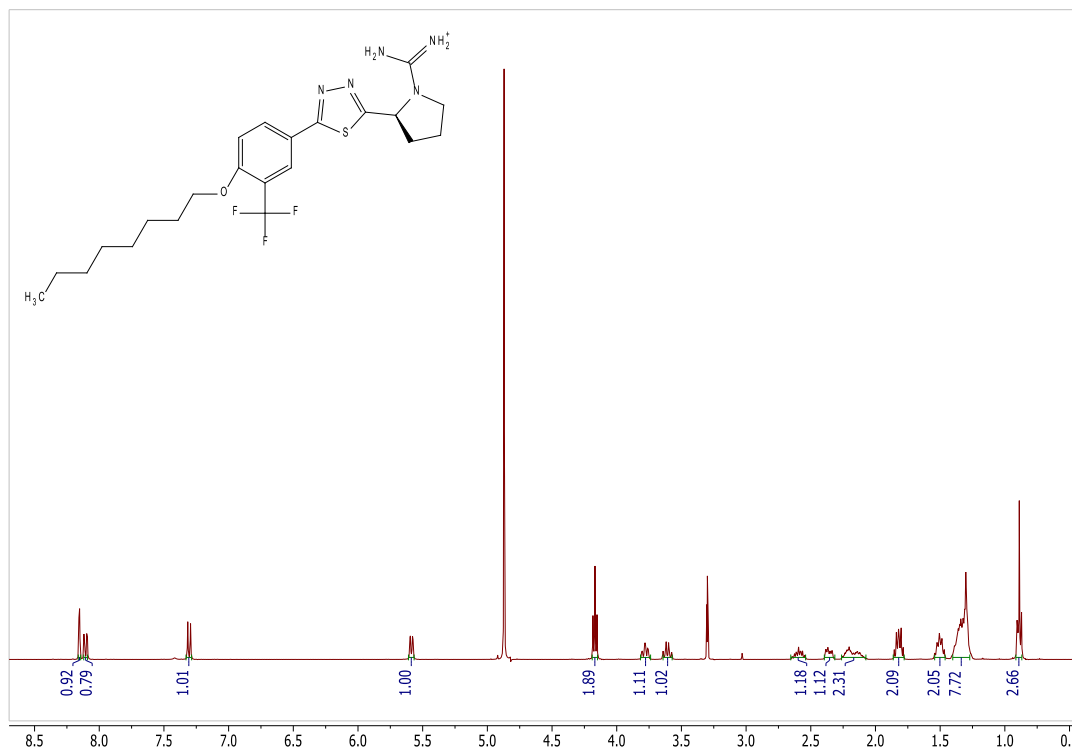
$^{13}\text{C}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-yl)methylene)carbamate –



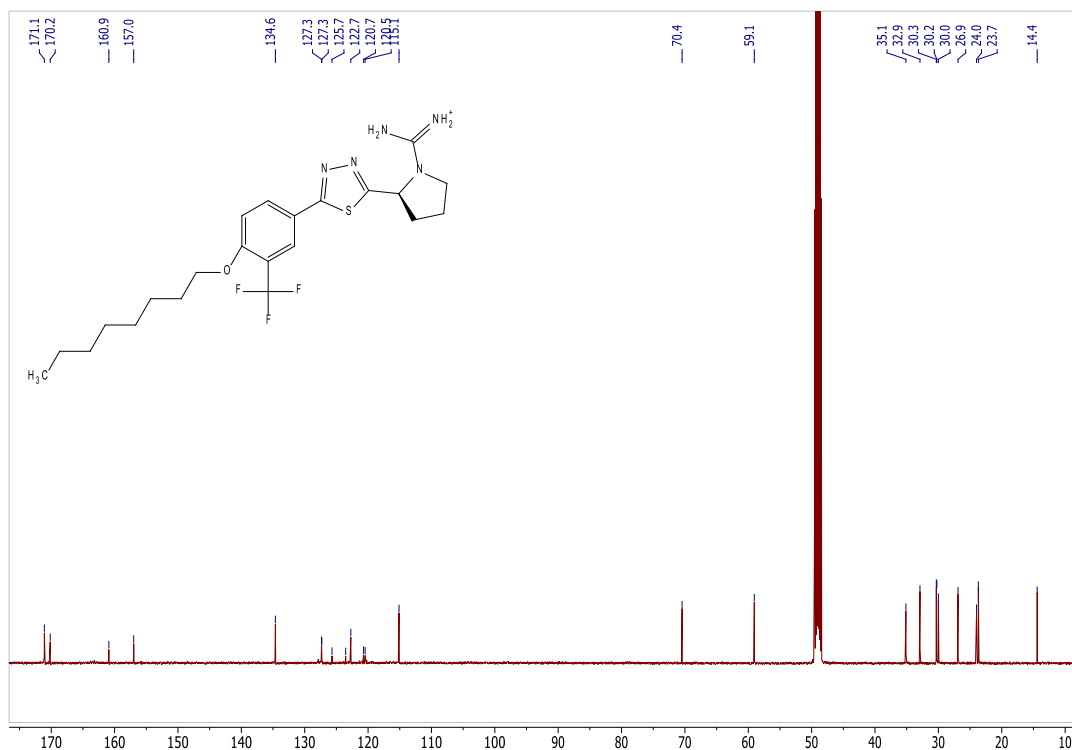
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-yl)methylene)carbamate –



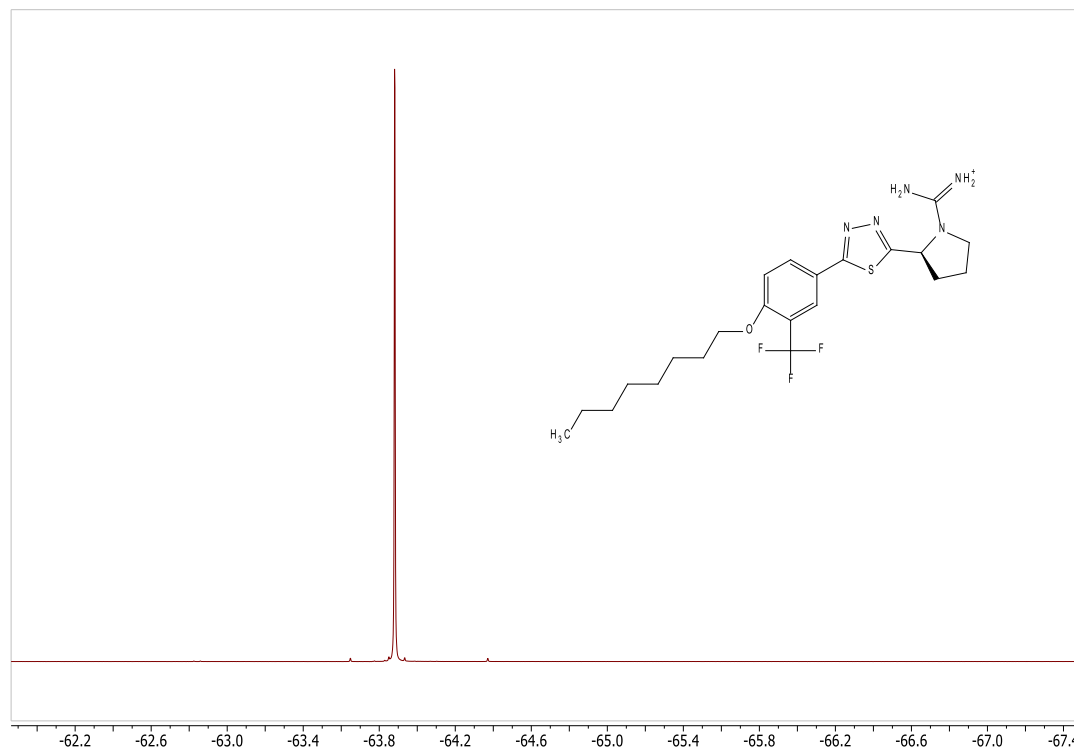
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.18**–



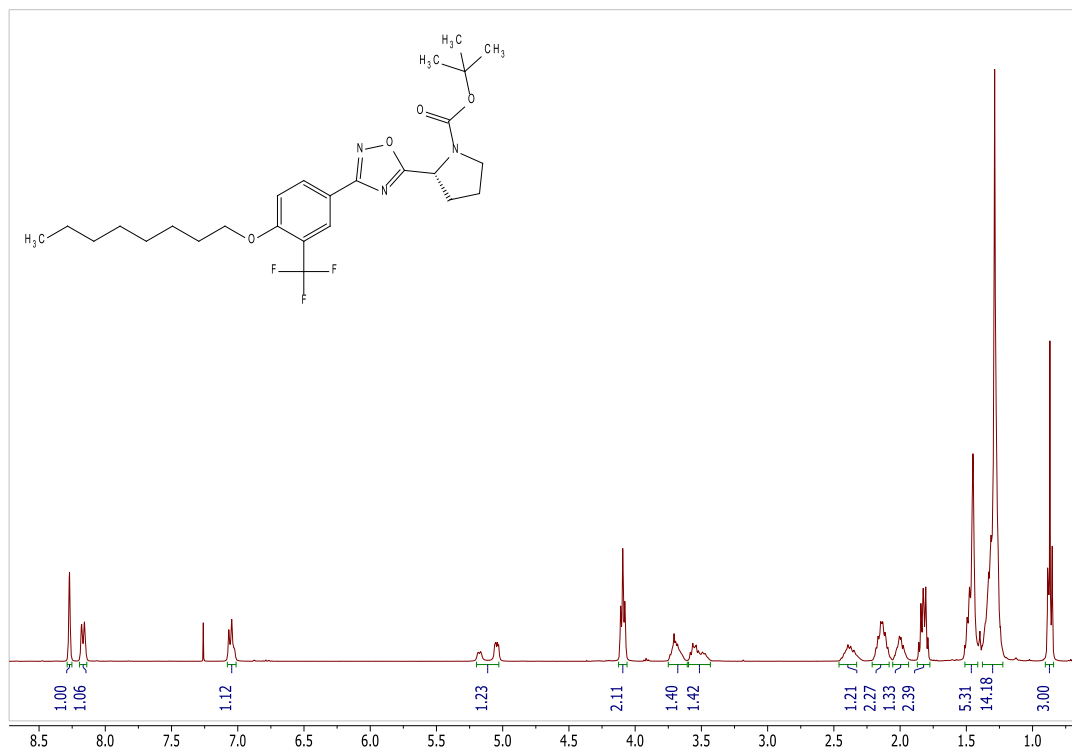
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.18**–



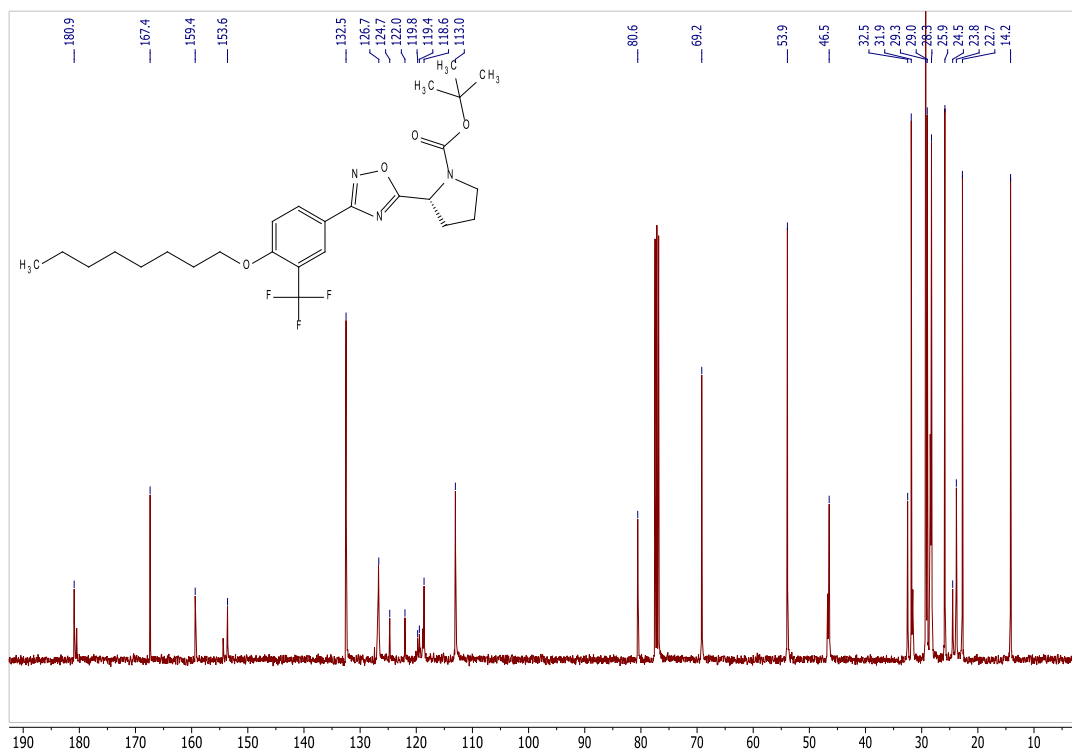
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.18**–



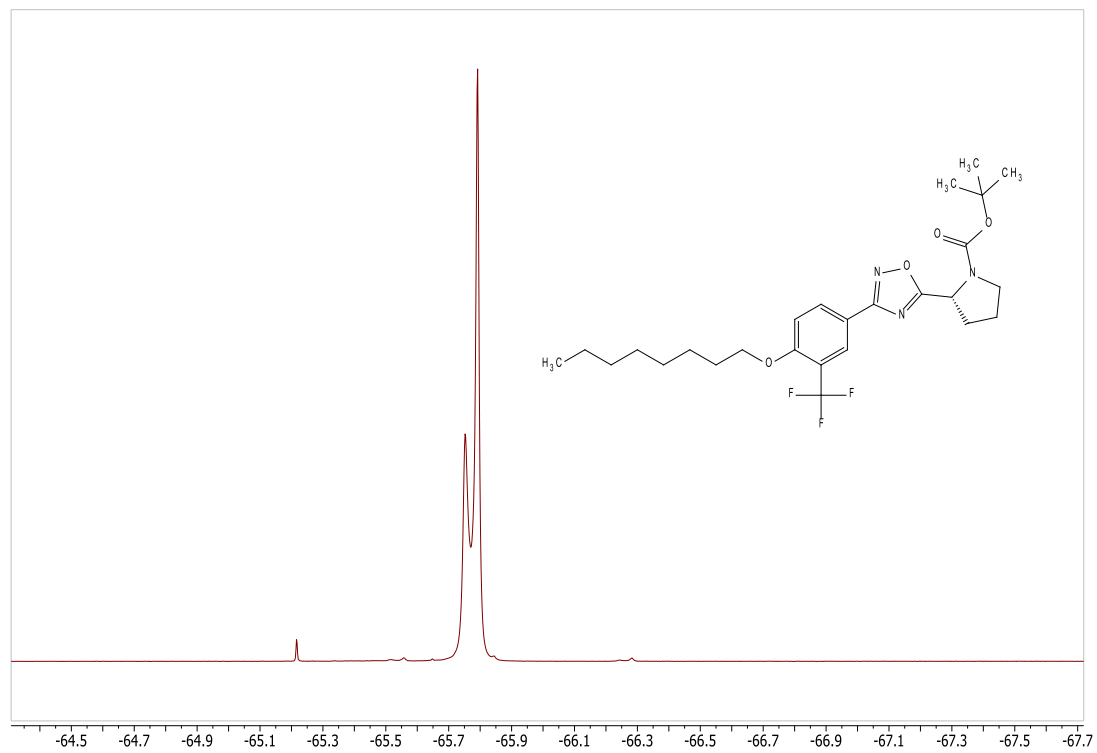
<sup>1</sup>H-NMR Spectrum for (*R*)-*tert*-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.19a**–



<sup>13</sup>C-NMR Spectrum for (*R*)-*tert*-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.19a**–

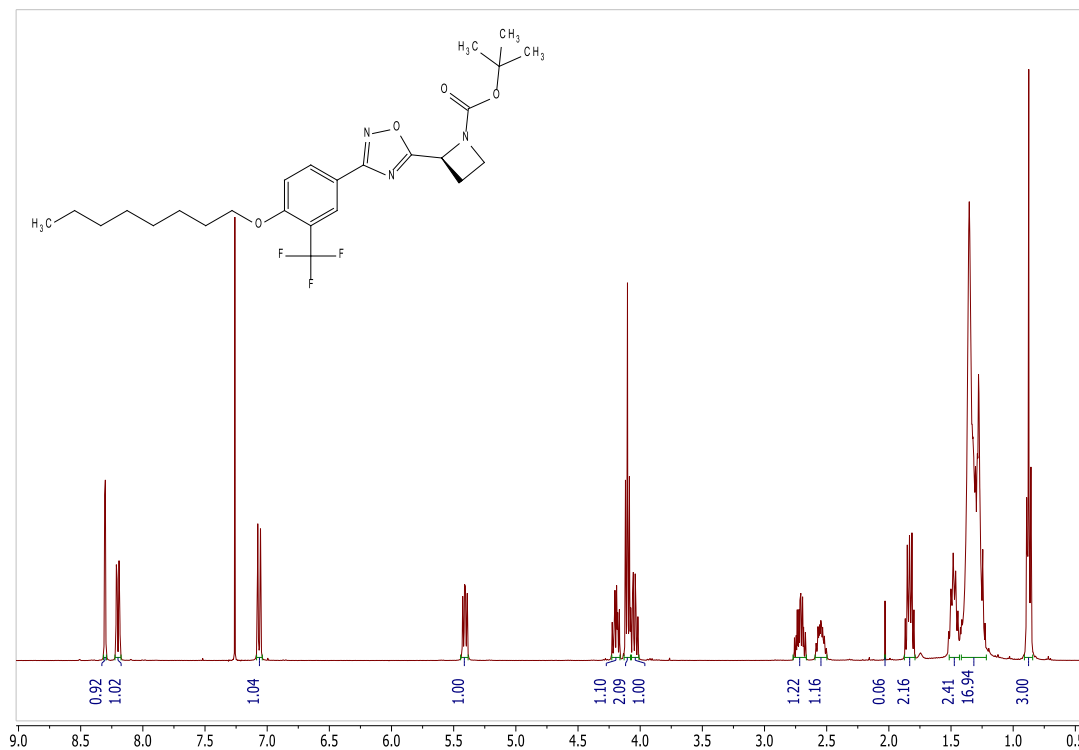


$^{19}\text{F}$ -NMR Spectrum for (*R*)-*tert*-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.19a**

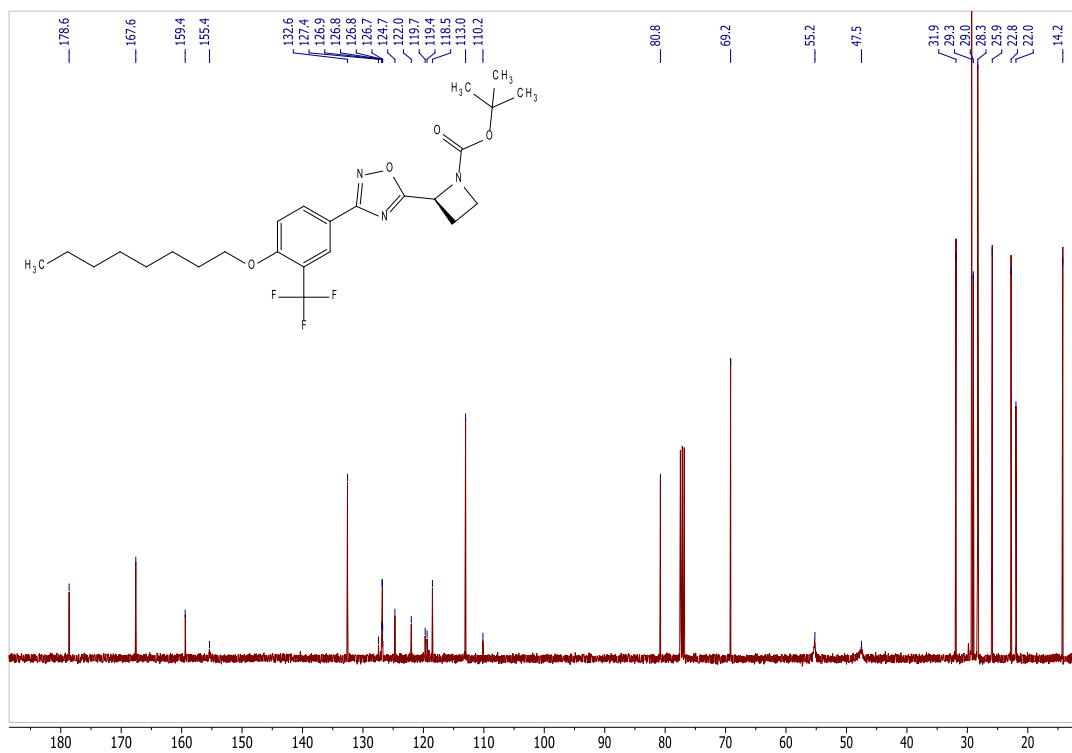




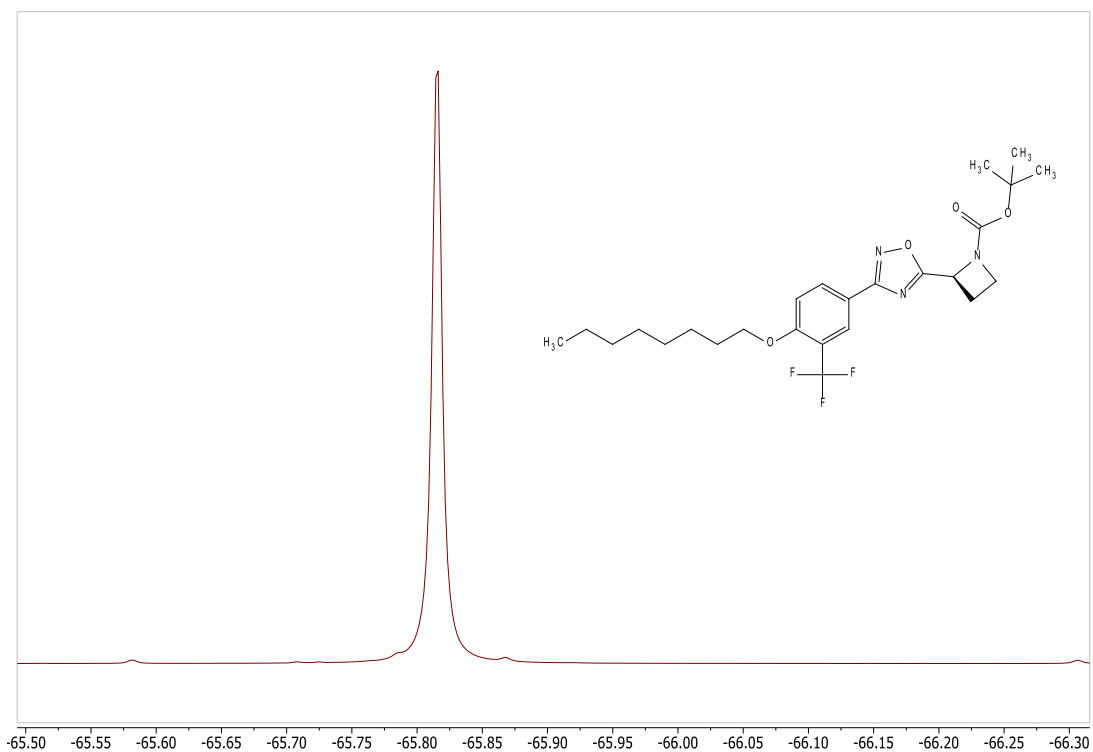
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate **3.19b**—



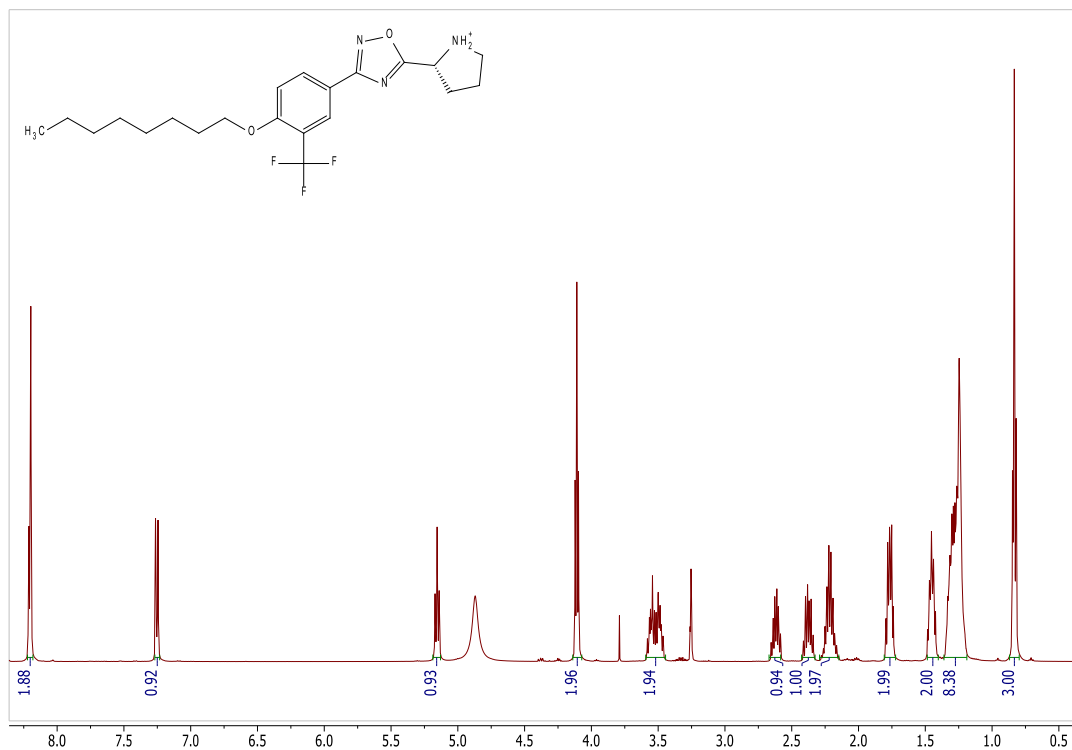
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate **3.19b**—



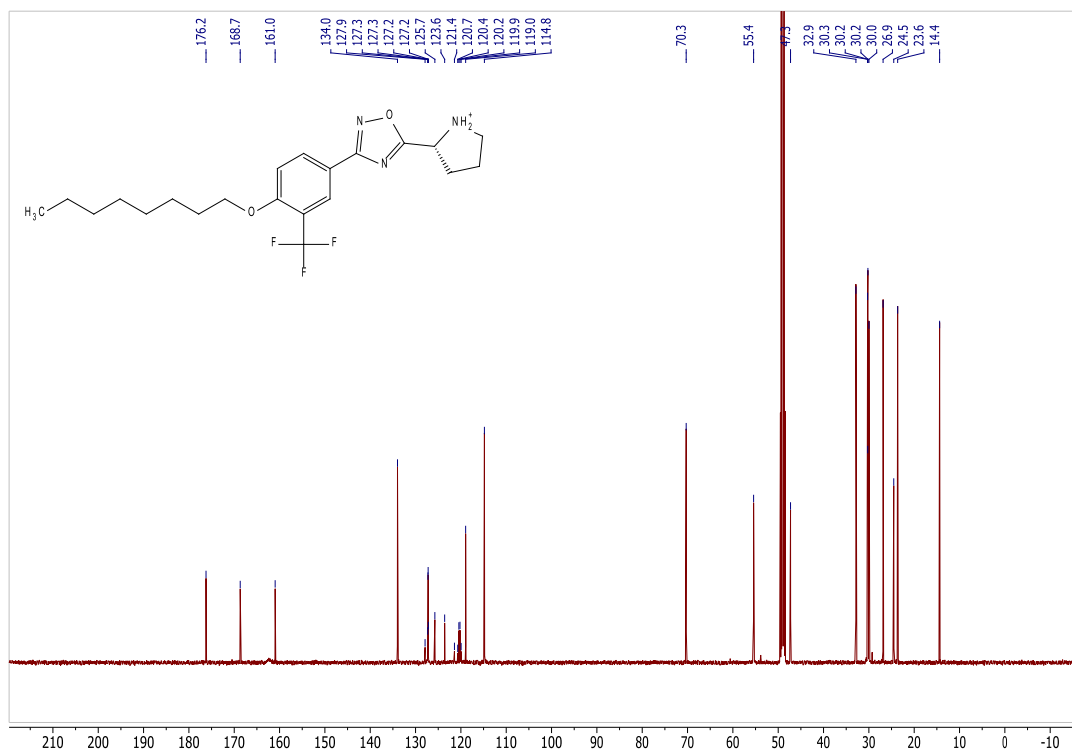
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate **3.19b**



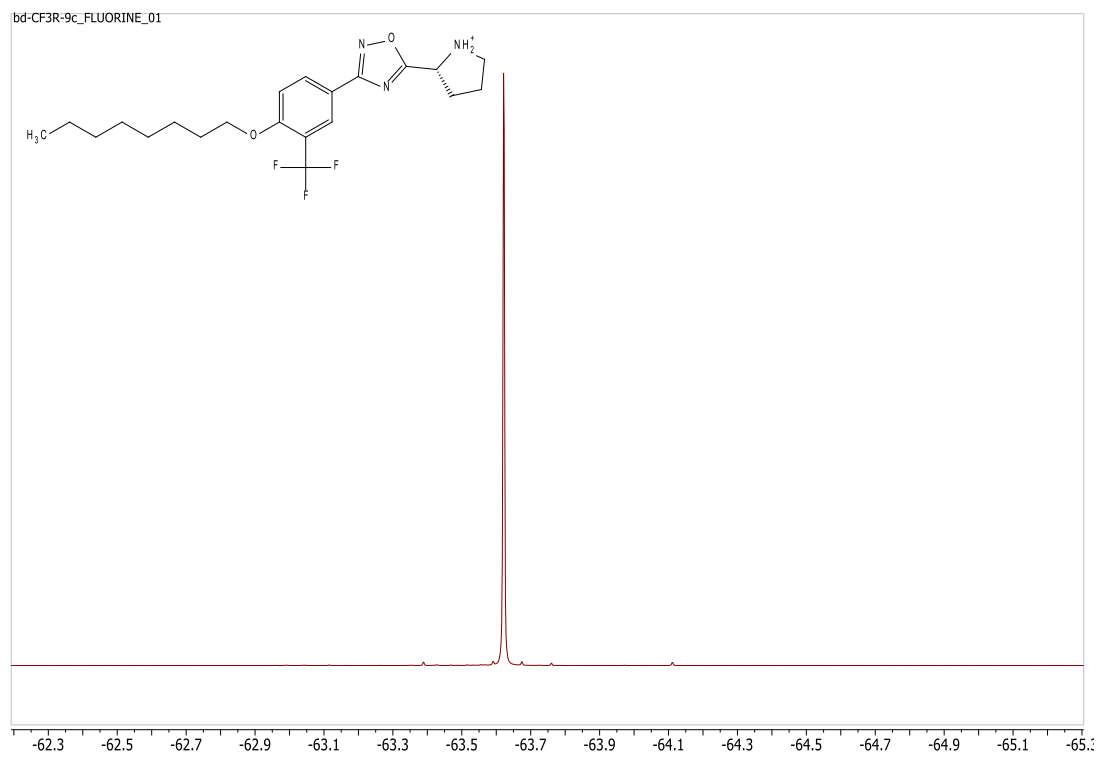
<sup>1</sup>H-NMR Spectrum for (R)-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



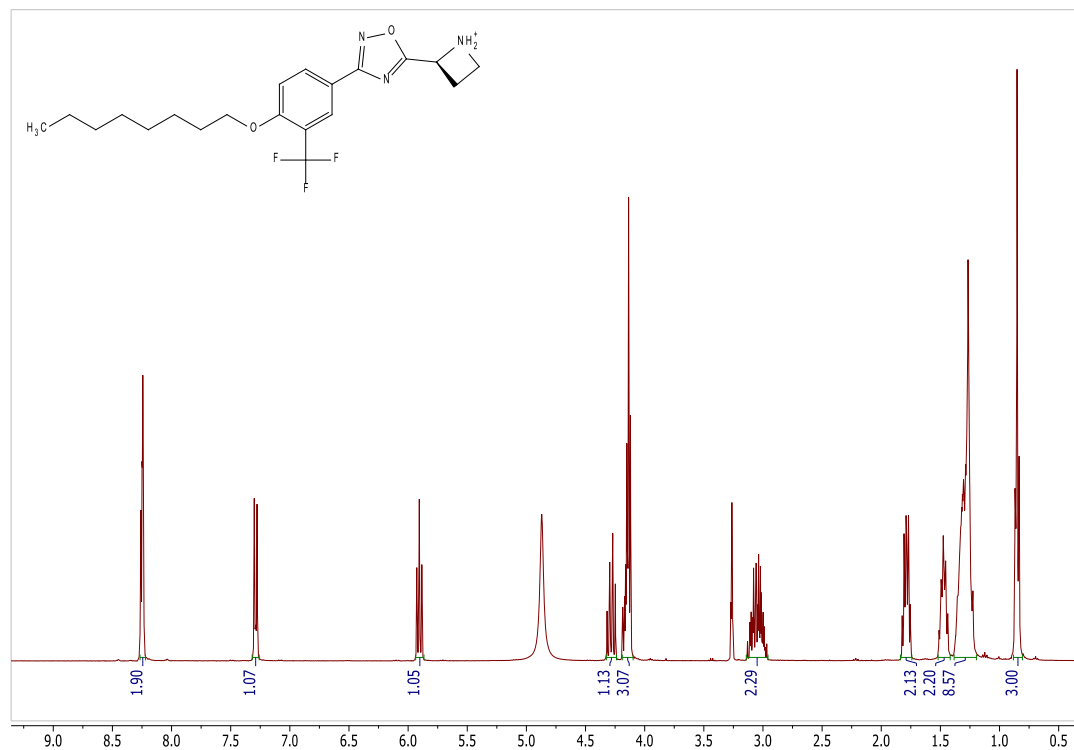
<sup>13</sup>C-NMR Spectrum for (R)-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



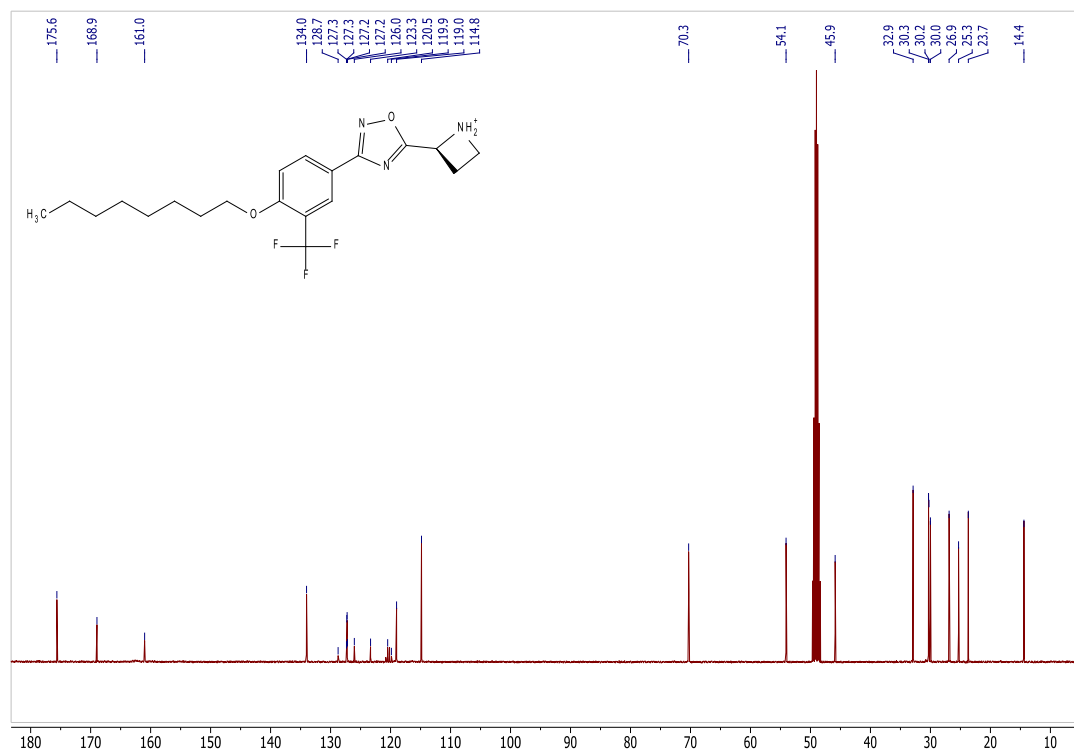
<sup>19</sup>F-NMR Spectrum for (*R*)-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



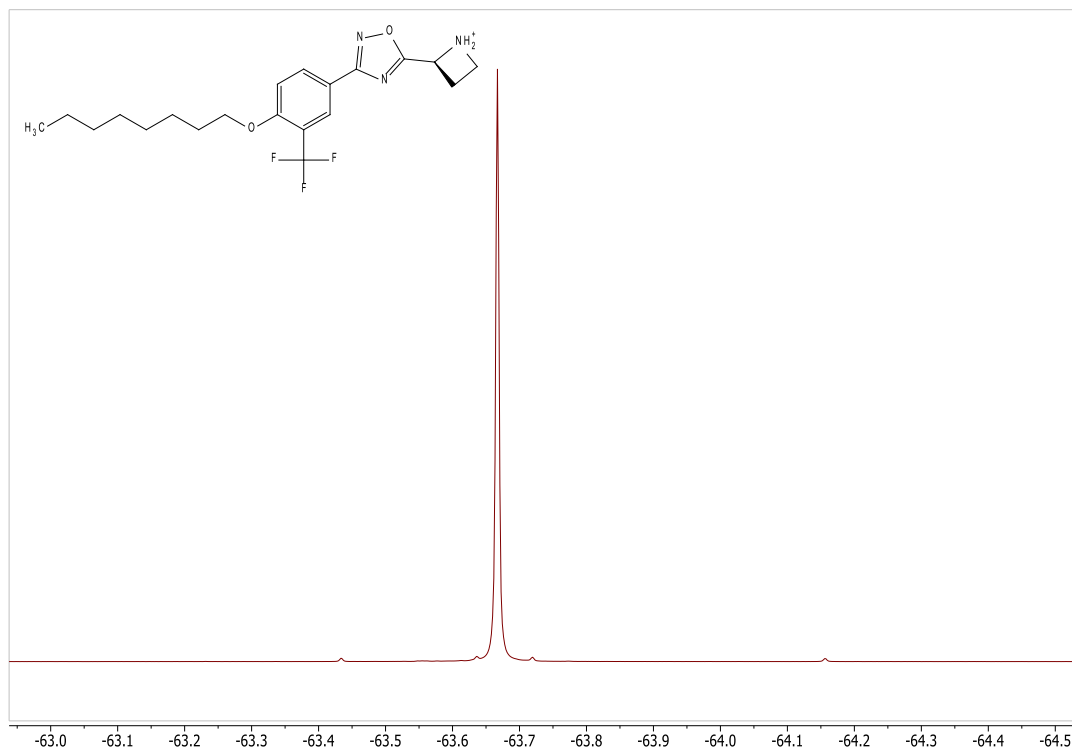
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-ium 2,2,2-trifluoroacetate –



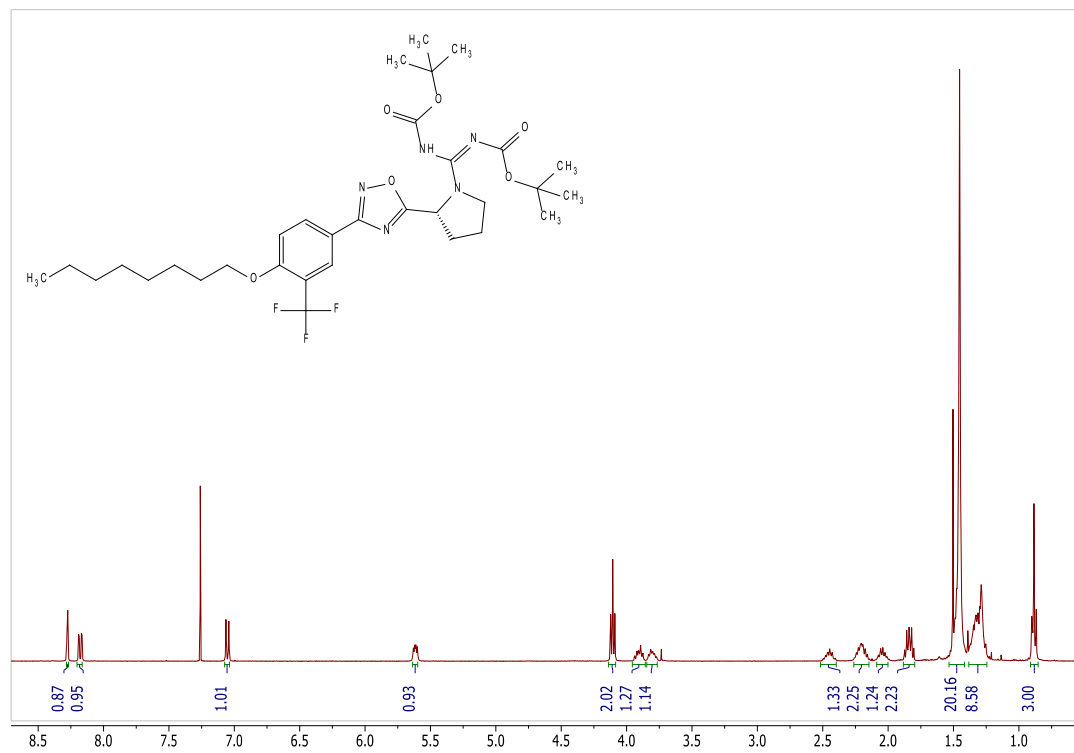
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-ium 2,2,2-trifluoroacetate –



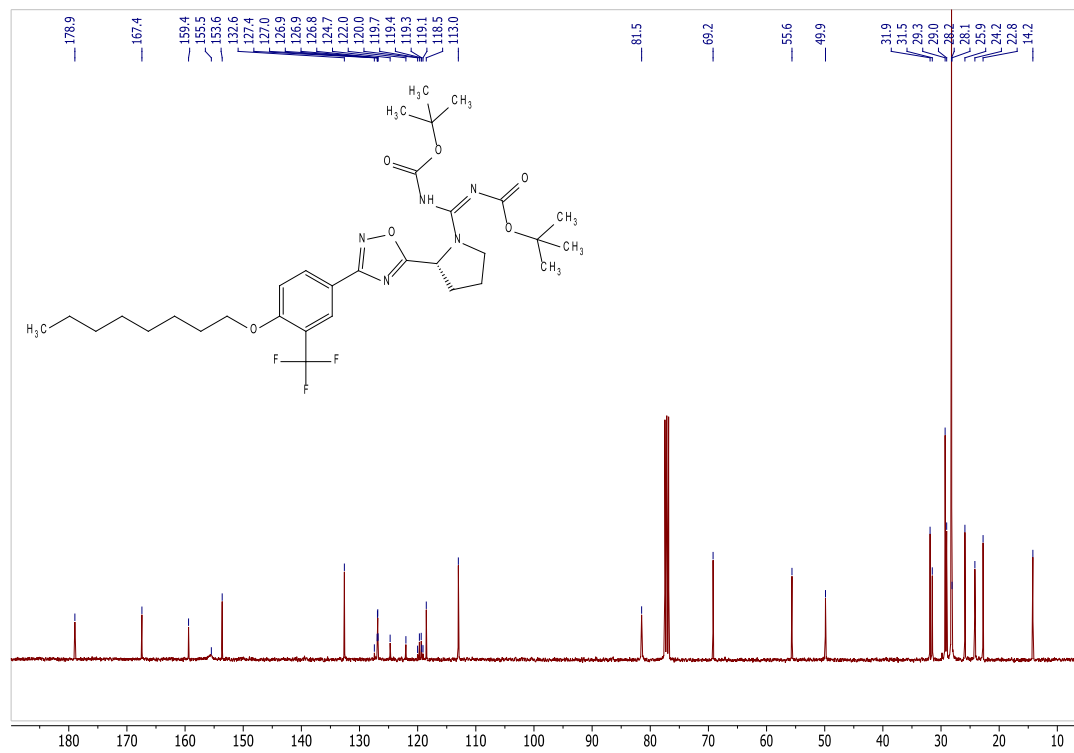
$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-ium 2,2,2-trifluoroacetate –



<sup>1</sup>H-NMR Spectrum for (*R*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –

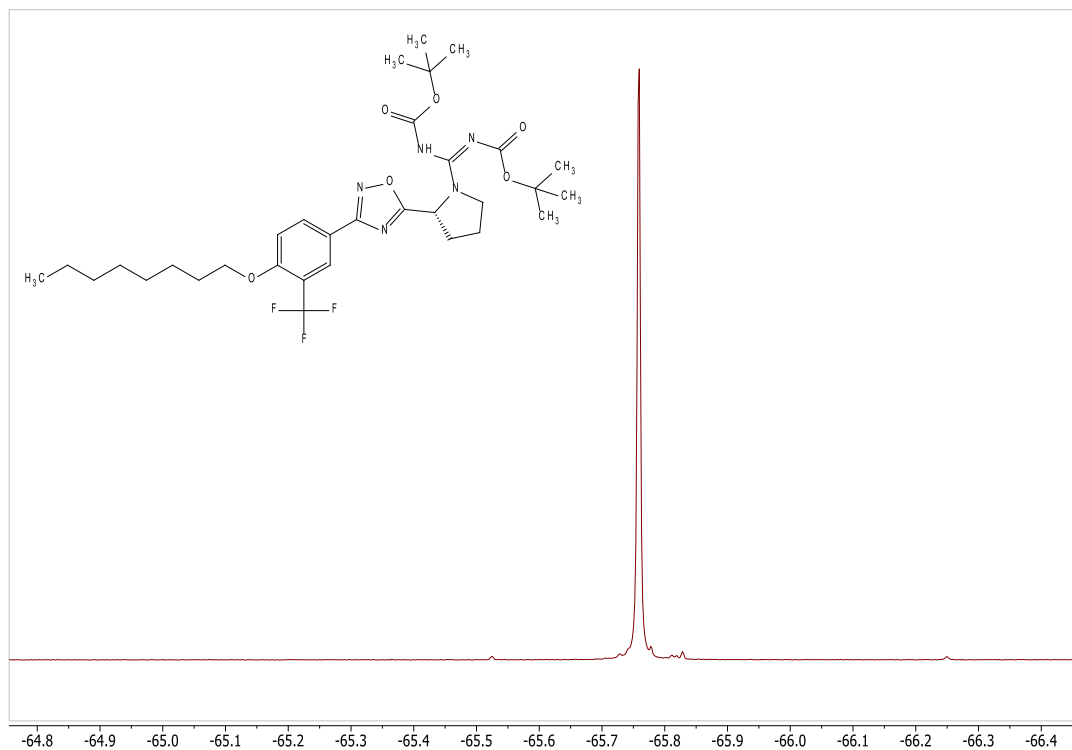


<sup>13</sup>C-NMR Spectrum for (*R*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –

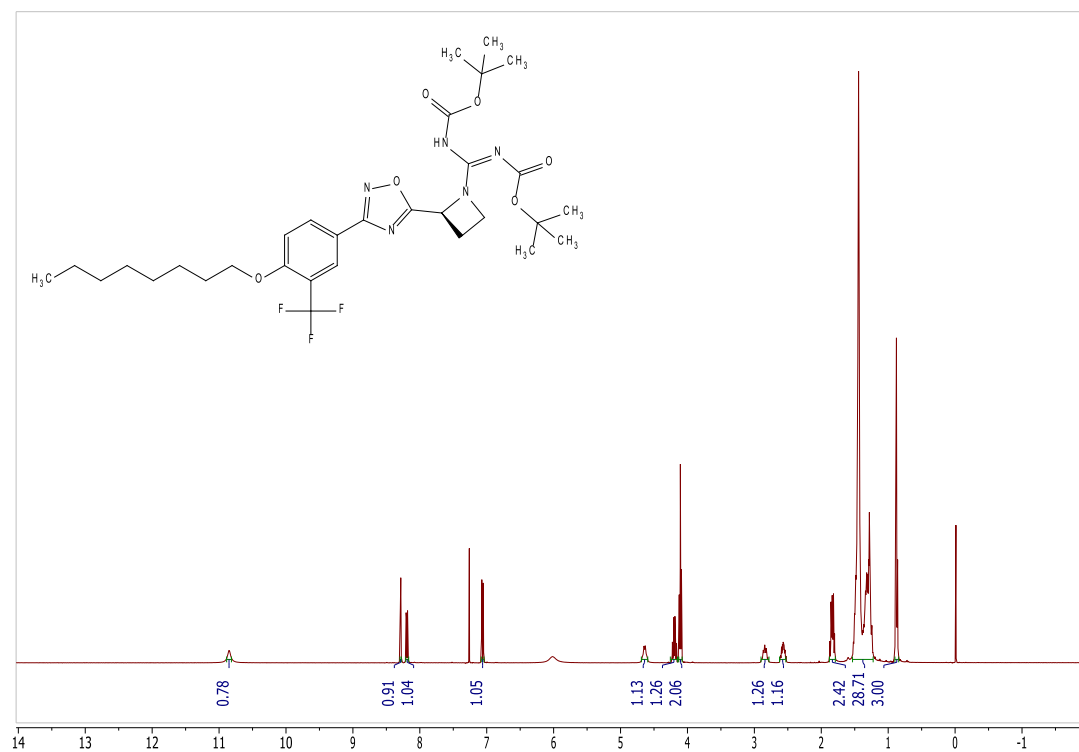




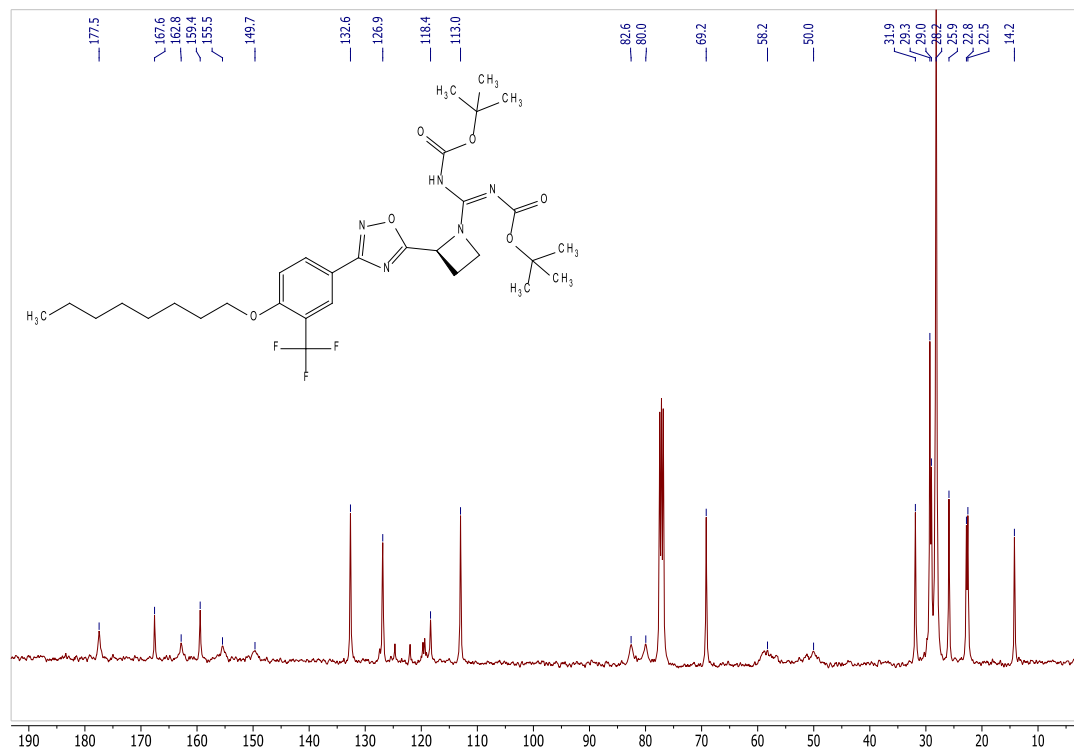
$^{19}\text{F}$ -NMR Spectrum for (*R*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



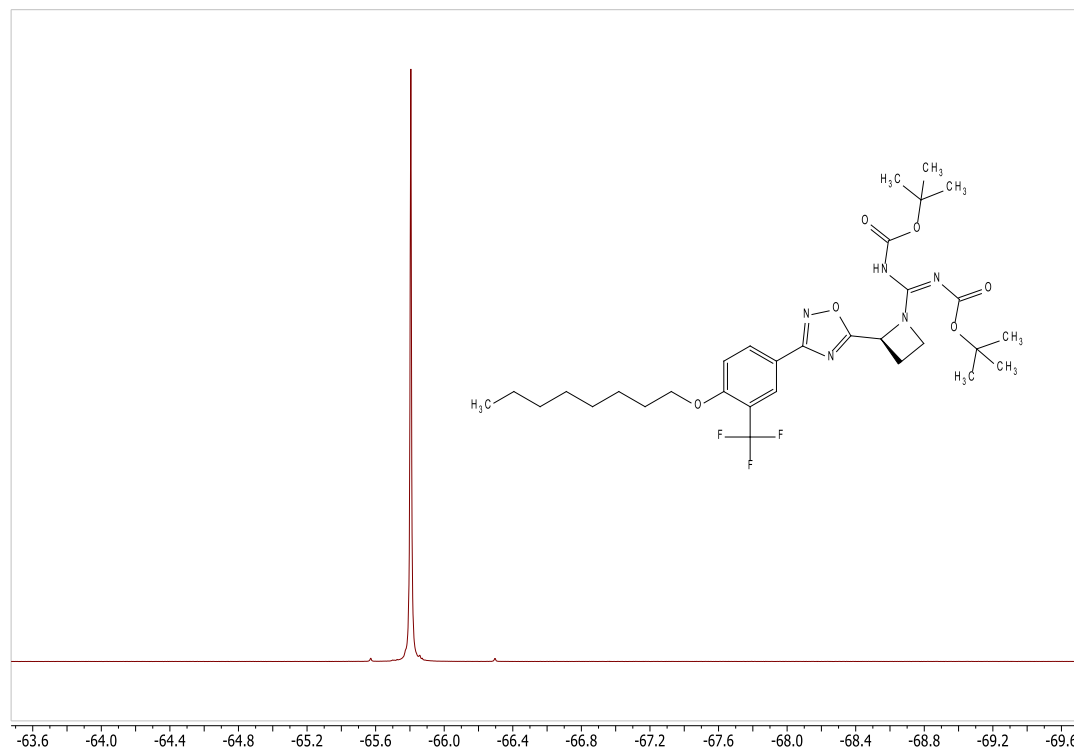
<sup>1</sup>H-NMR Spectrum for (S)-tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methylene)carbamate –



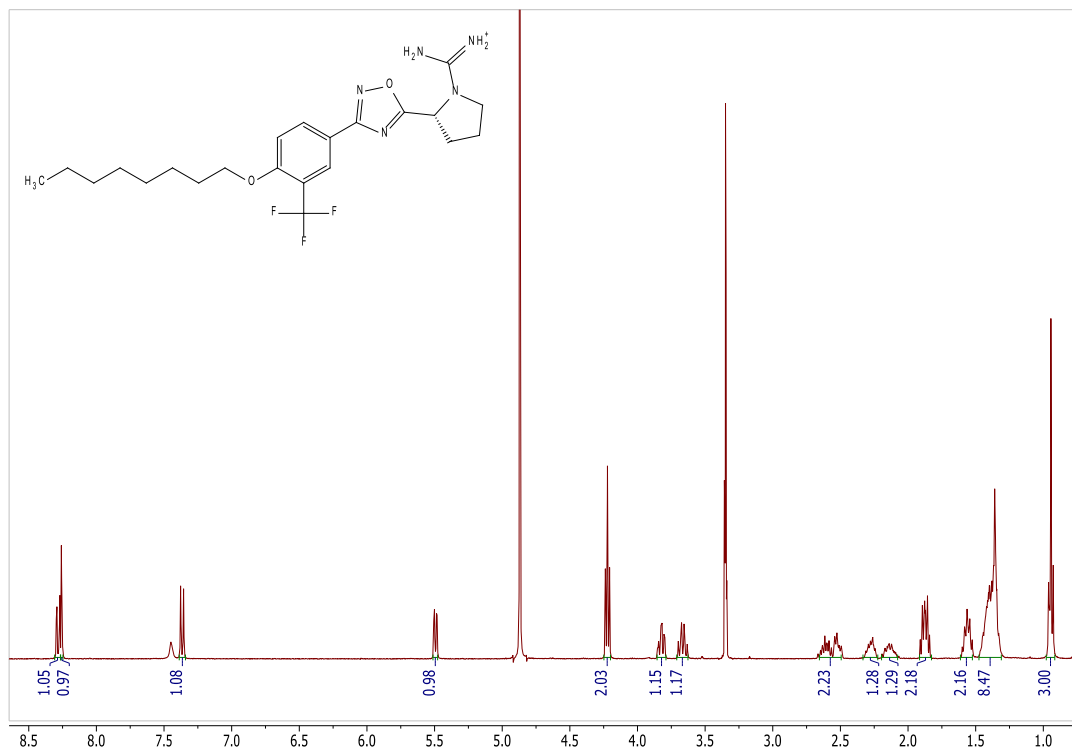
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methylene)carbamate –



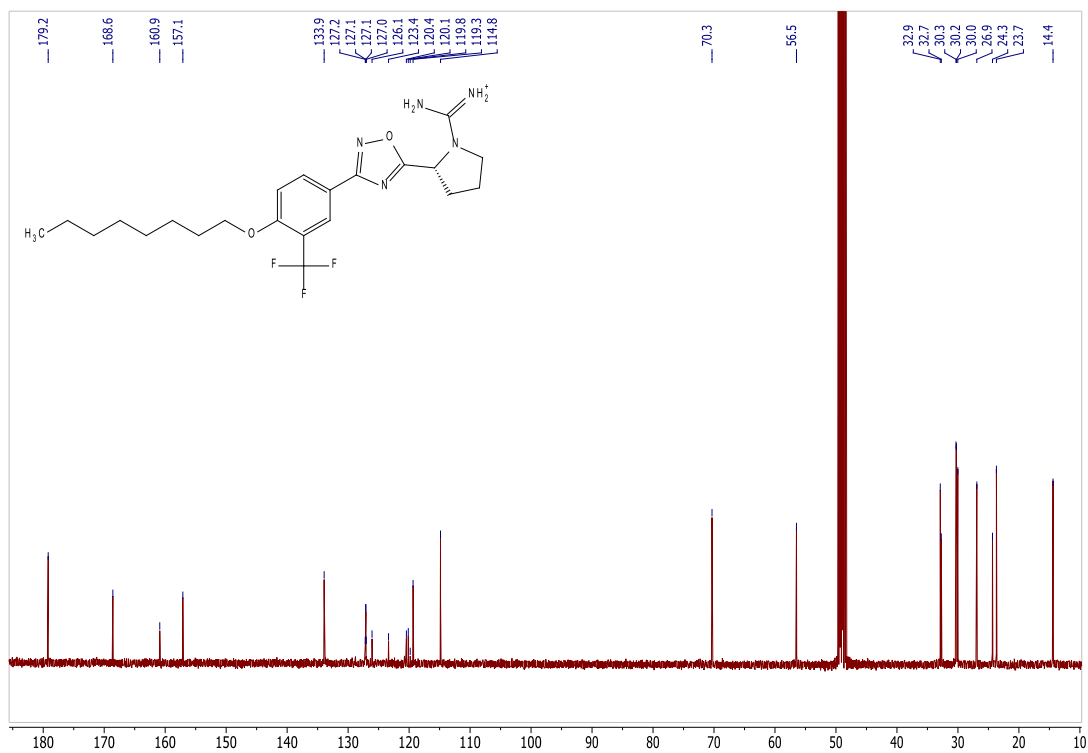
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methylene)carbamate –



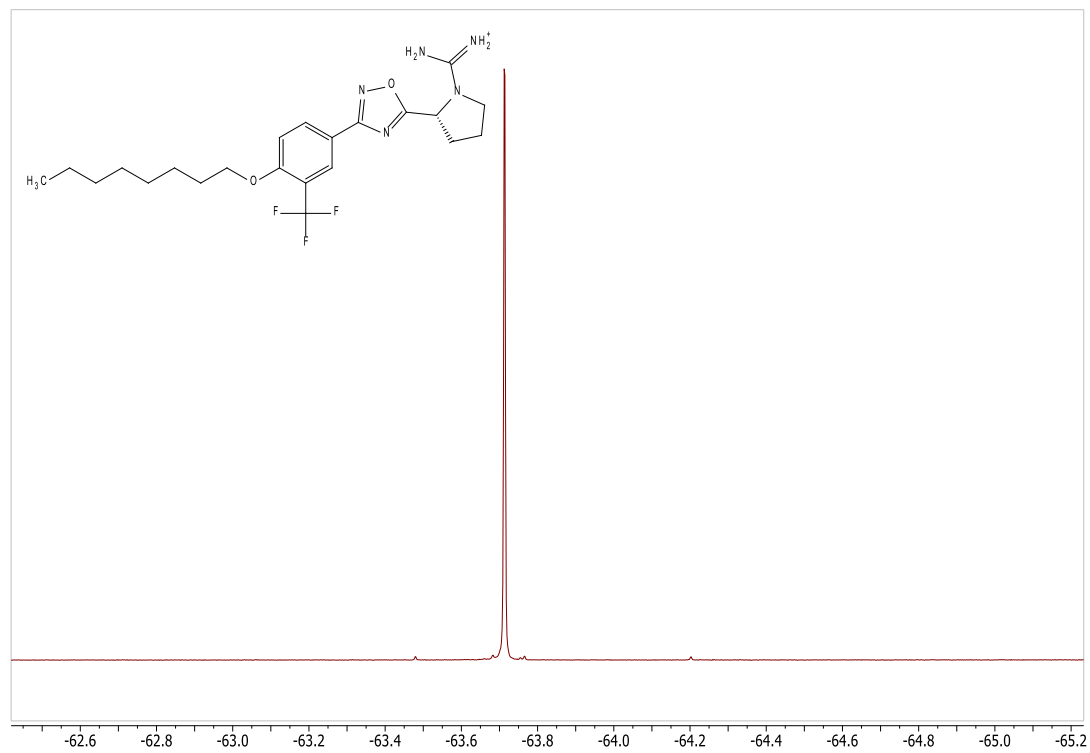
<sup>1</sup>H-NMR Spectrum for (*R*)-amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.20a** –



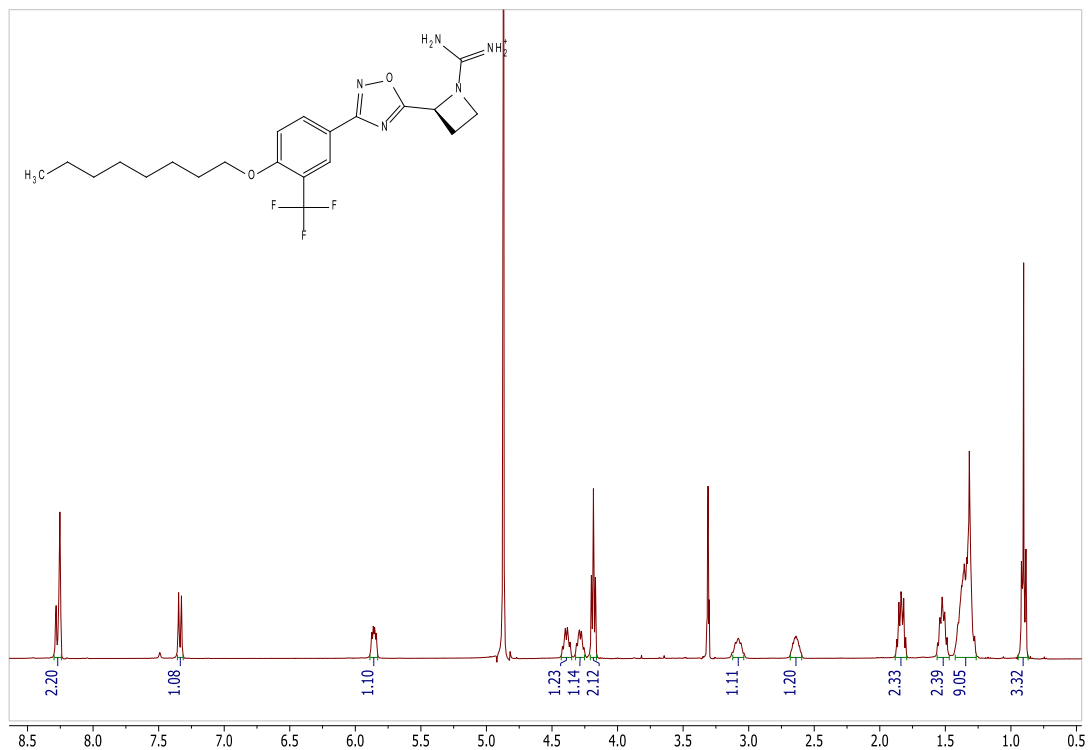
<sup>13</sup>C-NMR Spectrum for (*R*)-amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.20a** –



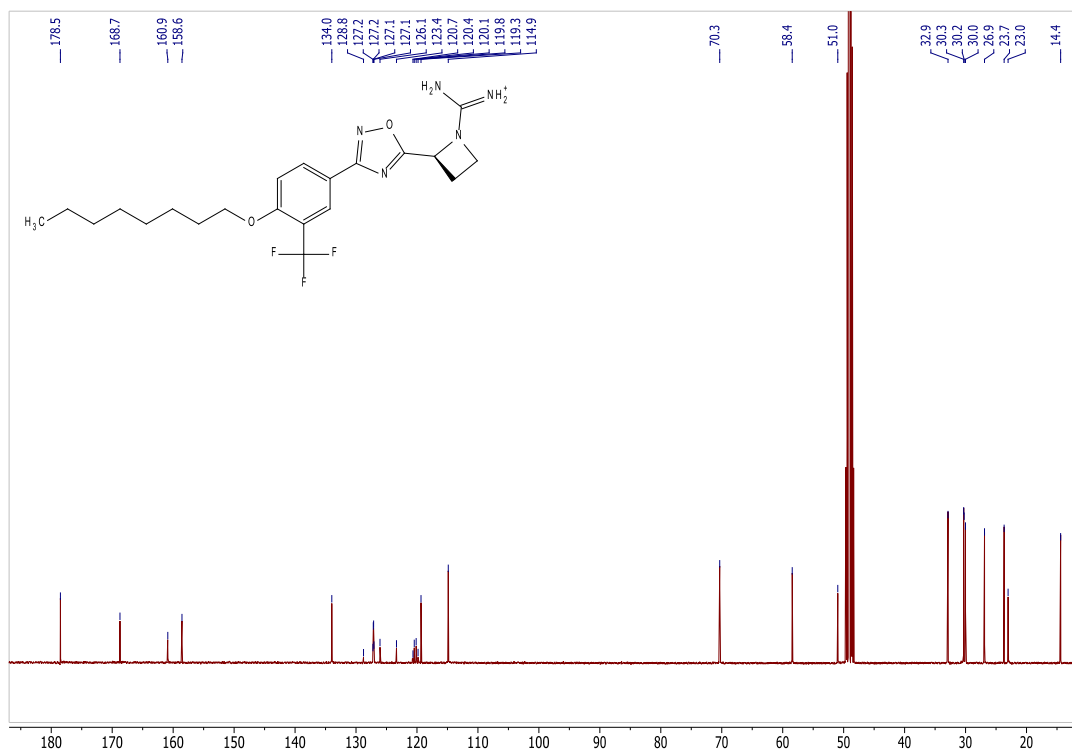
$^{19}\text{F}$ -NMR Spectrum for (*R*)-amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.20a** –



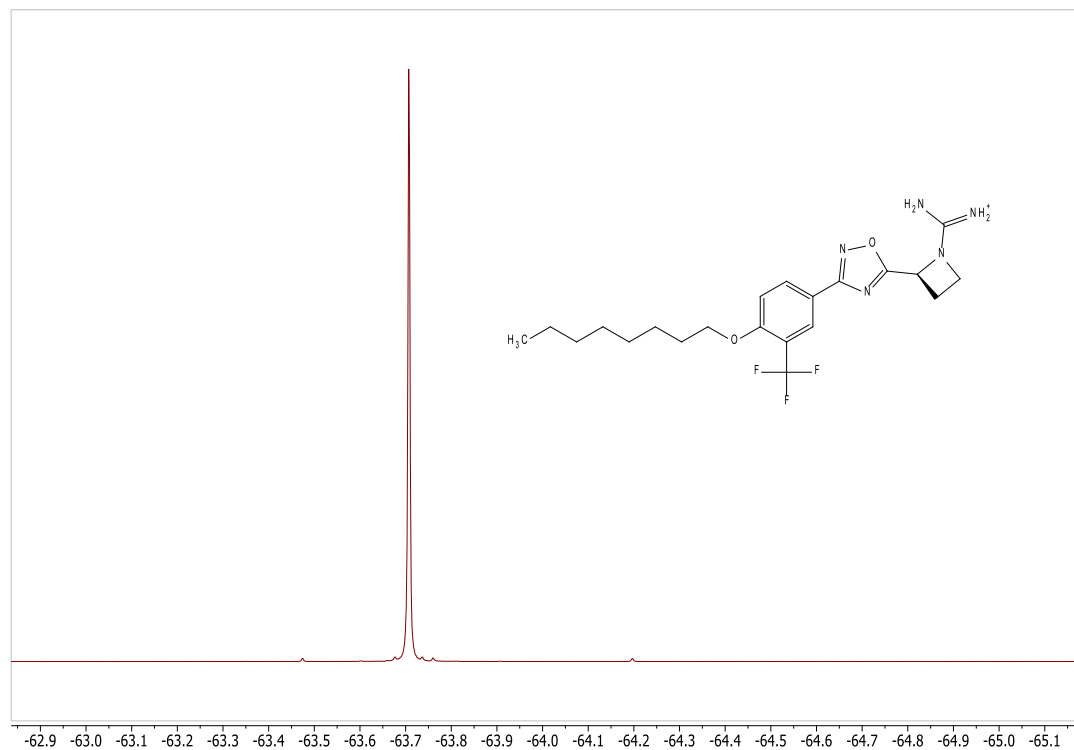
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methaniminium chloride **3.20b** –



<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methaniminium chloride **3.20b** –

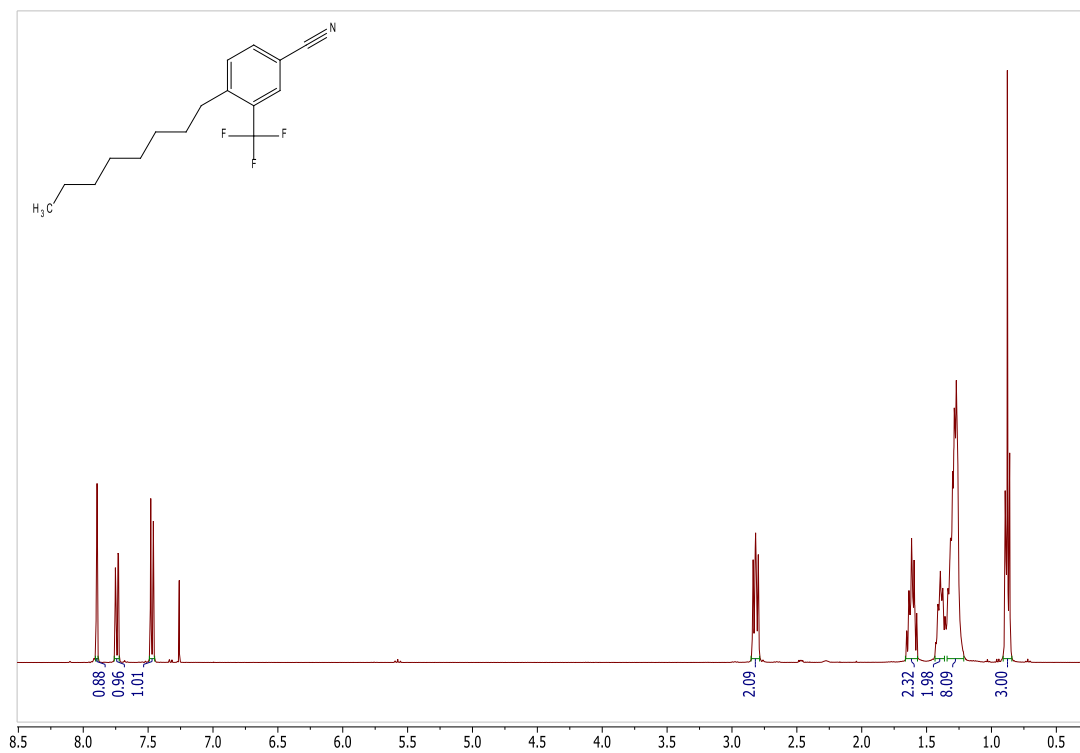


$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-yl)methaniminium chloride **3.20b** –

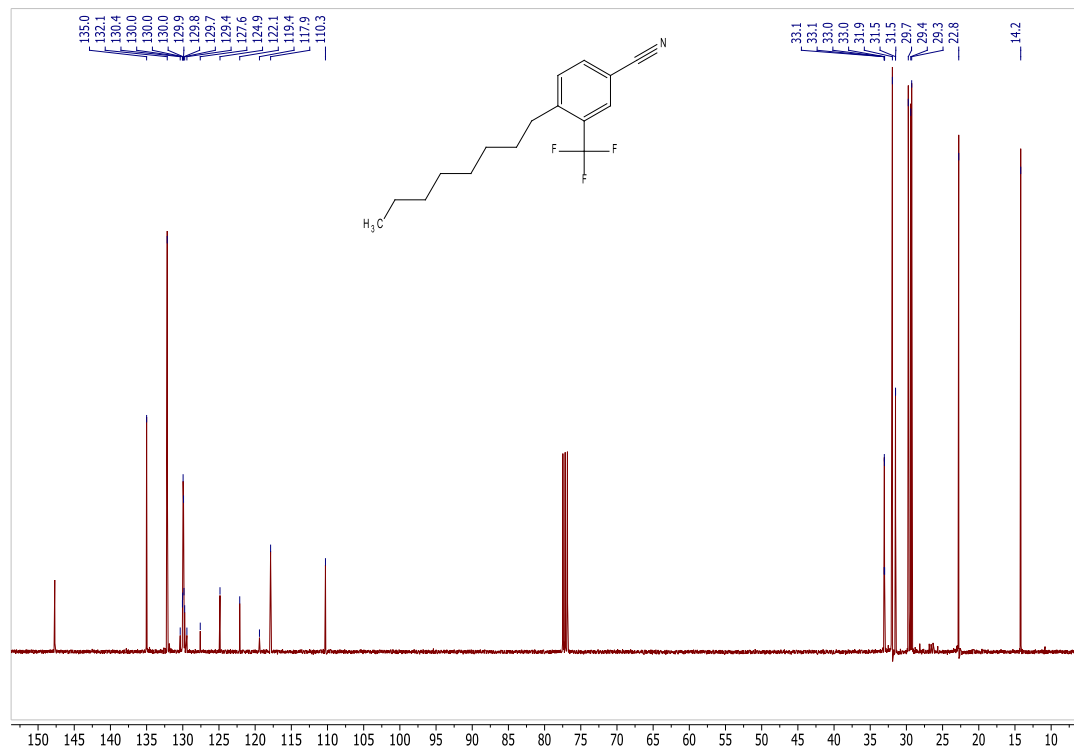




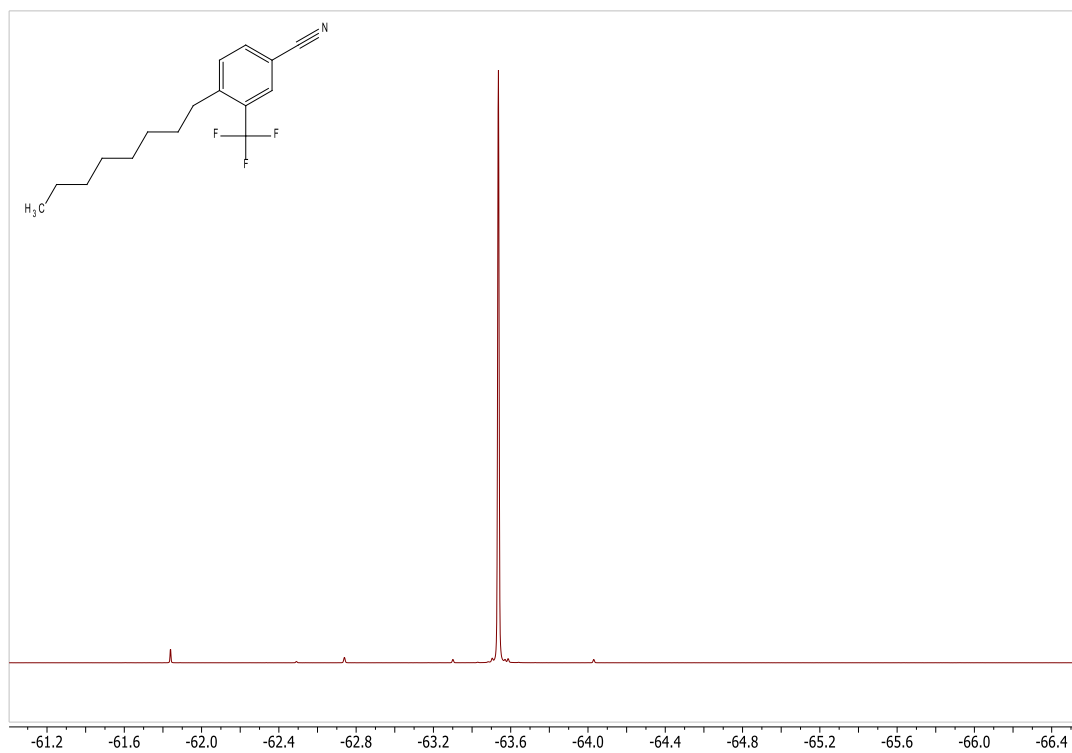
<sup>1</sup>H-NMR Spectrum for 4-octyl-3-(trifluoromethyl)benzonitrile **3.22a** –



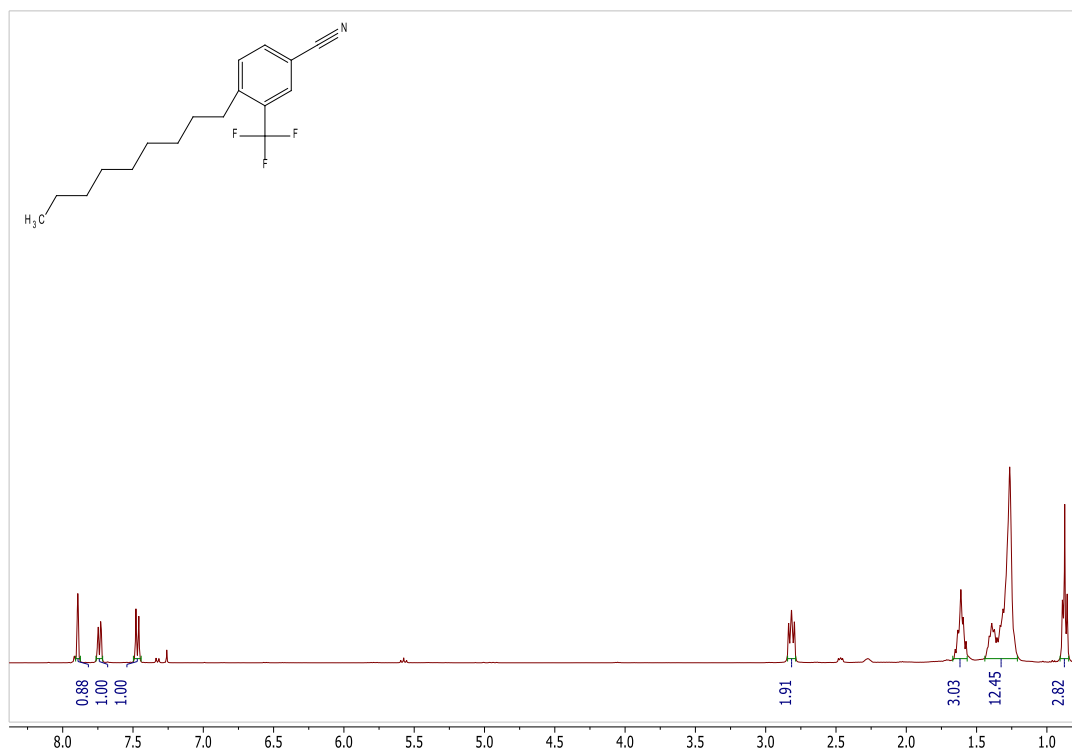
<sup>13</sup>C-NMR Spectrum for 4-octyl-3-(trifluoromethyl)benzonitrile **3.22a** –



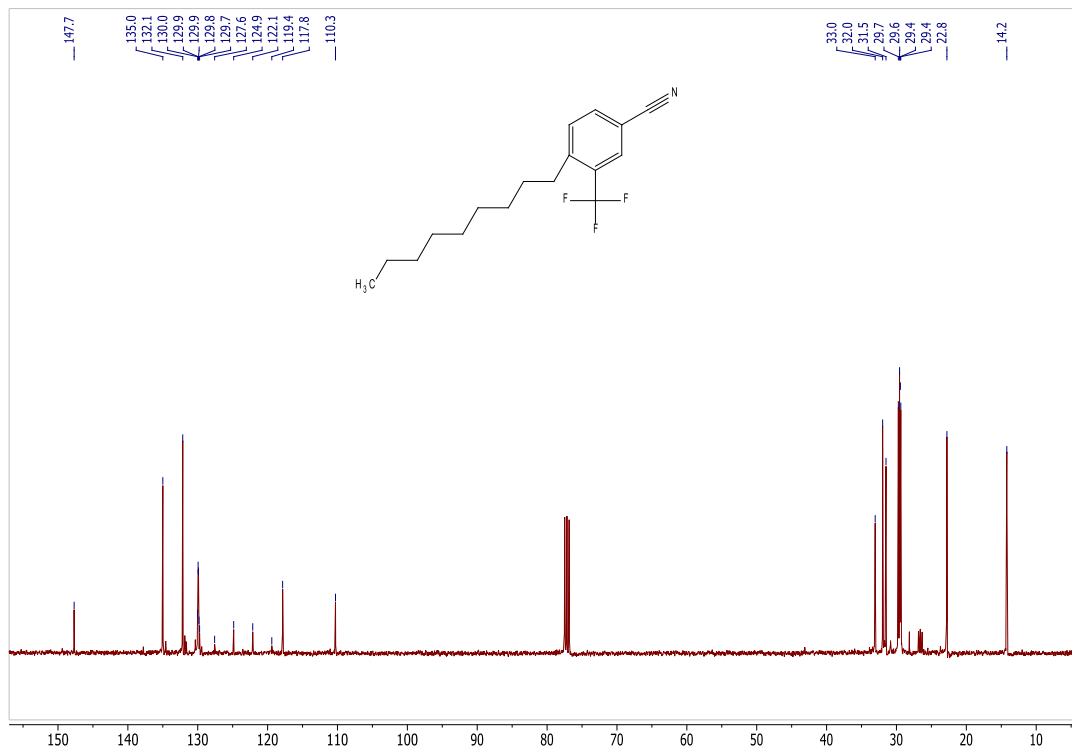
<sup>19</sup>F-NMR Spectrum for 4-octyl-3-(trifluoromethyl)benzonitrile **3.22a** –



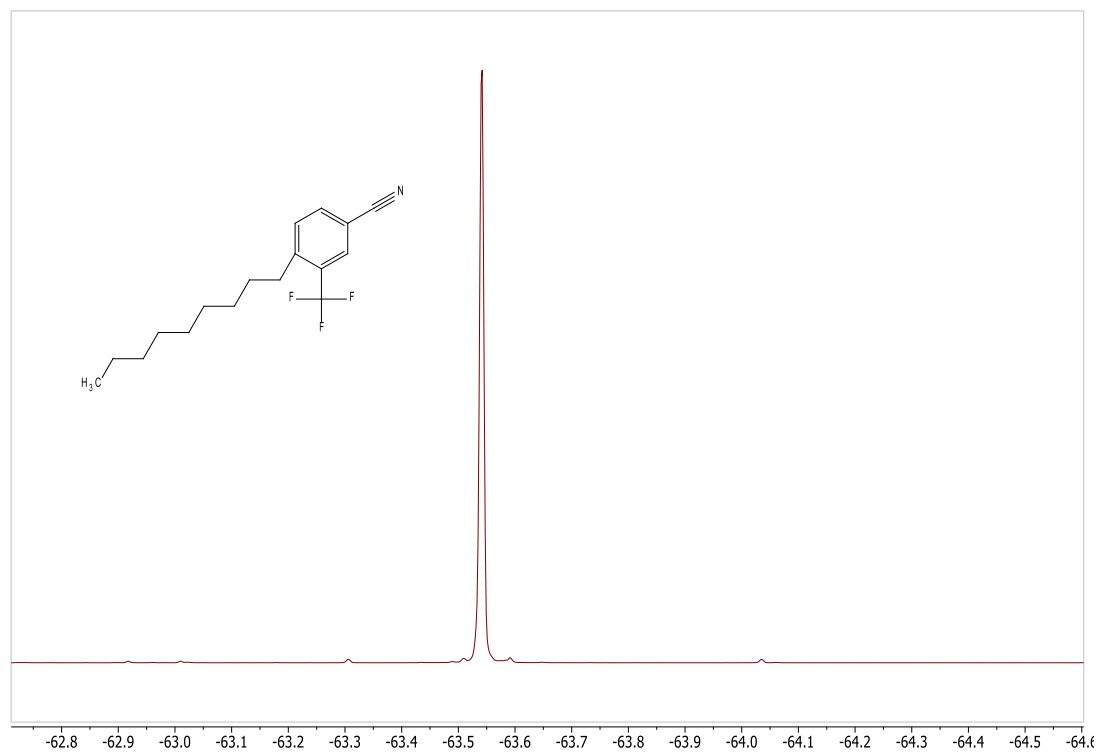
<sup>1</sup>H-NMR Spectrum for 4-nonyl-3-(trifluoromethyl)benzonitrile **3.22b** –



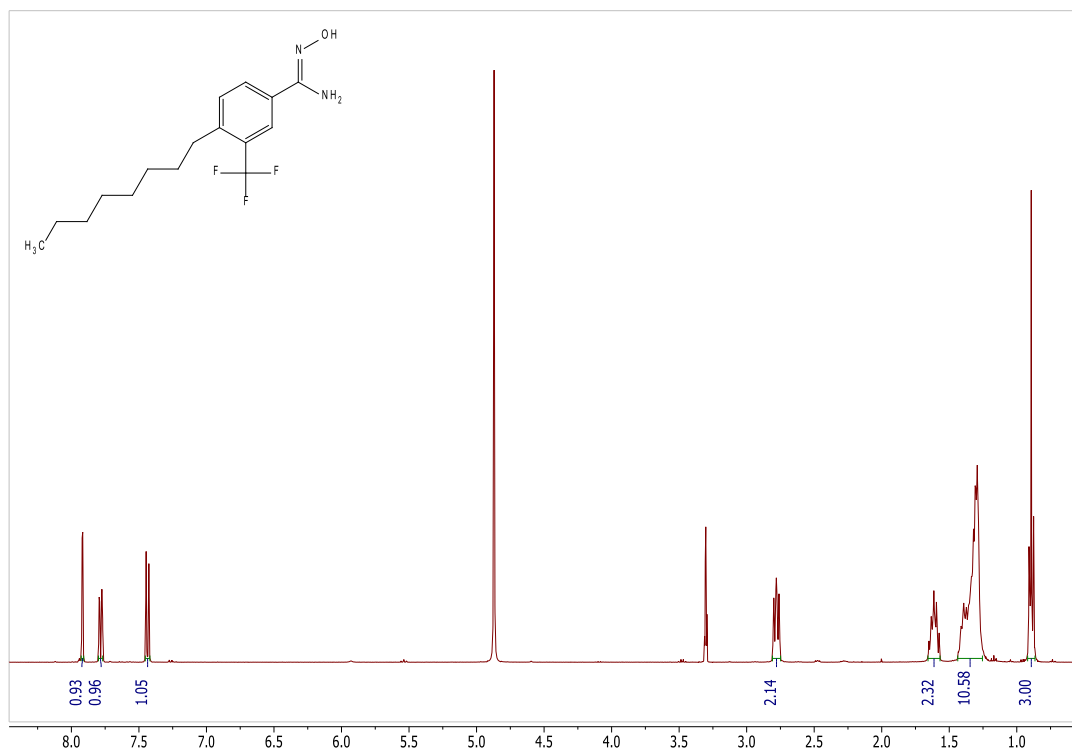
<sup>13</sup>C-NMR Spectrum for 4-nonyl-3-(trifluoromethyl)benzonitrile **3.22b** –



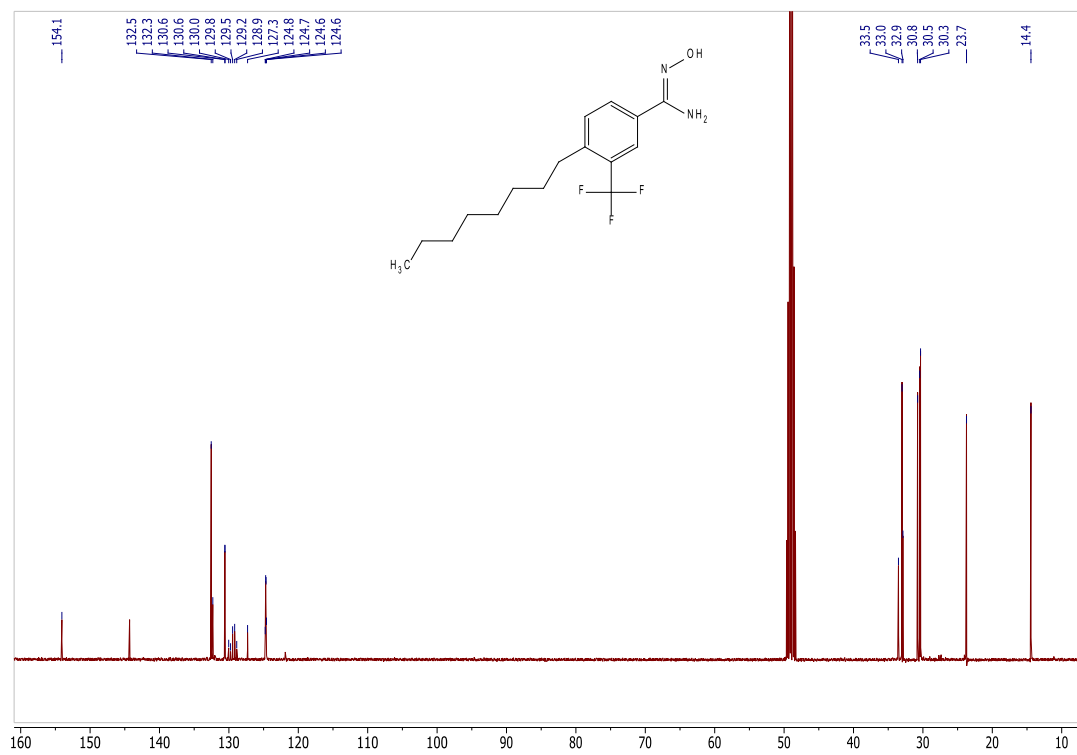
$^{19}\text{F}$ -NMR Spectrum for 4-nonyl-3-(trifluoromethyl)benzonitrile **3.22b** –



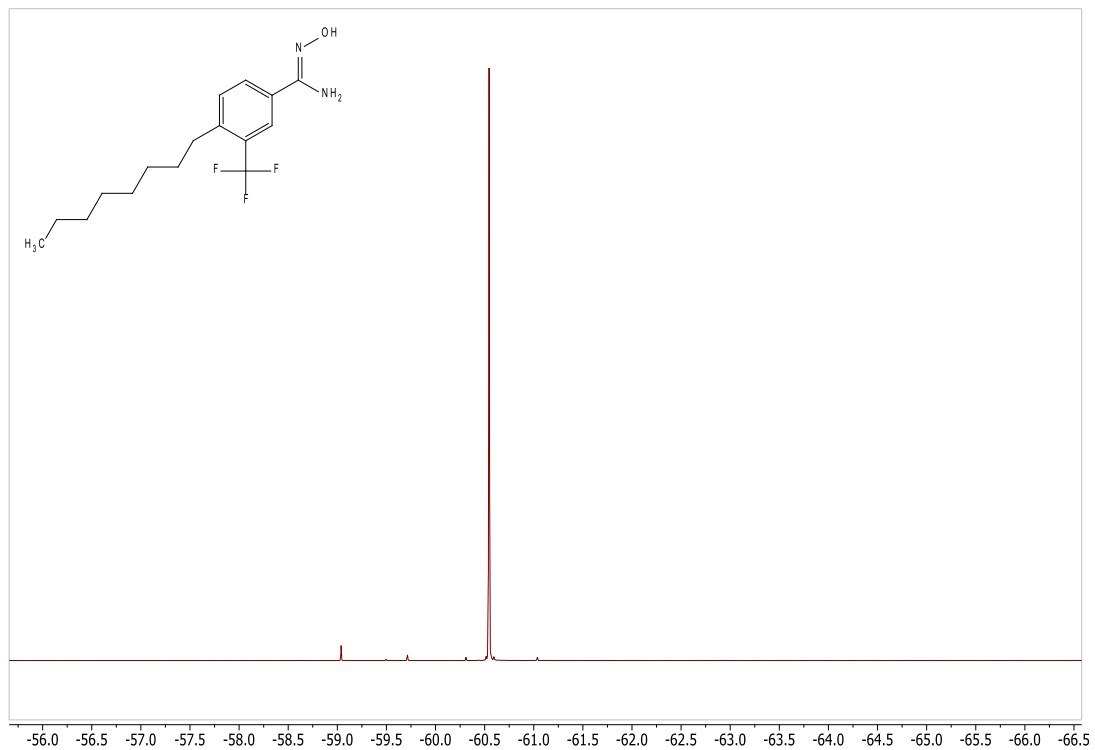
<sup>1</sup>H-NMR Spectrum for (Z)-hydroxy-4-octyl-3-(trifluoromethyl)benzimidamide –



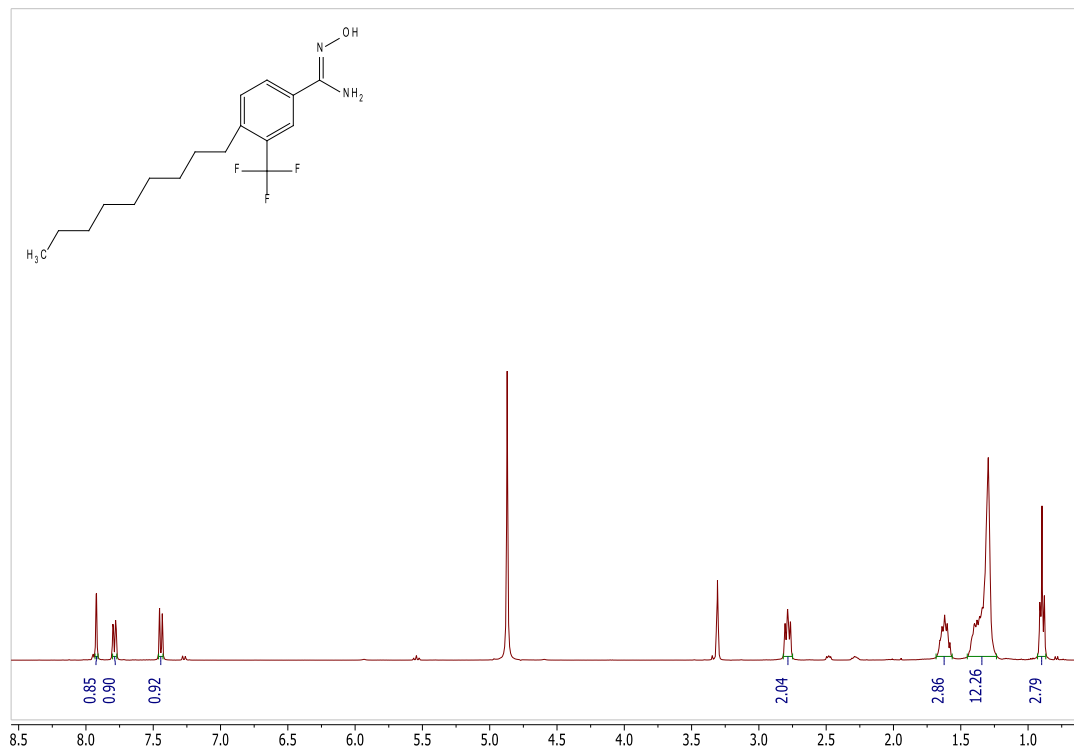
<sup>13</sup>C-NMR Spectrum for (Z)-hydroxy-4-octyl-3-(trifluoromethyl)benzimidamide –



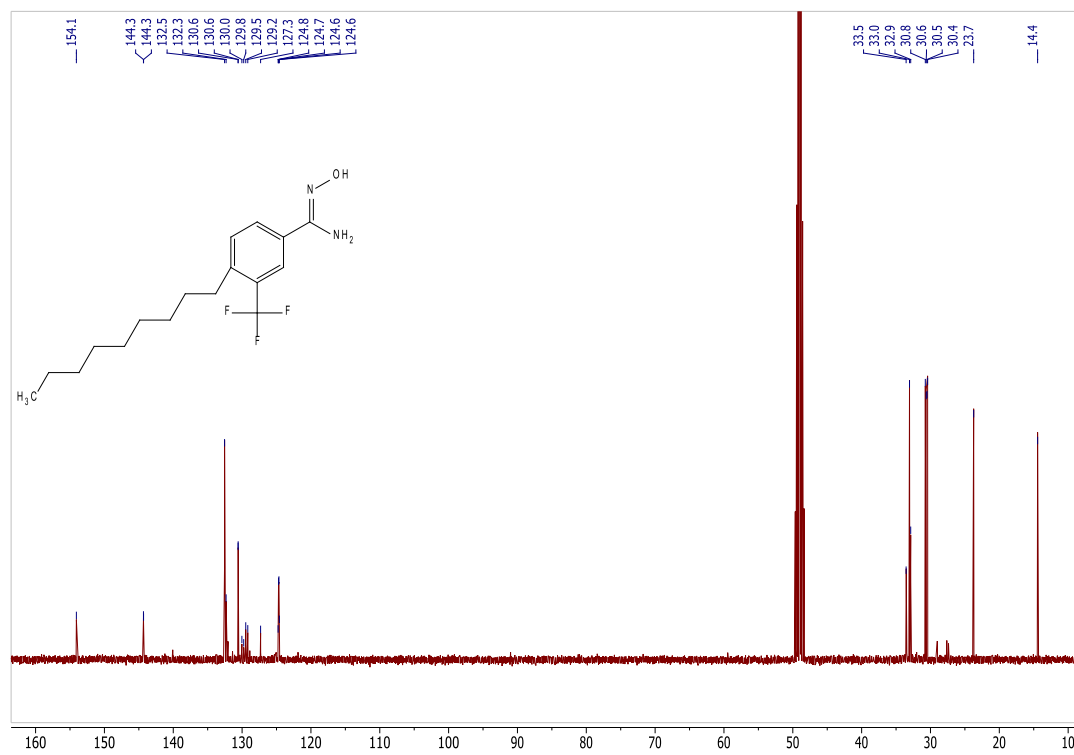
<sup>19</sup>F-NMR Spectrum for (Z)-hydroxy-4-octyl-3-(trifluoromethyl)benzimidamide –



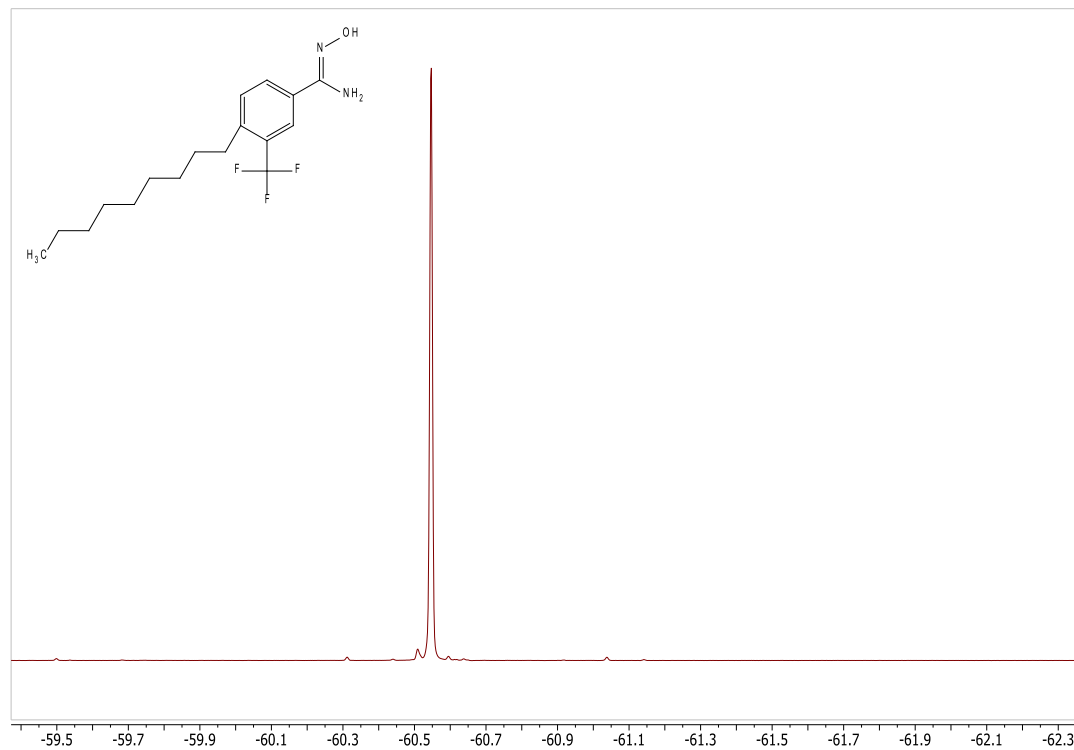
<sup>1</sup>H-NMR Spectrum for (Z)-hydroxy-4-nonyl-3-(trifluoromethyl)benzimidamide –



<sup>13</sup>C-NMR Spectrum for (Z)-hydroxy-4-nonyl-3-(trifluoromethyl)benzimidamide –

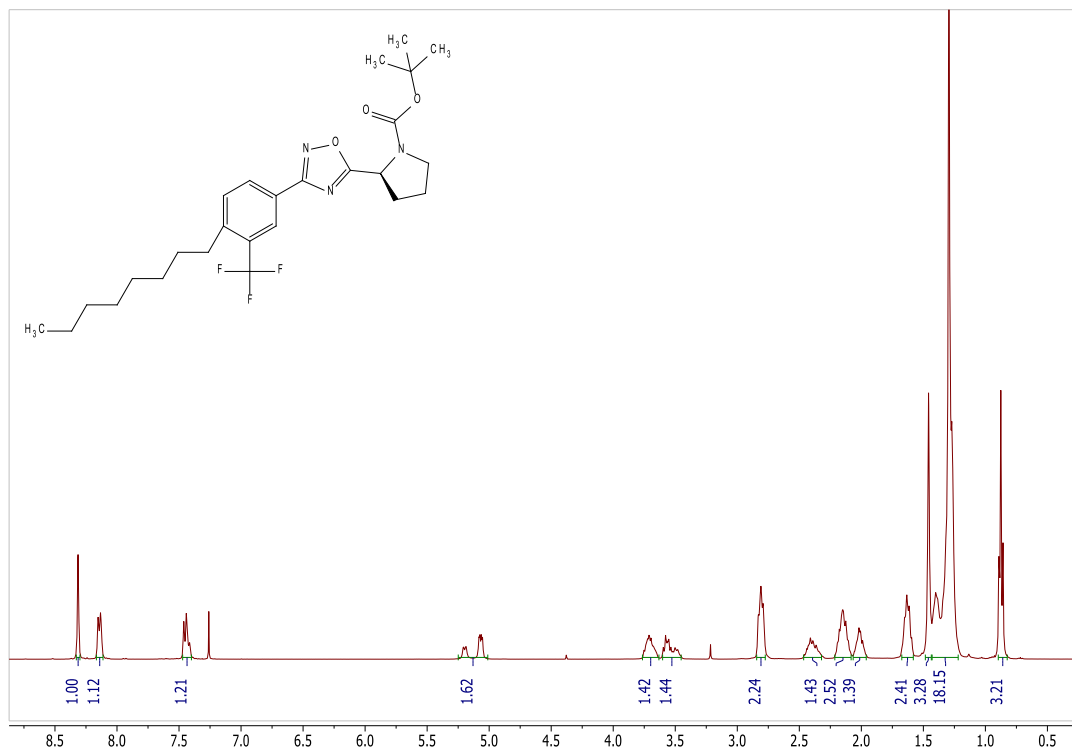


<sup>19</sup>F-NMR Spectrum for (Z)-hydroxy-4-nonyl-3-(trifluoromethyl)benzimidamide –

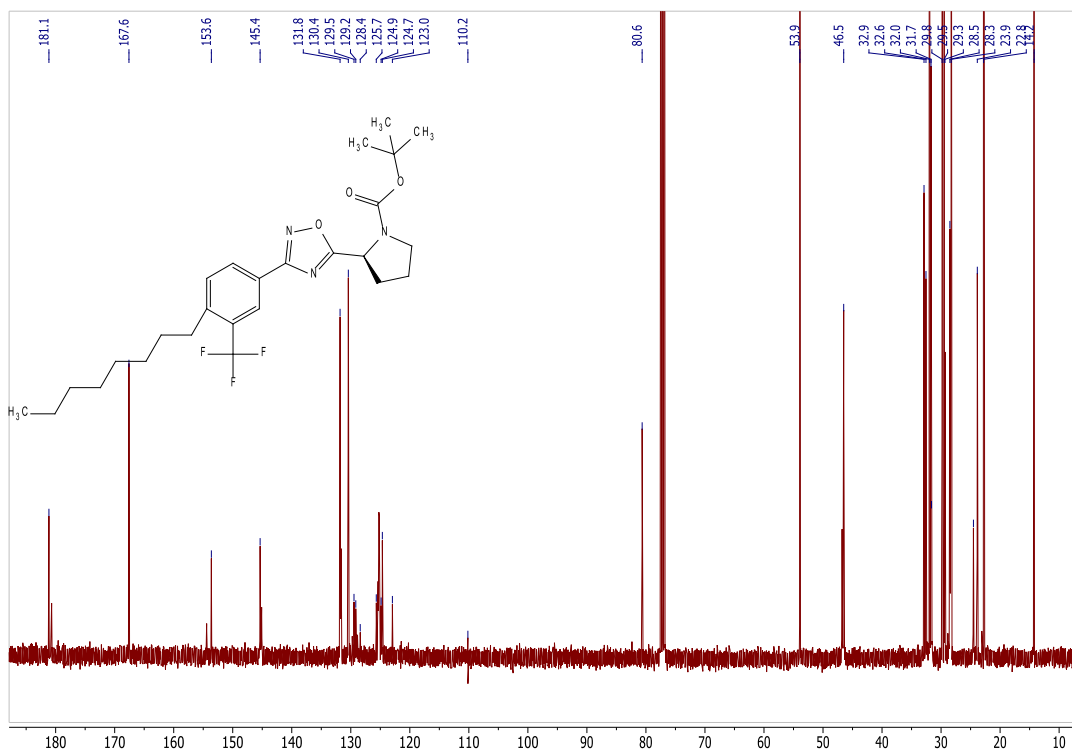




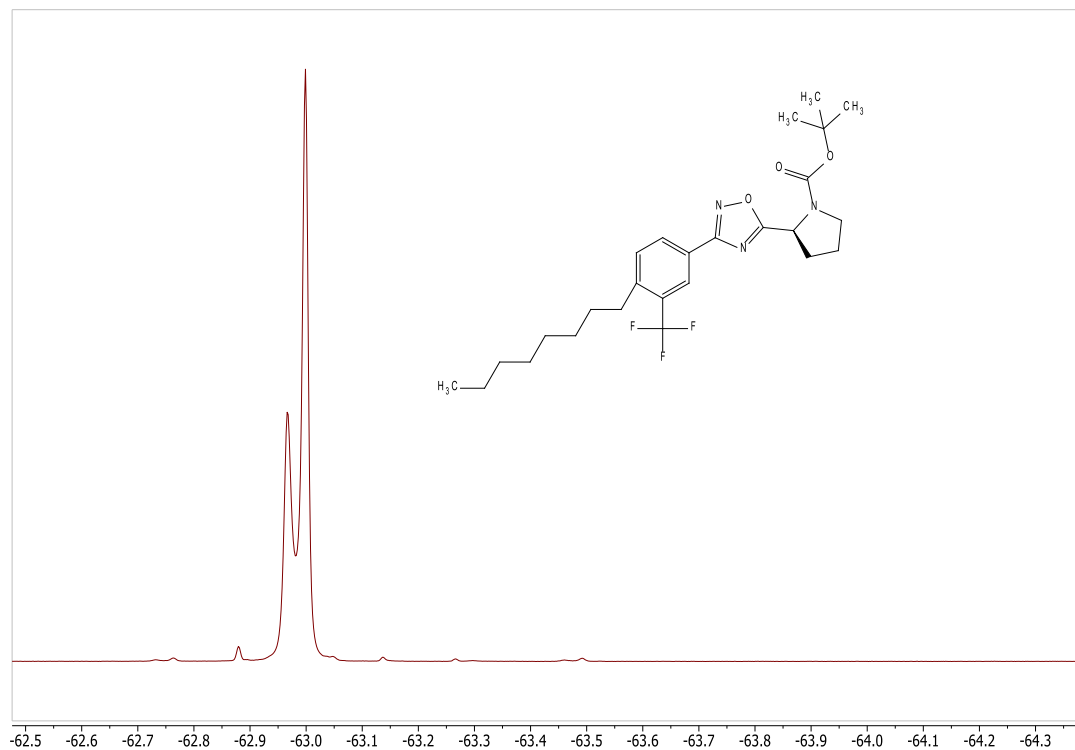
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



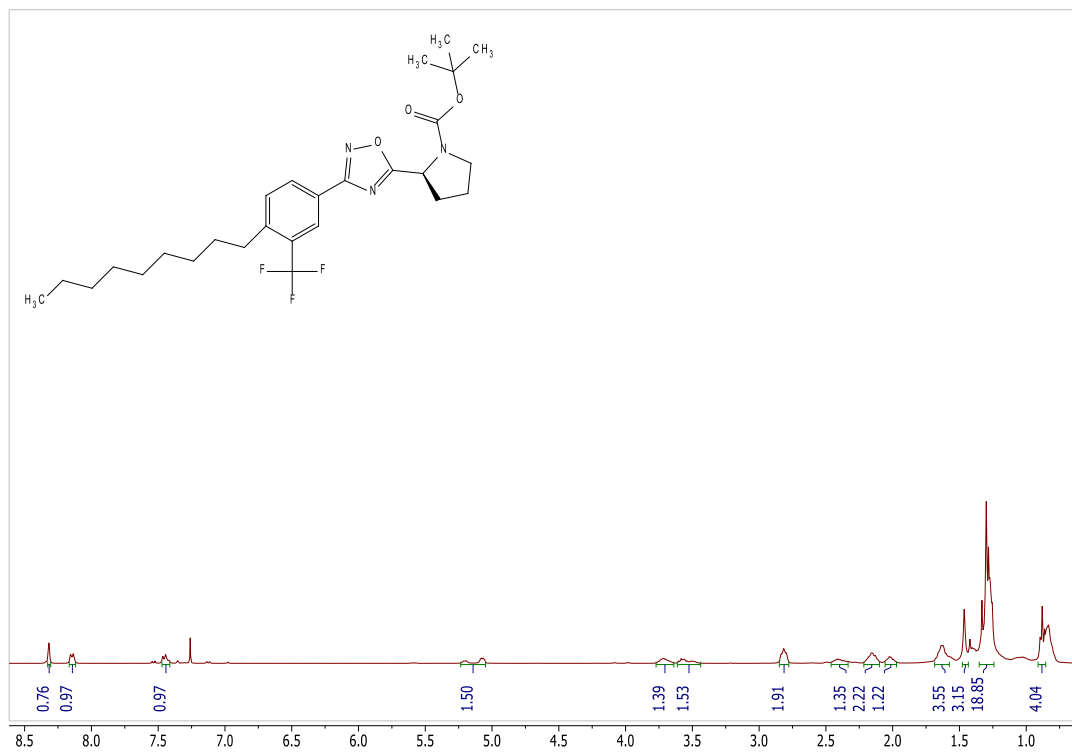
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



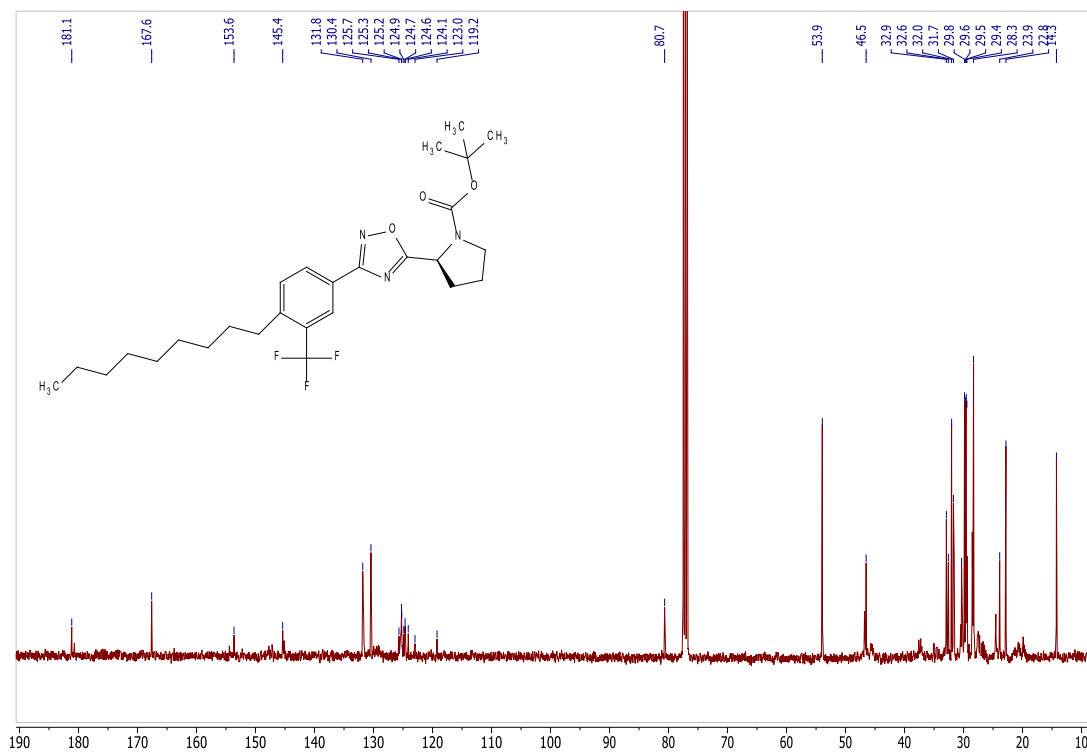
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



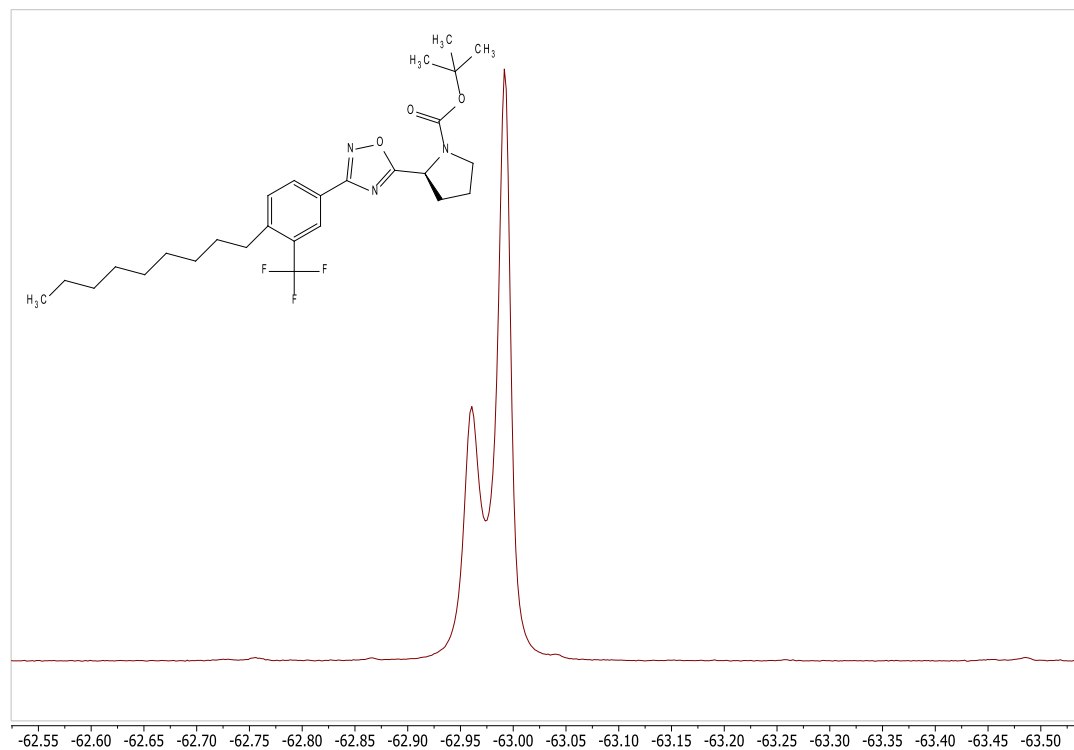
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



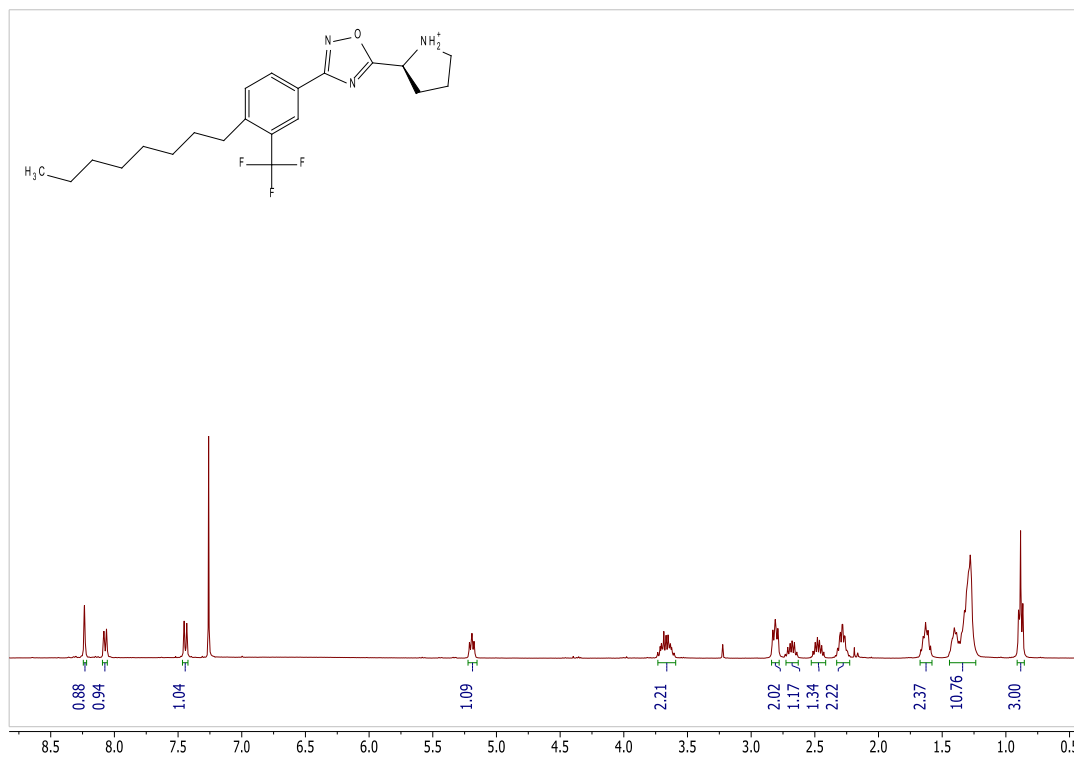
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



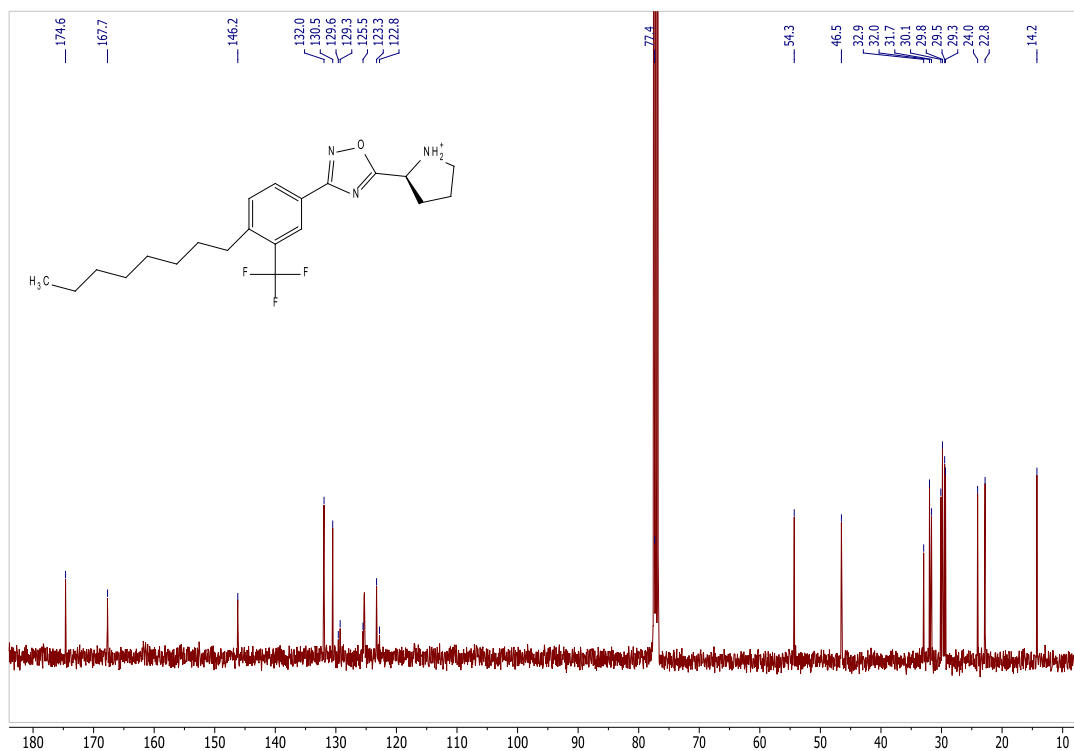
<sup>19</sup>F-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



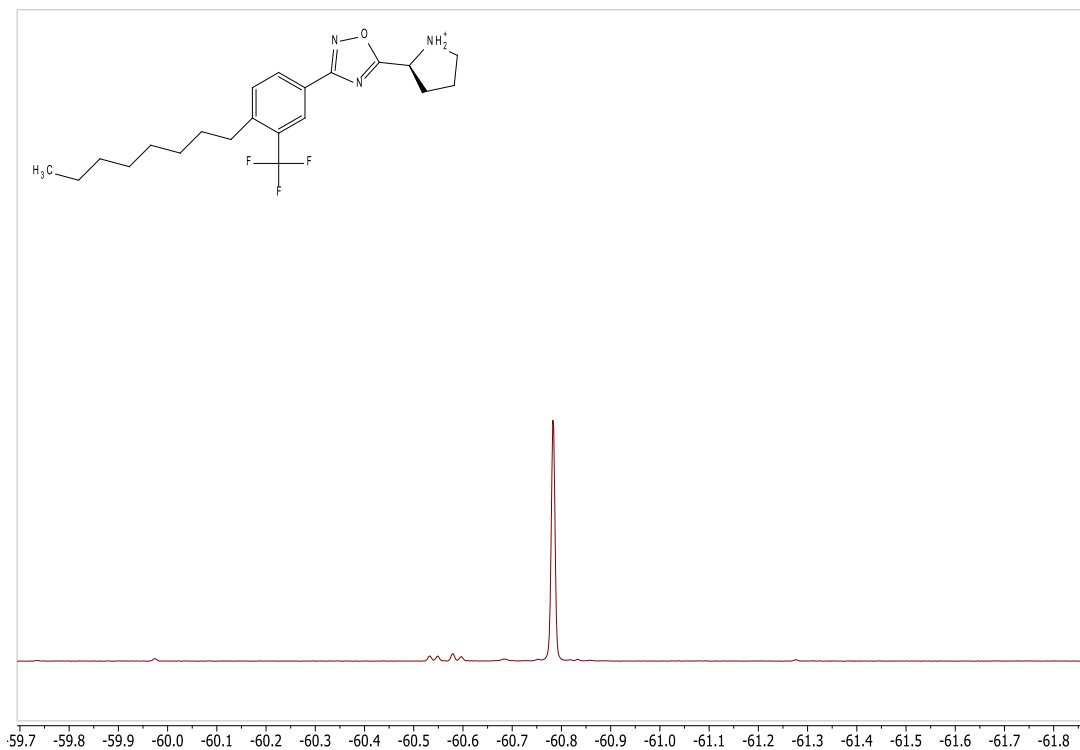
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



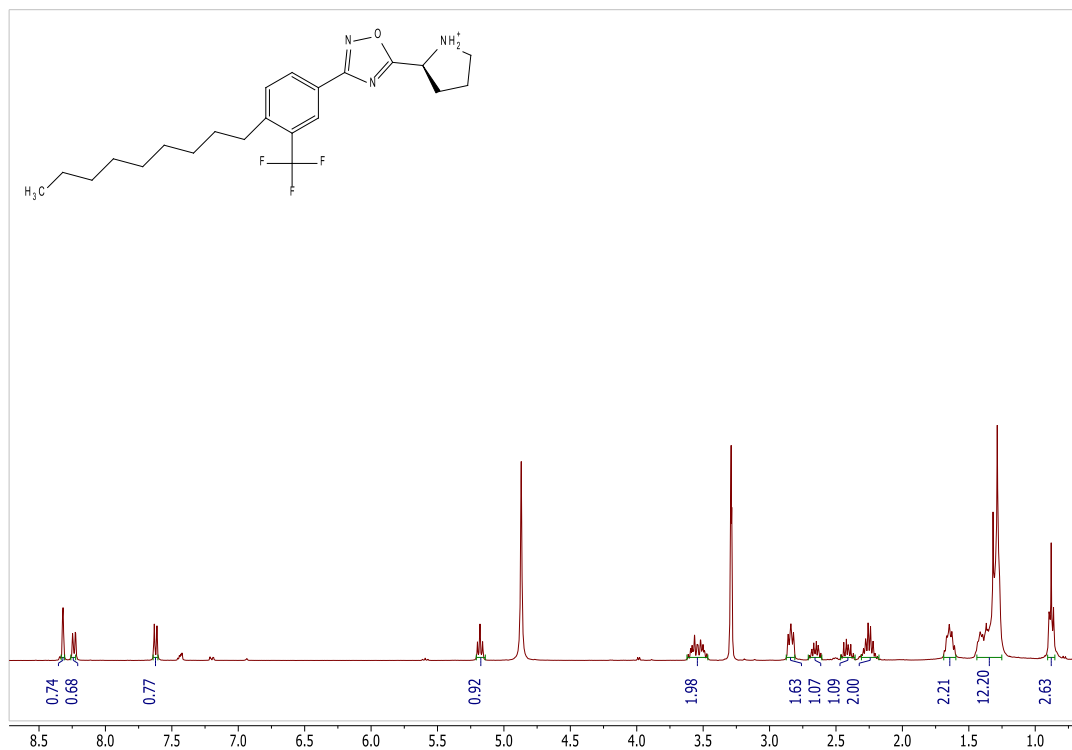
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



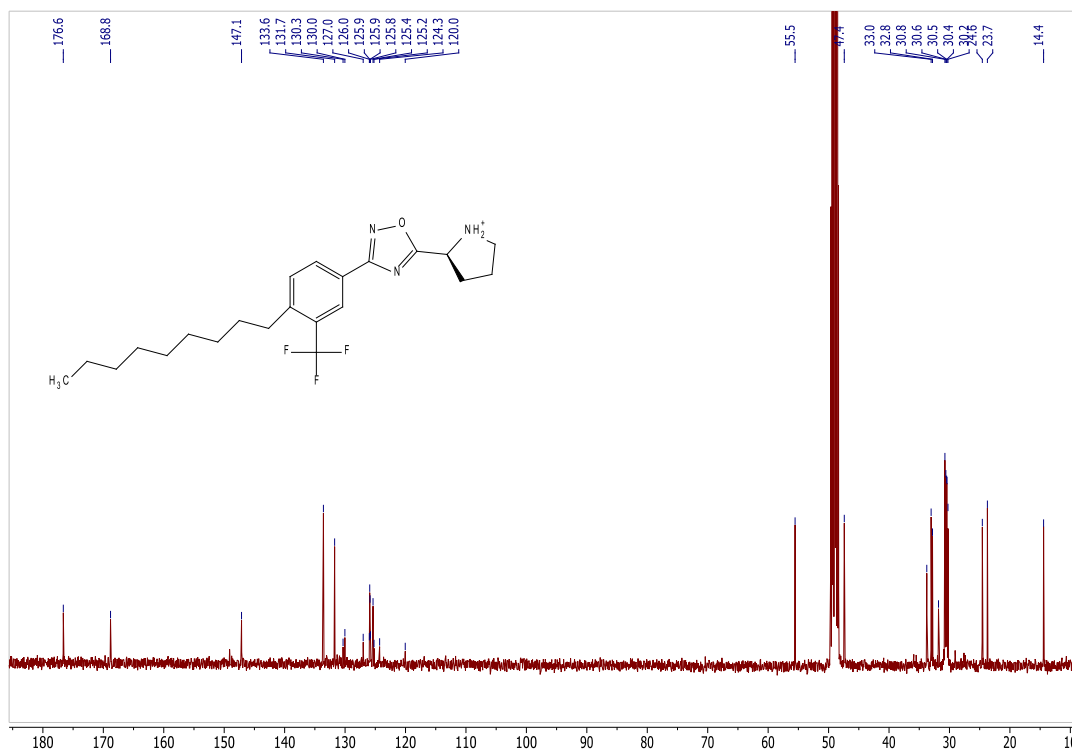
$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



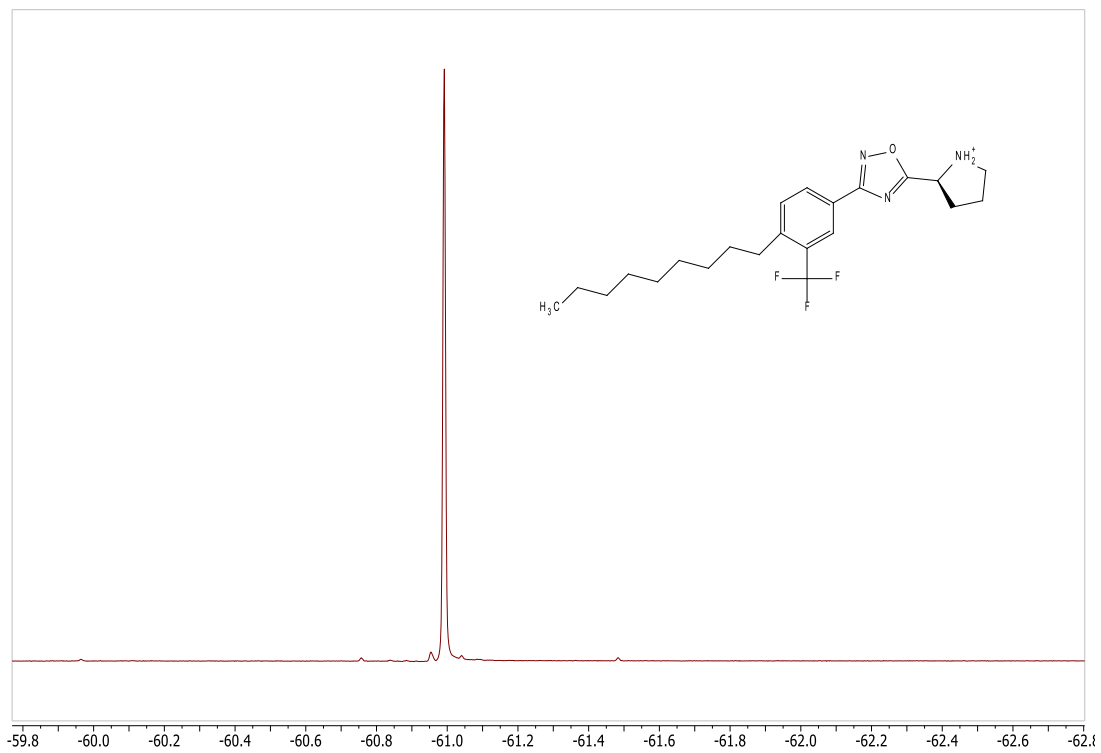
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –



<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –

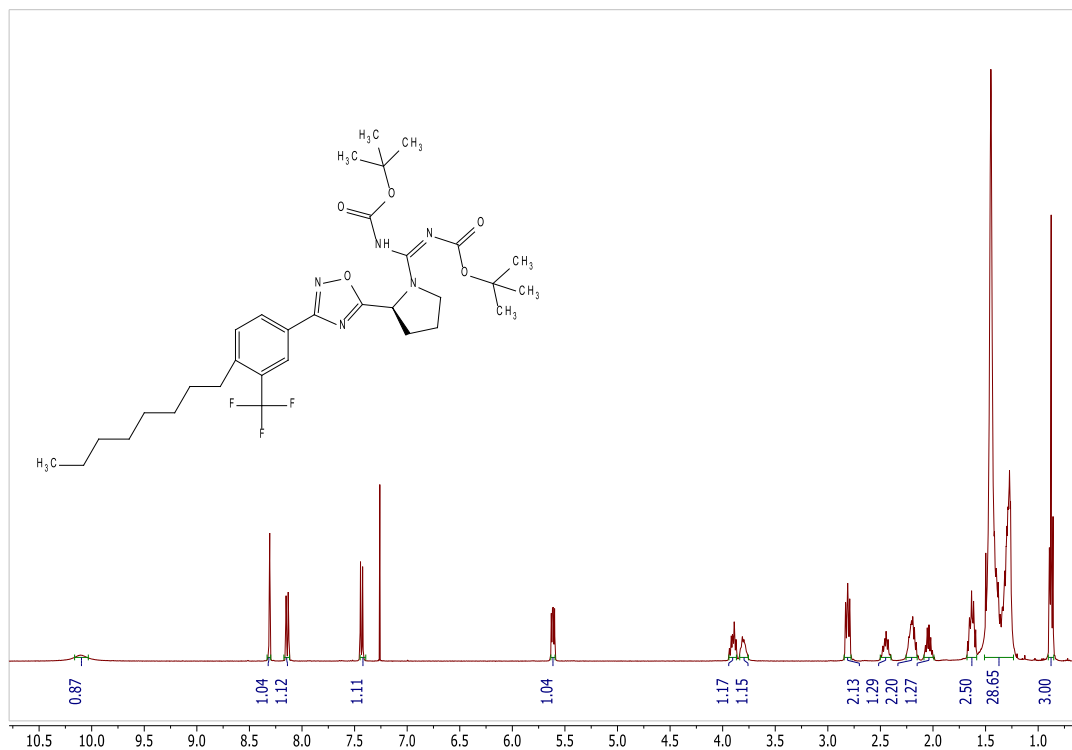


$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate –

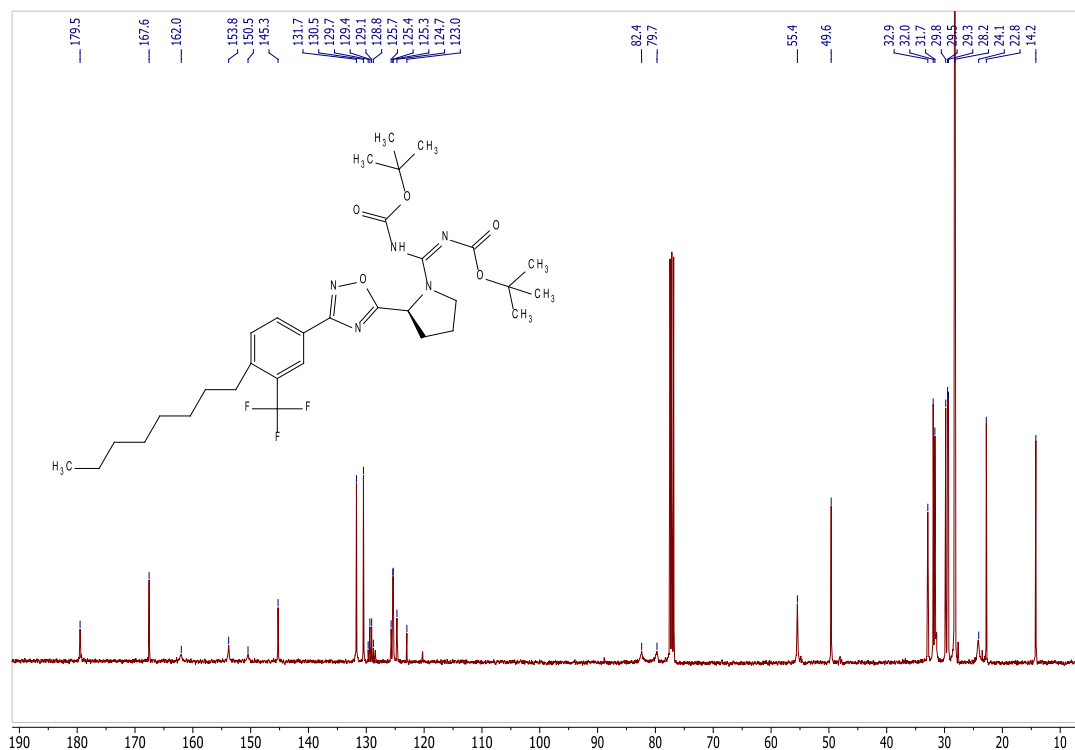




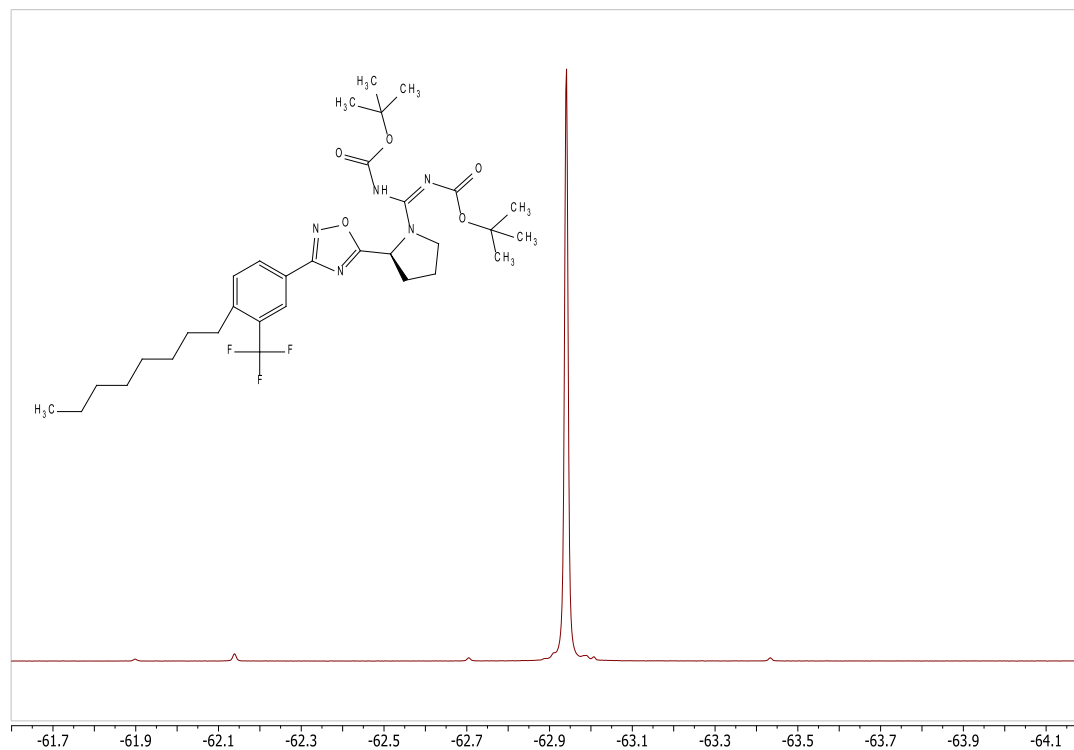
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



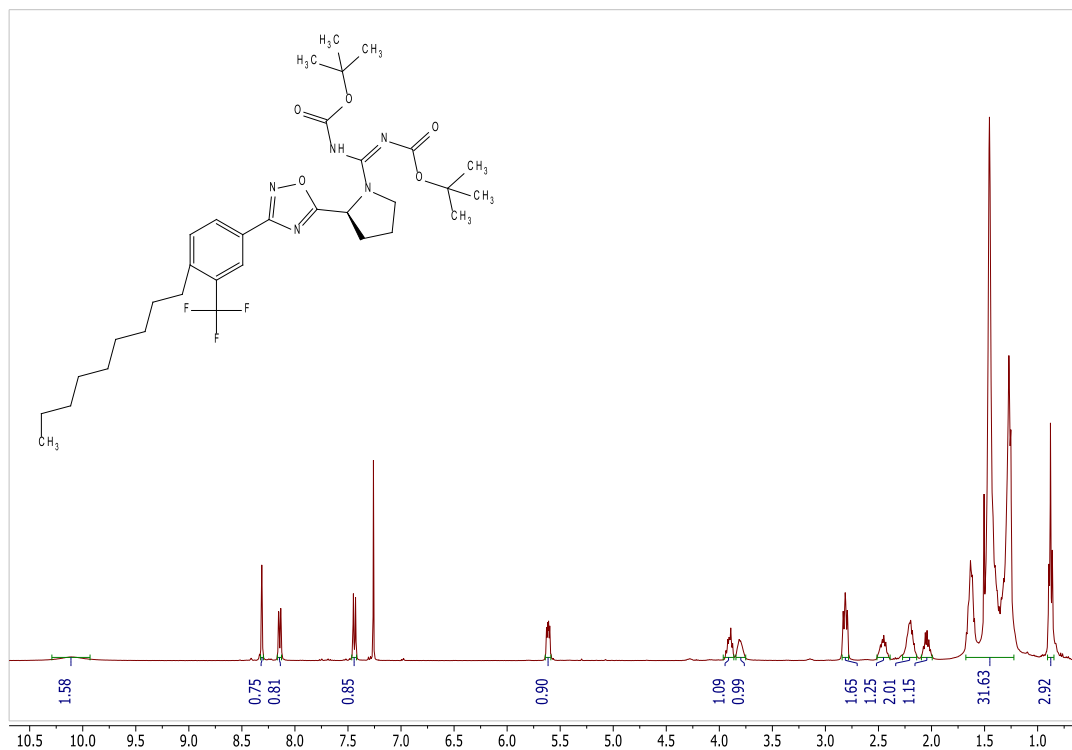
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



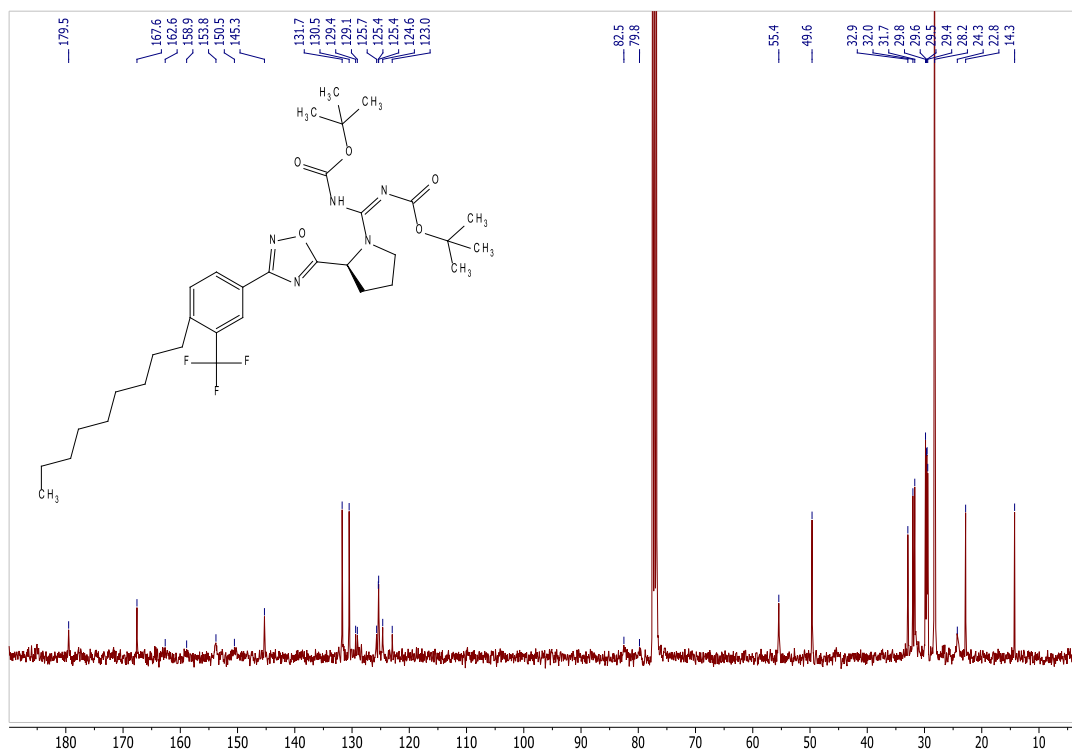
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



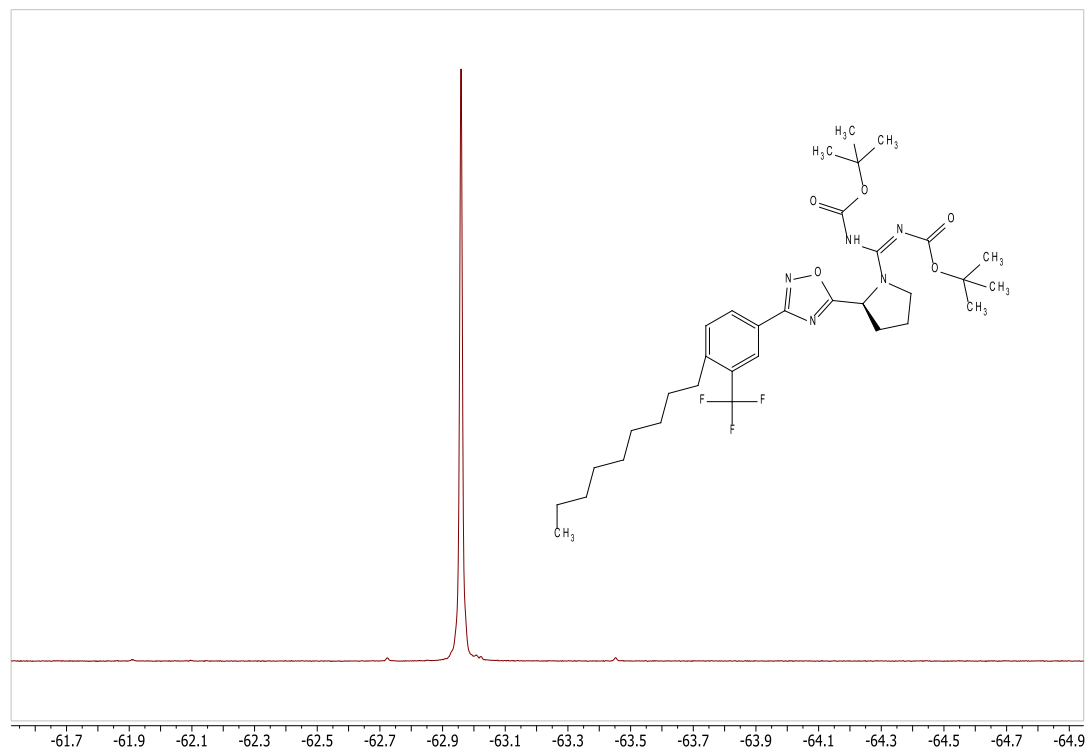
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



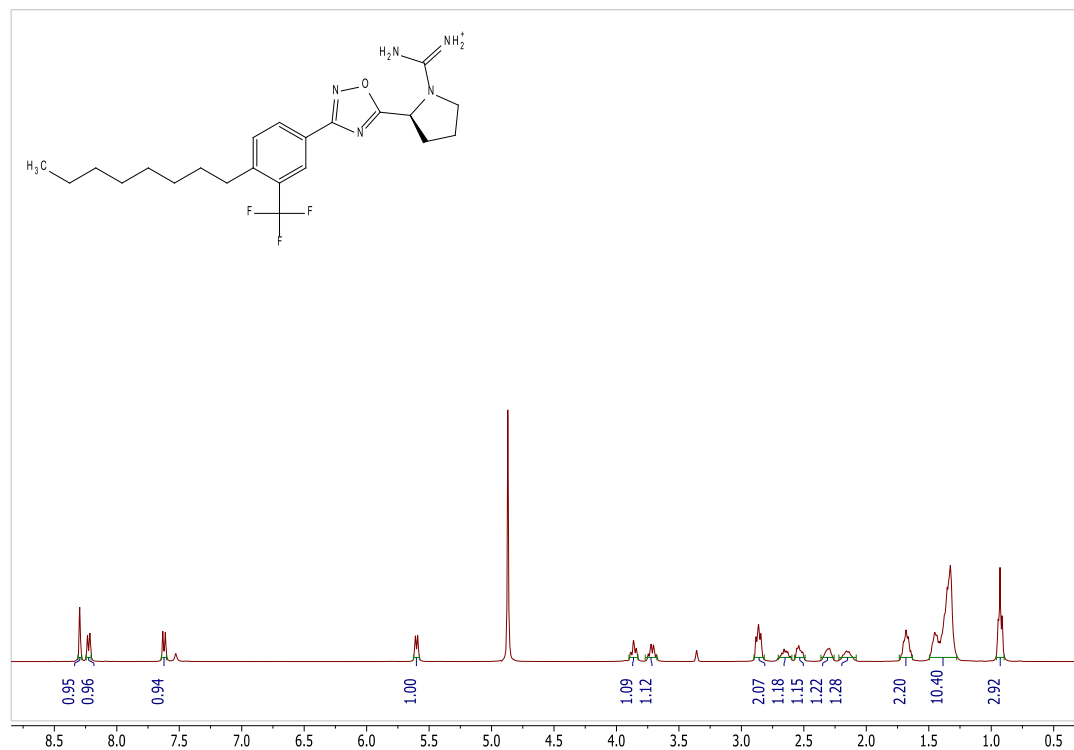
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



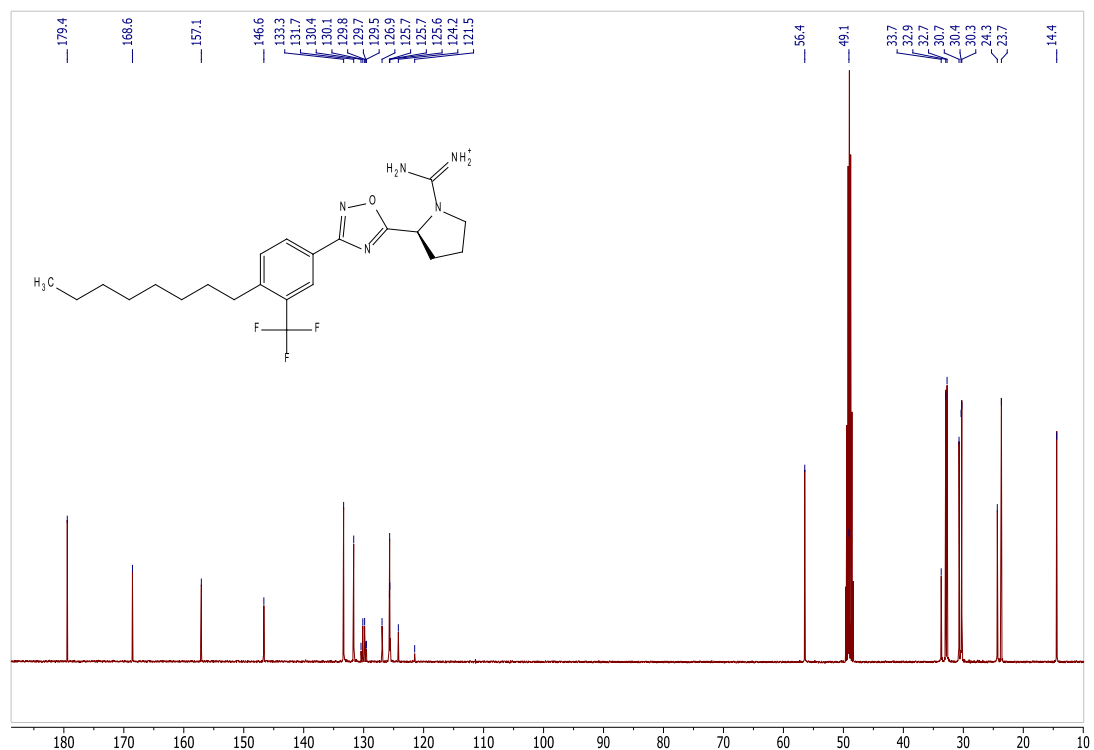
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate –



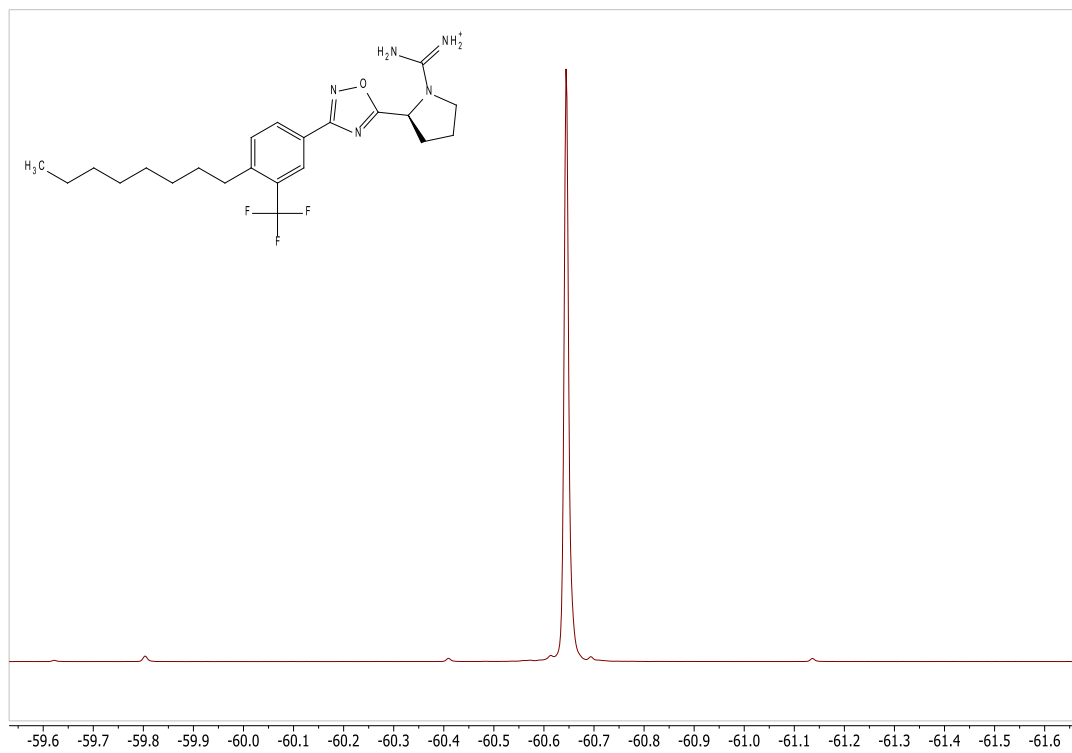
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.23a** –



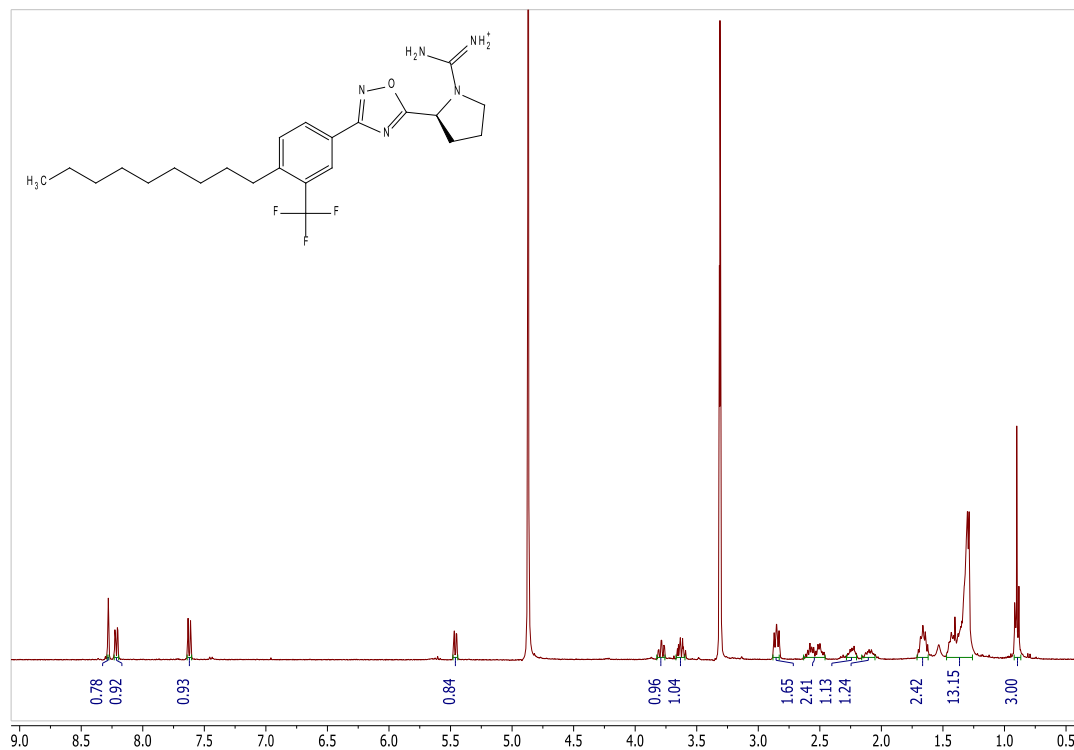
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.23a** –



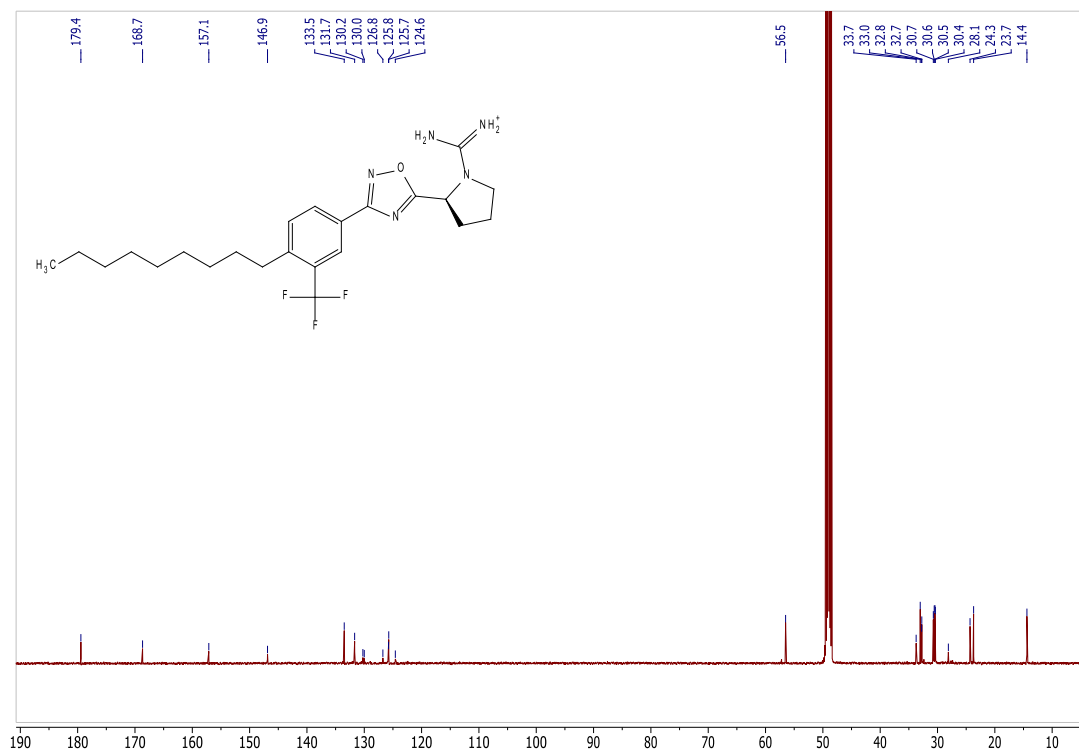
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-octyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.23a** –



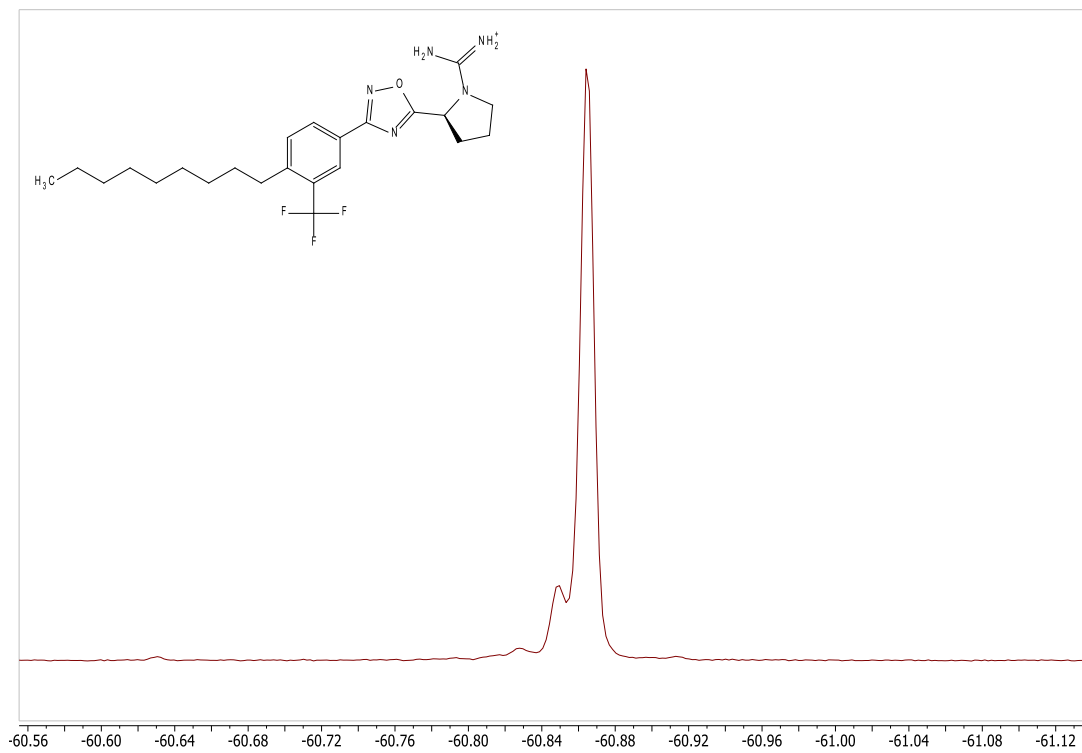
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.23b** –



<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.23b** –

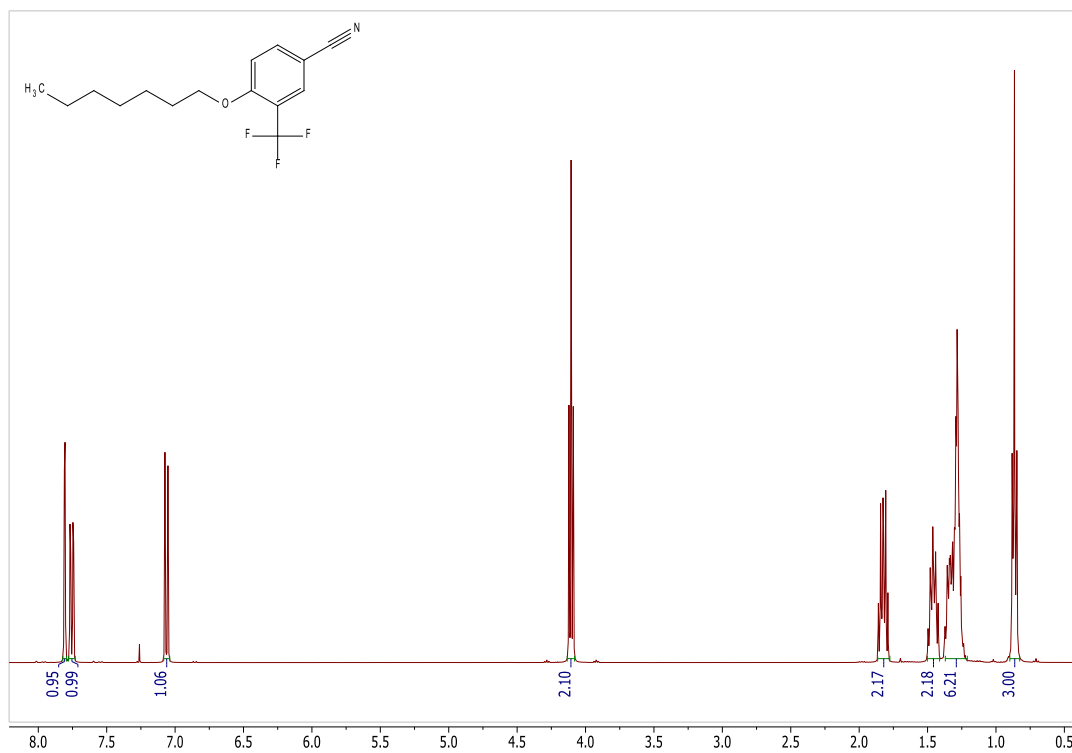


$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-nonyl-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.23b** –

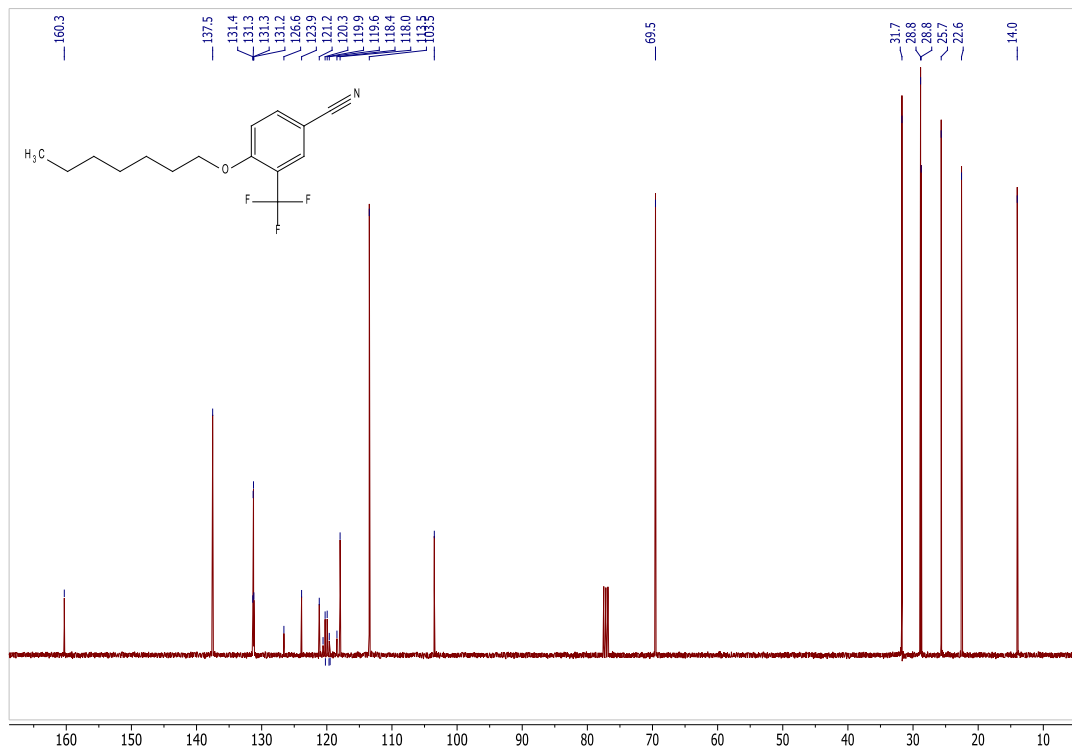




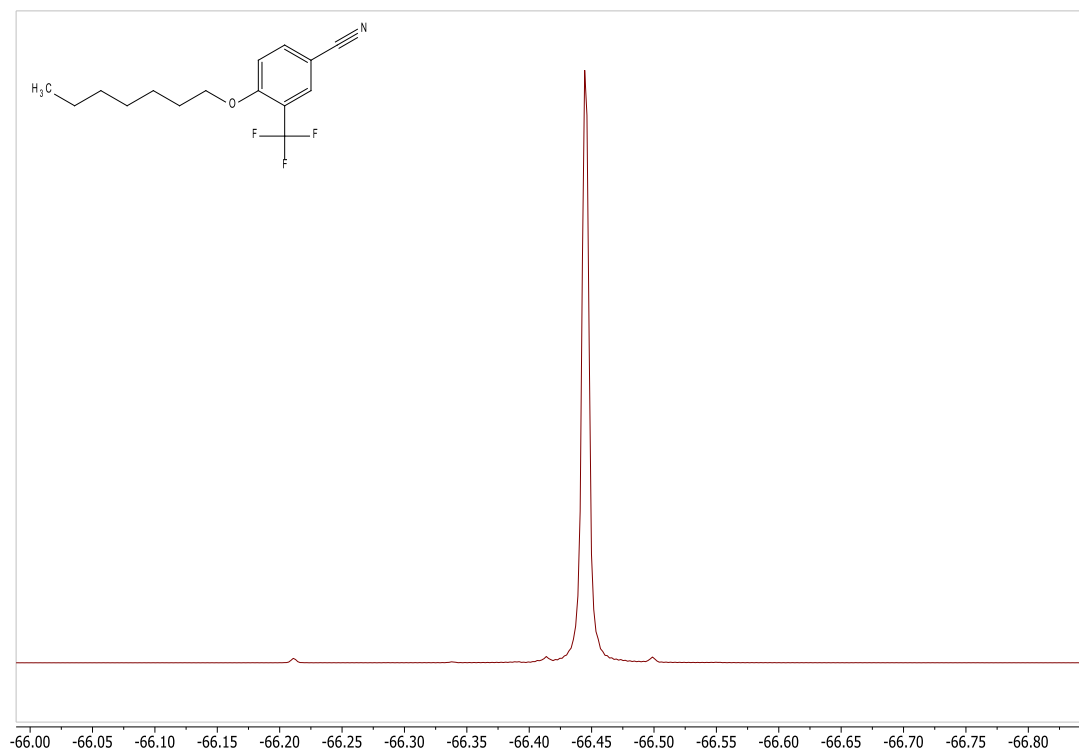
<sup>1</sup>H-NMR Spectrum for 4-(heptyloxy)-3-(trifluoromethyl)benzonitrile **3.25a** –



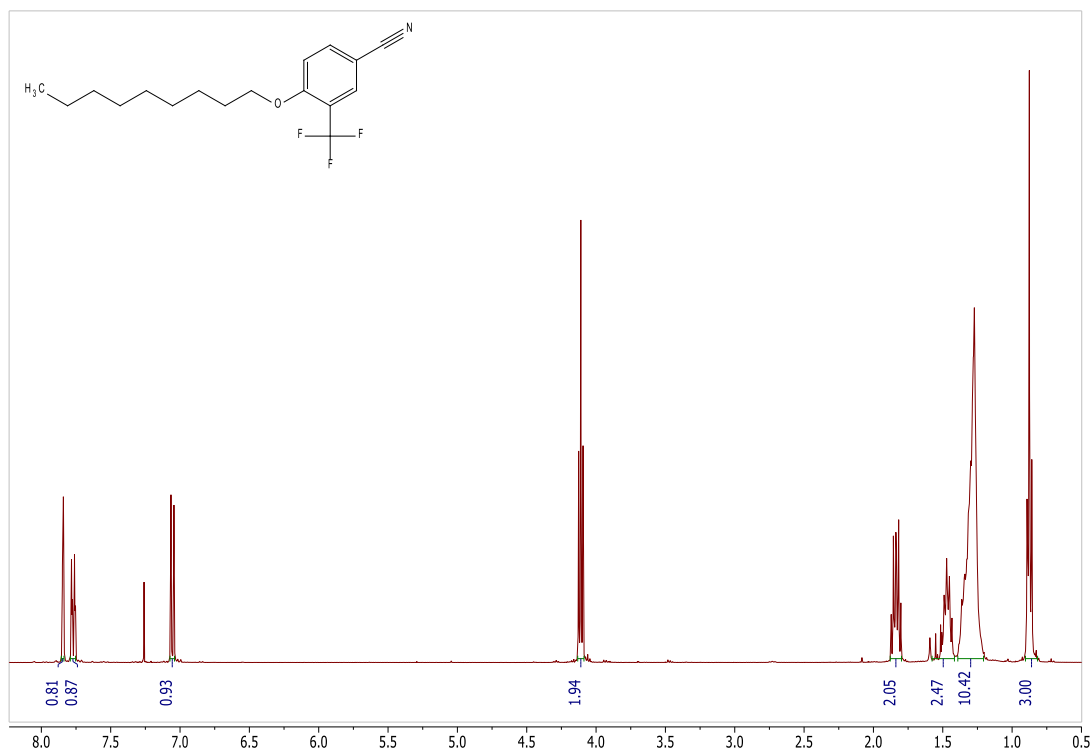
<sup>13</sup>C-NMR Spectrum for 4-(heptyloxy)-3-(trifluoromethyl)benzonitrile **3.25a** –



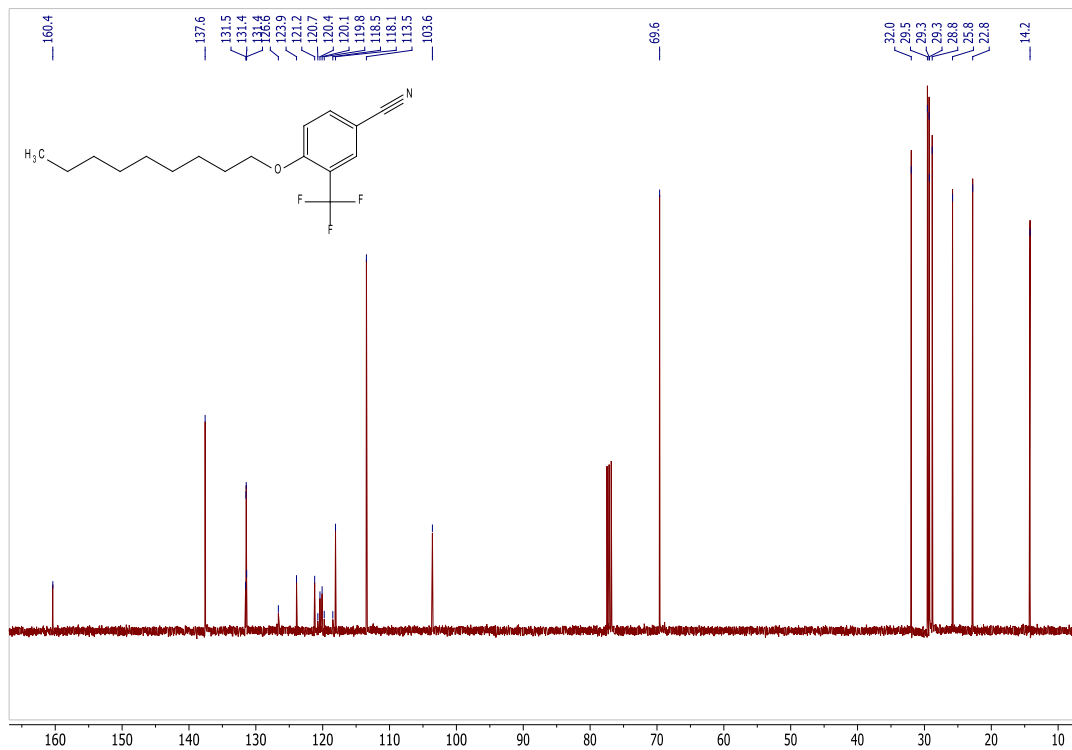
<sup>19</sup>F-NMR Spectrum for 4-(heptyloxy)-3-(trifluoromethyl)benzonitrile **3.25a** –



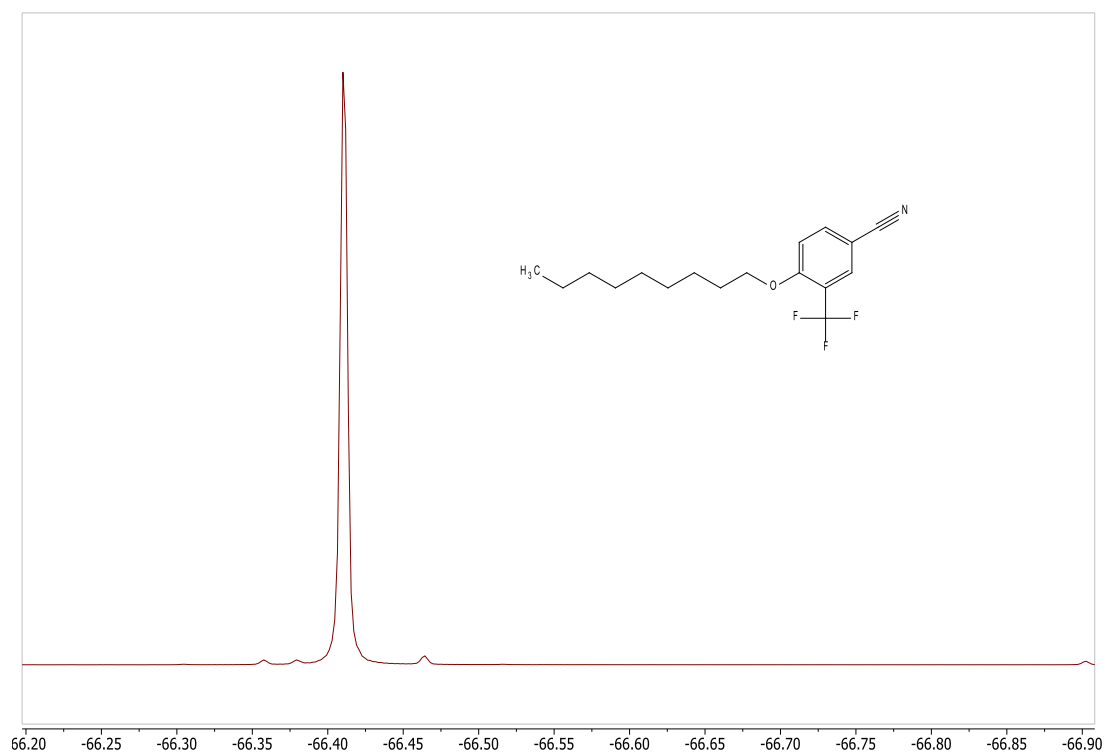
<sup>1</sup>H-NMR Spectrum for 4-(nonyloxy)-3-(trifluoromethyl)benzonitrile **3.25b** –



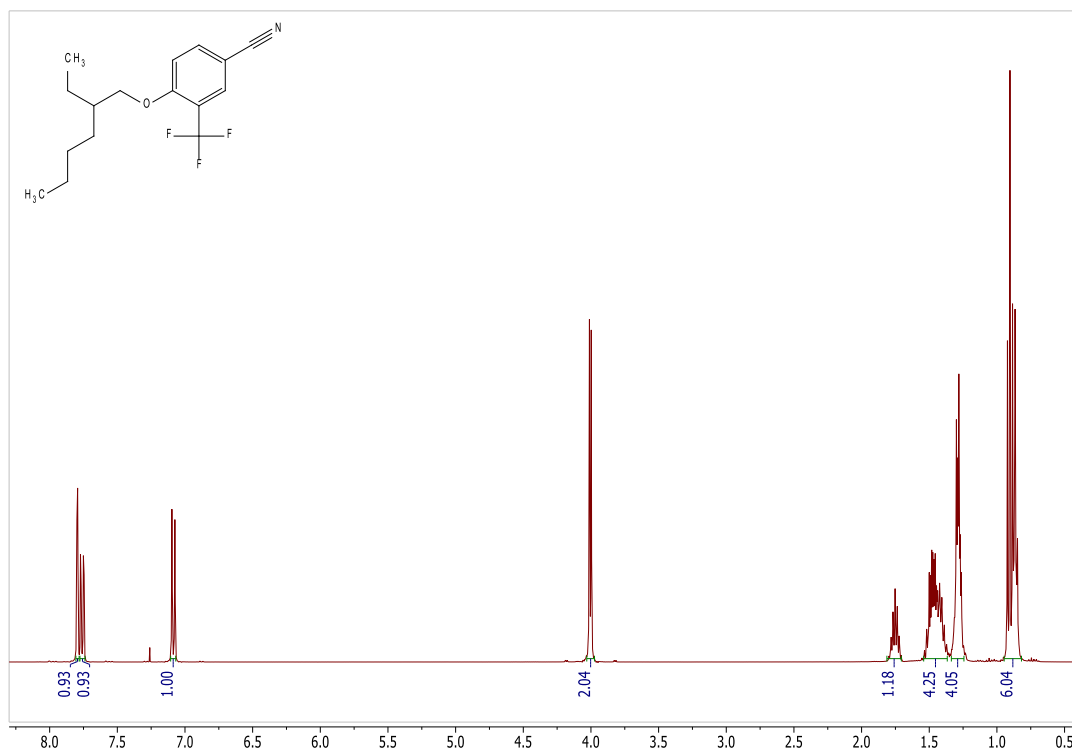
<sup>13</sup>C-NMR Spectrum for 4-(nonyloxy)-3-(trifluoromethyl)benzonitrile **3.25b** –



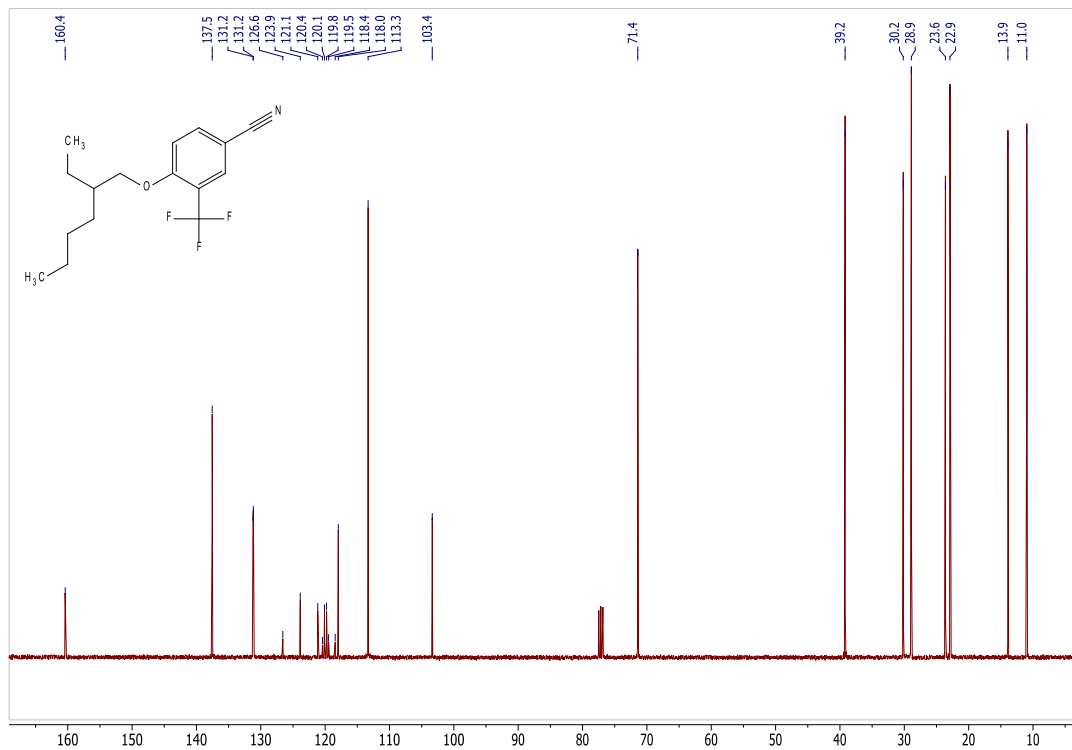
<sup>19</sup>F-NMR Spectrum for 4-(nonyloxy)-3-(trifluoromethyl)benzonitrile **3.25b** –



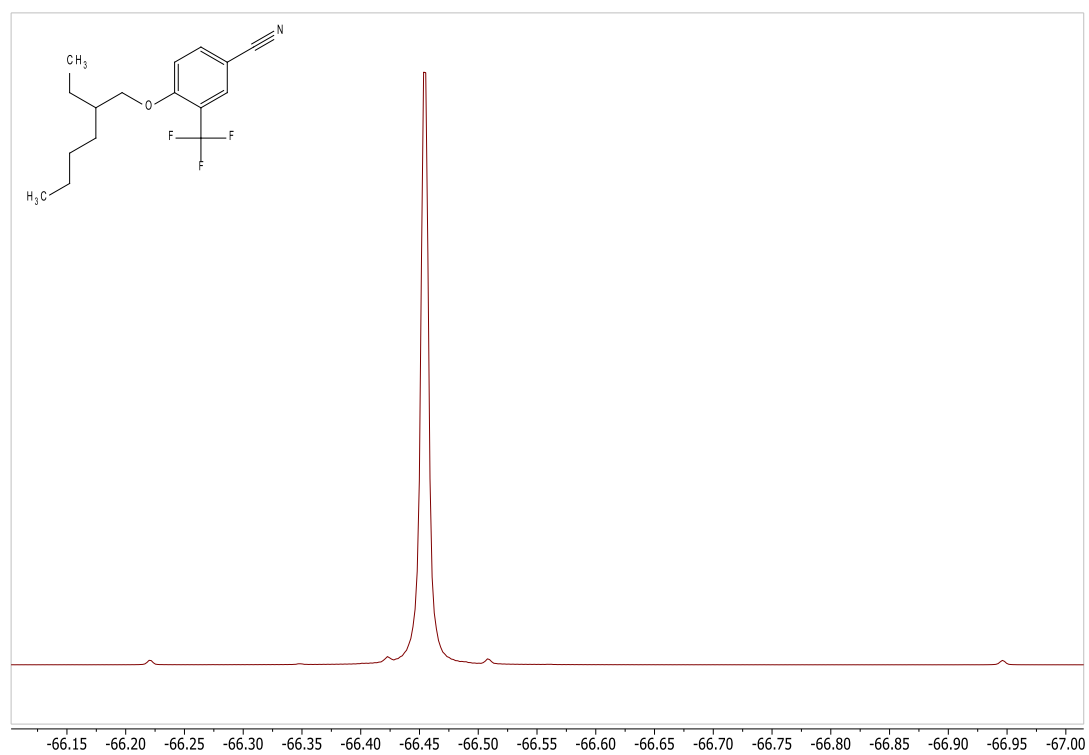
<sup>1</sup>H-NMR Spectrum for 4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)benzonitrile **3.25c** –



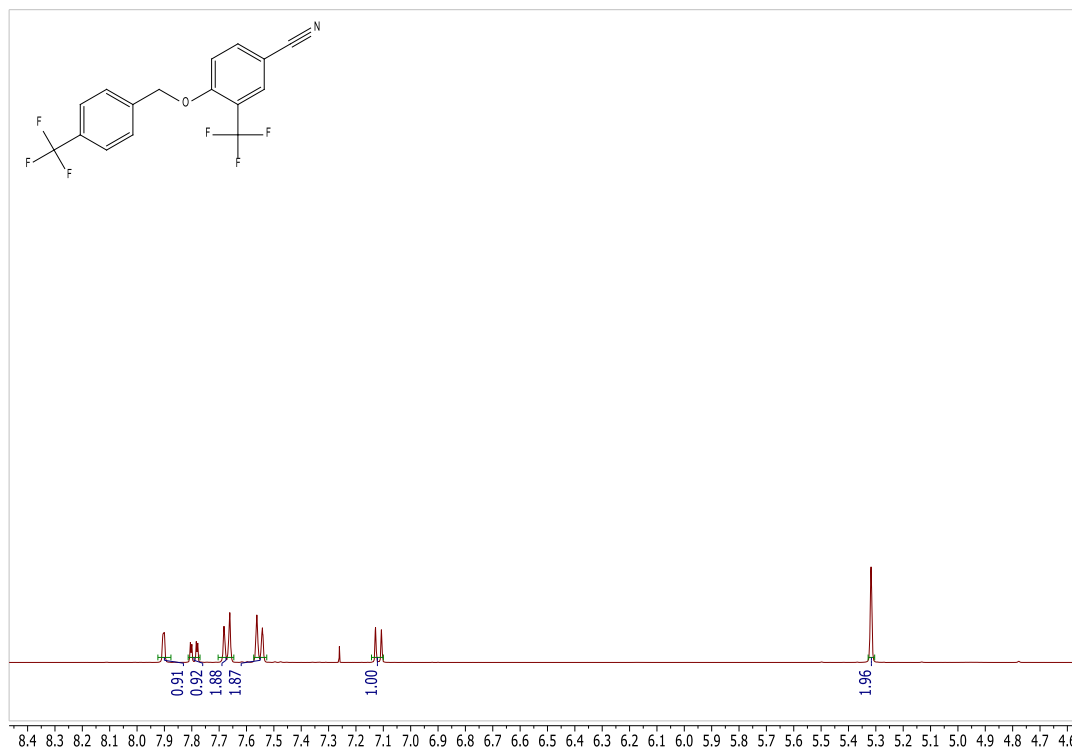
<sup>13</sup>C-NMR Spectrum for 4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)benzonitrile **3.25c** –



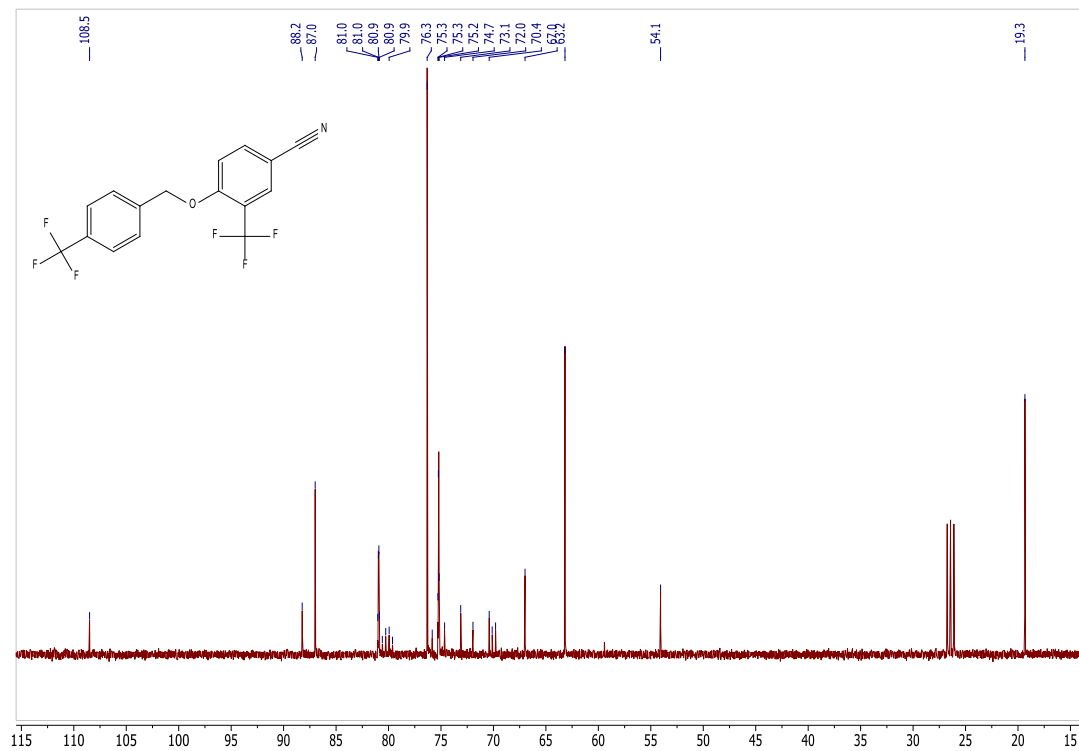
<sup>19</sup>F-NMR Spectrum for 4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)benzonitrile **3.25c** –



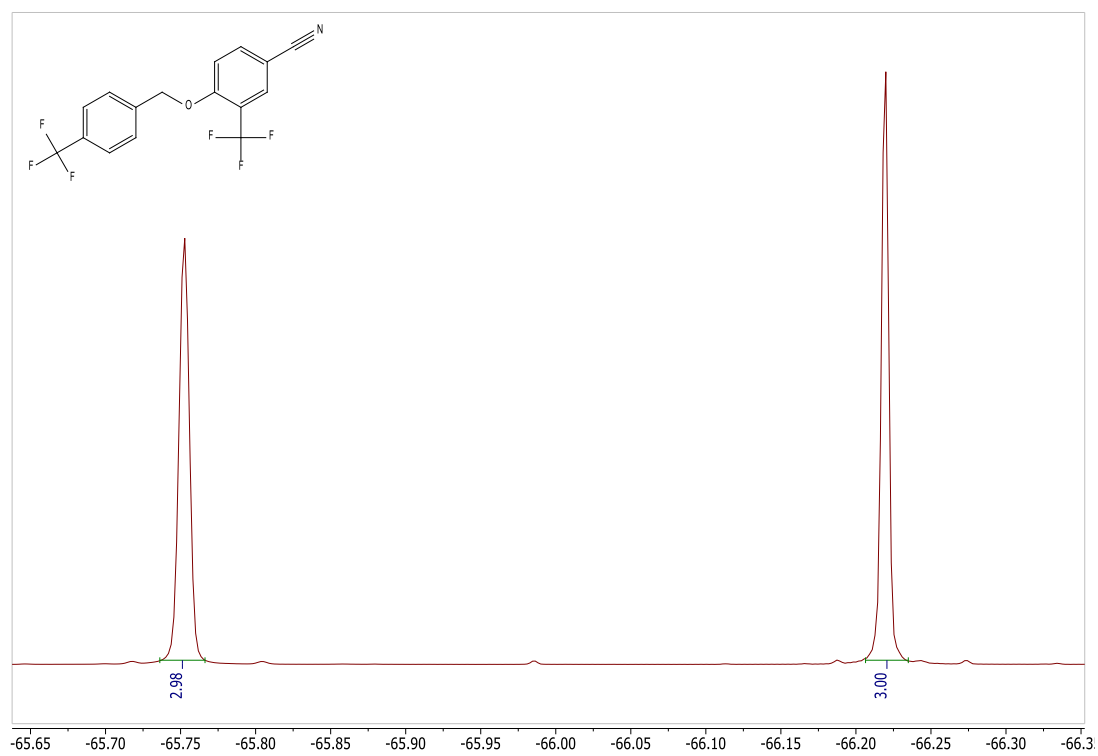
<sup>1</sup>H-NMR Spectrum for 3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)benzonitrile **3.25d**



<sup>13</sup>C-NMR Spectrum for 3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)benzonitrile **3.25d**

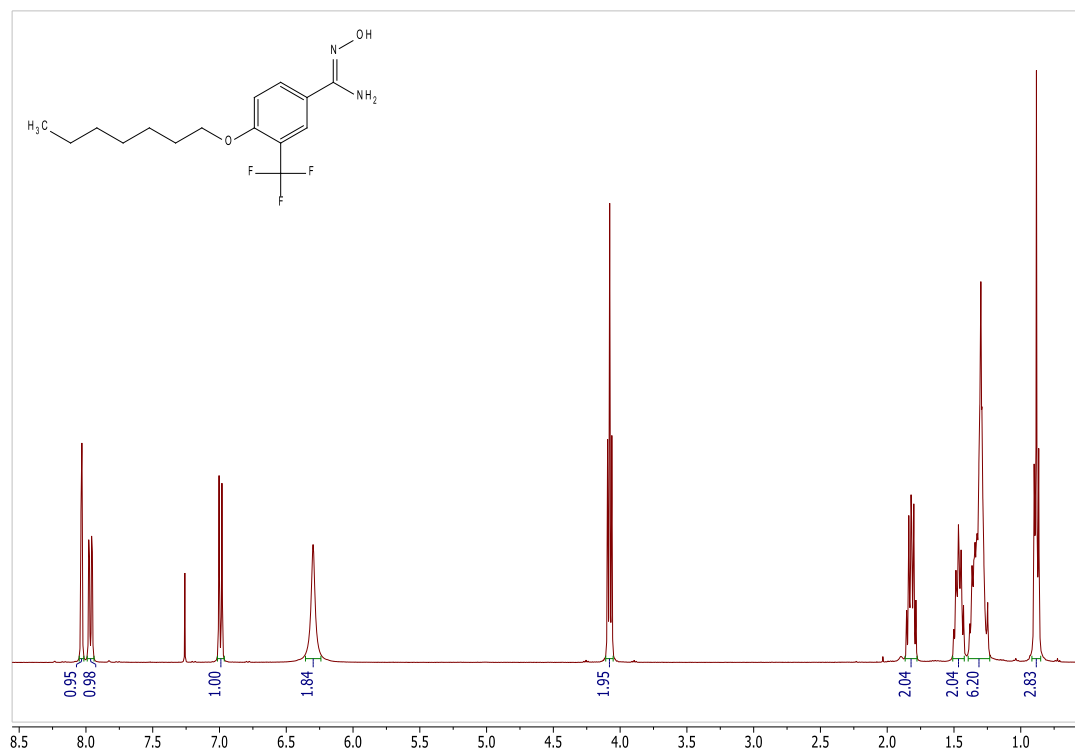


<sup>19</sup>F-NMR Spectrum for 3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)benzonitrile **3.25d**

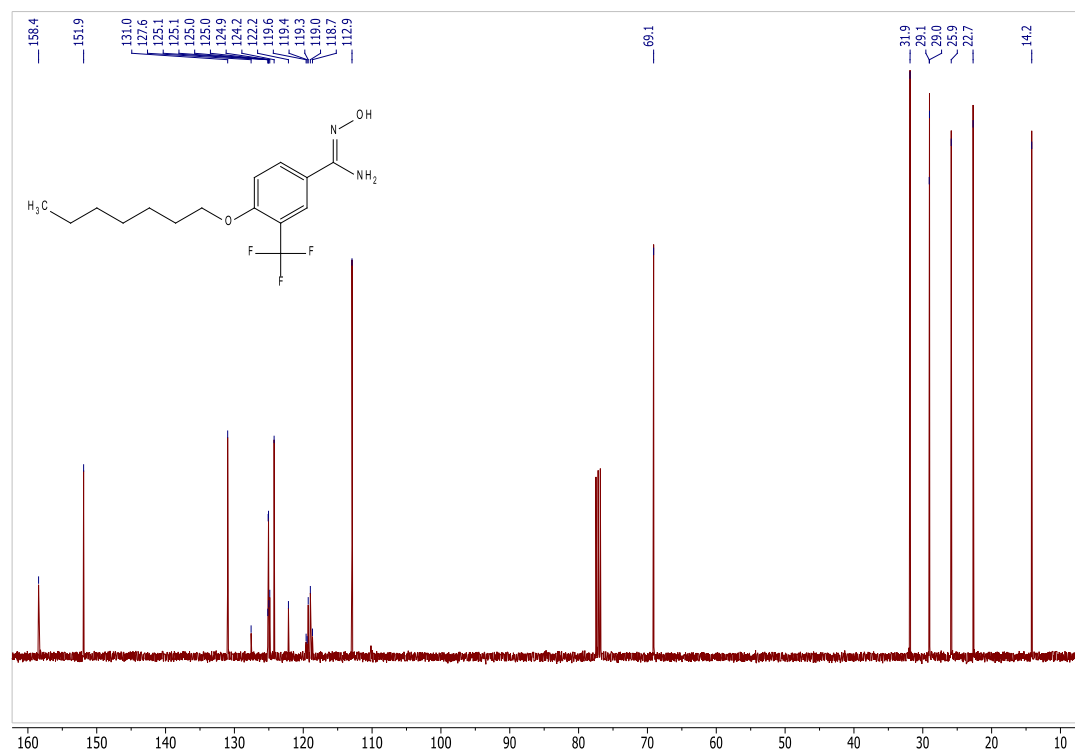




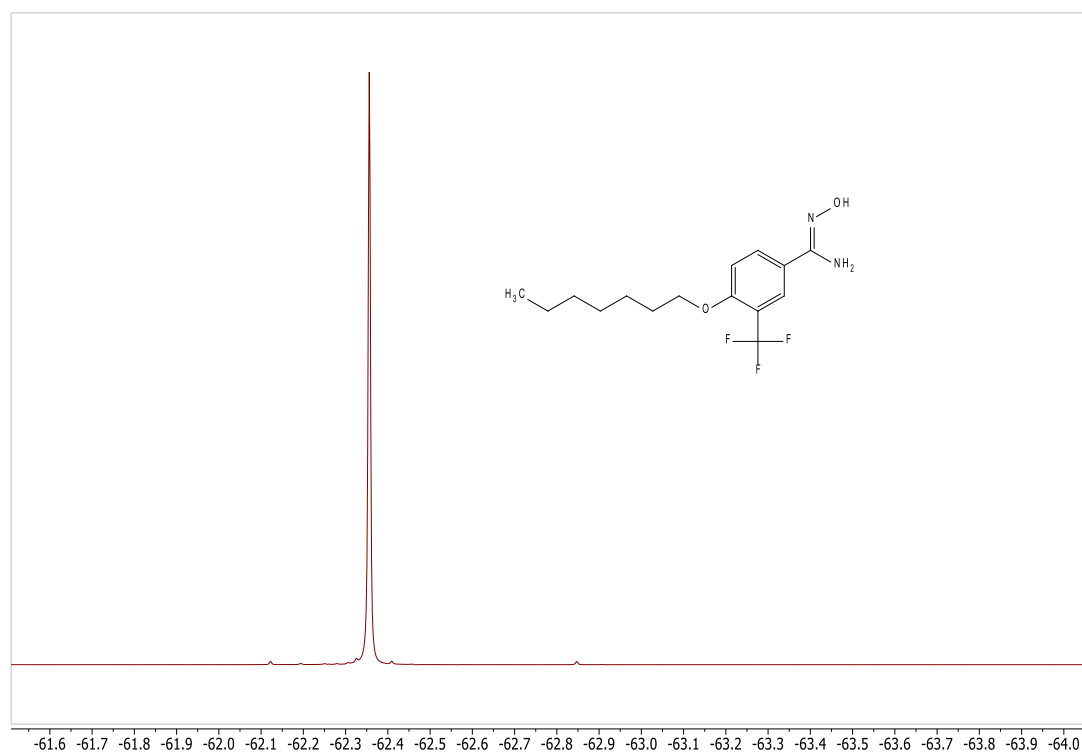
<sup>1</sup>H-NMR Spectrum for (Z)-4-(heptyloxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide **3.26a** –



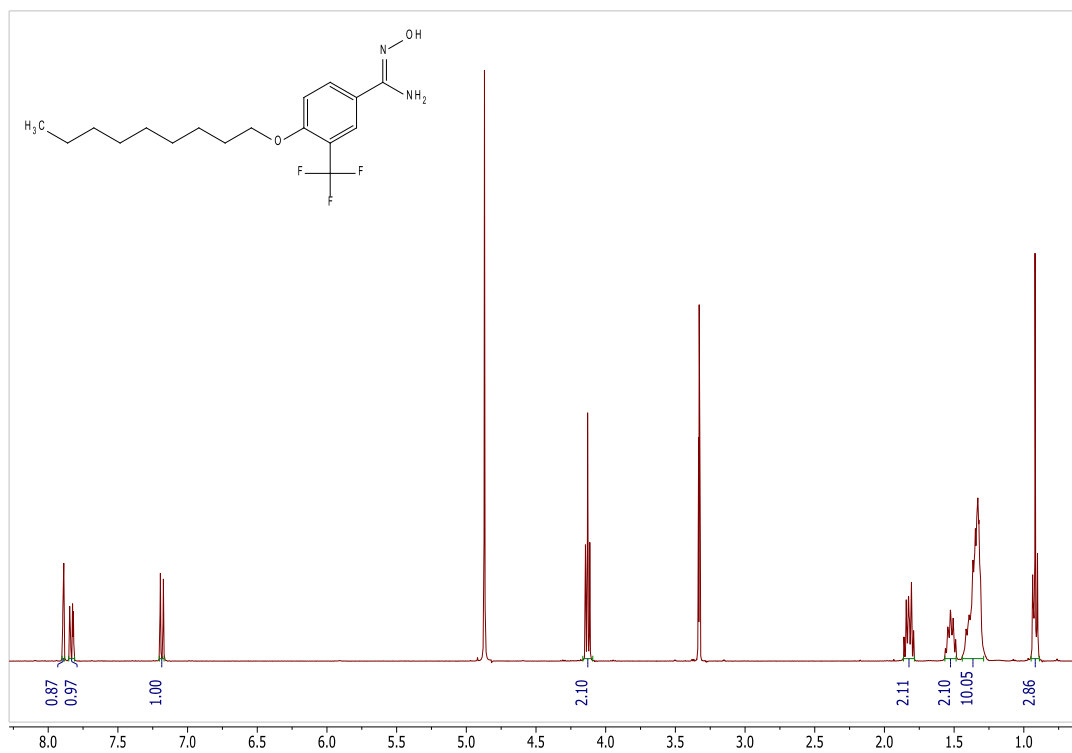
<sup>13</sup>C-NMR Spectrum for (Z)-4-(heptyloxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide **3.26a** –



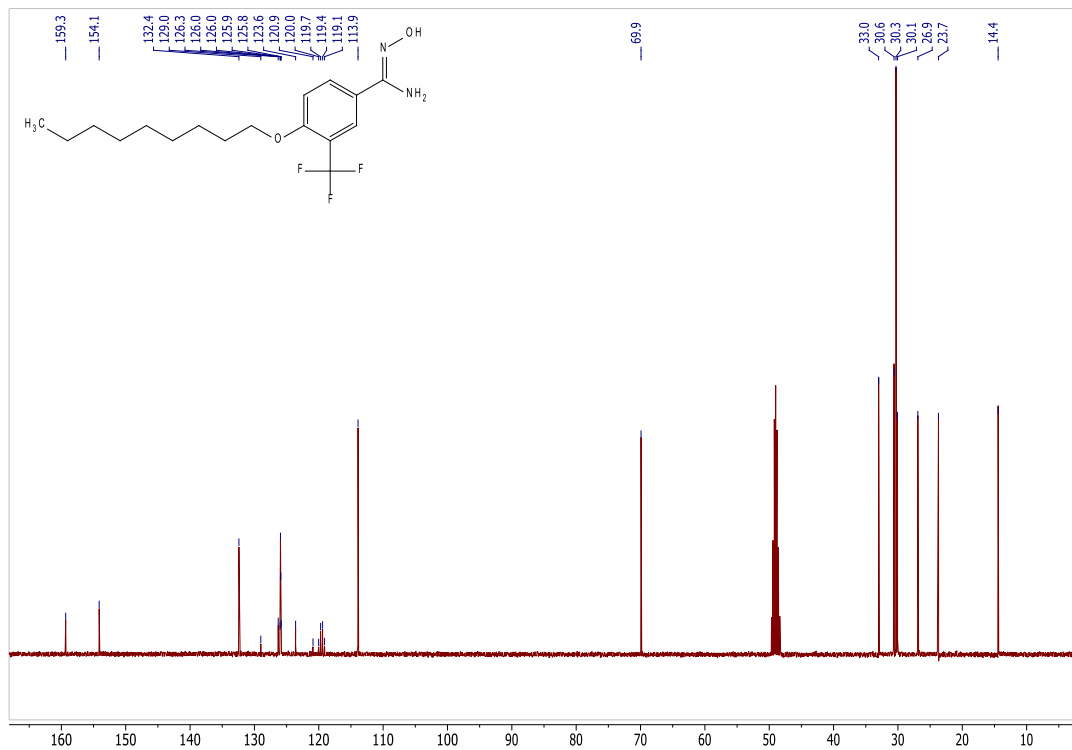
<sup>19</sup>F-NMR Spectrum for (Z)-4-(heptyloxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide **3.26a** –



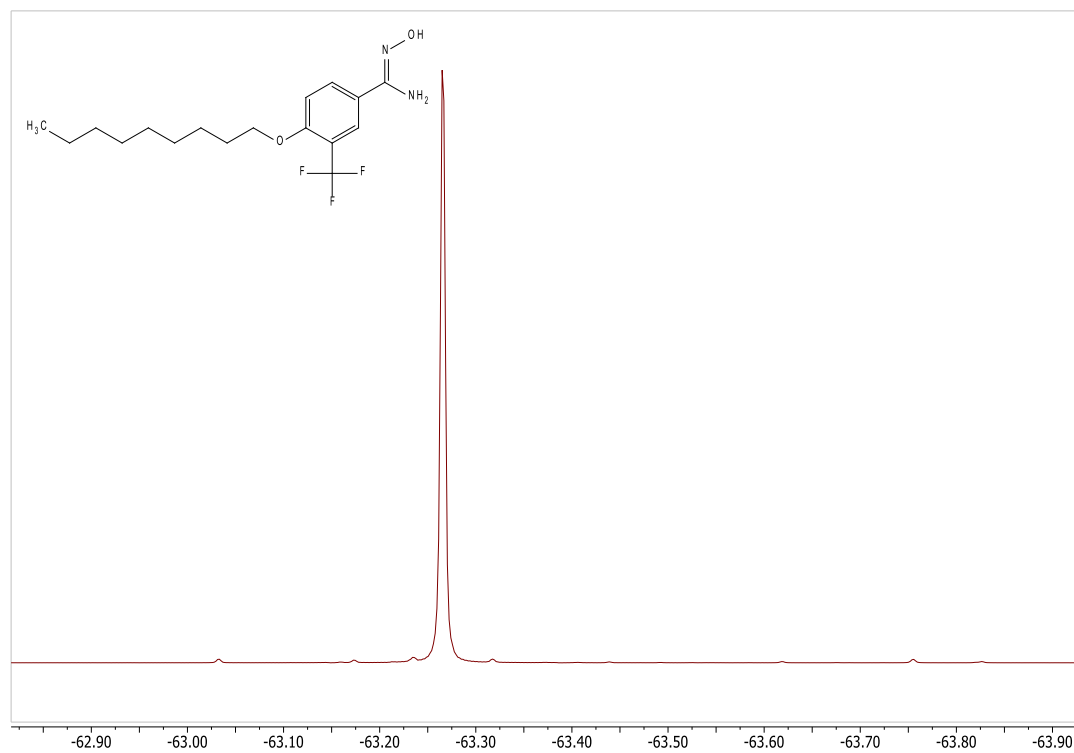
<sup>1</sup>H-NMR Spectrum for (Z)-4-(nonyloxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide **3.26b** –



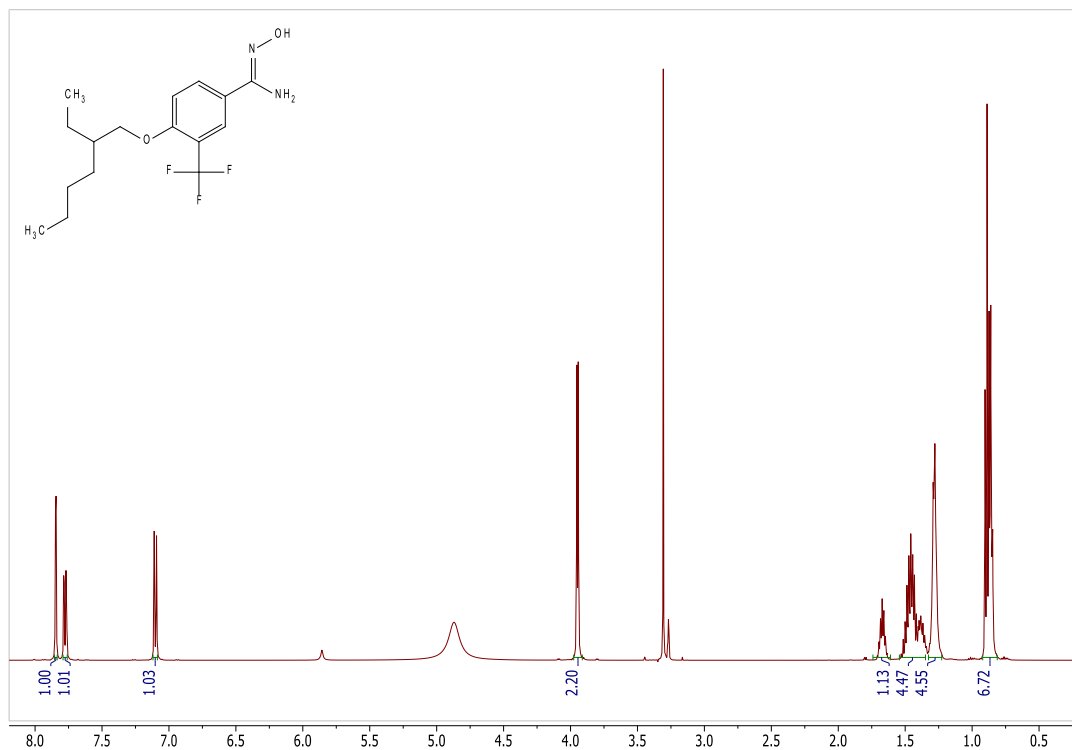
<sup>13</sup>C-NMR Spectrum for (Z)-4-(nonyloxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide **3.26b** –



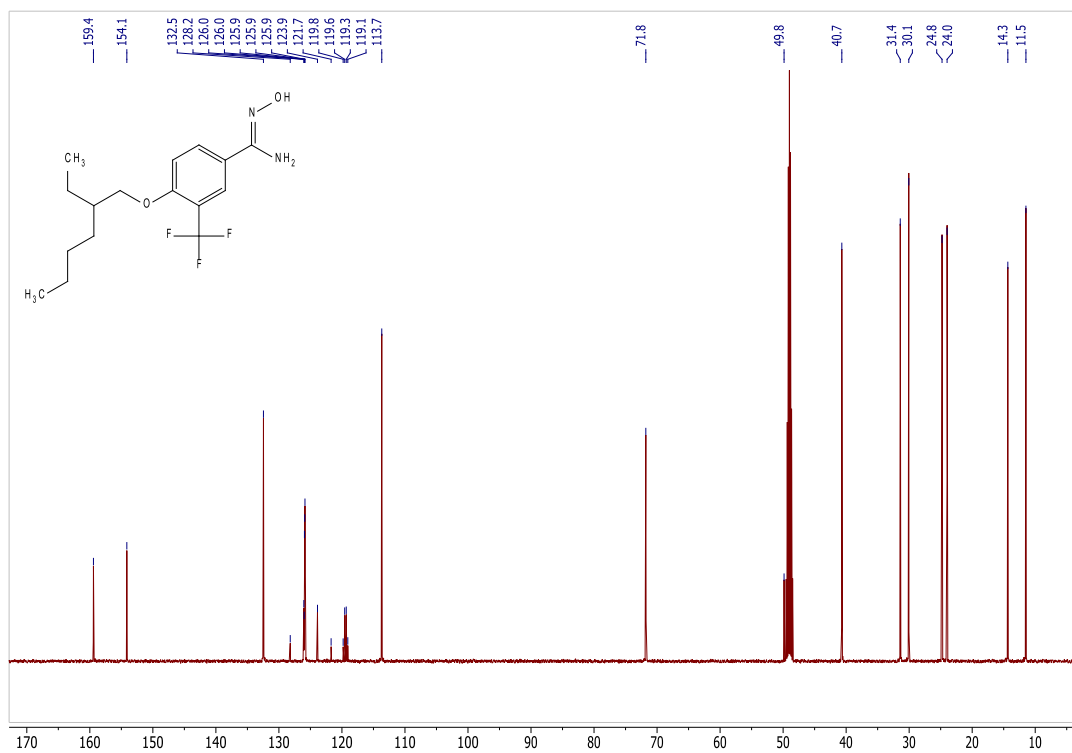
<sup>19</sup>F-NMR Spectrum for (Z)-4-(nonyloxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide **3.26b** –



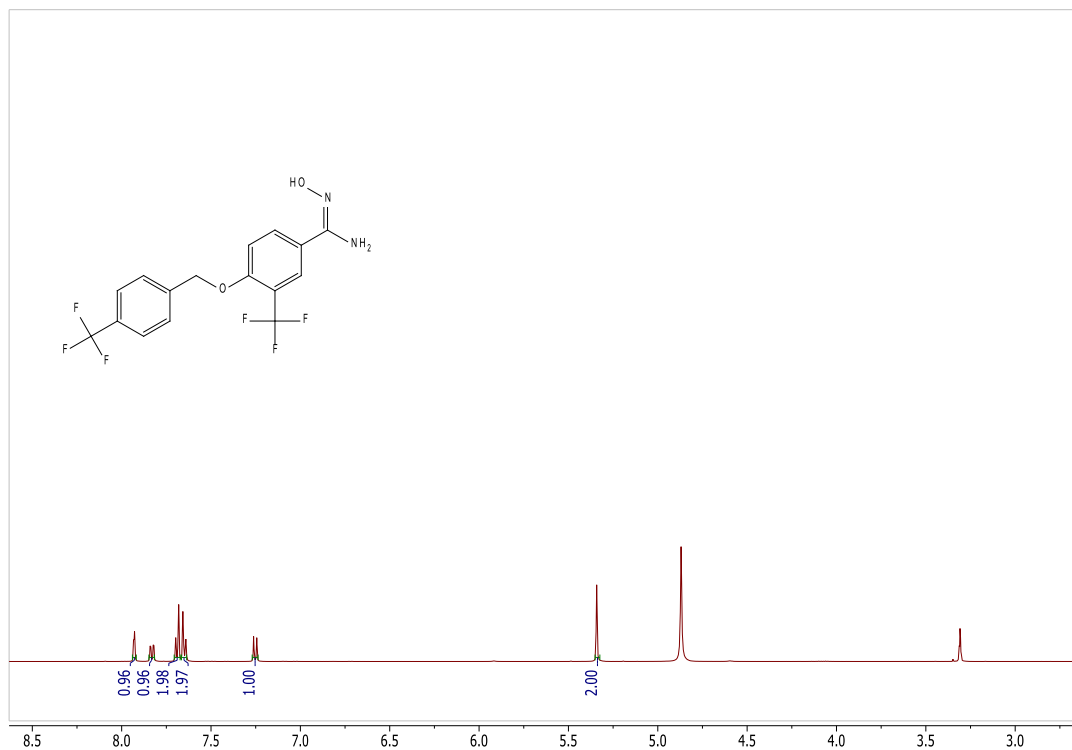
<sup>1</sup>H-NMR Spectrum for (Z)-4-((2-ethylhexyl)oxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide  
3.26c –



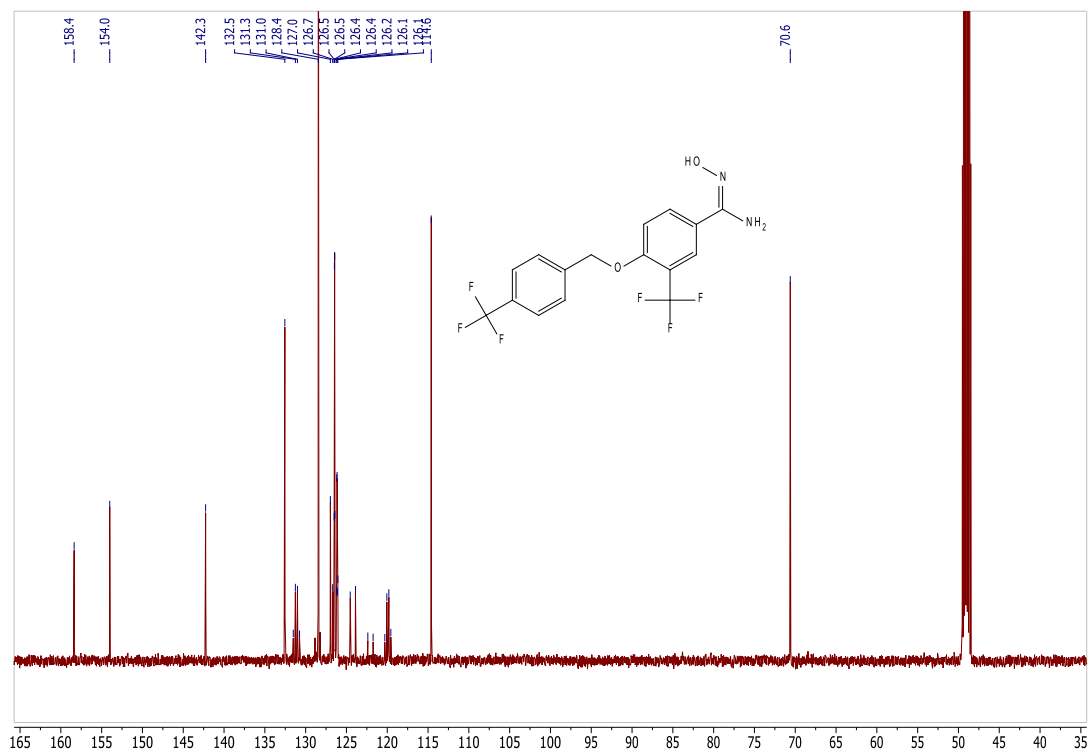
<sup>13</sup>C-NMR Spectrum for (Z)-4-((2-ethylhexyl)oxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide  
3.26c –



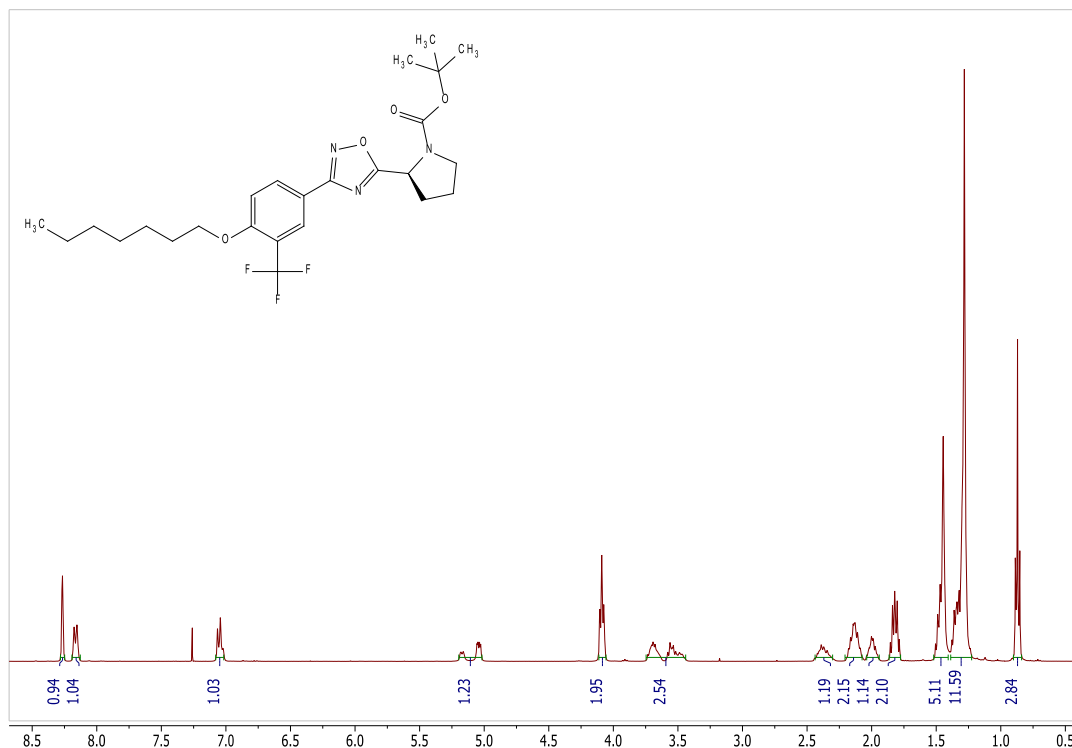
<sup>1</sup>H-NMR Spectrum for (Z)-N'-hydroxy-3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)benzimidamide **3.26d** –



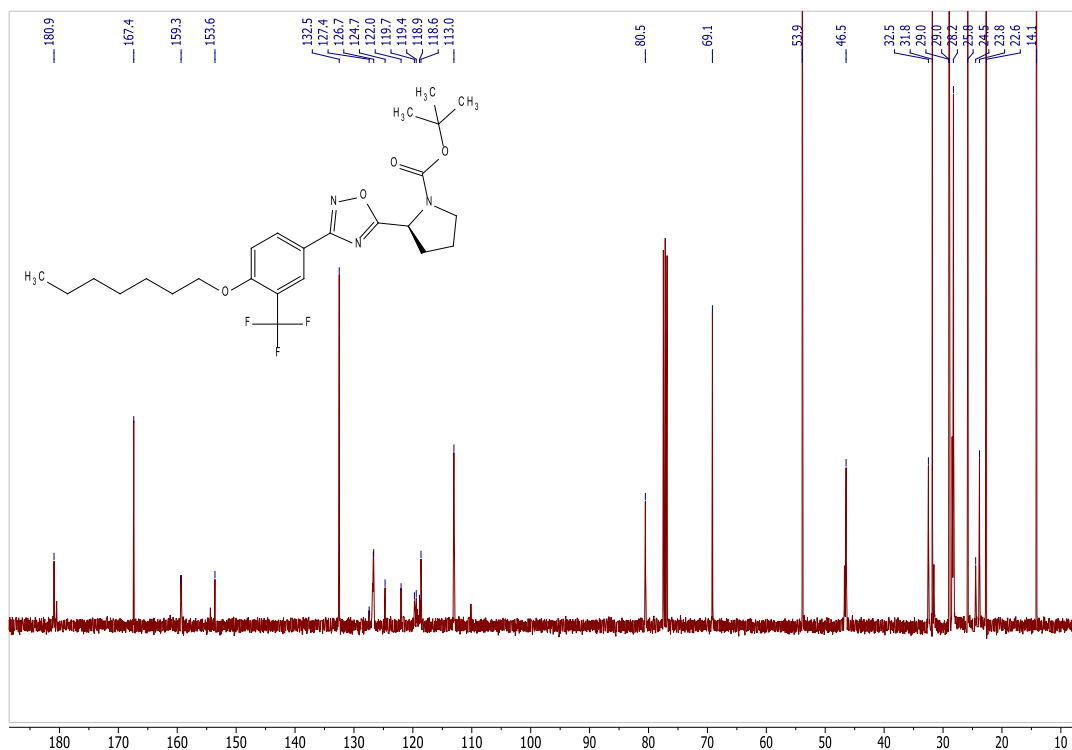
<sup>13</sup>C-NMR Spectrum for (Z)-N'-hydroxy-3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)benzimidamide **3.26d** –



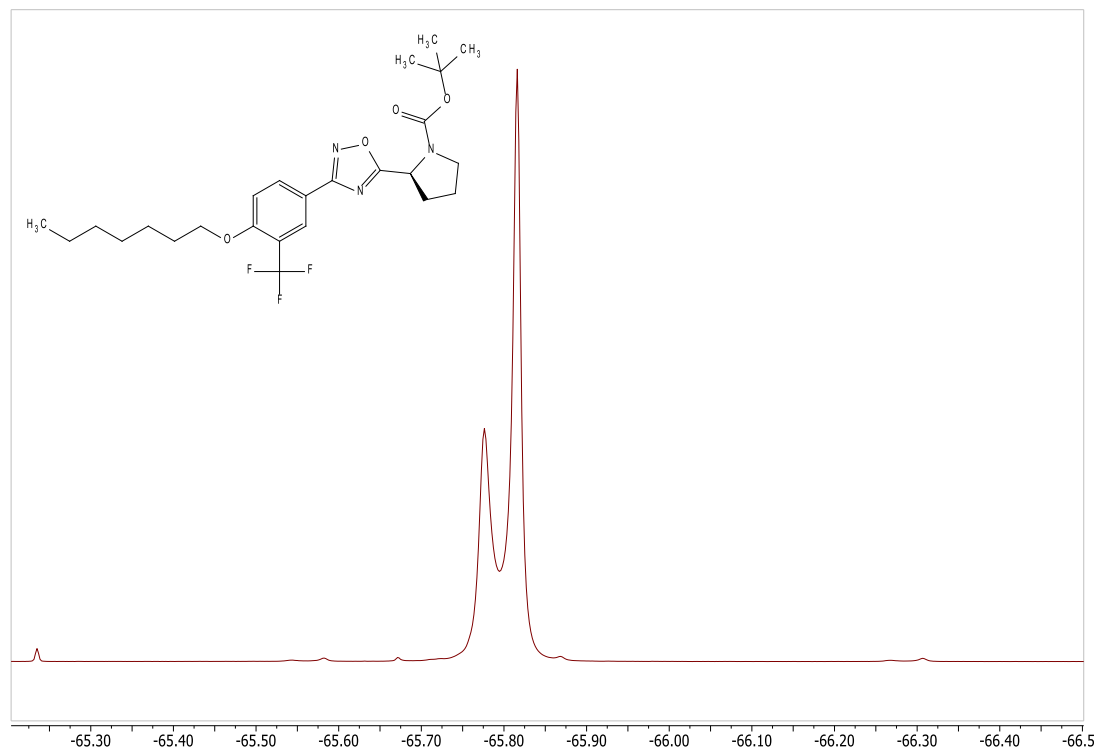
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –

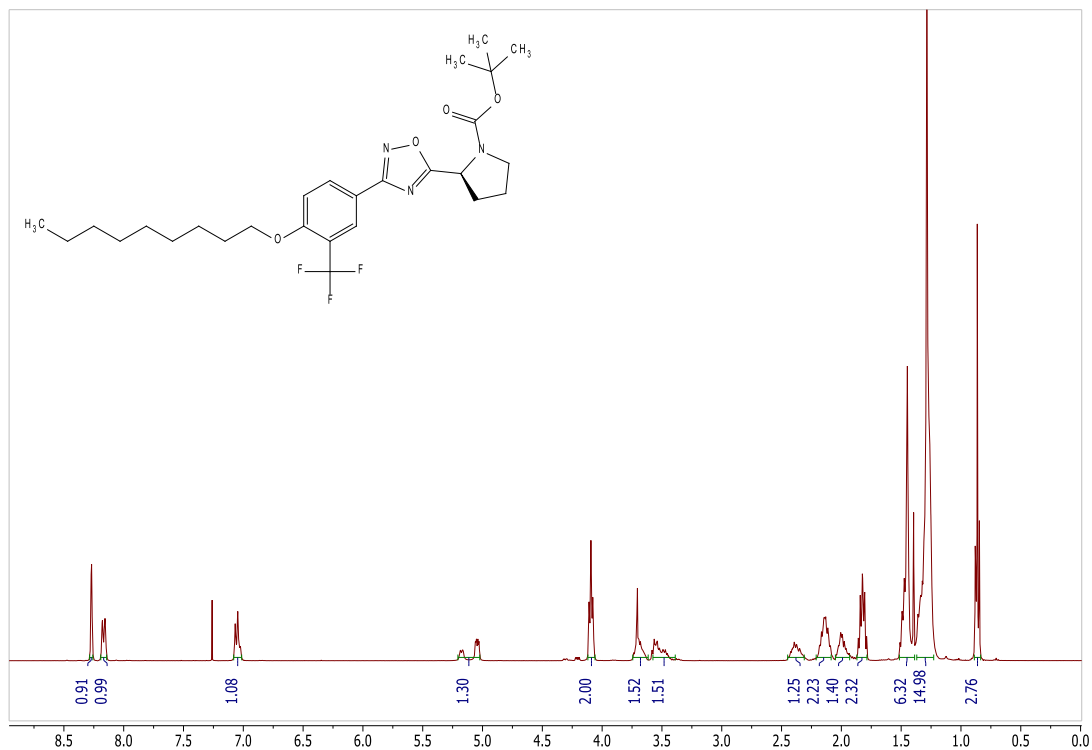


$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –

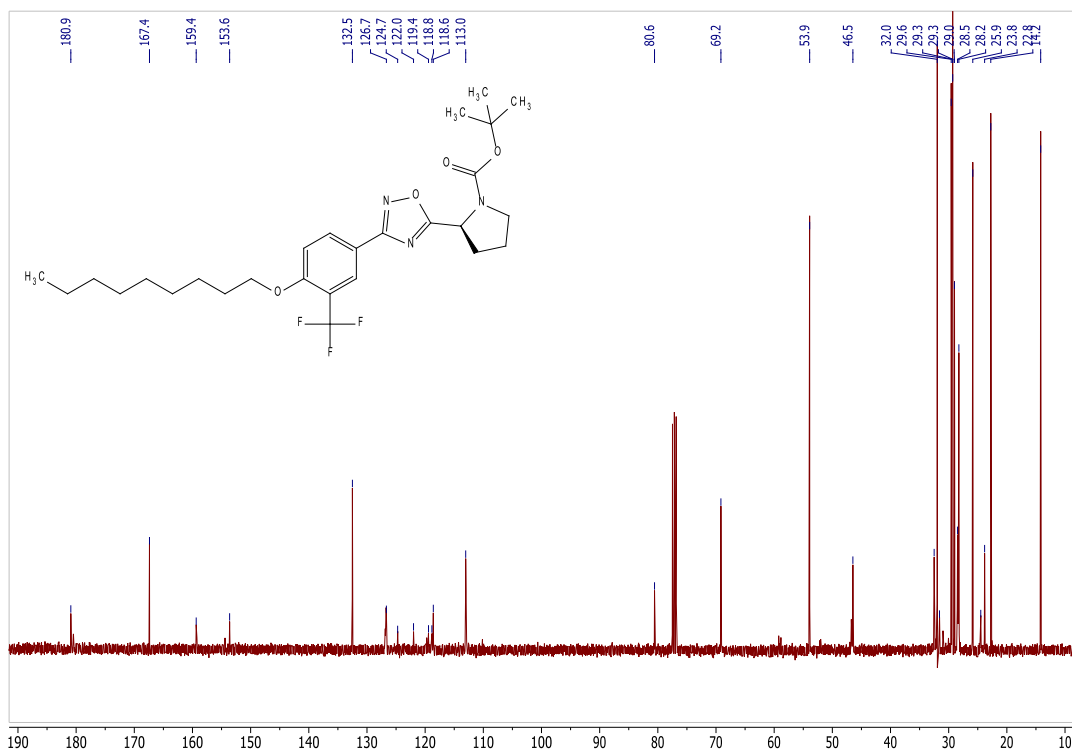




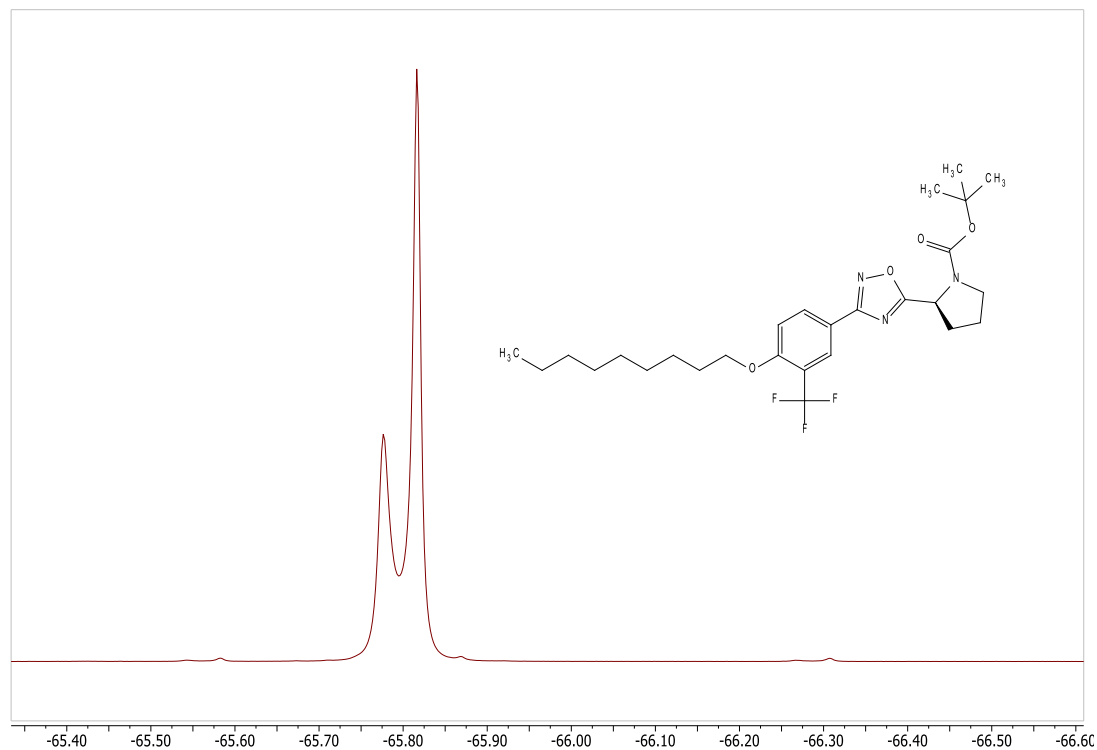
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



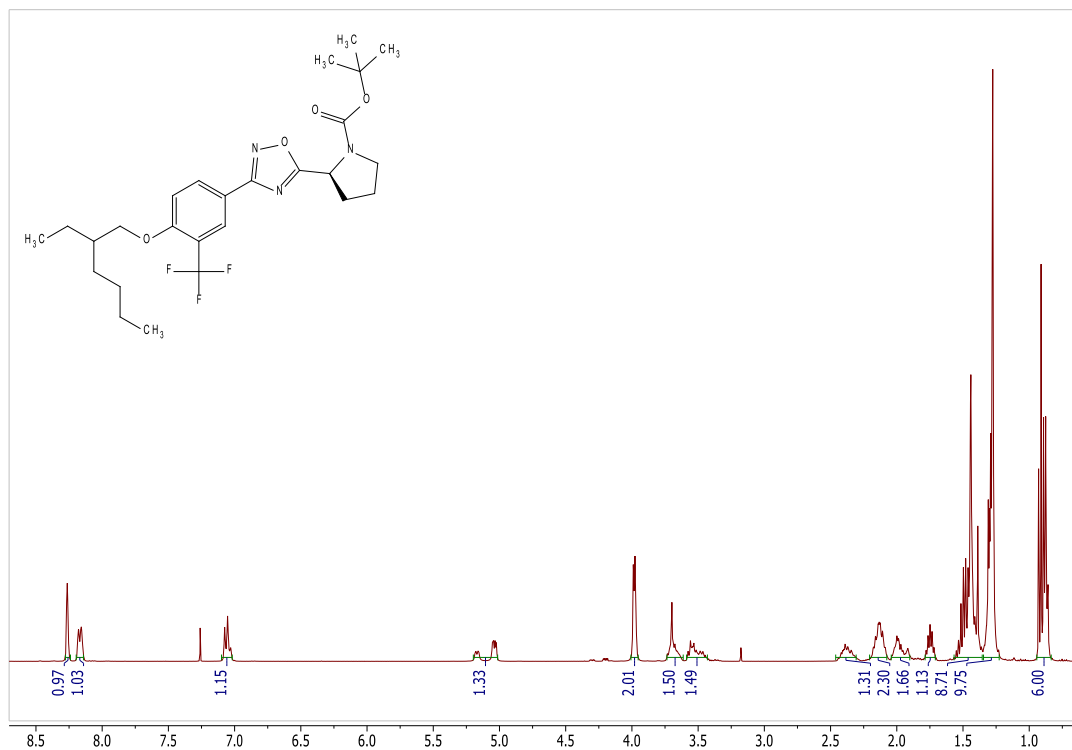
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



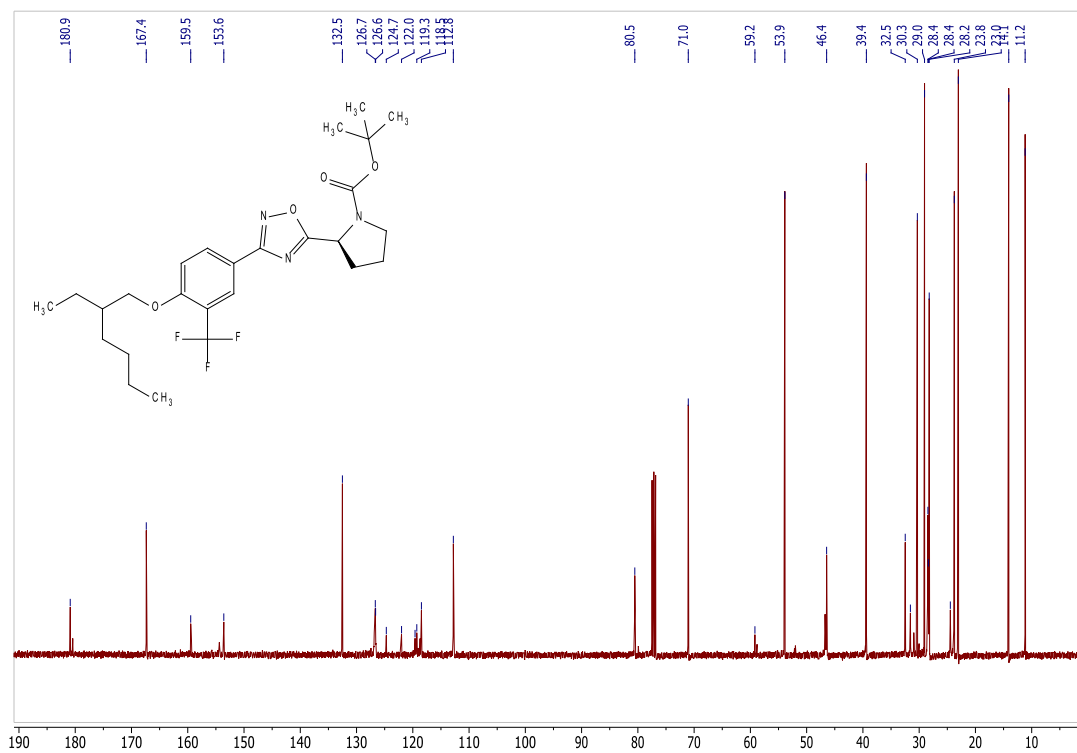
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate –



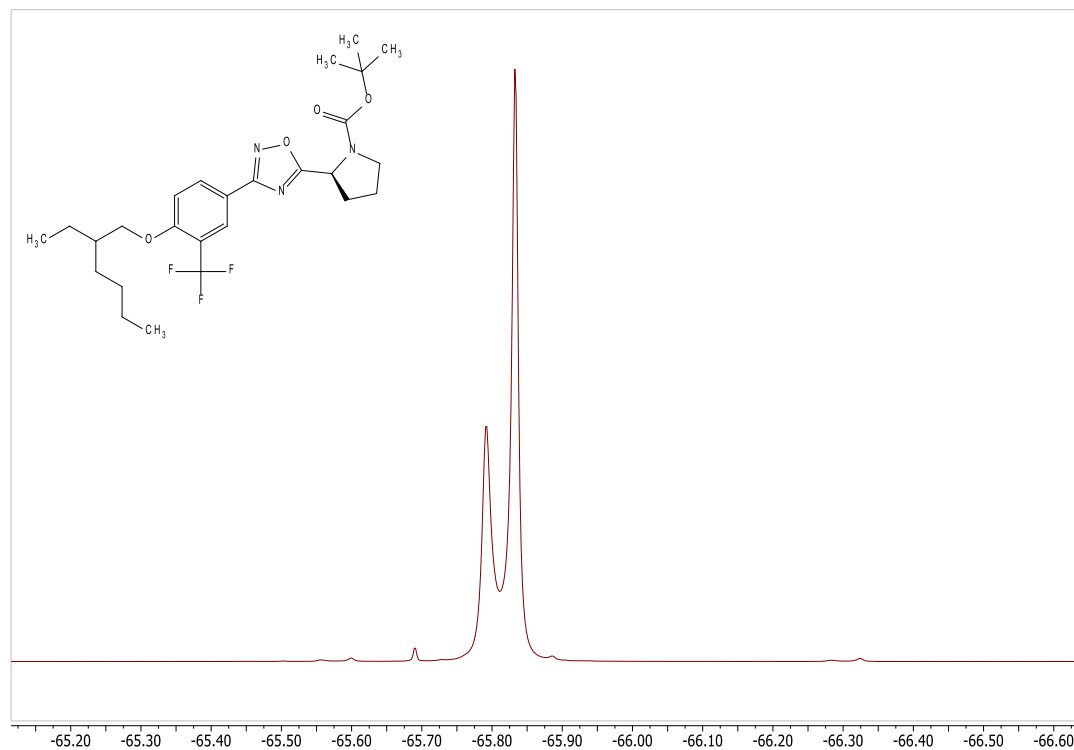
<sup>1</sup>H-NMR Spectrum for (2*S*)-*tert*-butyl 2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate-



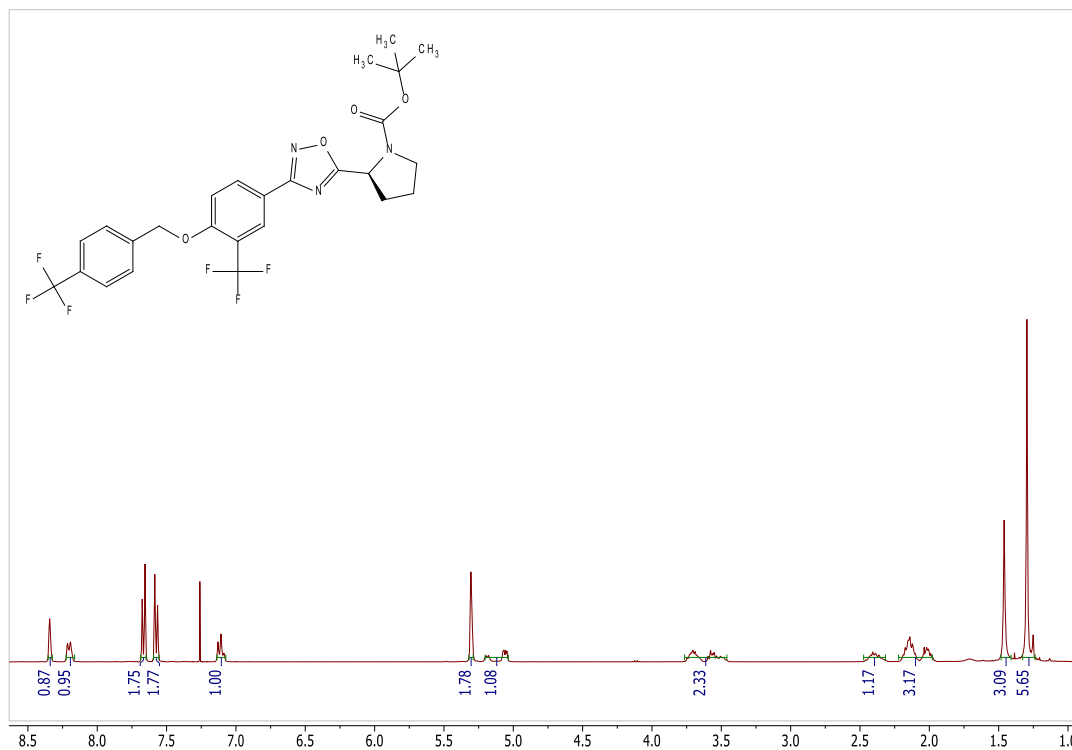
<sup>13</sup>C-NMR Spectrum for (2*S*)-*tert*-butyl 2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate-



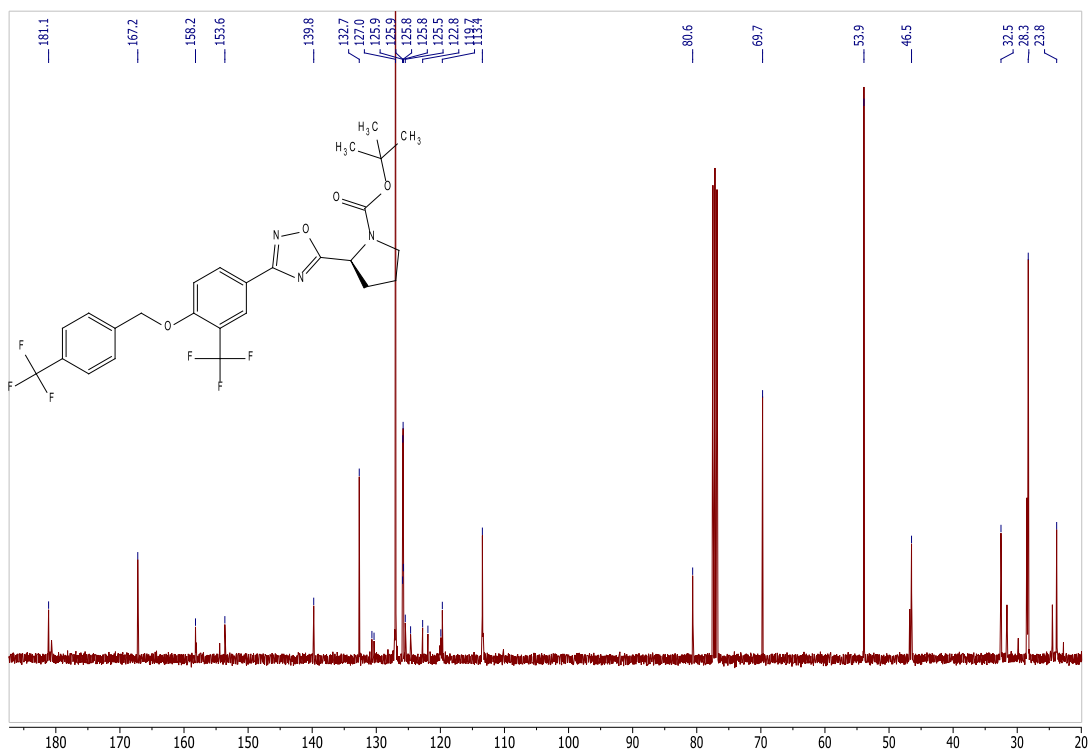
$^{19}\text{F}$ -NMR Spectrum for (2*S*)-*tert*-butyl 2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate-



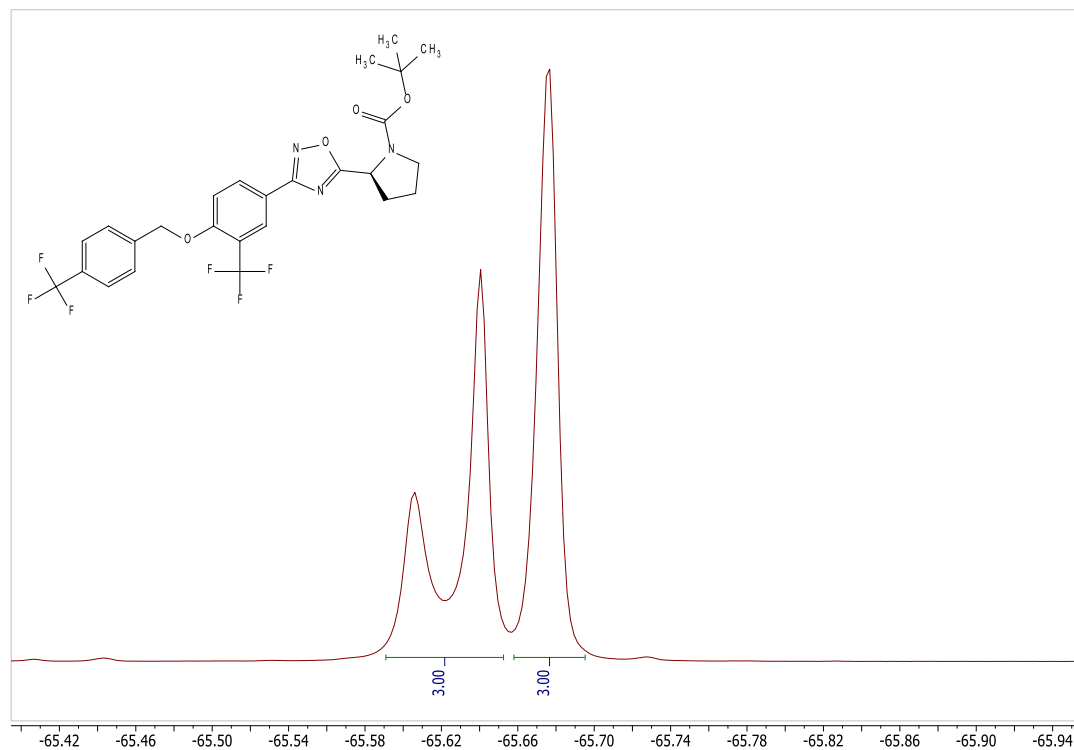
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate -



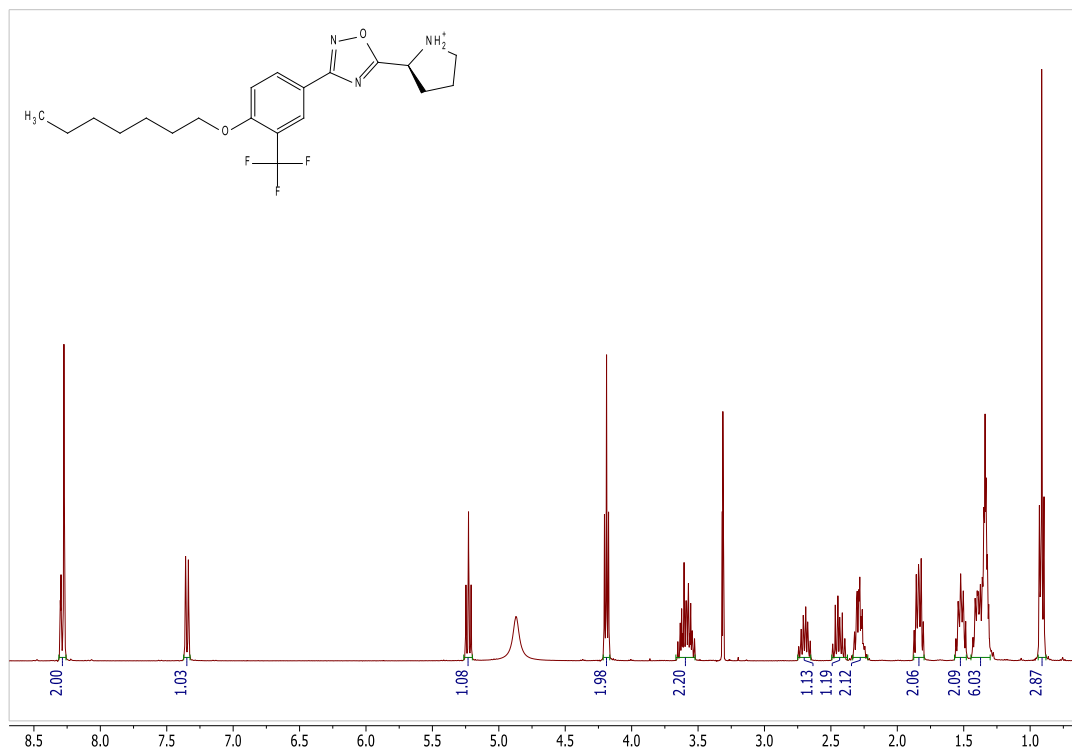
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate -



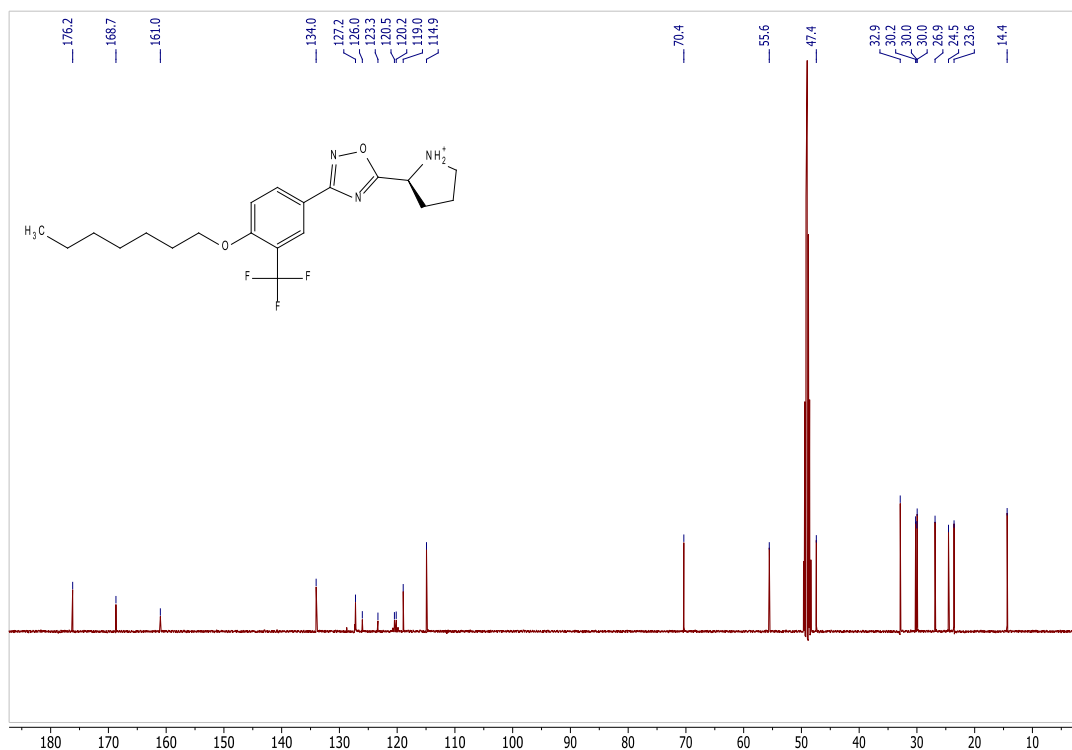
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate -



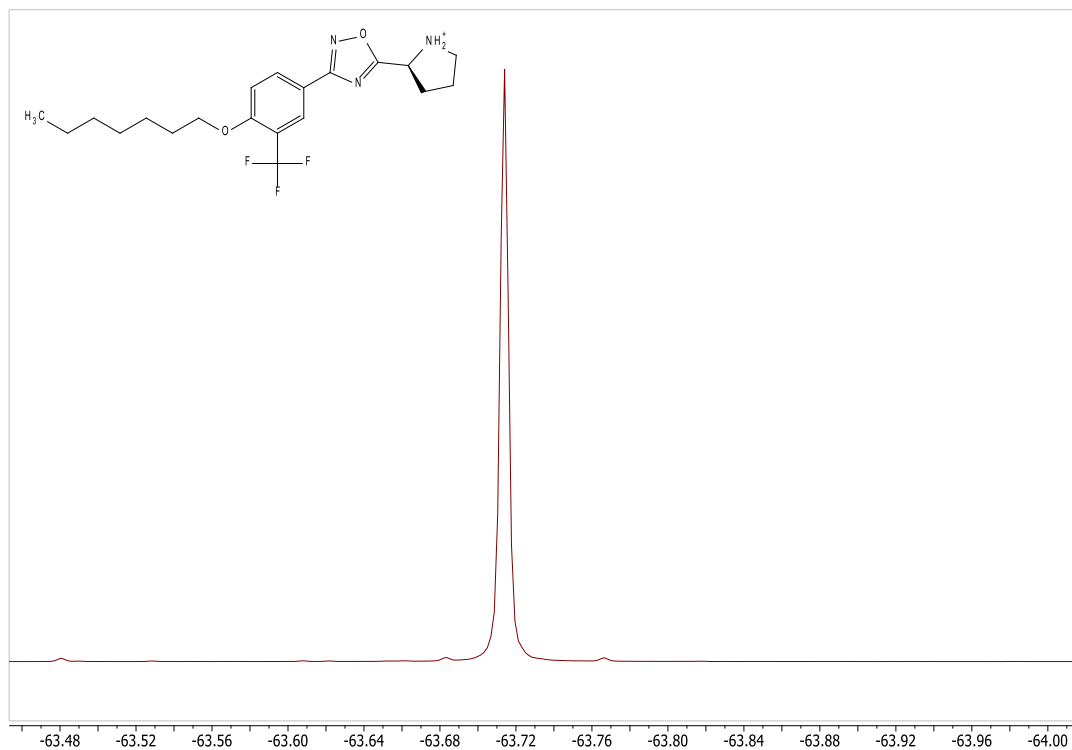
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium chloride -



<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium chloride -

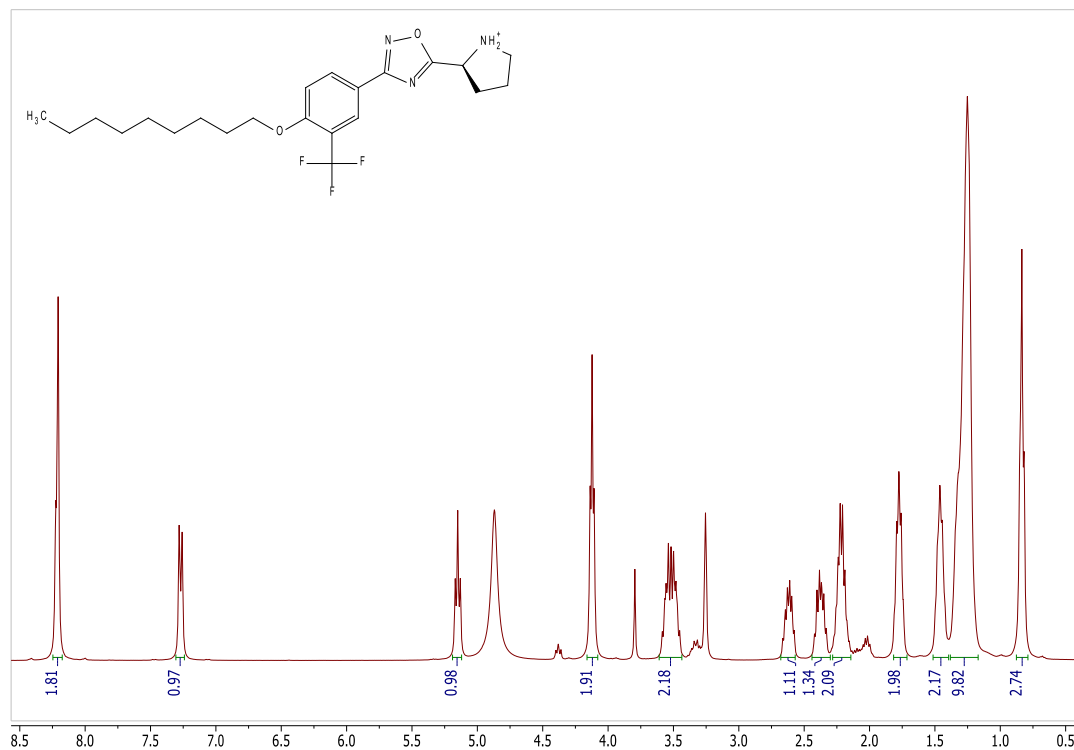


<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium chloride -

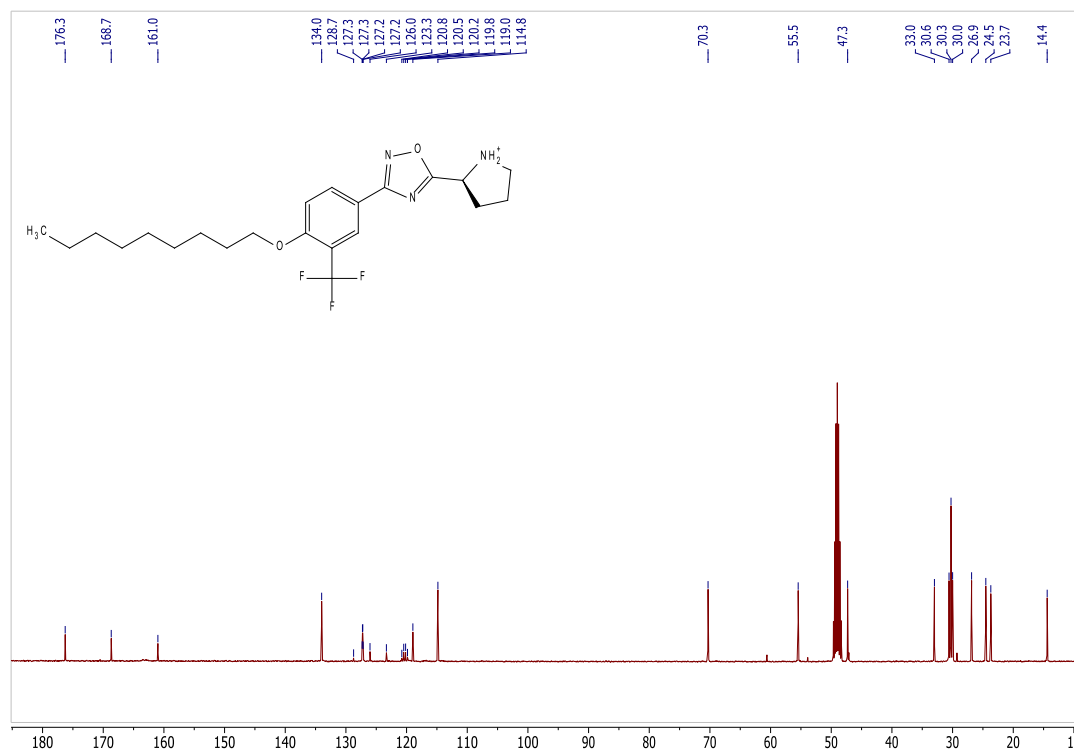




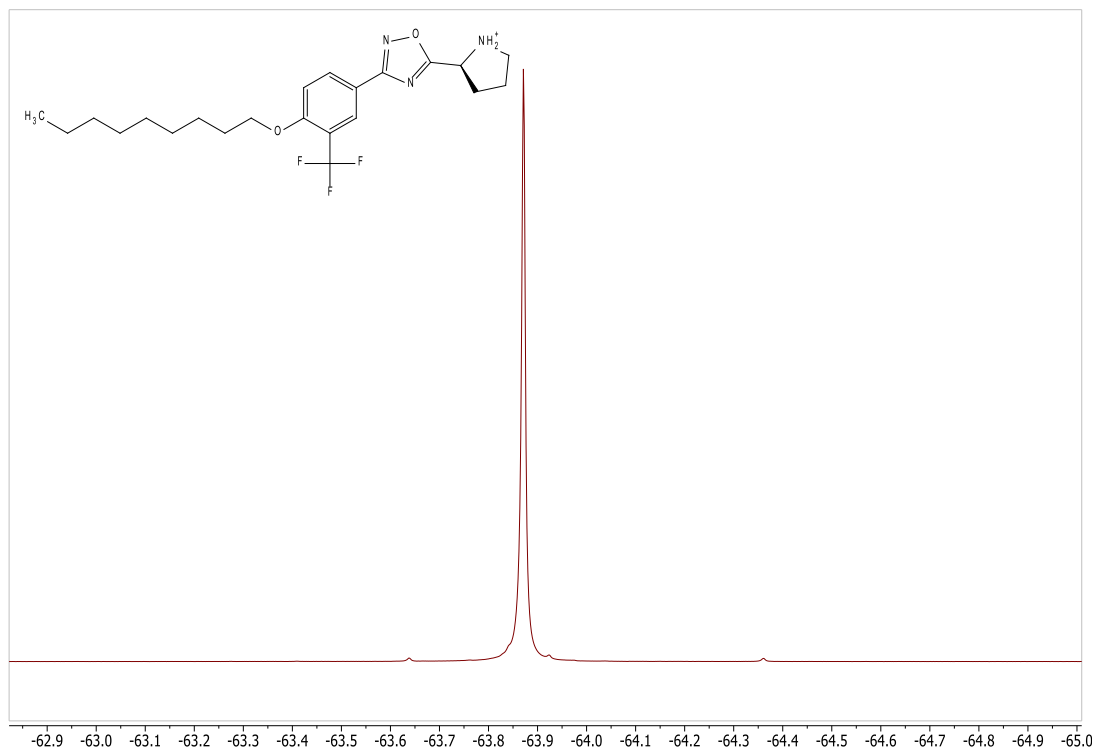
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



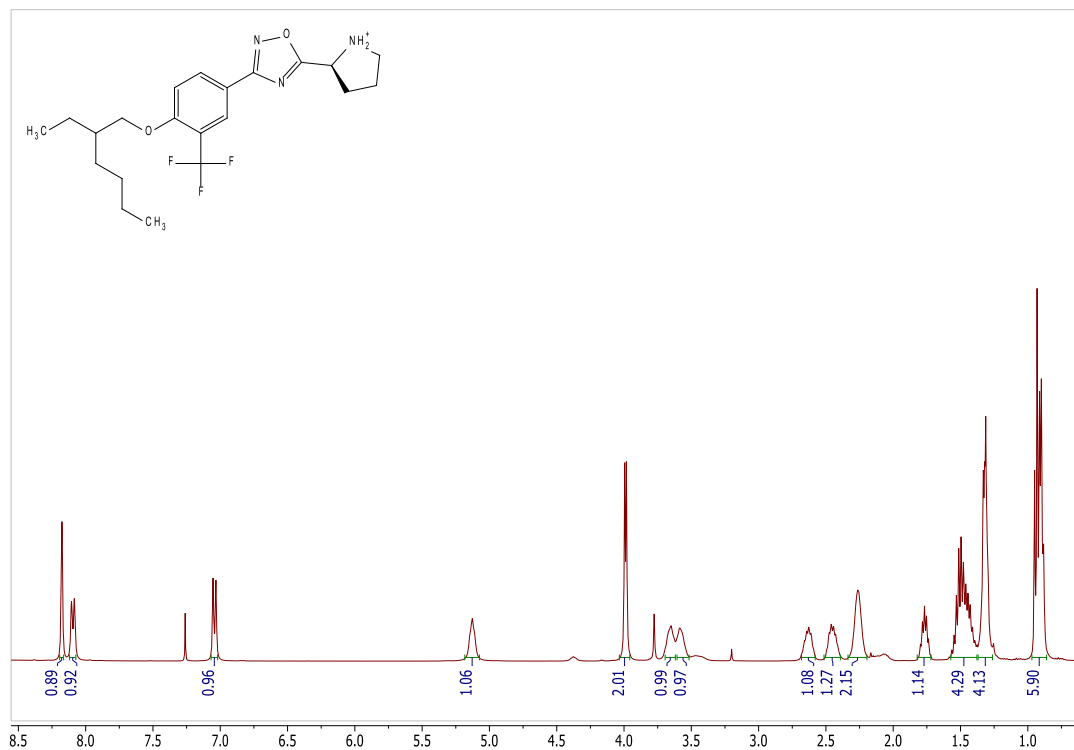
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



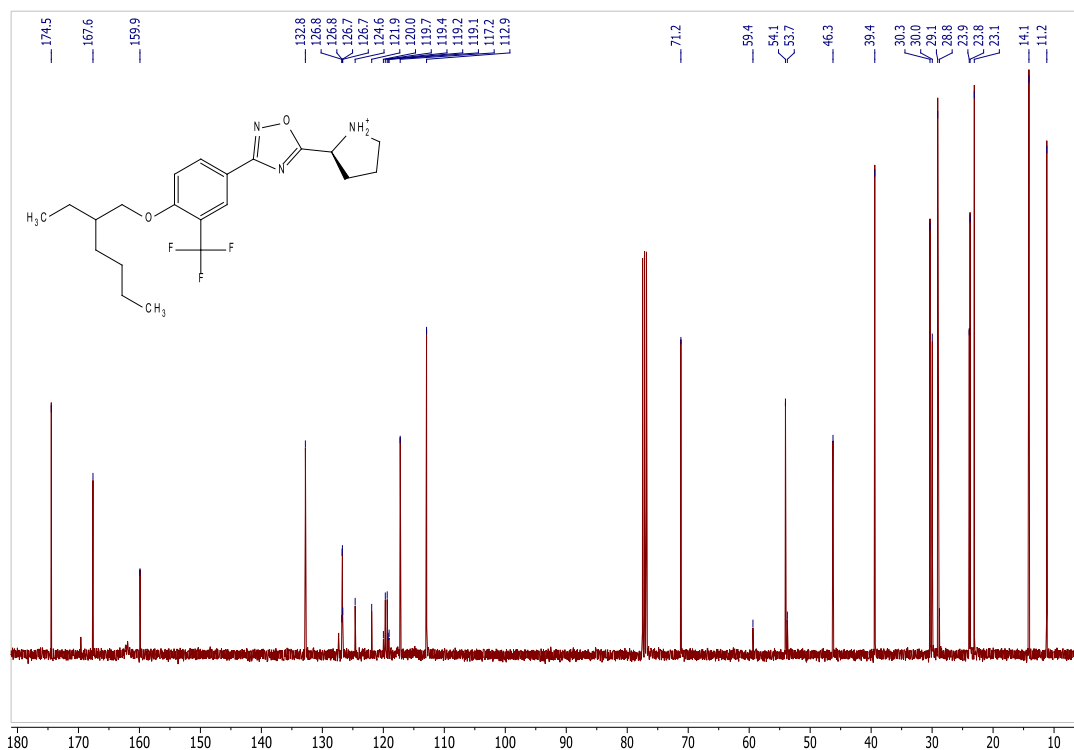
<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



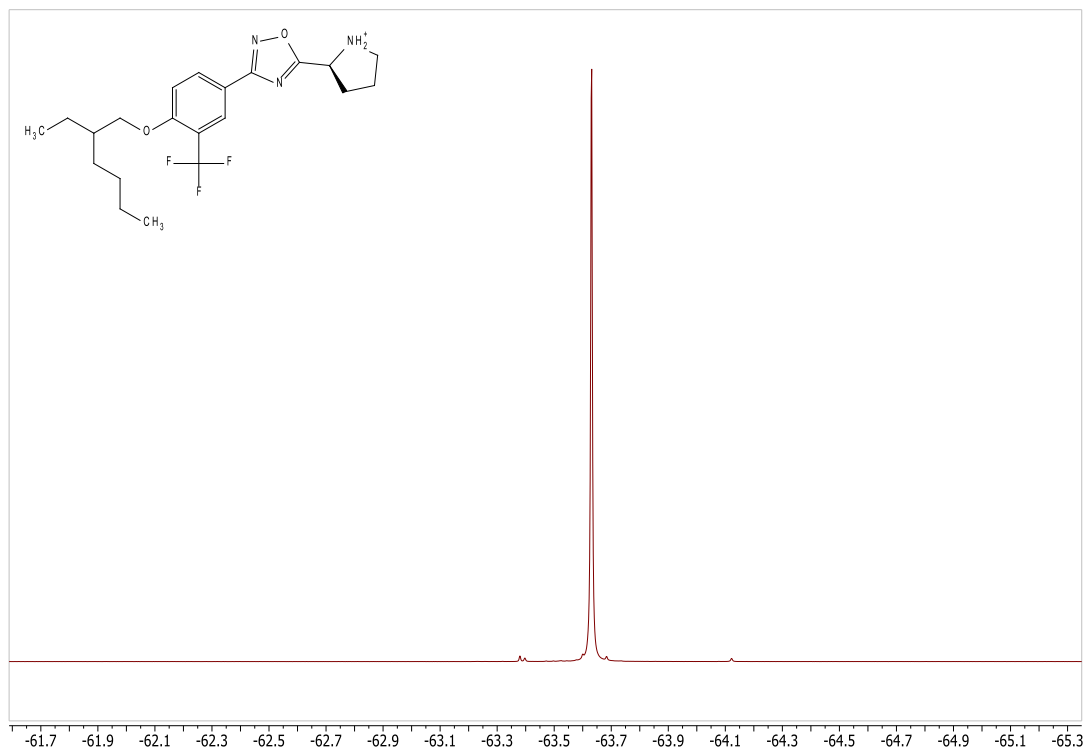
<sup>1</sup>H-NMR Spectrum for (2*S*)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



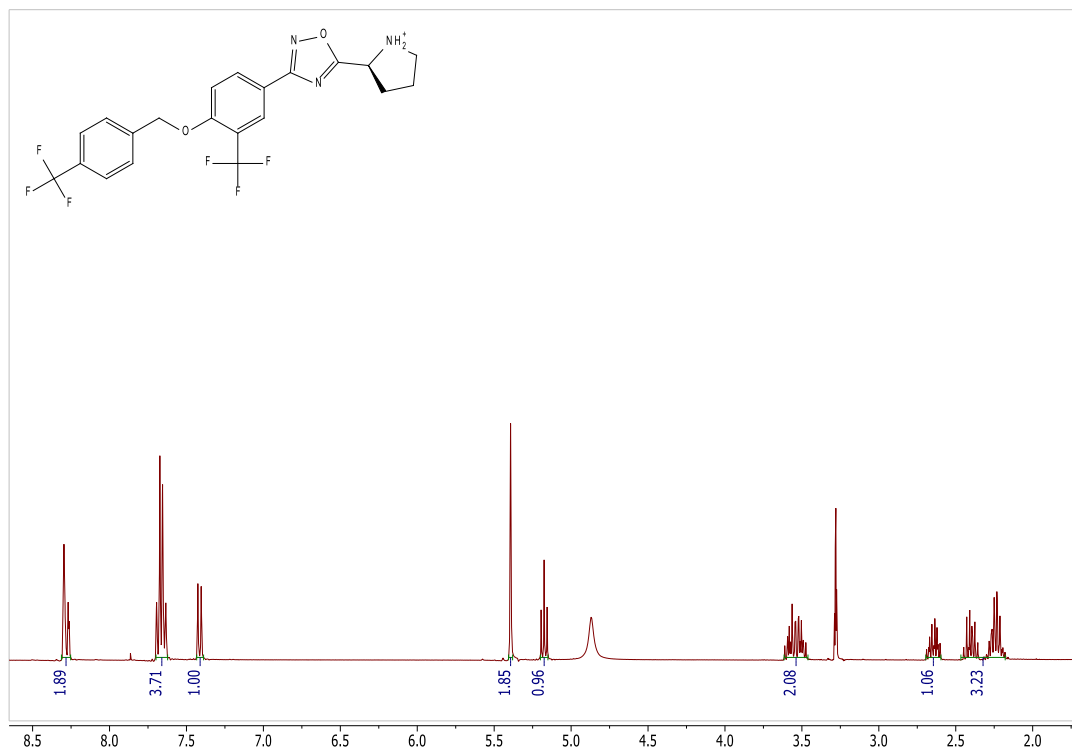
<sup>13</sup>C-NMR Spectrum for (2*S*)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



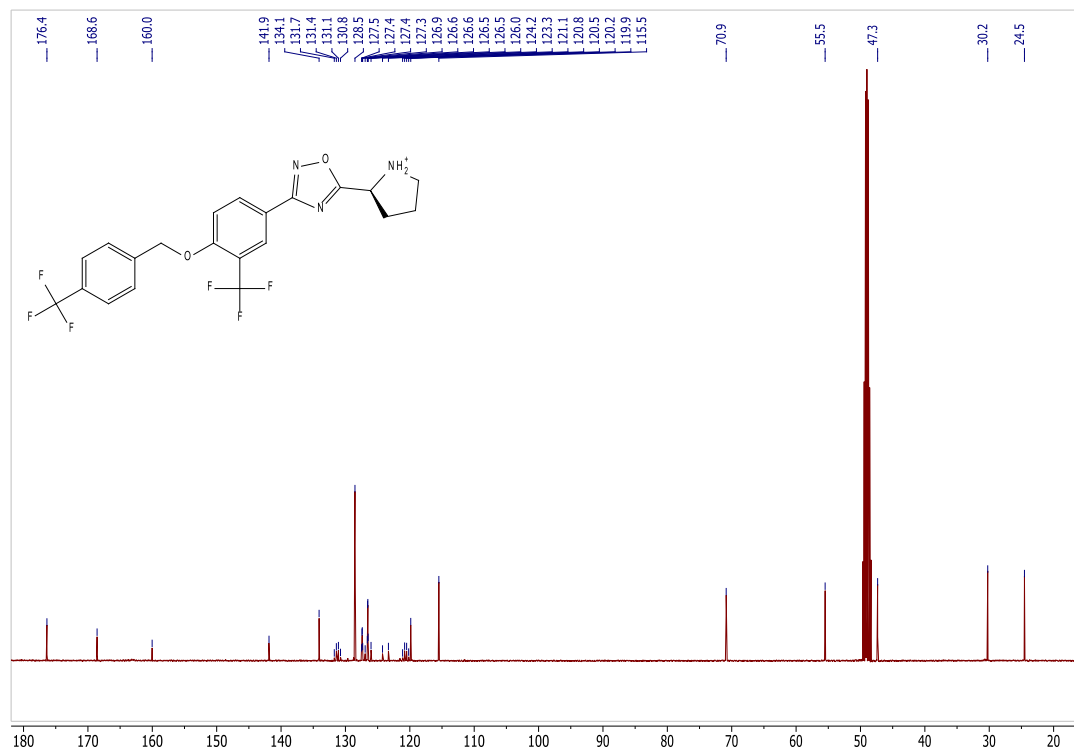
$^{19}\text{F}$ -NMR Spectrum for (2*S*)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



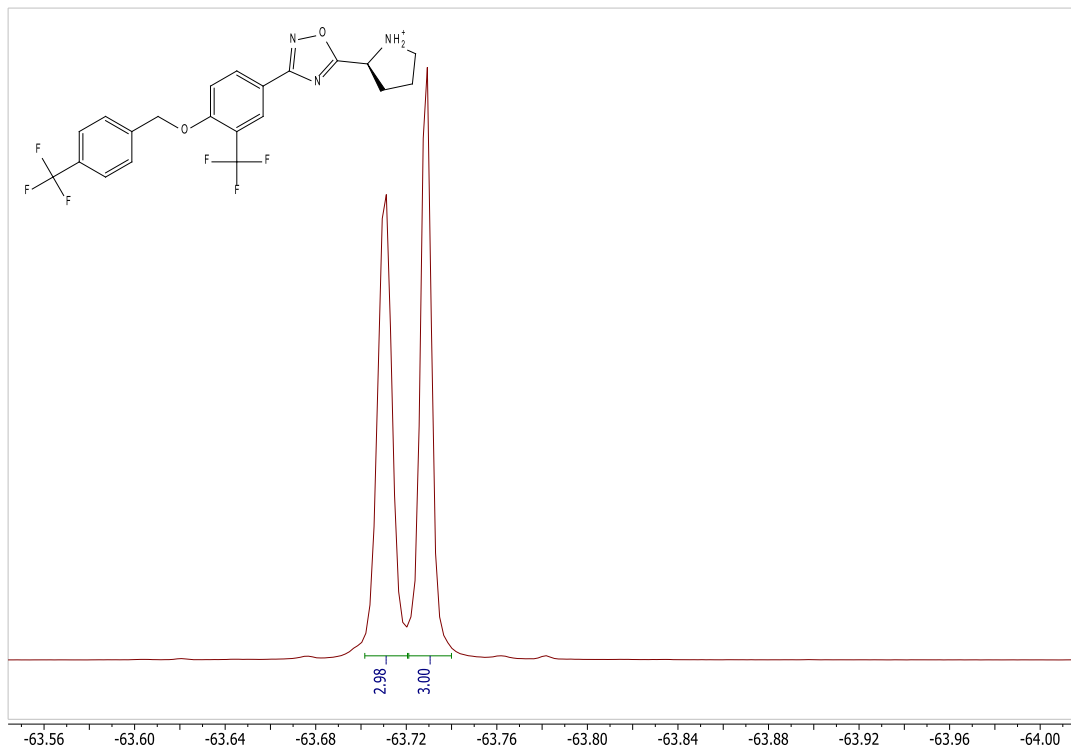
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



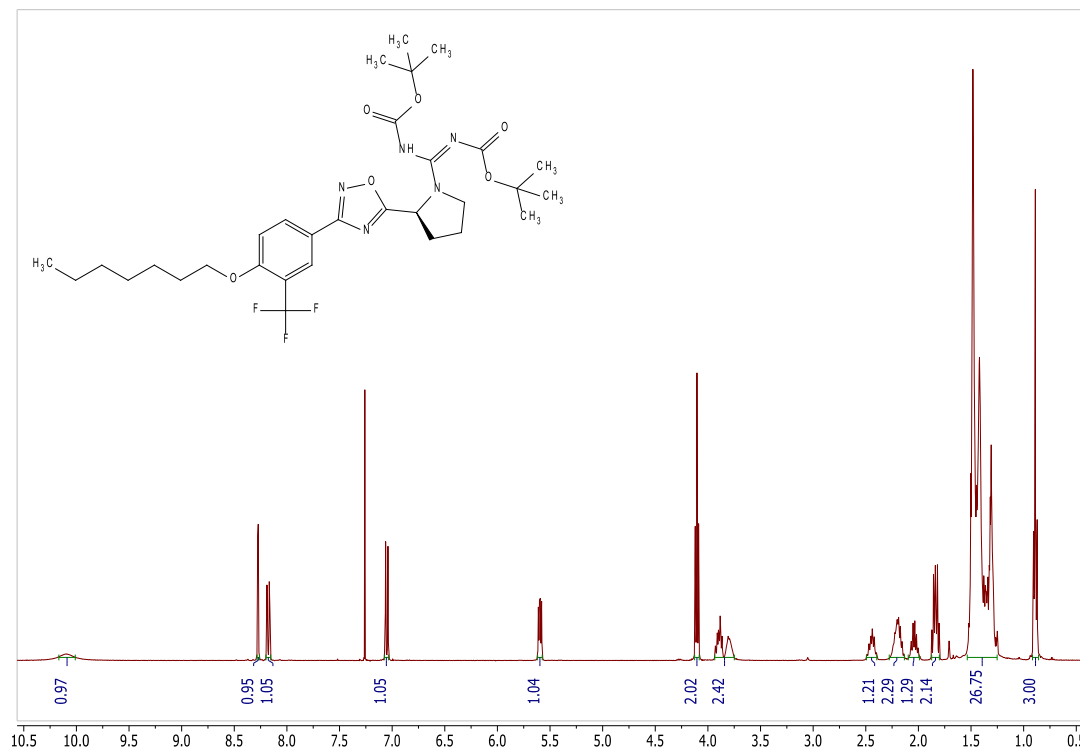
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -

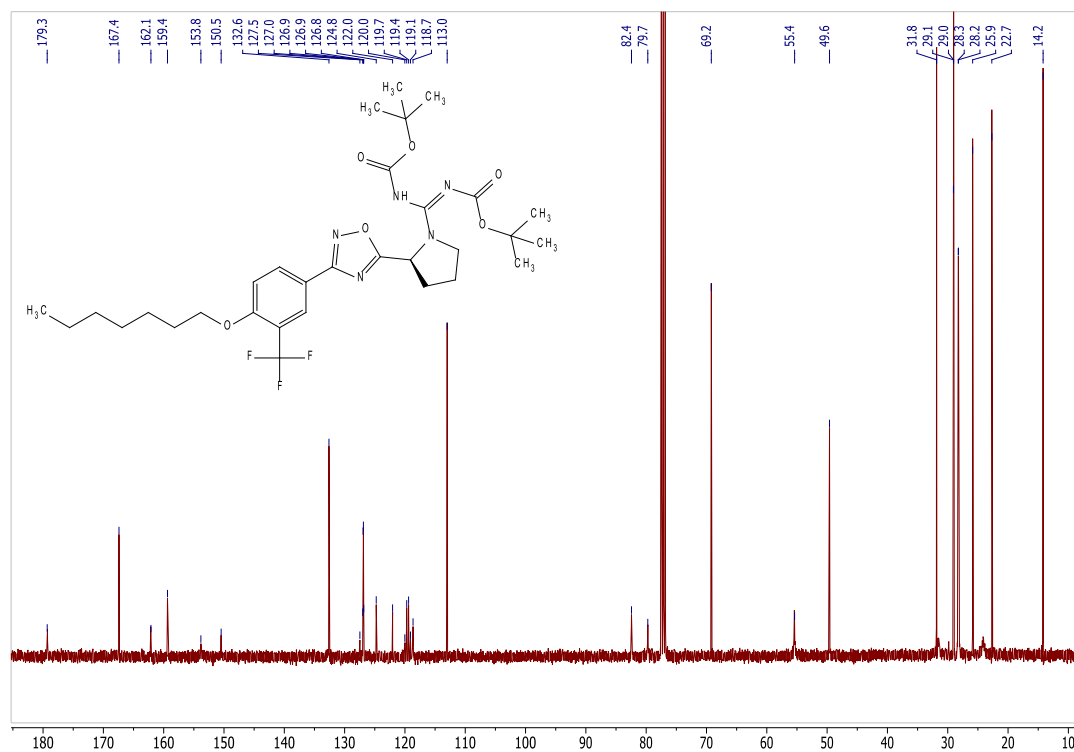


<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -

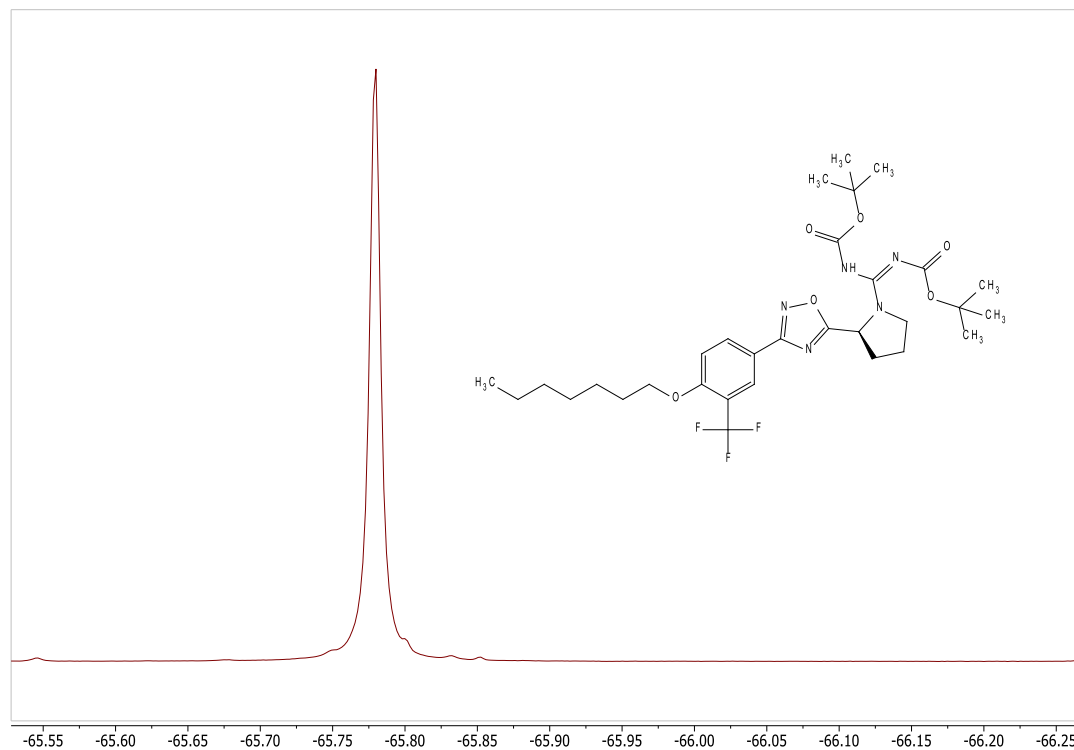




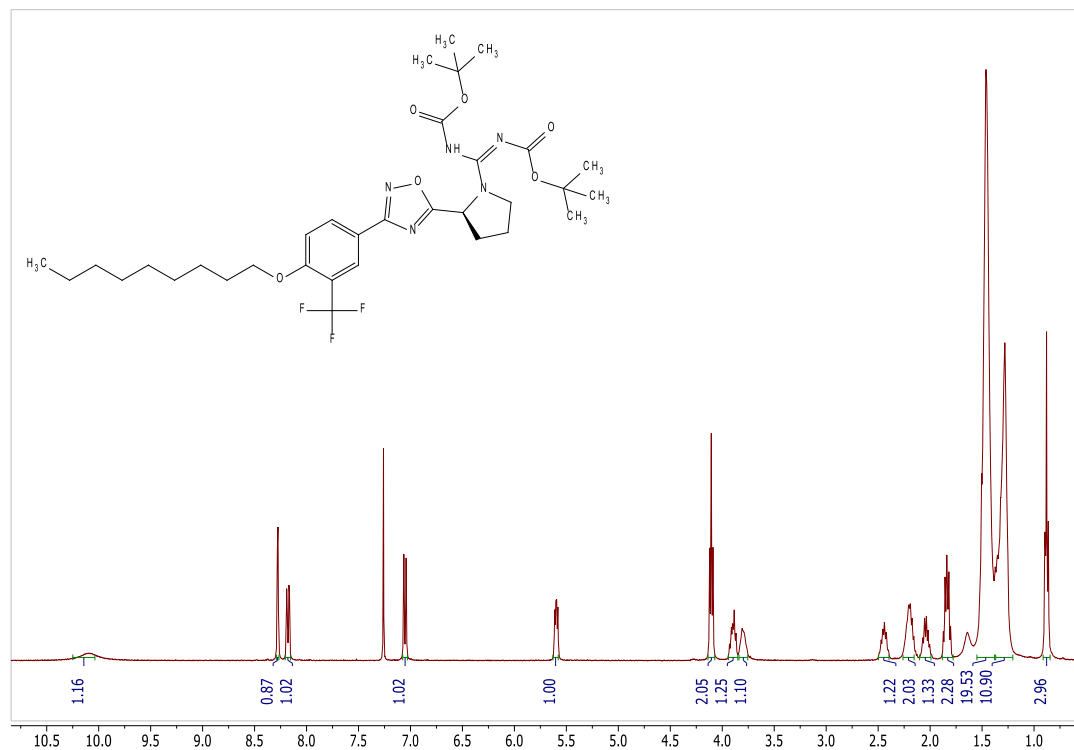
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



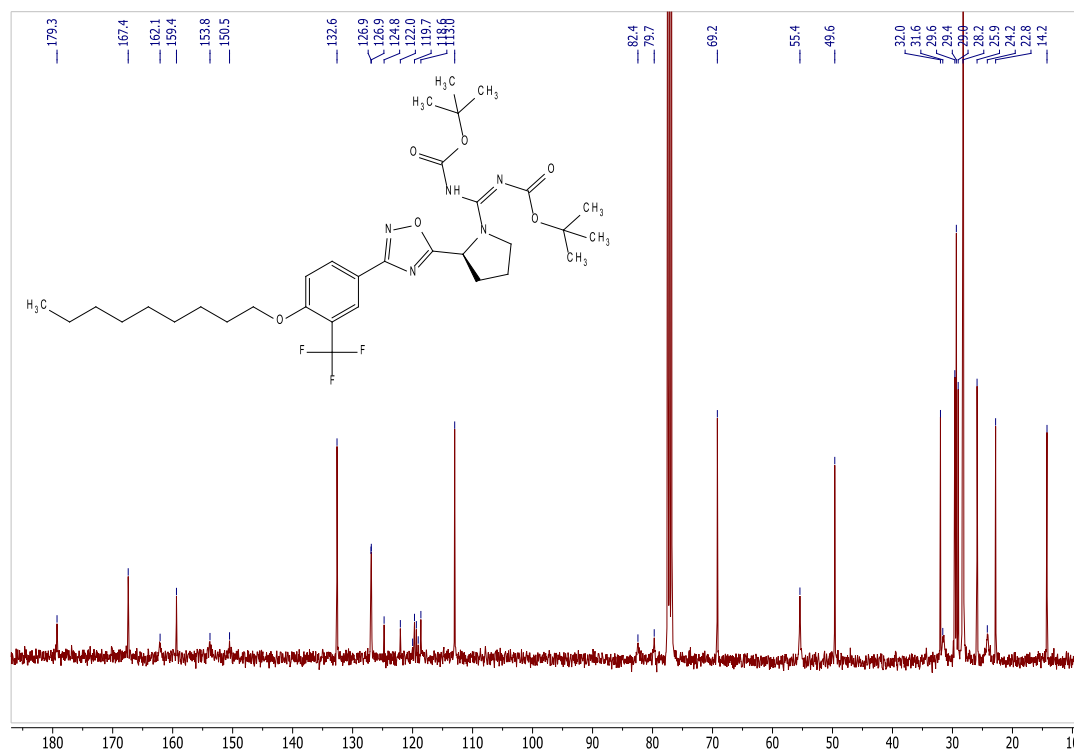
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



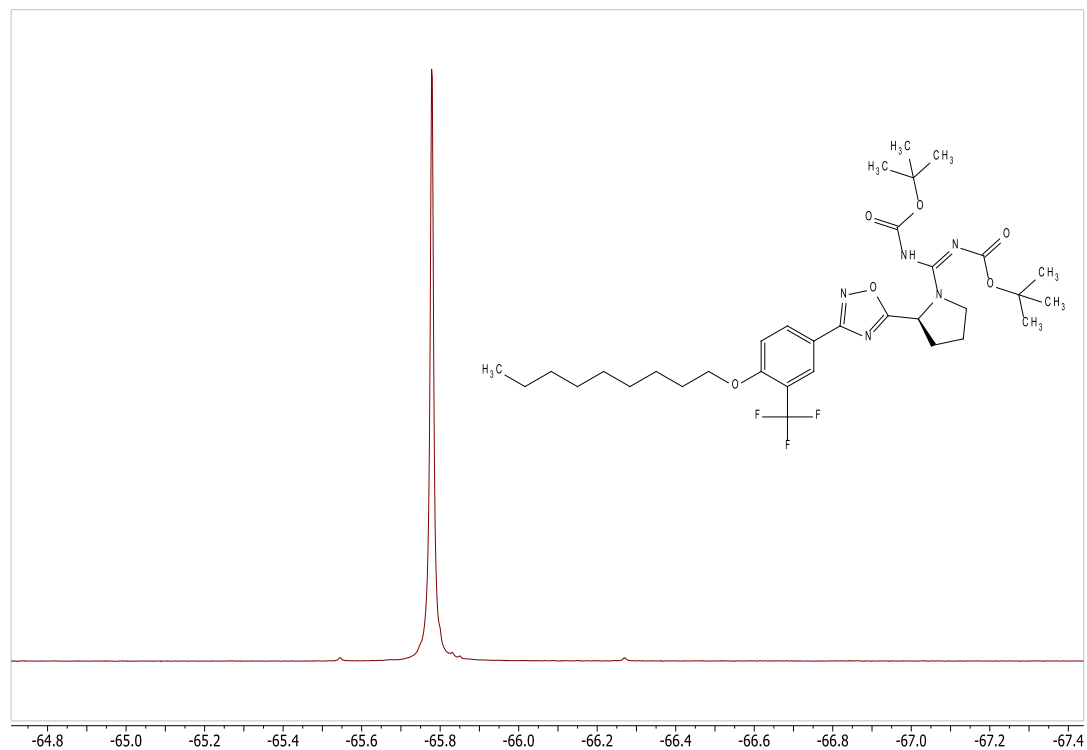
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



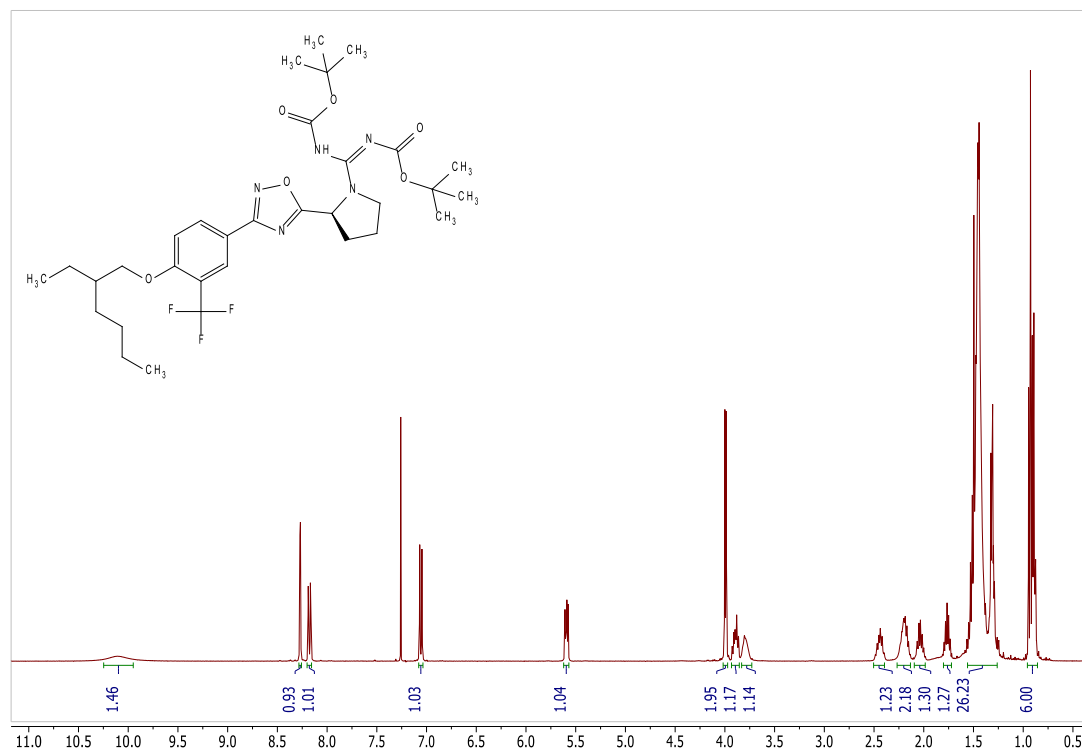
<sup>13</sup>C-NMR Spectrum for (S)-tert-butyl (((tert-butoxycarbonyl)amino)(2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



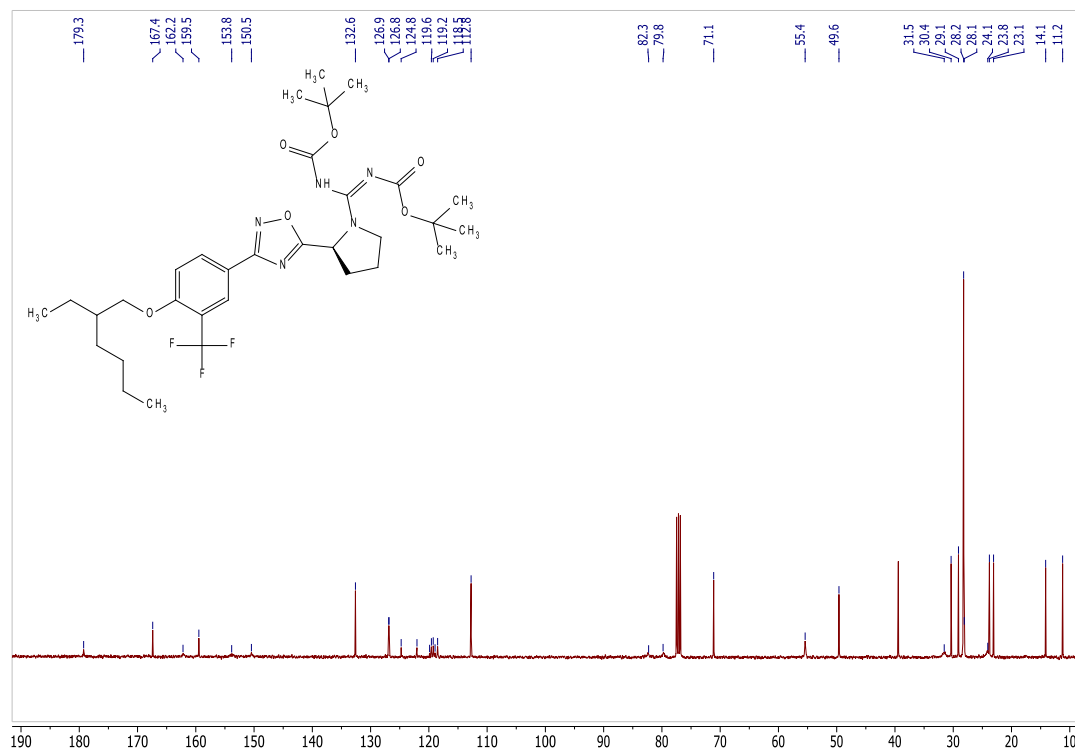
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



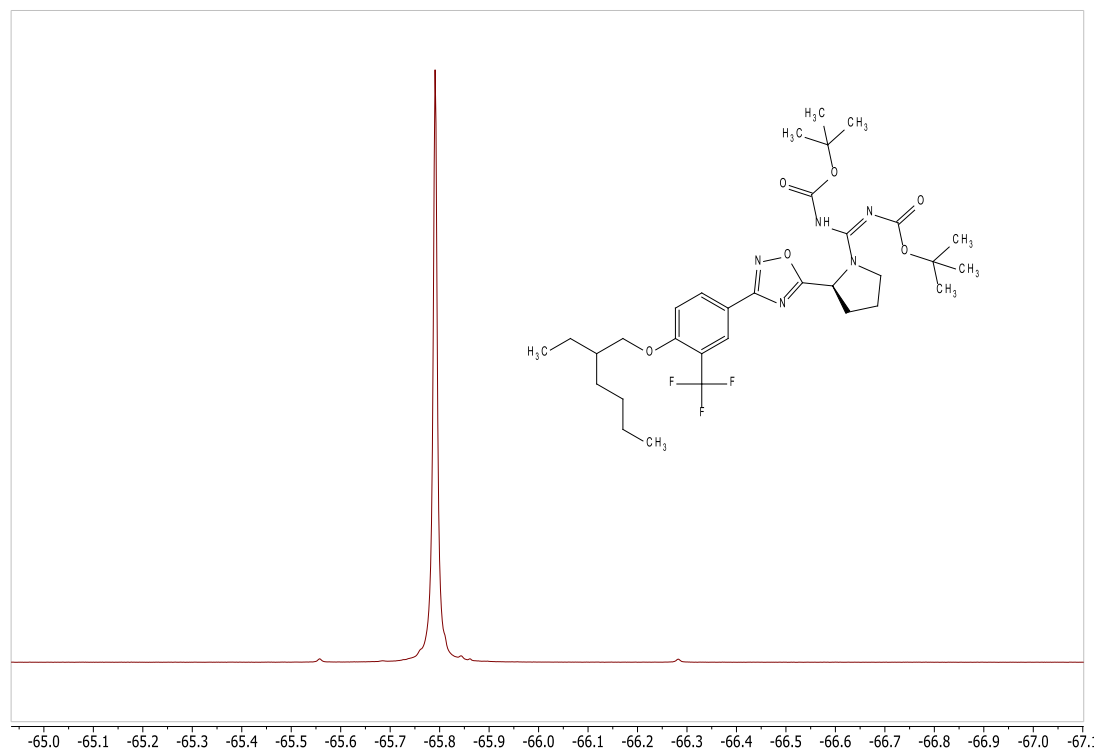
<sup>1</sup>H-NMR Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)((*2S*)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



<sup>13</sup>C-NMR Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)((*2S*)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -

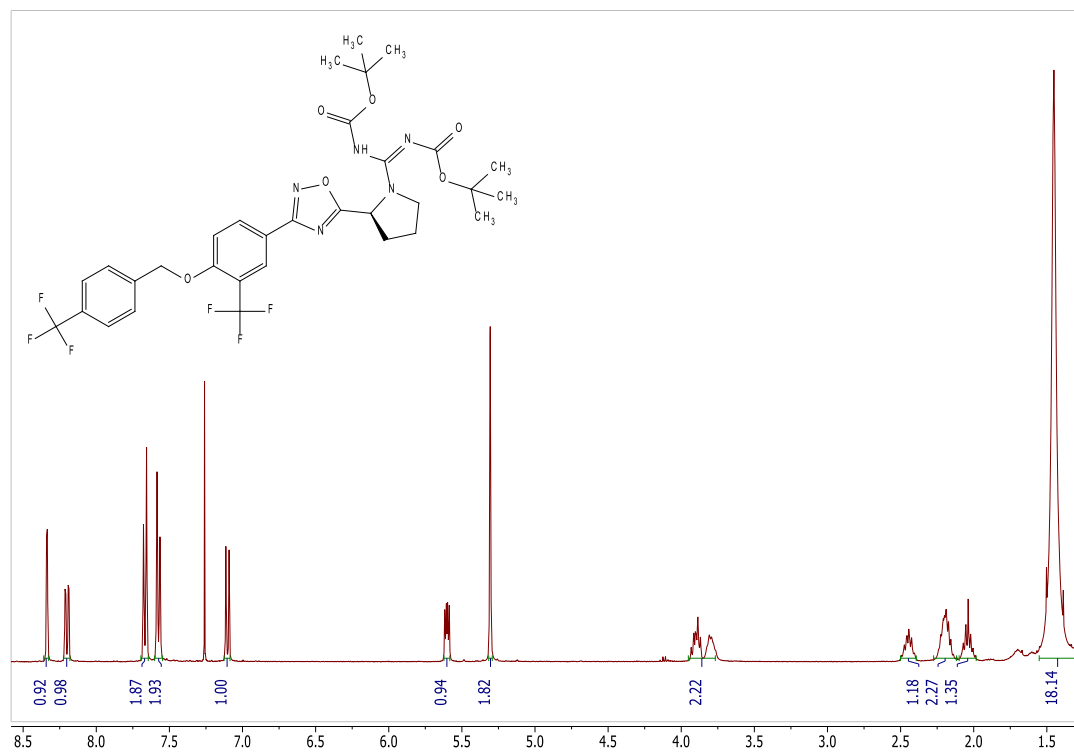


$^{19}\text{F}$ -NMR Spectrum for *tert*-butyl (((*tert*-butoxycarbonyl)amino)((*2S*)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -

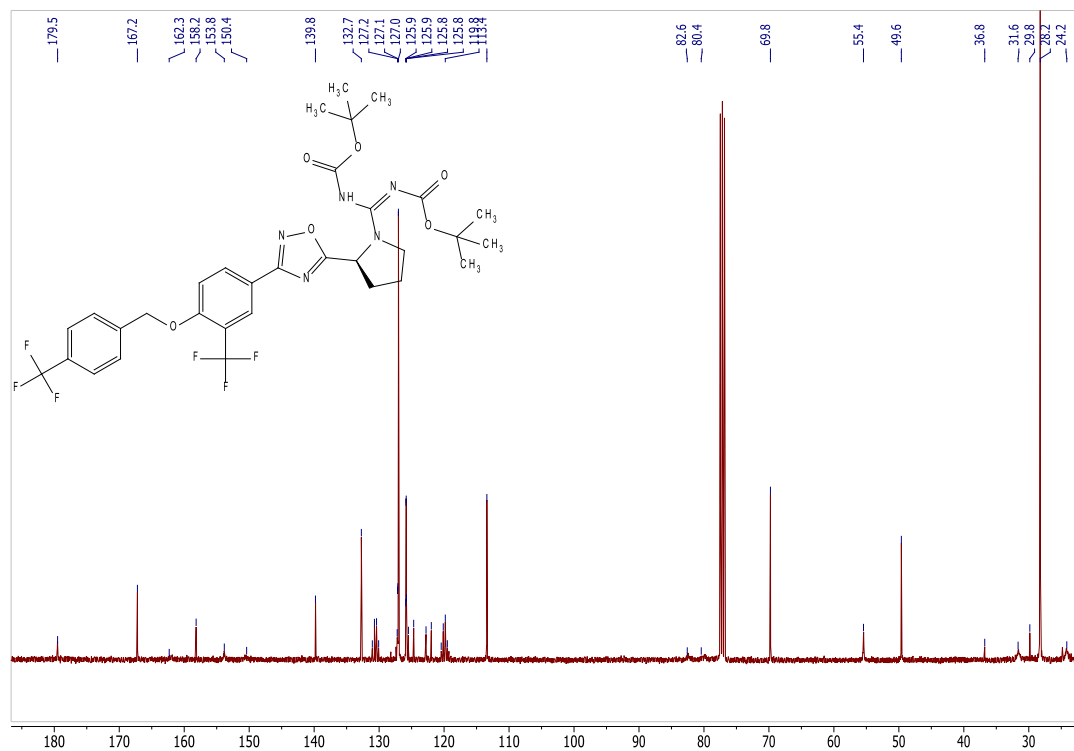




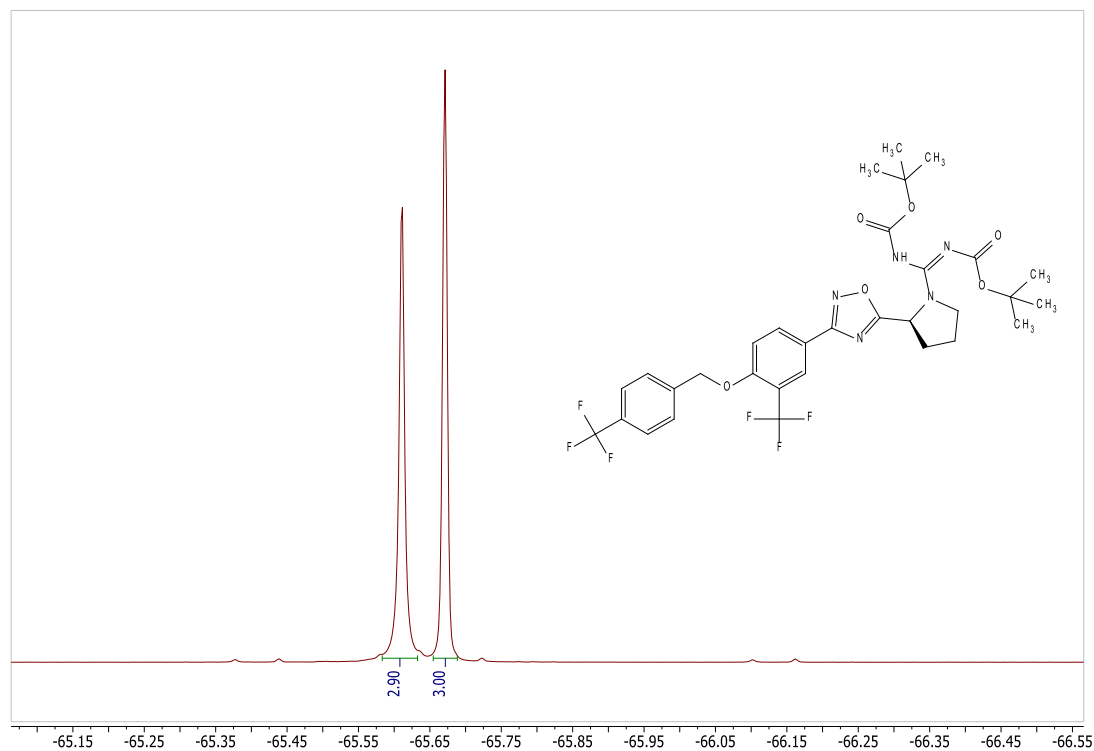
$^1\text{H-NMR}$  Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



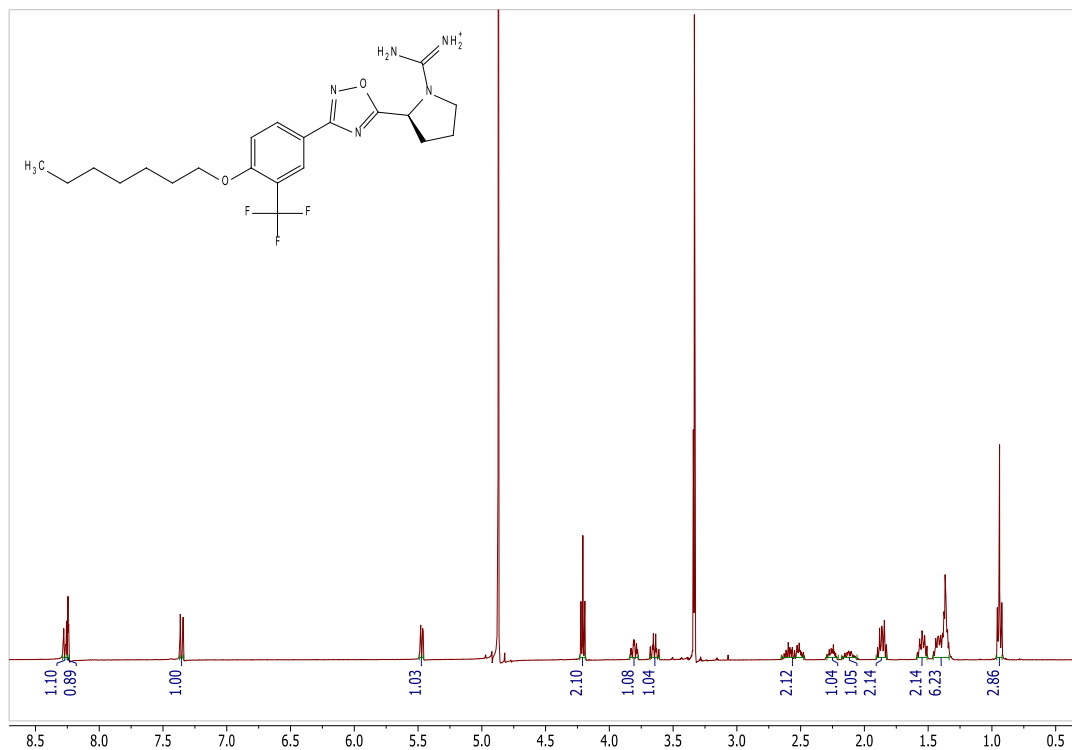
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



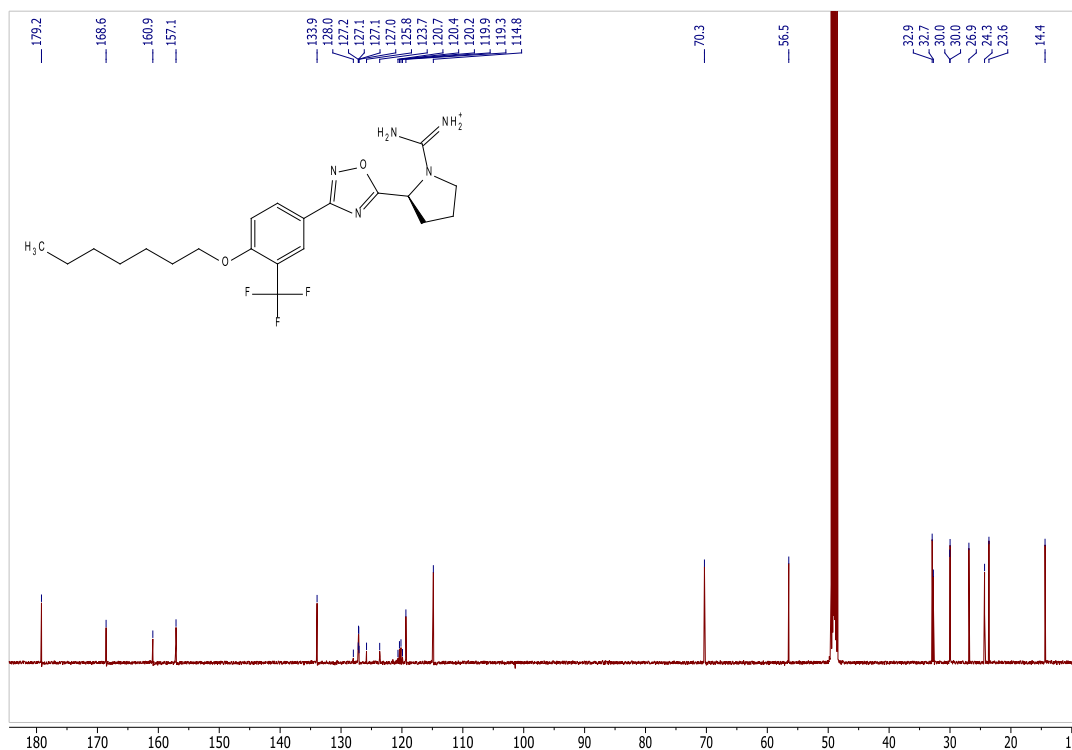
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



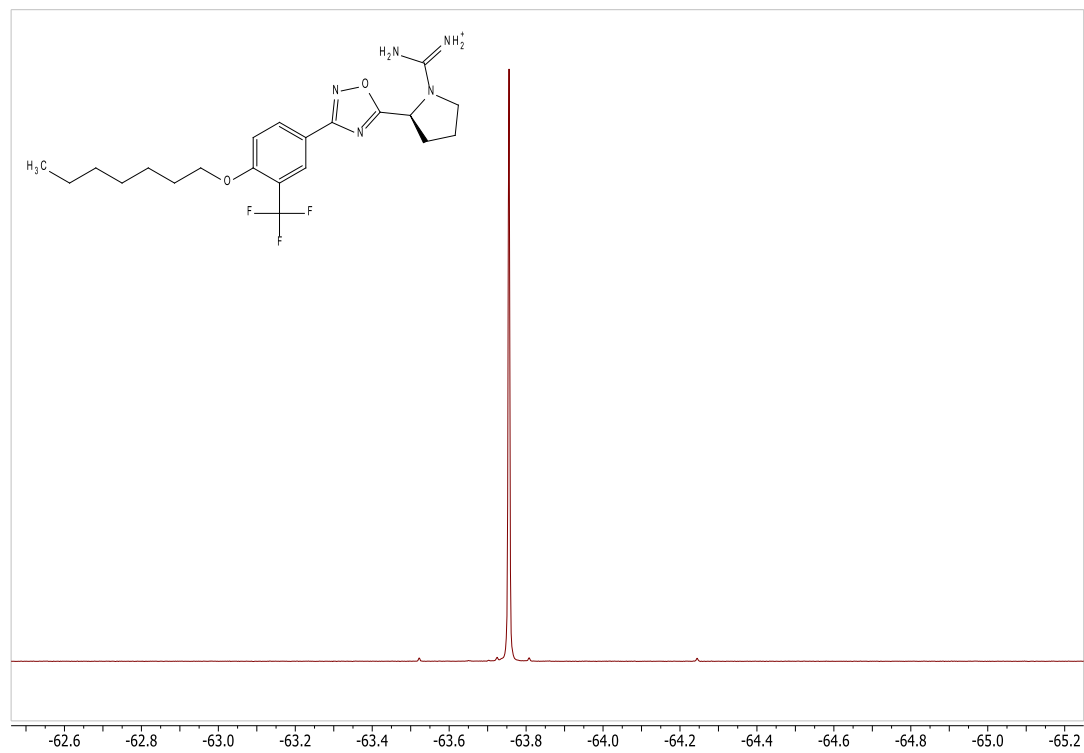
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27a** -



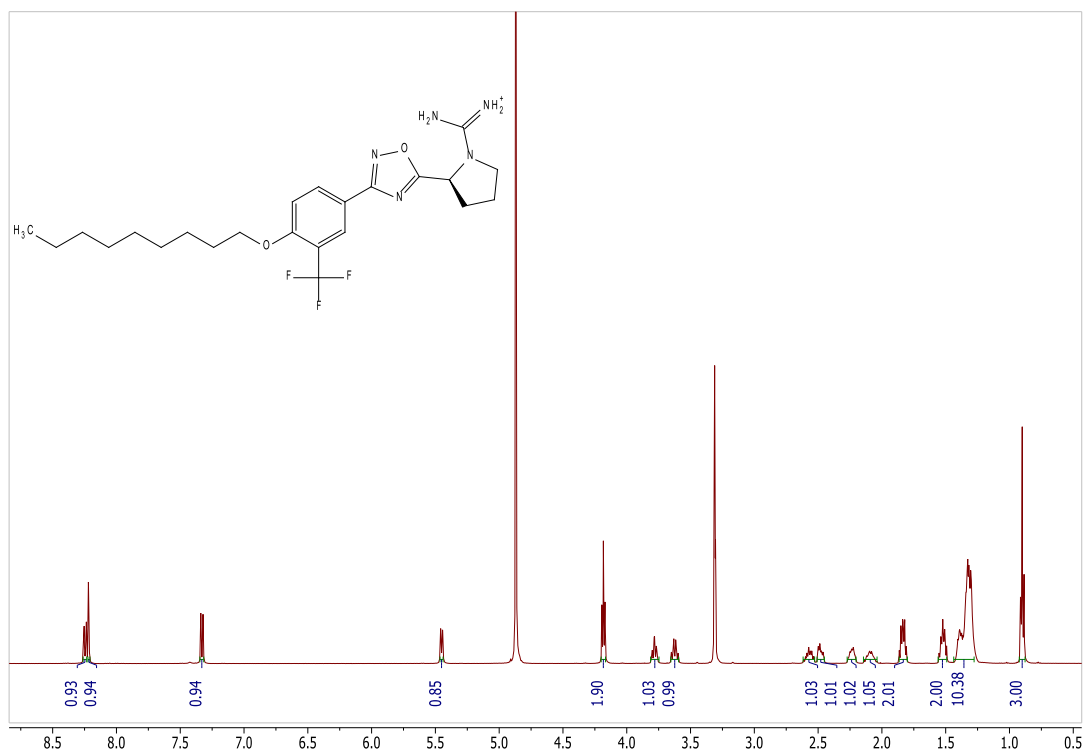
<sup>13</sup>C-NMR Spectrum for (S)-amino(2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27a** -



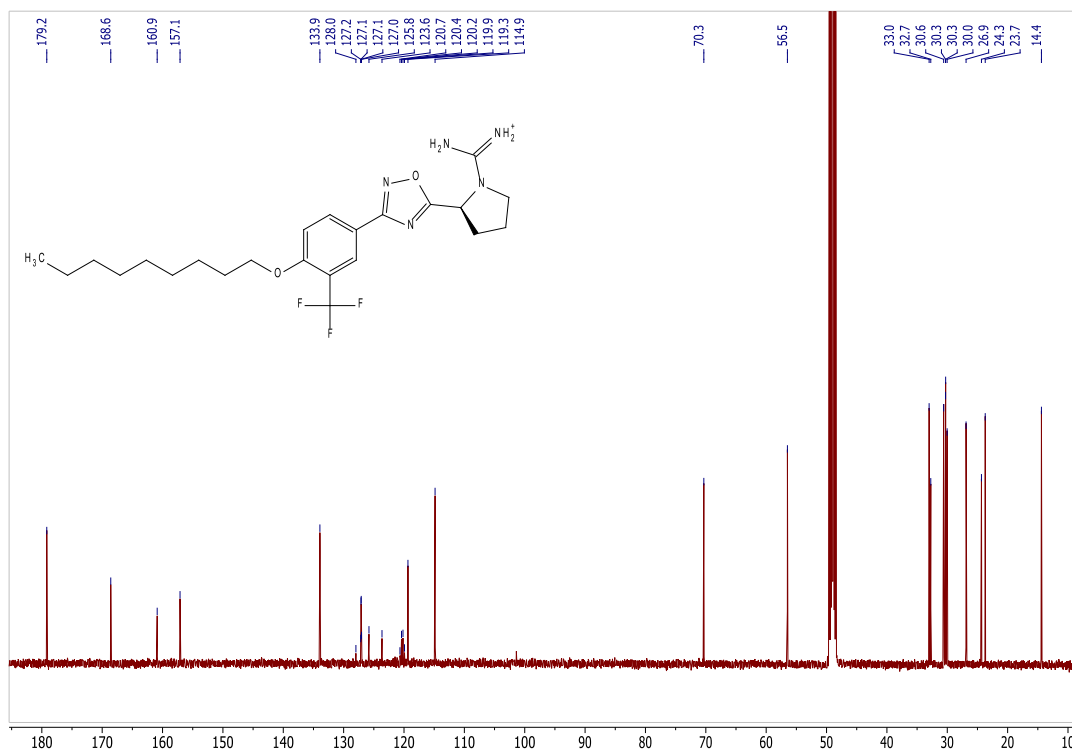
$^{19}\text{F}$ -NMR Spectrum for (S)-amino(2-(3-(4-(heptyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27a** -



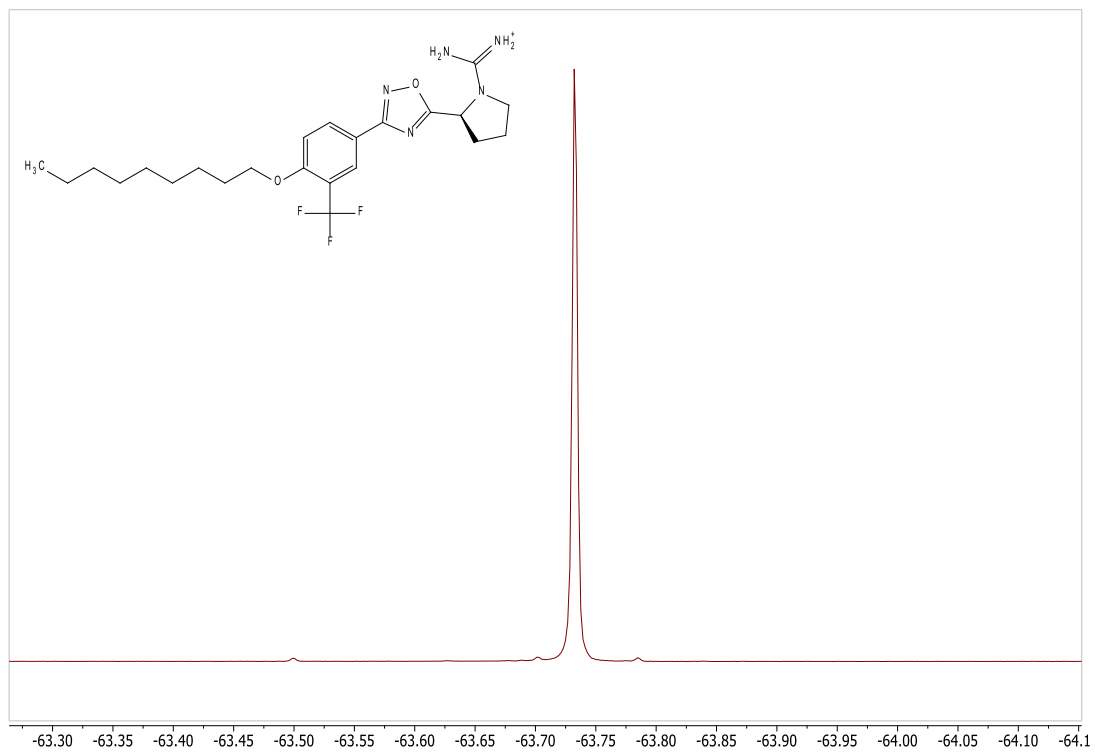
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27b** -



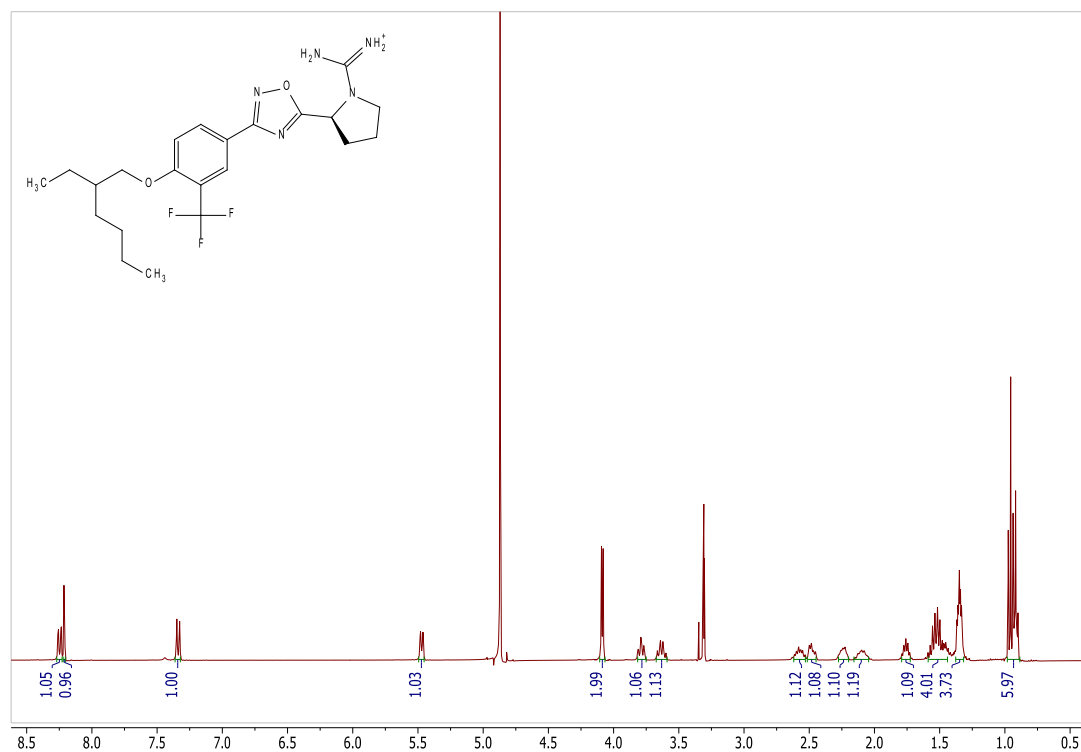
<sup>13</sup>C-NMR Spectrum for (S)-amino(2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27b** -



$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27b** -

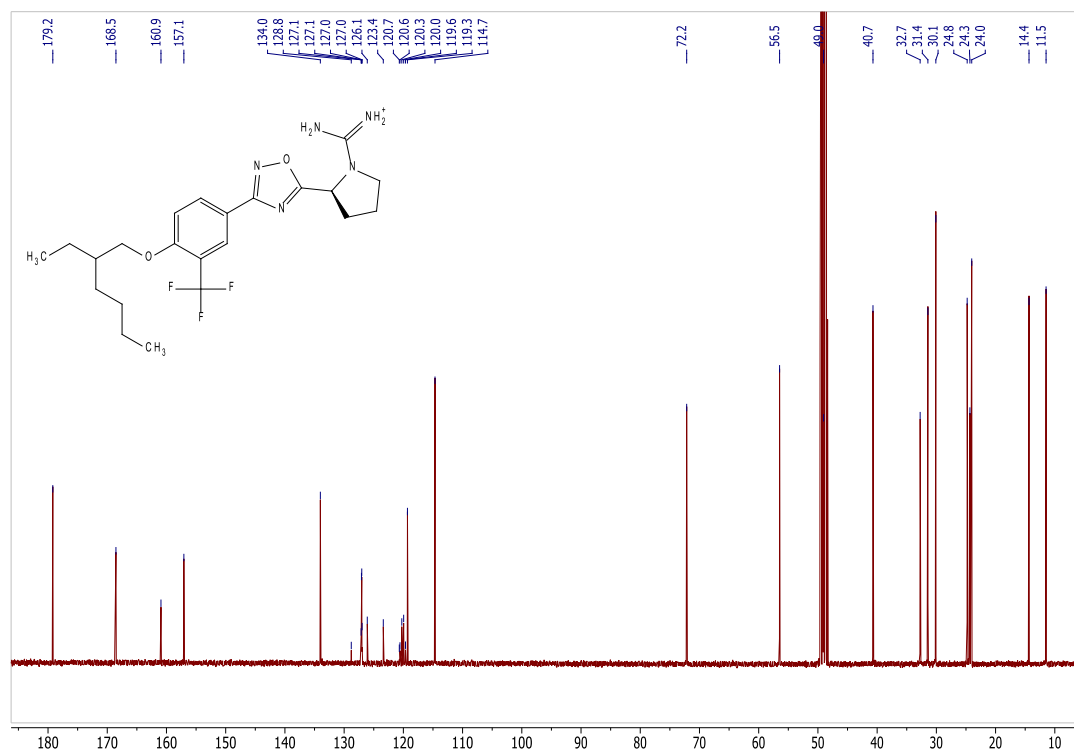


<sup>1</sup>H-NMR Spectrum for amino((2*S*)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27c** -

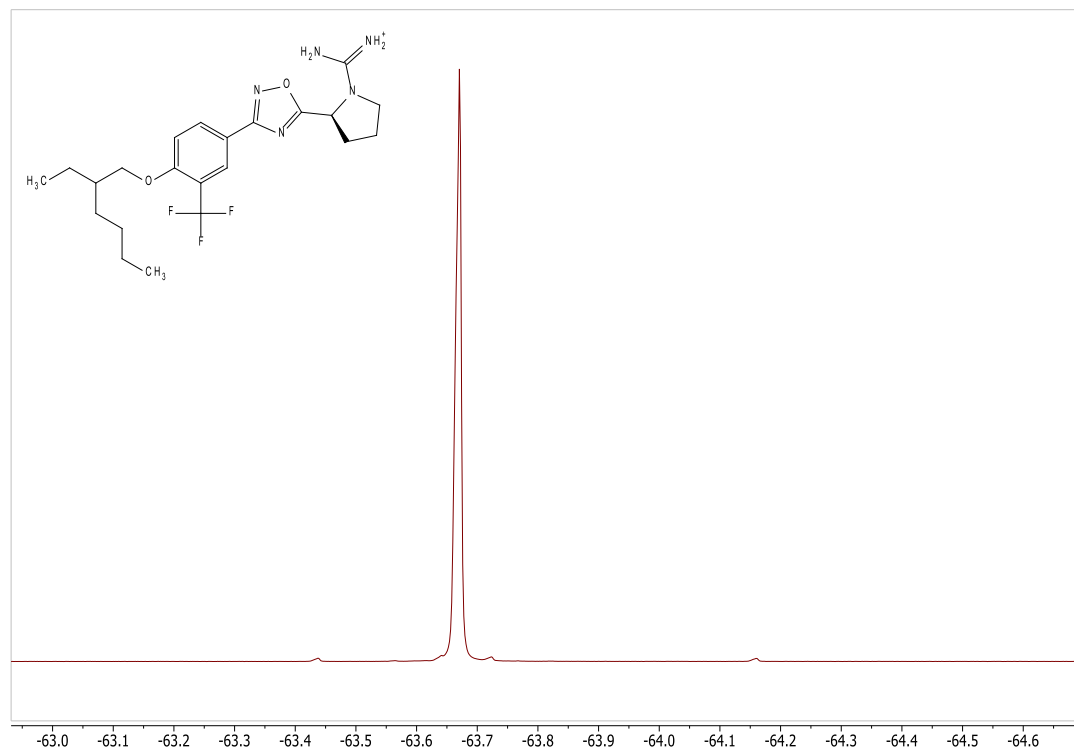




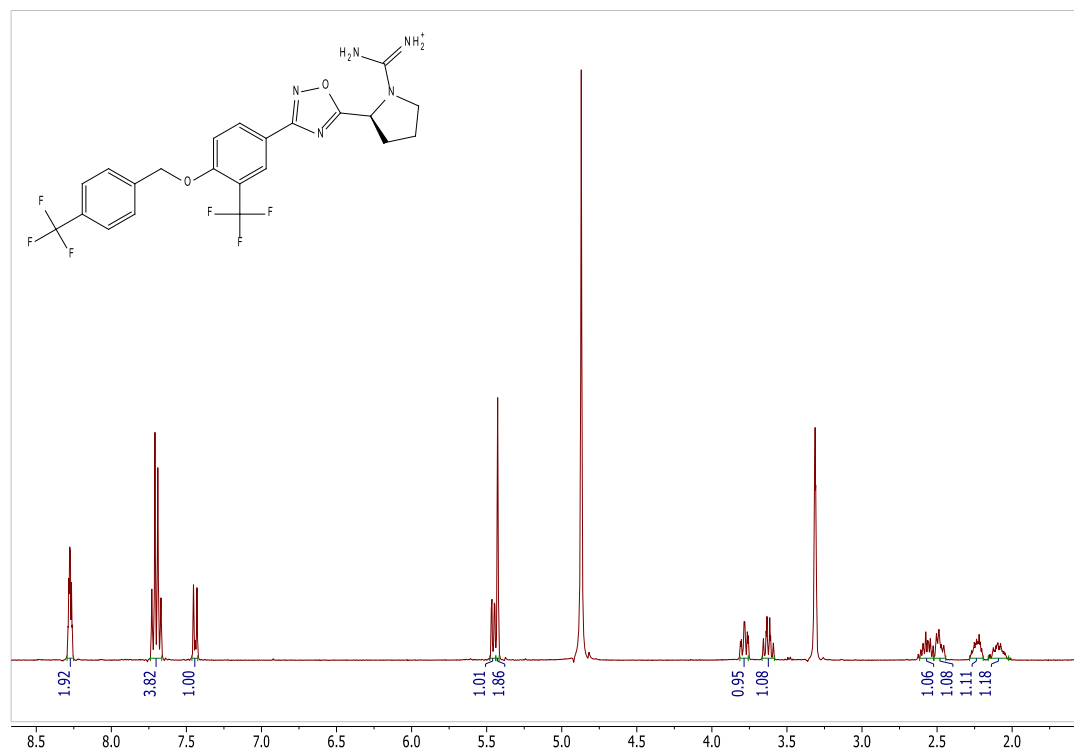
<sup>13</sup>C-NMR Spectrum for amino((2*S*)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27c** -



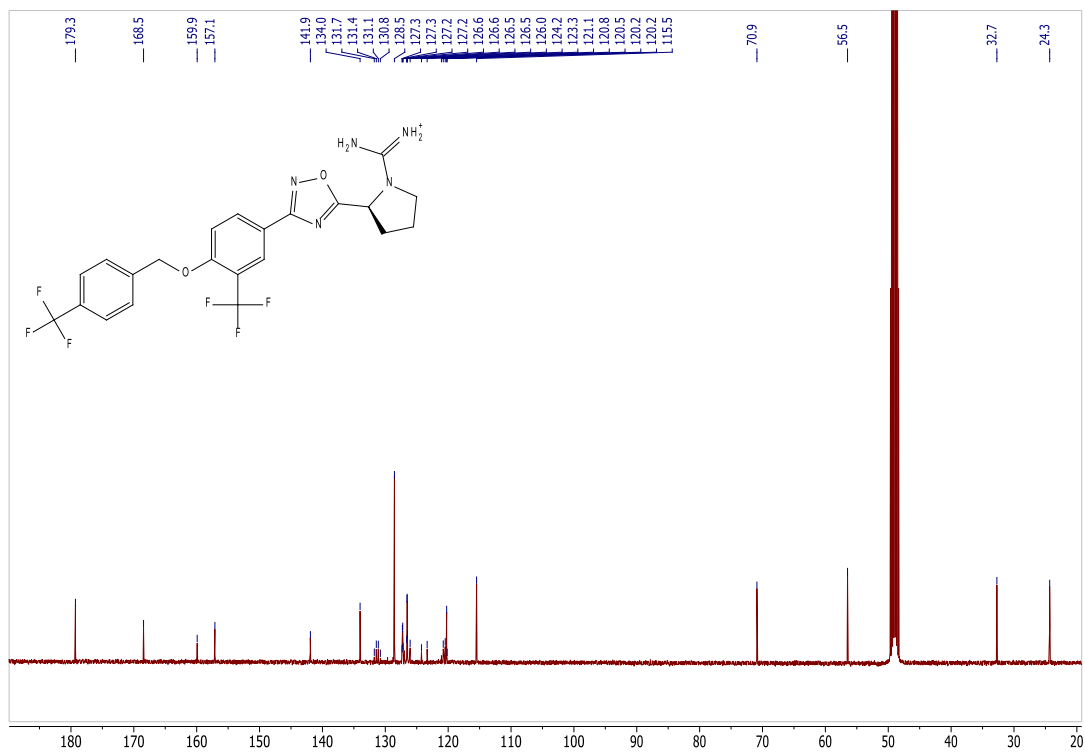
$^{19}\text{F}$ -NMR Spectrum for amino((2*S*)-2-(3-(4-((2-ethylhexyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27c** -



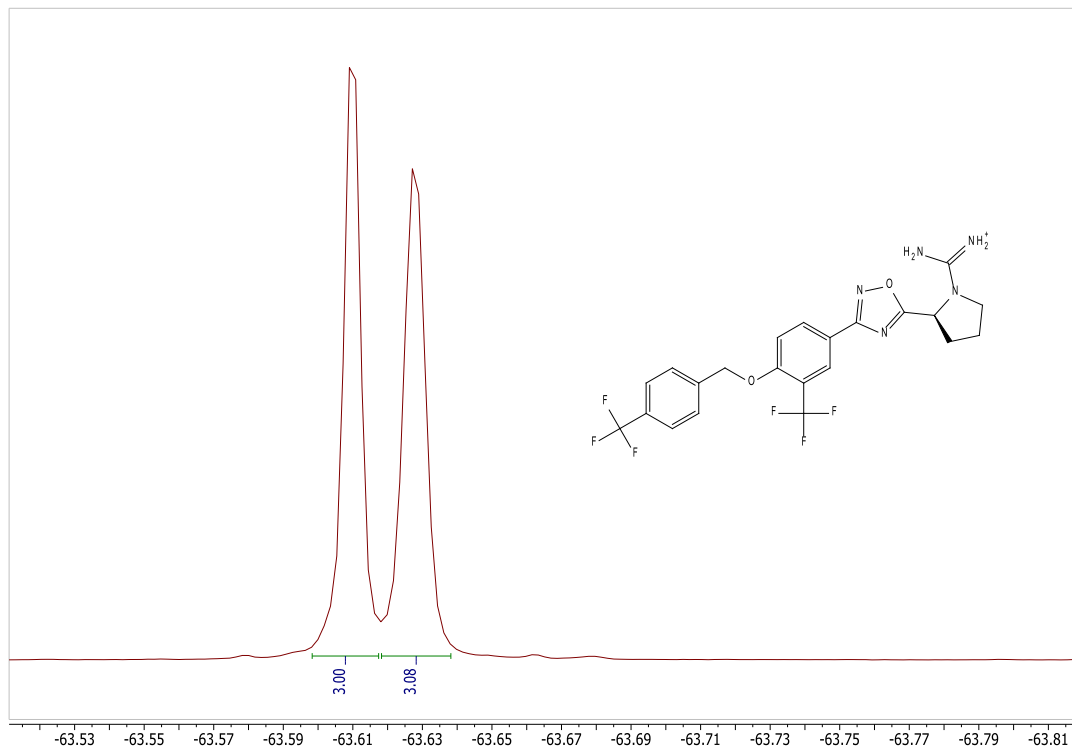
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27d** -



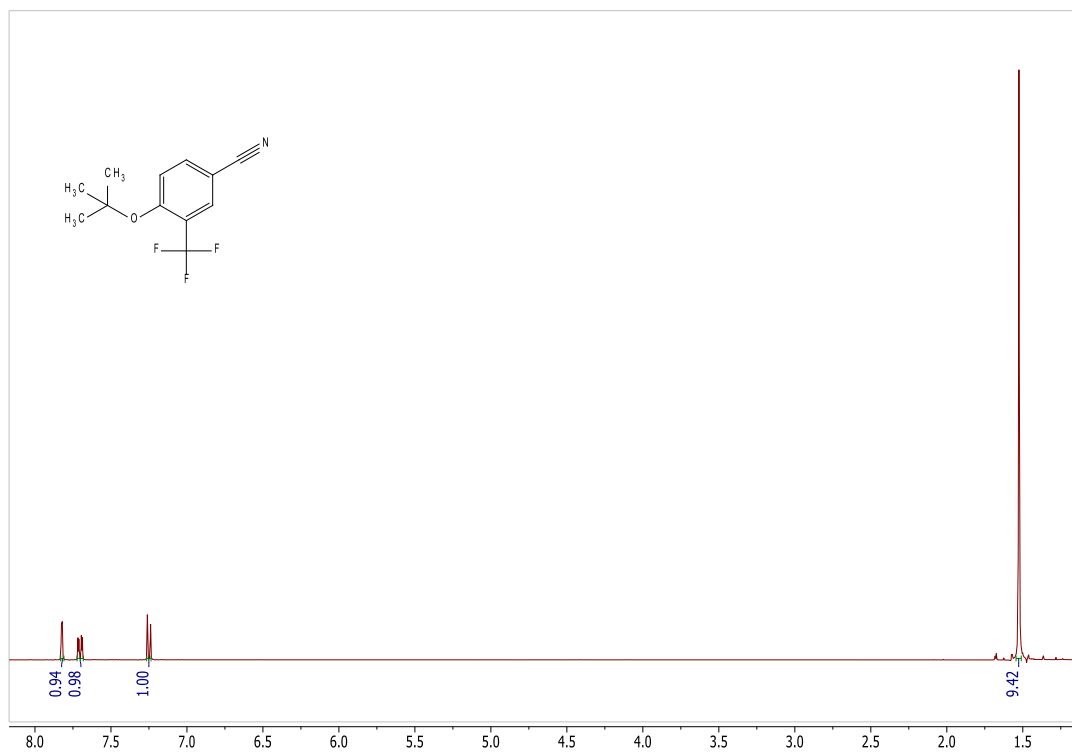
$^{13}\text{C}$ -NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27d** -



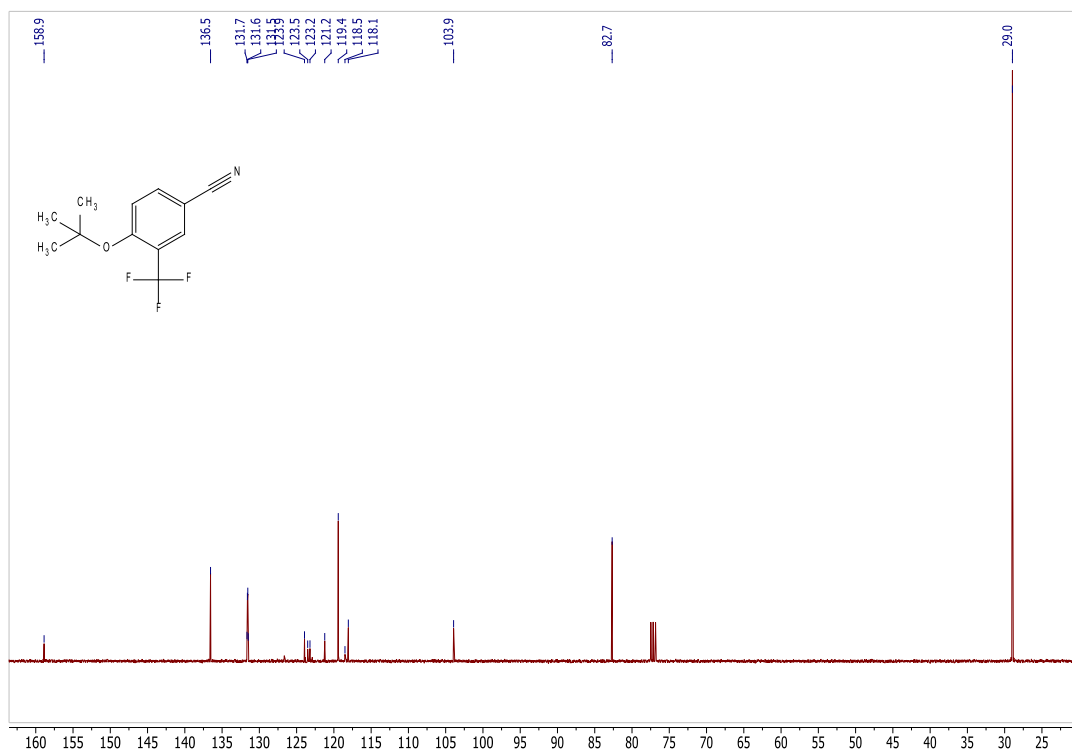
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(3-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.27d** -



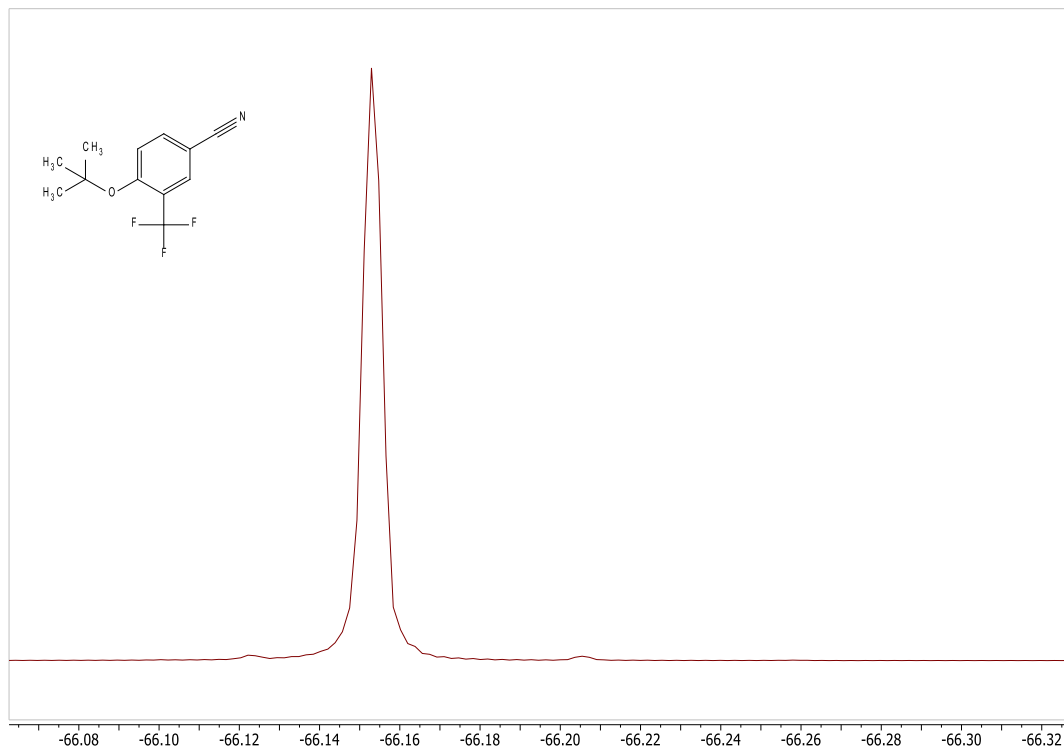
<sup>1</sup>H-NMR Spectrum for 4-(*tert*-butoxy)-3-(trifluoromethyl)benzonitrile -



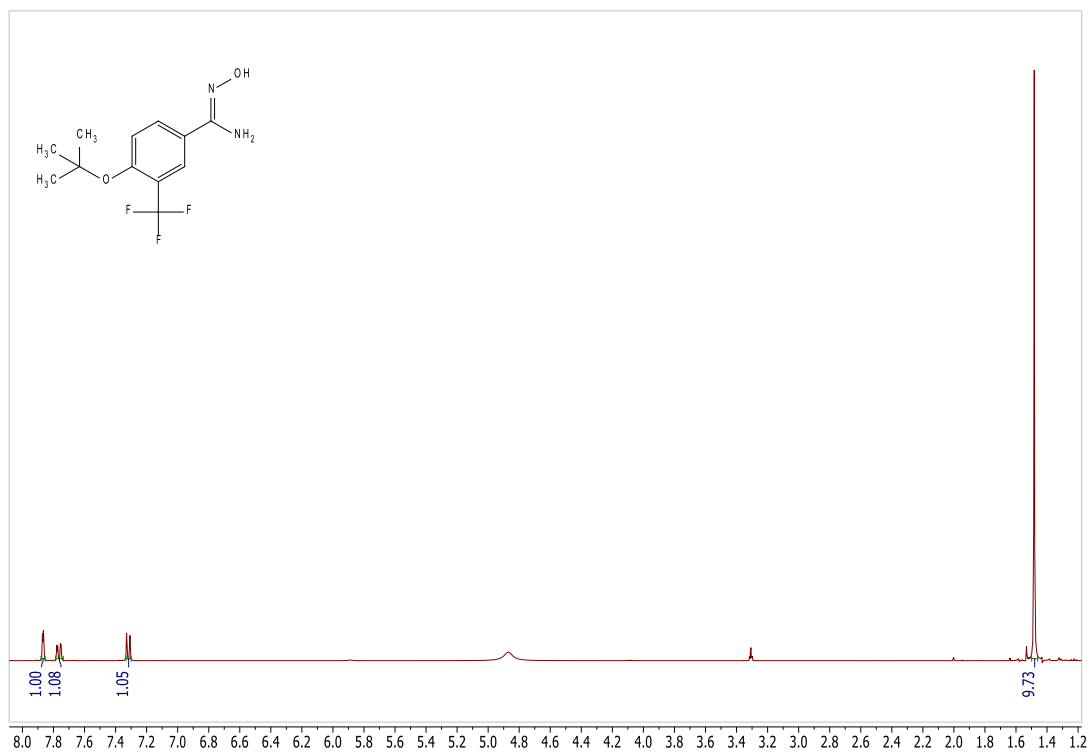
<sup>13</sup>C-NMR Spectrum for 4-(*tert*-butoxy)-3-(trifluoromethyl)benzonitrile -



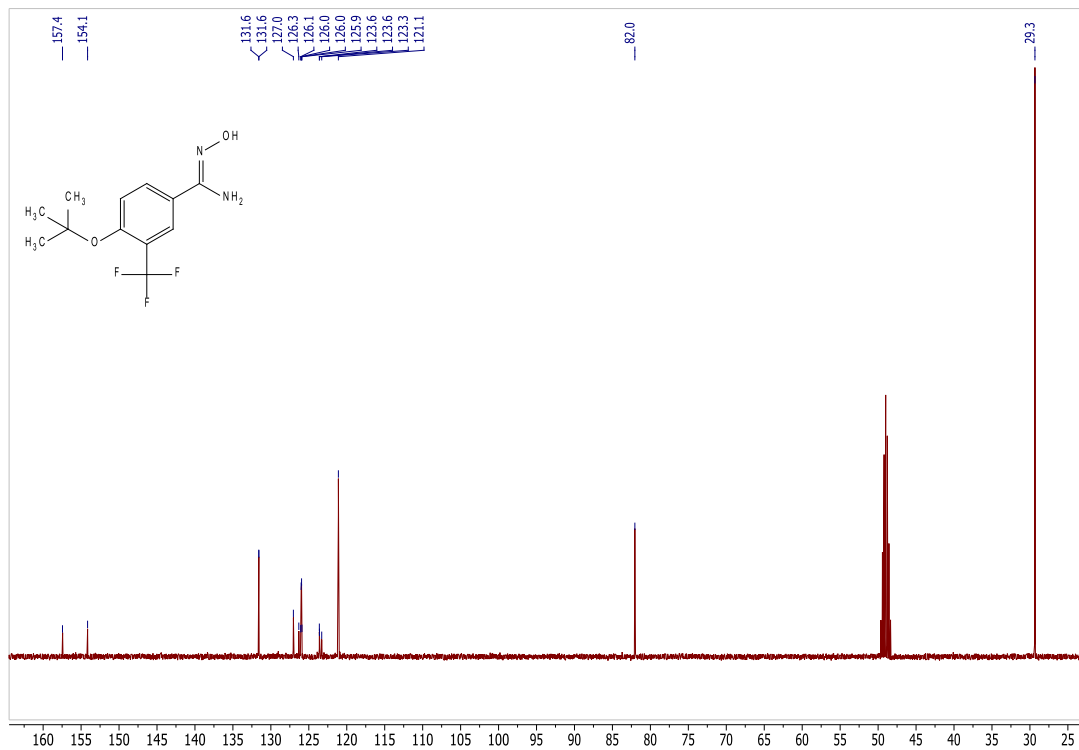
$^{19}\text{F}$ -NMR Spectrum for 4-(*tert*-butoxy)-3-(trifluoromethyl)benzonitrile -



<sup>1</sup>H-NMR Spectrum for (Z)-4-(tert-butoxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide -

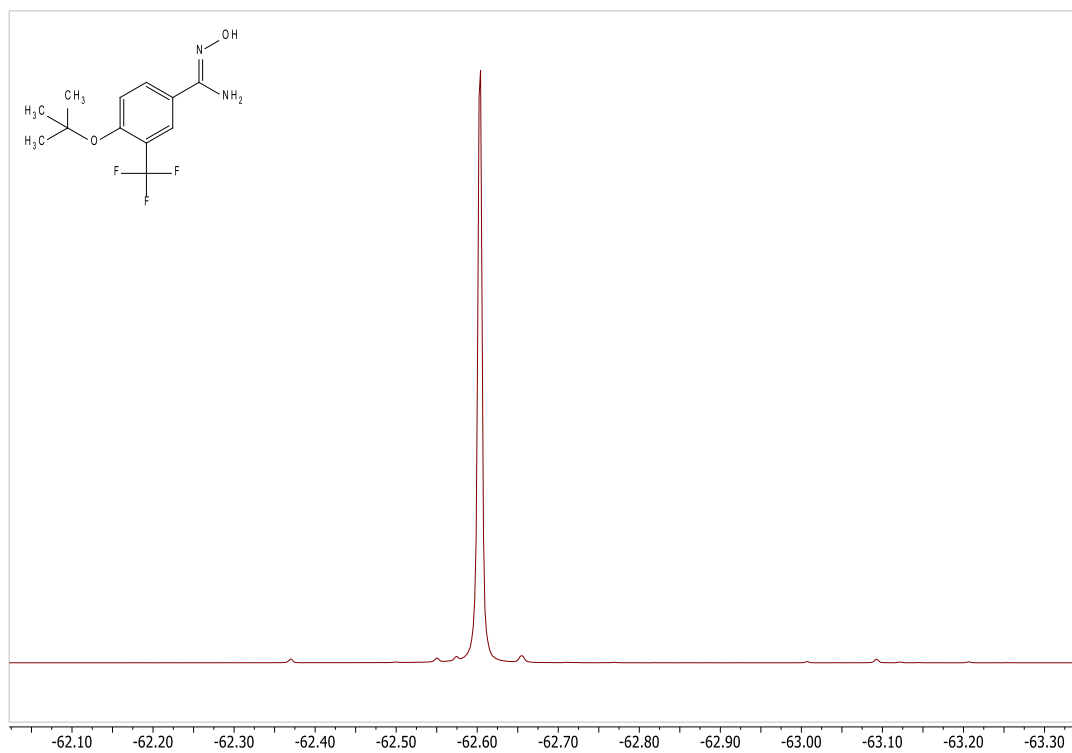


<sup>13</sup>C-NMR Spectrum for (Z)-4-(tert-butoxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide -

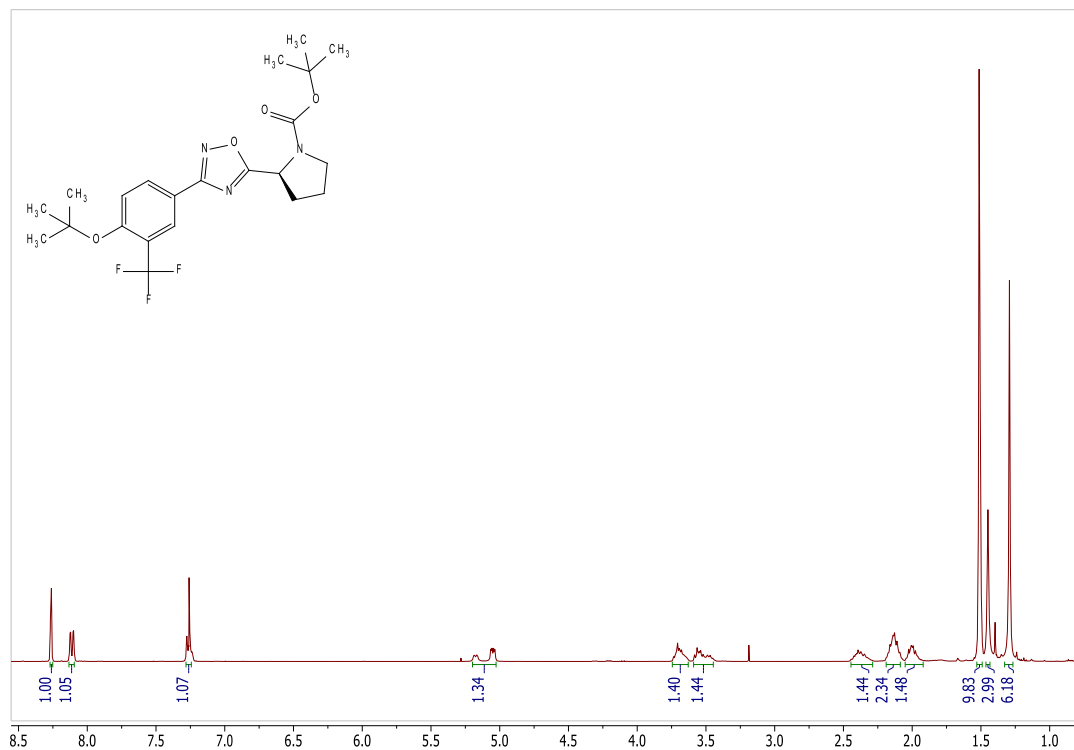




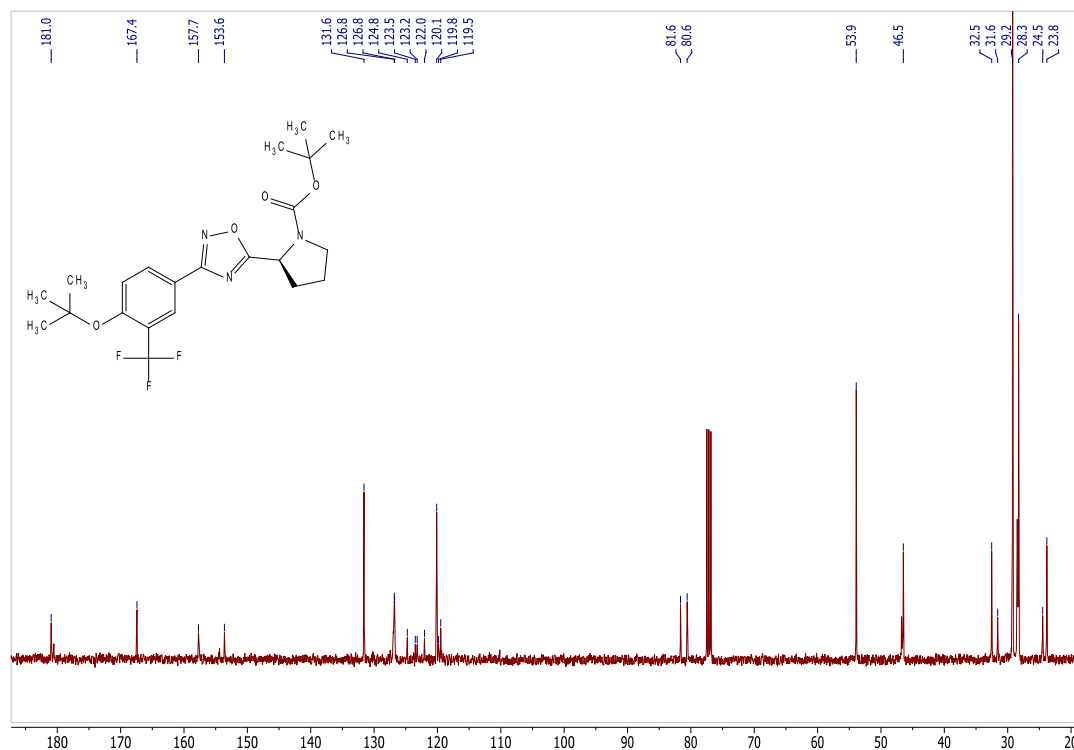
$^{19}\text{F}$ -NMR Spectrum for (Z)-4-(tert-butoxy)-N'-hydroxy-3-(trifluoromethyl)benzimidamide -



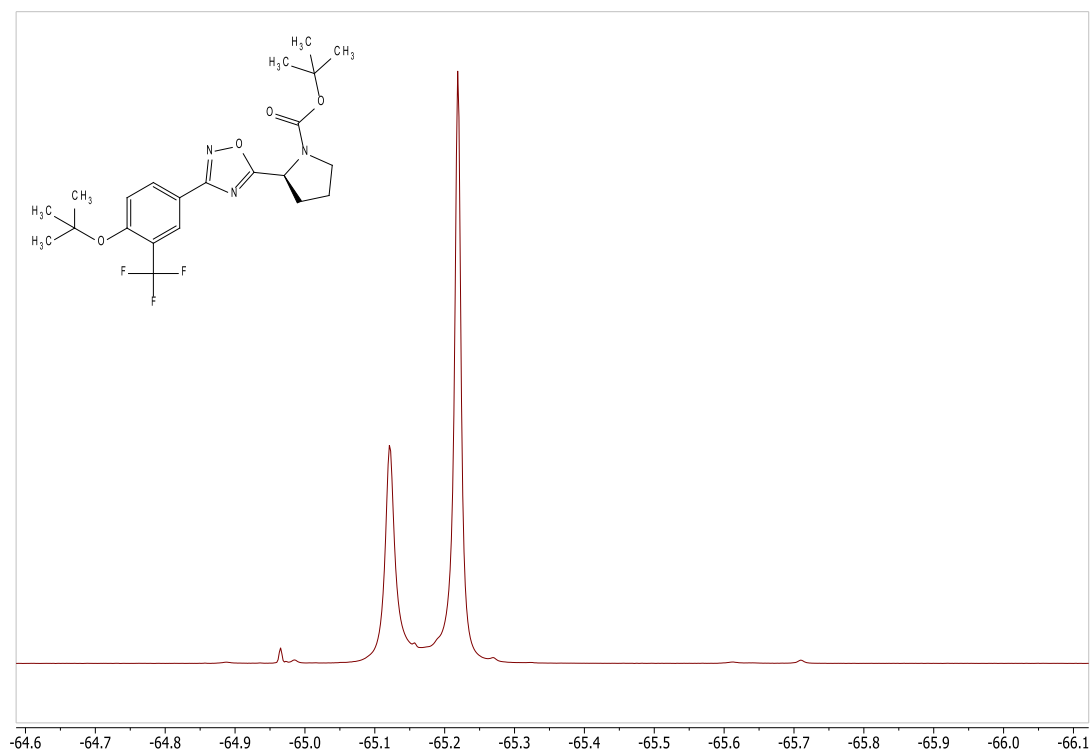
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(*tert*-butoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate -



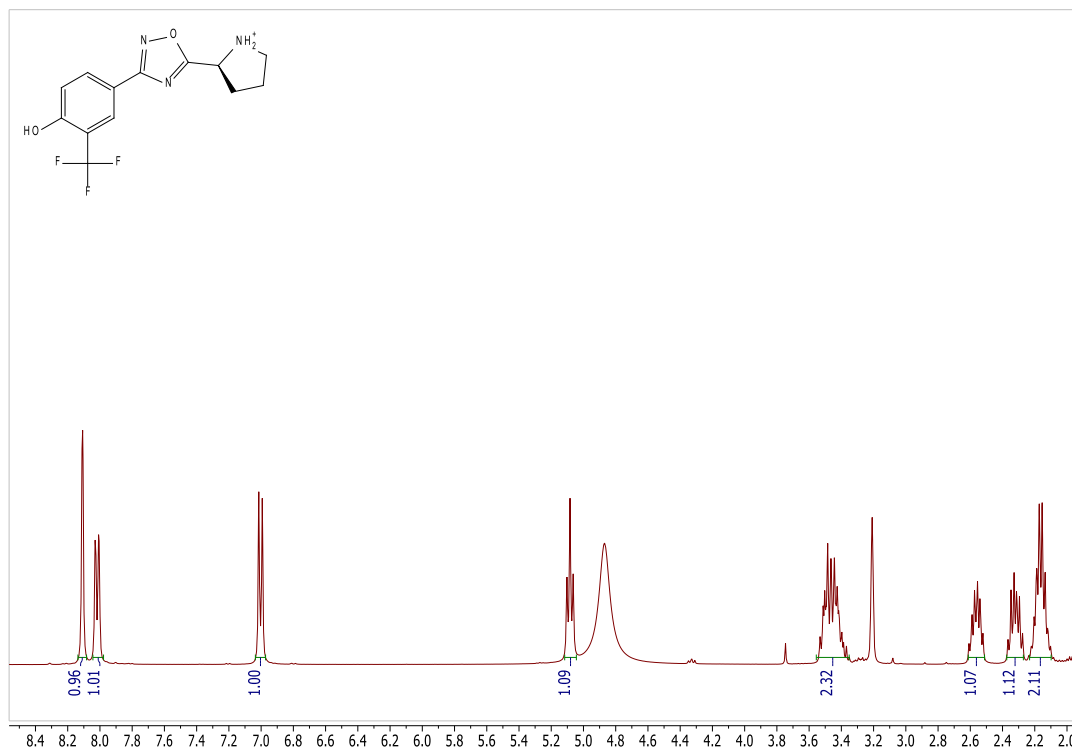
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(*tert*-butoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate -



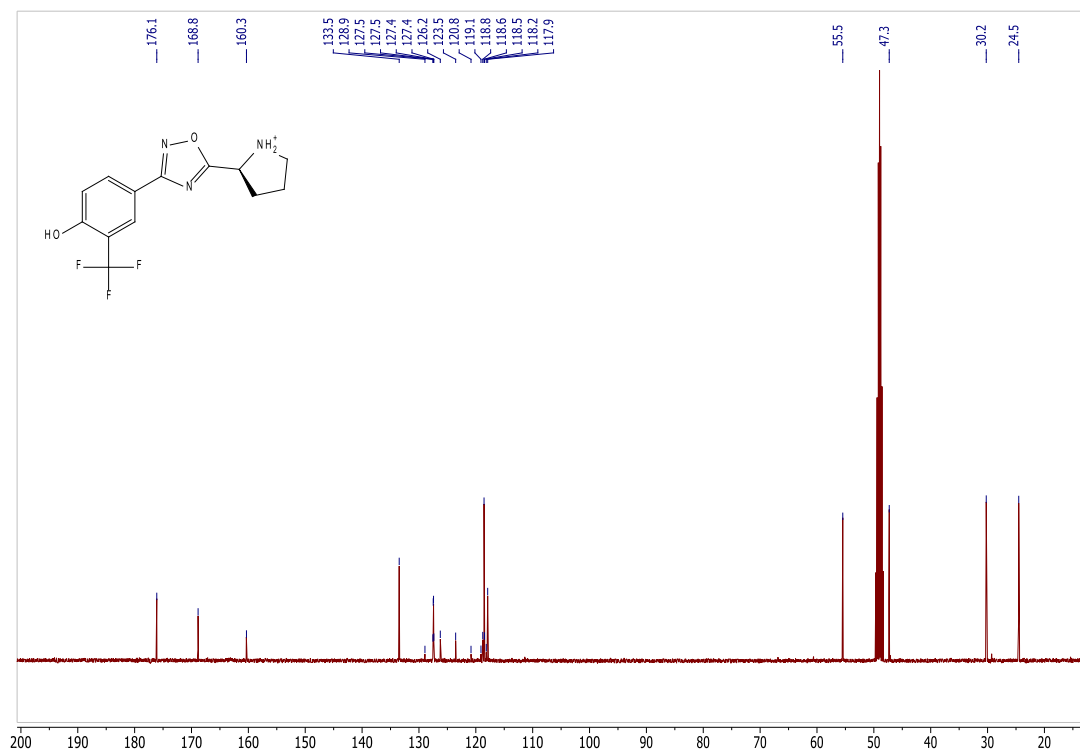
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(*tert*-butoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate -



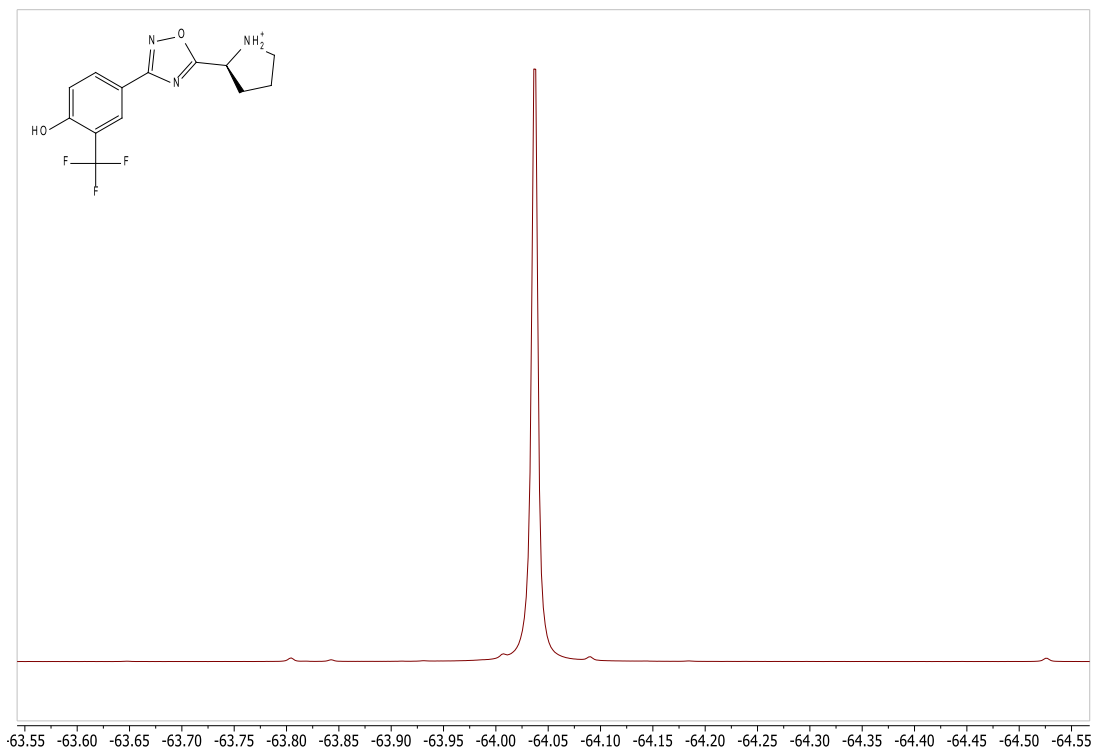
<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.28** -



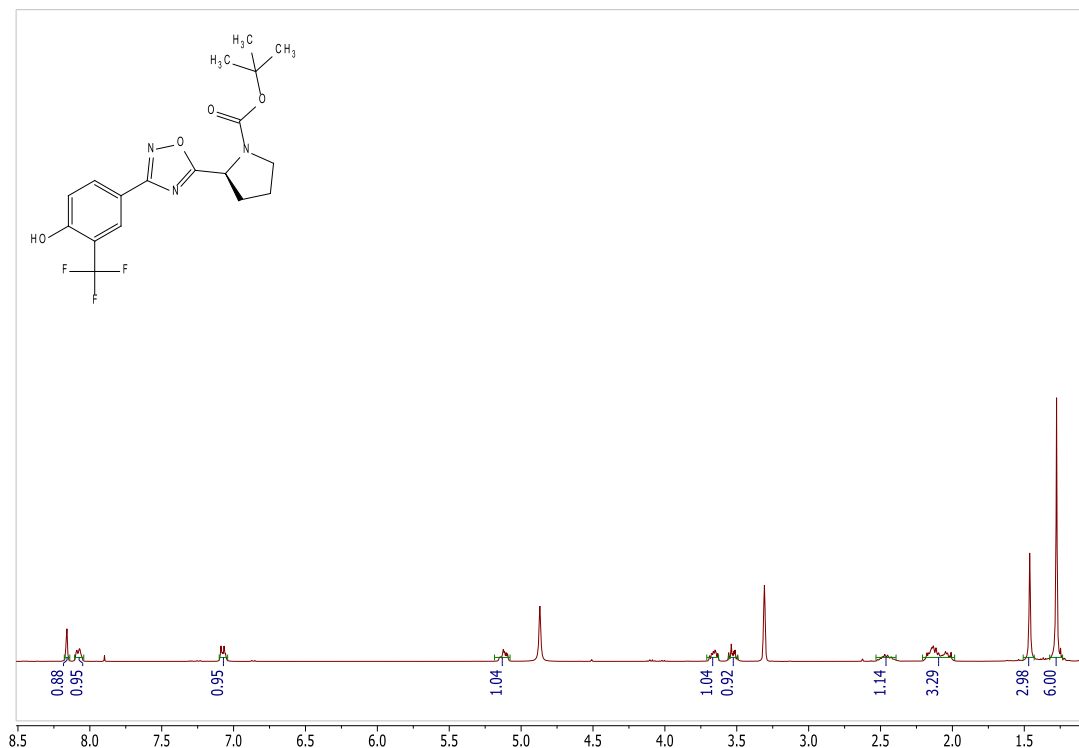
<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.28** -



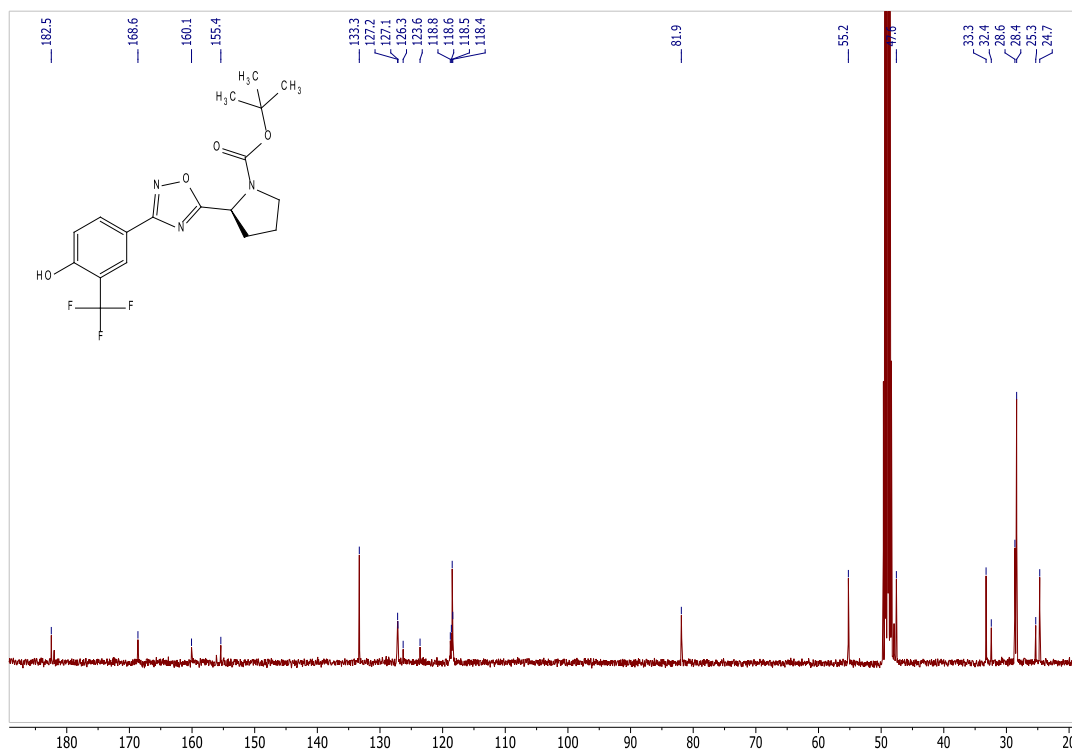
$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(3-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate **3.28** -



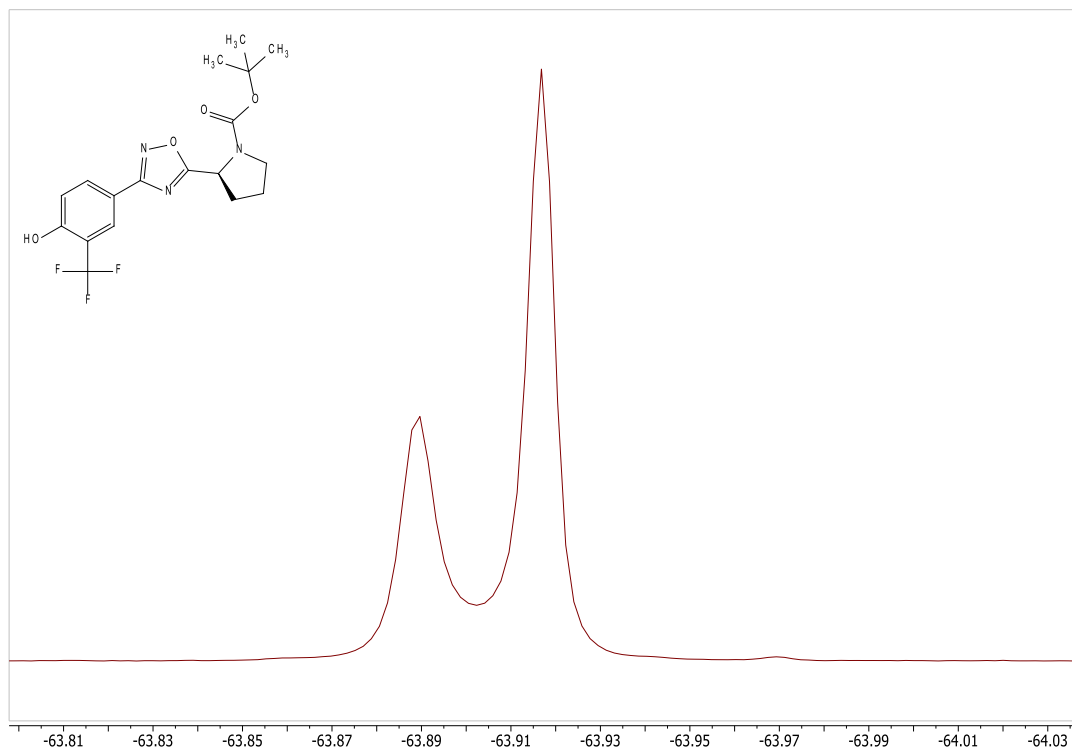
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.29** -



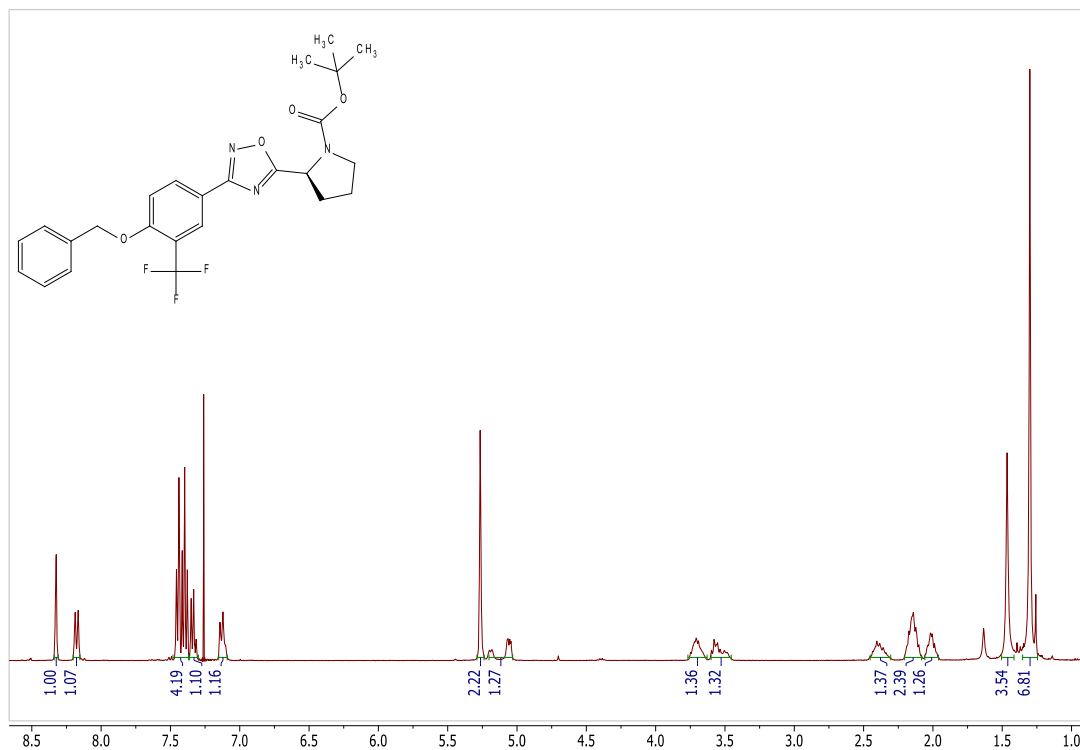
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.29** -



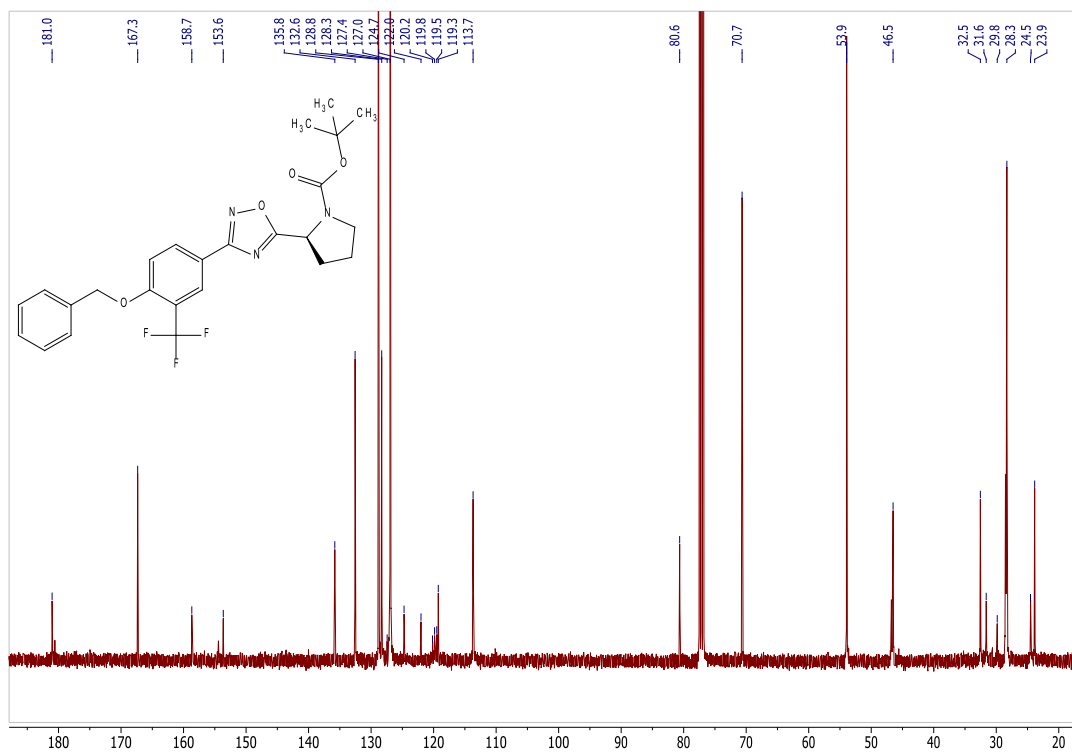
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.29** -



<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30a** -

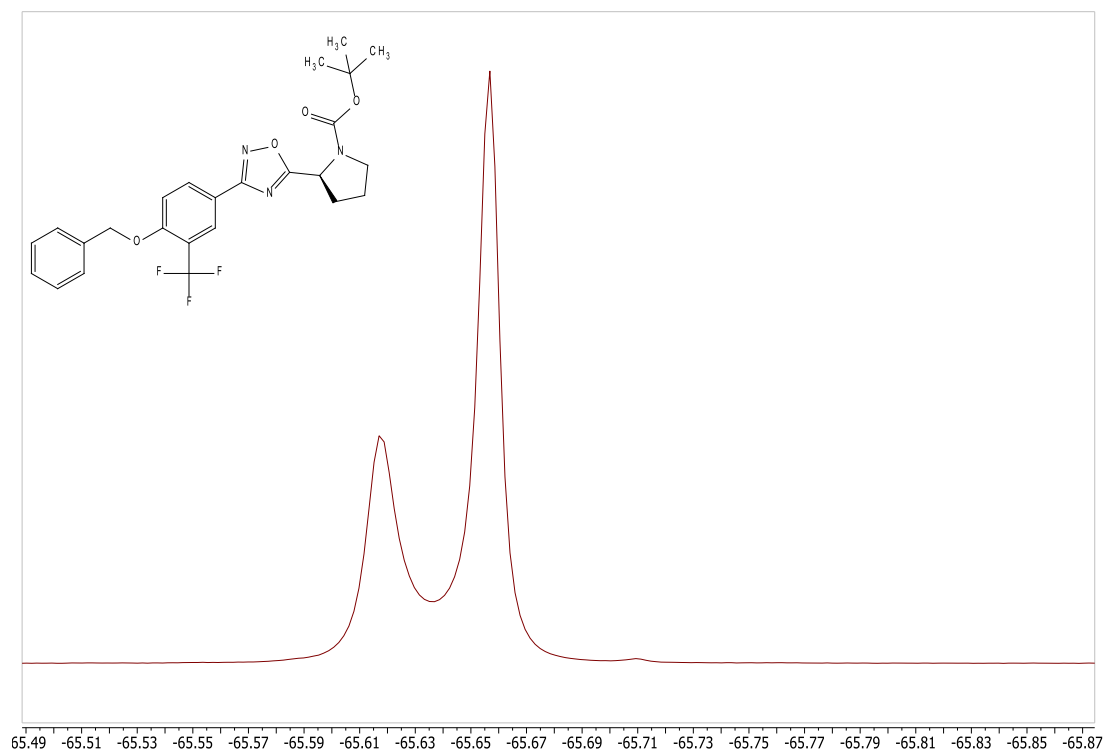


<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30a** -

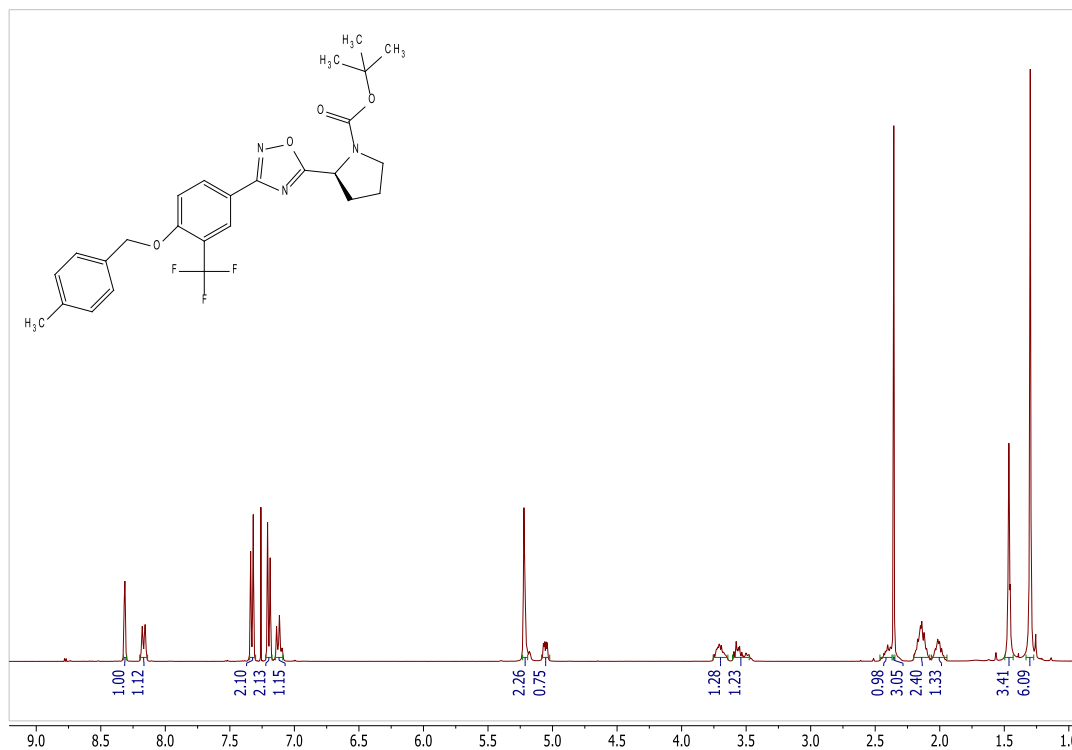




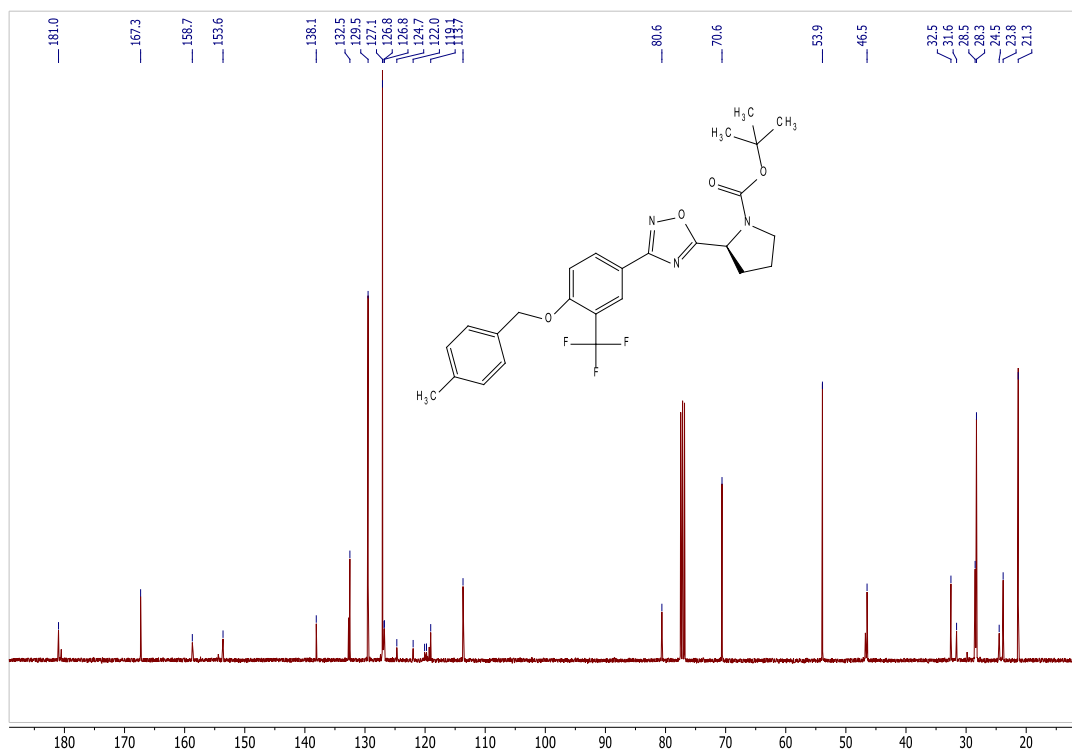
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30a** -



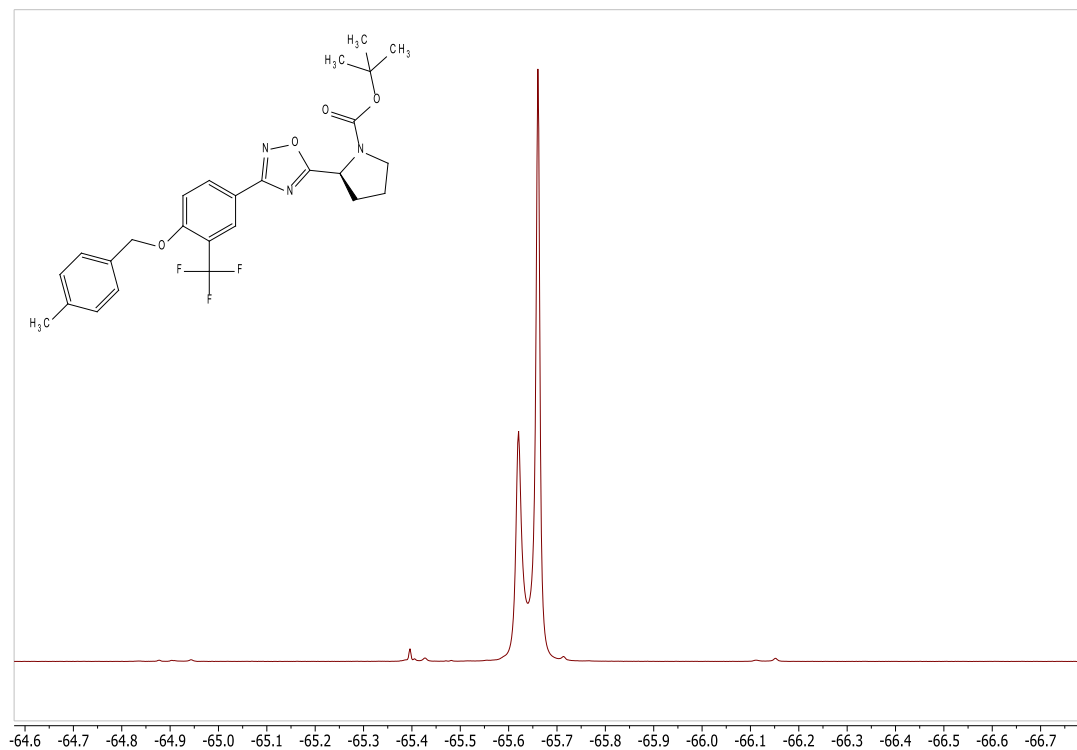
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30b** -



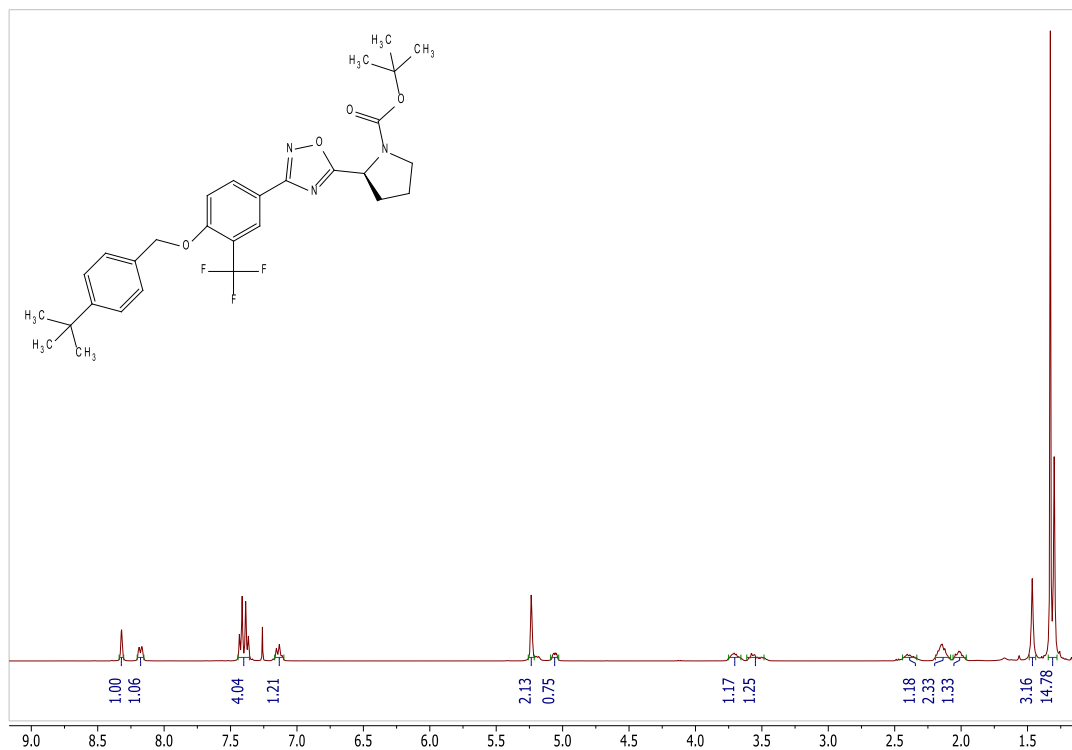
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30b** -



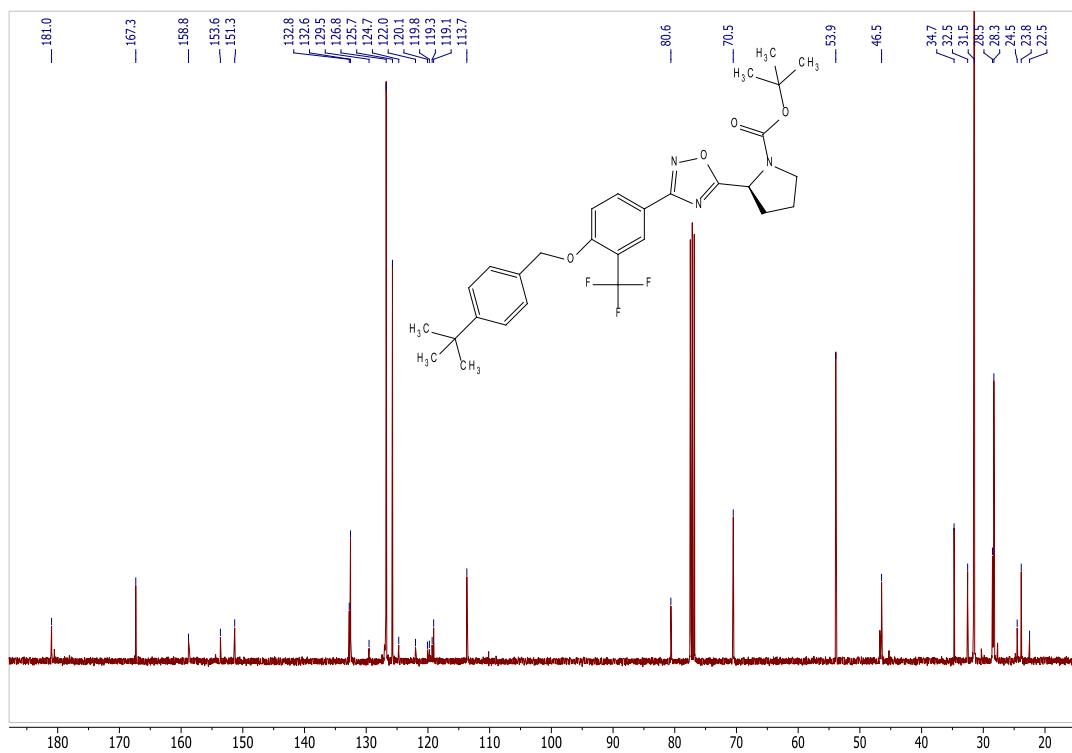
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30b** -



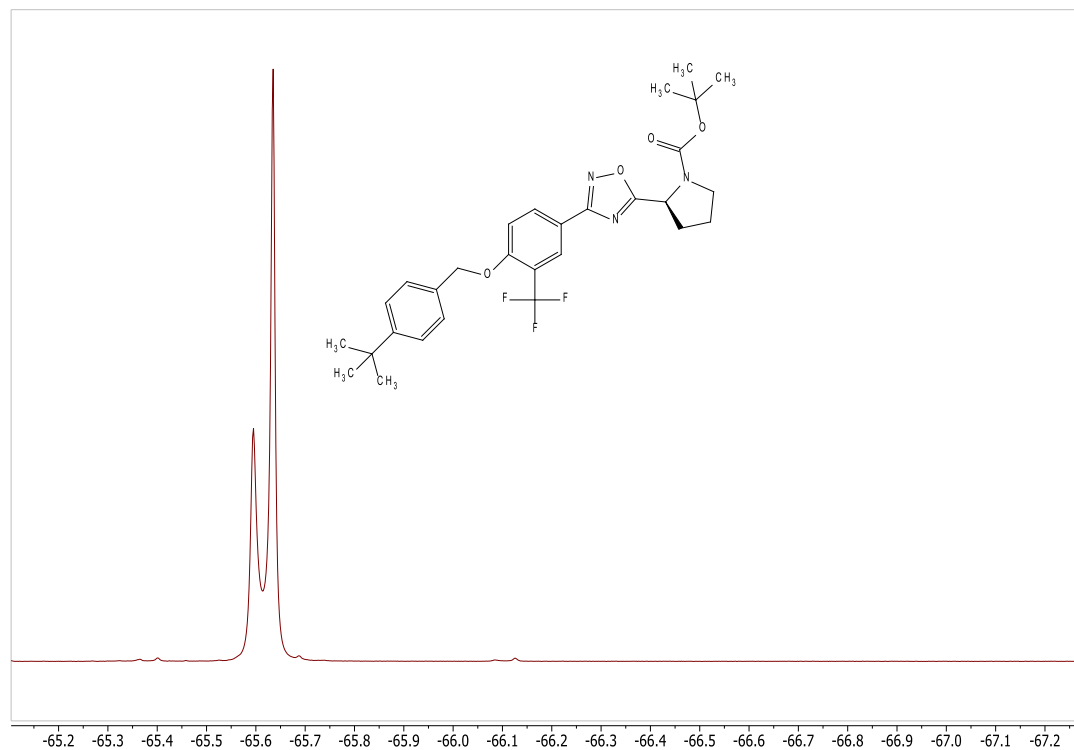
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30c** -



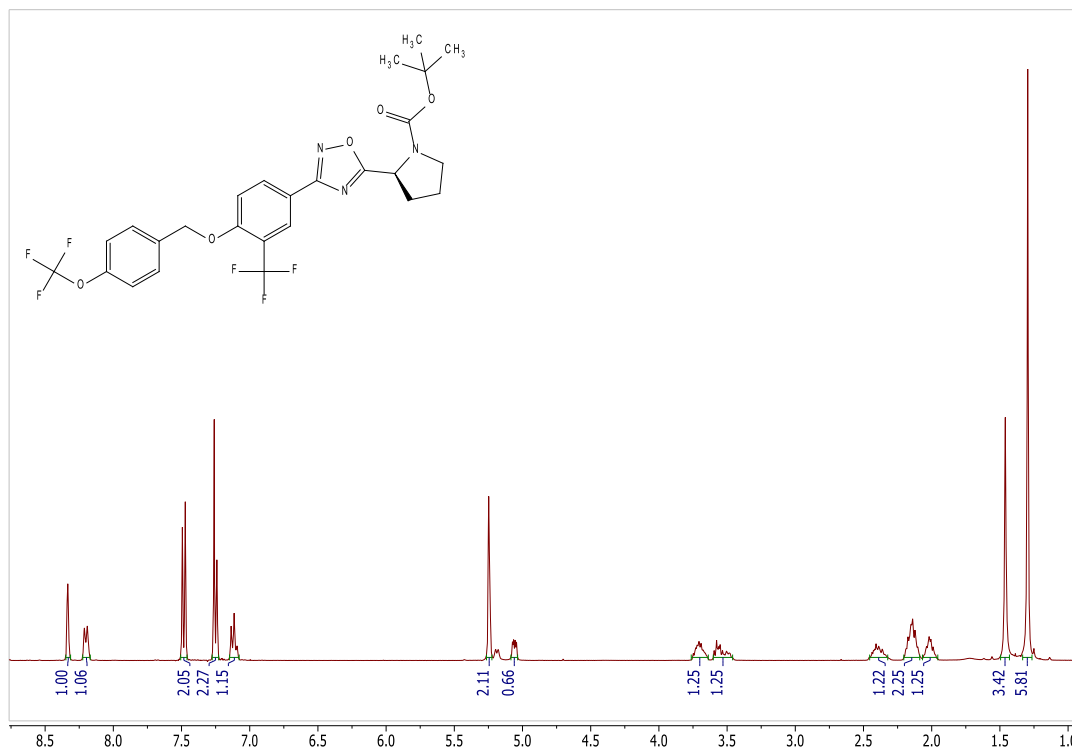
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30c** -



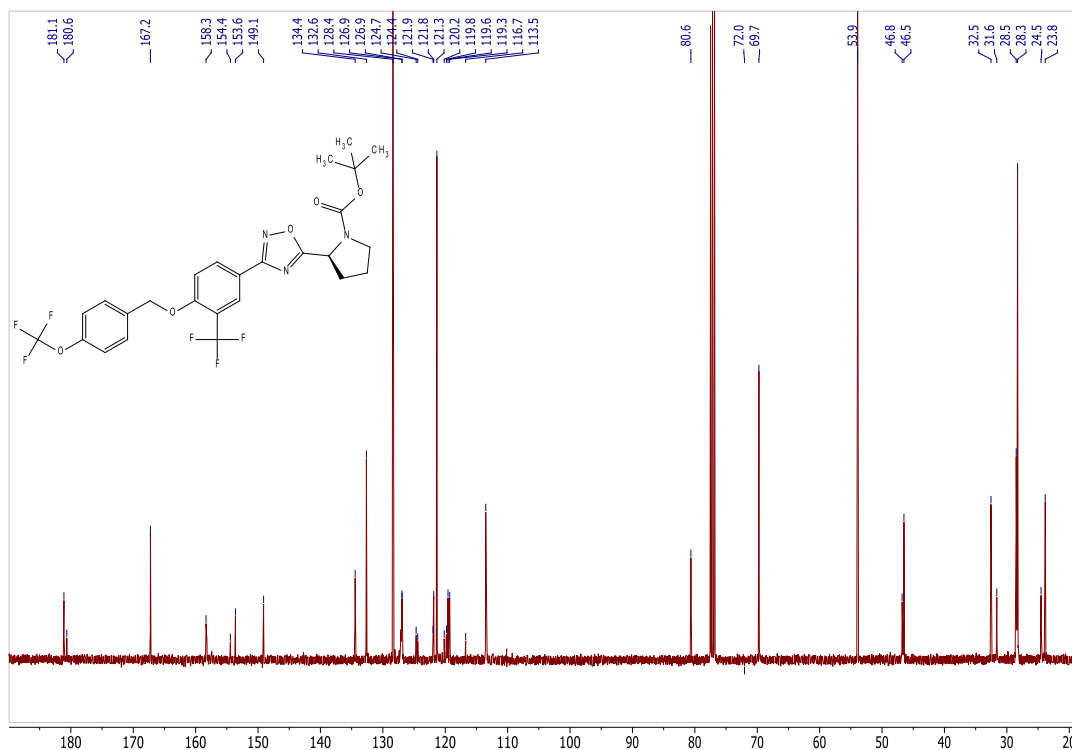
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30c** -



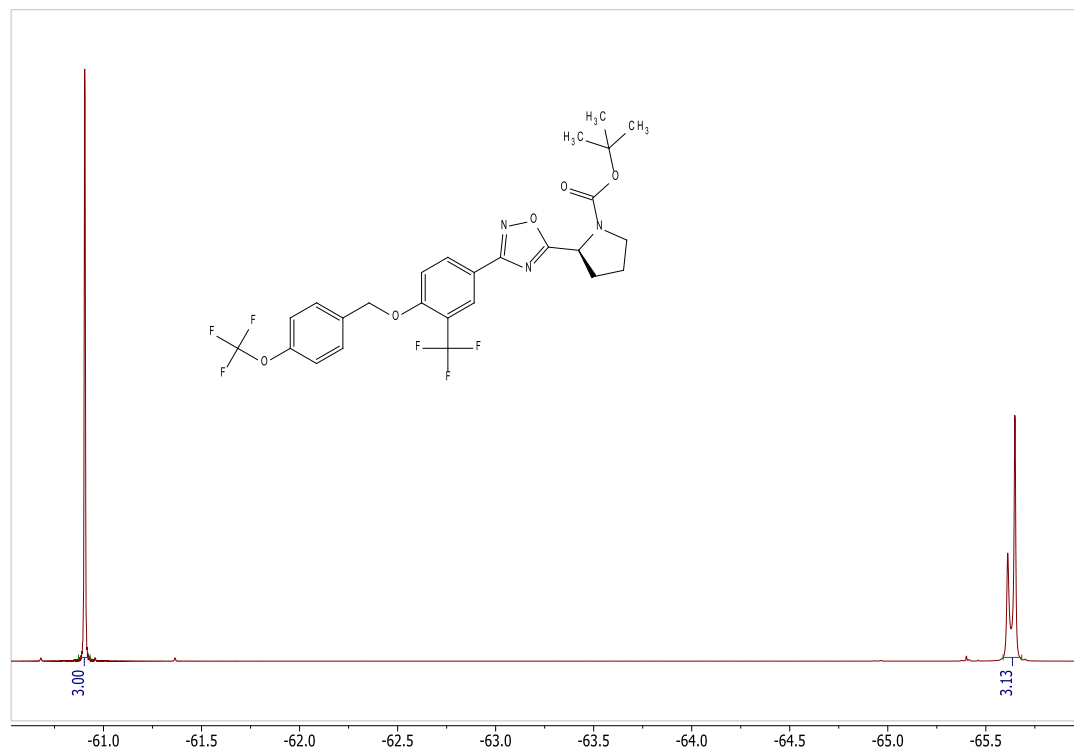
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30d** -



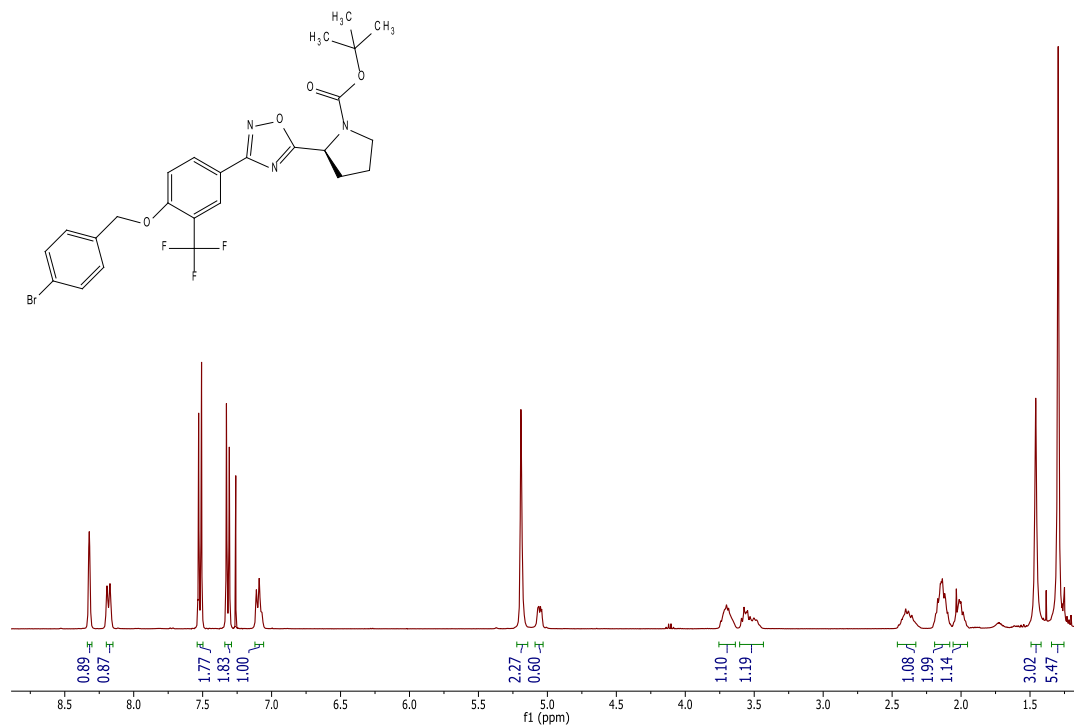
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30d** -



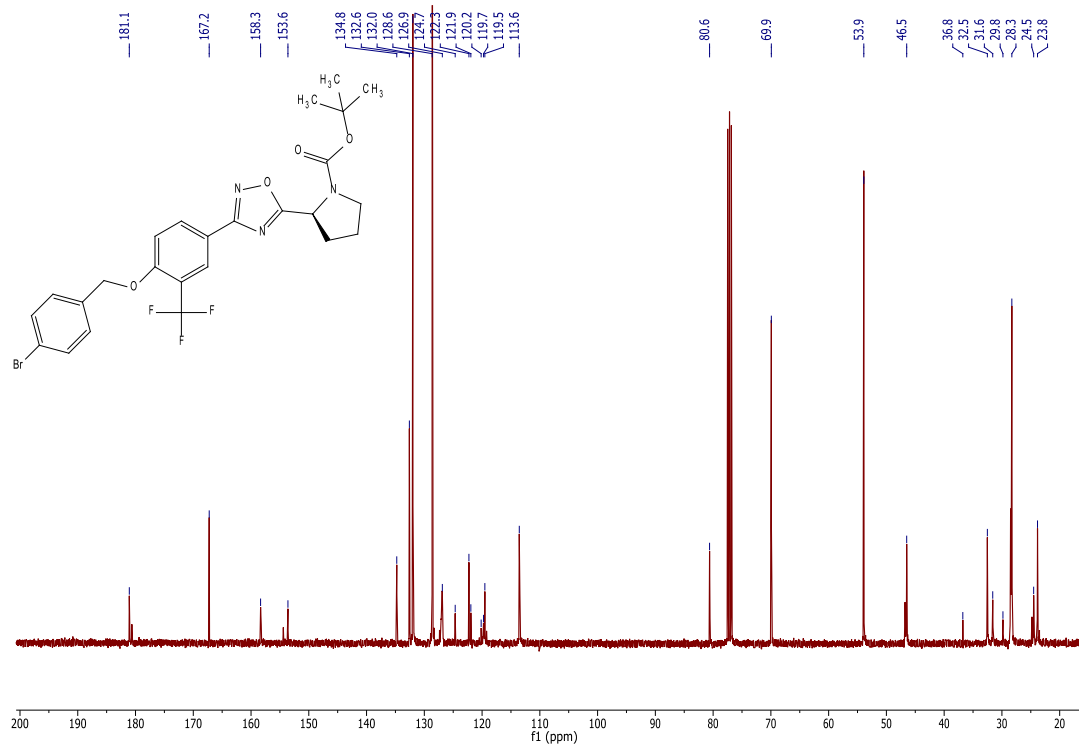
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30d** -



<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30e** -

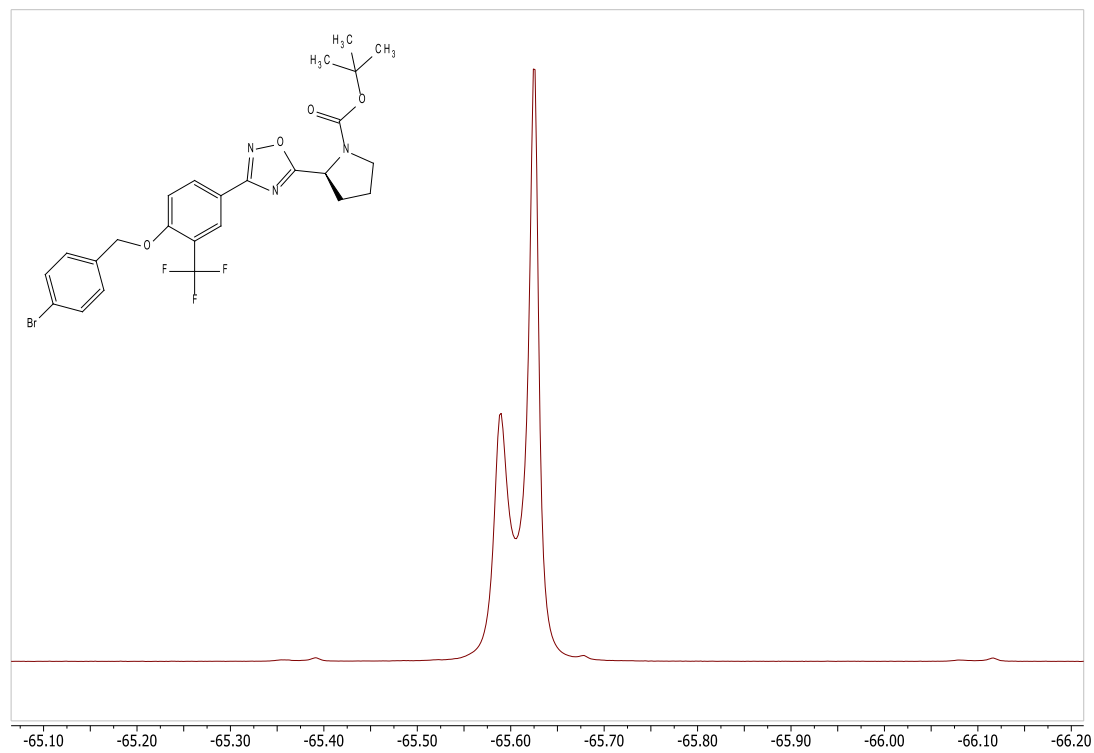


<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30e** -

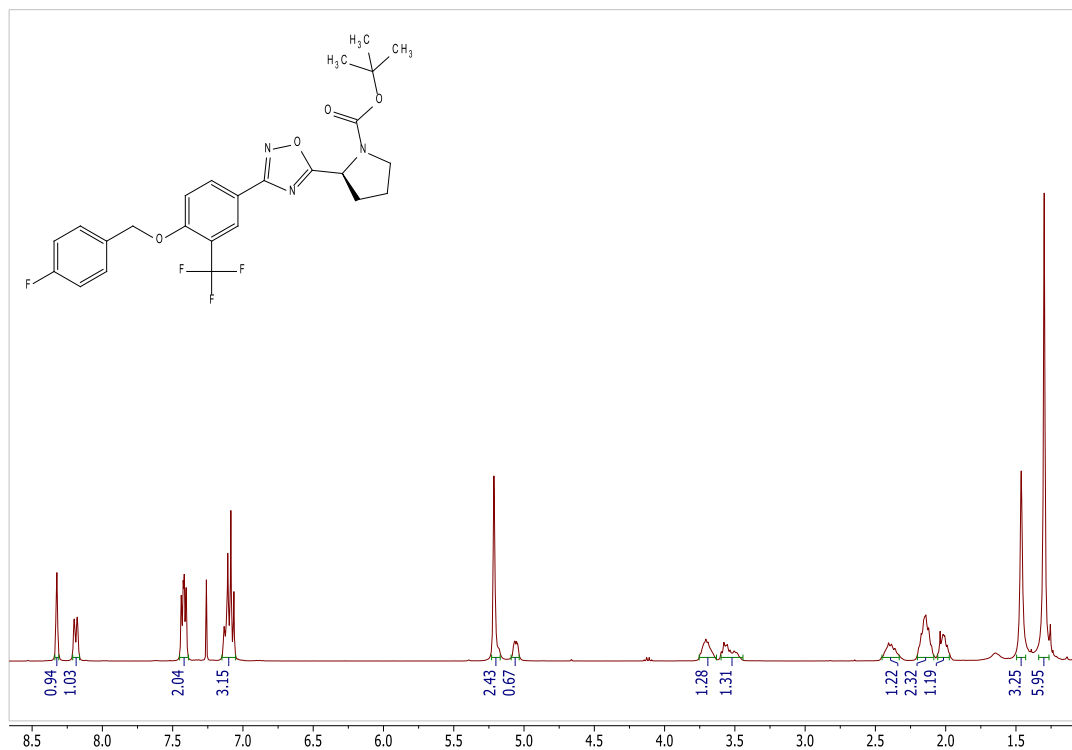




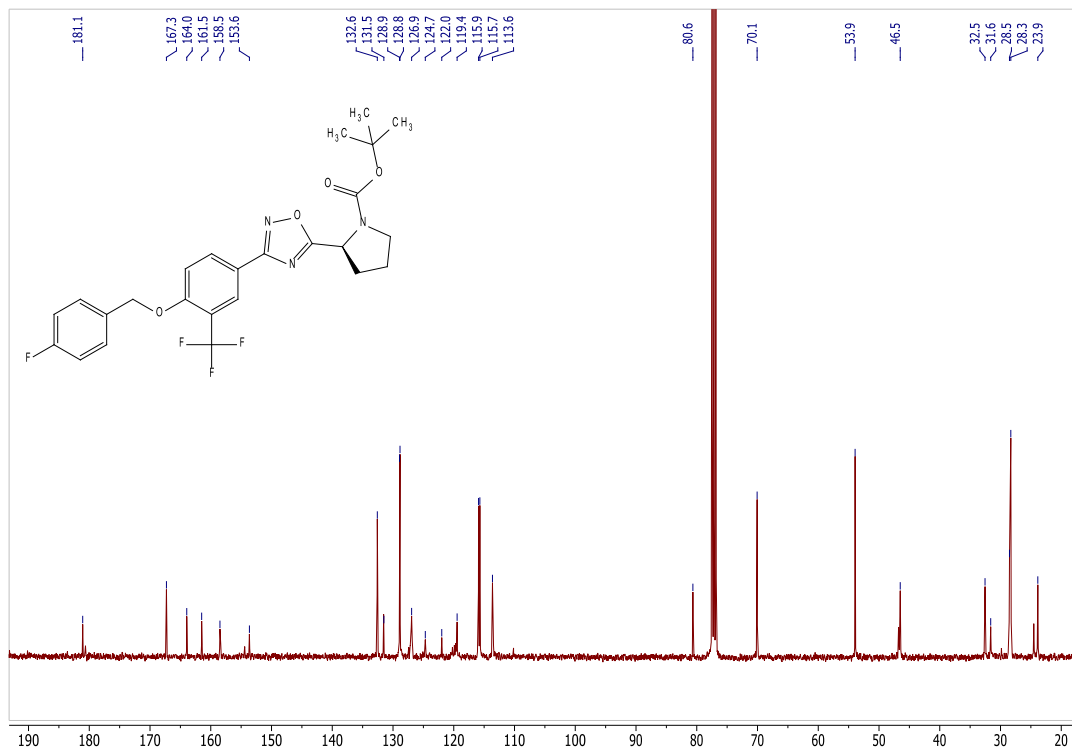
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30e** -



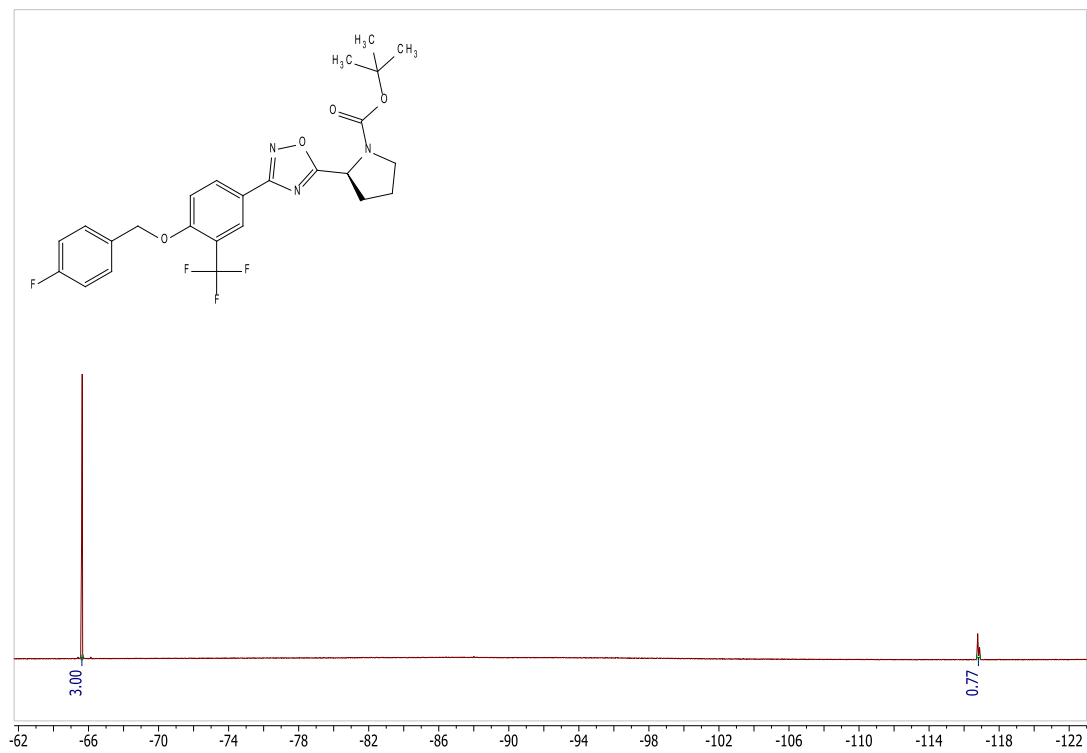
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30f** -



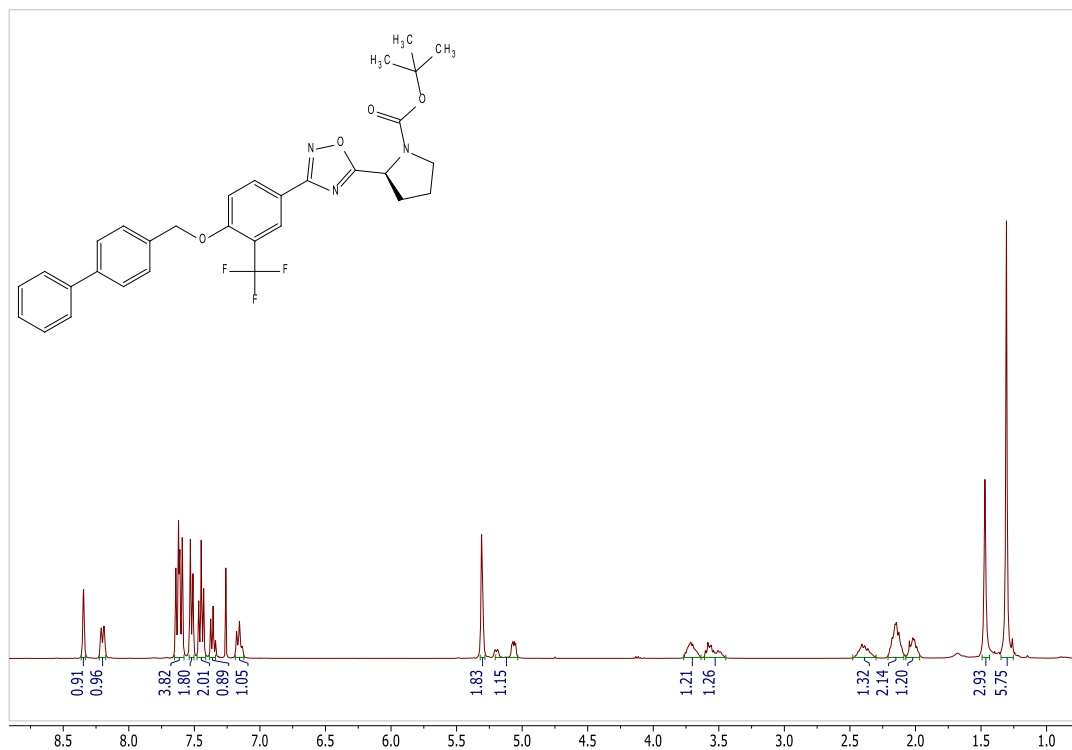
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30f** -



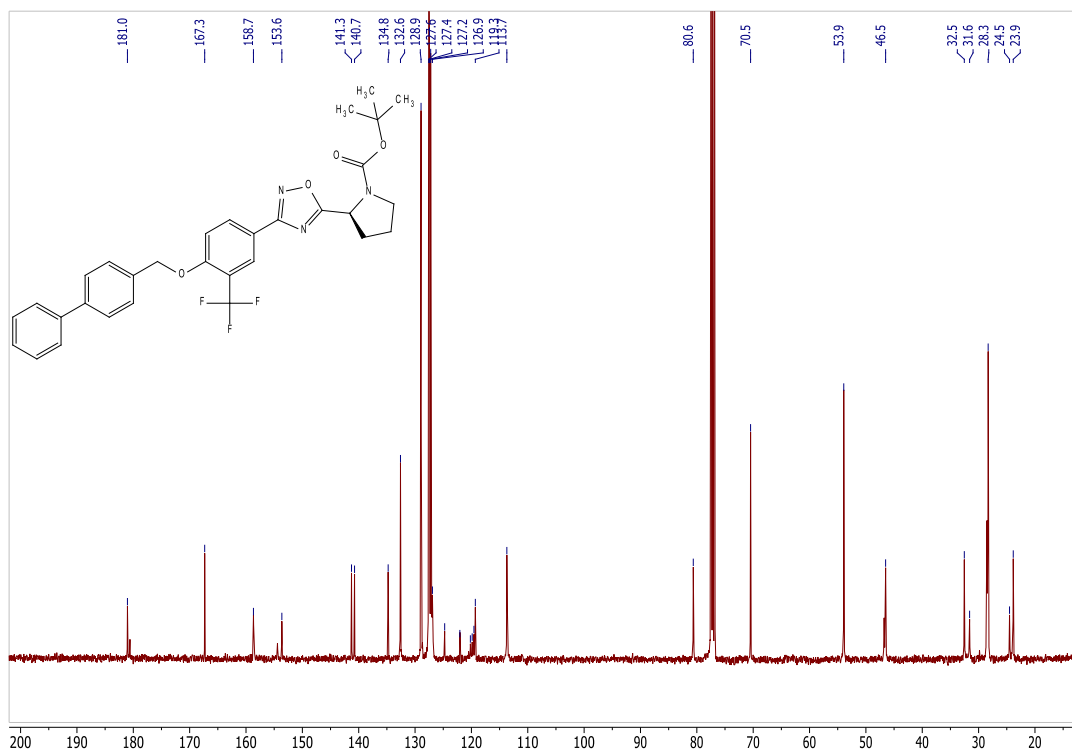
<sup>19</sup>F-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30f** -



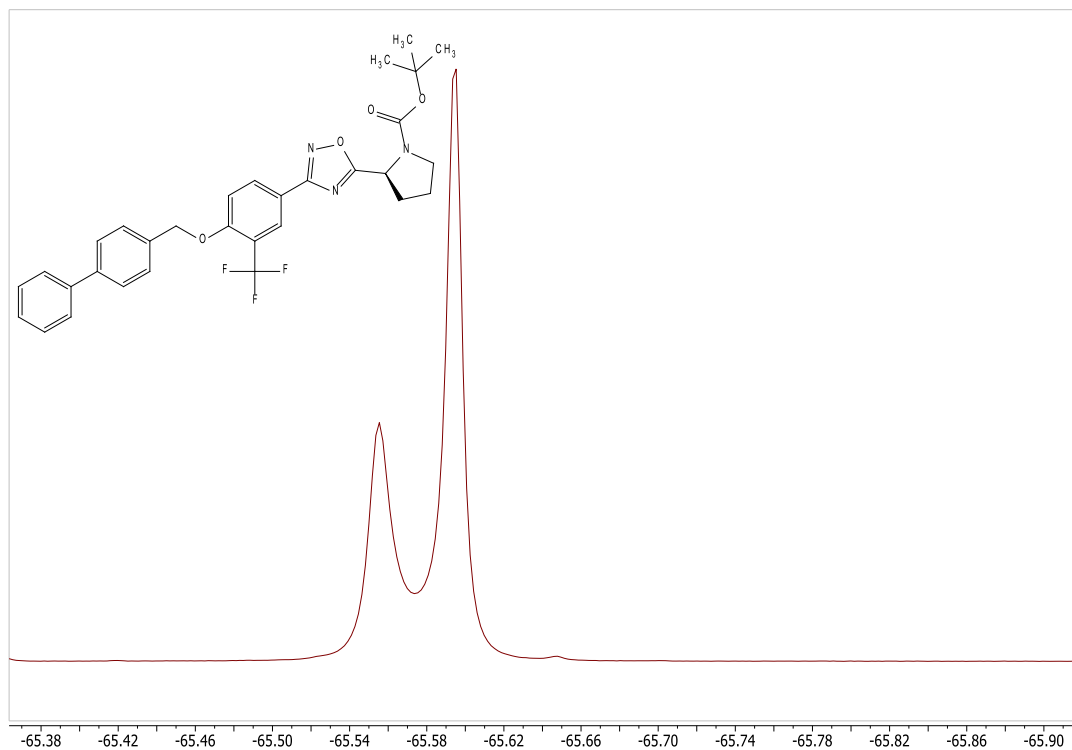
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30g** -



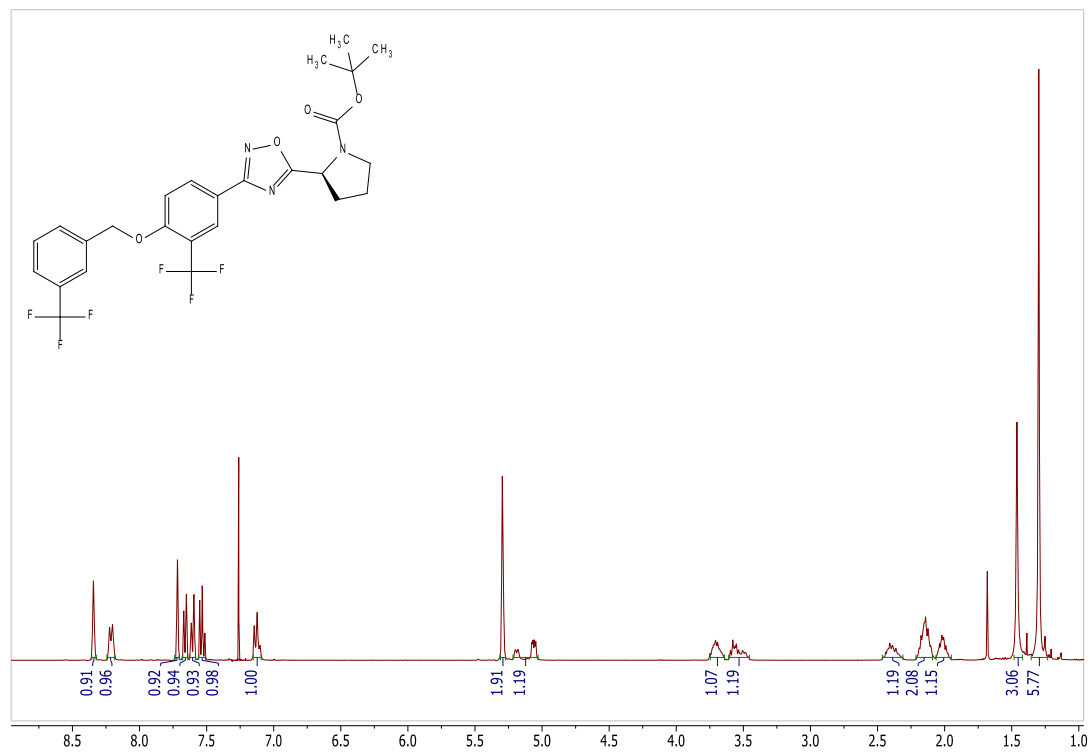
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30g** -



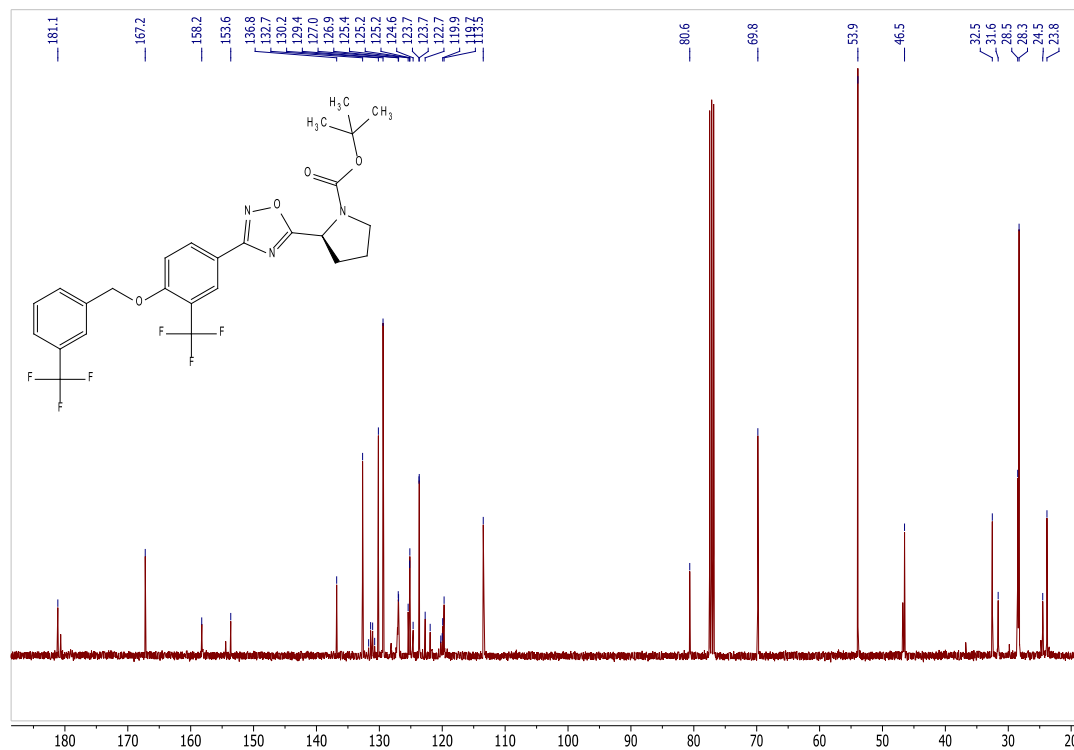
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30g** -



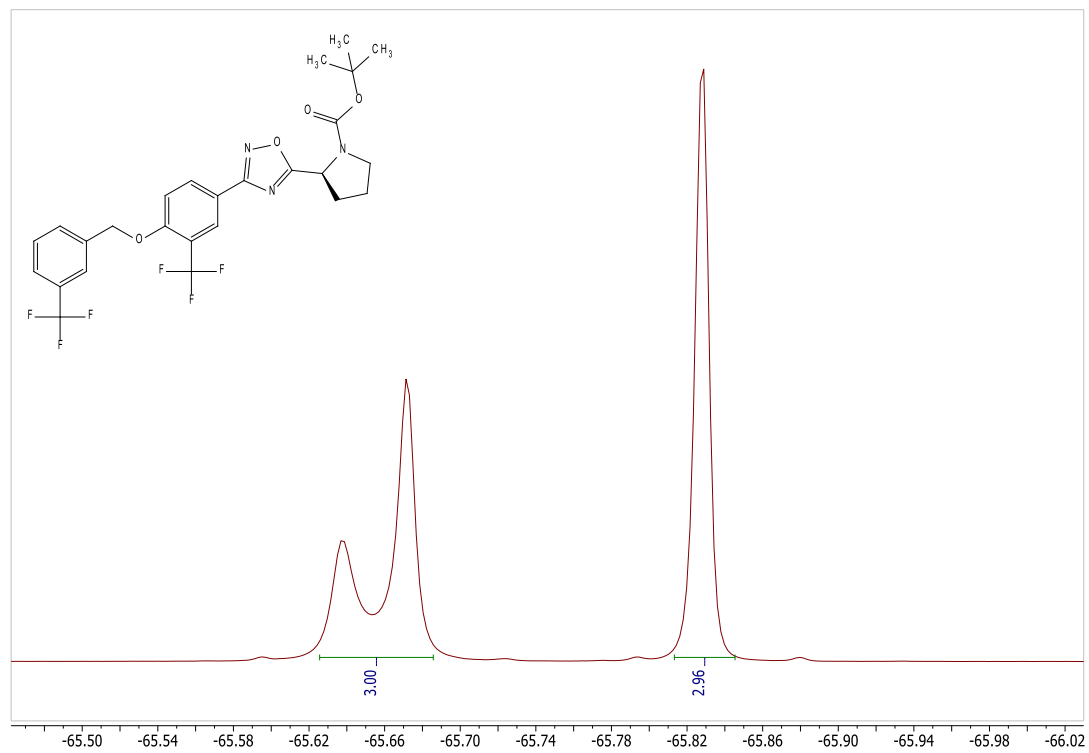
<sup>1</sup>H-NMR Spectrum for (S)-tert-butyl 2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30h** -



<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30h** -

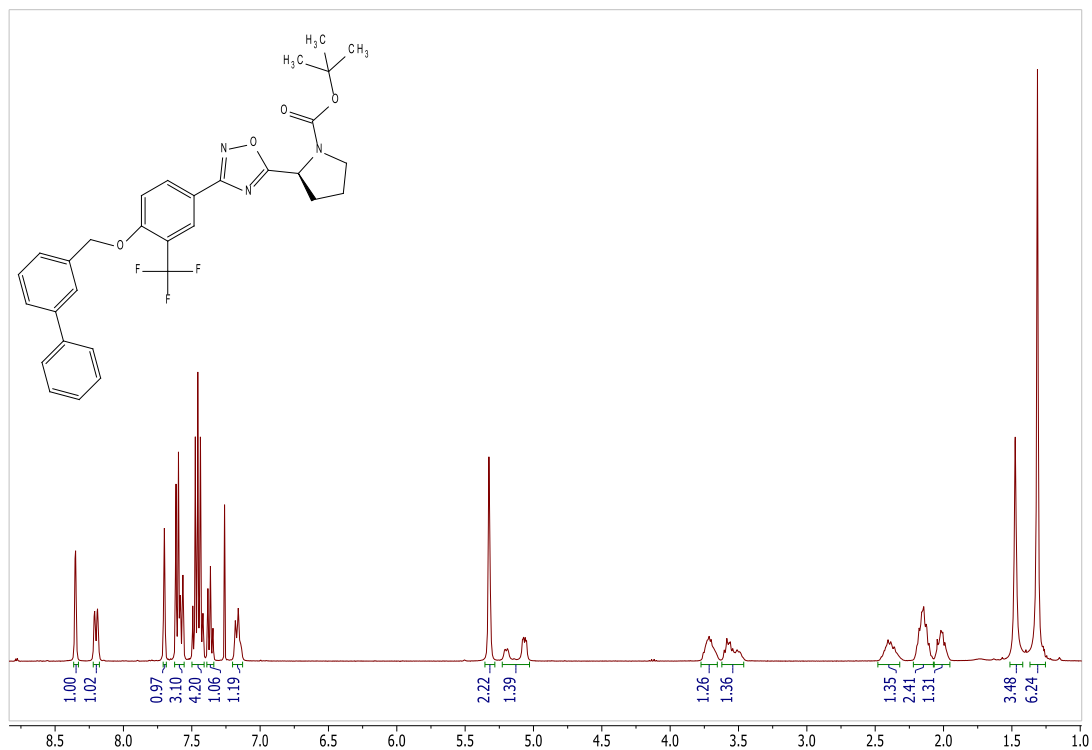


$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30h** -

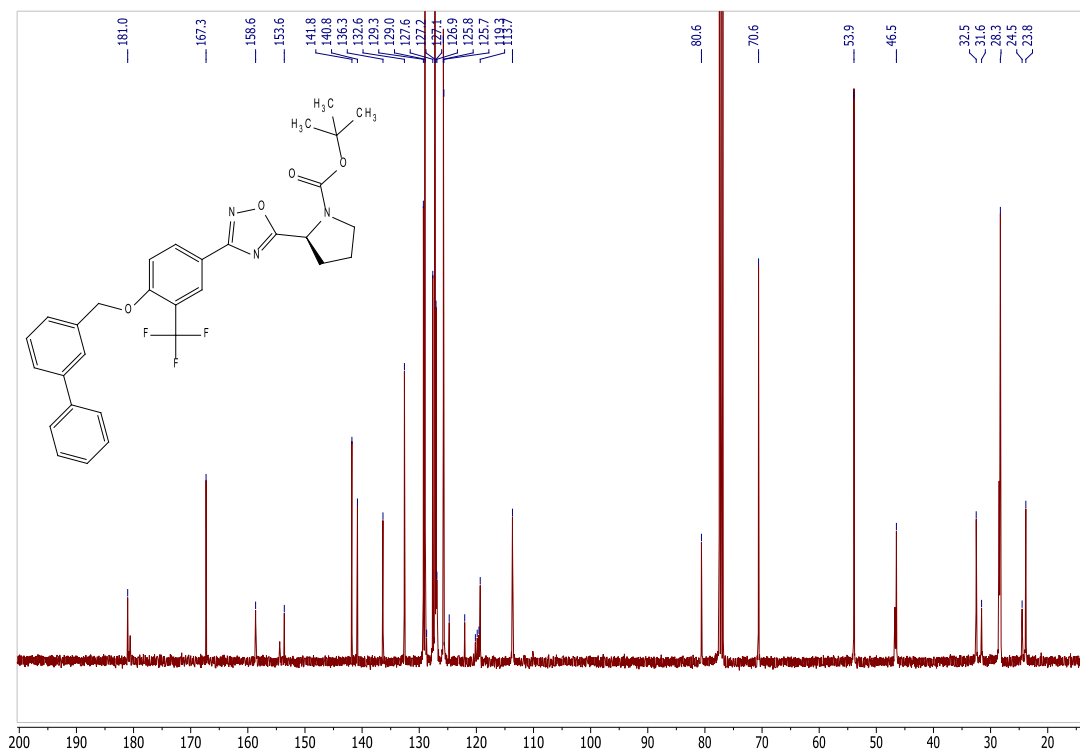




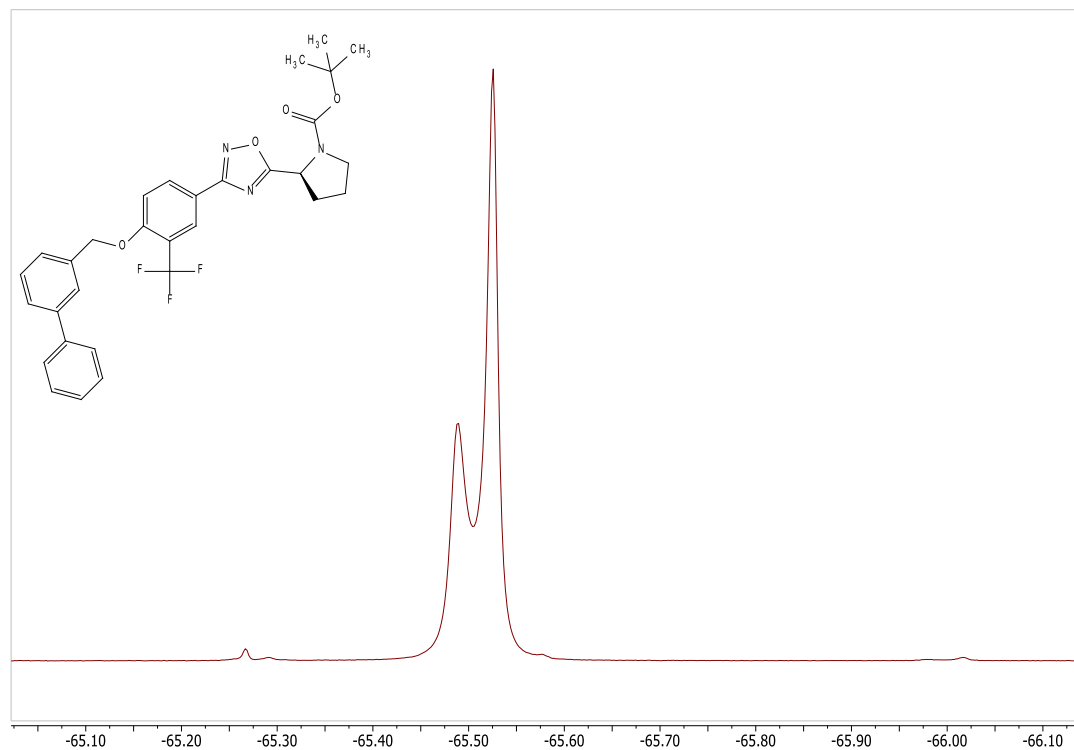
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30i** -



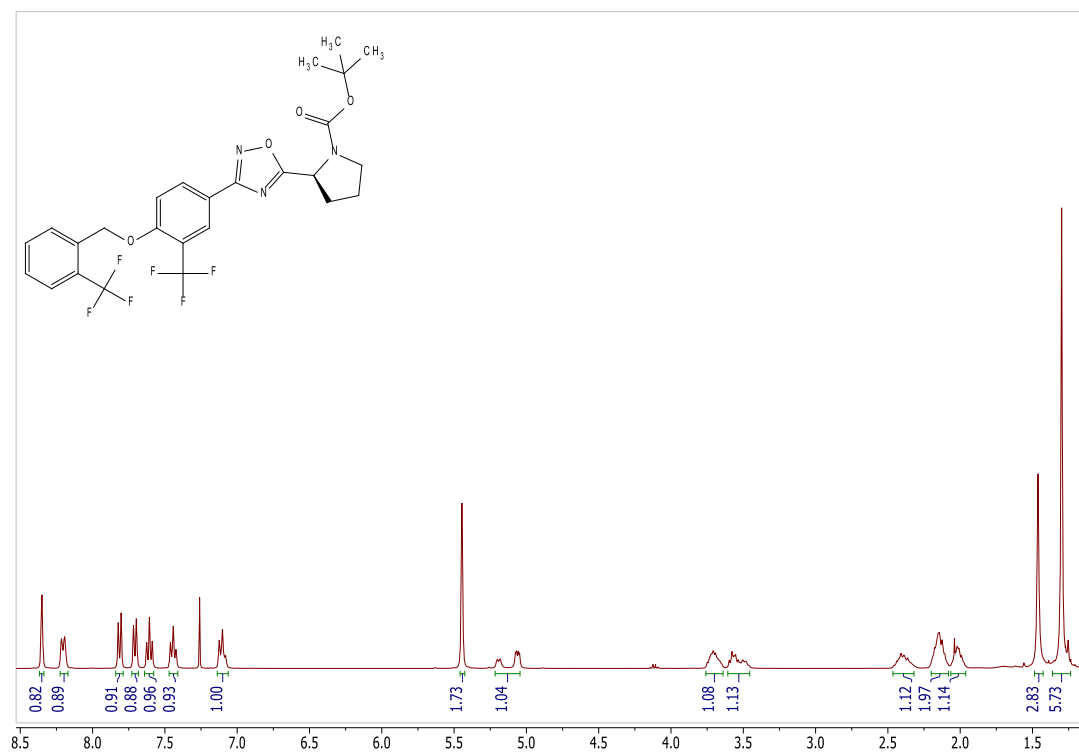
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30i** -



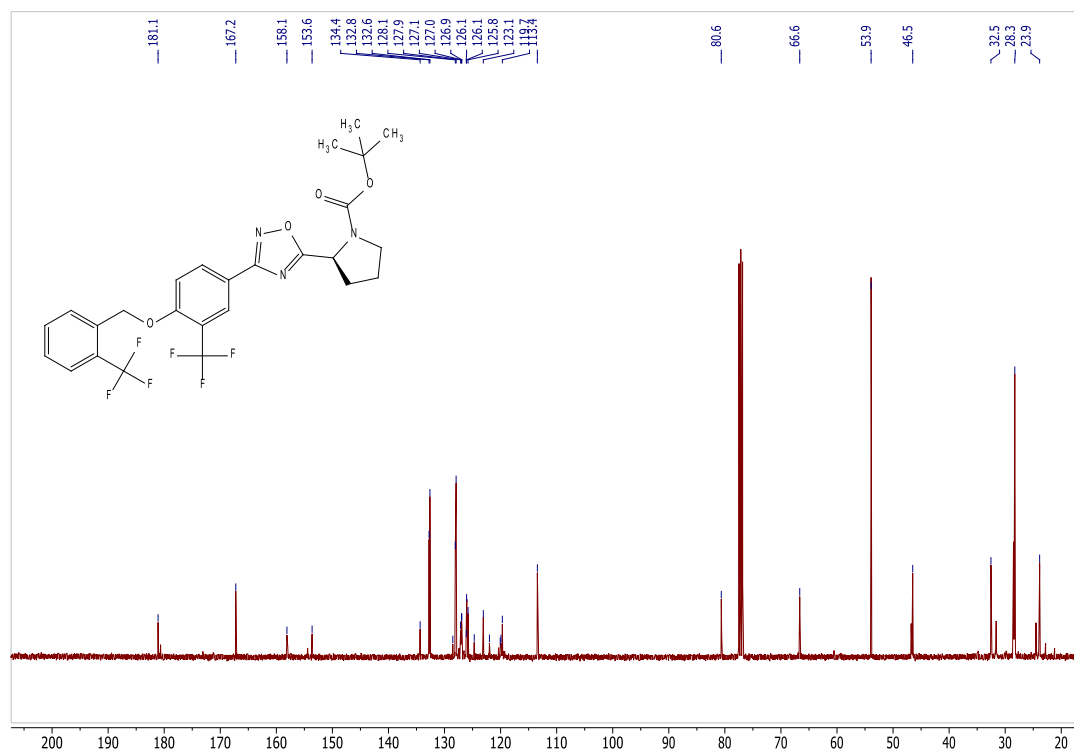
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30i** -



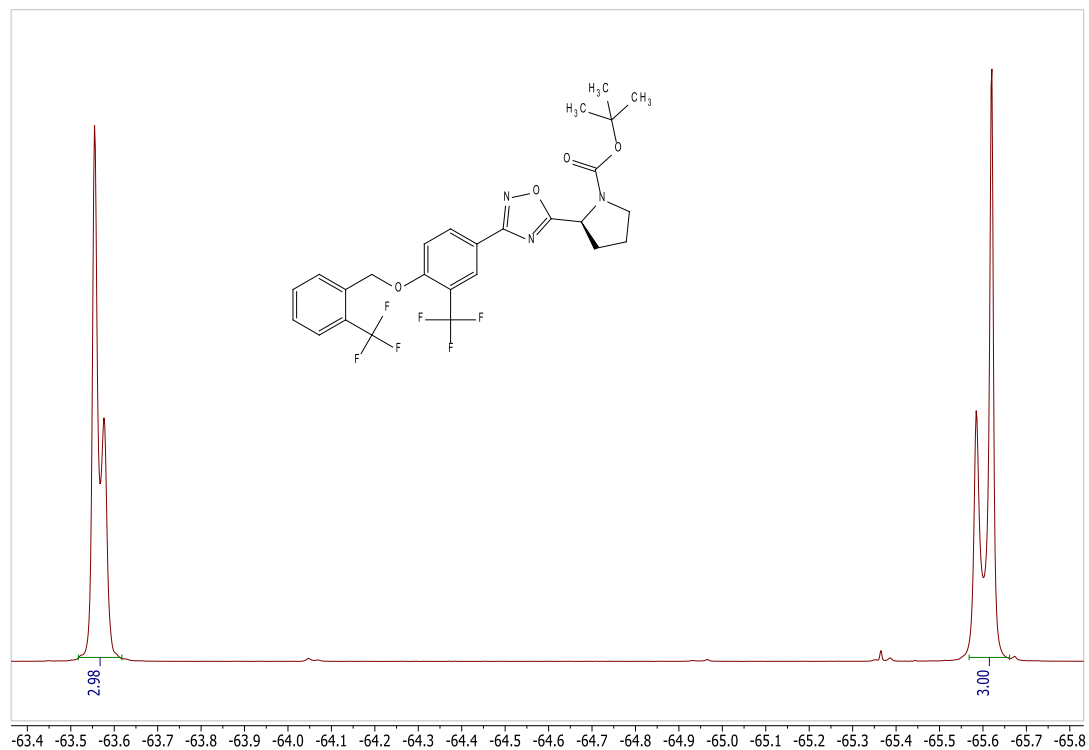
<sup>1</sup>H-NMR Spectrum for (S)-tert-butyl 2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30j** -



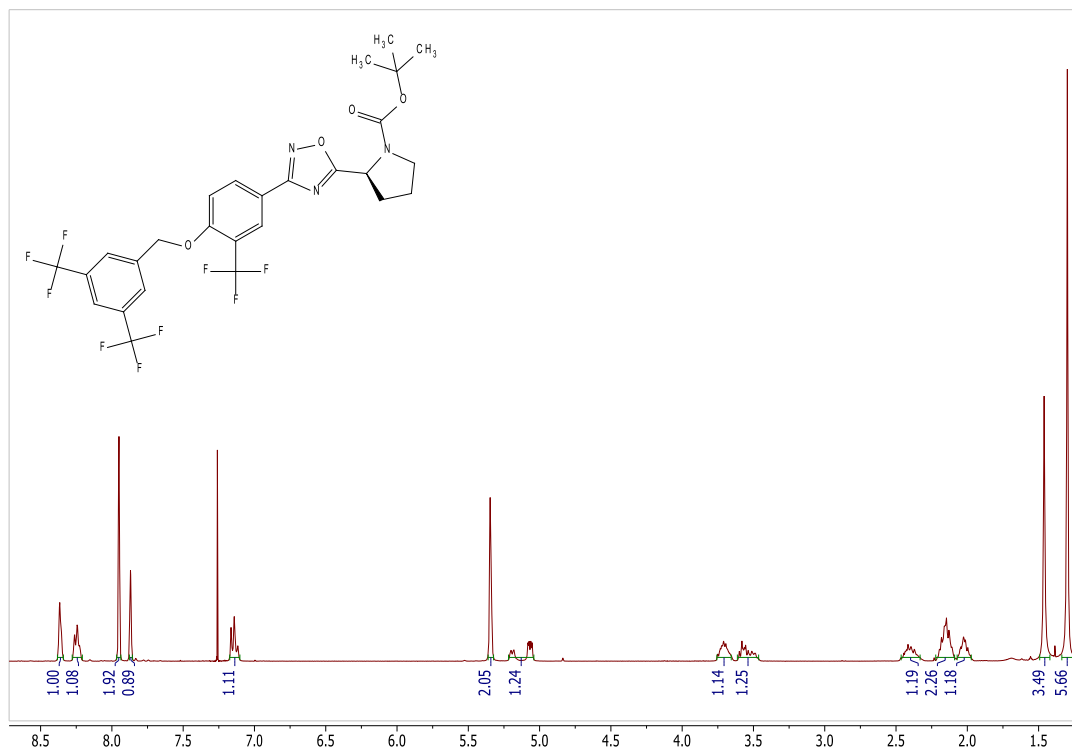
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30j** -



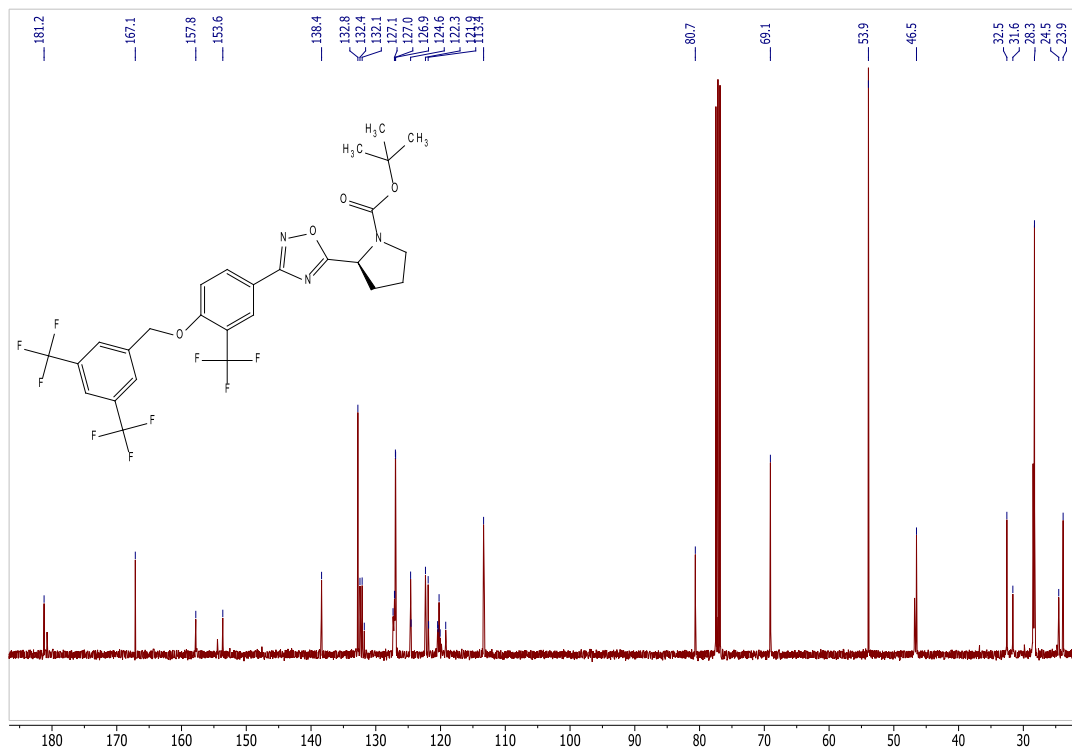
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30j** -



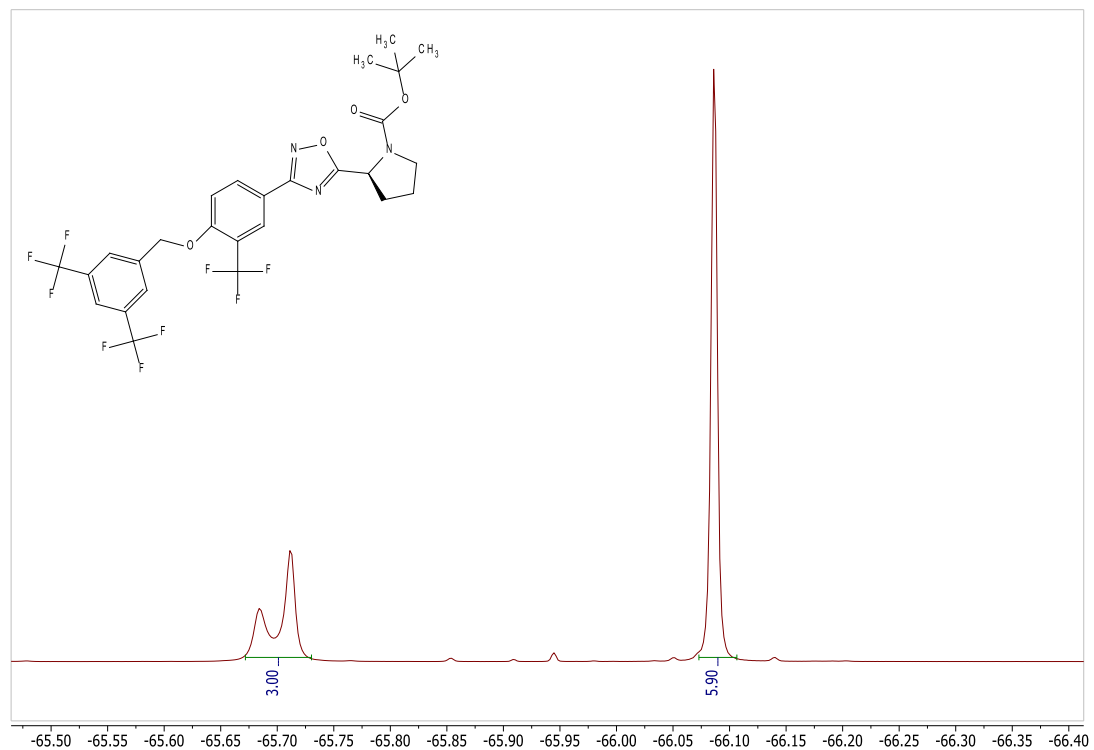
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30k** -



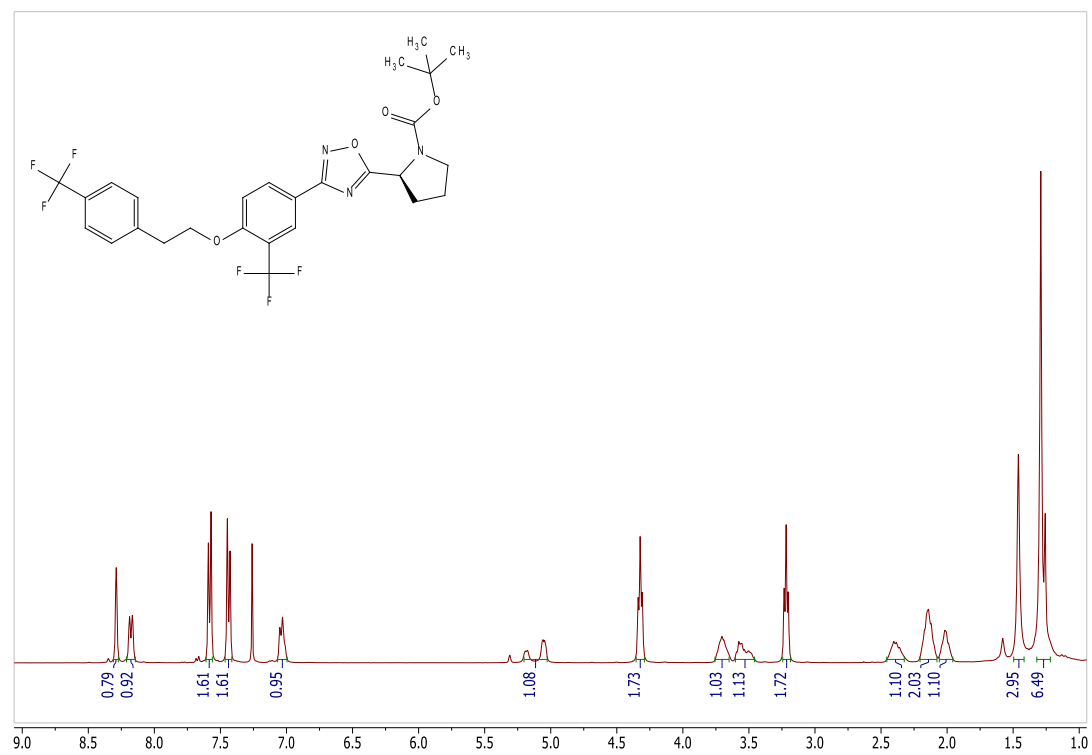
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30k** -



$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30k** -

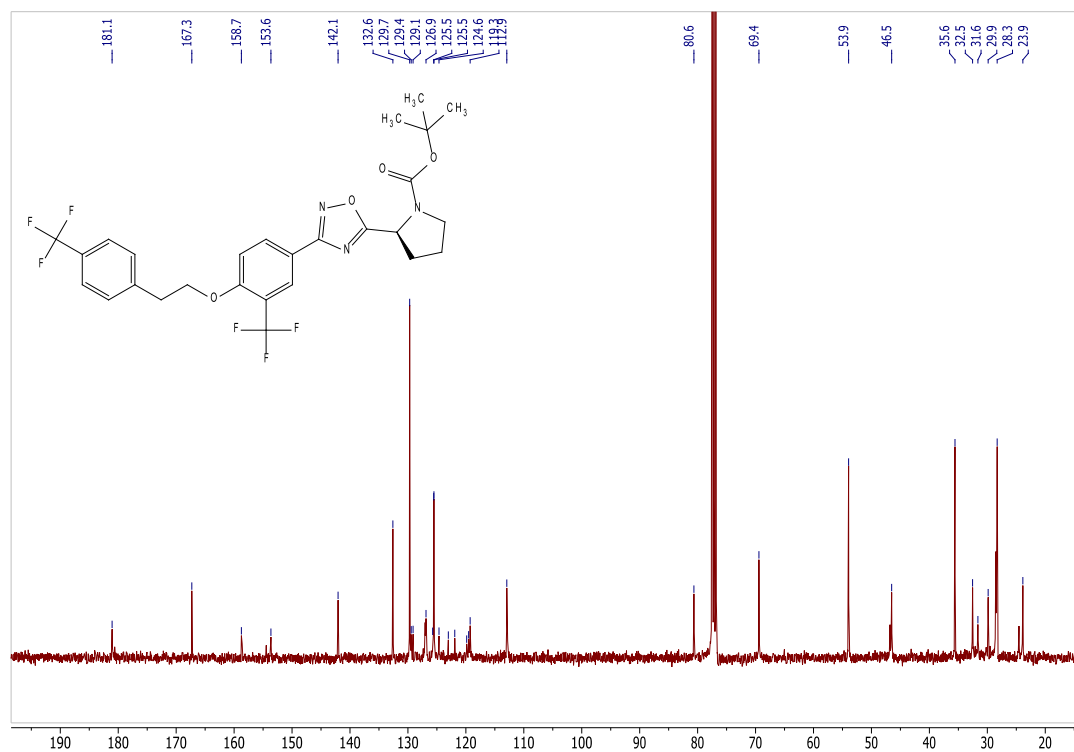


<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.301** -

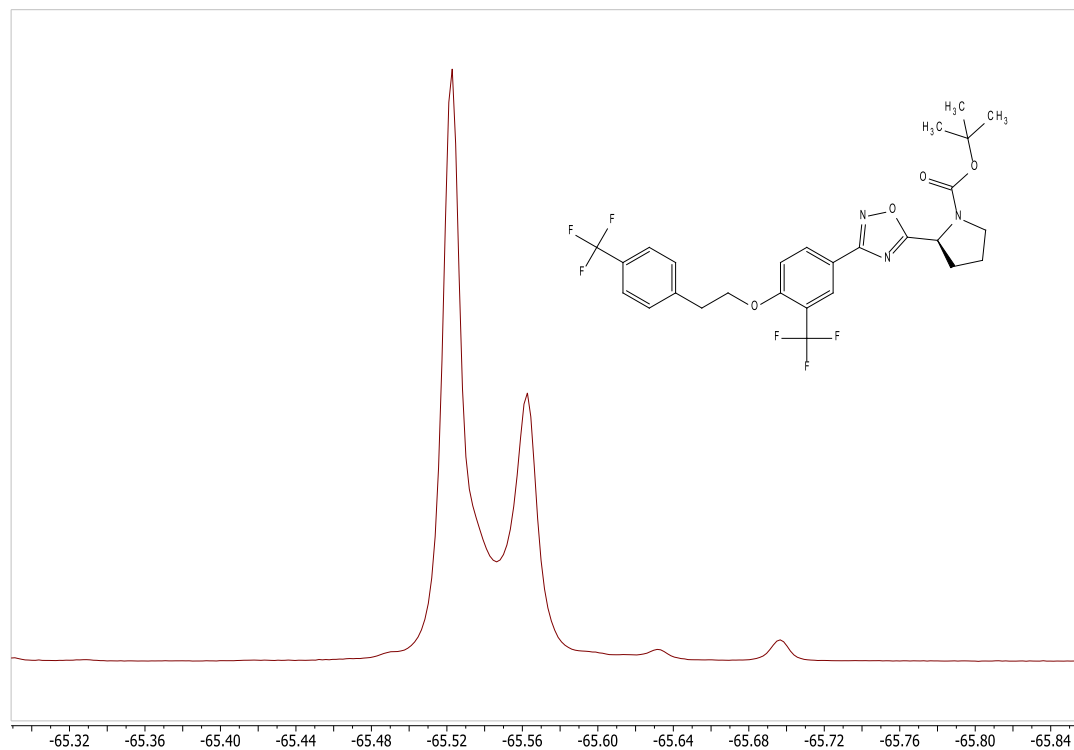




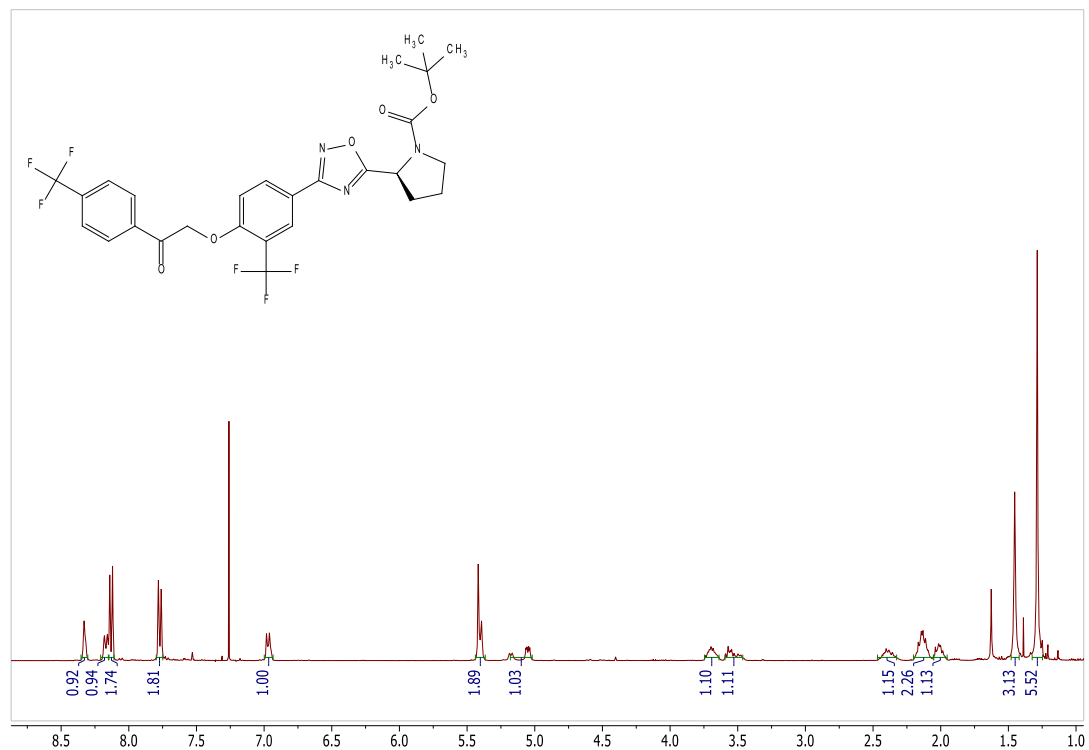
$^{13}\text{C}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.301** -



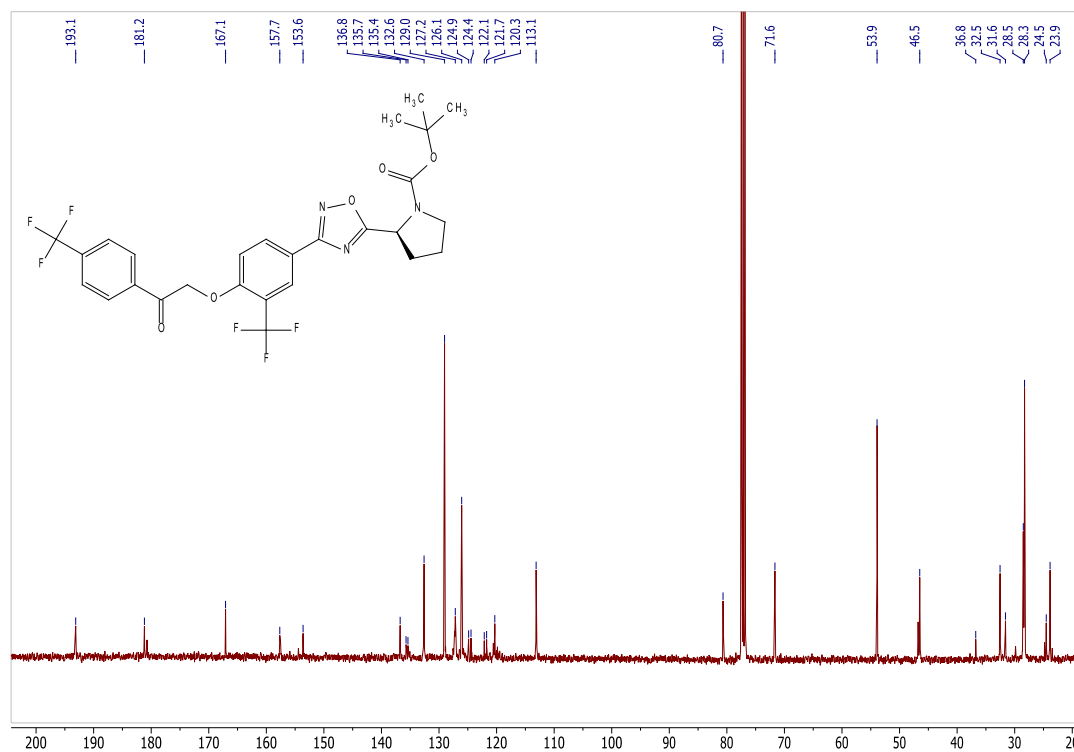
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.301** -



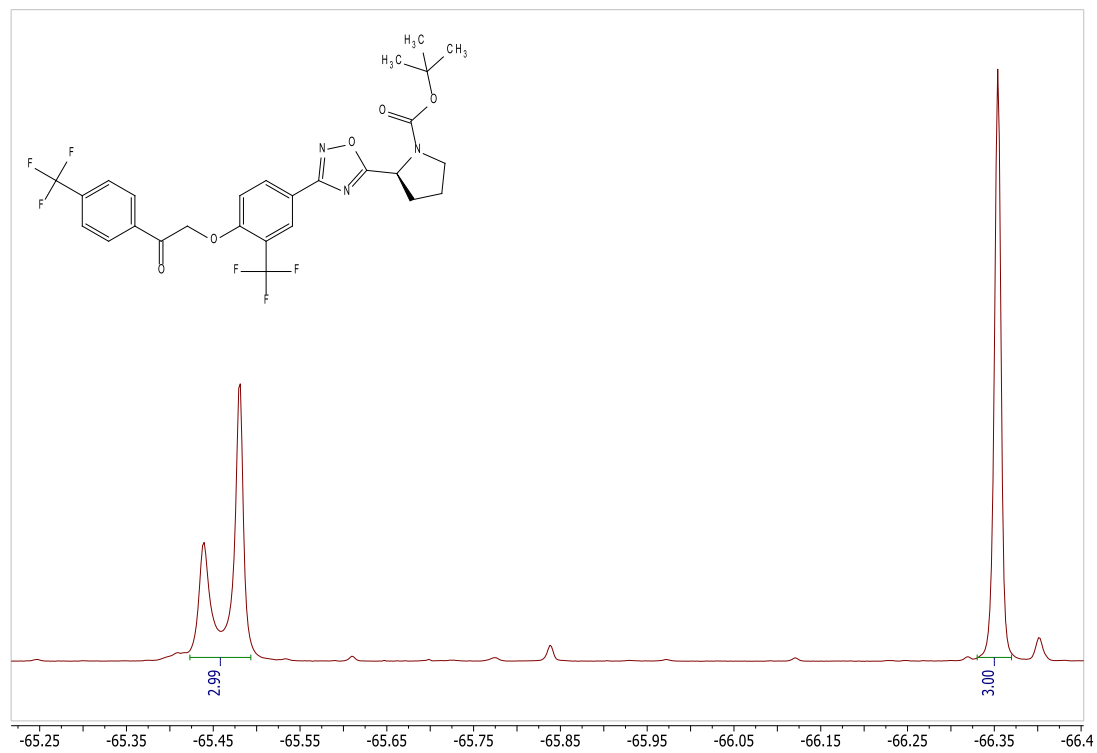
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30m** -



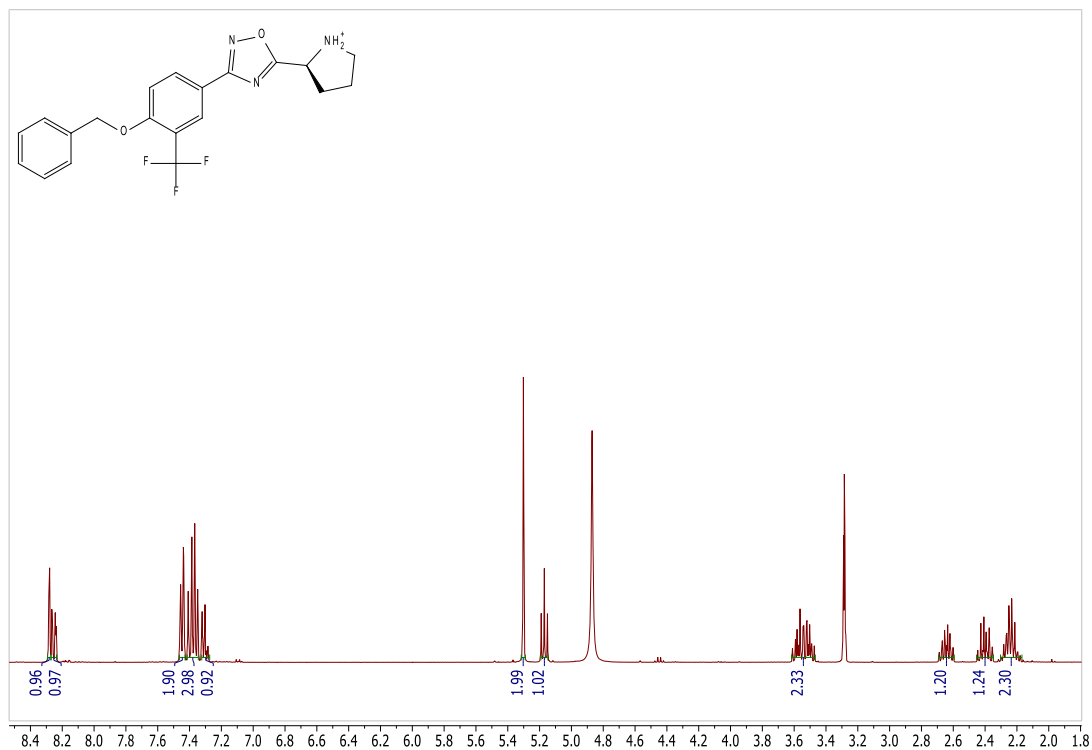
$^{13}\text{C}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30m** -



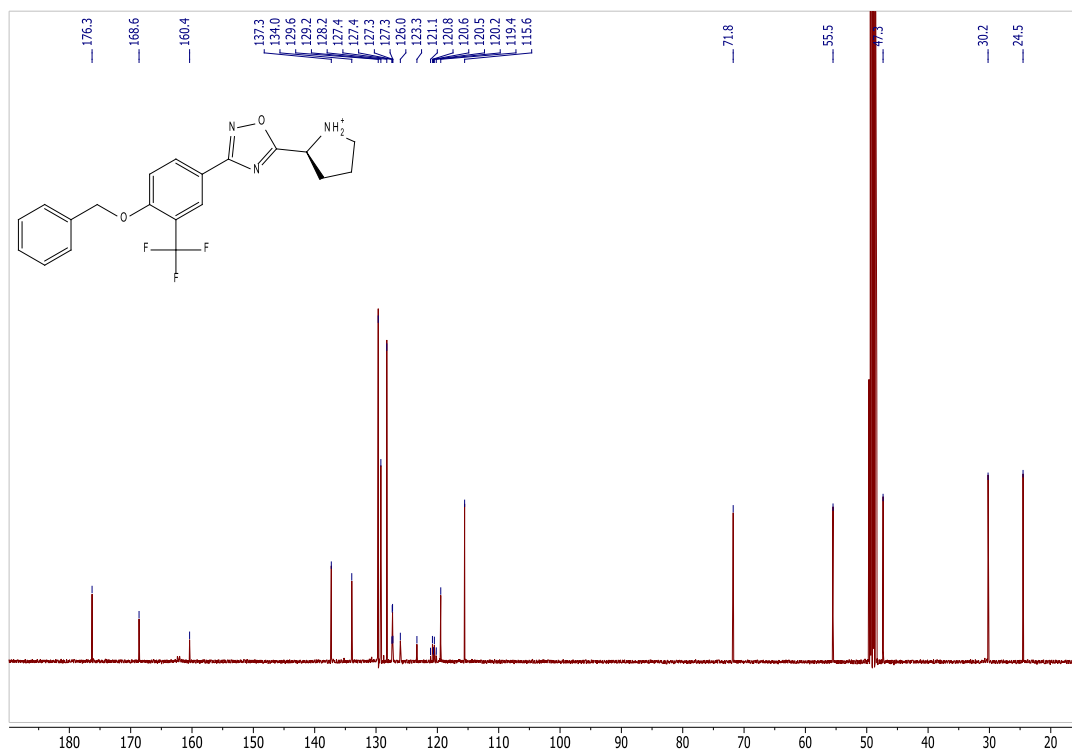
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.30m** -



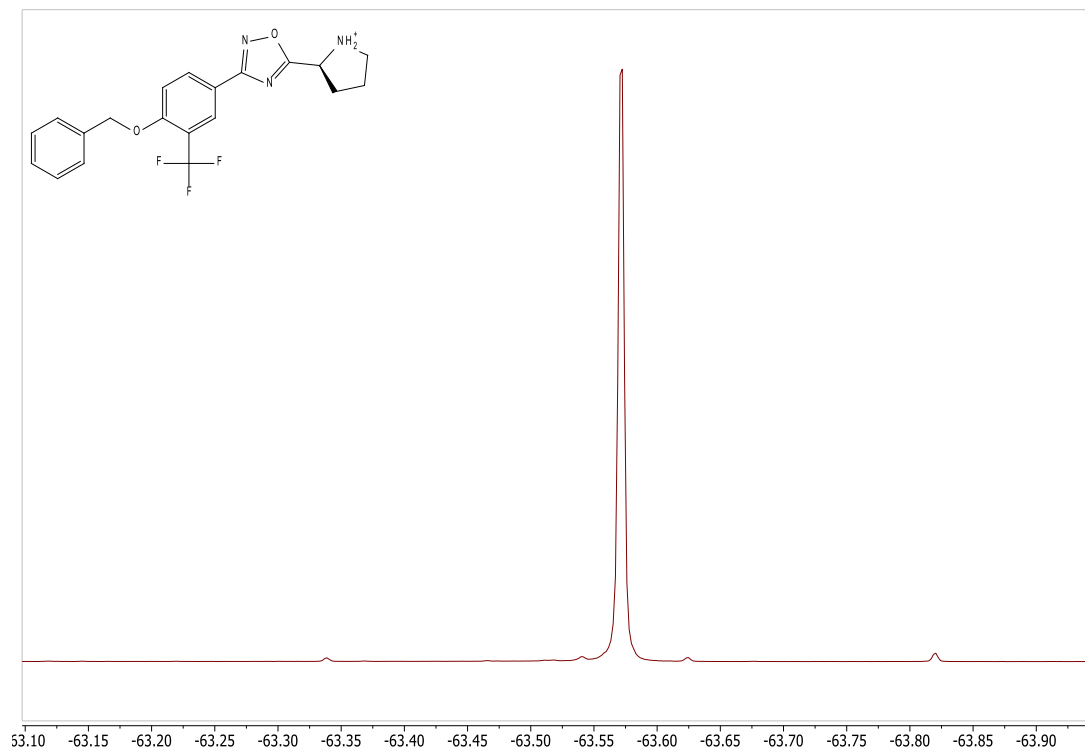
<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



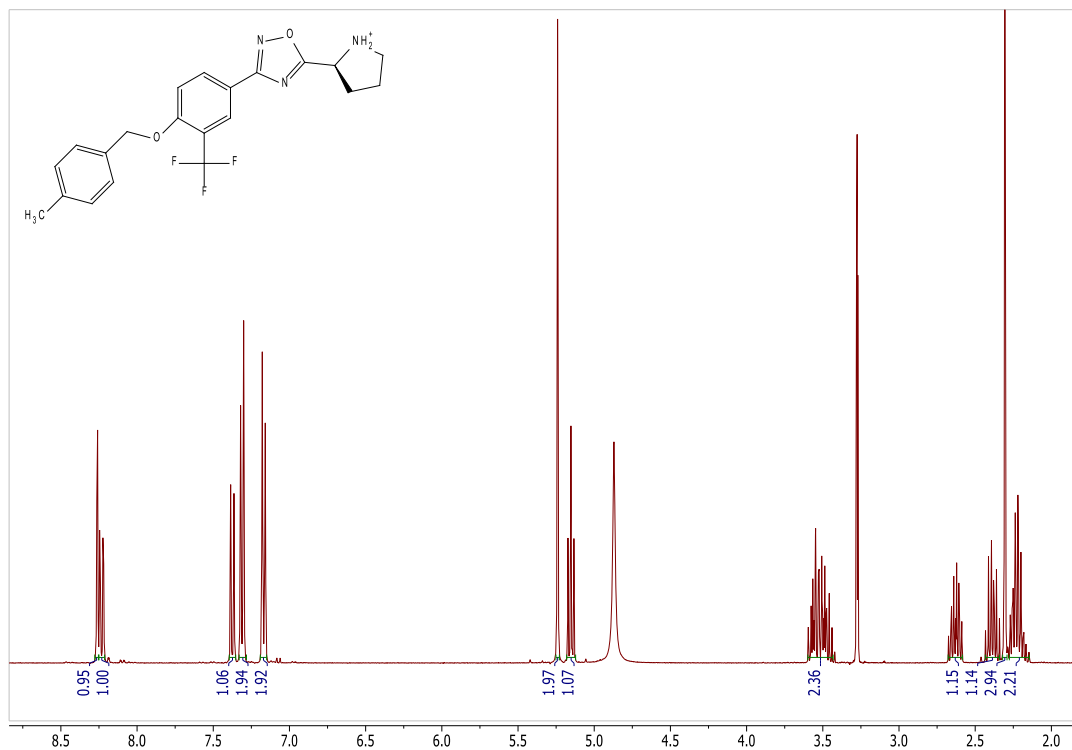
<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



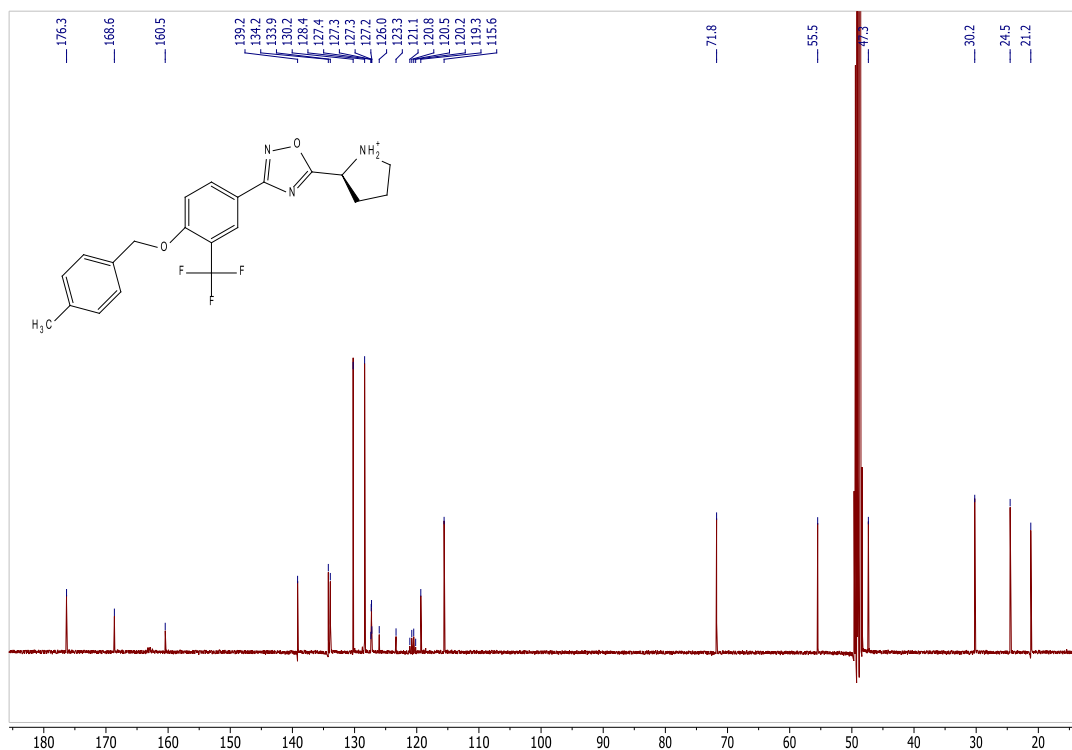
<sup>19</sup>F-NMR Spectrum for (*S*)-2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



<sup>1</sup>H-NMR Spectrum for (*S*)-2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -

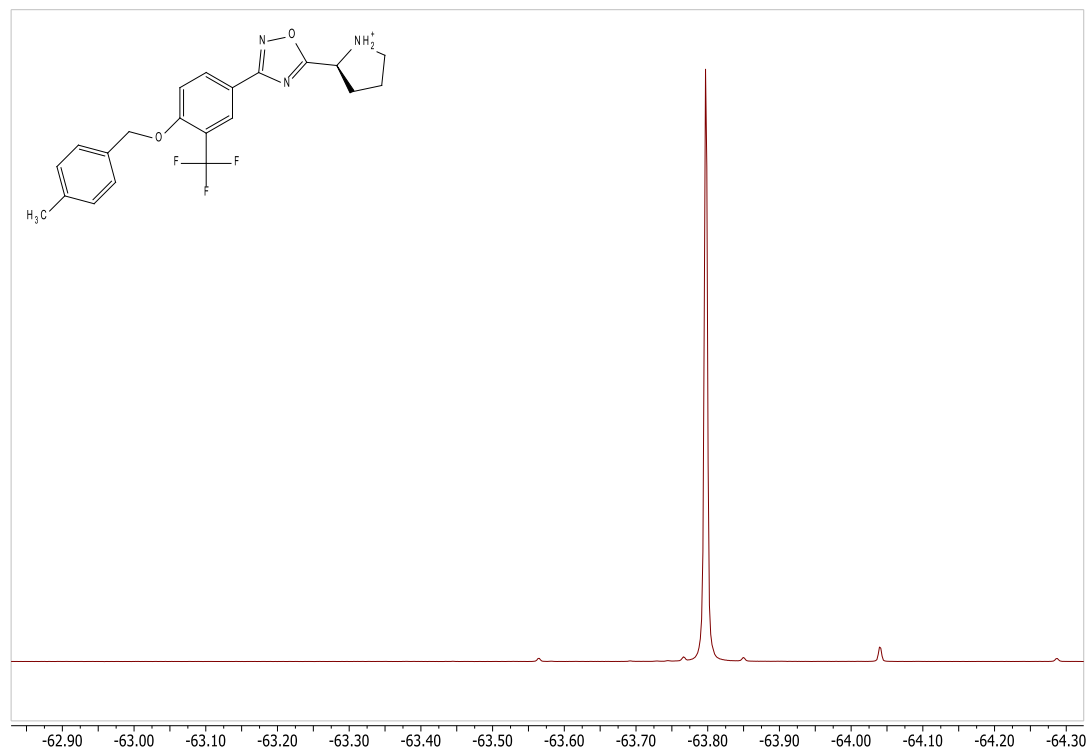


<sup>13</sup>C-NMR Spectrum for (*S*)-2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -

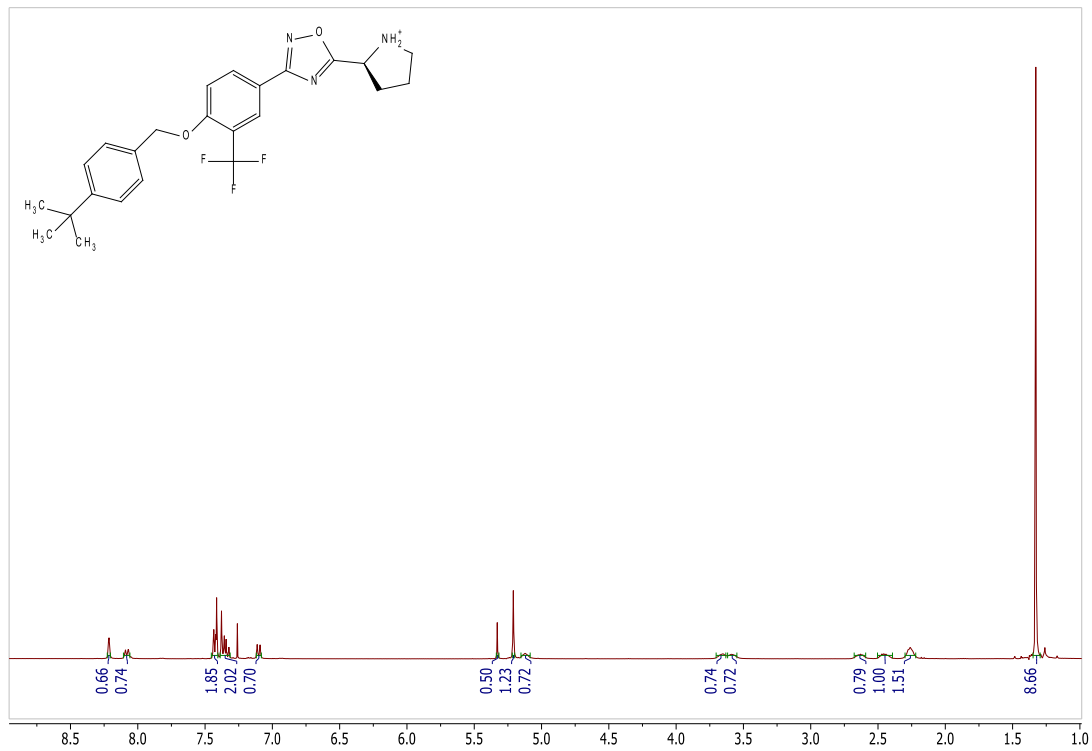




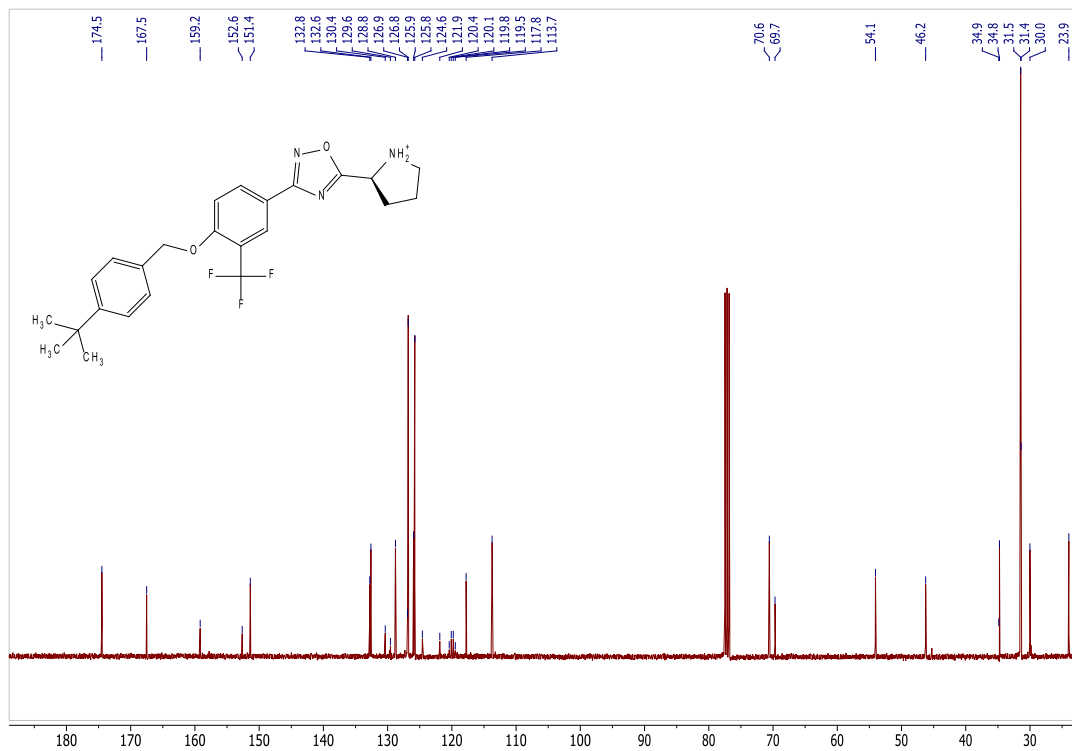
<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



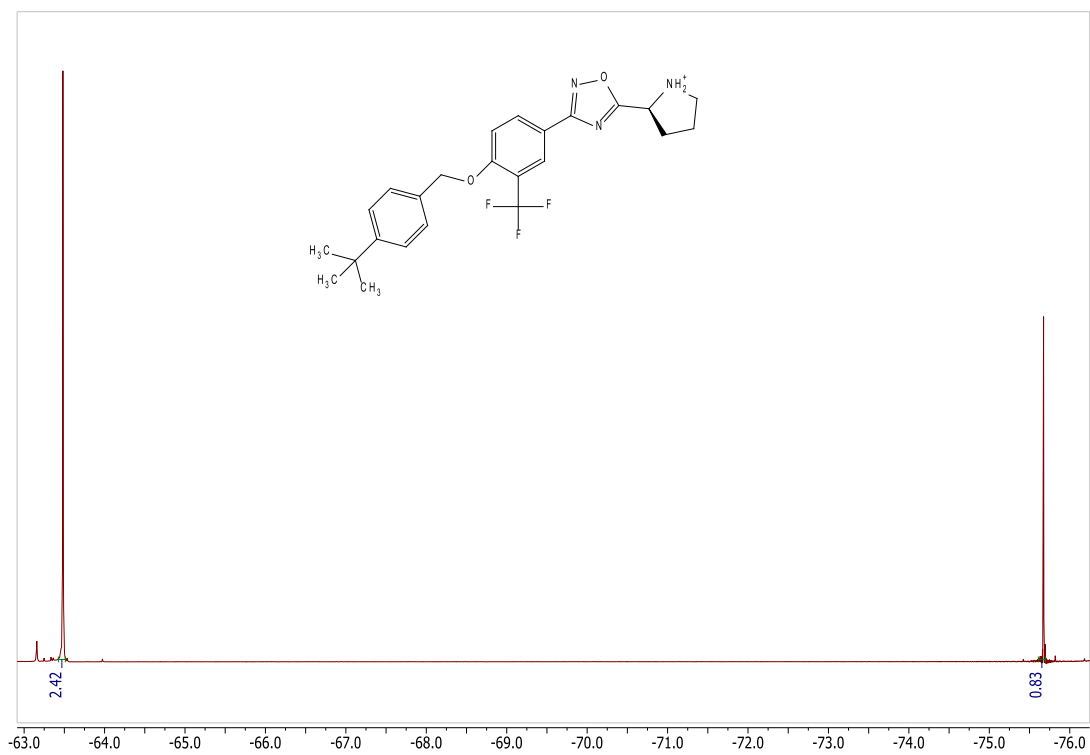
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-((4-*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-ylpyrrolidin-1-ium 2,2,2-trifluoroacetate -



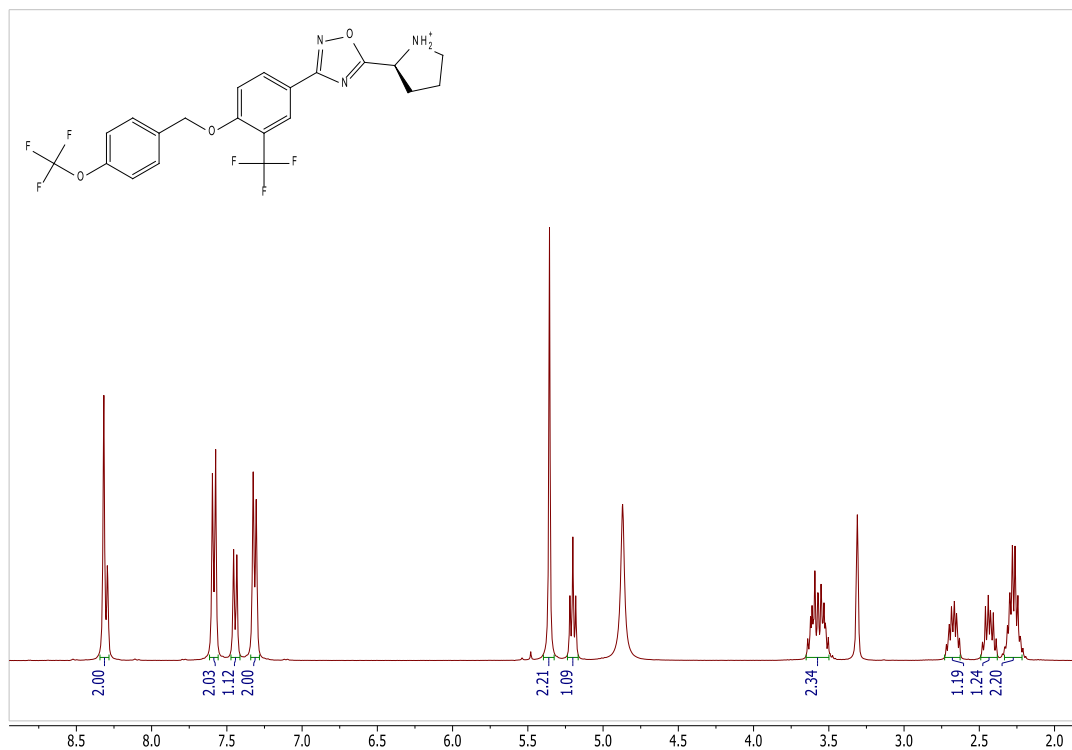
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-((4-*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-ylpyrrolidin-1-ium 2,2,2-trifluoroacetate -



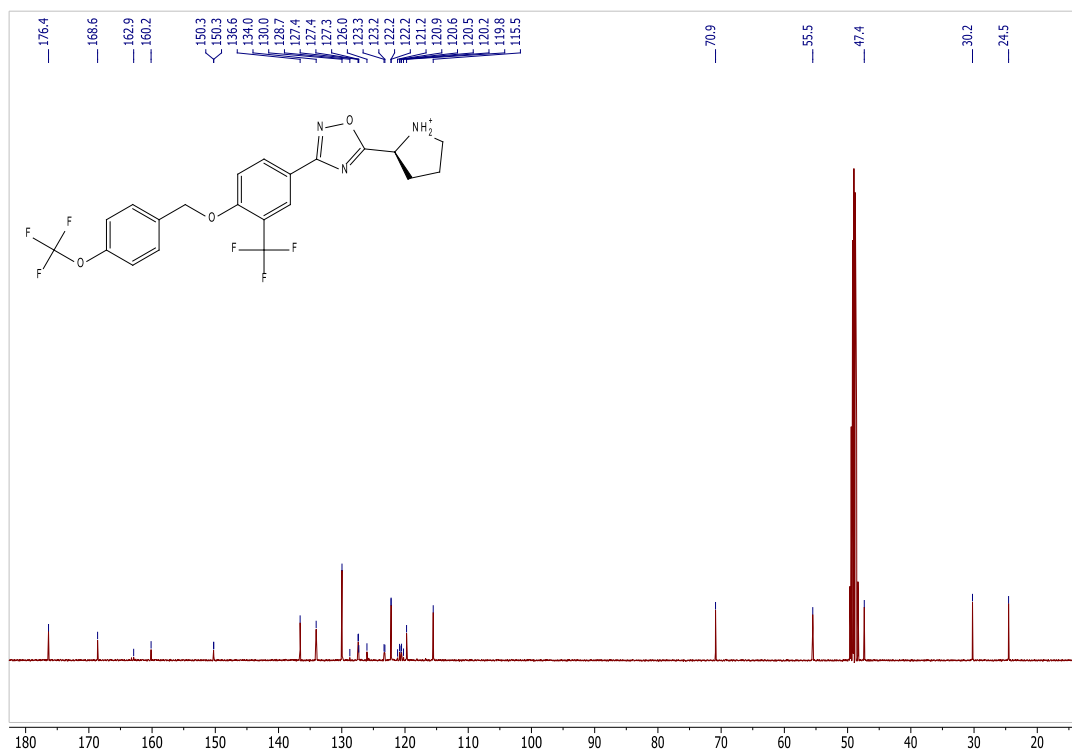
$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(3-(4-((4-*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



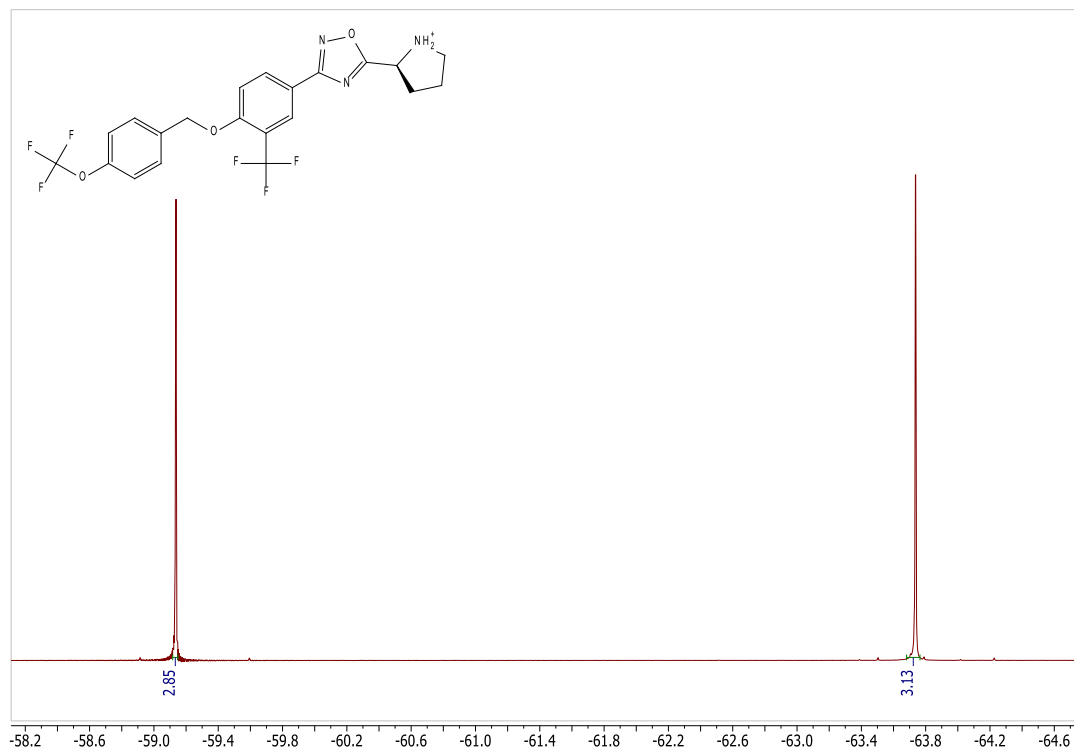
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



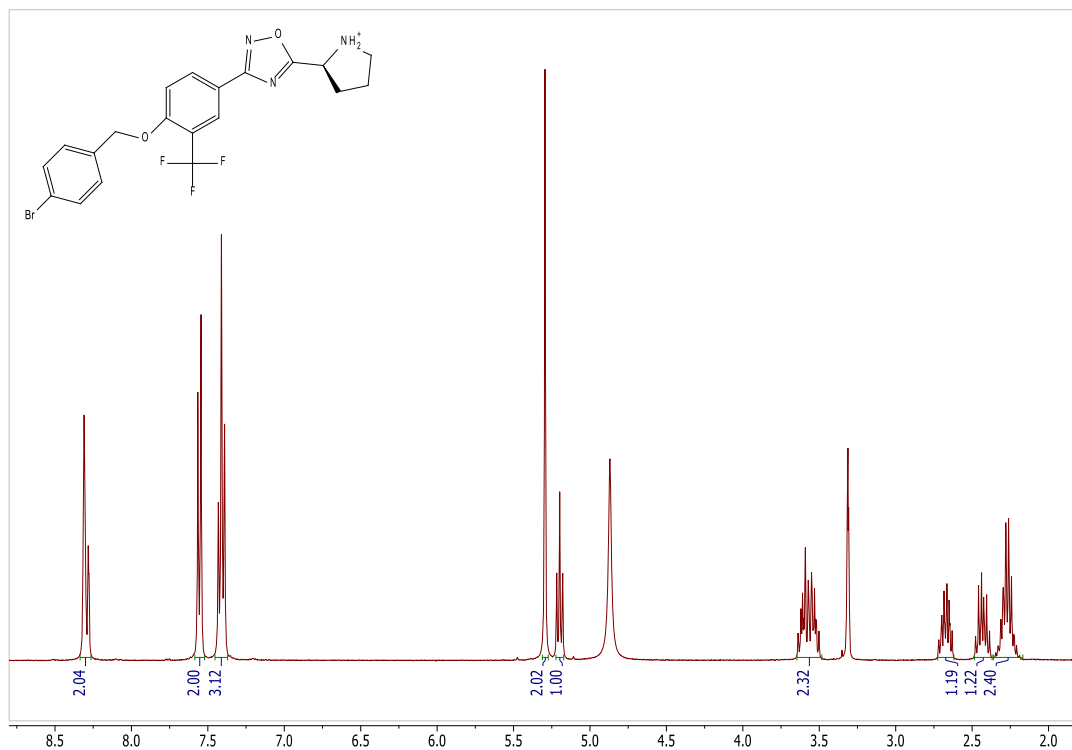
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



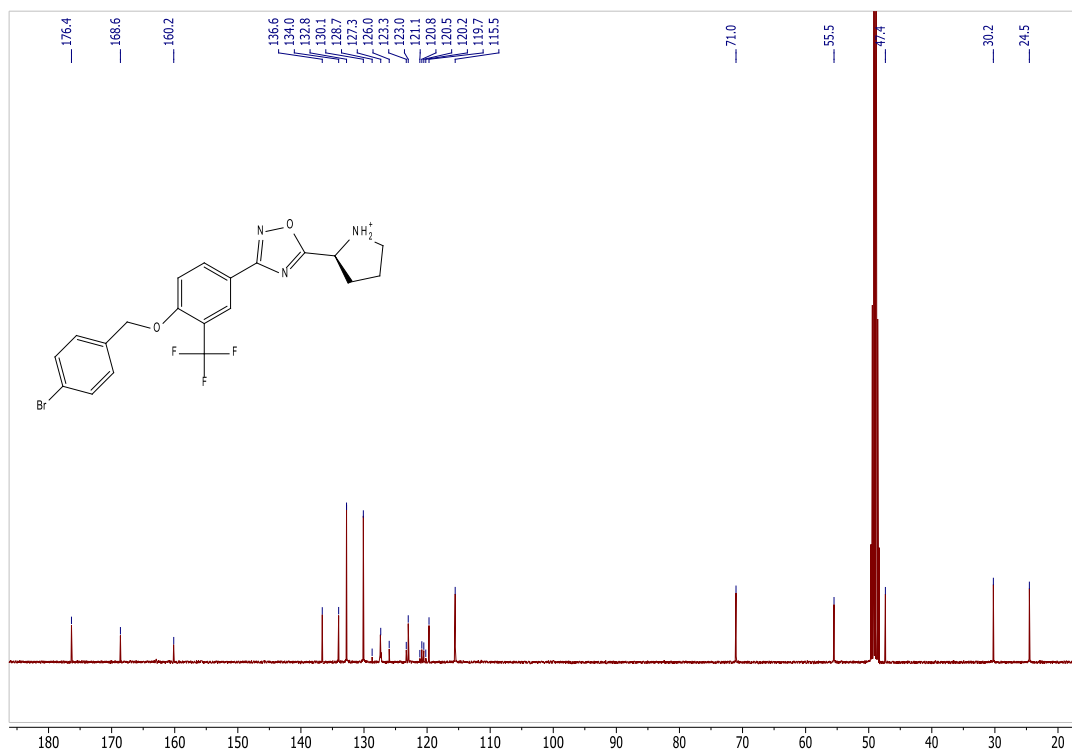
<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



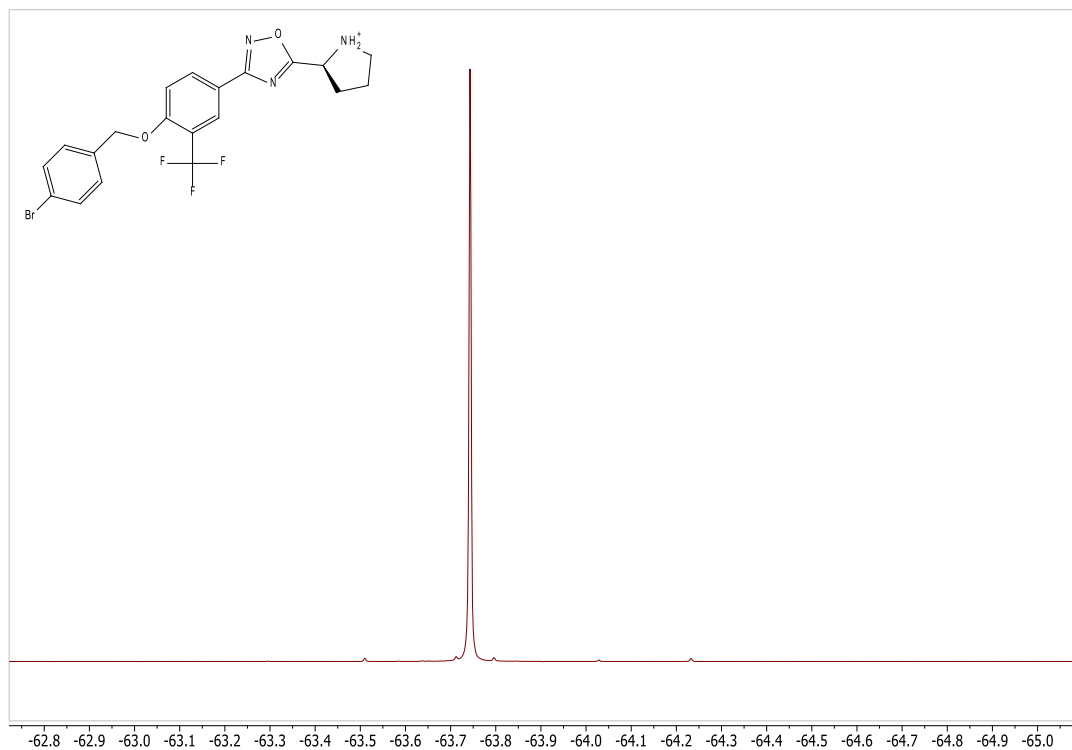
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



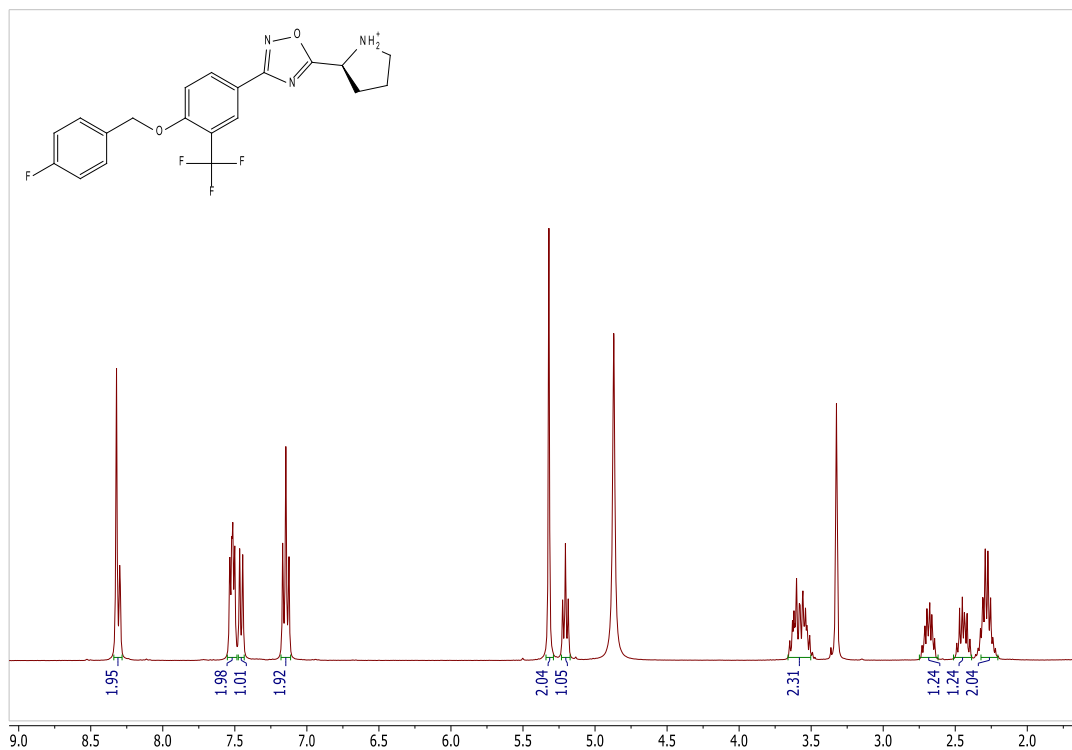
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



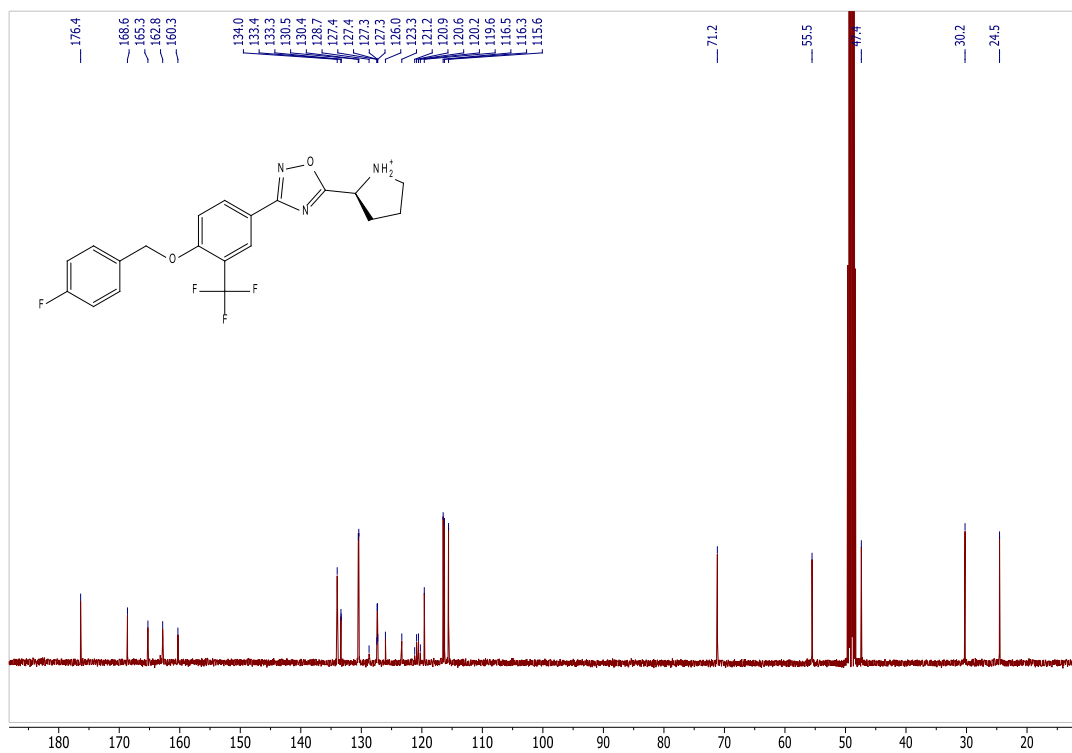
$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -

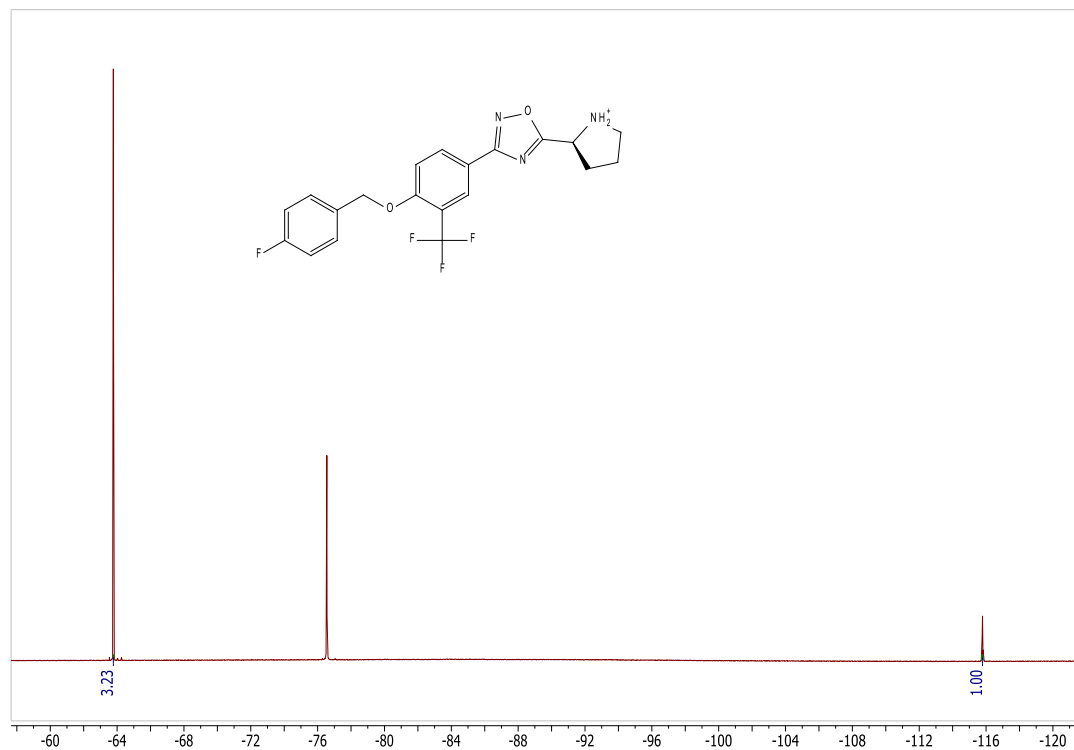


<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -

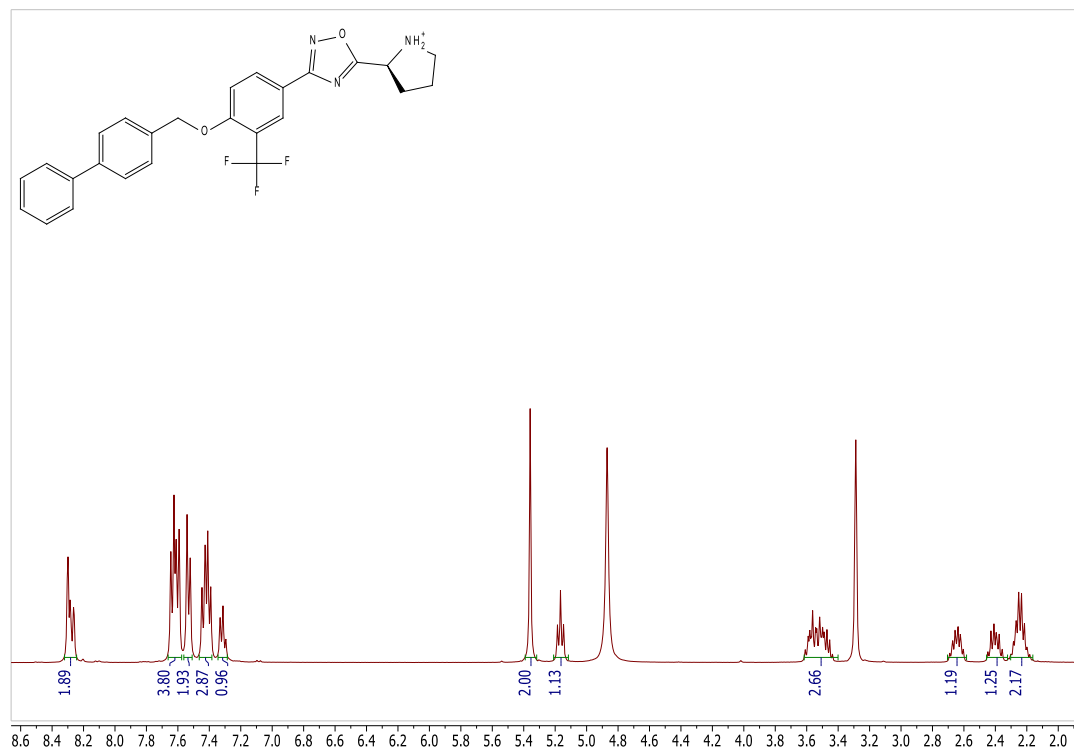




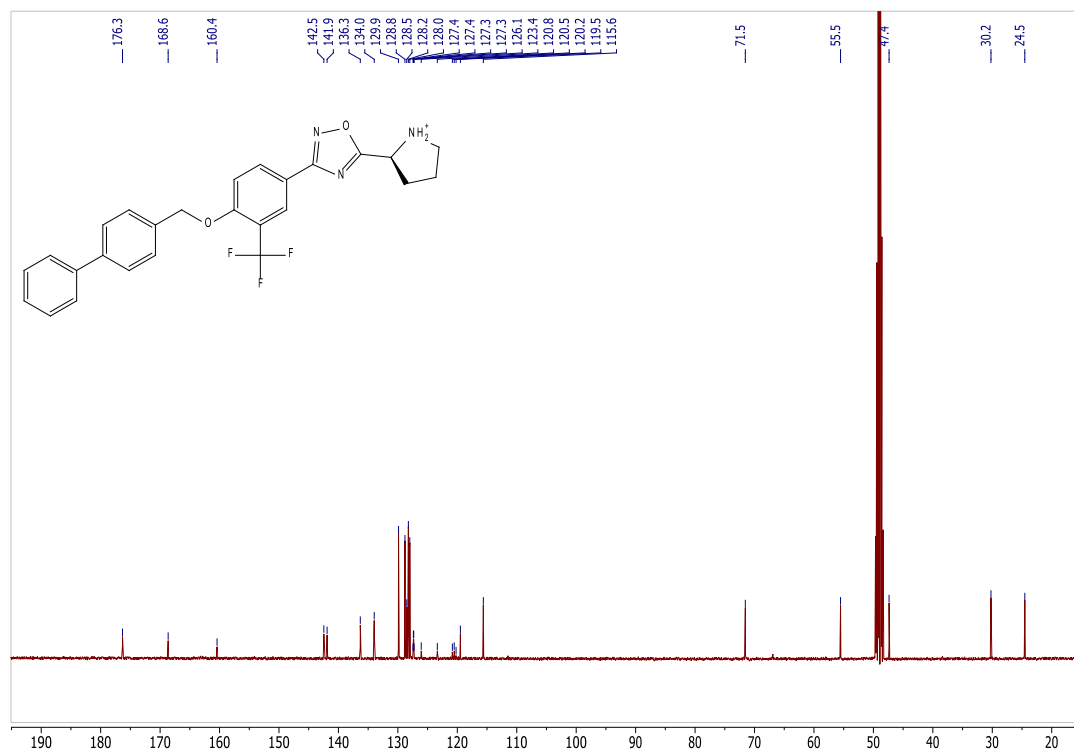
<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



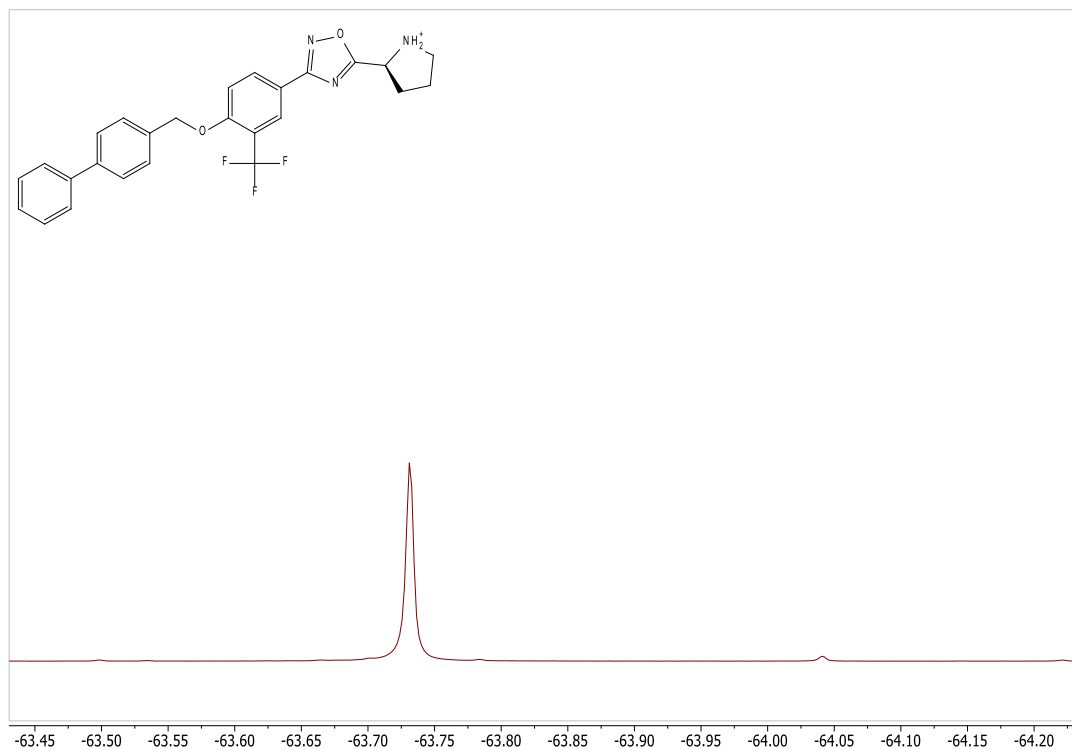
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



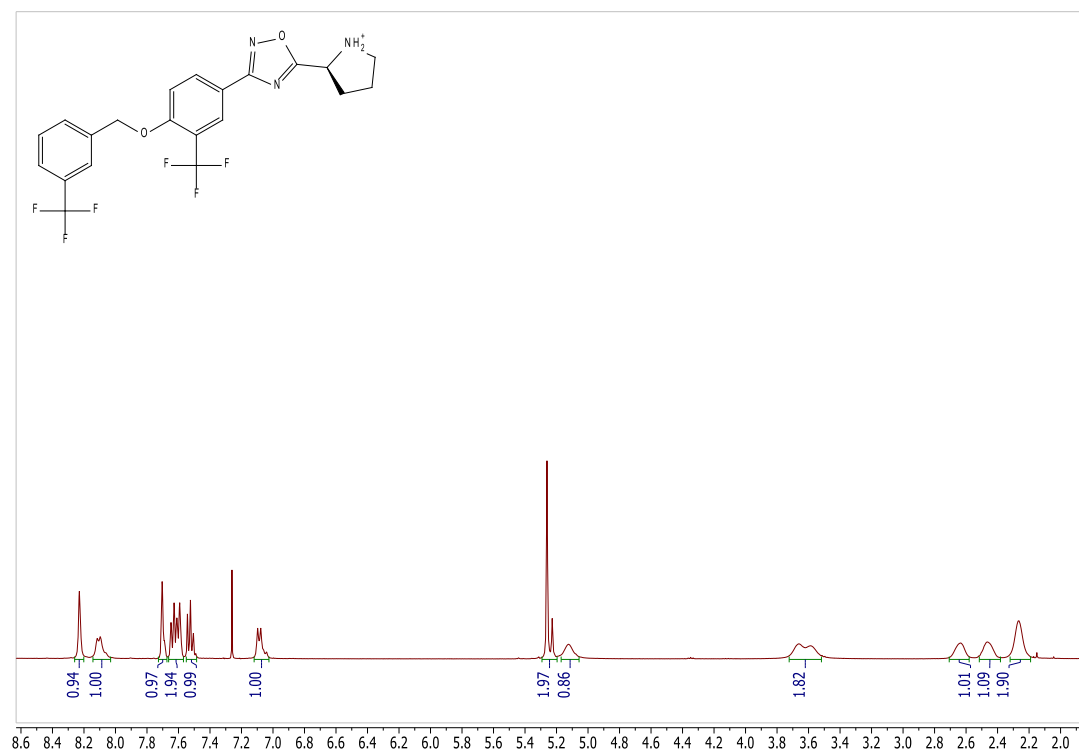
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



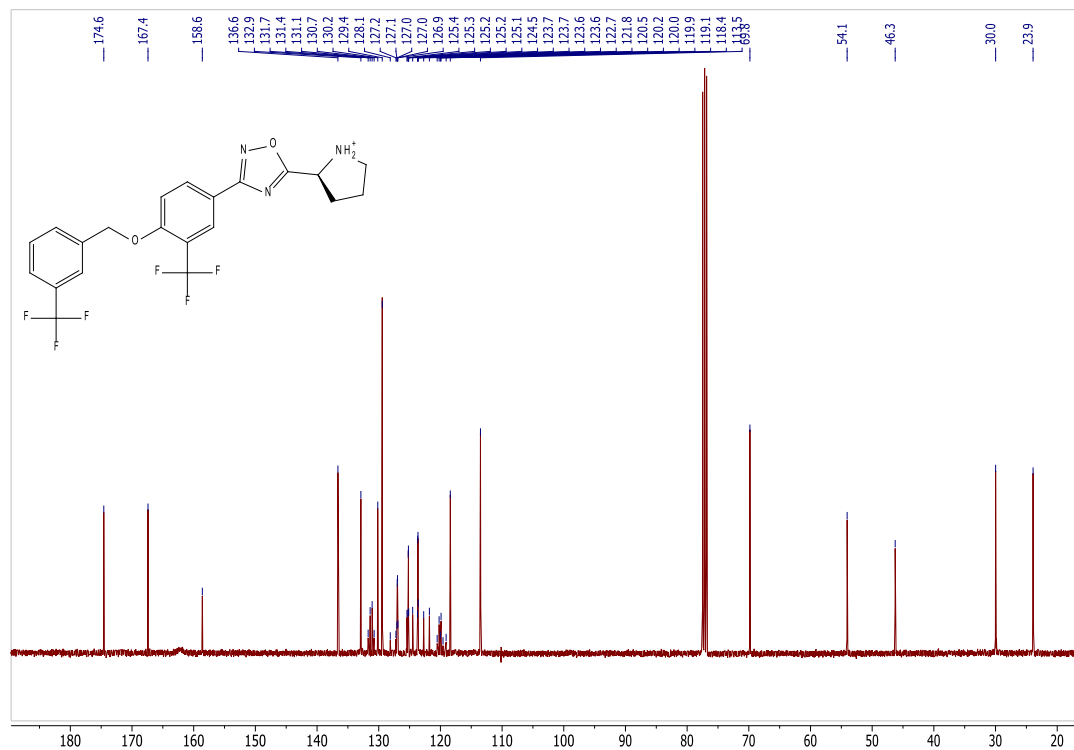
<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



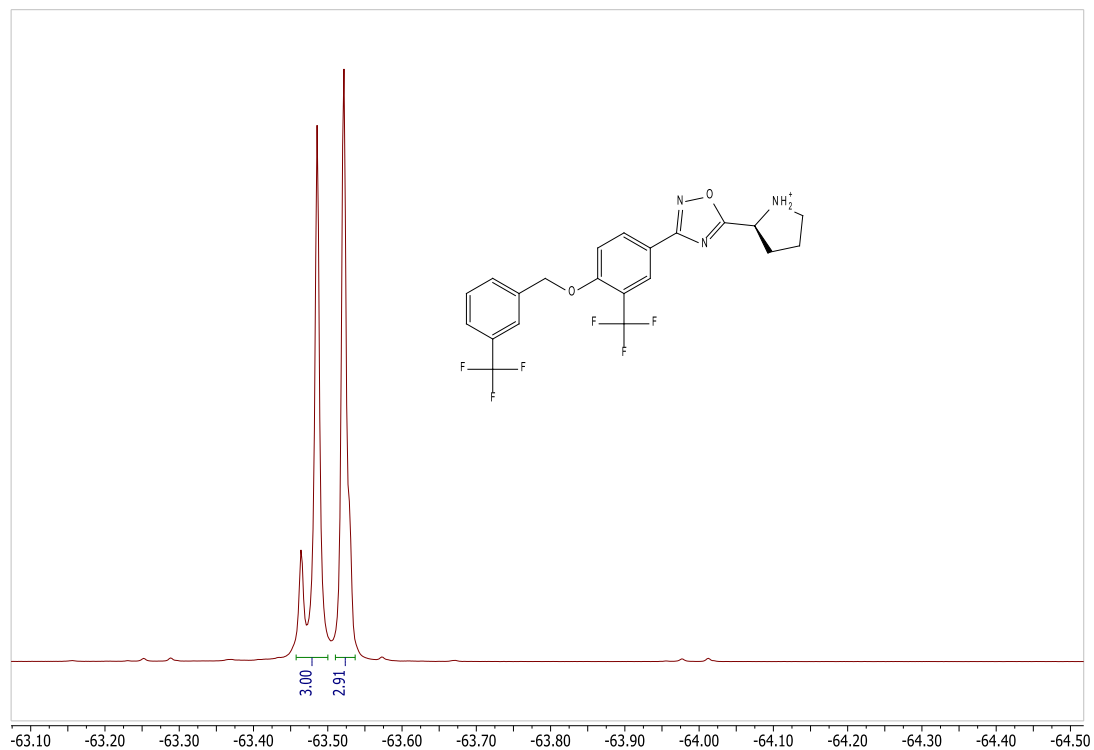
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



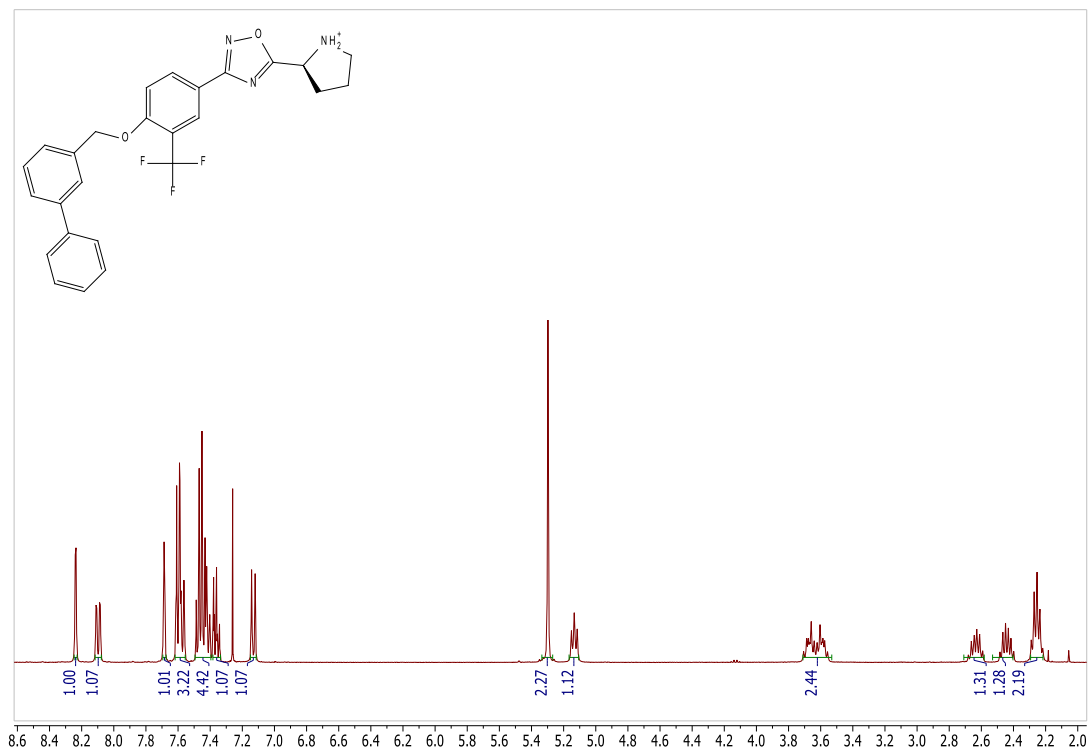
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



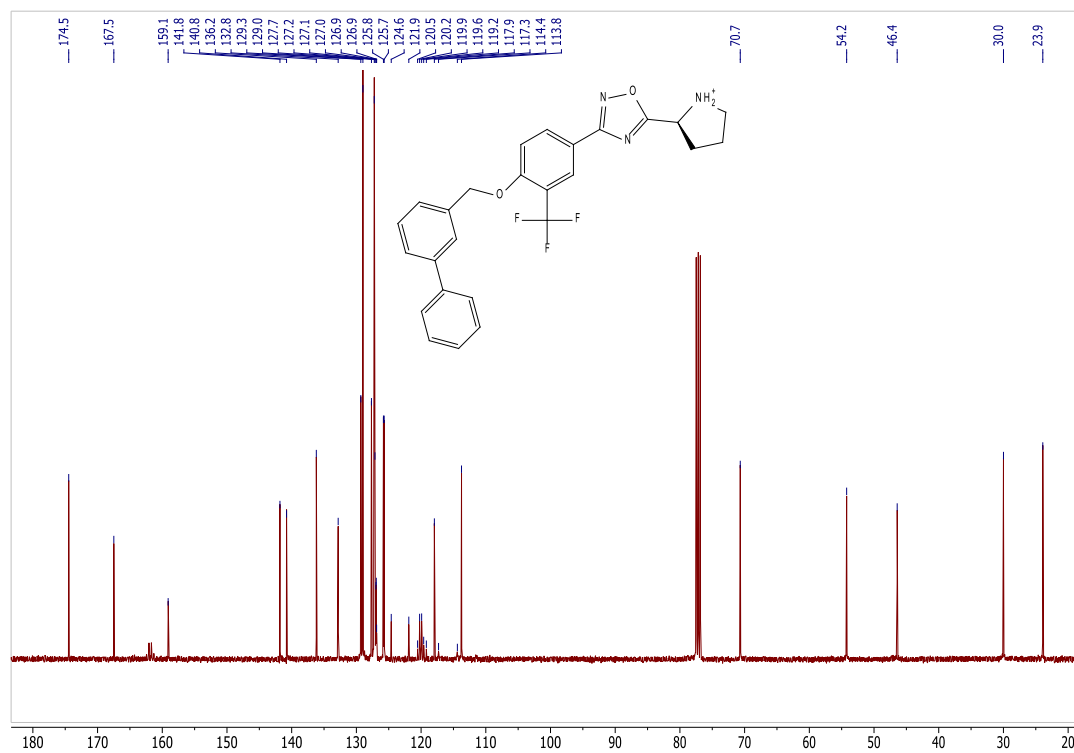
<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



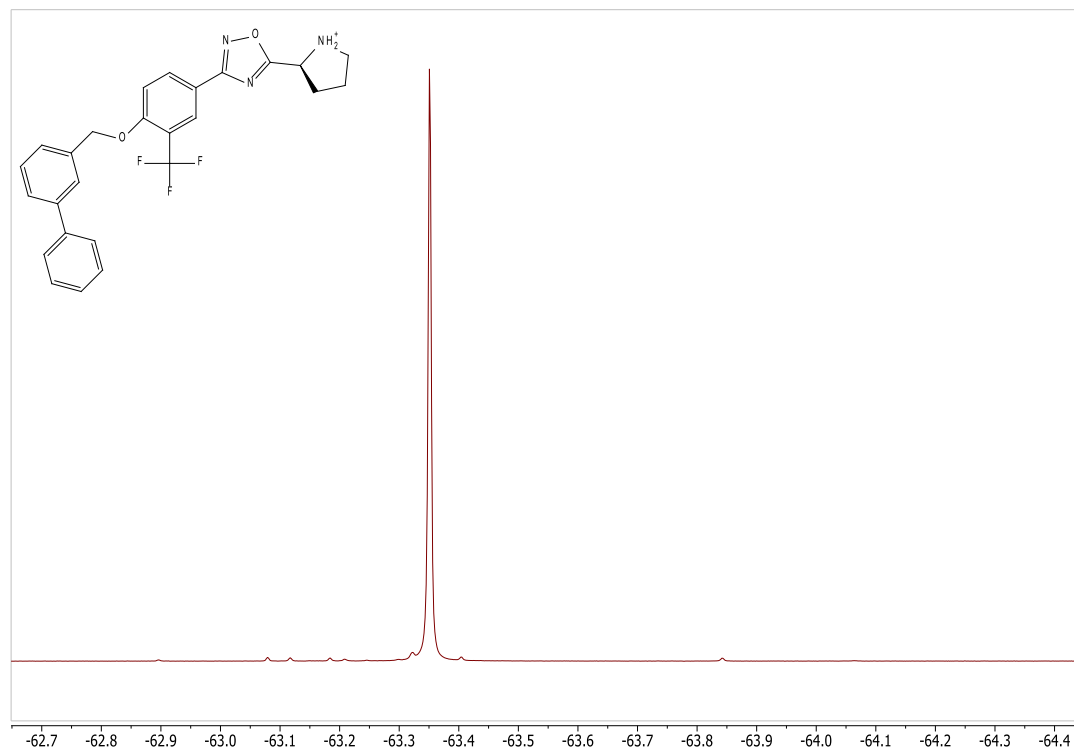
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -

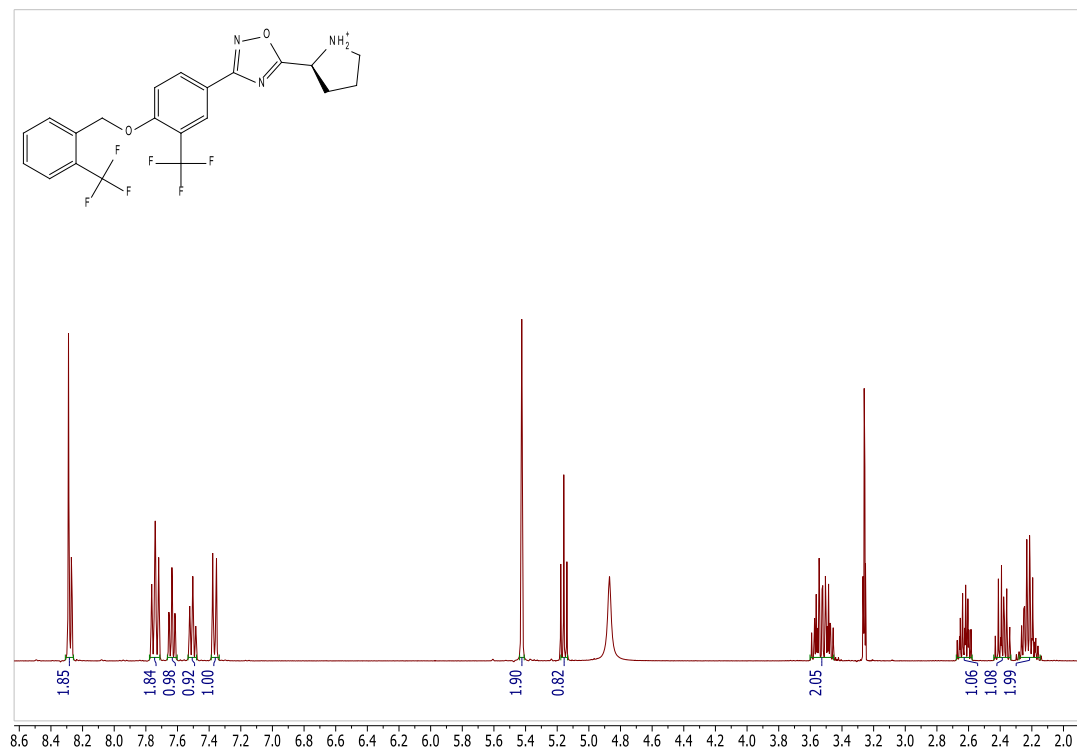


$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -

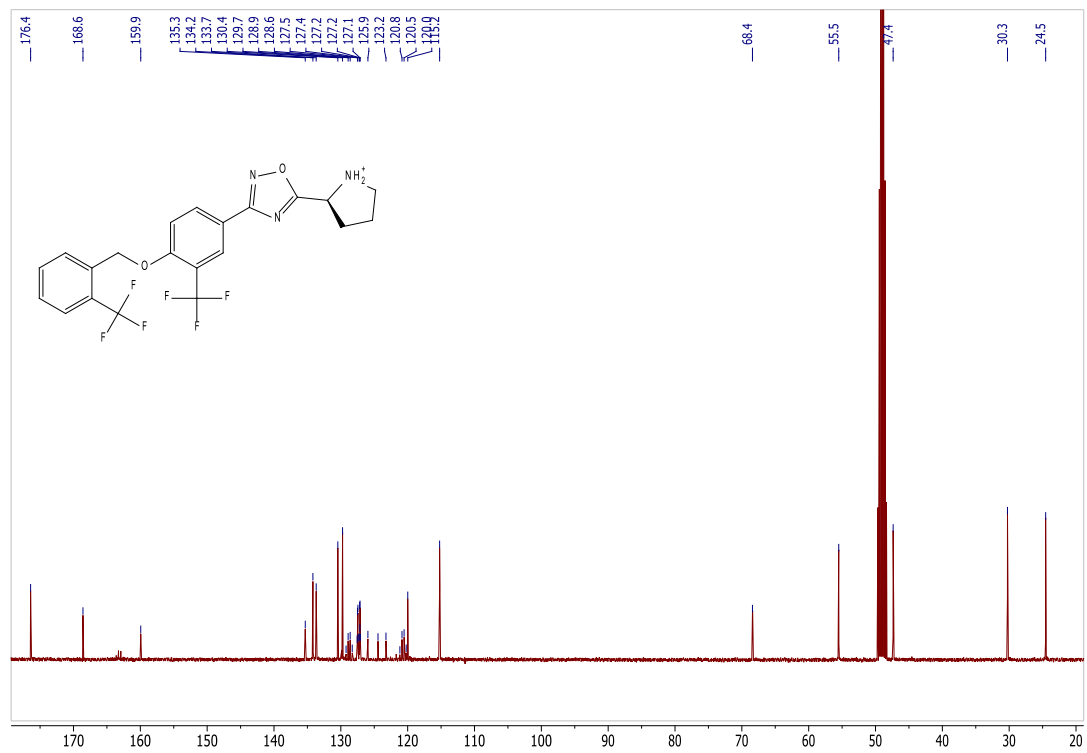




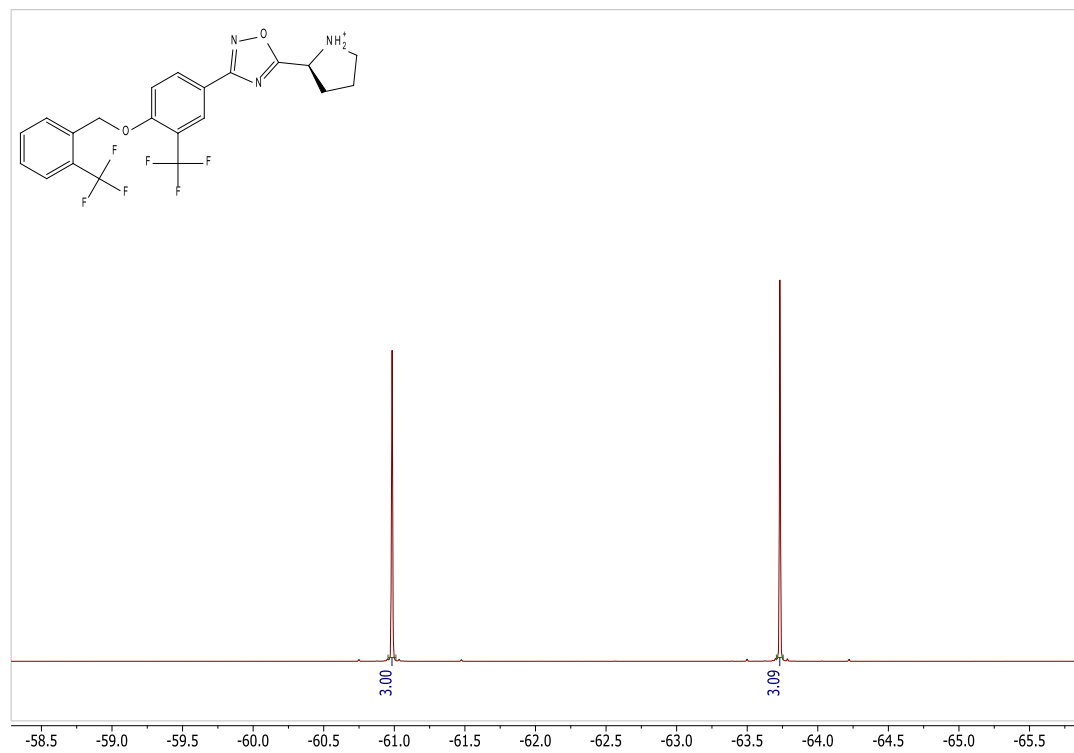
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



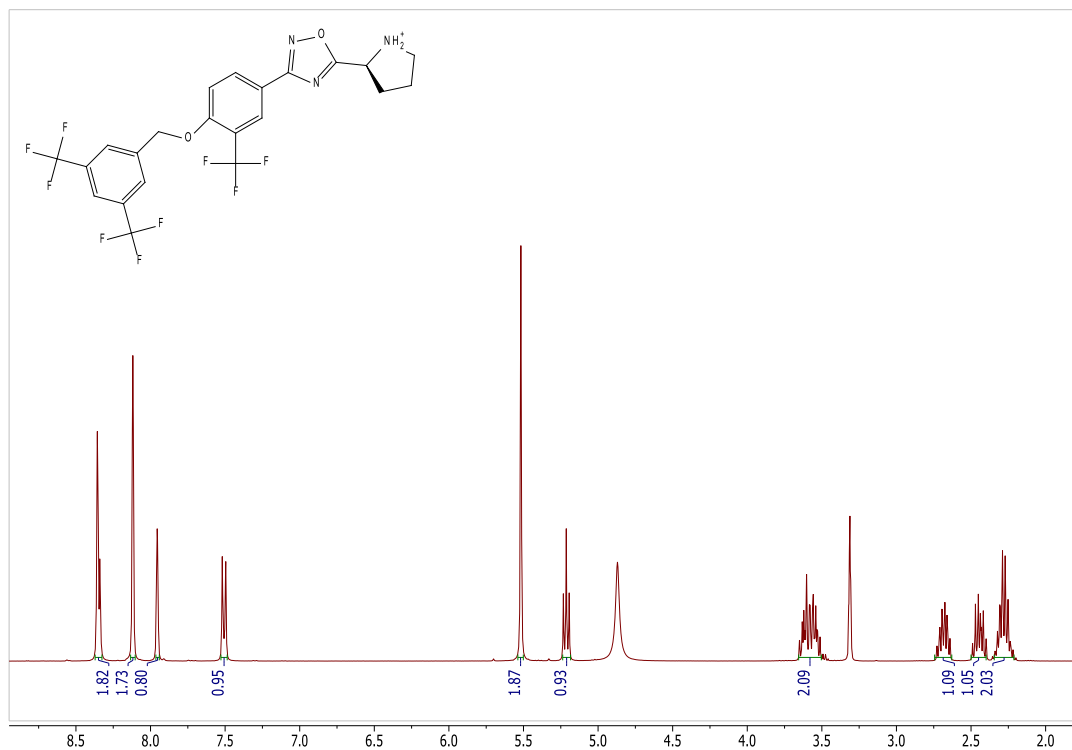
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



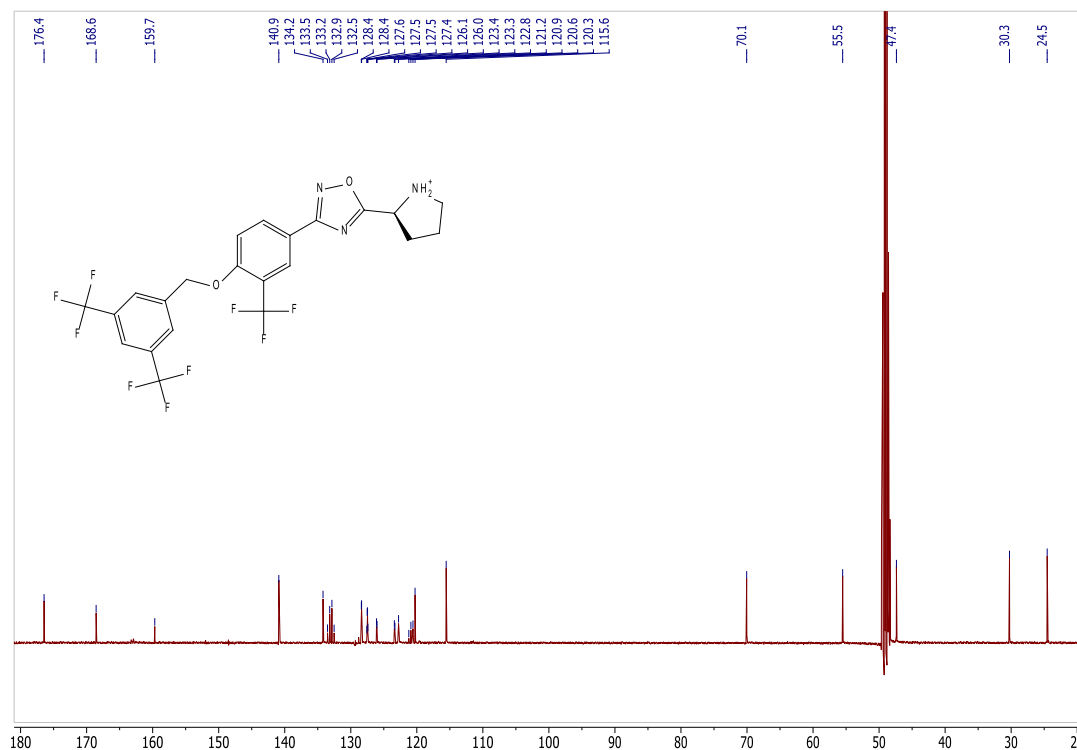
<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



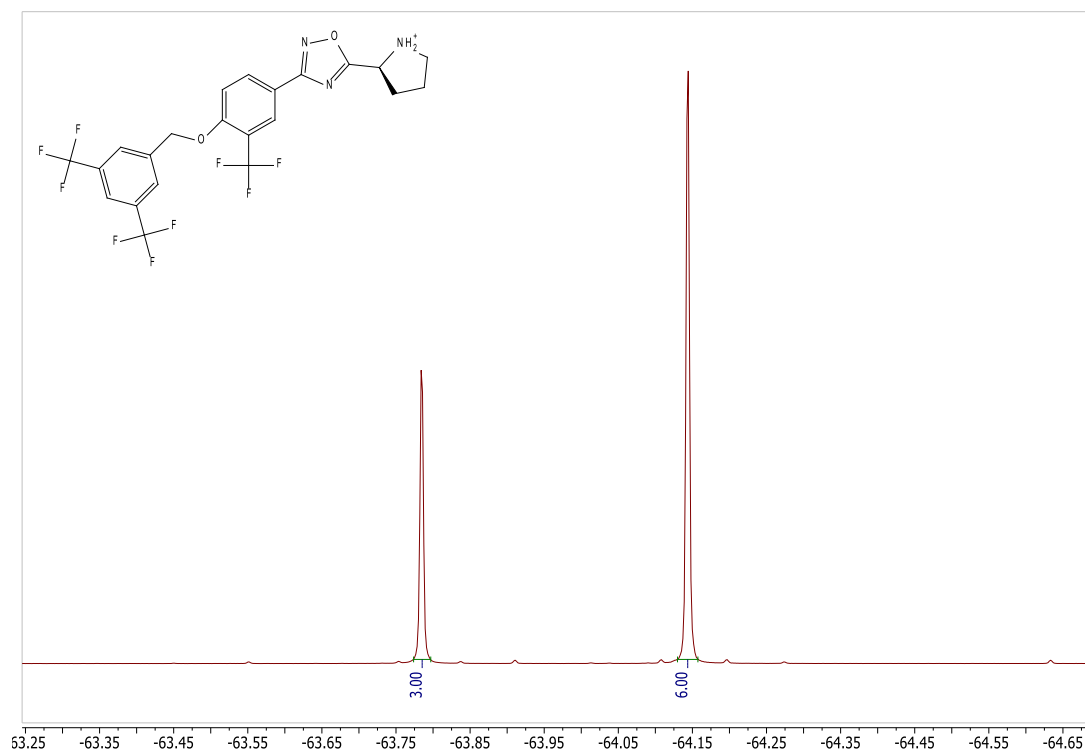
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



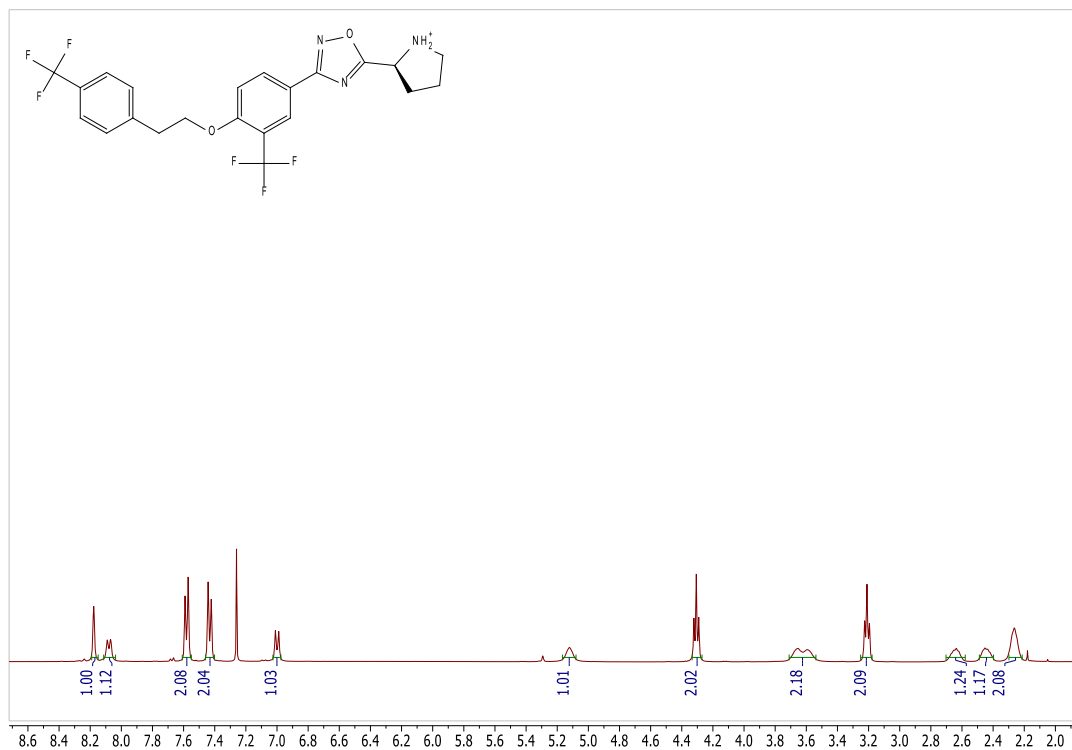
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



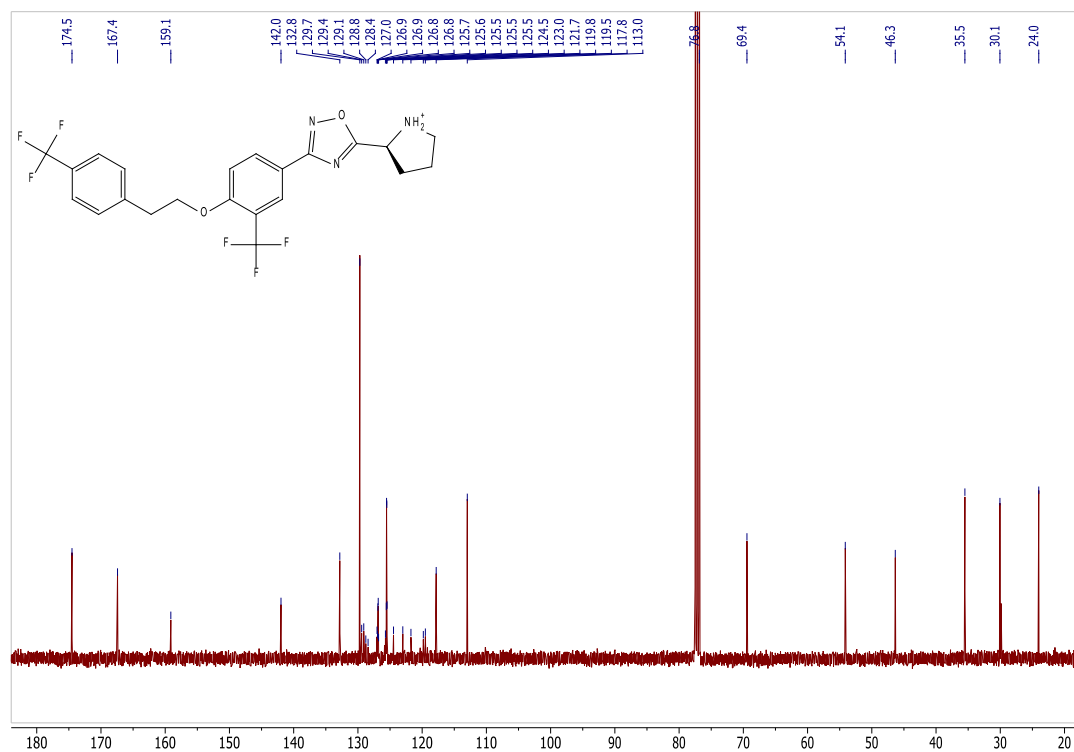
<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



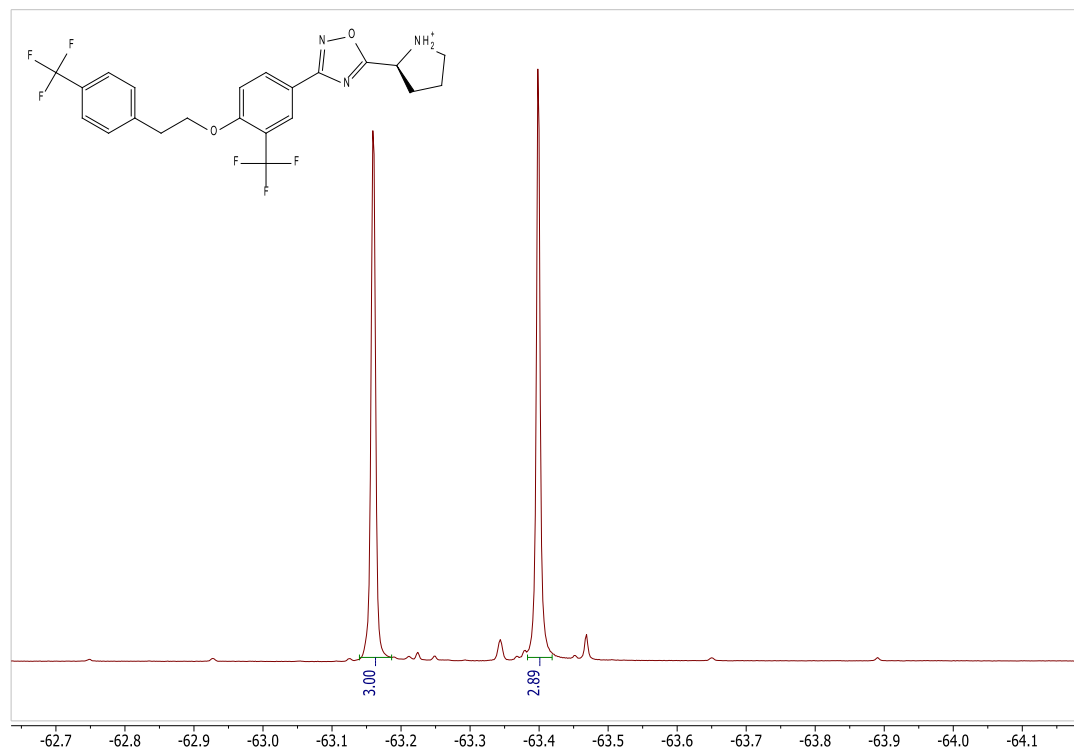
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -

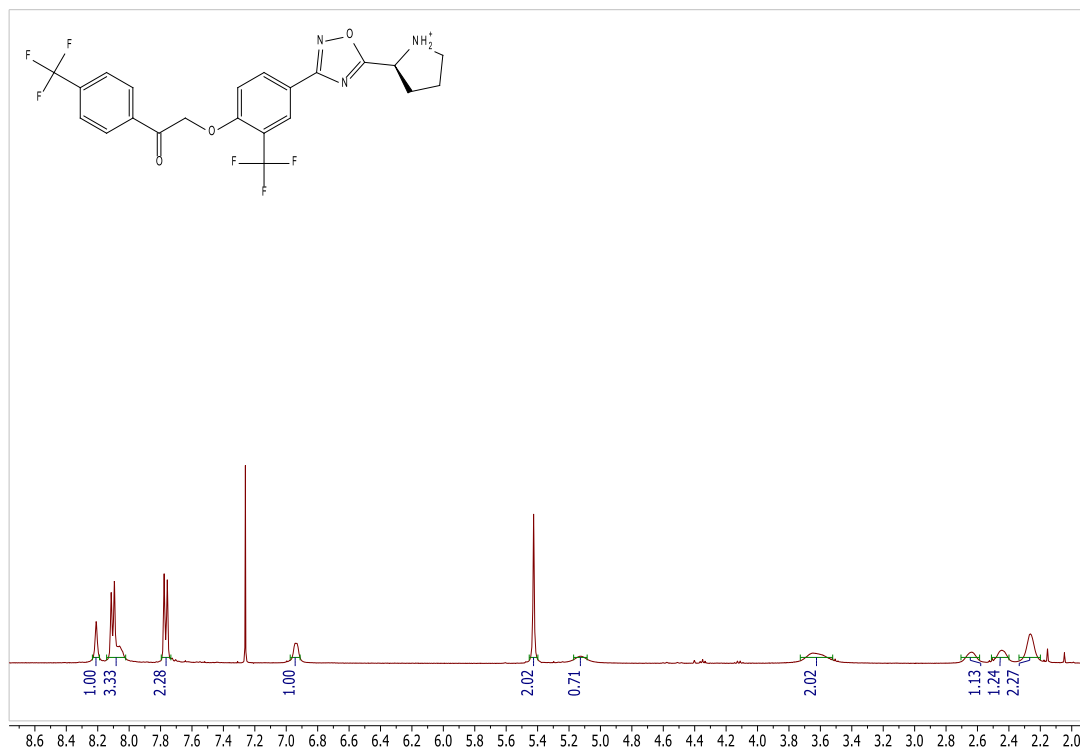


<sup>19</sup>F-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -

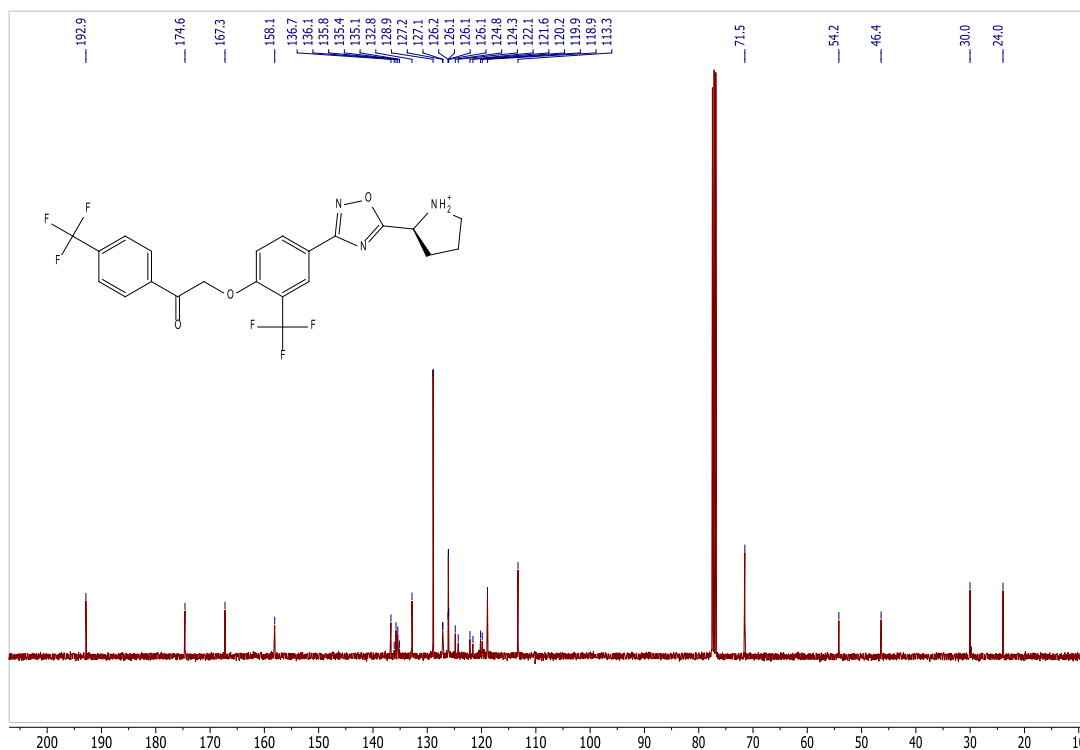




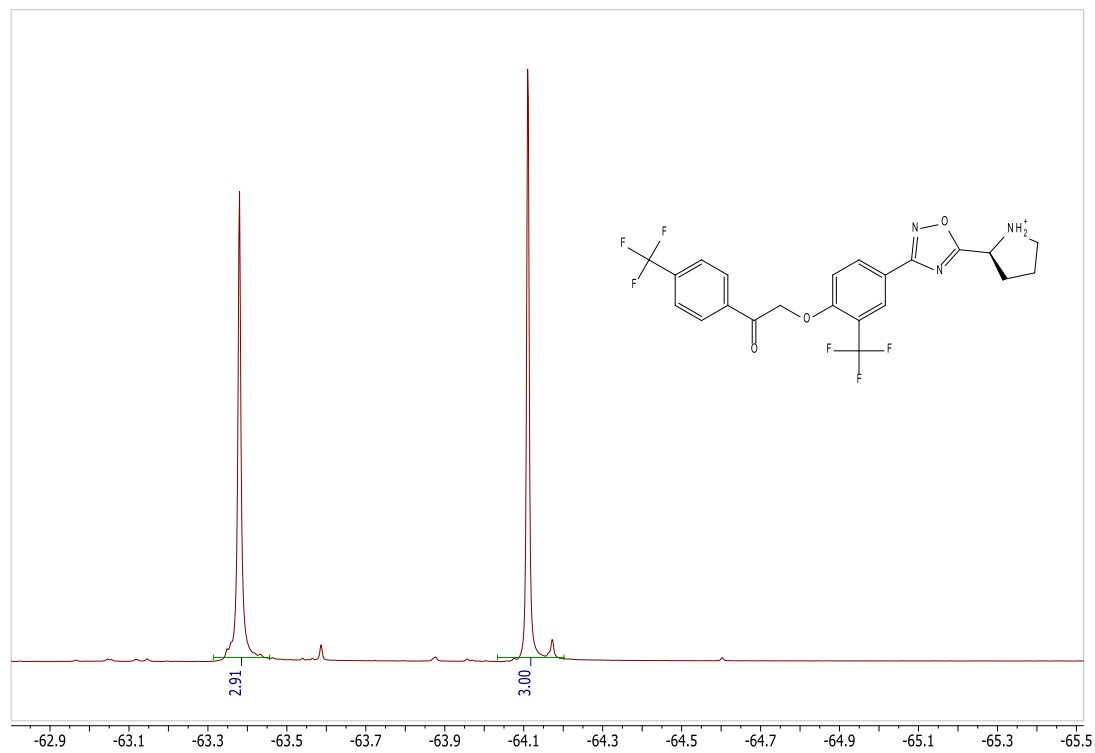
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



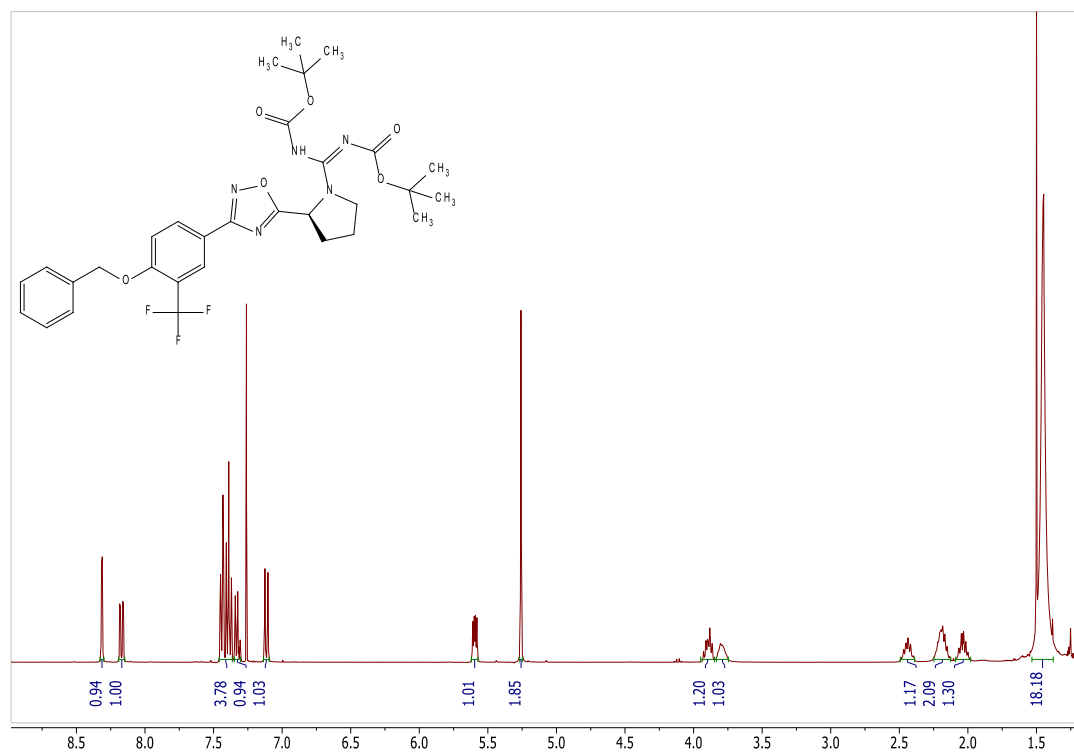
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



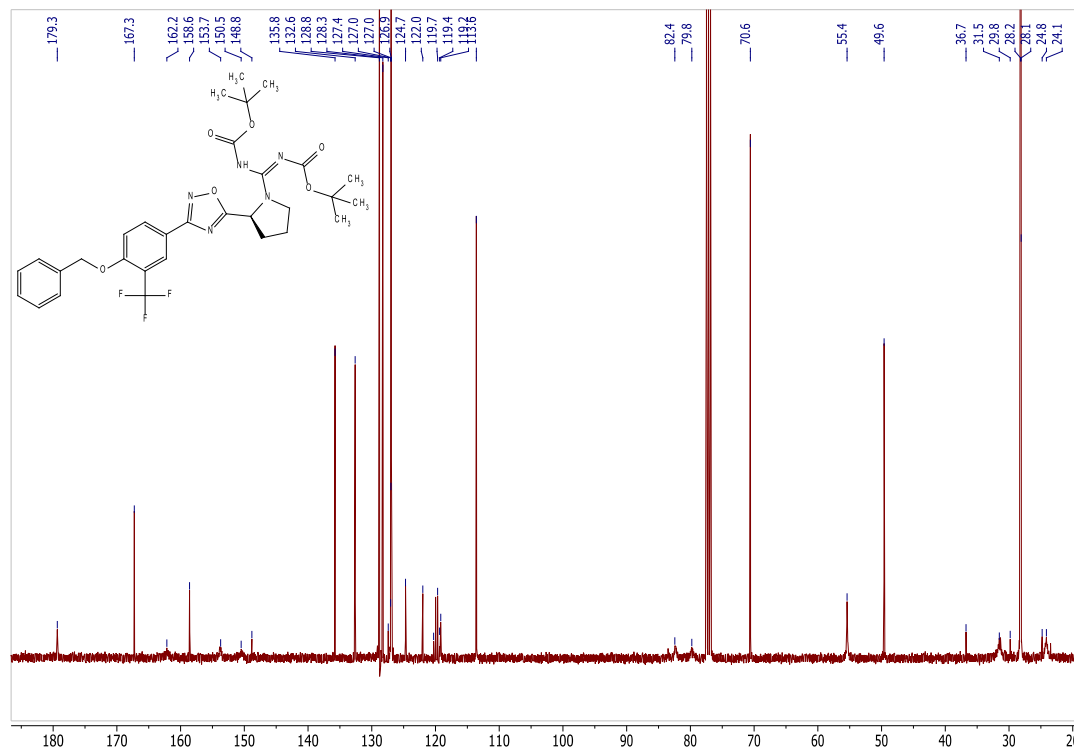
$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



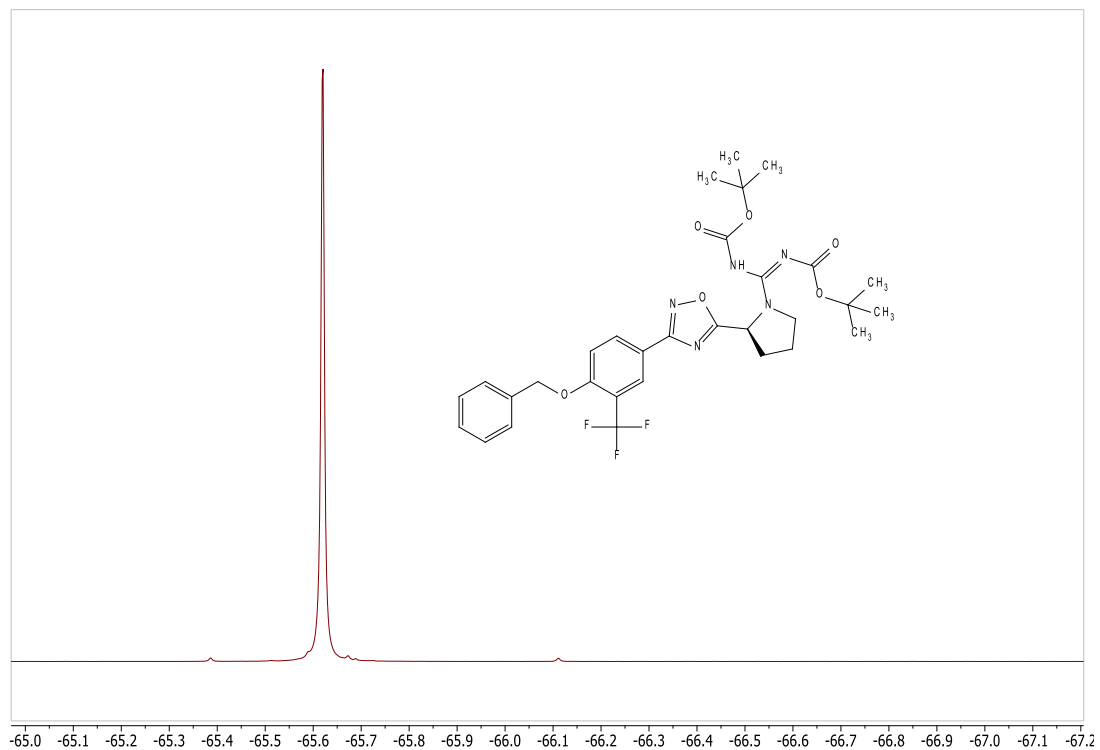
$^1\text{H-NMR}$  Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31a** -



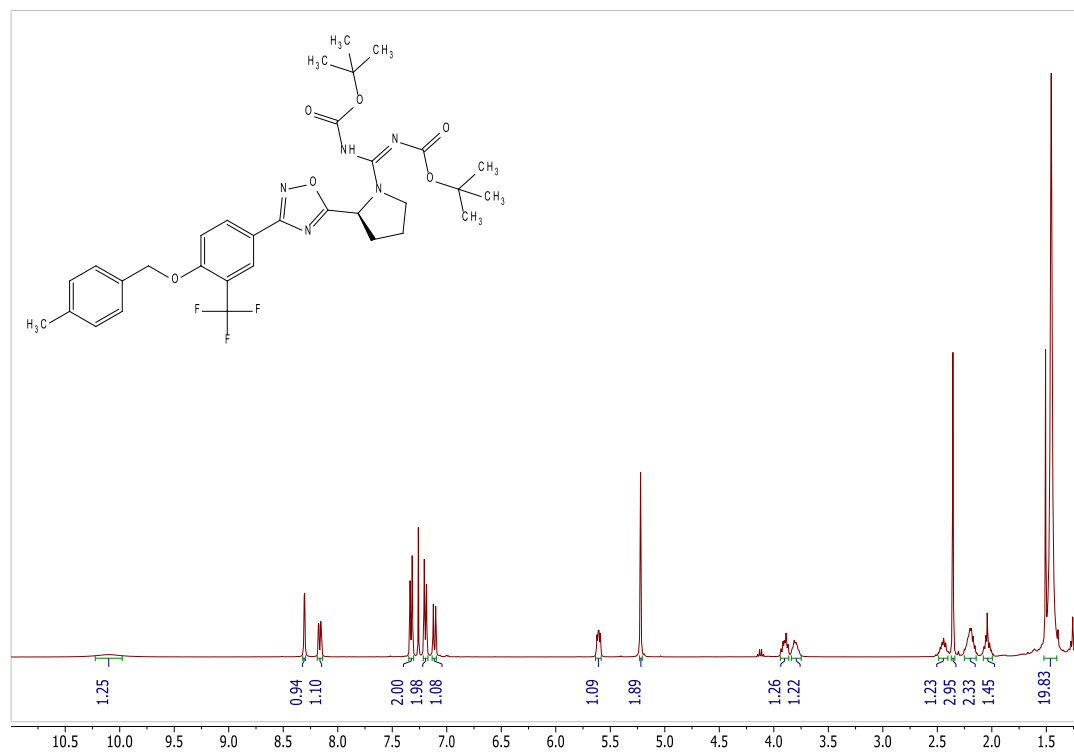
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31a** -



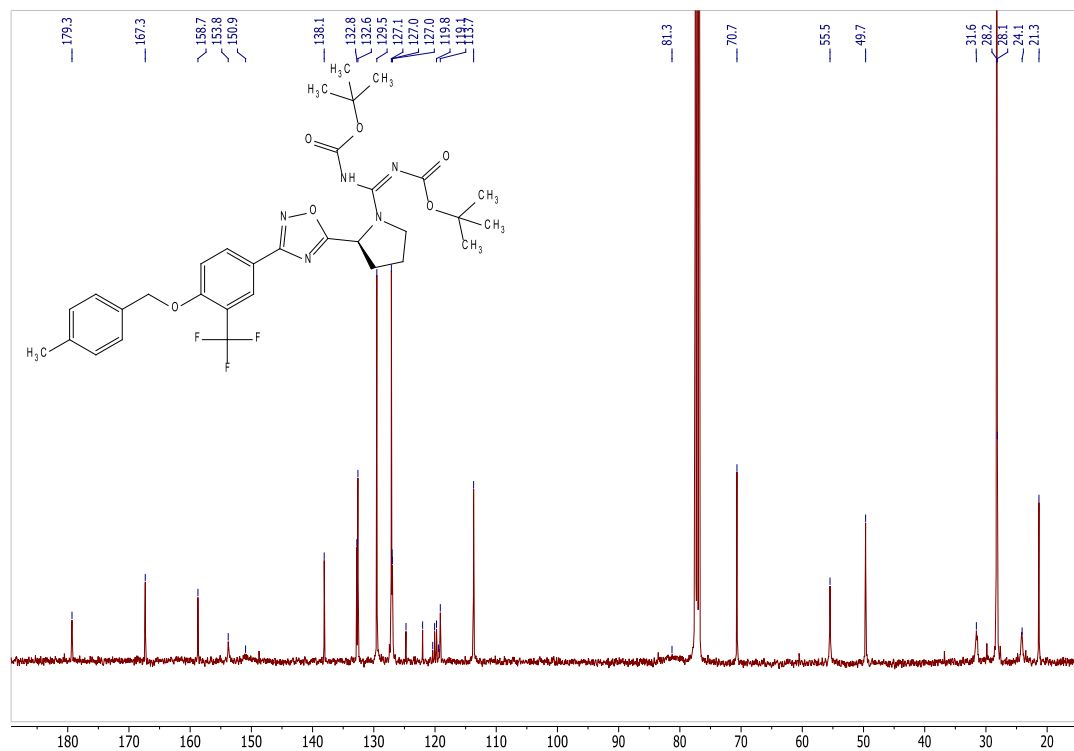
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31a** -



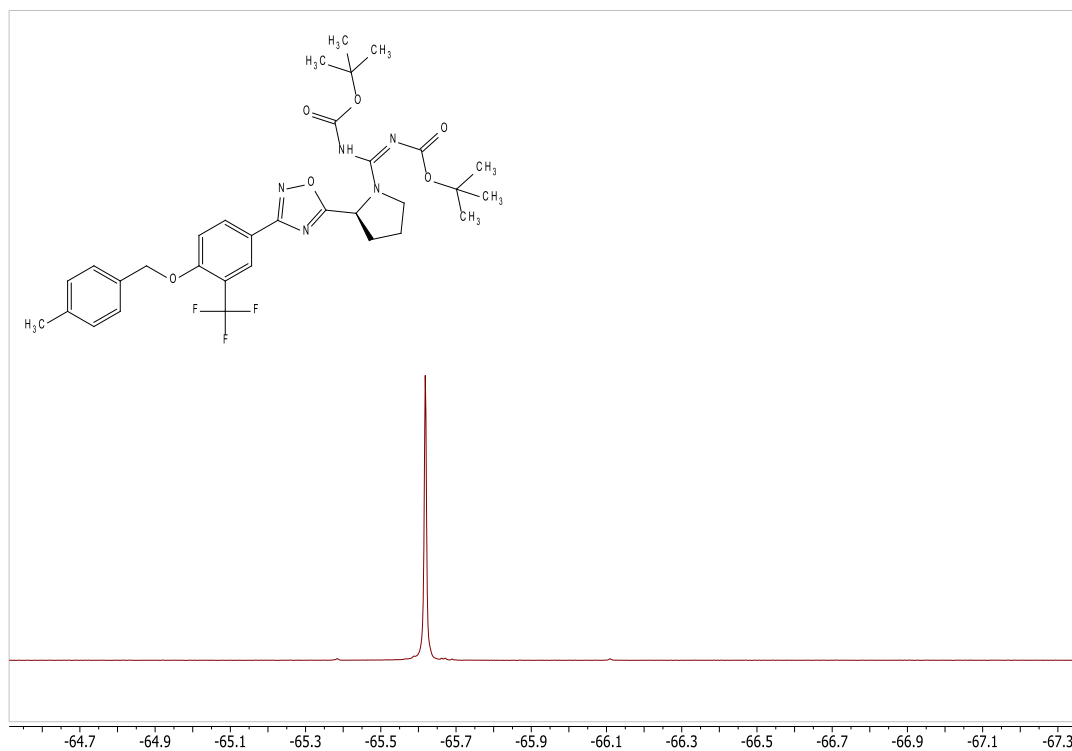
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31b** -



$^{13}\text{C}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31b** -

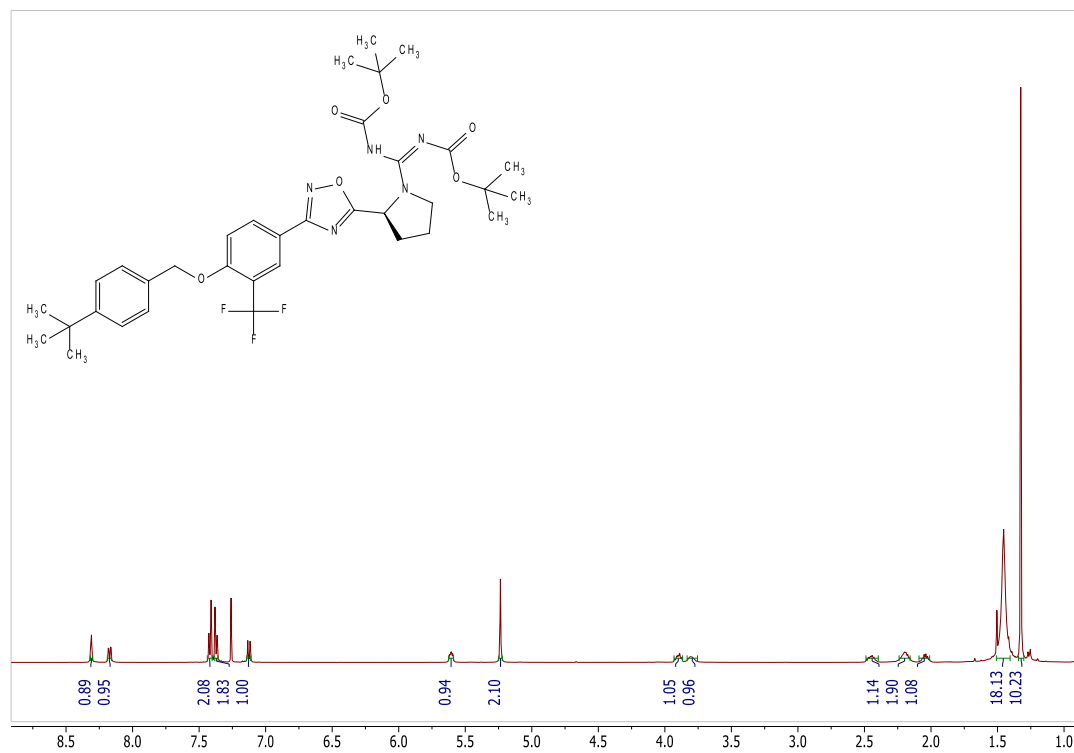


$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31b** -

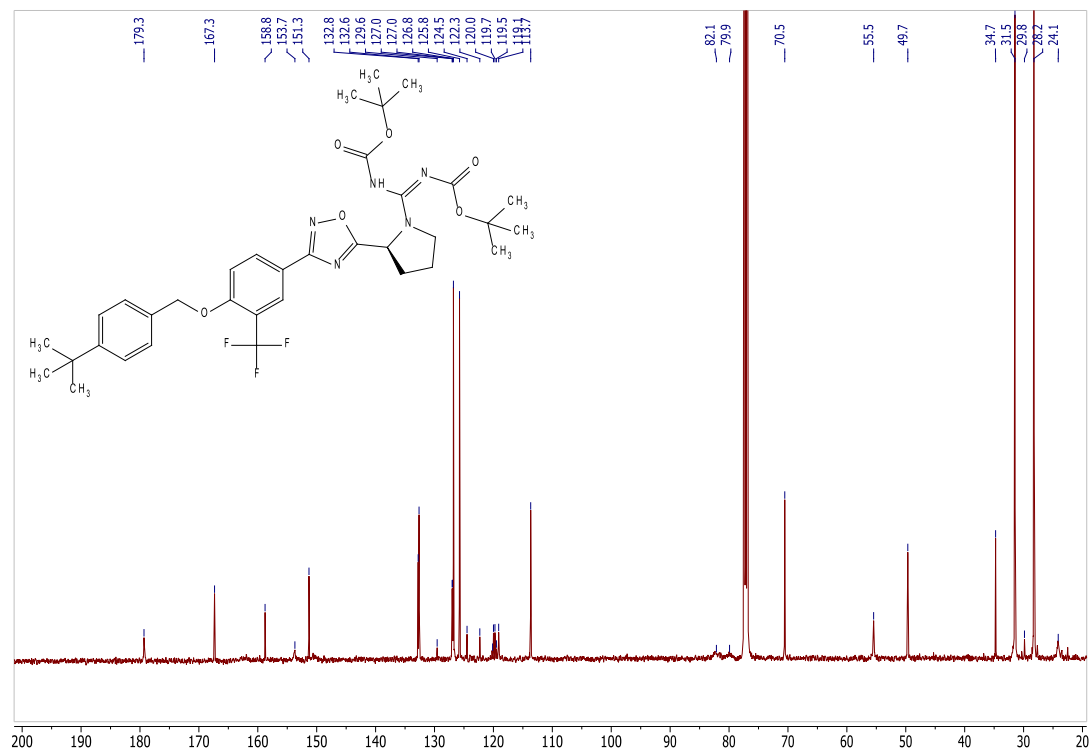




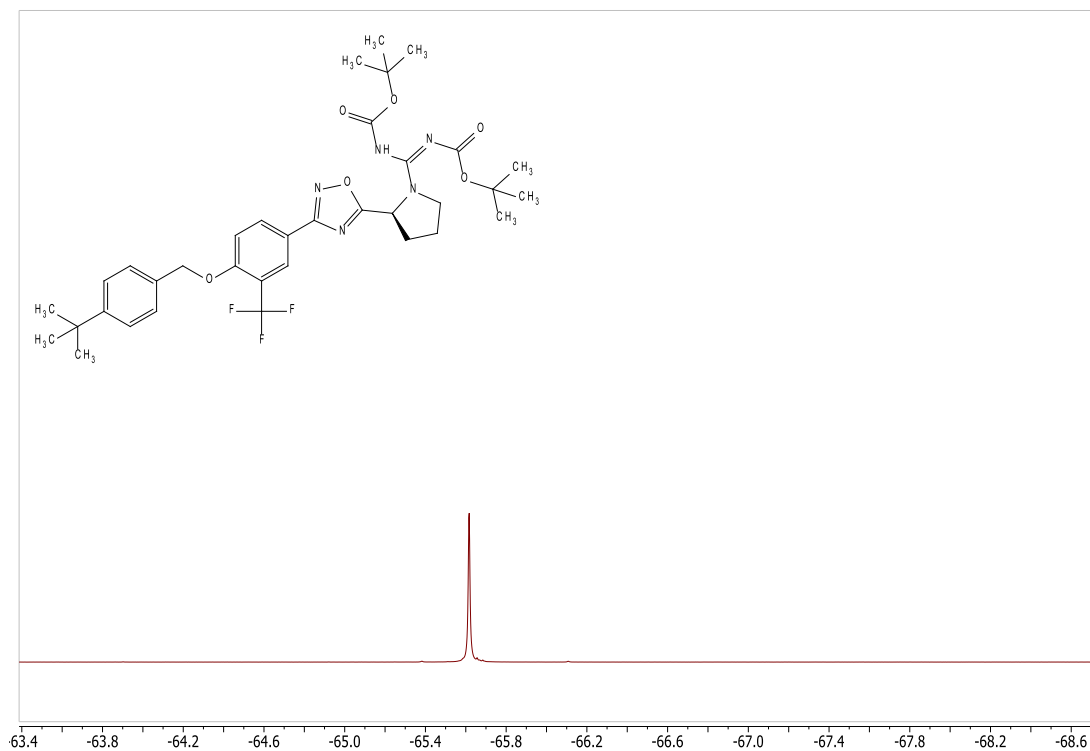
$^1\text{H-NMR}$  Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-((4-*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31c** -



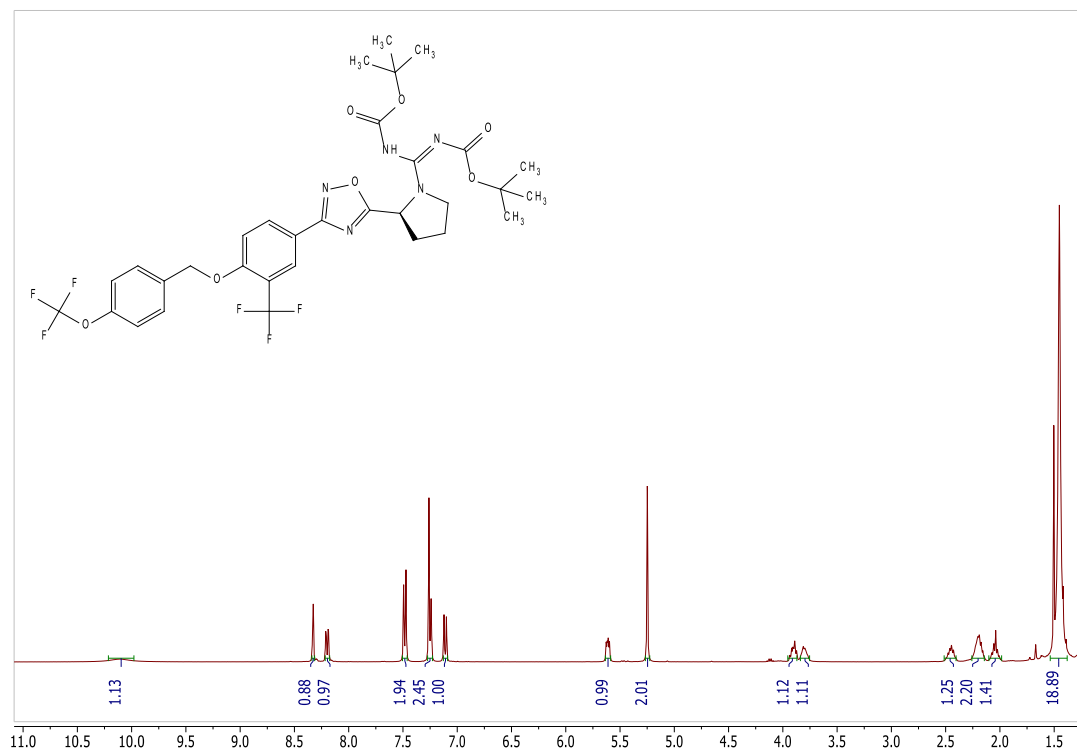
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-((4-*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31c** -



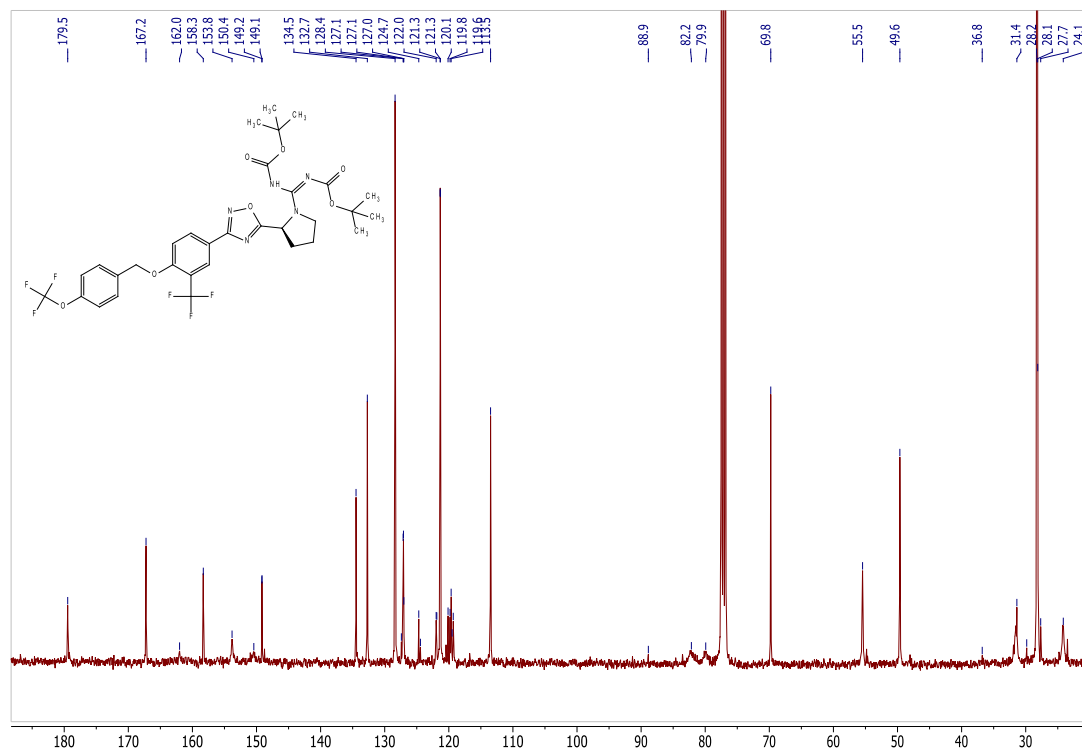
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-((4-*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31c** -



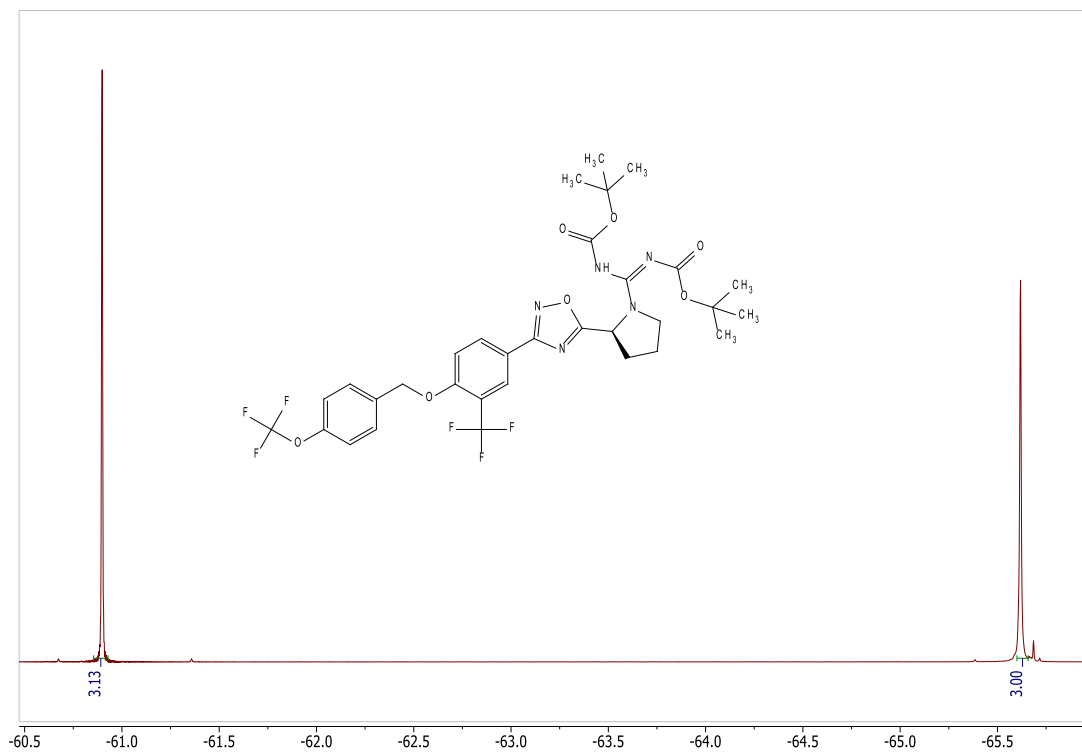
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31d** -



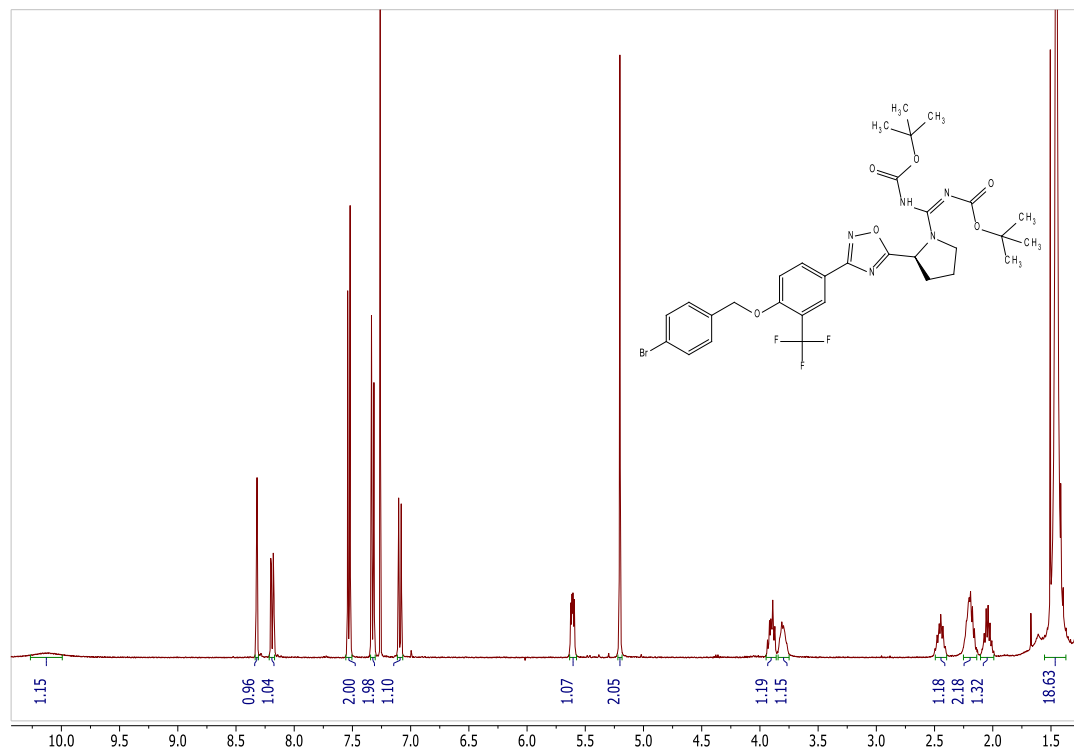
$^{13}\text{C}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31d** -



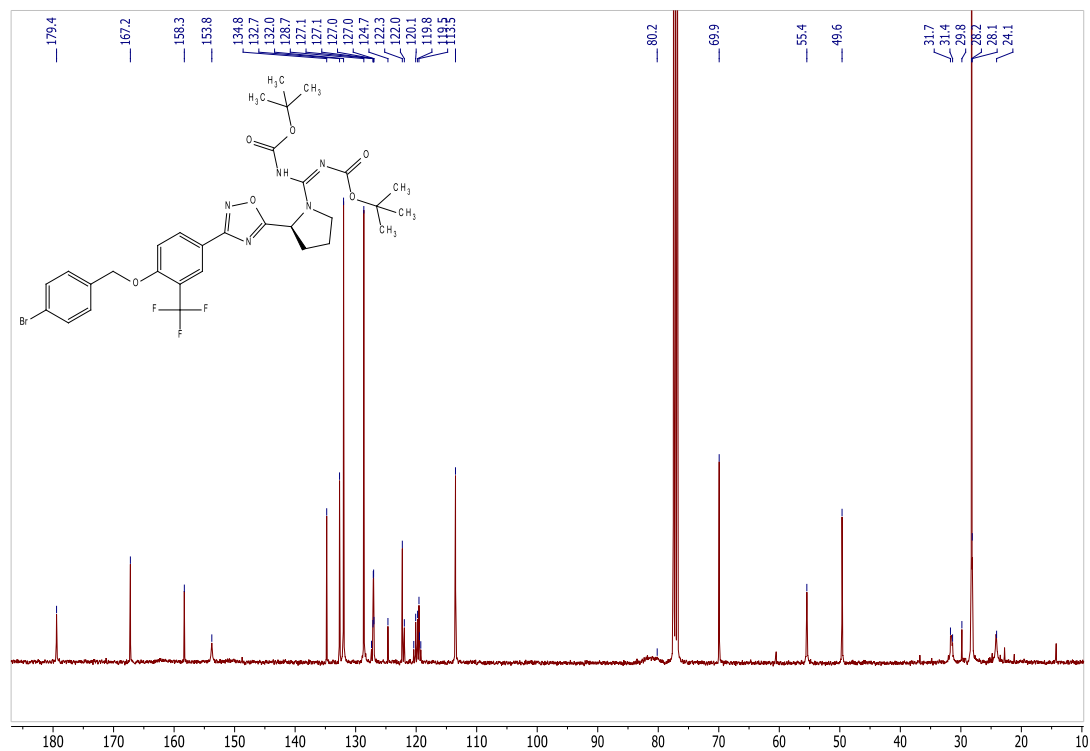
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31d** -



$^1\text{H-NMR}$  Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31e** -

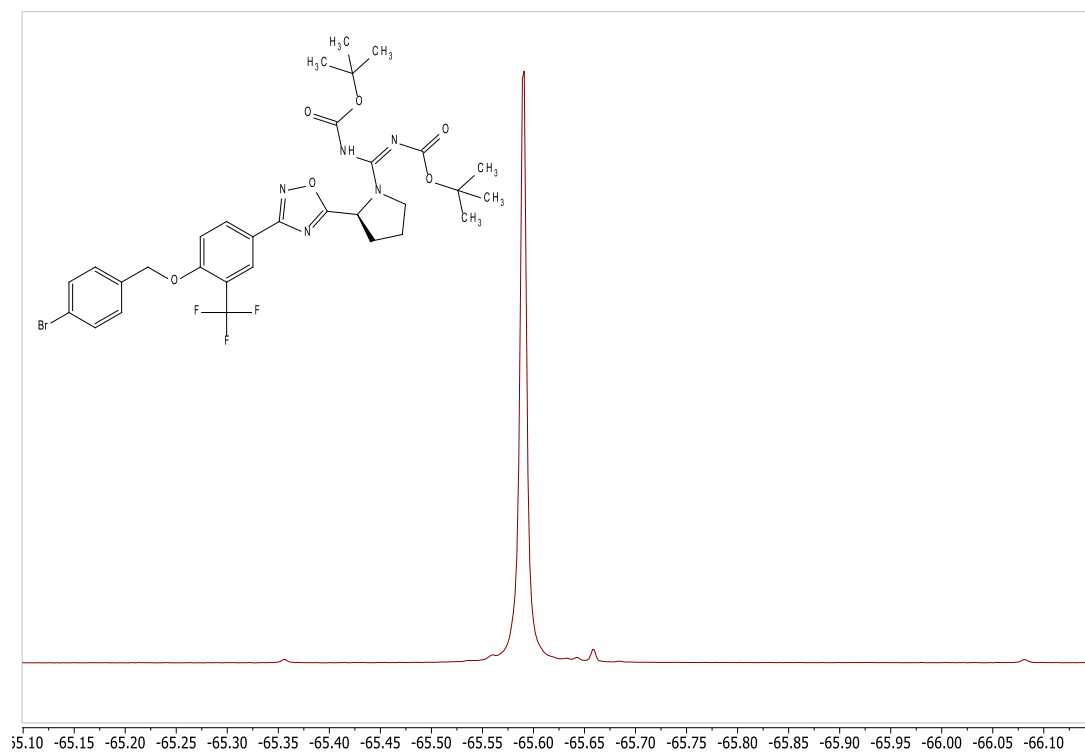


<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31e** -

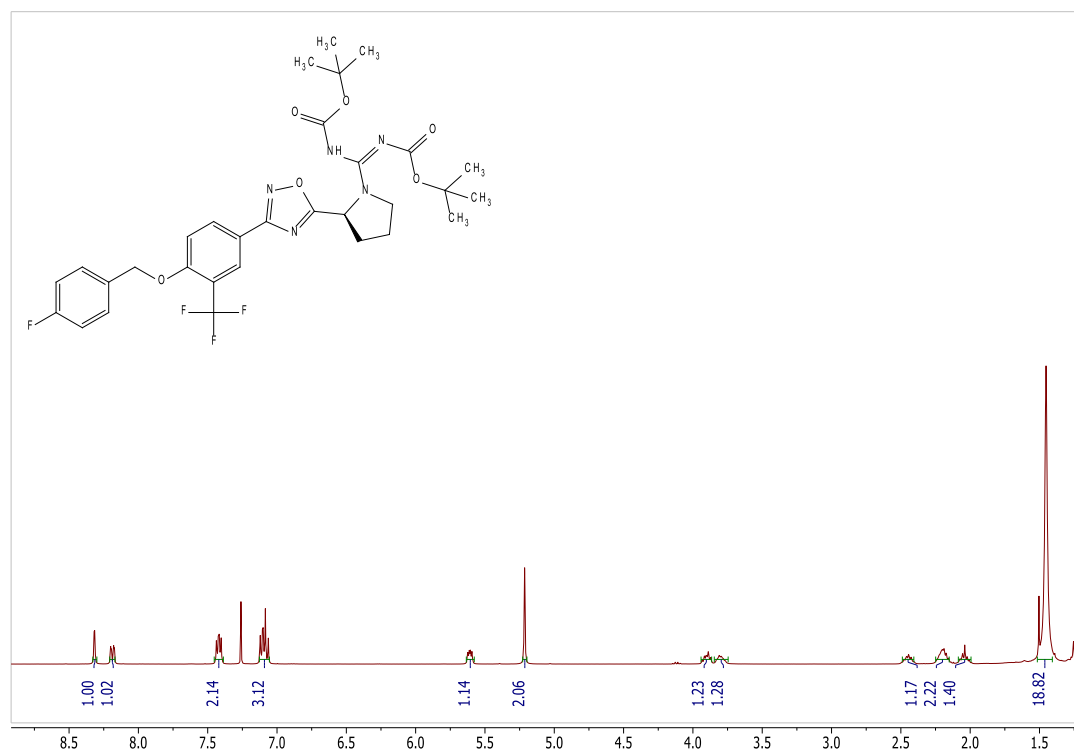




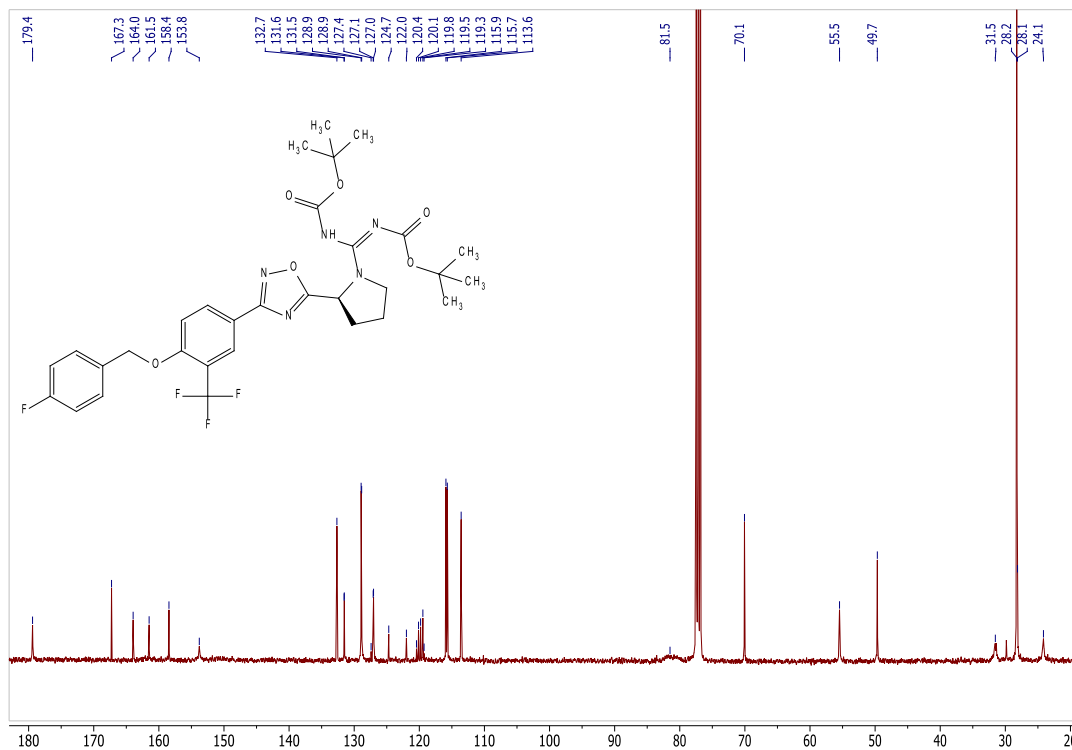
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31e** -



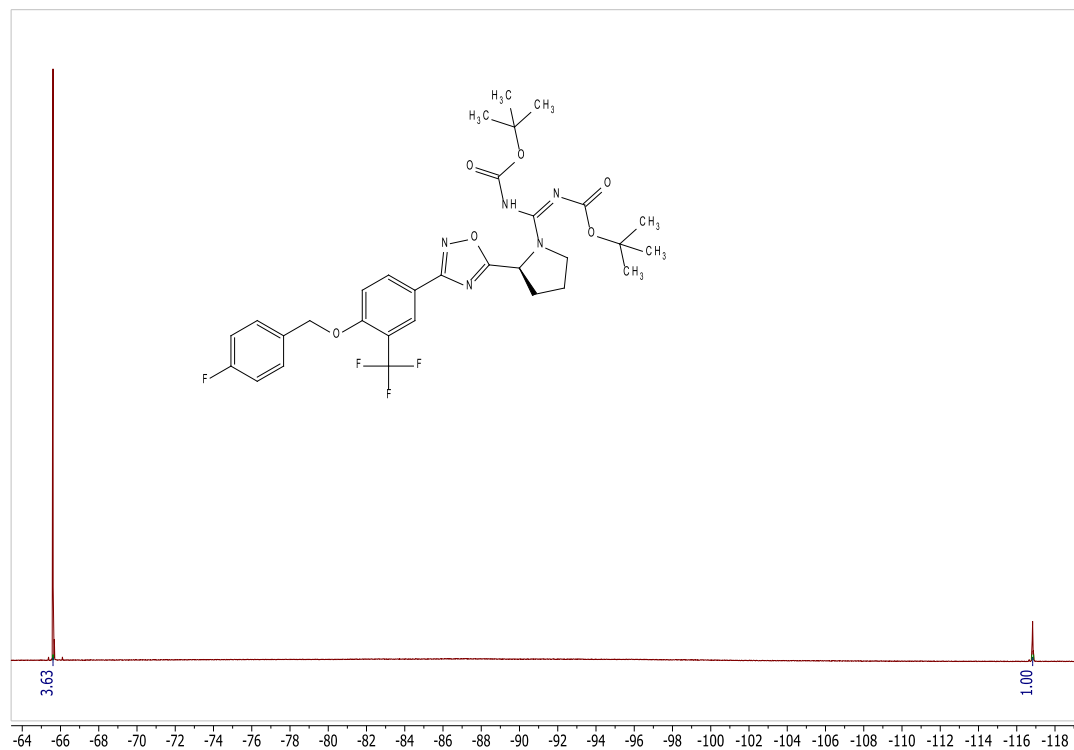
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31f** -



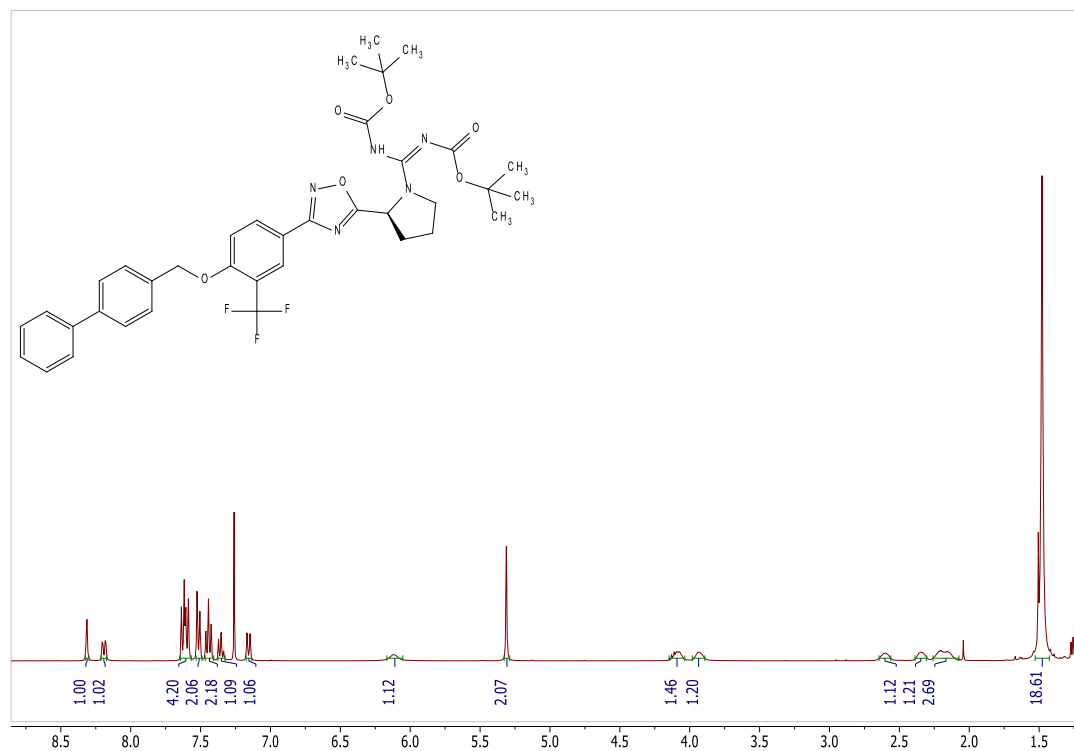
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31f** -



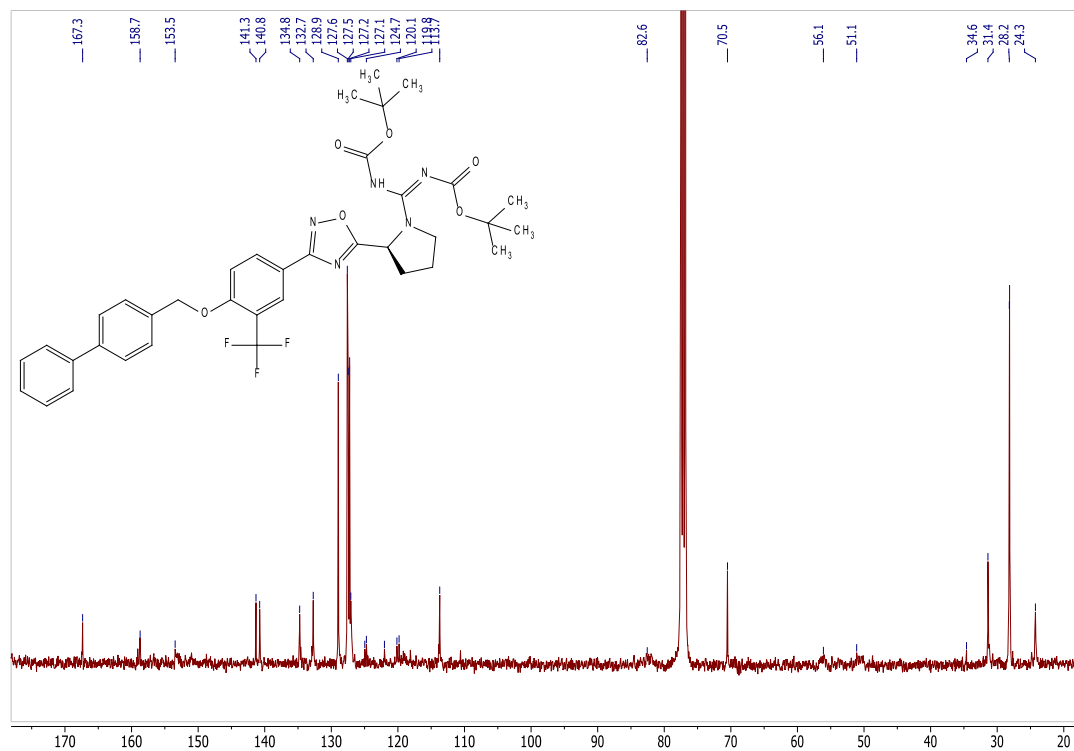
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31f** -



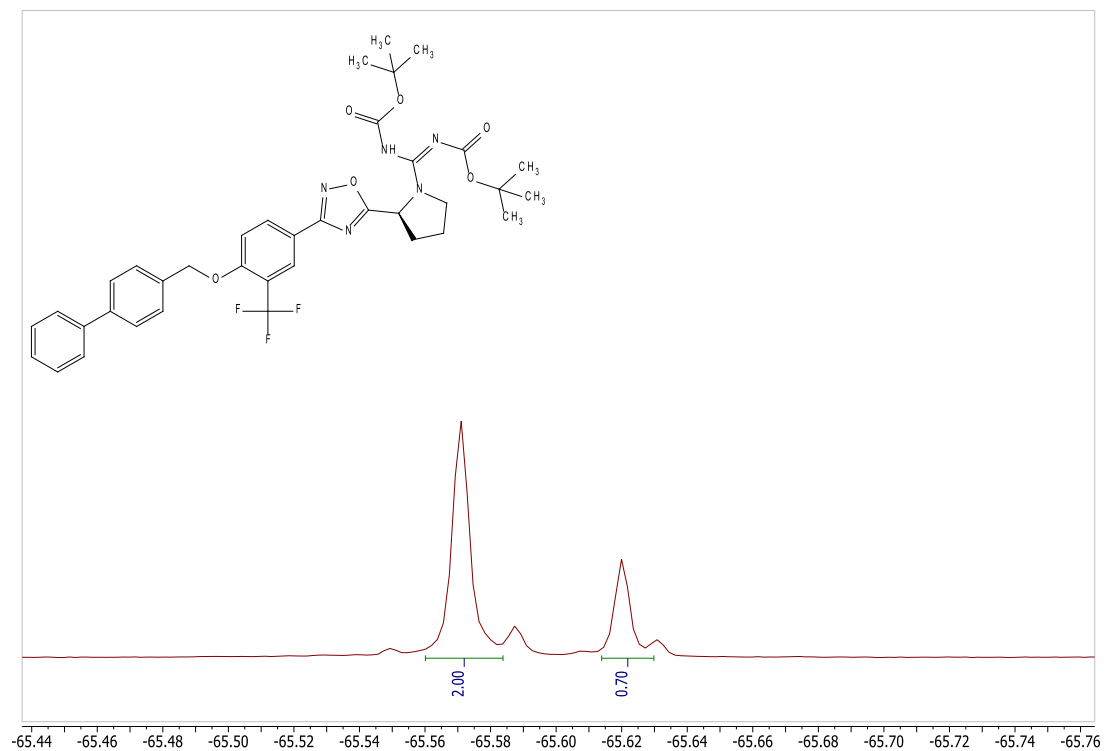
<sup>1</sup>H-NMR Spectrum for (S)-tert-butyl ((2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((tert-butoxycarbonyl)amino)methylene)carbamate **3.31g** -



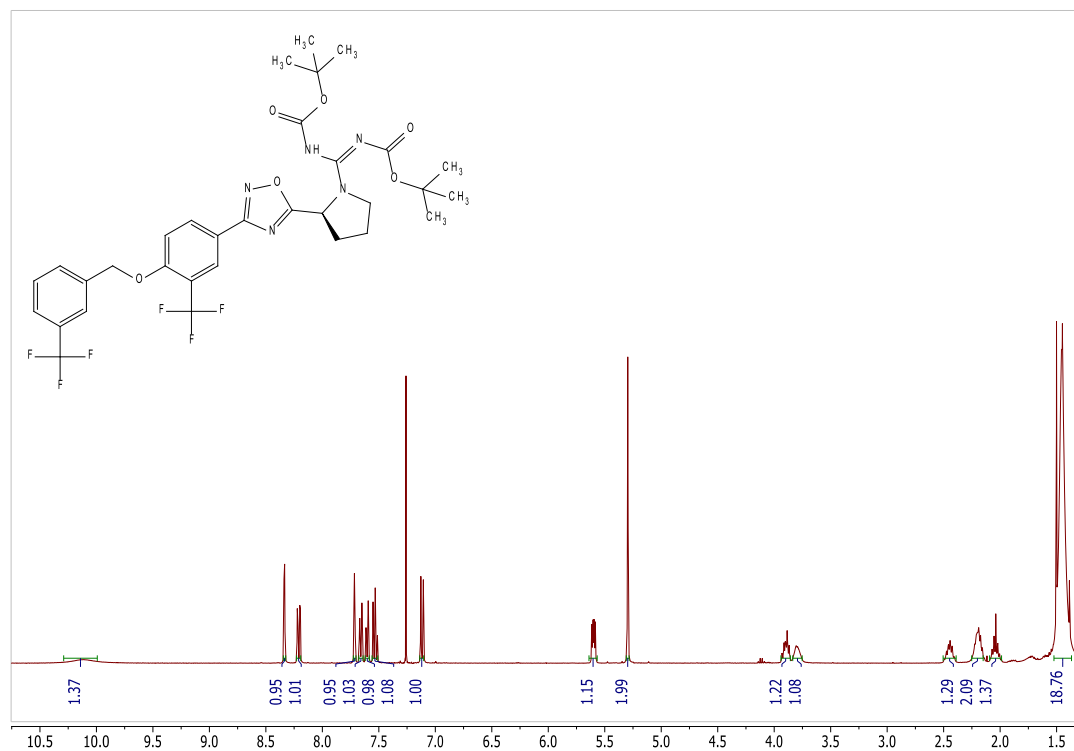
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31g** -



$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31g** -

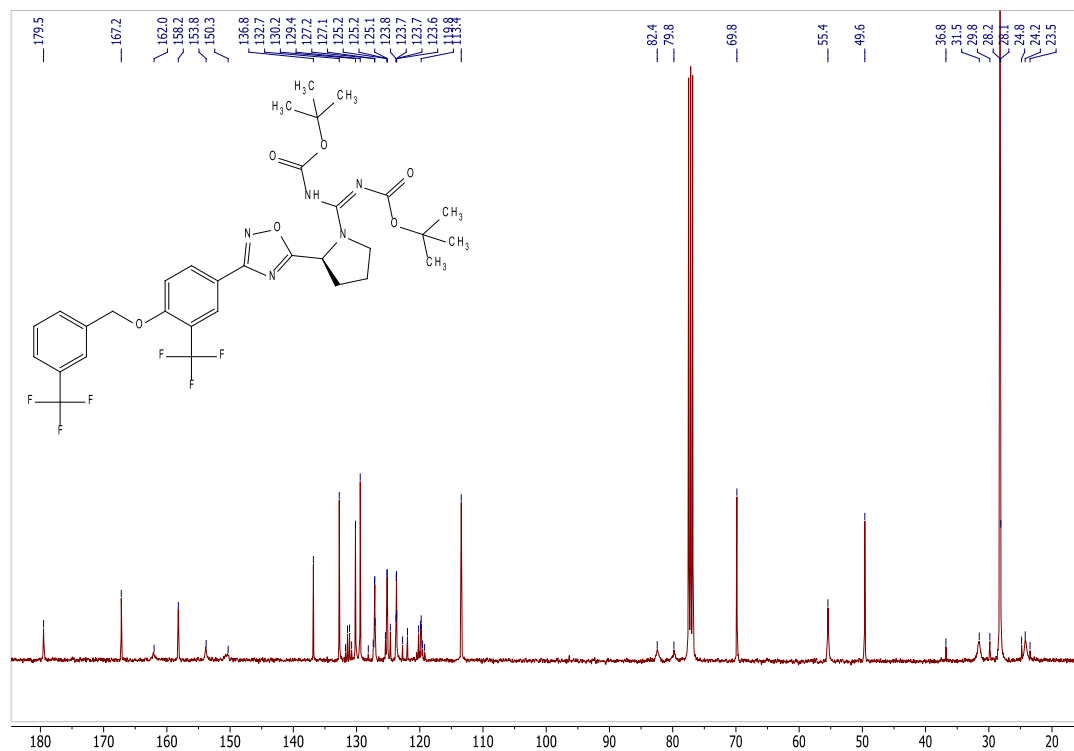


$^1\text{H-NMR}$  Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31h** -

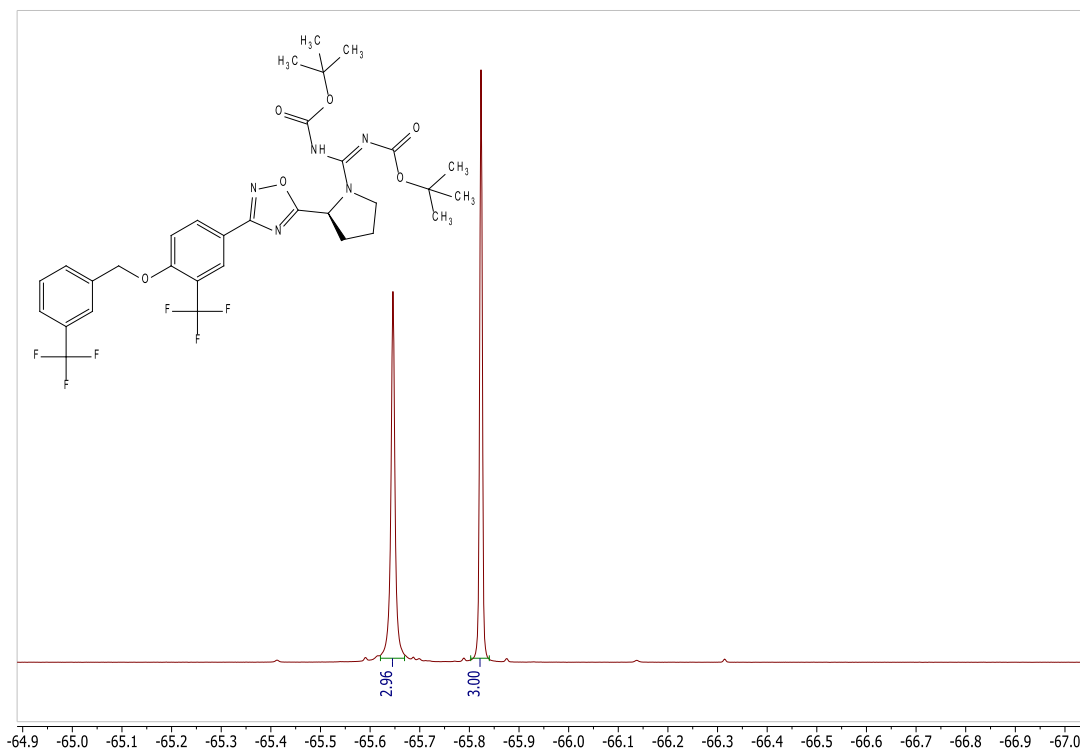




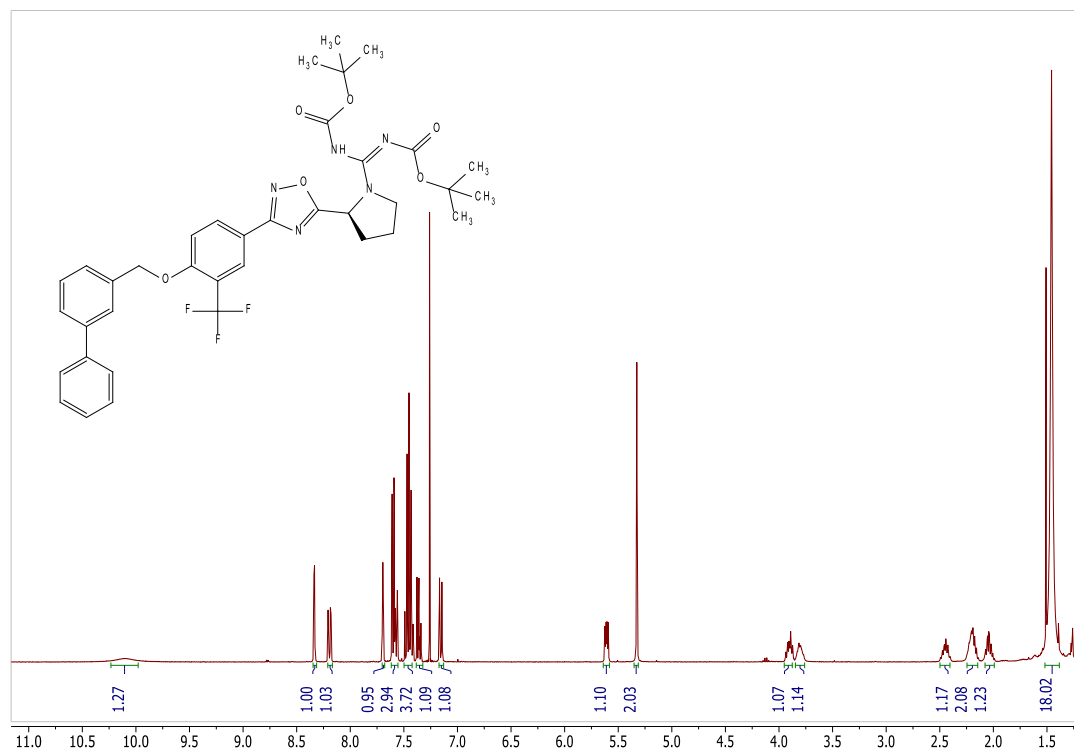
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31h** -



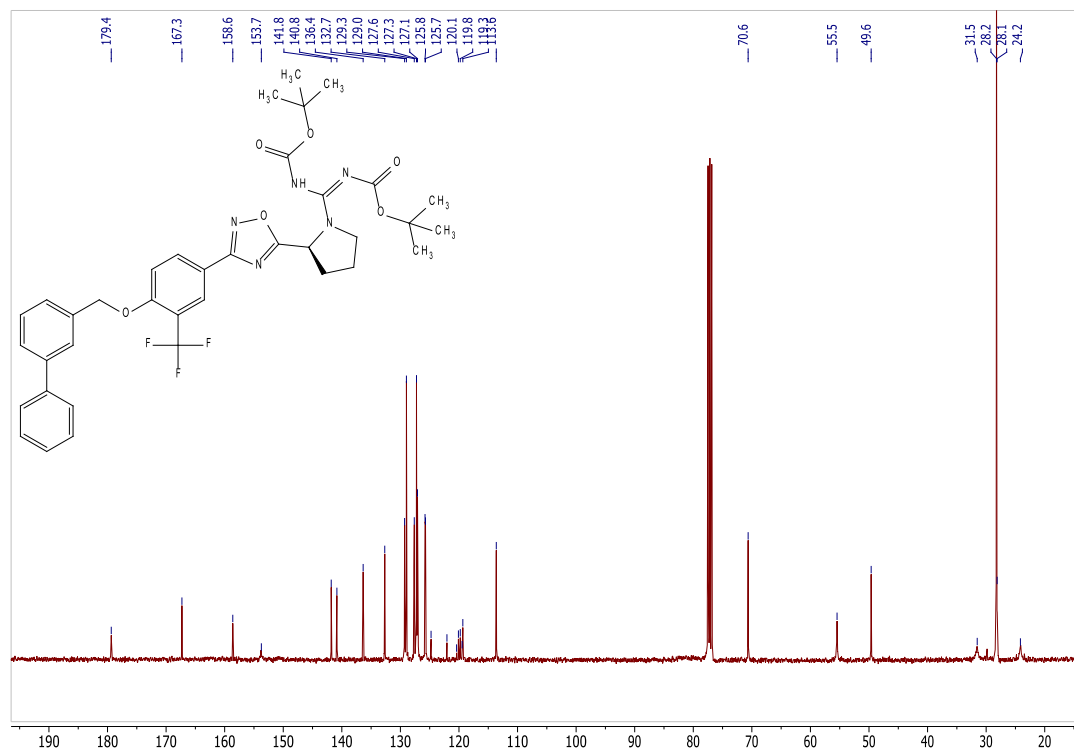
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31h** -



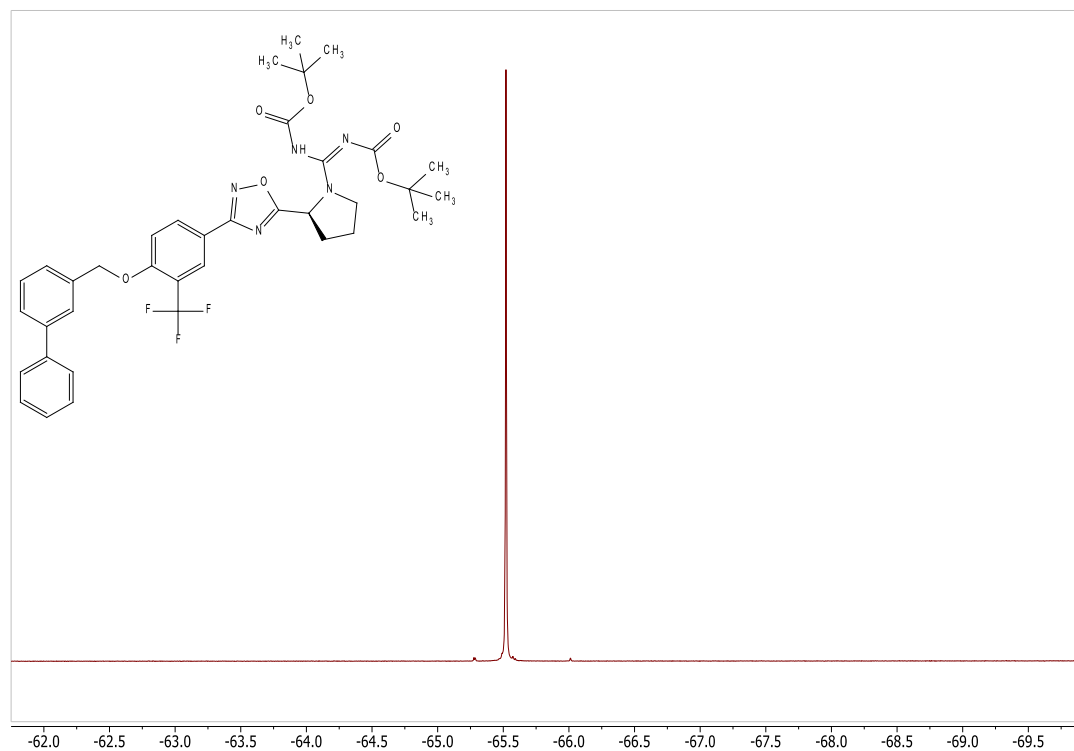
<sup>1</sup>H-NMR Spectrum for (S)-tert-butyl ((2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((tert-butoxycarbonyl)amino)methylene)carbamate **3.31i** -



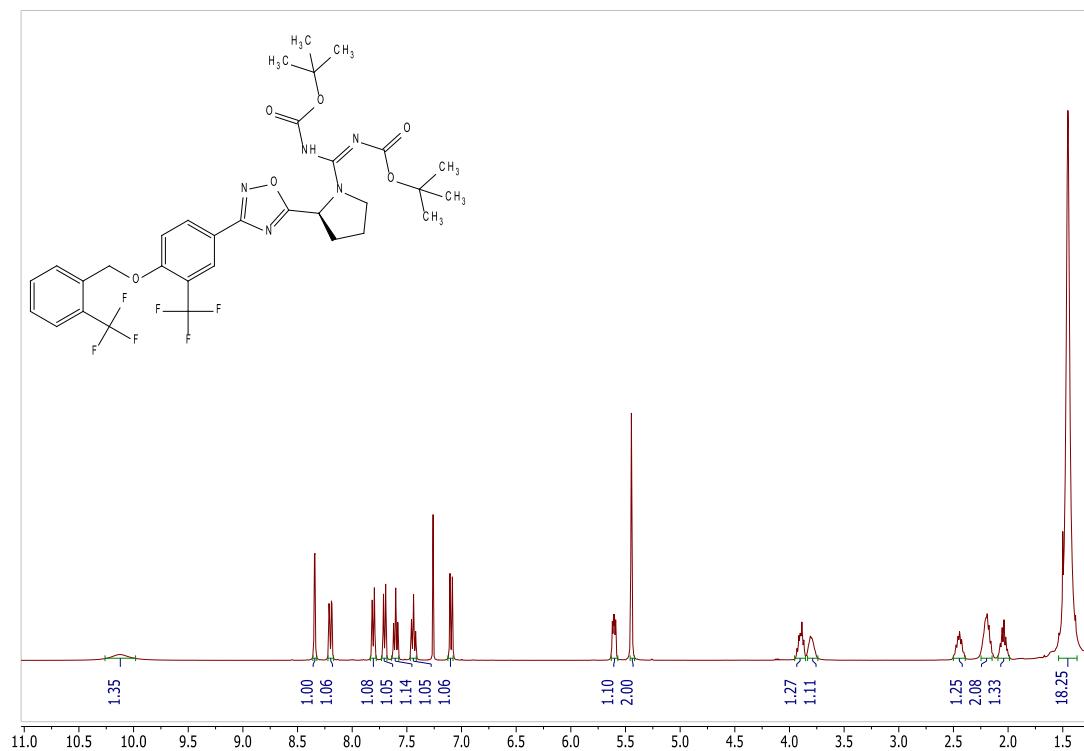
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31i** -



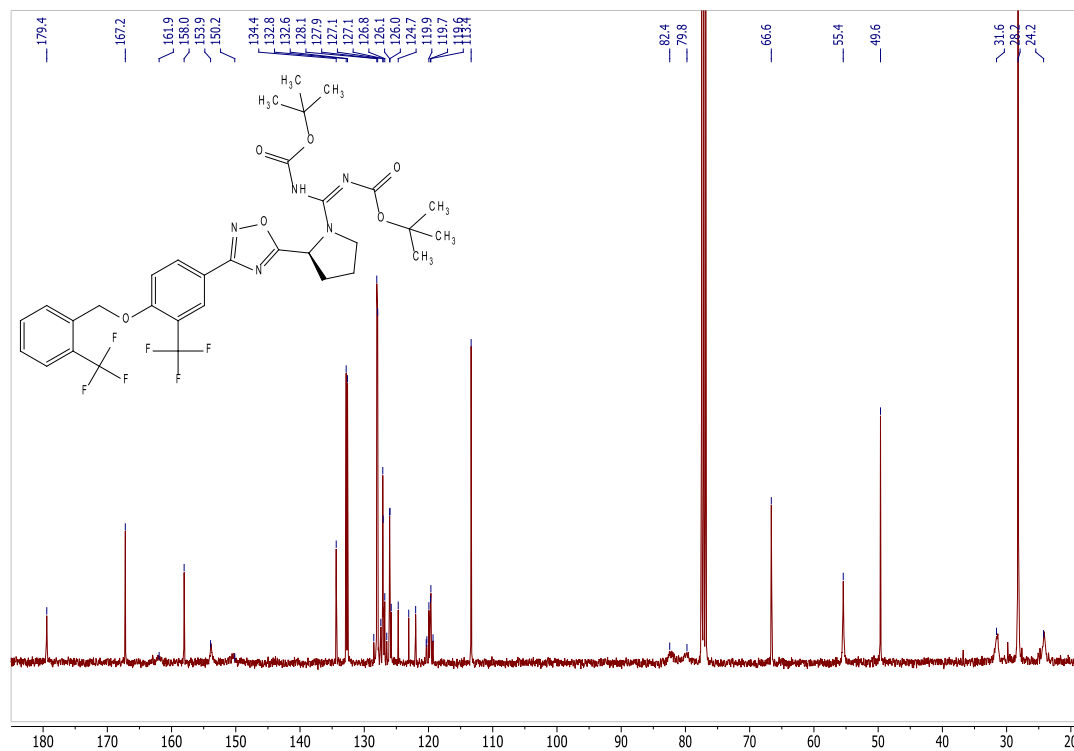
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31i** -



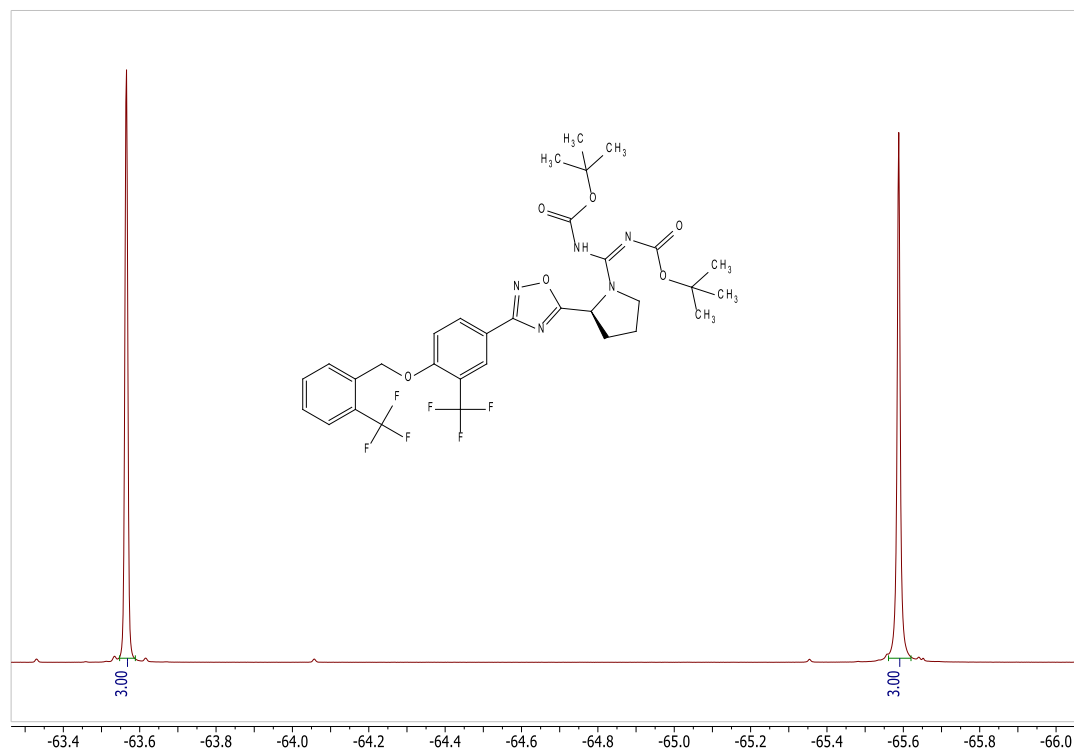
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31j** -



$^{13}\text{C}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31j** -

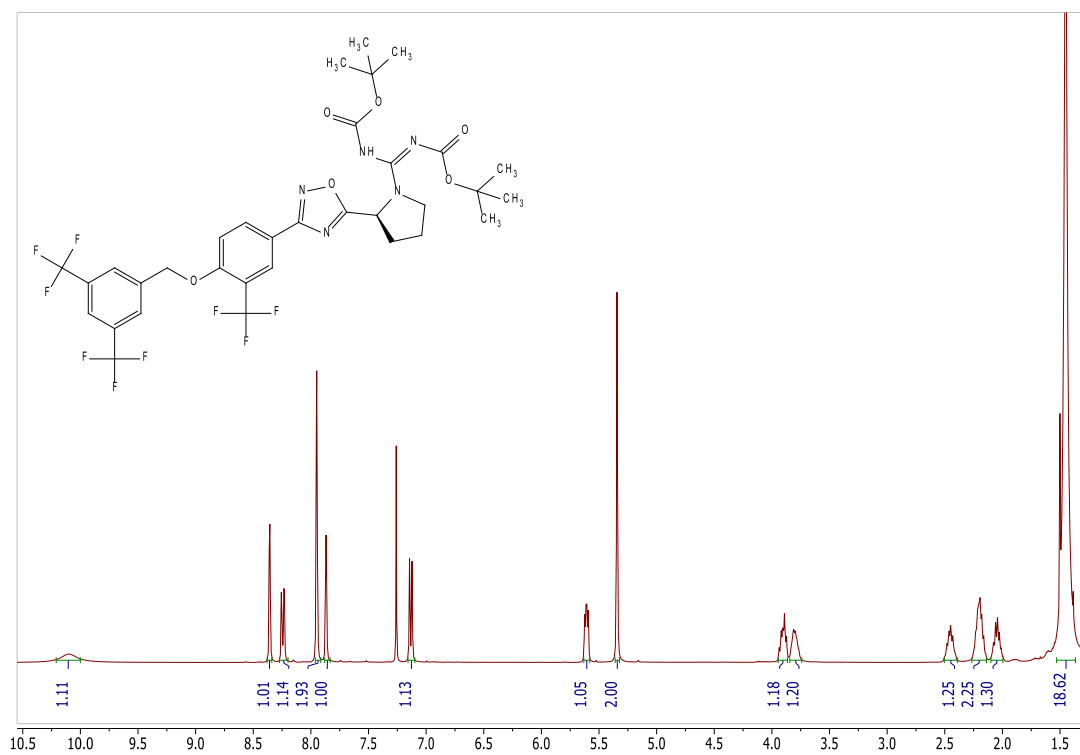


$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31j** -

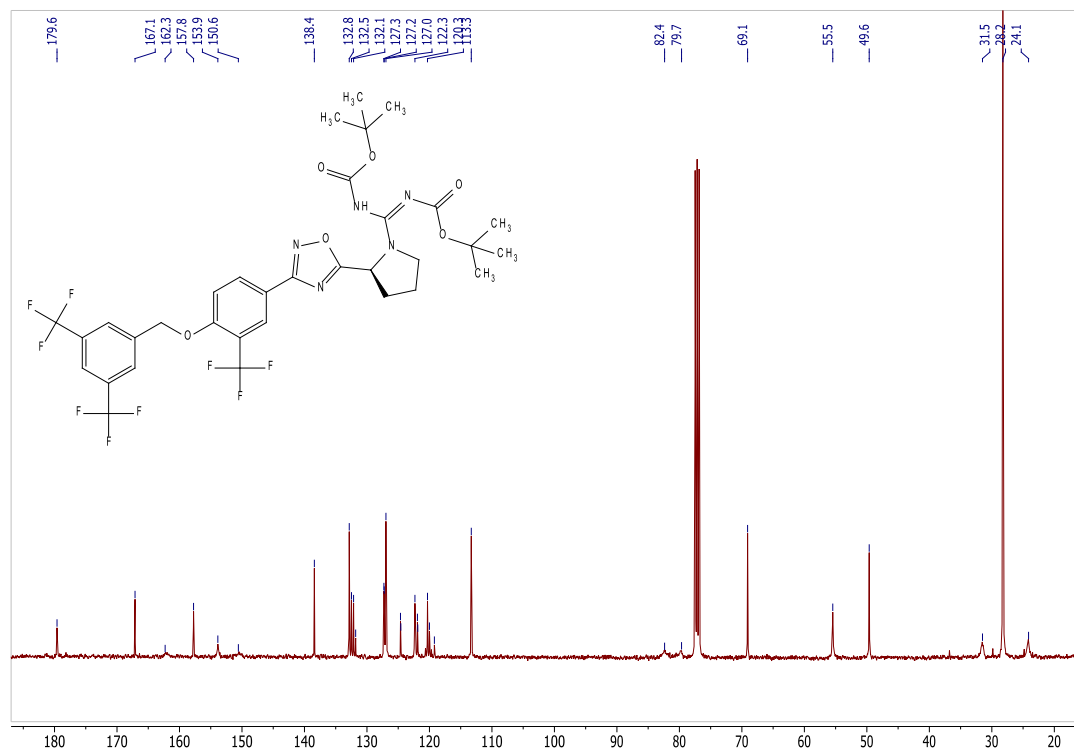




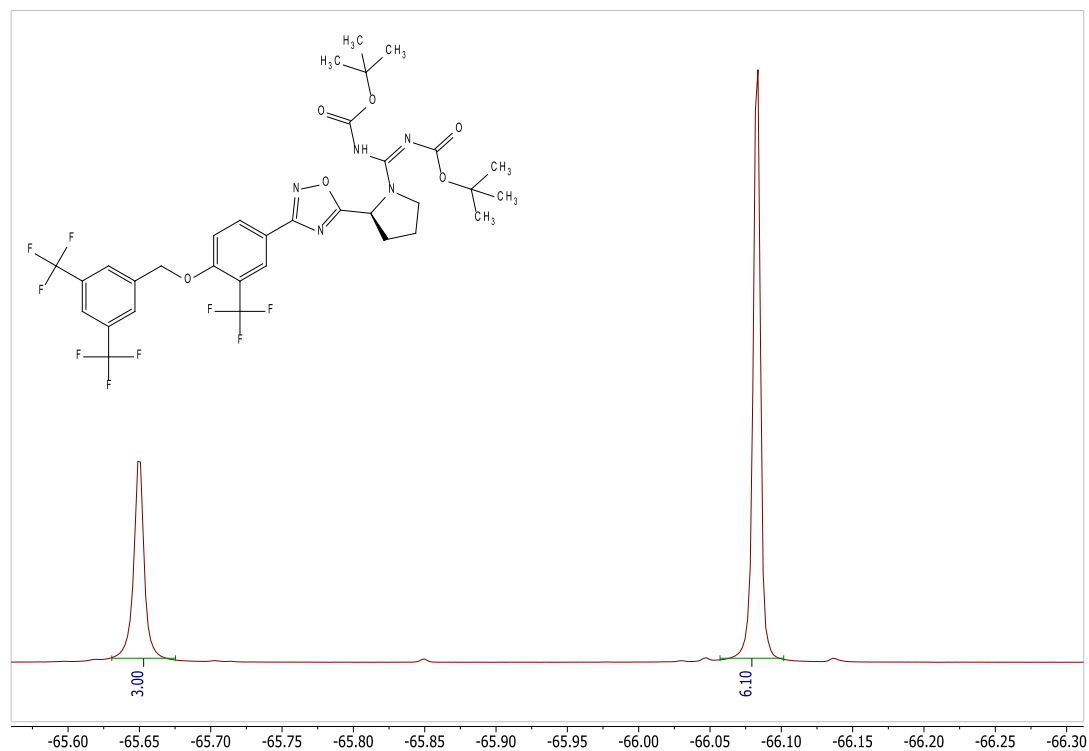
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31k** -



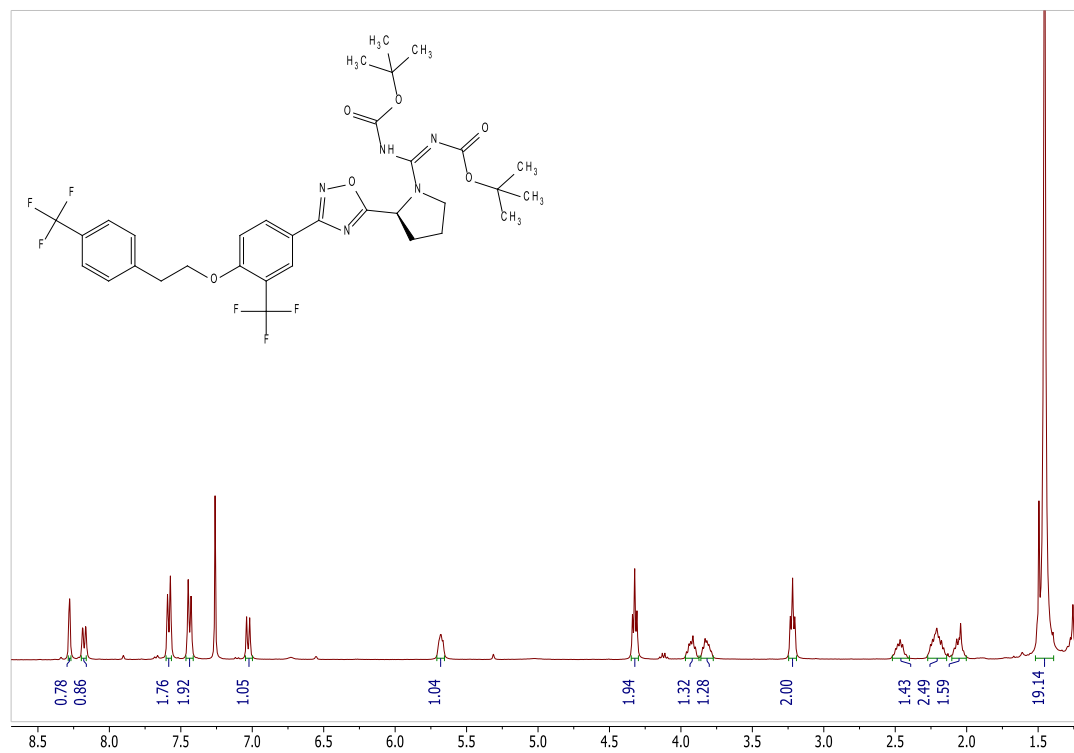
$^{13}\text{C}$ -NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31k** -



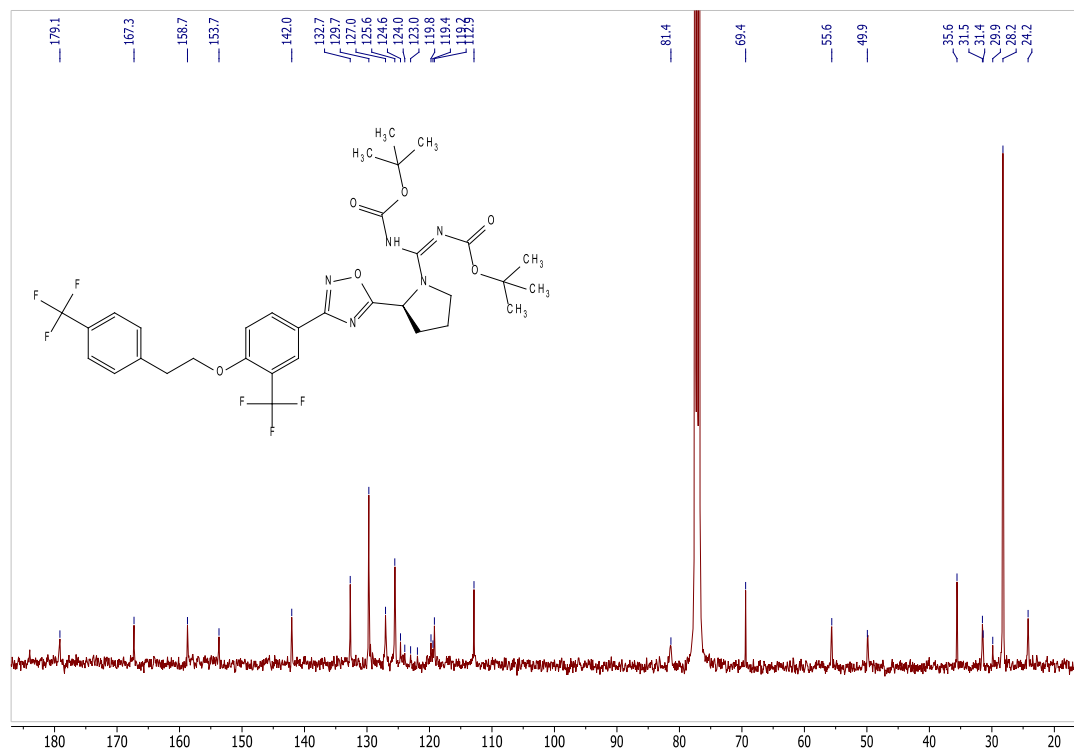
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl ((2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)((*tert*-butoxycarbonyl)amino)methylene)carbamate **3.31k** -



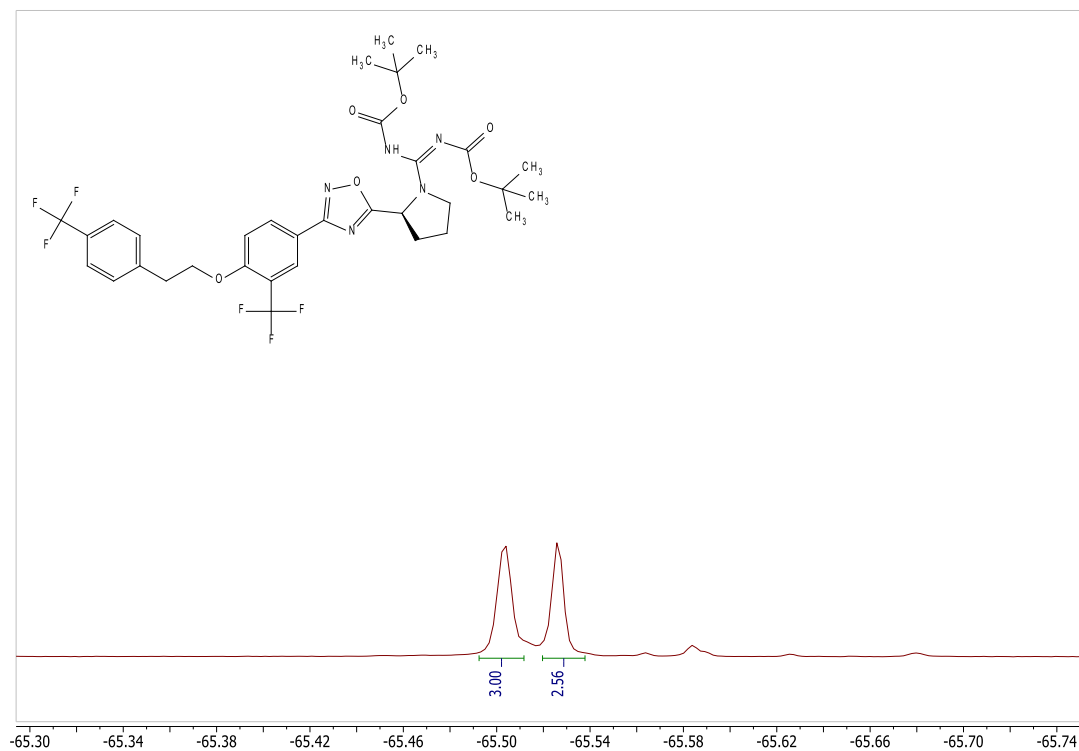
<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.311** -



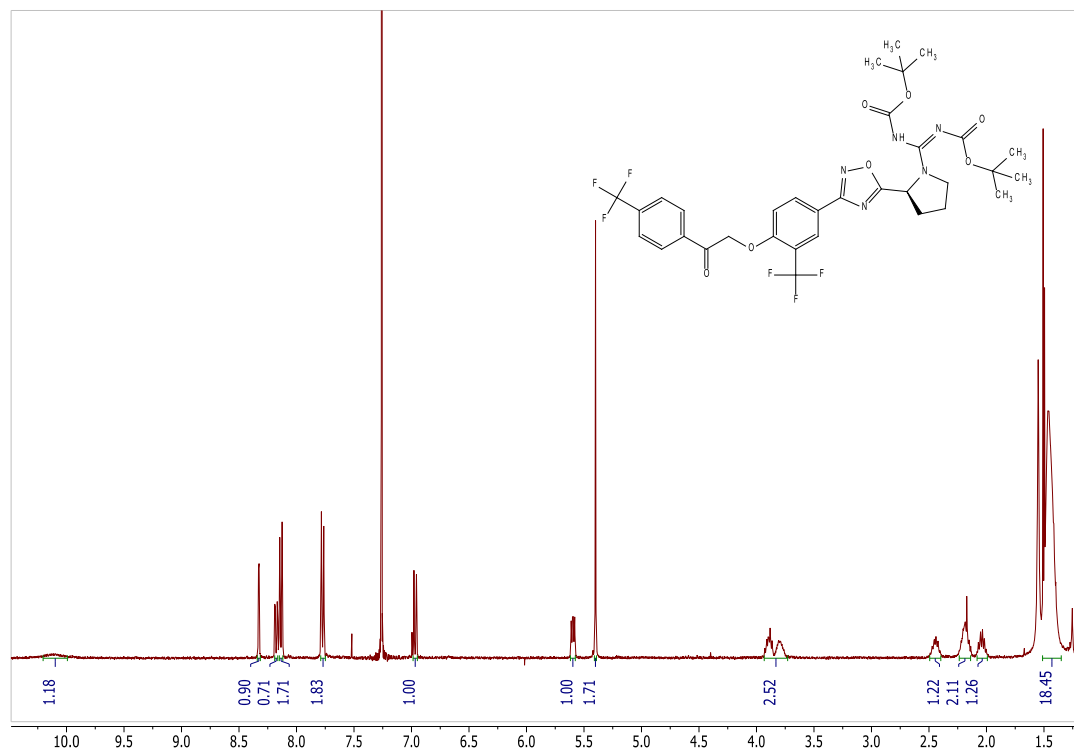
$^{13}\text{C}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.311** -



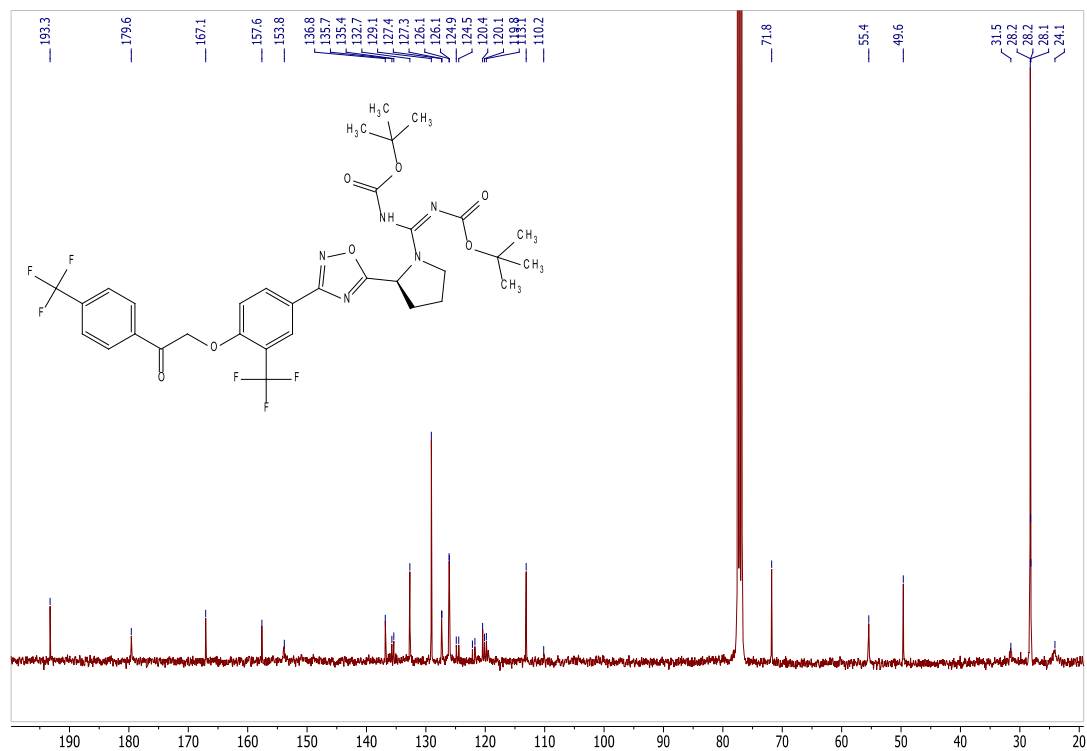
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.311** -



<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31m** -

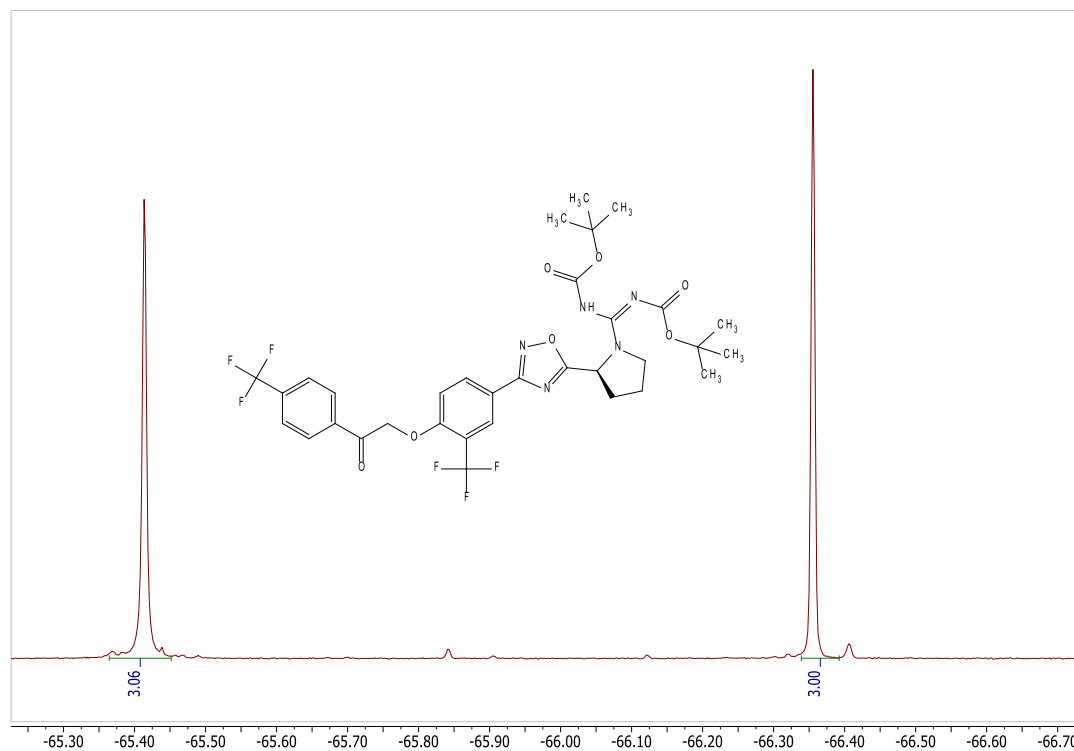


$^{13}\text{C}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31m** -

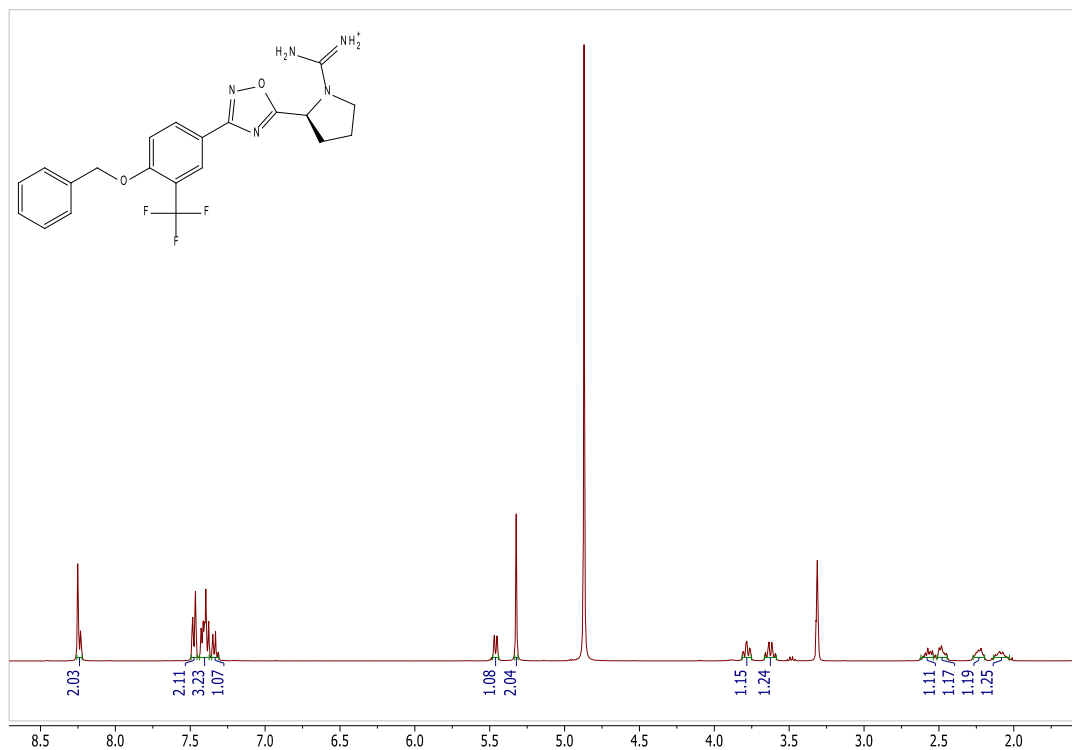




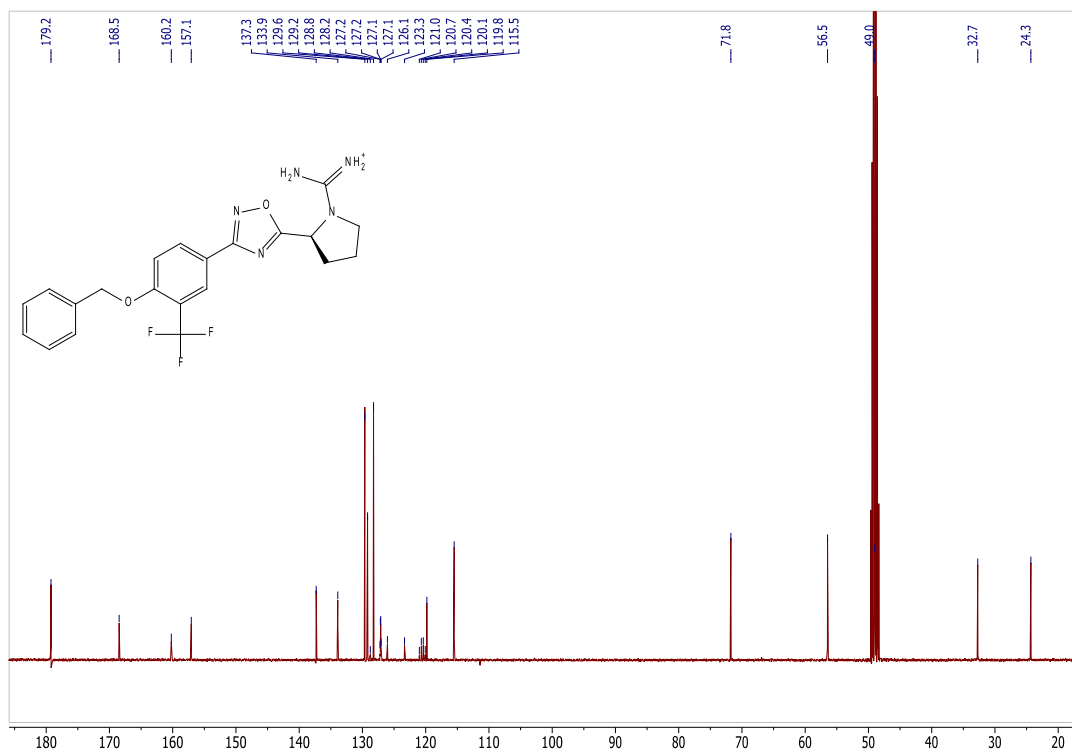
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate **3.31m** -



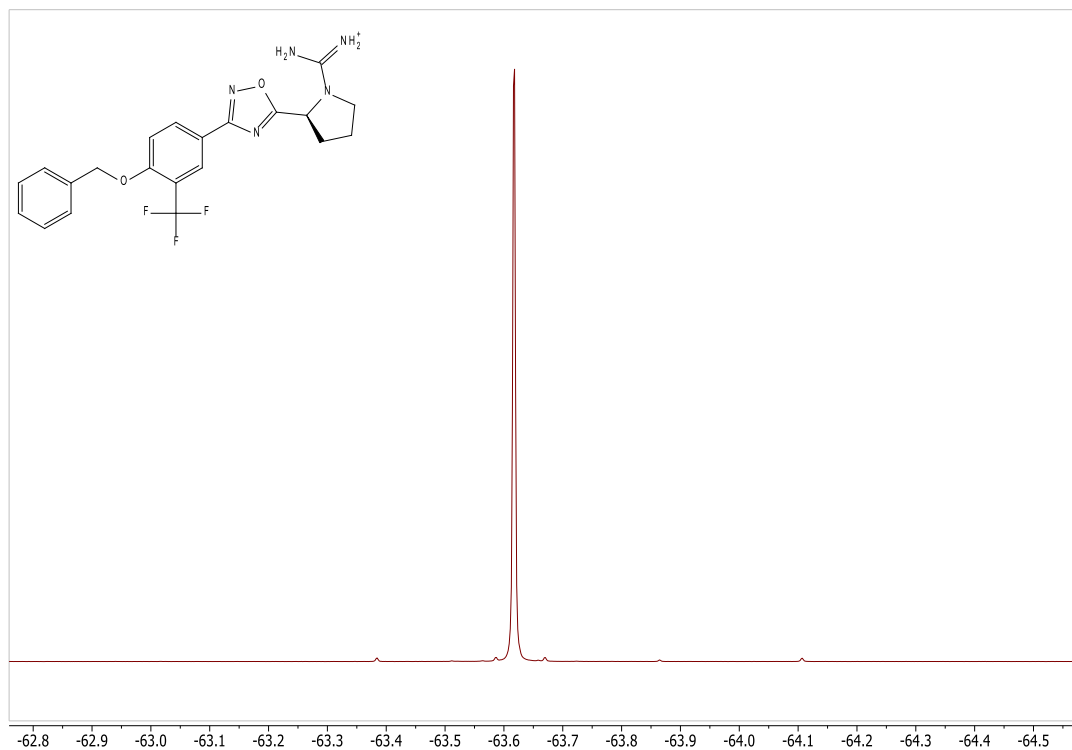
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32a** -



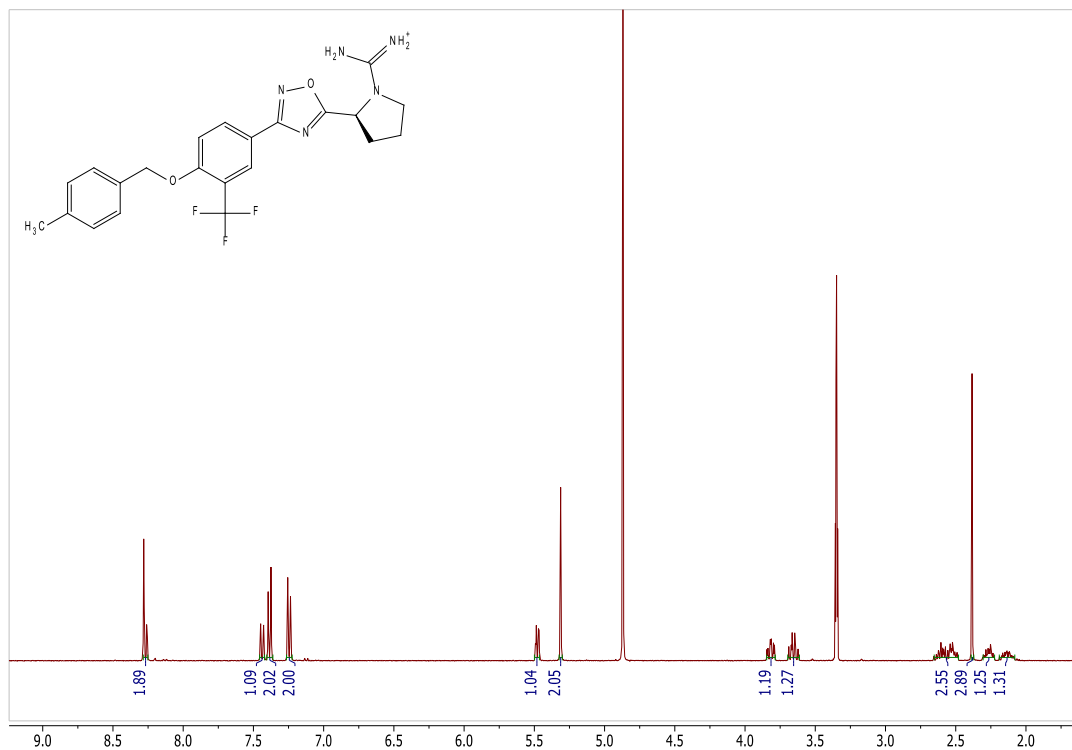
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32a** -



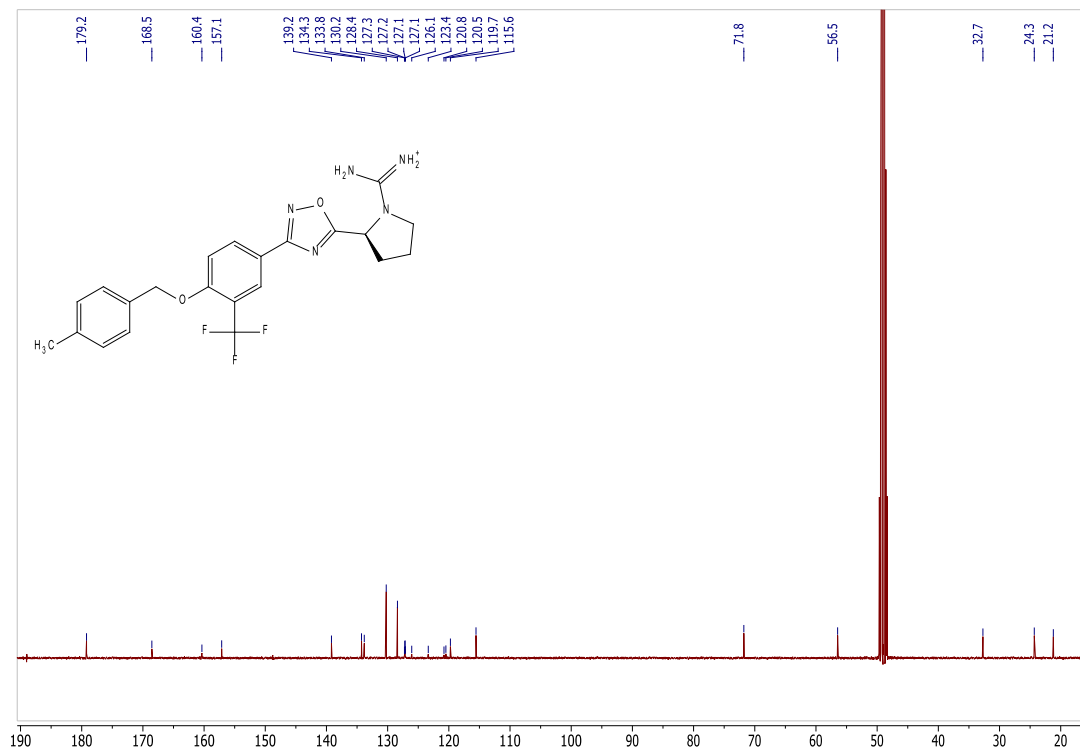
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32a** -



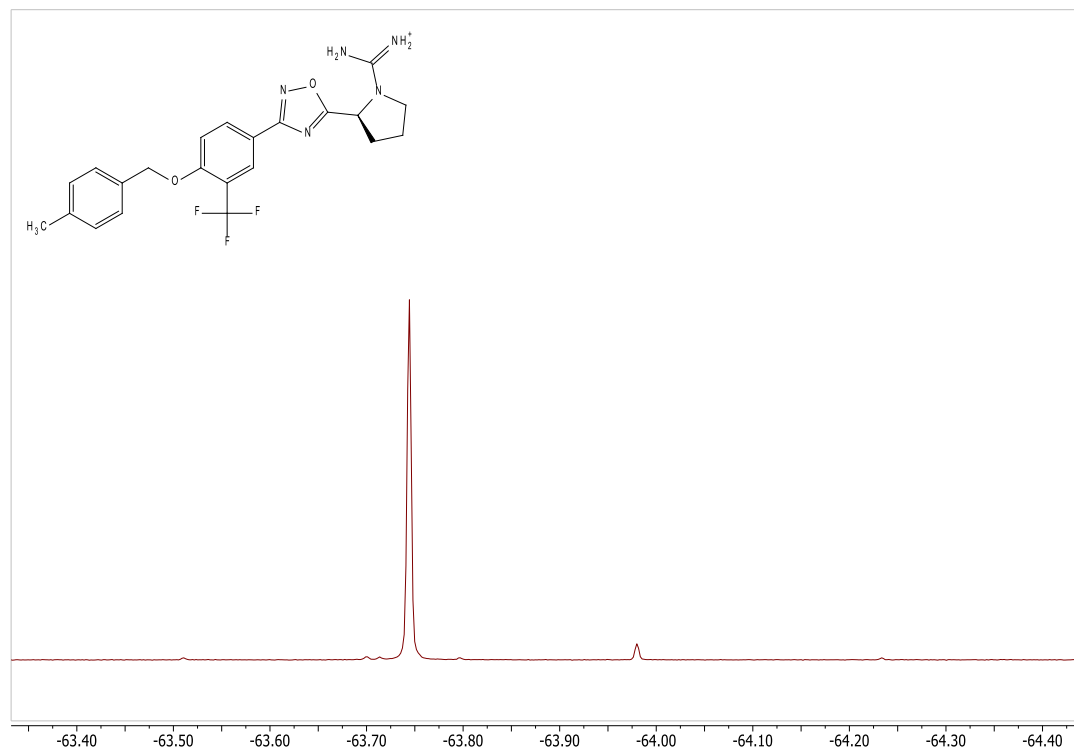
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32b** –



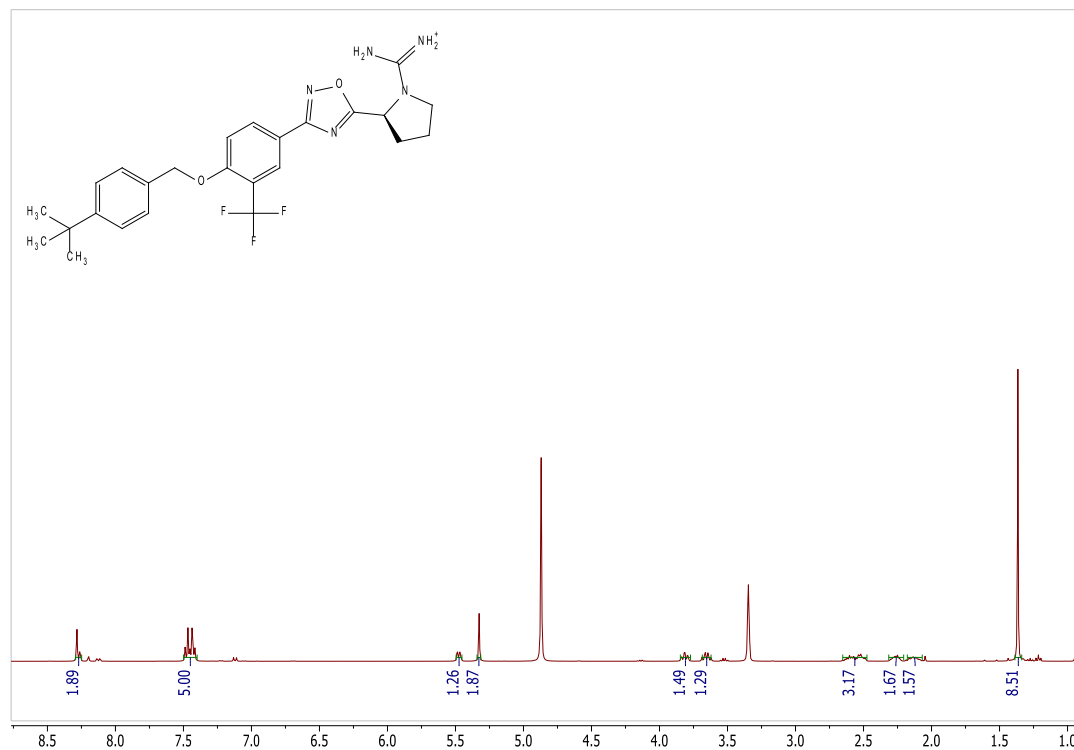
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32b** -



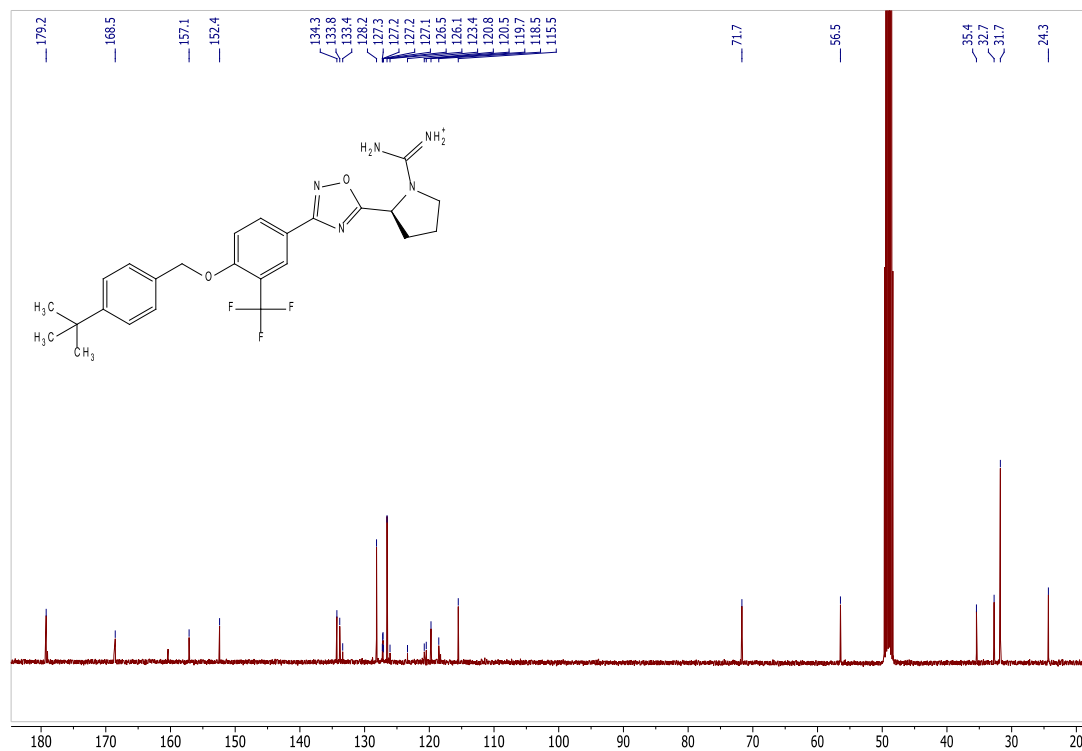
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-((4-methylbenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32b** -



<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-((*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32c** -

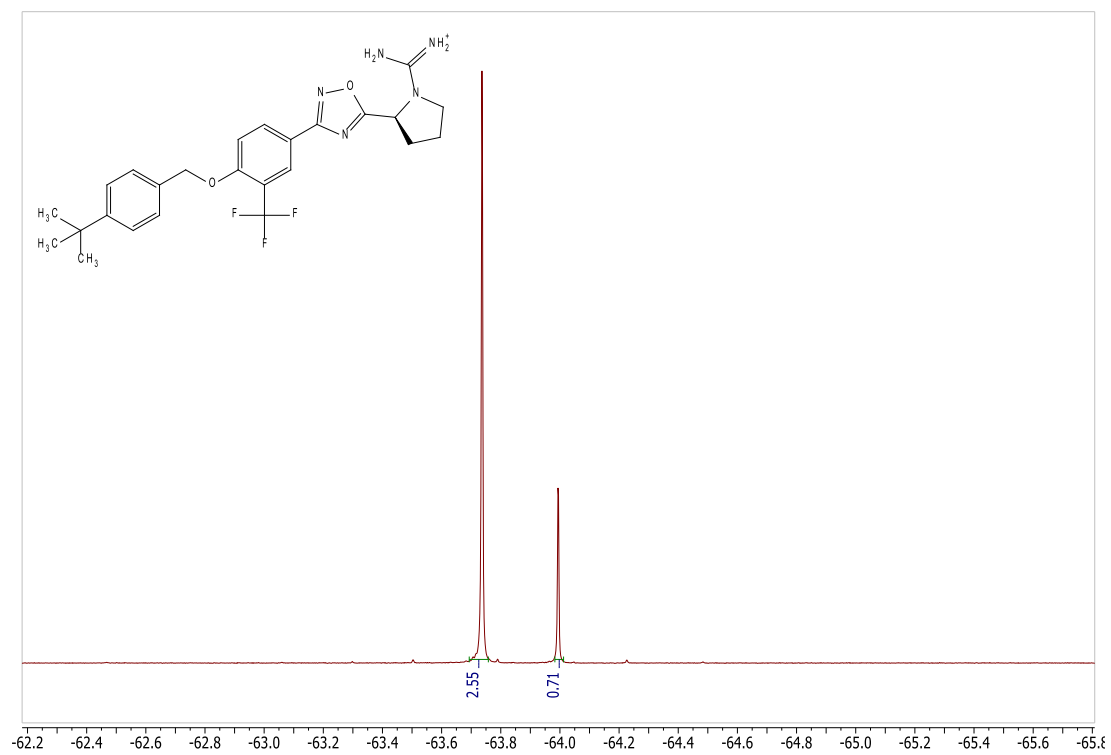


<sup>13</sup>C-NMR Spectrum for (S)-amino(2-(3-(4-((4-*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32c** –

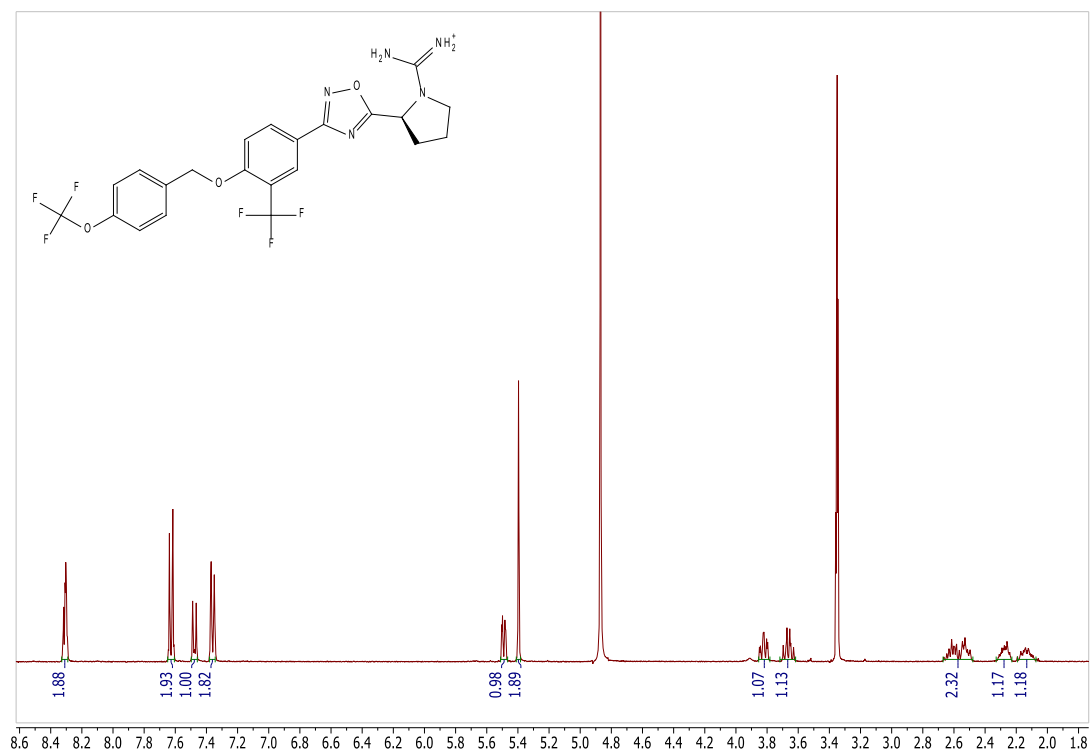




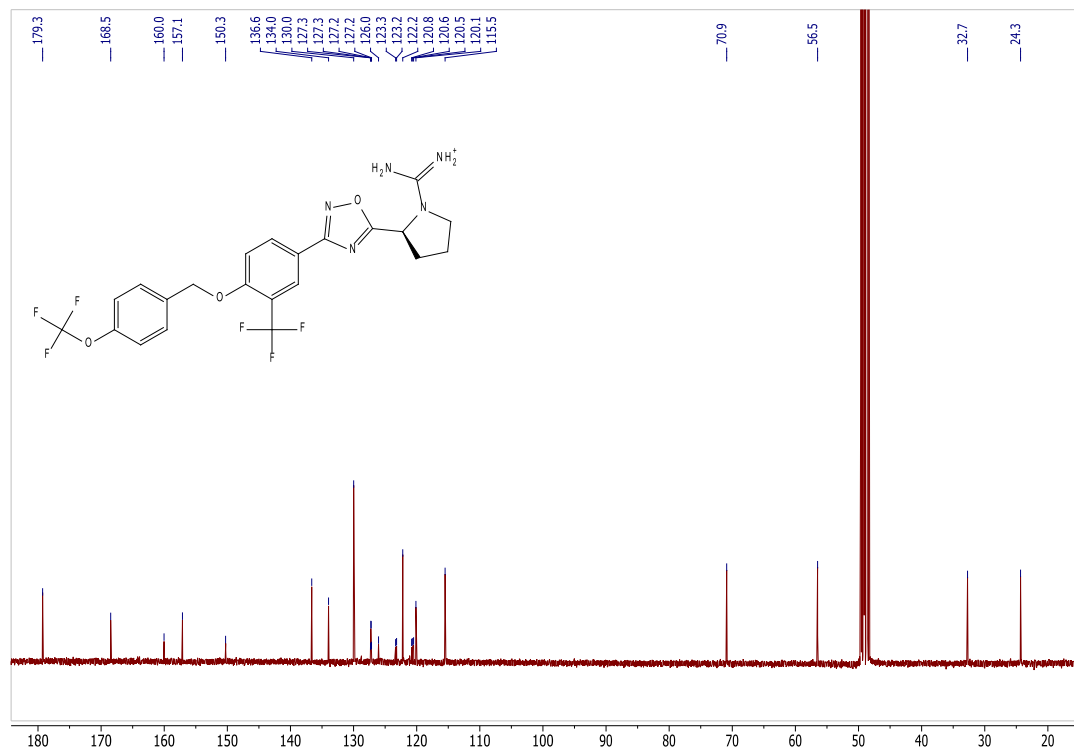
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-((4-*tert*-butyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32c** -



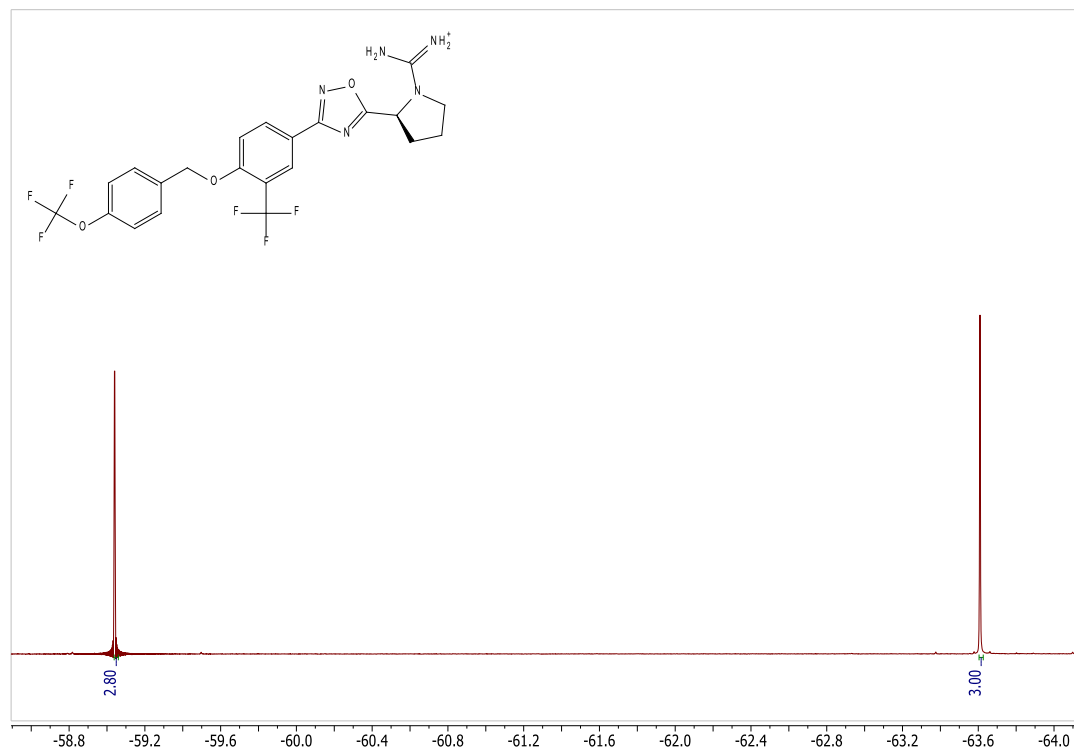
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32d** -



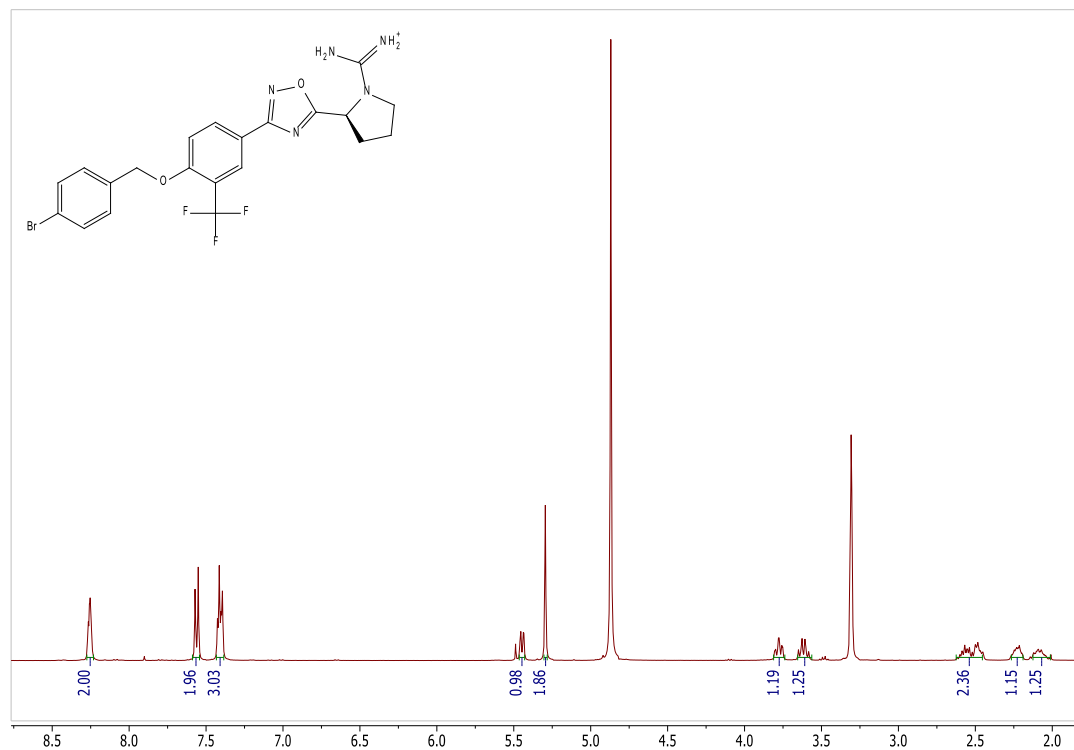
<sup>13</sup>C-NMR Spectrum for (S)-amino(2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32d** -



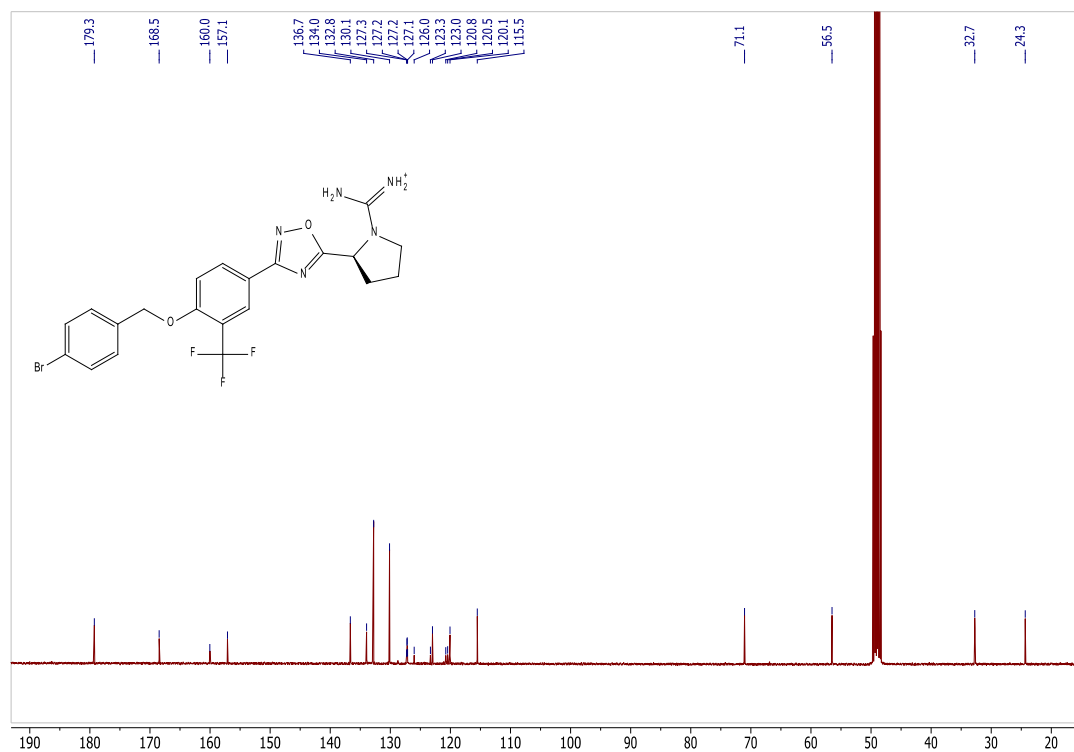
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-((4-(trifluoromethoxy)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32d** -



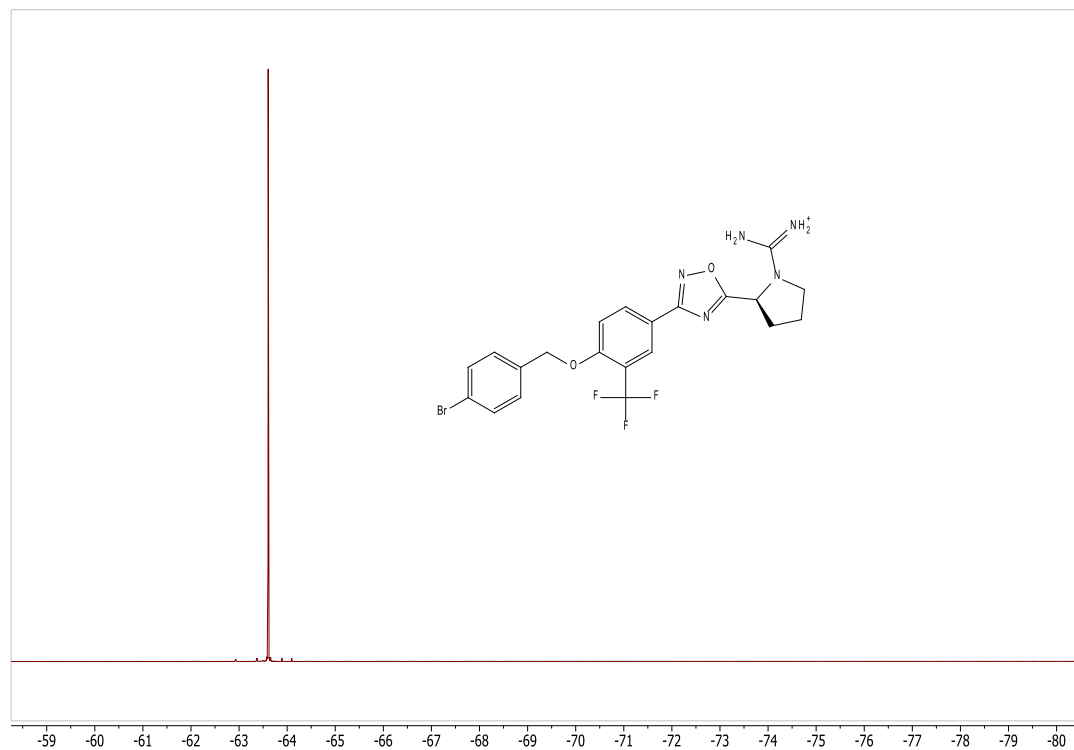
<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32e** -



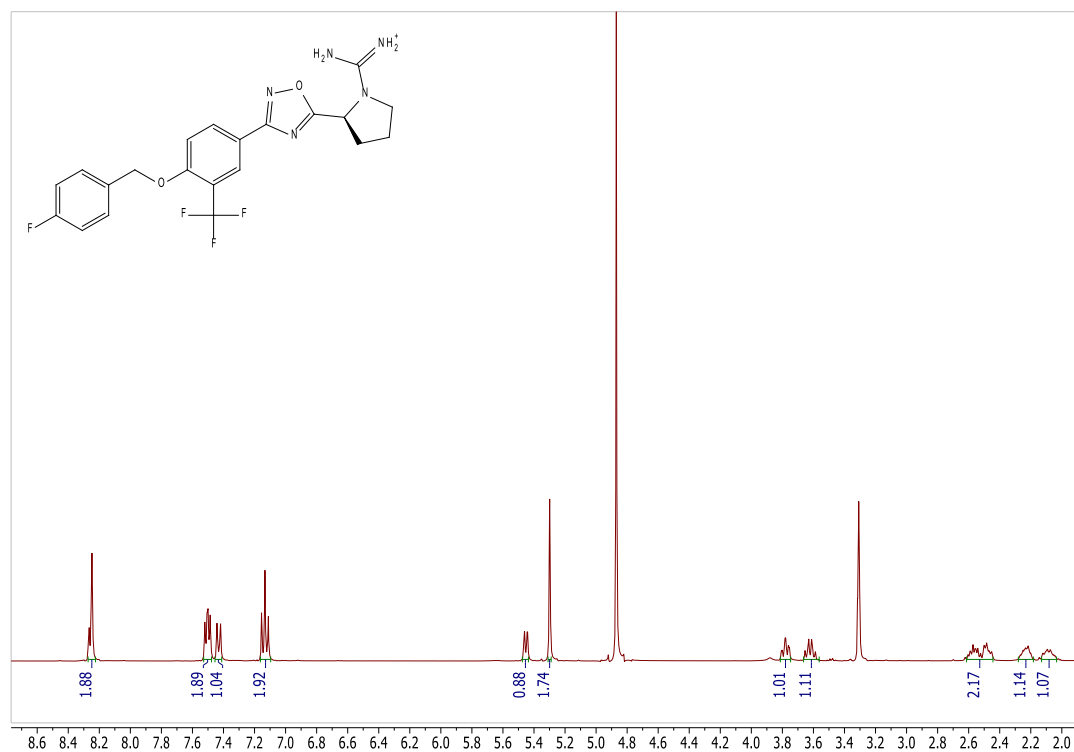
<sup>13</sup>C-NMR Spectrum for (*S*)-amino(2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32e** -



$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-((4-bromobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32e** -

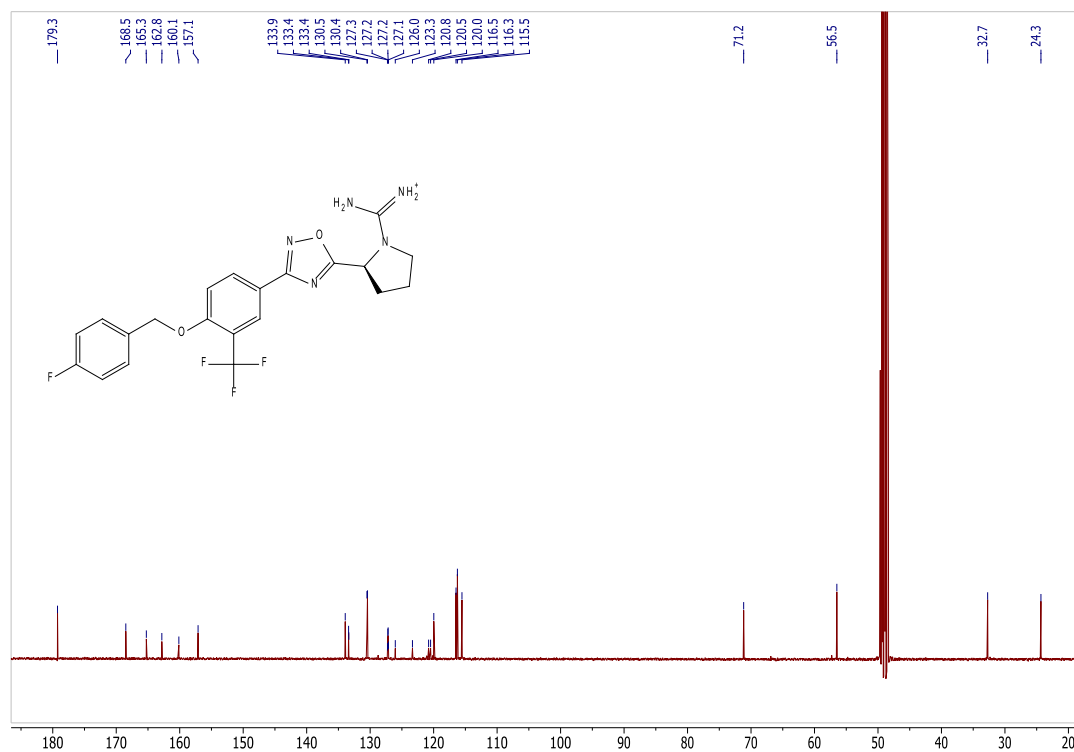


<sup>1</sup>H-NMR Spectrum for (*S*)-amino(2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32f** -

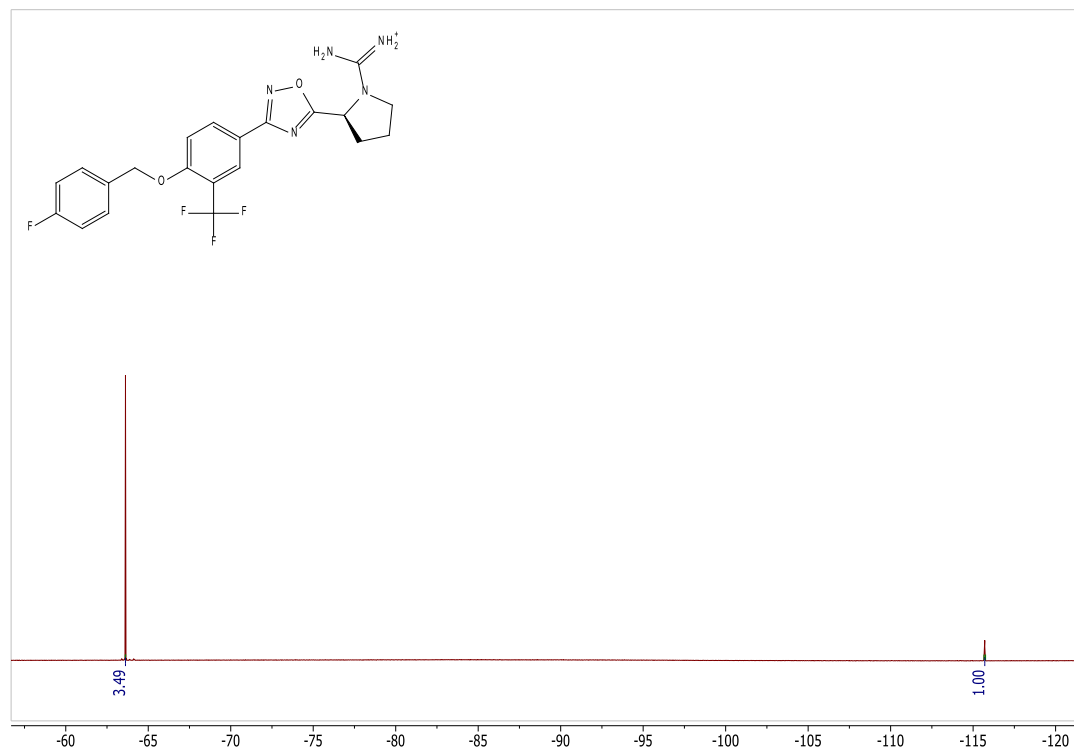




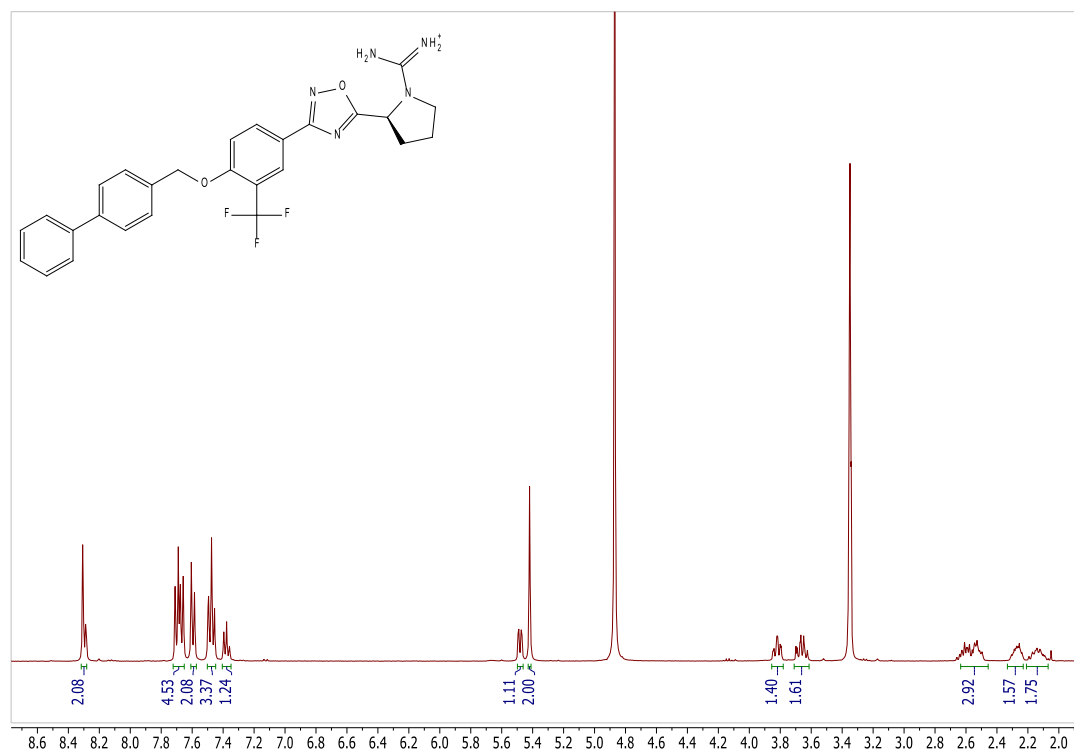
<sup>13</sup>C-NMR Spectrum for (S)-amino(2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32f** -



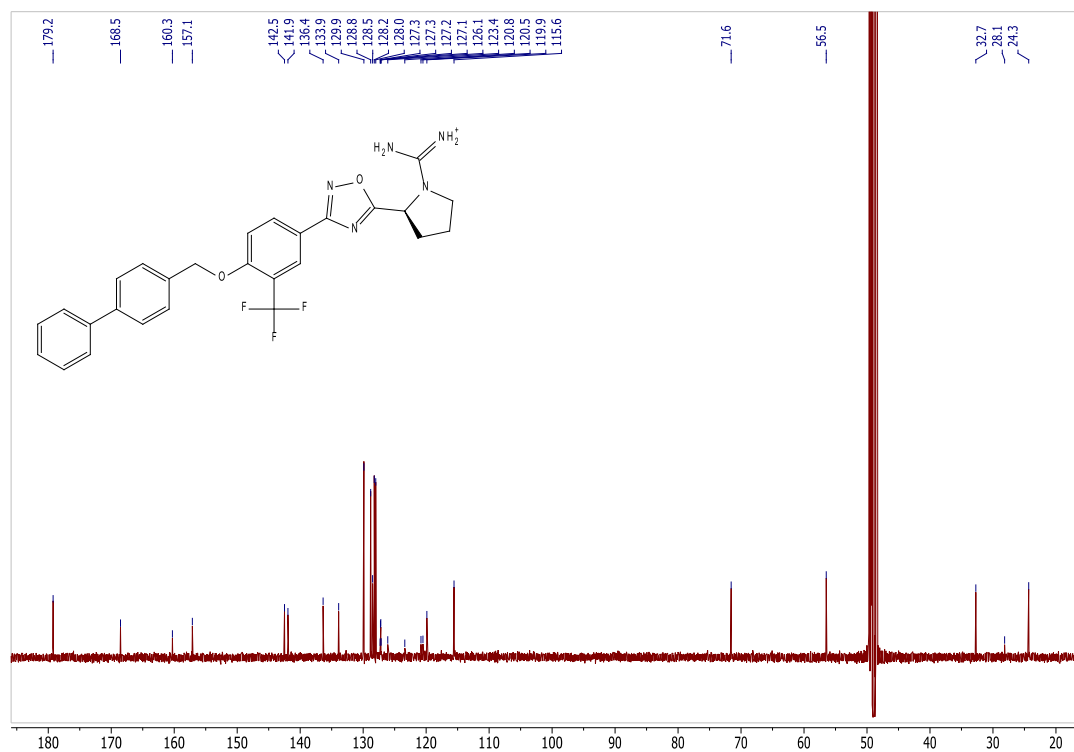
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-((4-fluorobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32f** -



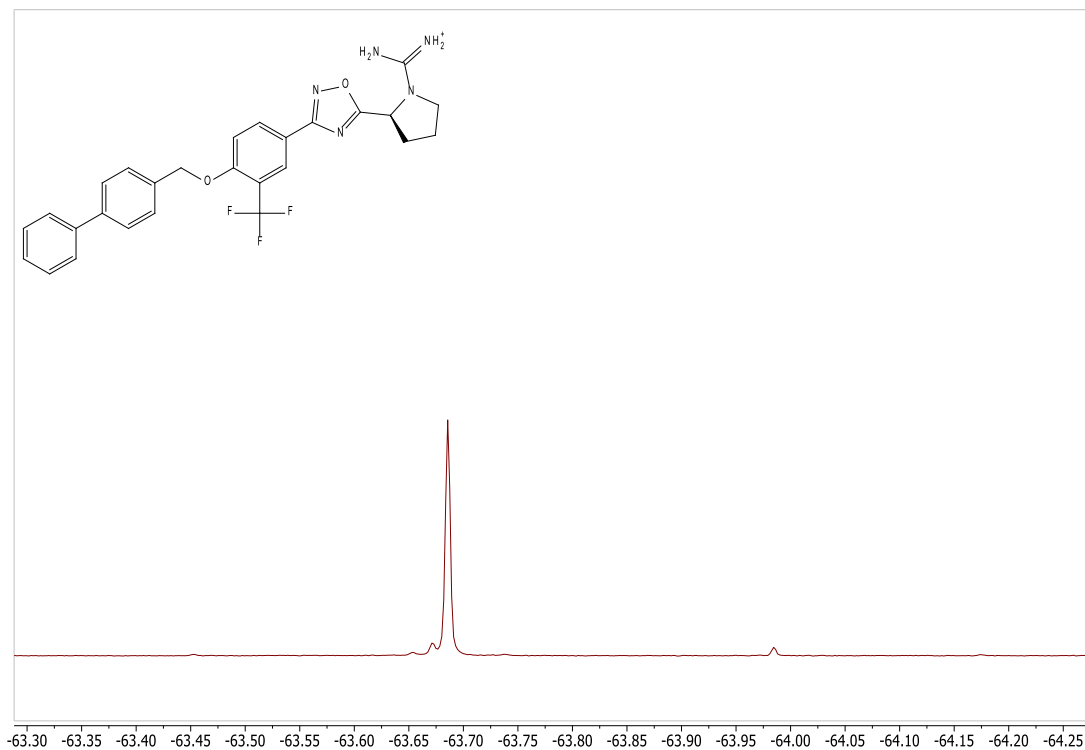
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)(amino)methaniminium 2,2,2-trifluoroacetate **3.32g** -



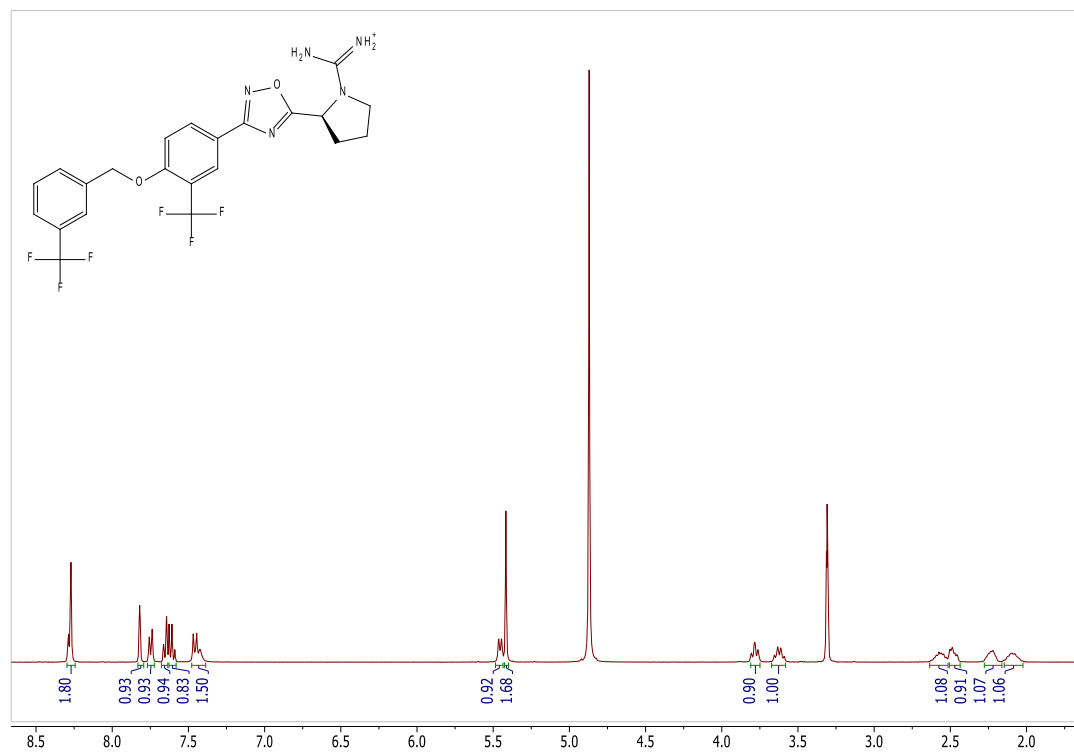
$^{13}\text{C}$ -NMR Spectrum for (*S*)-(2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)(amino)methaniminium 2,2,2-trifluoroacetate **3.32g** -



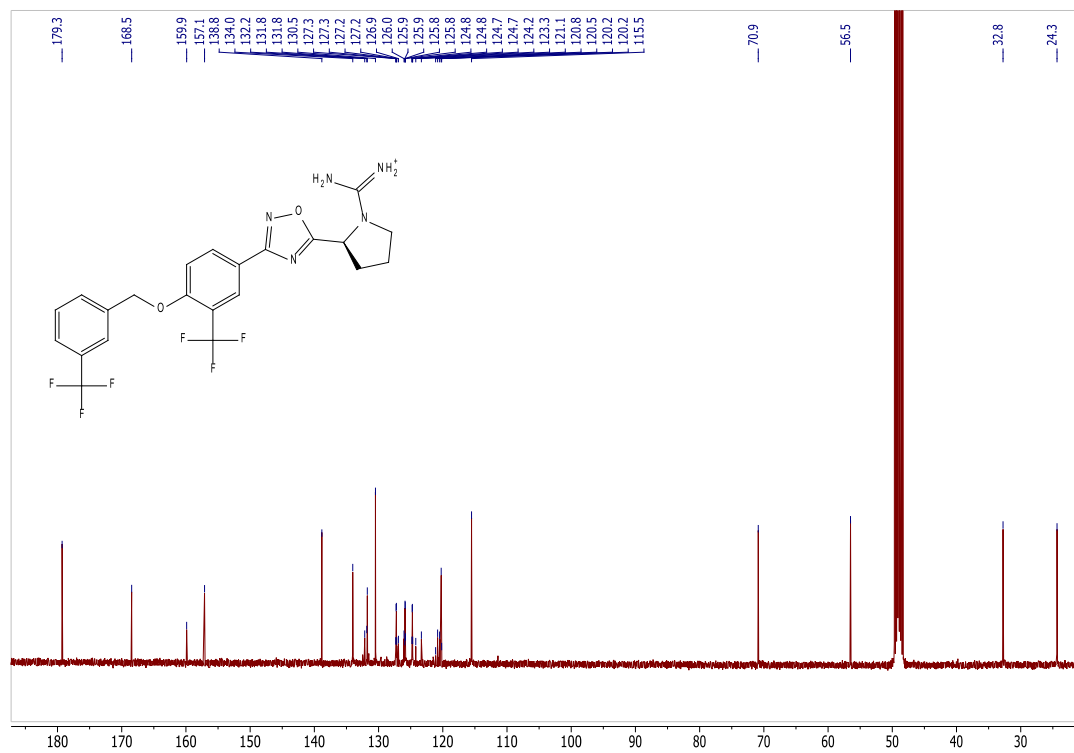
$^{19}\text{F}$ -NMR Spectrum for (*S*)-(2-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)(amino)methaniminium 2,2,2-trifluoroacetate **3.32g** -



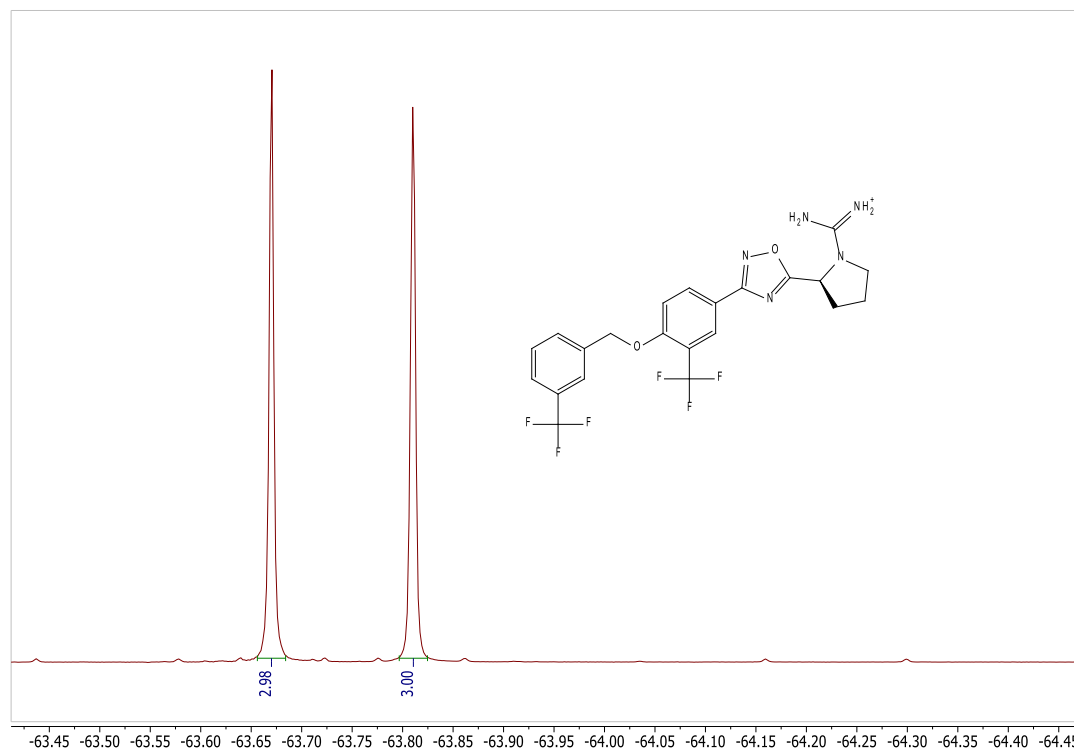
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32h** -



$^{13}\text{C}$ -NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32h** -

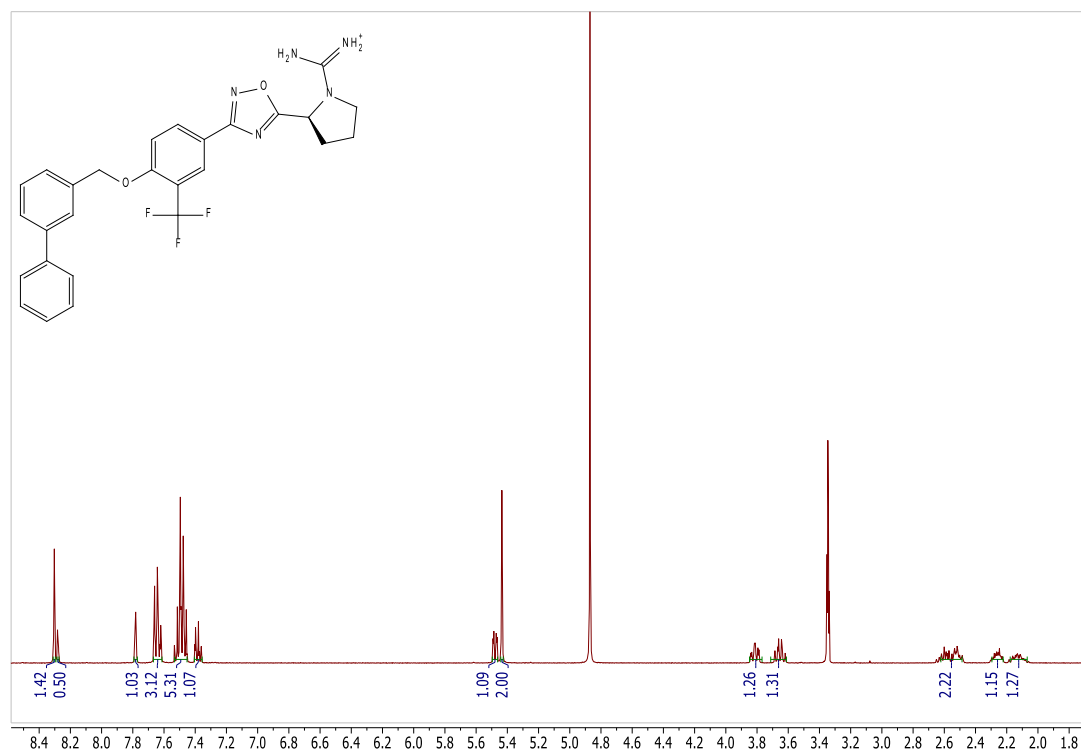


$^{19}\text{F}$ -NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-((3-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32h** -

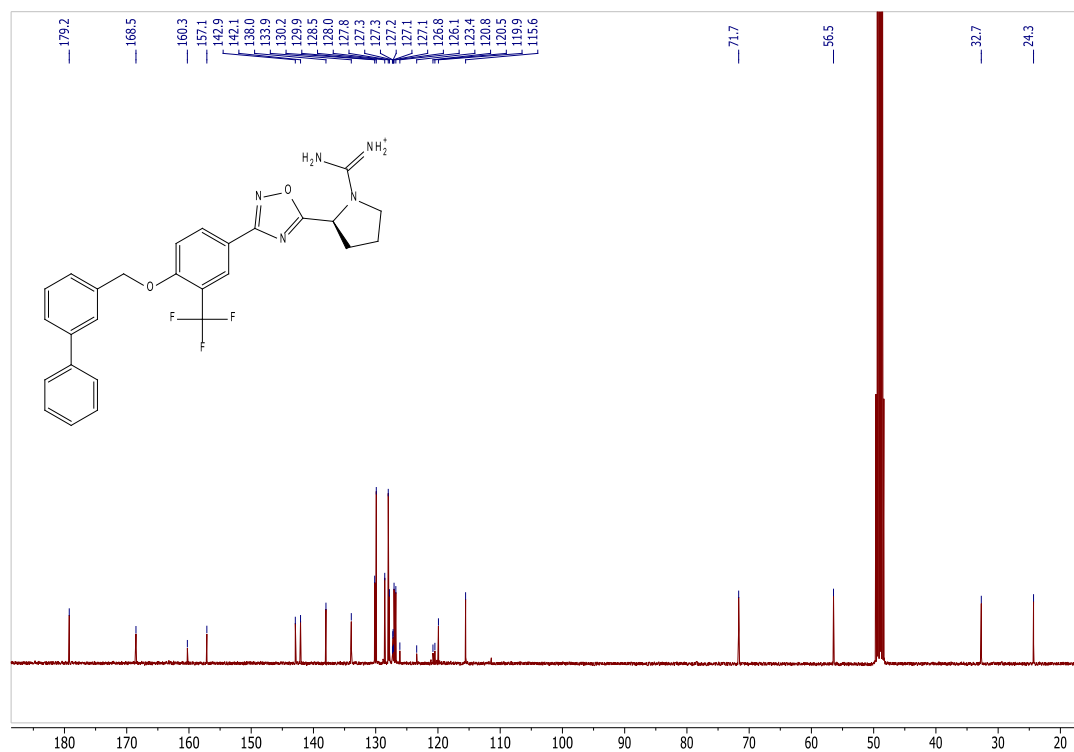




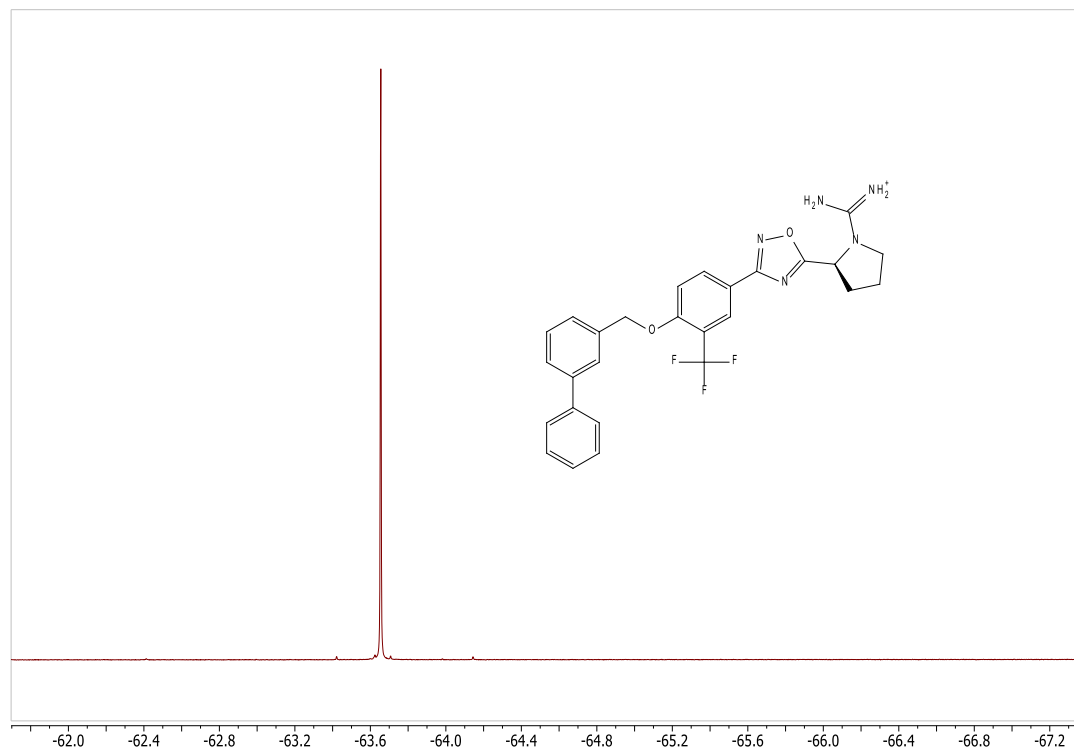
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)(amino)methaniminium 2,2,2-trifluoroacetate **3.32i** -



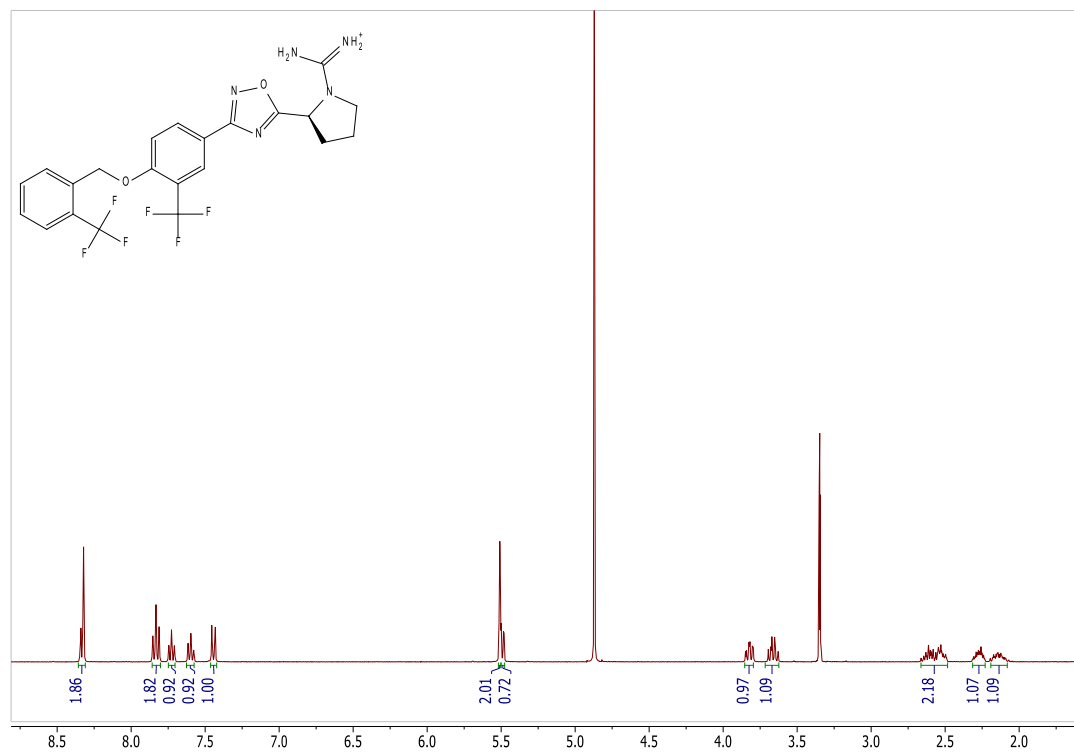
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)(amino)methaniminium 2,2,2-trifluoroacetate **3.32i** -



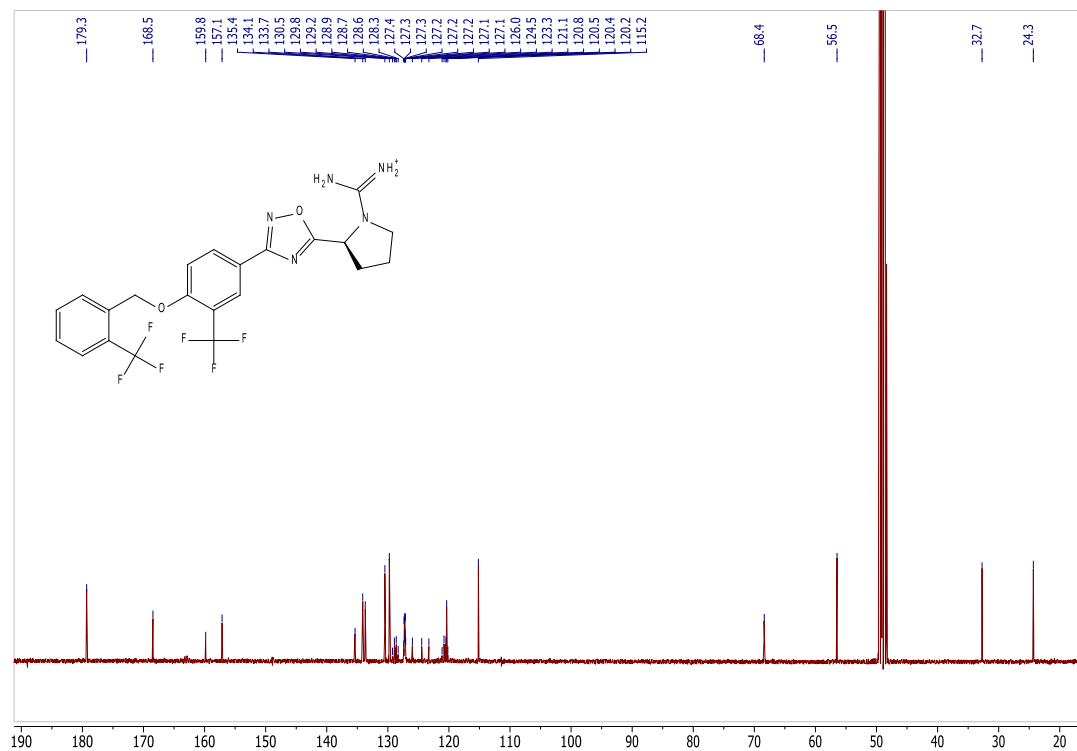
$^{19}\text{F}$ -NMR Spectrum for (*S*)-(2-(3-(4-([1,1'-biphenyl]-3-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)(amino)methaniminium 2,2,2-trifluoroacetate **3.32i** -



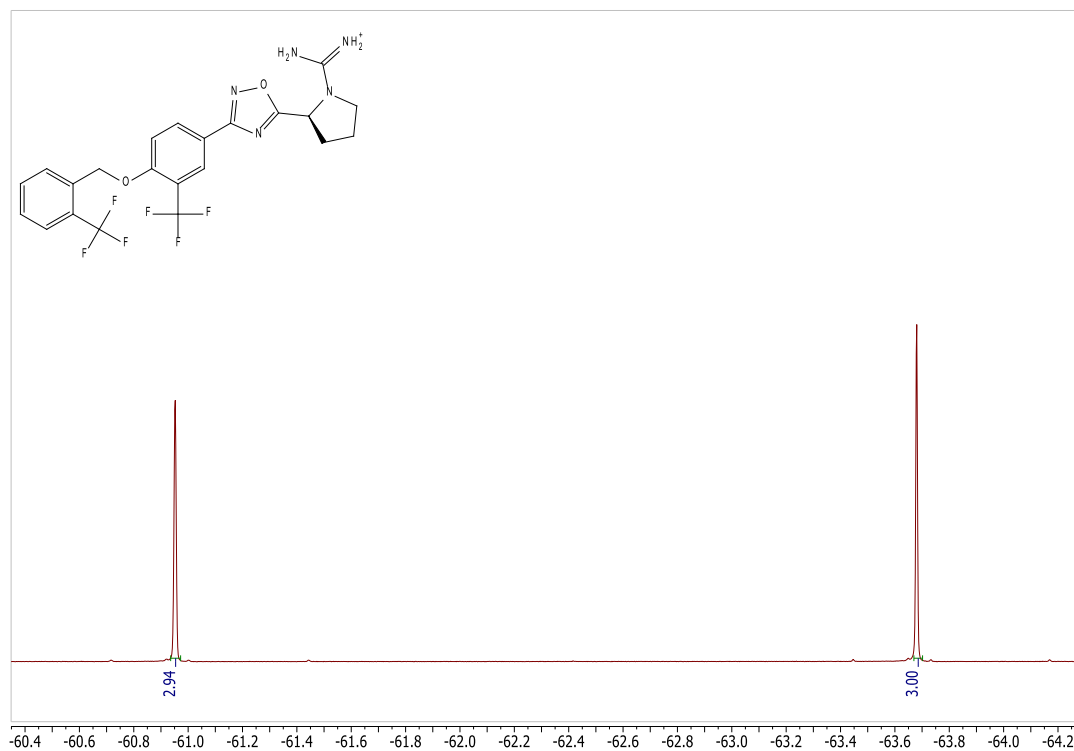
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32j** -



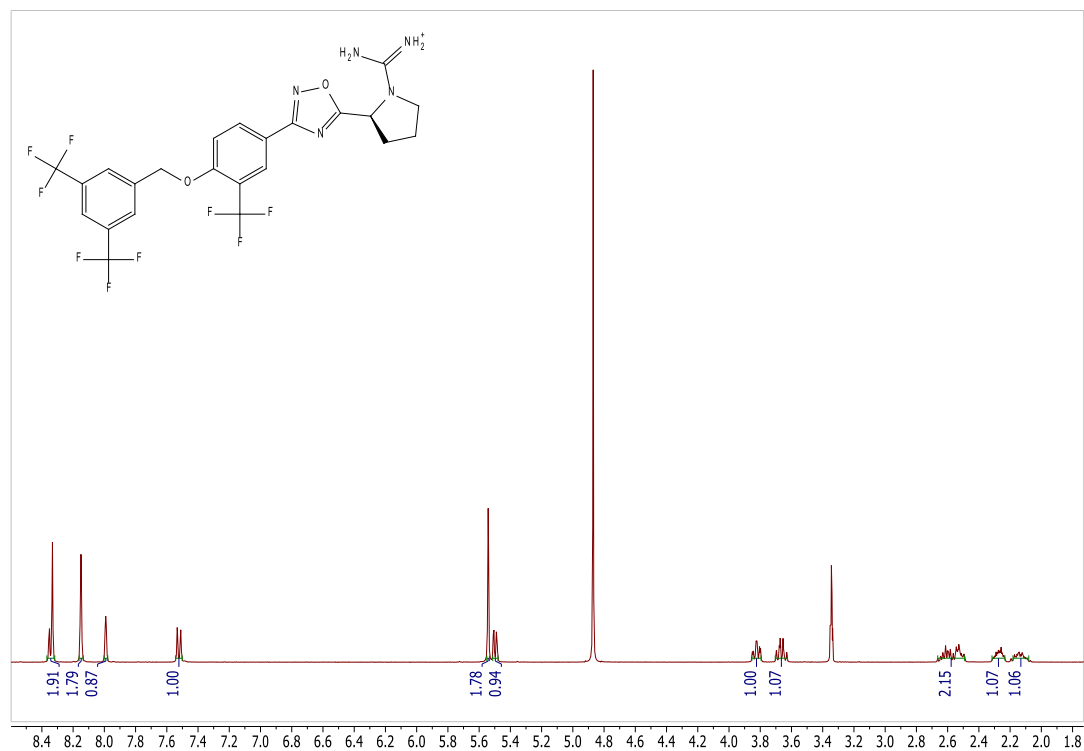
$^{13}\text{C}$ -NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32j** -



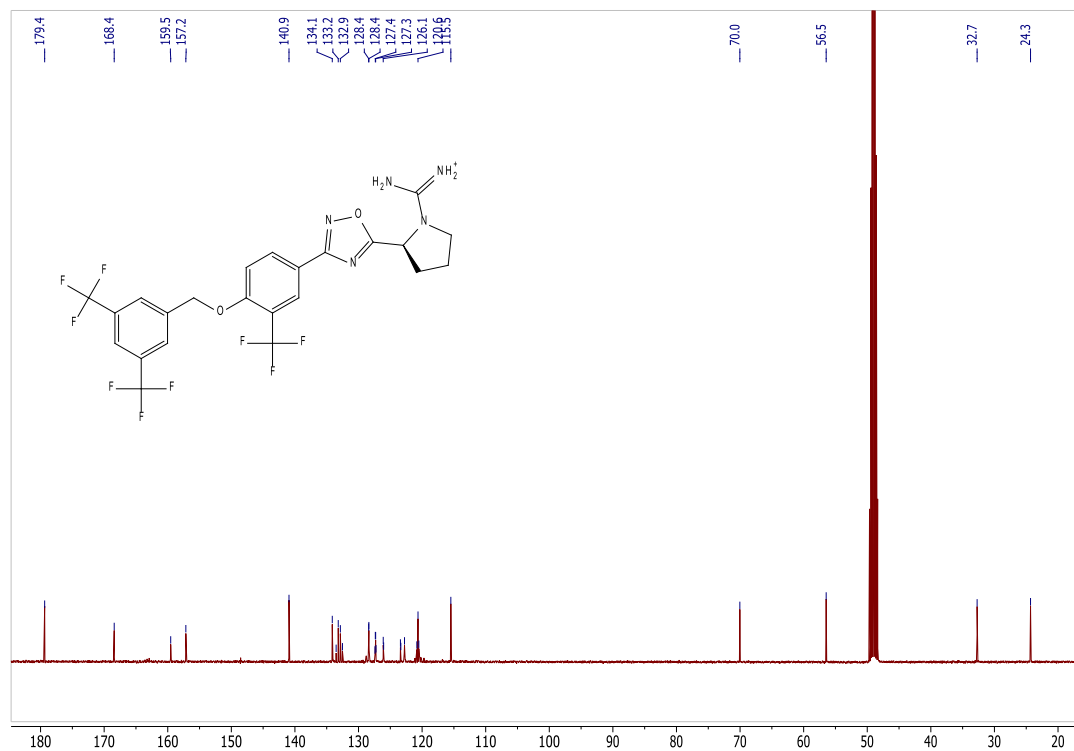
<sup>19</sup>F-NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-((2-(trifluoromethyl)benzyl)oxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32j** -



<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32k** -

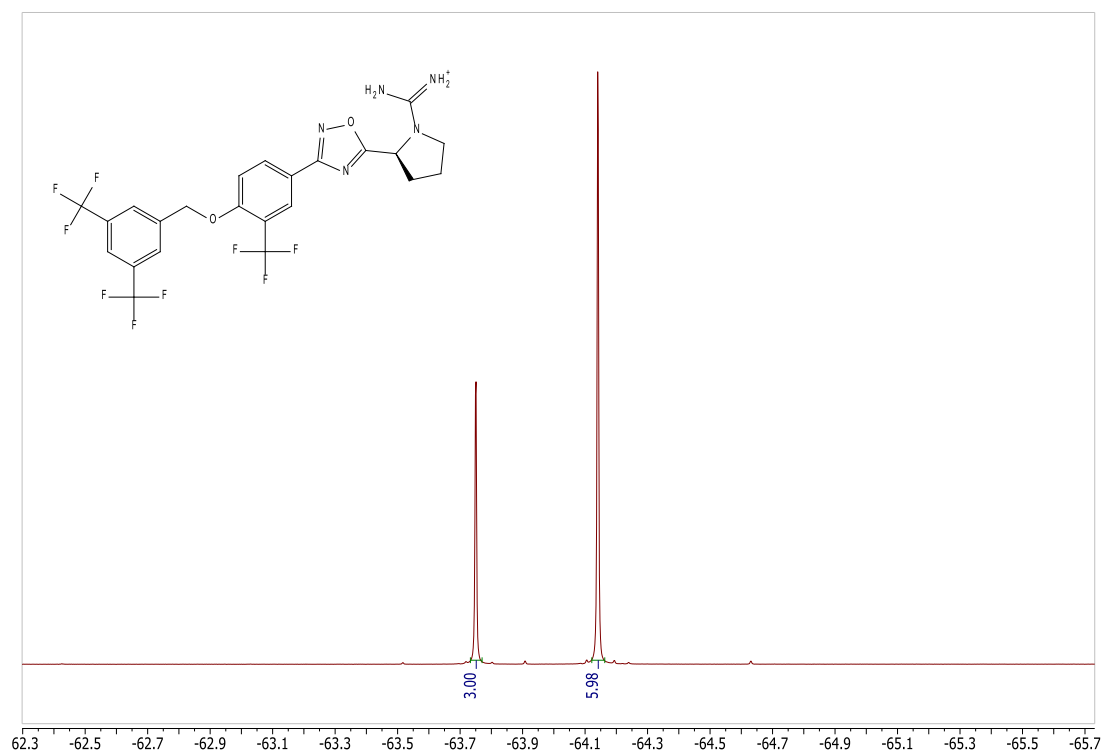


$^{13}\text{C}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32k** -

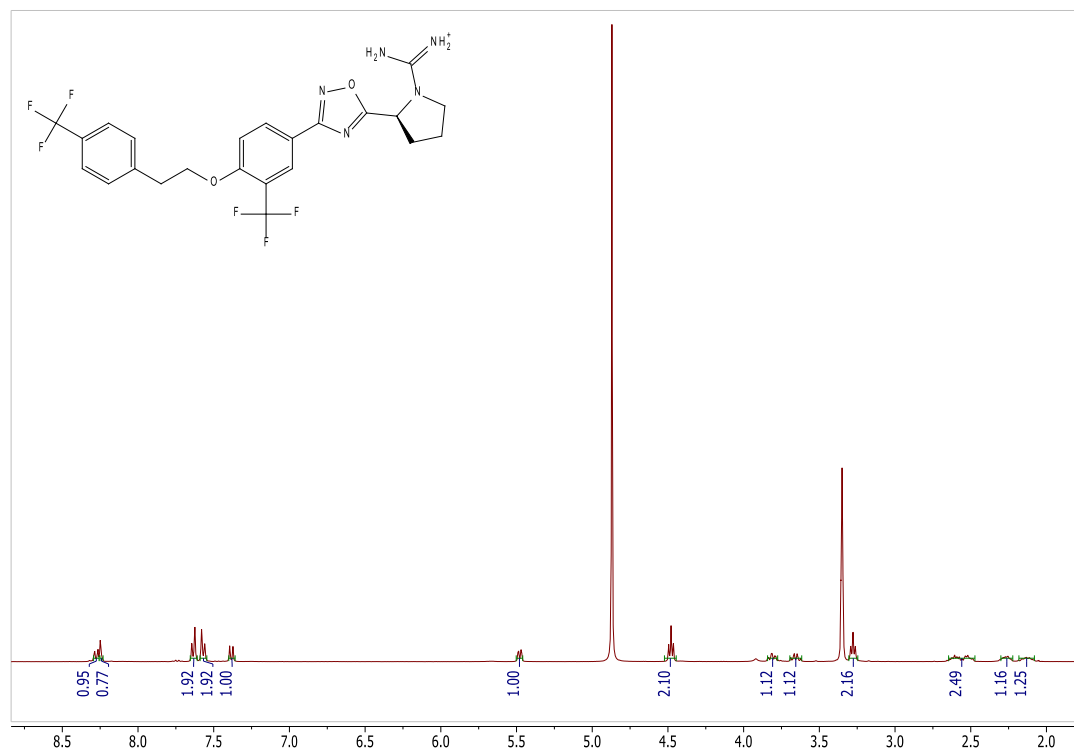




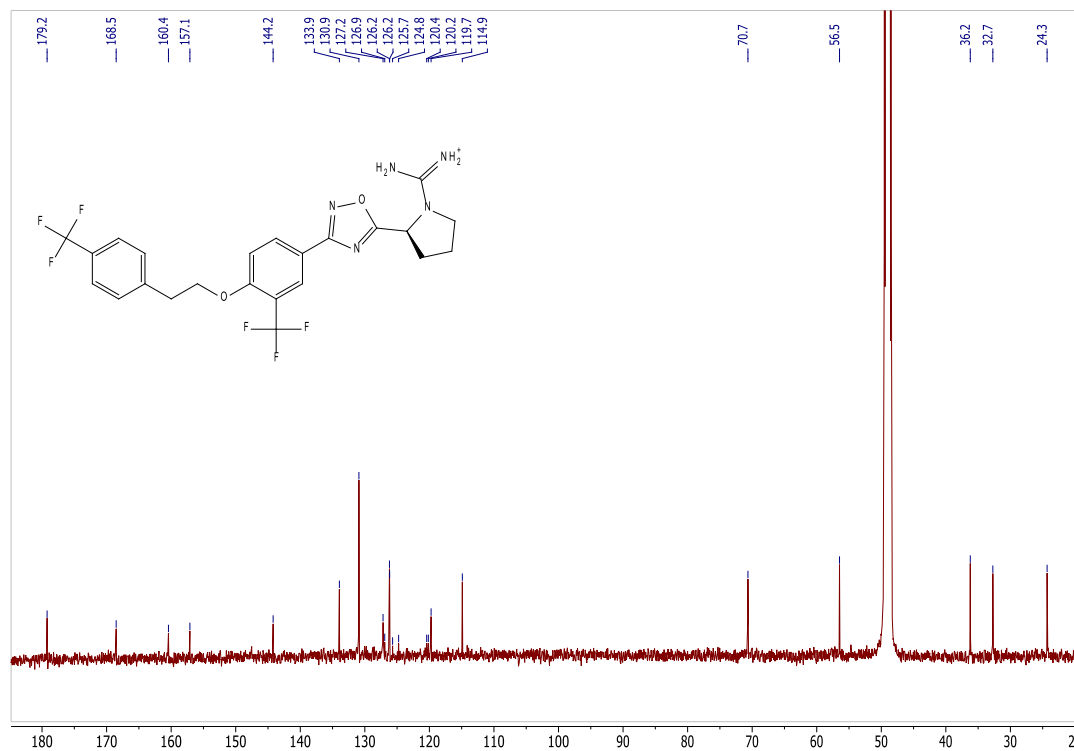
$^{19}\text{F}$ -NMR Spectrum for (S)-amino(2-(3-(4-((3,5-bis(trifluoromethyl)benzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.32k** -



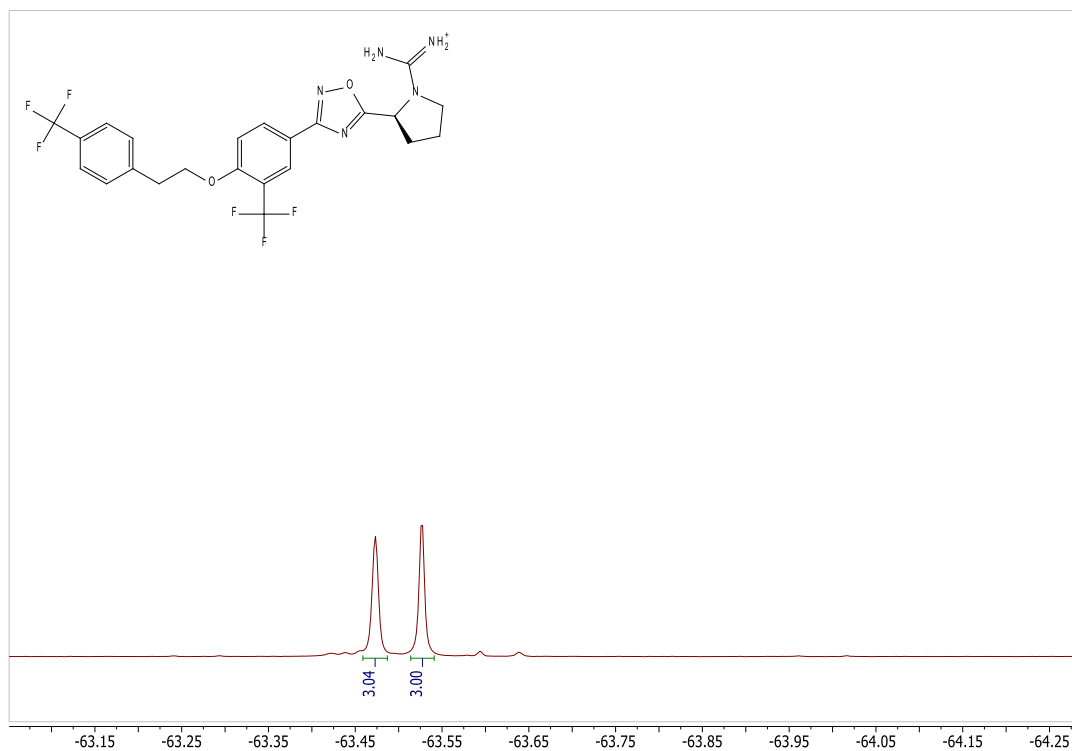
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.321** -



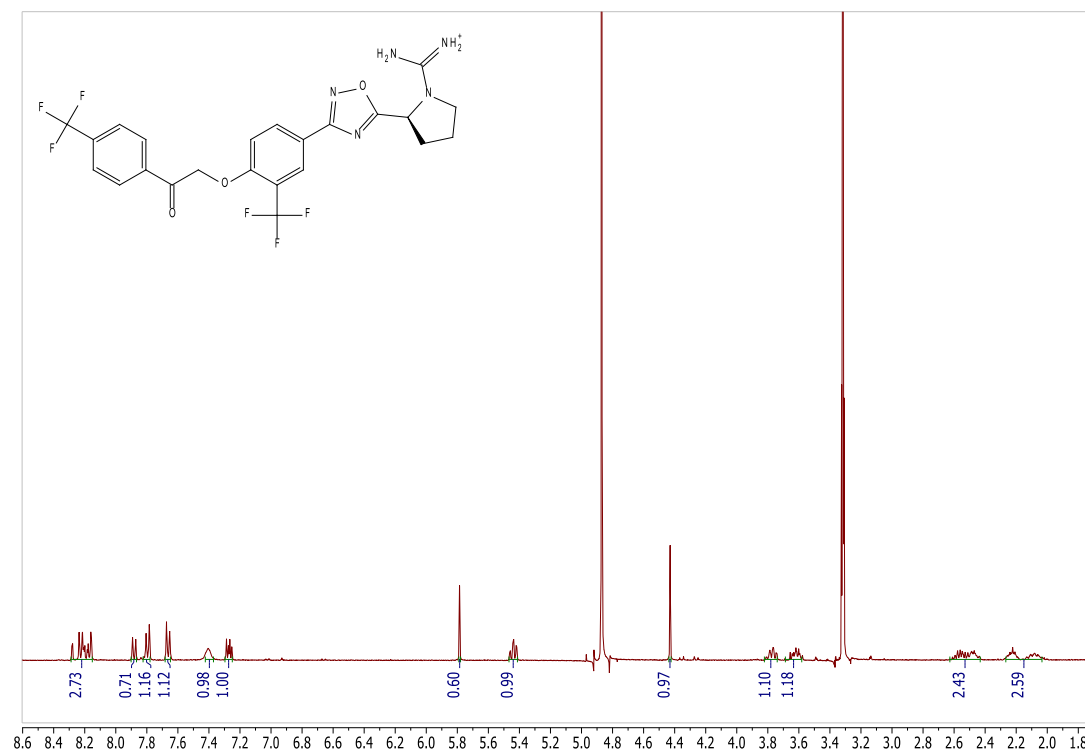
$^{13}\text{C}$ -NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.321** -



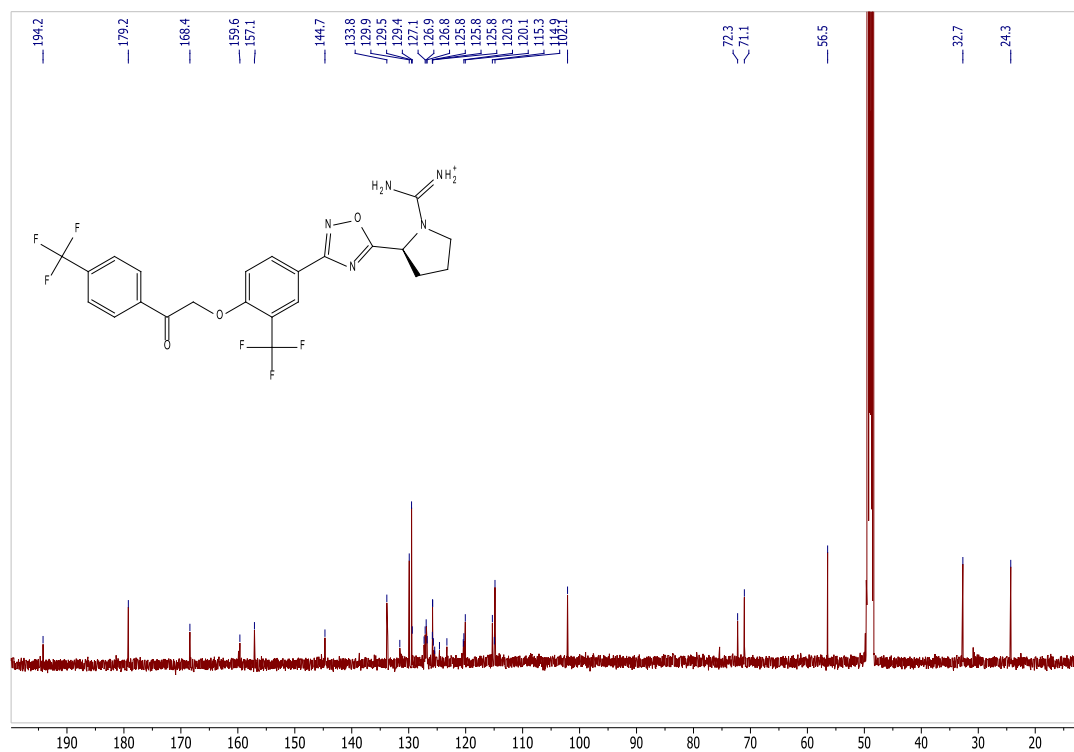
$^{19}\text{F}$ -NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.321** -



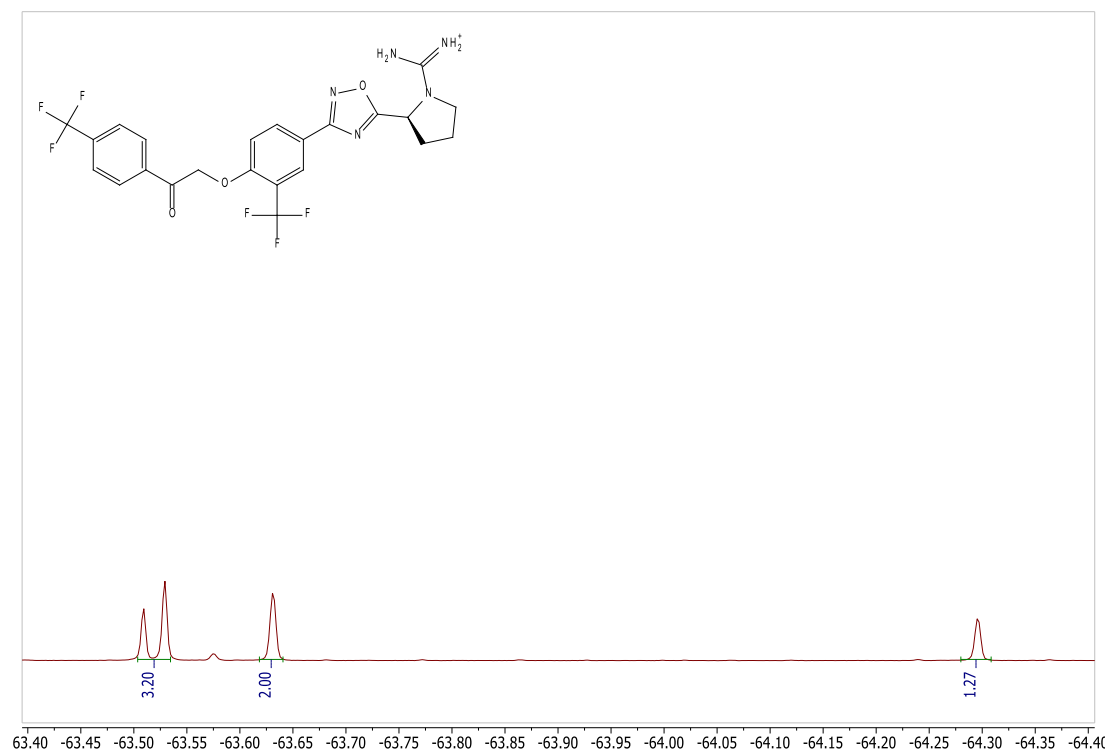
<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32m** -



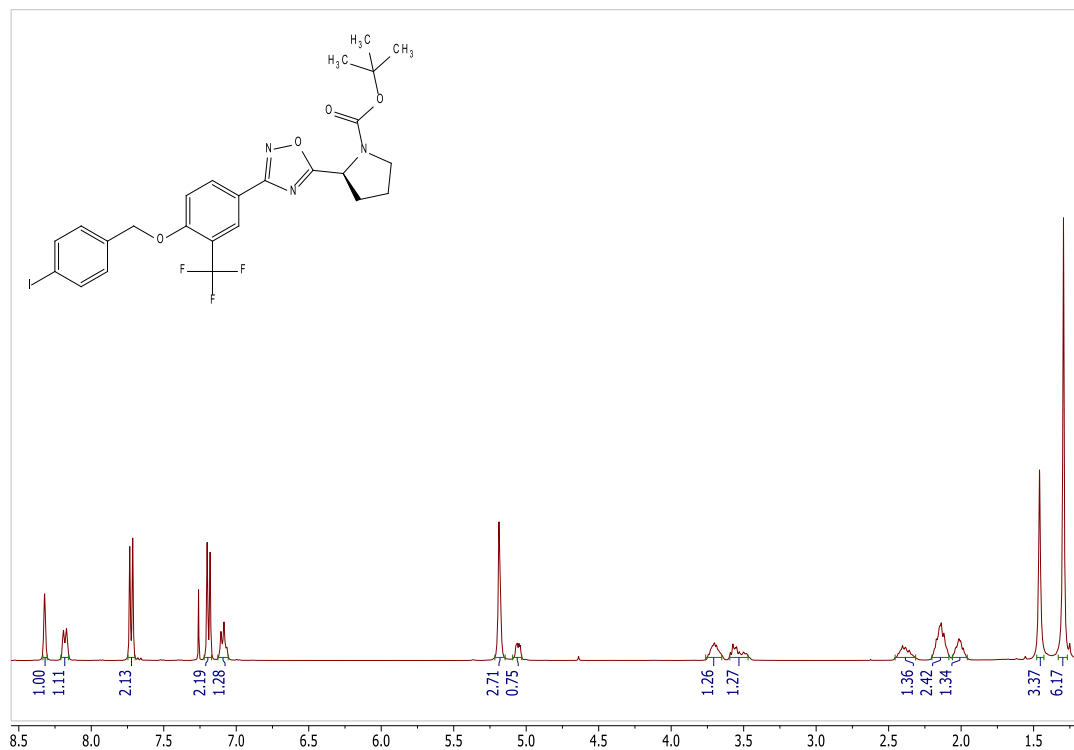
<sup>13</sup>C-NMR Spectrum for (S)-amino(2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32m** -



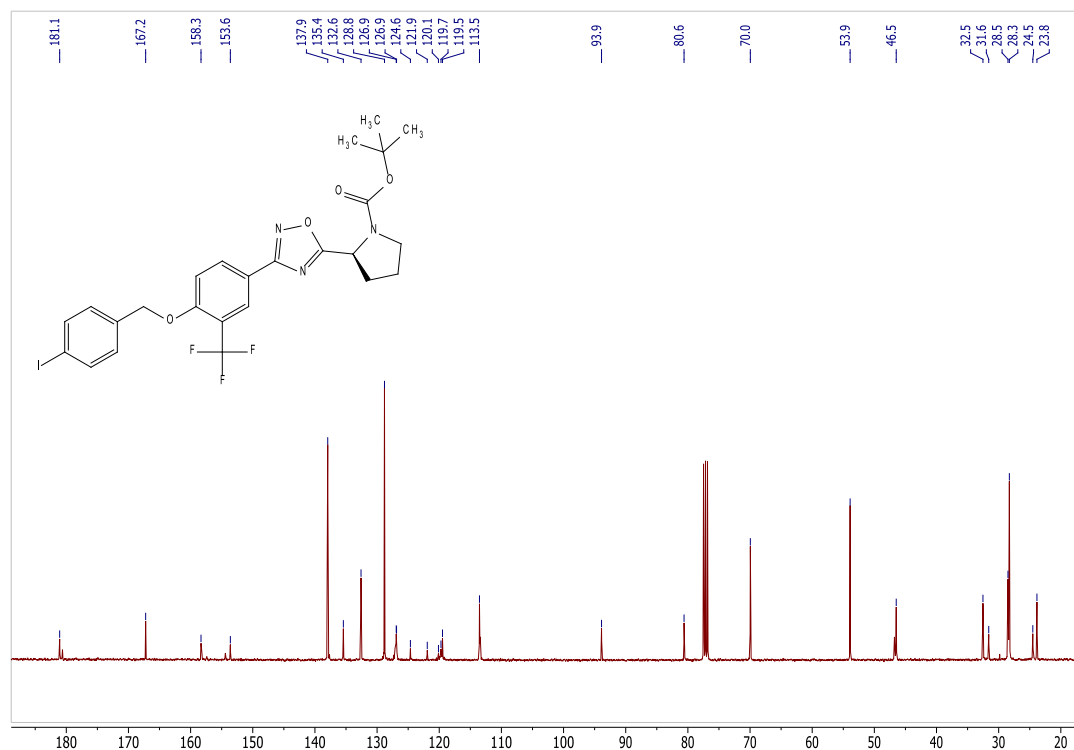
$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(4-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium chloride **3.32m** -



<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-iodobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.33** -

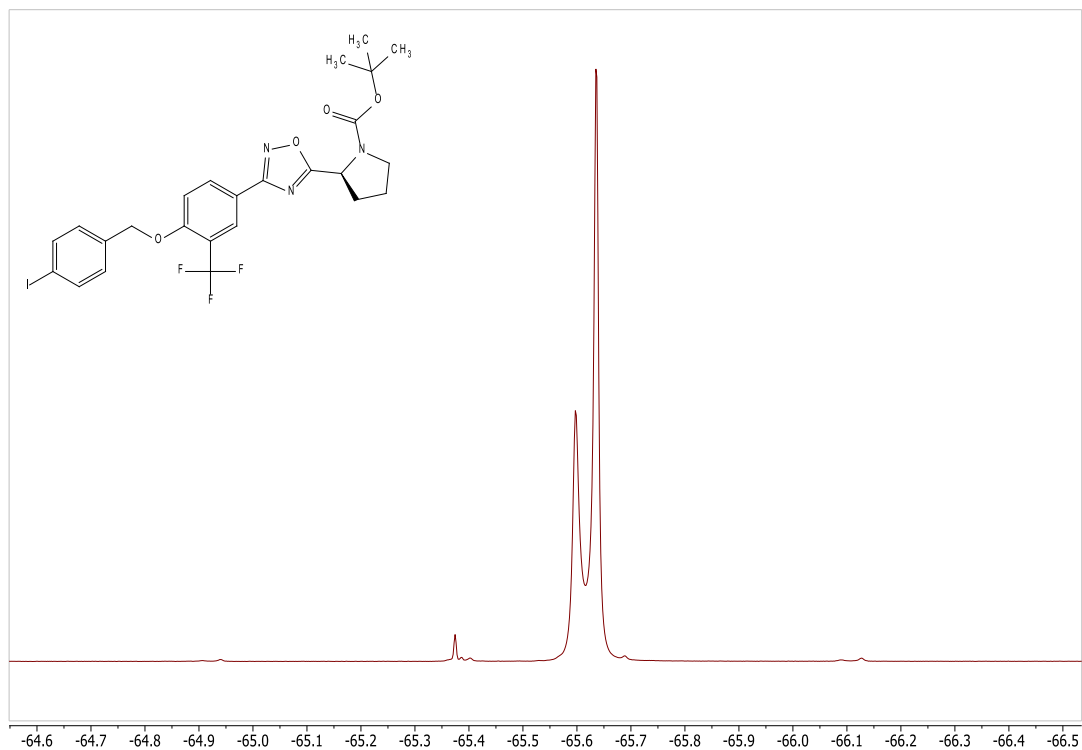


<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-iodobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.33** -

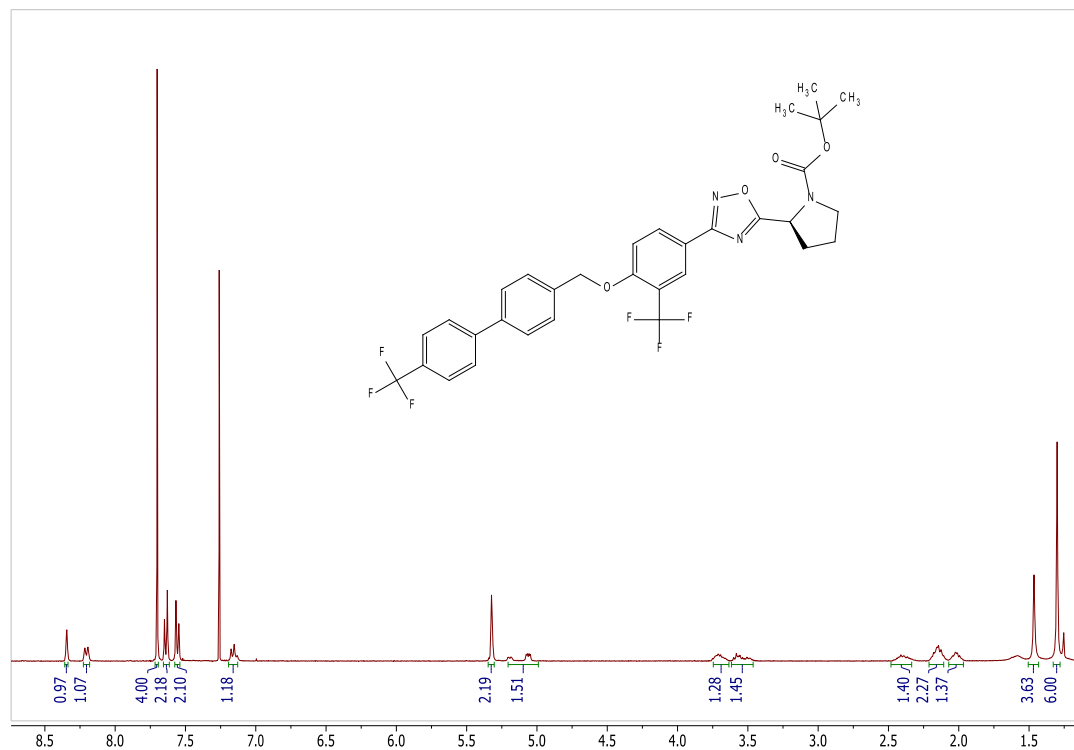




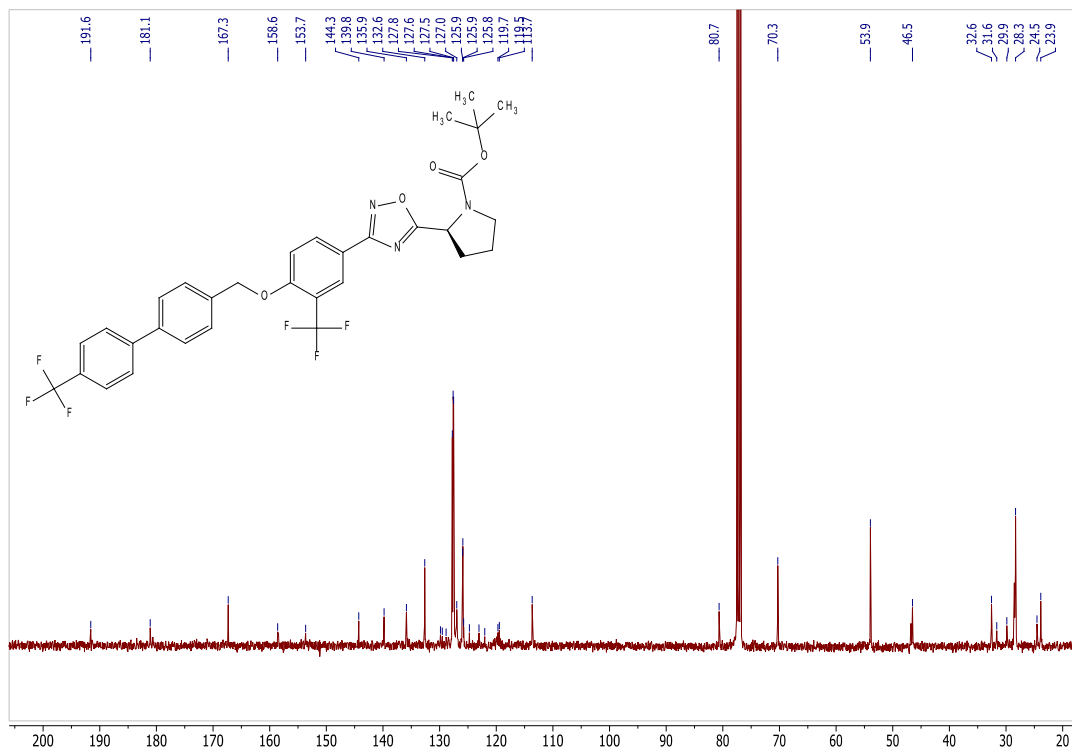
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(4-((4-iodobenzyl)oxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.33** -



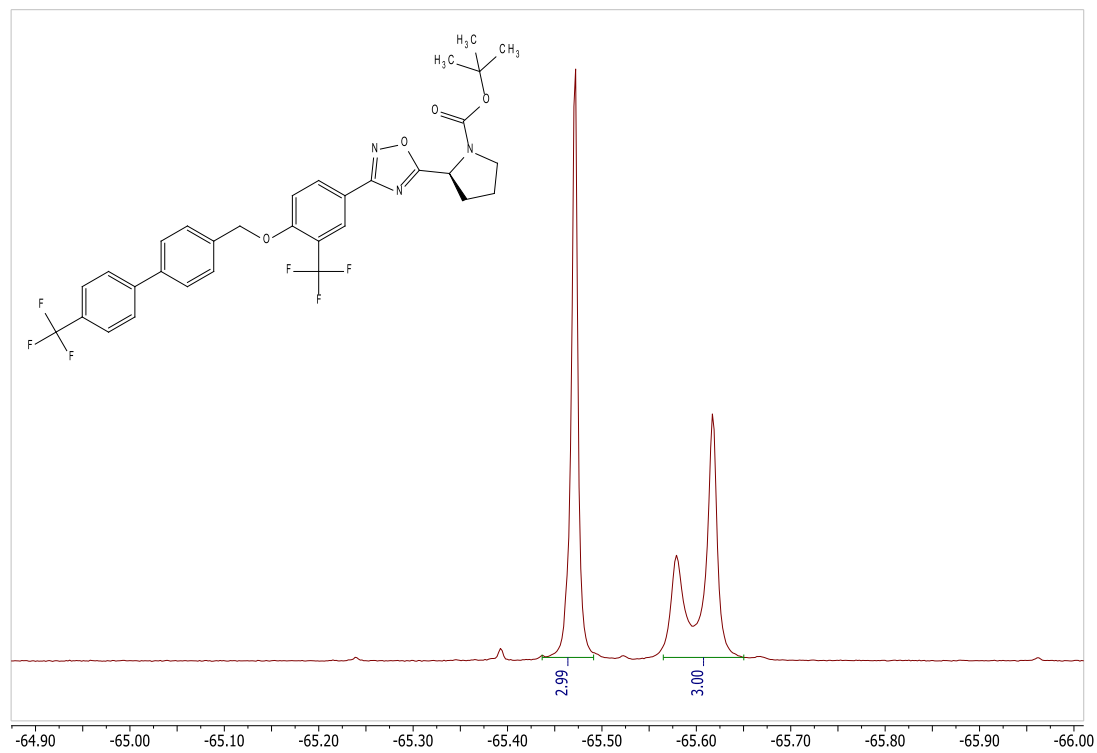
$^1\text{H-NMR}$  Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.34** -



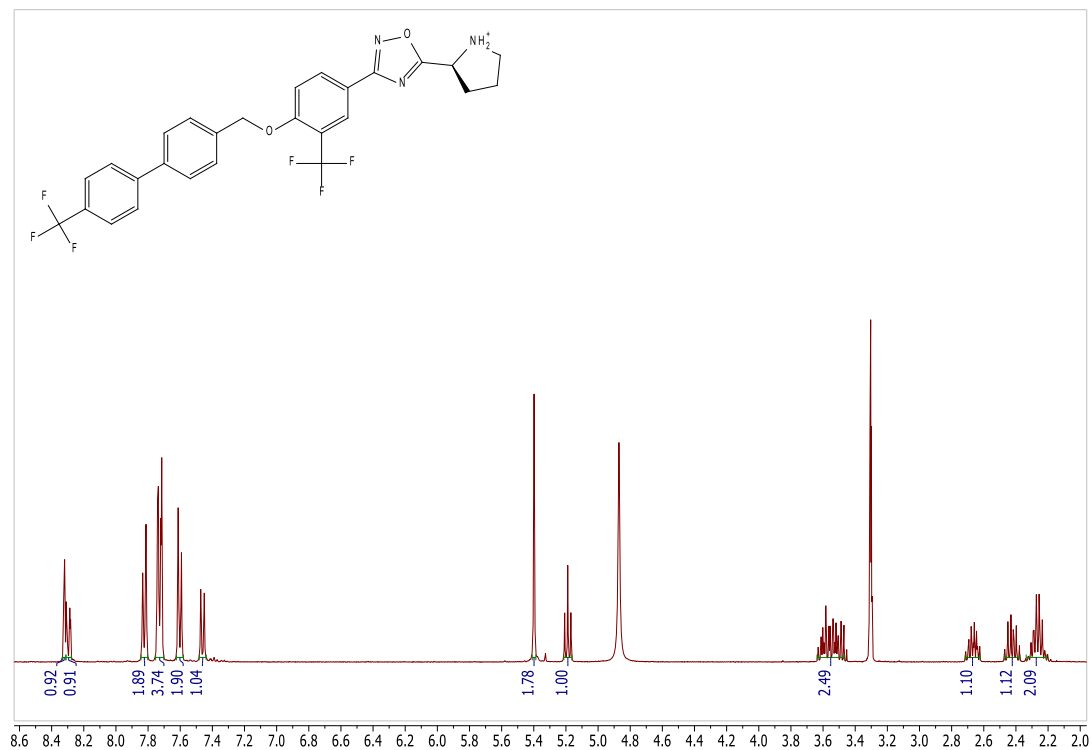
<sup>13</sup>C-NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.34** -



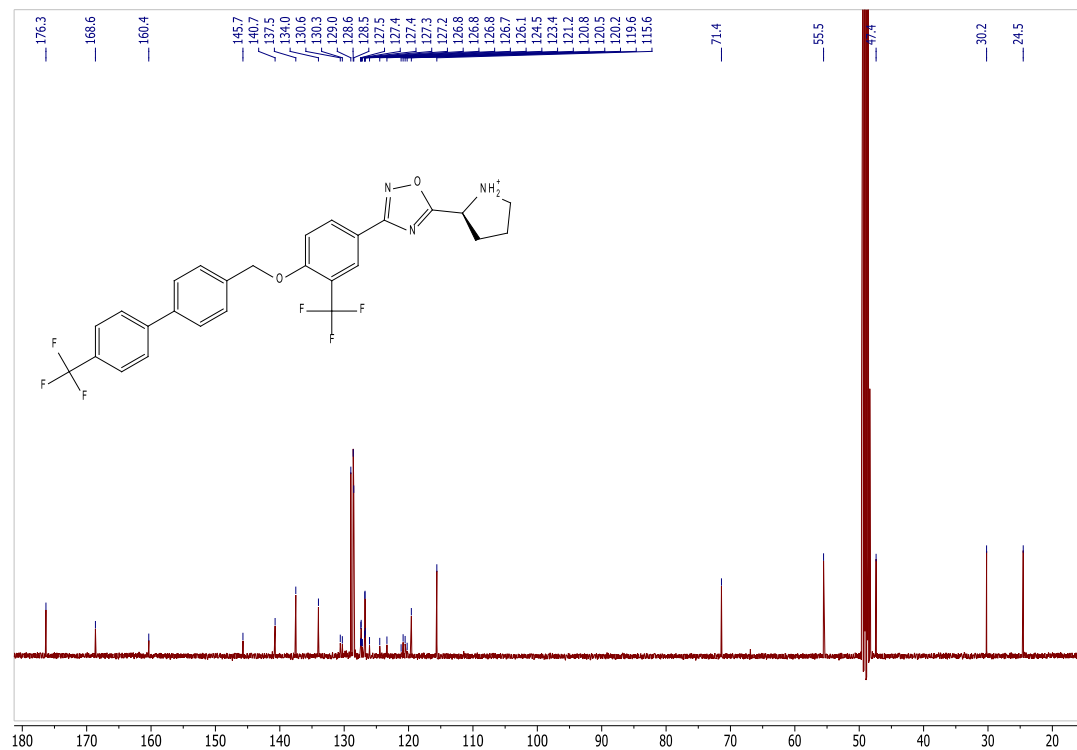
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl 2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate **3.34** -



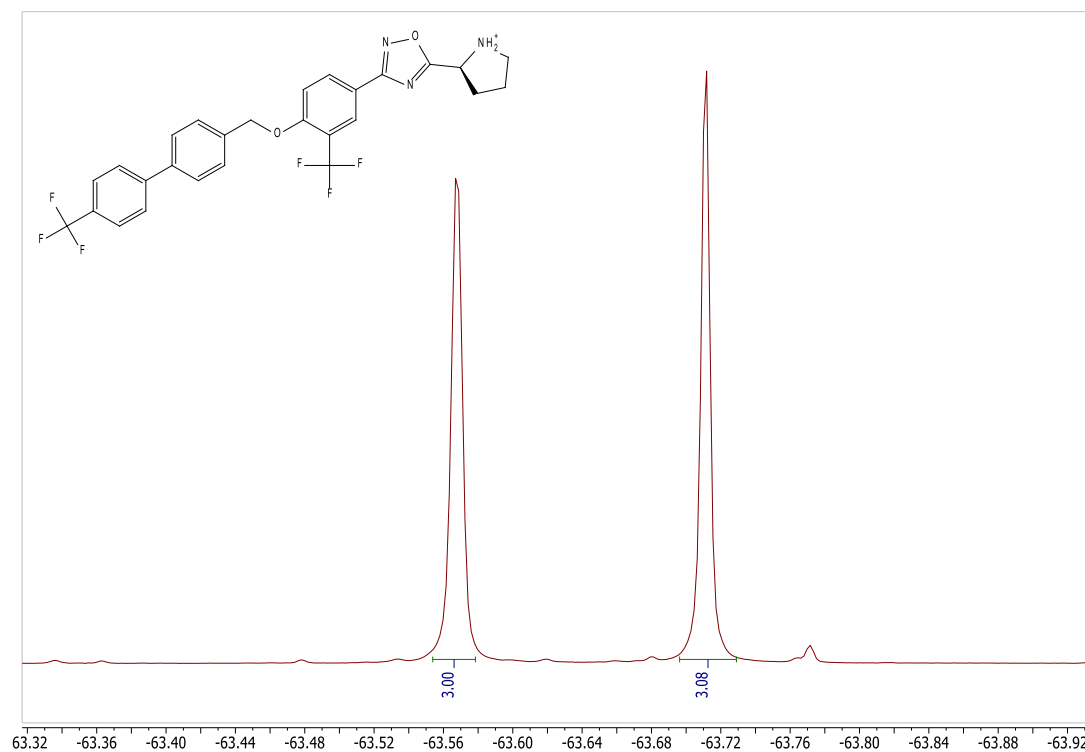
<sup>1</sup>H-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



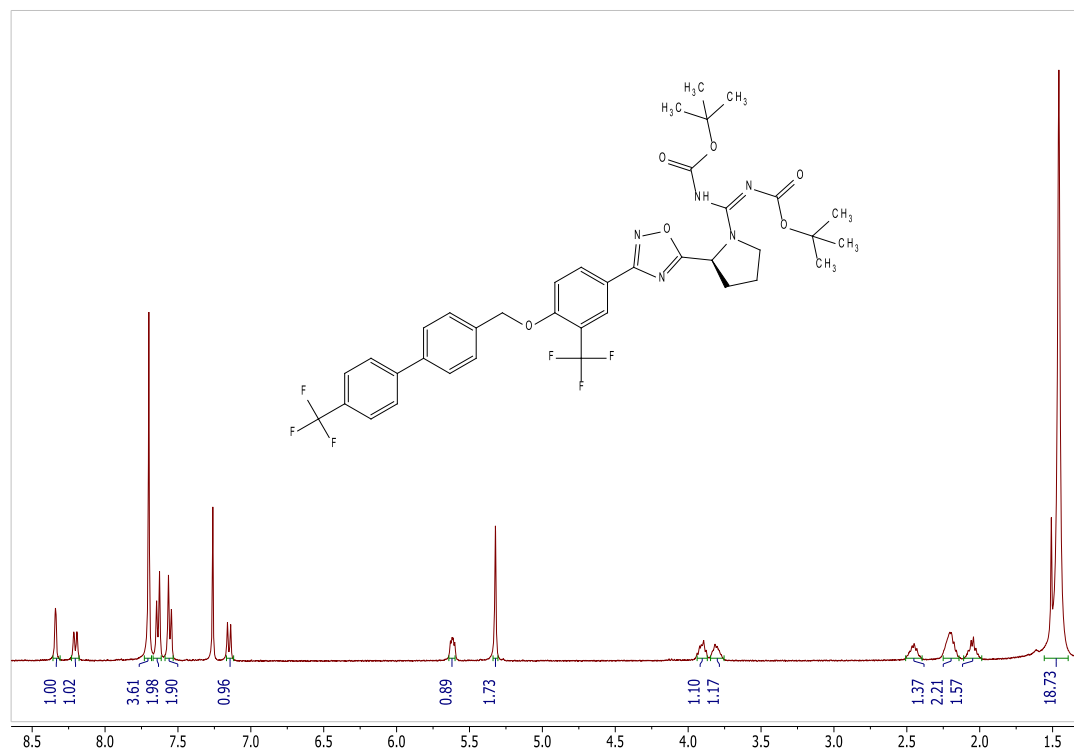
<sup>13</sup>C-NMR Spectrum for (S)-2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -



$^{19}\text{F}$ -NMR Spectrum for (*S*)-2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-ium 2,2,2-trifluoroacetate -

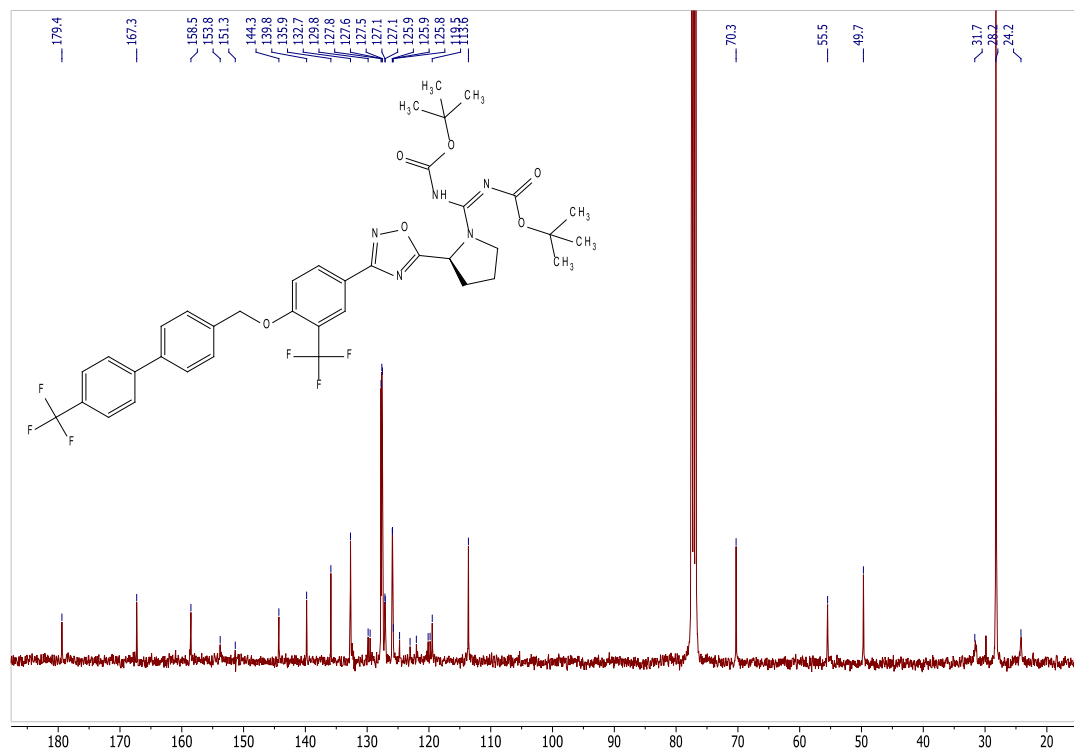


<sup>1</sup>H-NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -

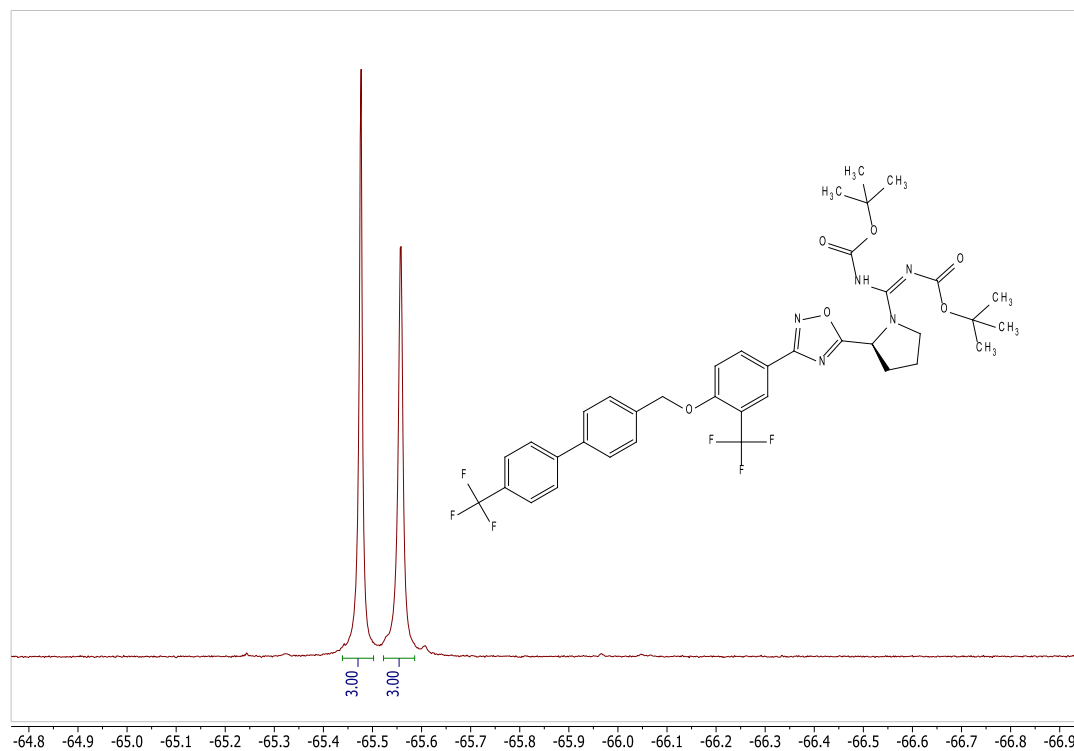




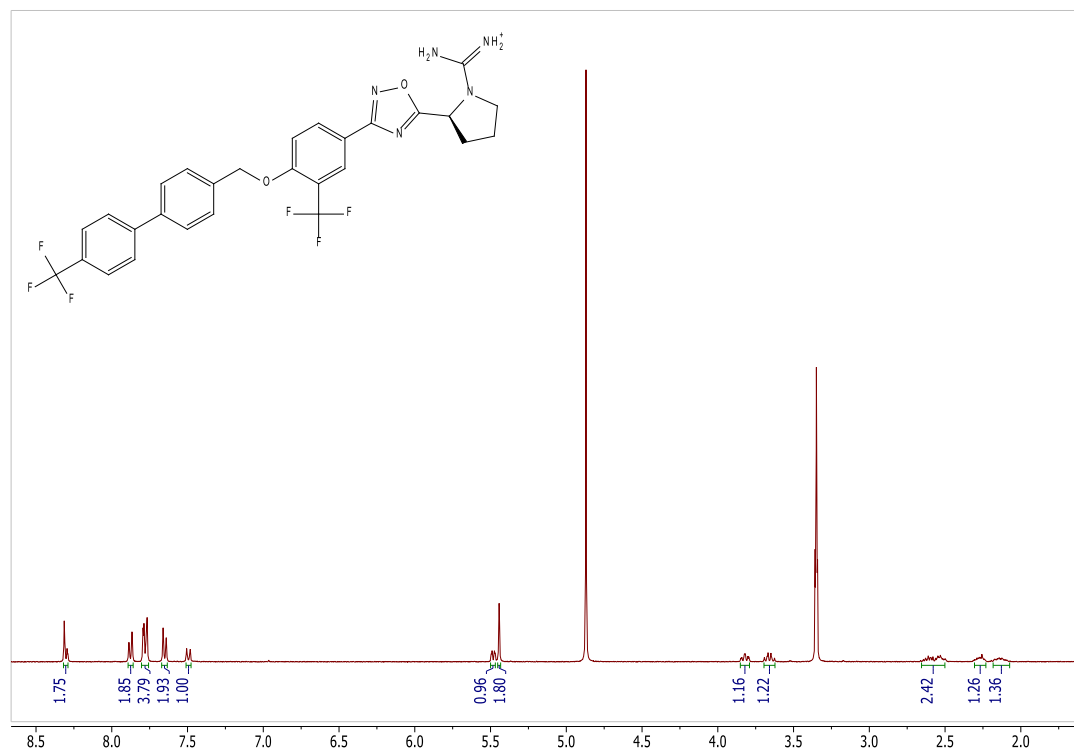
$^{13}\text{C}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



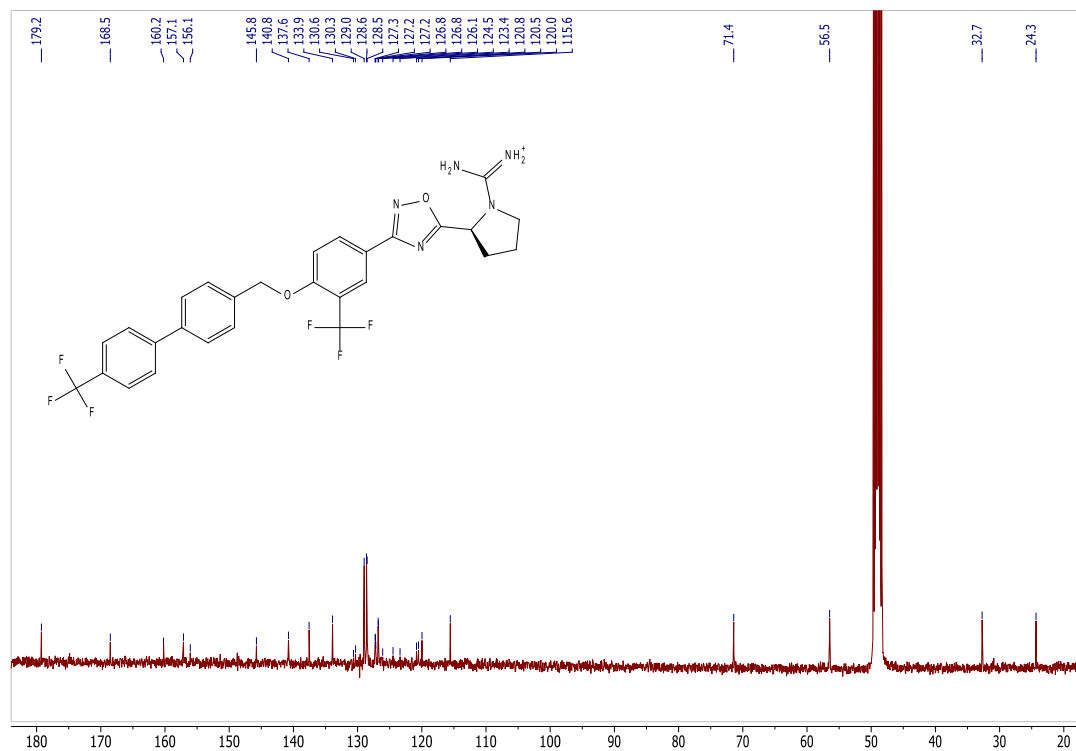
$^{19}\text{F}$ -NMR Spectrum for (*S*)-*tert*-butyl (((*tert*-butoxycarbonyl)amino)(2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methylene)carbamate -



<sup>1</sup>H-NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.35** -



<sup>13</sup>C-NMR Spectrum for (S)-amino(2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.35** -



$^{19}\text{F}$ -NMR Spectrum for (*S*)-amino(2-(3-(3-(trifluoromethyl)-4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methoxy)phenyl)-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)methaniminium 2,2,2-trifluoroacetate **3.35** -

