

Novel Antimalarial Compounds from the Optimization of the Malaria Box

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ABSTRACT

Malaria continues to threaten human beings, causing a staggering number of more than 400,000 deaths each year. Although effective treatment and prevention methods are available, rapidly emerging resistance towards existing drugs is of great concern, and the need for novel antimalarial compounds are still urgent. The Malaria Box lead molecules MMV008138 and MMV665831 are promising in this regard, due to their apparently novel antimalarial mechanisms of action.

The target of MMV008138 is the *Pf*IspD enzyme in the MEP pathway, which is absent in humans. This difference makes the *Pf*IspD a great target. However, while MMV008138 shows potency against *Plasmodium falciparum*-infected human erythrocytes in vitro, no efficacy was observed in a humanized mouse model or a *P. berghei* infected mouse in vivo. In order to block potential metabolic spots and to probe for steric demand, a series of analogous featuring C1-deuteration, methyl substitution on B- and C-ring, and an ethylene bridge were prepared. The effect of various substitution on the tetrahydro- β -carboline conformation and D-ring orientation was studied.

In the course of preparing the C1-Me analog of MMV008138 featuring 2',4'-dichloro substitution, unexpected ring-expanded azepane products were isolated. Later it was found that the desired product could be isolated when the imine formed was treated with acid at lower temperature. Other intermediates possessing a 2'-substituent were also isolated under the low temperature acid treatment protocol,

which upon heating in acid gave the ring-expanded azepane we initially isolated. A mechanism was proposed to account for the formation of the azepane as well as other intermediates. The driving force of the expansion reaction was explored, and the hypothesis that the steric interaction between the 2'-substituent and the C1-Me was supported via DFT calculation and conformational analysis.

MMV665831 is another potent hit from the Malaria Box, and it appears to inhibit the hemoglobin endocytosis process of *P. falciparum*. The structure–activity relationship of MMV665831 was studied with analogues featuring modifications on C2-benzamide, C3-ester, C-7 phenol, as well as the phenolic Mannich base moiety. Modifications at phenolic Mannich base moiety leads to the discovery of an analogue that is twice as potent toward cultured *P. falciparum* compared to MMV665831. We were worried the phenolic Mannich base moiety might act as the precursor of toxic quinone methide intermediates, and designed two analogs to block this potential toxicophore. Although the modification resulted in reduced potency, this result proved that the potency of MMV665831 does not stem from the formation of quinone methides. Unfortunately, MMV665831 did not reduce parasitemia in *P. berghei*-infected mice. Fast hepatocyte metabolism was observed for MMV665831, and the loss of in vivo efficacy was discussed in comparison with other phenolic Mannich bases with similar hepatocyte stability.

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GENERAL AUDIENCE ABSTRACT

In the fight against malaria, one concerning issue is the rapidly emerging resistance towards existing drugs. The continuous development of antimalarials with novel mechanism of action is greatly needed. To accelerate the development of novel antimalarials, an open access ensemble of 400 compounds that are toxic to the malaria parasite known as the Malaria Box, has been made available. My work involves the optimization of two compounds from this ensemble, MMV008138 and MMV665831.

MMV008138 kills the malaria parasite by inhibiting an enzyme named *Pf*IspD, which is absent in human. In the parasite an enzyme called *Pf*IspD is responsible for the biosynthesis of IPP and DMAPP, two chemical building blocks that are essential for all cells. It is unlikely that MMV008138 will interrupt with the biosynthesis of IPP and DMAPP in human, since we use another enzyme to synthesize them. Although MMV008138 shows great *in vitro* potency, but did not protect a live mouse from malaria infection. The lack of *in vivo* efficacy could stem from the rapid metabolism of MMV008138, and analogs aimed to prevent metabolism were designed and prepared. While preparing analogs featuring 2'-substitution, the desired product was not found, but other unexpected by-products were isolated. The conditions that leads to both the desired products and the by-products were found, and the mechanistics detail of this unexpected reaction were studied.

During the blood-stage, which causes malaria symptoms in human, the *Plasmodium falciparum* parasite invades and feeds on human red blood cells (erythrocytes). The parasite destroys human hemoglobin through a multistep process that begins by transporting the hemoglobin from the red blood cell into itself, a process called endocytosis. MMV665831 appears to interfere with this endocytosis process of *P. falciparum*, thus starving the parasite of its food. Analogs of MMV665831 were prepared to probe for the effect on potency, and one compound that is twice as potent in cultured parasites was found. The structure of MMV665831 contains a potentially unstable moiety, which might lead to toxicity in humans. Two analogs with the problematic moiety removed were designed and prepared, and one still shows antimalarial activity, showing that the reactivity of the potentially unstable moiety is not the reason for the antimalarial activity of MMV665831. However, MMV665831 did not protect *P. berghei*-infected mice (murine malaria) *in vivo*, and the reason for the loss of efficacy was discussed.

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For Yuye Wu and Guowen Ding

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Chapter 1. Malaria, Antimalarials, the Malaria Box, and New Therapeutic Strategies

Introduction

Malaria has been a misfortune for humans since ancient times. Descriptions of malaria symptoms have been found in *Nei Ching* as early as 2700 BCE. The first confirmed human malaria case dates back to 450 CE.¹ Despite the long history, malaria still remains a threatening global disease. An estimated 3.2 billion people are at risk of malaria. In 2017 alone, approximately 219 million cases of malaria occurred worldwide. An estimated 435,000 of these cases were fatal, including 266,000 children under the age of five.²

***Plasmodium* and its life cycle**

Malaria is a mosquito-borne disease caused by *Plasmodium* genus parasites. Of the *Plasmodium* parasites, five species can affect humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovalei* and *P. knowlesi*.³ With the exception of *P. knowlesi*, which is transmitted from malaria-infected monkeys to humans (zoonotic transmission), all other parasites are spread from humans to humans via *Anopheles* mosquito bites. Of all the five *Plasmodium* parasites, *P. falciparum* and *P. vivax* are responsible for over 95% of all cases. *P. falciparum* occurs primarily in the African continent, killing more people than all the other four species combined, while *P. vivax* can suffer colder temperatures and higher altitudes, and is thus spread more widely around the world, more commonly seen in many places than *P. falciparum*.

When an infected female *Anopheles* mosquito sucks human blood for a meal, several sporozoites can be transferred from mosquito saliva to human blood. Sporozoites then enter, reproduce and develop in liver cells, creating tissue schizonts containing tens of thousands of merozoites,⁴ which later rupture and go into the blood and attack erythrocytes. Each infected erythrocyte can produce new merozoites, which can again attack other erythrocytes. Merozoites live through a few asexual life cycles before developing into gametocytes, the sexual life stage.³ During blood-feeding by *Anopheles* mosquitos, gametocytes can be transferred to the mosquito and produce new sporozoites, becoming potentially dangerous for other humans (Figure 1-1).⁵⁻⁶

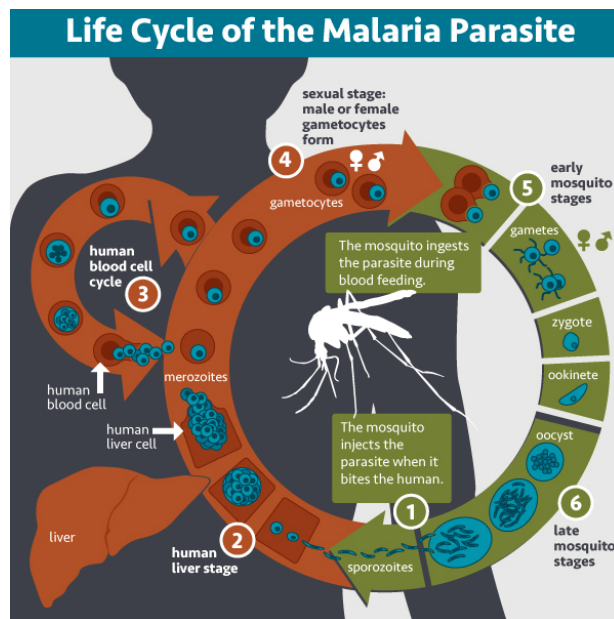


Figure 1-1. The life cycle of the malaria parasite (Source:

<https://www.niaid.nih.gov/diseases-conditions/malaria-parasite>, last accessed 2020

Mar. 17th)

The development of antimalarial candidates with novel mechanisms of action is critical to compete with the rapidly emerging resistance.⁷ In the efforts to develop such candidates, a relict plastid known as the apicoplast is a promising target. I will discuss this organelle and its function below.

Antimalarial progress and goals

The United Nations listed eradication of malaria in its *Millennium Development Goals 2000*.⁸ Taking into account population growth, the malaria incidence rate dropped continuously from 2000 to 2015. A total reduction of 37% was observed, thanks to the renaissance in the research and development of chemical vector control methods⁹ and malaria medicines.¹⁰⁻¹² As expected, with decreasing morbidity, malaria mortality rates also decreased. Yet despite these trends, malaria still remains a major public health problem for many countries. Over 80% of malaria incidences and deaths cluster in fewer than 20 countries. Morbidity and mortality rates also decrease more slowly in these high-burden areas. In 2015, WHO developed *Global Technical Strategy for Malaria 2016–2030*,¹³ aiming for reducing at least 90% of global mortality and morbidity in 2030 compared to 2015.

Available Malaria Drugs and Drug Resistance

Many drugs are currently available for malaria treatment, but resistance to these drugs has also developed rapidly.¹⁴⁻¹⁵ The leading treatment for malaria, artemisinin-based combination therapy (ACT), has proven to be highly effective. However, malarial drug resistance keeps emerging rapidly around the world; the need for new medicines is still urgent.

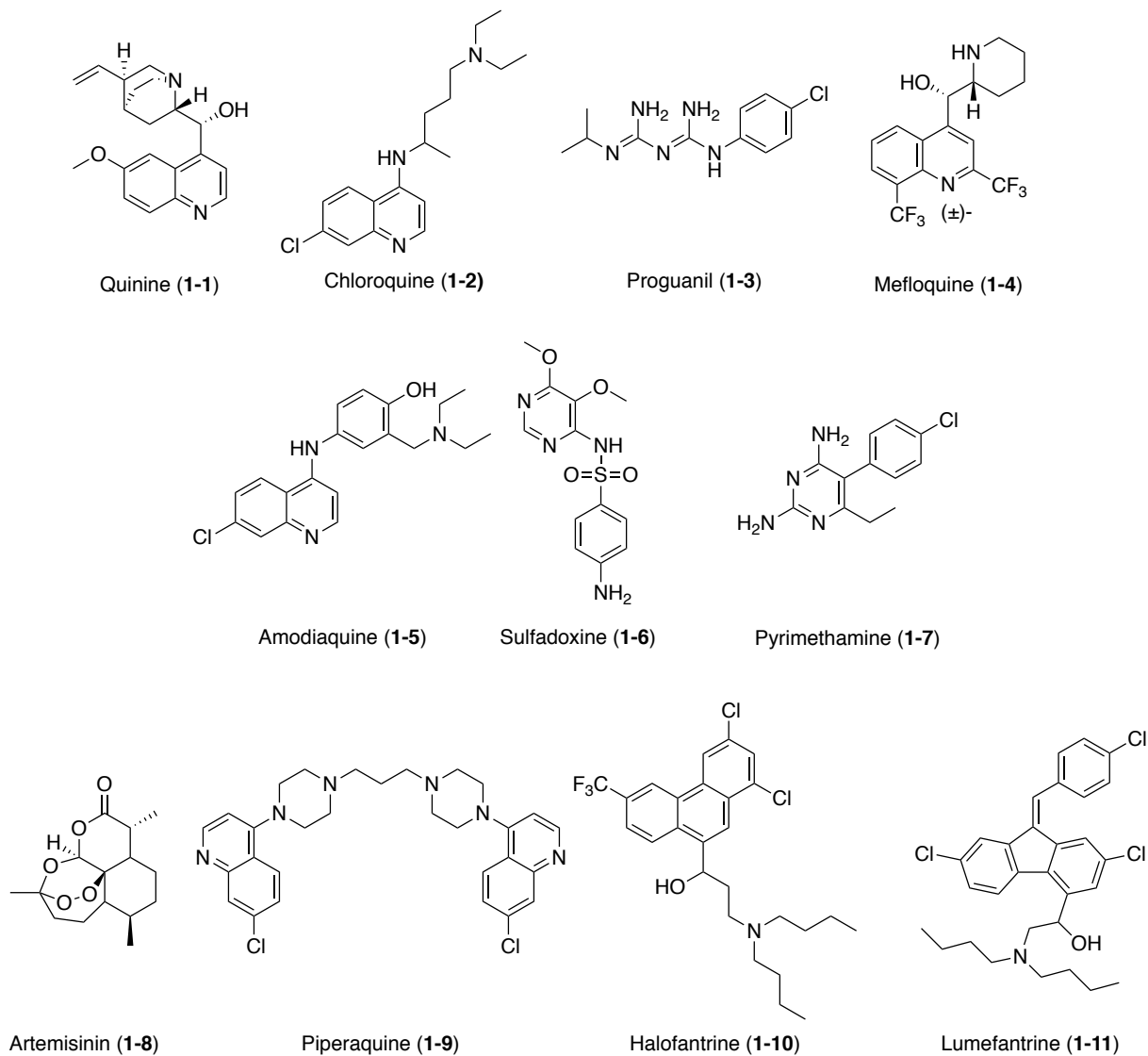


Figure 1-2. Selected Antimalarial drugs

A. Quinine

Quinine (1-1) has been used for the treatment of malaria starting nearly 400 years ago.¹⁶ Extracted from cinchona tree bark, quinine was used to treat malaria and cyclic fevers. Even now it remains an important treatment method for uncomplicated malaria.¹⁷ Its intravenous applicability makes it the only therapeutic option for severe malaria.¹⁸ The first documented case of resistance to quinine was reported in 1910,

and since then patients have been given higher doses of it over the years.¹⁹ Quinine resistance is commonly seen recently, and thus a combination of it with other drugs is often recommended. The very distinct and unpleasant taste of quinine stops people from taking it regularly. Reversible but severe side effects such as vomiting, diarrhea, potential to cause arrhythmia, severe hypoglycemia caused by insulin release, and stomach cramps can also be observed. As a monotherapy, treatment with quinine requires taking the medicine for 7 days. This long-term treatment often is hard for the patient because of its repulsive characteristics.

B. Chloroquine

Historically, chloroquine (**1-2**) was used widely for the treatment and prophylaxis of malaria. Thanks to its low cost and good tolerability, it was once the best single drug.²⁰ However, following the initially attempted eradication of malaria in the late 1950s, massive use of chloroquine led to worldwide independent development of resistant *P. falciparum* strains.²¹⁻²³ Although its massive use was halted in 1969, as of 2015, more than 80% of field isolates of *P. falciparum* were still chloroquine resistant,²³ and in some regions this approached 100%.²⁴ However, most *P. vivax*, *P. ovalei*, and *P. malariae* parasites remain sensitive, making chloroquine the first choice for treating *P. vivax* malaria.¹⁴

One common adverse effect mostly seen in African patients is pruritus (severe itching of skin).²⁵⁻²⁶ The combination of chloroquine and proguanil (**1-3**) is usually used for prophylaxis purposes; this combination generally has tolerability,¹⁴ but a higher chance of mouth ulcers and gastrointestinal upset is found compared to other prophylaxis methods.²⁷

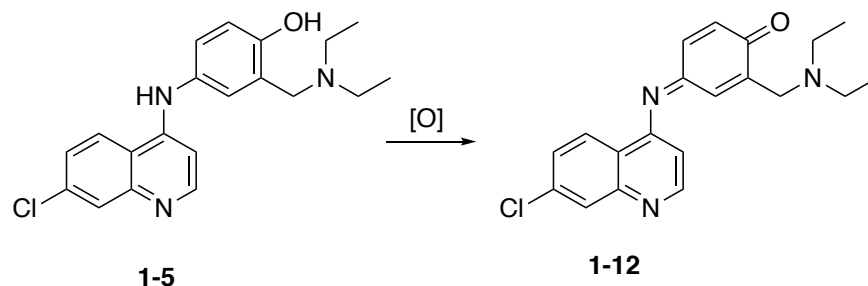
C. Mefloquine

Mefloquine (**1-4**) has a similar structure to **1-1** in that it is a substituted quinolin-4-yl methanol, and is effective against asexual stages of *P. falciparum*,¹⁴ it is highly effective against most quinoline-resistant *Plasmodium* strains.²⁸ It proves to be a very effective prophylactic drug²⁹ and is widely used in Asia. Due to *P. falciparum*'s multi-drug resistance, mefloquine or mefloquine/artemisinin analog combination became the only treatment for some areas.¹⁵ In most endemic areas, mefloquine is widely used for treatment and prophylaxis.¹⁵ Mefloquine is generally well tolerated. But occasional neuropsychiatric adverse effects can occur to some patients, including headaches, dizziness, insomnia, nightmares, and anxiety. Adverse effects on travelers and the military were often reported by the media, which have given mefloquine a bad reputation in recent years.³⁰⁻³² In 2013, FDA added a “black box warning” to mefloquine due the risk of psychiatric side effects.³³

D. Amodiaquine

Amodiaquine (**1-5**) is structurally similar to chloroquine, in that it is a 4-aminoquinoline. The aliphatic side chain of chloroquine was replaced with a 4-aminophenol ring, that also contains a phenolic Mannich base moiety, similar to the MMV665831 (**4-1**) discussed in Chapter 4. The structural similarity of amodiaquine to chloroquine results in cross-resistance—amodiaquine shares *P. falciparum* strain sensitivity with chloroquine.¹⁴ Considering its low price, it is still used for treatment of malaria in developing countries.³⁴ However, the *para*-aminophenol structure is redox active under physiological conditions and can be transformed to quinone imine (**1-12**) via oxidative metabolism *in vivo* (Scheme 1-1).³⁵ The quinone imine formed is

hepatotoxic and may cause agranulocytosis, which is a life threatening disease.³⁶ This largely limits the application of amodiaquine.



Scheme 1-1. Redox activity of **1-5**

E. Sulfadoxine/pyrimethamine

The combination of the dihydropteroate synthase inhibitor sulfadoxine (**1-6**) and the dihydrofolate reductase inhibitor pyrimethamine (**1-7**), known as S/P or Fansidar[®], took chloroquine's place as the first-line antimalarial.¹⁷ However the development of strains with mutated *dhps* and *dhfr* genes limits the efficacy of this combination.³ However, due to its low price, the combination of S/P with compounds **1-1**, **1-5**, or artesunate is still widely used in Africa. As a treatment, S/P is well tolerated; it is also used for intermittent preventative treatment for pregnant women. As prophylaxis, S/P has been contraindicated, due to severe adverse effects such as toxic epidermal necrolysis and Stevens–Johnson syndrome.¹⁴

F. Artemisinin

Artemisinin (**1-8**) and its synthetic derivatives are currently the most active drugs against the *P. falciparum* parasite. It is isolated from *Artemisia annua* (an herb employed in Chinese traditional medicine). Ms. Tu Youyou shared the 2015 Nobel Prize in medicine for her important role in the discovery of artemisinin. Artemisinin

contains an unusual peroxide bridge. Although the mechanism of action is not clear as of 2016, it is commonly believed that the peroxide bridge is cleaved and creates free radicals, which could attack susceptible proteins in the *P. falciparum* parasite.³⁷

G. Piperaquine

Piperaquine (**1-9**) is a bis-4-aminoquinoline first synthesized in 1960 in France. It was used extensively in China and Indonesia for the following 20 years.³⁸ Generally, for *P. falciparum* and *P. vivax*, piperaquine has better tolerability while possessing the same efficacy as chloroquine. With these advantages, it took over chloroquine's position as the first line antimalarial recommended by the Chinese National Malaria Control Program, and 140 million adult doses were distributed. The overuse of this drug quickly resulted in piperaquine-resistant *P. falciparum* strains. Later in the 1980s, the rise of artemisinin derivatives gradually became mainstream antimalarials. Piperaquine has recently re-emerged as a combinational drug for ACT due to its low cost, tolerability, and low resistance in Africa regions. The combination of piperaquine and dihydroartemisinin shows good tolerability and efficacy, and also shows higher efficacy against *P. vivax* than artesunate/amodiaquine.

H. Halofantrine/lumefantrine

Halofantrine (**1-10**) and lumefantrine (**1-11**) do not have quinoline structures but still possess the β/γ amino alcohol moiety seen in compounds **1-1** and **1-4**. Halofantrine is effective against chloroquine-resistant *Plasmodium* strains but causes cardiac arrhythmia in some cases.¹⁴ Lumefantrine also exhibits good efficacy against chloroquine resistant *Plasmodium* strains, although less potently. Furthermore,

compound **1-11** does not have the risk of causing cardiac arrhythmia.³⁹ In vitro synergism with artemether has also been reported.⁴⁰

Mechanism of action of quinoline-based antimalarial drugs

Inhibition of heme crystallization to hemozoin in the acidic food vacuole is one common mechanism proposed for quinoline-based antimalarial drugs.⁴¹ Quinoline-based drugs (in particular 4-aminoquinolines) are considered to act on ferriprotoporphyrin IX (FPIX) heme in the food vacuole of *Plasmodium* species.⁴² During the trophozoite stage of the intraerythrocytic cycle, hemoglobin is proteolyzed, giving FPIX.⁴³ In the parasite vacuole, the absence of the heme oxygenase pathway would result in FPIX remaining in its toxic free state.⁴⁴⁻⁴⁶ Thus the parasite will pack the FPIX into its “head-to-tail” oxo-bridged dimers, which then polymerize into crystalline hemozoin, also known as malaria pigments. The crystalline form of FPIX is nontoxic to the parasite. It is believed that quinoline-based antimalarials can inhibit the formation of hemozoin, thereby thwarting the detoxification and killing the parasite.⁴⁷ This is clearly the consensus mechanism for chloroquine (**1-2**). Interestingly, mefloquine (**1-4**) has also been proved to inhibit heme crystallization in vitro,⁴⁸ and can associate with parasite-derived hemozoin.⁴⁹ Mefloquine can also reduce the hemozoin level in vitro,⁴¹ although mefloquine is considerably less potent than chloroquine in this activity.

However, resistance to mefloquine and chloroquine in *Plasmodium* strains emerge from different mechanisms.⁴⁸ *Pf*CRT and *Pf*MDR1 are two *Plasmodium* parasite food vacuole transporters. These transporters can control the transport of quinoline-based drugs at the food vacuole membrane. Chloroquine-resistant strains

containing mutant *PfCRT* have been shown to transport chloroquine out of the food vacuole. Decreased chloroquine concentration in the food vacuole leads to less inhibition of hemozoin formation, thus and more heme-induced toxicity.

Mefloquine resistance on the other hand is associated, not with the mutant *PfCRT*, but rather the upregulation of *PfMDR1*. The upregulation of *PfMDR1* results in increase of solutes pumping, including mefloquine, into the food vacuole. When *PfMDR1* is genetically downregulated, mefloquine shows a higher potency. Ghavami et al. have thus argued that if the mefloquine-resistance mechanism involves pumping mefloquine out of the food vacuole, then clearly the target of mefloquine does not reside in the food vacuole, but rather outside.⁵⁰ Mefloquine is observed to inhibit cytosomal endocytosis of host hemoglobin.⁵¹⁻⁵³ Chloroquine, on the other hand, is proposed to inhibit vesicle trafficking. The proposal that mefloquine's antimalarial action is due to inhibition of hemoglobin uptake by the parasite received further experimental support in published work from Ghavami et al.⁵⁰ As described above, the usefulness of our current antimalarial "toolbox" is decreasing as drug resistance emerges. As a recent review pointed out, "The glass is still half empty",⁷ and development of new drugs is still needed.

The Malaria Box

GlaxoSmithKline,⁵⁴ Novartis,⁵⁵ and St. Jude Children's Research Hospital, Memphis⁵⁶ screened approximately 6 million compounds against the blood-stage *P. falciparum*, and found approximately 0.5% of these compounds with sub-micromolar potency. The HTS results were published in order to help with: i) identification of new biological pathways and revealing new targets for drug development; ii)

providing a starting point for hit-to-lead optimization; and iii) serving as a clue to identify new compounds capable of killing parasites and pathogens other than *P. falciparum*. However, the overwhelmingly large number of hit compounds is not practical for the majority of researchers to study.

To provide a practical collection of hits, the so-called “Malaria Box” effort was launched.⁵⁷ The collection of 20,000 hits was filtered and simplified, and the result of this simplification effort is a collection of 400 compounds known as the Malaria Box.⁵⁷ (Figure 1-3)

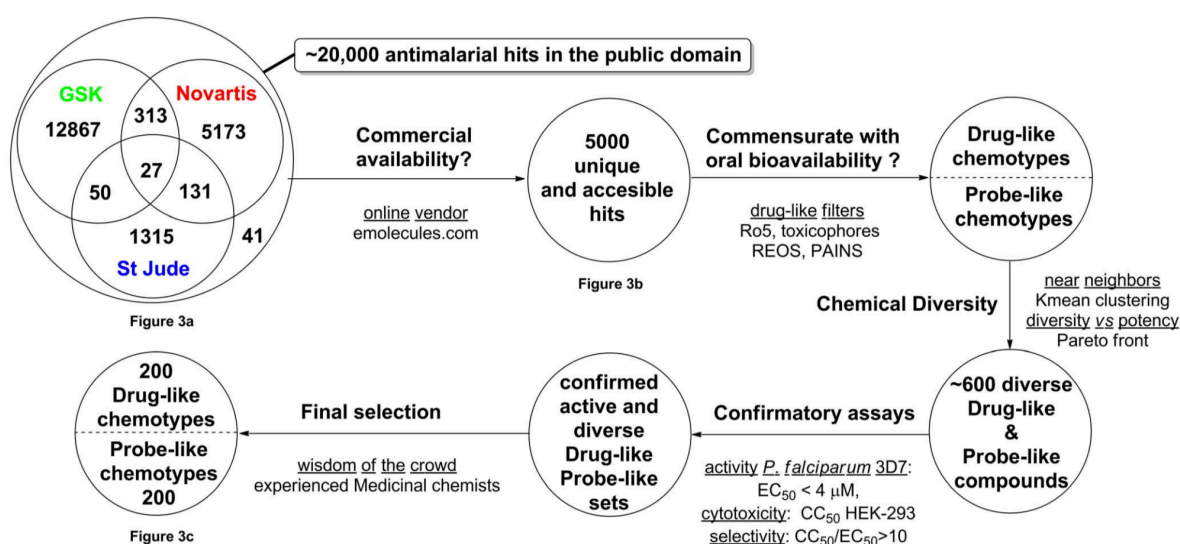


Figure 1-3. The selection process of the Malaria Box (adapted from Spangenburg et al., 2013⁵⁷)

The first selection criterion was commercial availability. Out of the 20,000 compounds, 5,034 commercially available hits were selected. The five-thousand compounds were then classified into two categories: drug-like and probe-like. Rule-of-5 screening was first applied to ensure oral-bioavailability; the structures of the

remaining compounds were then filtered for known toxicophores; the liability of the remaining set was screened with PAINS⁵⁸ (Pan Assay Interference Compounds) and REOS⁵⁹ (Rapid Elimination of Swill) filters. After the filters, 2,693 compounds did not violate any criteria, and are classified as the “drug-like” set, and the remaining 2,341 compounds are classified as the “probe-like” set.

The 5,034 commercially available compounds were further narrowed by clustering into representative subgroups to ensure chemical diversity, and results in a collection of 600 compounds. The potency of these compounds was confirmed with both *P. falciparum* 3D7 and K1 strains. A good correlation between activities of two strains (EC_{50}) was observed. All compounds had to exhibit a $EC_{50} < 4 \mu\text{M}$ for *P. falciparum* 3D7 strain to be qualified, and a >10-fold selectivity ratio against cytotoxicity (HEK-293 cell line) was also required. Finally, 400 compounds were picked by experienced medicinal chemists, and this group constitutes the final Malaria Box. Out of the 400 compounds, 200 were classified as “probe-like”, and 200 were classified as “drug-like”.⁵⁷

Two particular compounds in the Malaria Box form the basis of my PhD thesis projects. Our group collaborated with two biochemists from Virginia Tech to search for antimalarials with novel mechanism of action from the Malaria Box. Our collaboration with Dr. Cassera (now at University of Georgia) focuses on the optimization of MMV008138; on the other hand, the collaboration with Dr. Klemba works on another potent candidate MMV665831. To understand the antimalarial property of MMV008138, I will first discuss the apicoplast, an organelle of *P. falciparum*, and its relationship to a therapeutic strategy for antimalarial medication.

The apicoplast

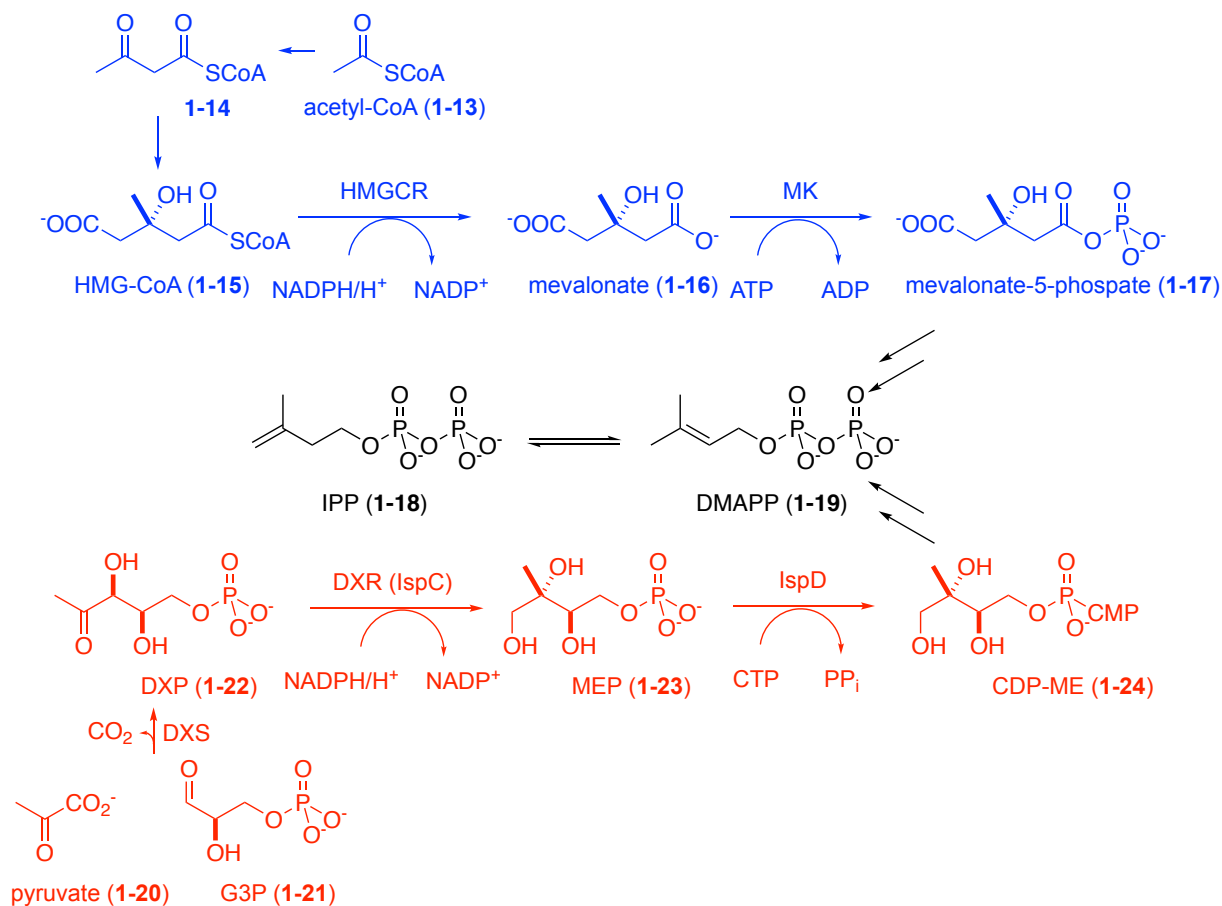
The *Plasmodium* parasite belongs to the phylum *Apicomplexa*, and possesses an organelle called the apicoplast. The apicoplast organelle was first discovered in the 1960s from *Eimeria* and *P. lophurae* and is distinct from the nuclear and mitochondrial genomes.⁶⁰⁻⁶¹ It was proposed that the *Apicomplexa* obtained the apicoplast from algae from the endosymbiosis process,⁶² and in 2008 evidence was found that apicomplexan parasites evolved from photosynthetic algal ancestors.⁶³ As the apicoplast was obtained from algae ancestors via endosymbiosis, many enzymes in the apicoplast differ fundamentally from that of humans.

Although the vestigial plastid has lost its ability for photosynthesis, other functions critical to parasite growth were retained.⁶⁴ Disrupting the biosynthetic pathways in the apicoplast can stop the replication of the parasite in the host. The indispensability of the apicoplast was validated with two approaches: i) chemical disruption of the apicoplast biosynthesis pathway; and ii) creation of mutant parasite strains that are unable to replicate the apicoplast. In both cases, the parasite can still survive in the host cell, but lacks the ability to infect new cells. This phenomenon is known as “delayed-death”. One possible explanation for this phenomenon is that the apicoplast is responsible for the synthesis of a compound that is directly or indirectly involved in the infection process.⁶⁴ The essential biological function of apicoplast, combined together with the distinct enzymatic origin, made the apicoplast an ideal target for developing novel antimalarials. The metabolic maps and biological functions of the apicoplast are well studied, and one of these potential pathways is the MEP pathway.

The MEP pathway

The isoprenoids are a group of over 55,000 compounds that exhibit various biological functions including antibacterial, anticancer, antiparasitic, anti-inflammatory, and antiviral properties.⁶⁵ The isoprenoids are mostly low molecular weight molecules. Despite the diverse medicinal application, their biological functions were not well investigated until the 1970s.⁶⁶

Isoprenoids are biosynthesized from two common building blocks: the isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP).⁶⁷ IPP and DMAPP were initially believed to be synthesized solely via the mevalonate pathway from acetyl-CoA building block.⁶⁸ However discrepancies seen in isotopic labeling studies led to the discovery of the 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway (also known as the non-mevalonate pathway), which uses pyruvate and D-glyceraldehyde 3-phosphate. (Scheme 1-2)



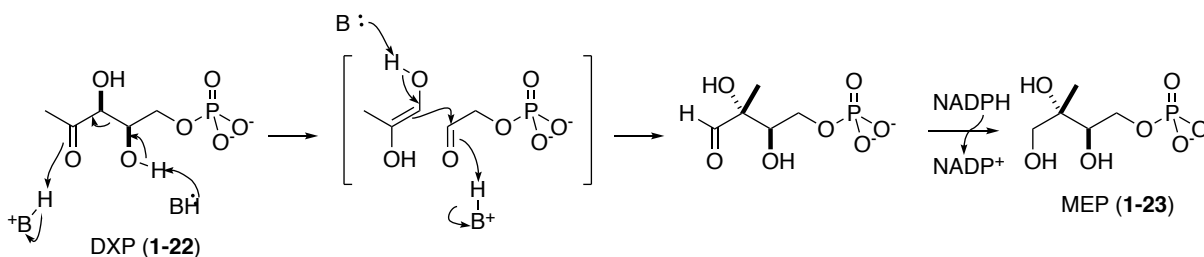
Scheme 1-2. The mevalonate pathway (blue) and the MEP pathway (red)

In the mevalonate pathway, two acetyl-CoA **1-13** were condensed to give acetoacetyl-CoA **1-14**, followed by another condensation with a third acetyl-CoA to give HMG-CoA **1-15**. Reduction of HMG-CoA gave mevalonate **1-16**, from which the mevalonate pathway got its name. The mevalonate was then phosphorylated twice, and subsequent decarboxylation and hydroxyl elimination yielded the IPP **1-18** and DMAPP **1-19**.

In the MEP pathway, instead of starting from acetyl-CoA **1-13**, pyruvate **1-20** and glyceraldehyde 3-phosphate (G3P) **1-21** were used as the starting material. Catalyzed by DXP synthase, pyruvate **1-20** and G3P **1-21** were condensed to give 1-

deoxyxylulose-5-phosphate (DXP) **1-22**. The rearrangement from DXP **1-22** to MEP **1-23** was proposed to happen via a retro-aldol/aldol reaction, followed by reduction.⁶⁹

(Scheme 1-3)



Scheme 1-3. DXP undergoes retroaldol/aldol-reduction to form MEP

The DXP **1-22** is first cleaved into an ene-diol and aldehyde via a retroaldol reaction, and recombined via an aldol reaction to achieve the skeletal rearrangement. Subsequent NADPH reduction converts the intermediate into MEP **1-23**. The MEP **1-23** is then coupled with cytidine 5'-triphosphate (CTP) catalyzed by the IspD enzyme to give methylerythritol cytidyl diphosphate (CDP-ME) **1-24**. Then CDP-ME **1-24** was phosphorylated, cyclized, ring-opened, and dehydrogenated to give IPP **1-18** and DMAPP **1-19**. (Scheme 1-2)

Both the mevalonate and the MEP pathway are biosynthetic pathways nature uses to produce isoprenoids precursors IPP **1-18** and DMAPP **1-19**. These two pathways are well-separated in different kingdoms.⁷⁰ Human, along with other animals, and fungi utilize the mevalonate pathway, while eubacteria and green algae utilize the MEP pathway. In plants, both the mevalonate and the MEP pathway are present, but the mevalonate pathway only happens in the cytosol. As discussed earlier, the *Plasmodium* parasite contains a relict plastid organelle called the apicoplast, which was obtained from algae from the endosymbiosis process. Like

green algae, the *Plasmodium* relies on the MEP pathway to produce IPP and DMAPP,⁷¹ which are essential for the parasite to infect other cells. Compounds that can selectively target the MEP pathway thus have potential to become a promising antimalarial drug.

MMV008138

As mentioned above, the *Plasmodium* parasite uses the MEP pathway to synthesize IPP and DMAPP. To identify compounds that target the MEP pathway, our collaborator Prof. Cassera examined the 400 compounds from the Malaria Box for their effects on asexual blood-stage *P. falciparum* Dd2 strain, with and without IPP supplementation. The IPP supplementation procedure, also known as the “IPP rescue” assay was developed by other workers to assess the effects of various compounds on the apicoplast.⁷¹

An IspC inhibitor fosmidomycin was used as a positive control. Fosmidomycin is structurally similar to DXP, the substrate of the IspC enzyme in the MEP pathway. (Figure 1-4) By inhibiting the IspC enzyme, which catalyzes the transformation from DXP to MEP, the MEP pathway is blocked, and the parasite could not perform the biosynthesis of IPP and DMAPP, which eventually results in the parasite death. Fosmidomycin has shown *in vivo* activity against mice infected with *P. vinckei*, and went to clinical trial in combination with clindamycin.⁷²

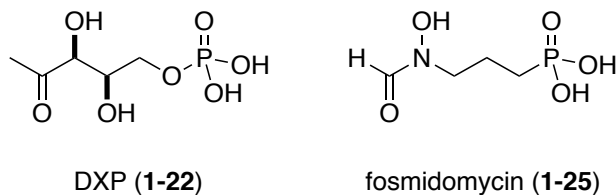
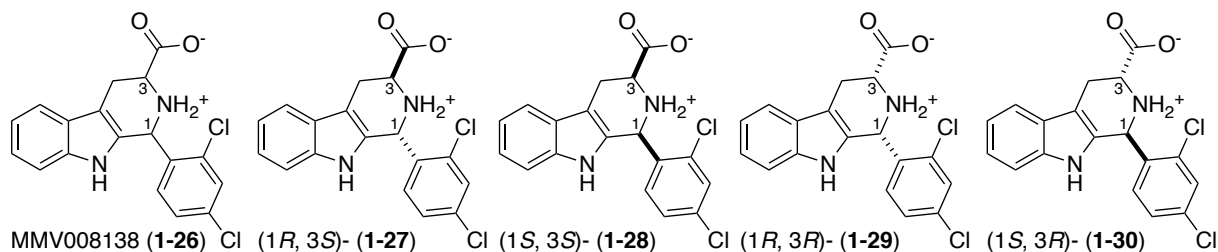


Figure 1-4. Fosmidomycin is structurally similar to the IspC substrate DXP

The *P. falciparum* treated with positive control fosmidomycin was 100% rescued following the addition of IPP, which is expected from an IspC inhibitor. For the 400 compounds in the Malaria Box, over 95% of the compounds showed parasite growth inhibition potency at 5 μ M, and after 200 μ M IPP was supplemented, only one compound showed $\geq 60\%$ IPP rescue. This compound was MMV008138 (1-26), which had a *P. falciparum* Dd2 growth inhibition IC_{50} of 210 ± 90 nM.⁷³ The structure of MMV008138 contains two stereocenters, but the absolute stereochemistry was not specified in the Malaria Box. To identify the active stereoisomer, all four stereoisomers 1-27 to 1-30 were prepared and tested against the *P. falciparum* Dd2 strain. (Table 1-1)

Table 1-1. *P. falciparum* Dd2 strain growth inhibition and % rescue with IPP supplement of MMV08138 and stereoisomers⁷³

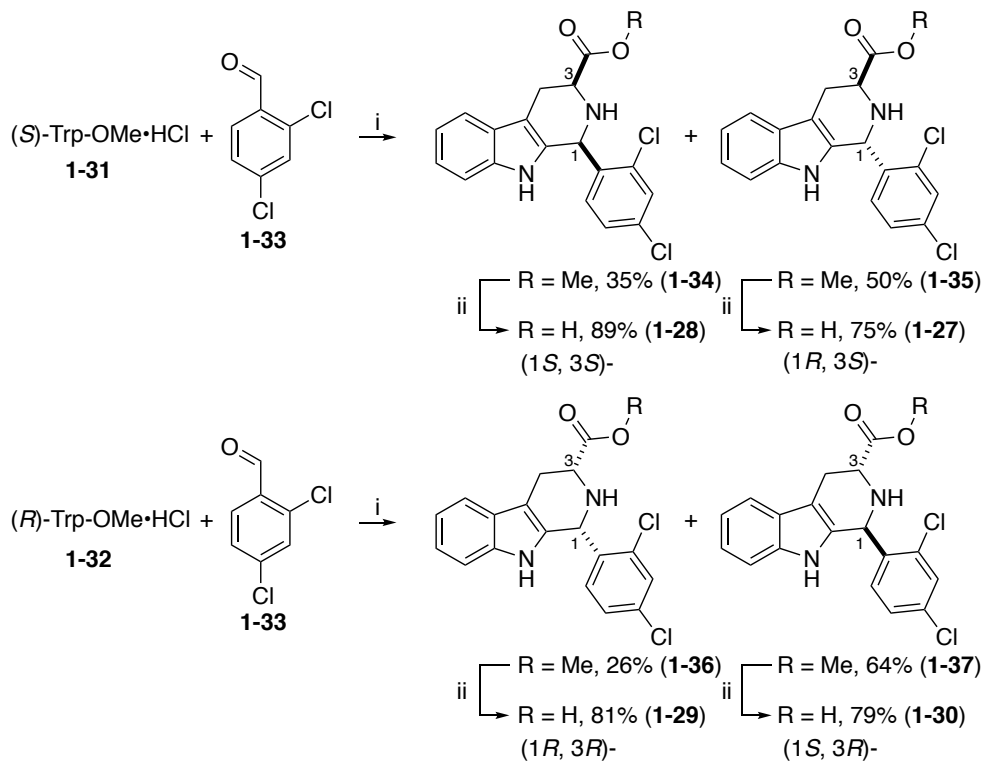


Compound	Absolute stereochemistry	<i>P. falciparum</i> Dd2 strain growth inhibition IC ₅₀ (nM)	% rescue (+ 200 μM IPP)
1-26	Not specified	210 ± 90	100% @ 2.5 μM
1-27	(1 <i>R</i> , 3 <i>S</i>)-	250 ± 70	100% @ 2.5 μM
1-28	(1 <i>S</i> , 3 <i>S</i>)-	>10,000	Not determined
1-29	(1 <i>R</i> , 3 <i>R</i>)-	3,000 ± 200	Not determined
1-30	(1 <i>S</i> , 3 <i>R</i>)-	>10,000	Not determined

The stereoisomers were readily prepared with the Pictet–Spengler reaction. Enantiopure L-tryptophan methyl ester hydrochloride **1-31** and D-tryptophan methyl ester hydrochloride **1-32** were separately condensed with 2,4-dichlorobenzaldehyde **1-33**, 4Å molecular sieves were added to remove the water generated; the resulting imine was treated with trifluoroacetic acid to facilitate the cyclization of the tetrahydro-β-carboline ring. The L-tryptophan methyl ester hydrochloride **1-31** gave a mixture of *cis*-/*trans*-diastereomers **1-34** and **1-35**; similarly the D-tryptophan methyl ester hydrochloride **1-32** gave **1-36** and **1-37**. The *cis*-/*trans*-diastereomers were

separated with column chromatography, then separately hydrolyzed with an Amberlyst hydroxide “catch-and-release” protocol to give the product **1-27** to **1-30**.⁷⁴

(Scheme 1-4)



Scheme 1-4. Synthesis of the stereoisomers of MMV008138. Reagents and conditions: (i) 4 Å molecular sieves, CH₂Cl₂, 20 h; TFA (2 equiv, 44 h). (ii) Amberlyst hydroxide, THF/MeOH/H₂O; AcOH, H₂O (Adapted from Yao et al. 2015⁷³)

Out of the four stereoisomers, only the (*1R, 3S*)-isomer **1-27** was equipotent to **1-26**, exhibiting a *P. falciparum* growth inhibition IC₅₀ of 250 ± 70 nM, which was similar to the potency of **1-26** at 210 ± 90 nM. All other three isomers **1-28** to **1-30** were not potent. The (*1R, 3R*)-isomer **1-30** had an IC₅₀ of 3,000 ± 200 nM, while the (*1S, 3S*)- and (*1S, 3R*)-isomers **1-28**, **1-29** showed no inhibition at > 10,000 nM.

These results suggested that the MMV008138 in the Malaria Box is the pure (1*R*, 3*S*)-isomer. In the IPP rescue assay **1-26** and **1-27** also have similar profile, further supported that MMV008138 in the Malaria Box is the (1*R*, 3*S*)-isomer.

After the absolute stereochemistry of the lead compound was determined, our group prepared various analogs of **1-27** featuring D-ring and C3-ester variations.^{73, 75} My work continued from here, following Dr. Maryam Ghavami's initial work on the B- and C-ring. My work will be discussed in Chapter 2, including the preparation, biological activity, and conformation study of B- and C-ring analogs. The ketone Pictet–Spengler reaction is a critical tool used to prepare many analogs in the following chapter, and a novel ring-expansion reaction was discovered by Dr. Ghavami while preparing C1-Me analogs. My work to establish the scope and mechanism of this expansion reaction will be discussed in Chapter 3, together with computational studies to explain the driving force of this expansion reaction.

Endocytosis of erythrocyte hemoglobin

Asexual reproduction of *P. falciparum* in human blood leads to clinical malaria symptoms. After infection, *P. falciparum* degrades up to 75% of host erythrocyte hemoglobin.⁷⁶⁻⁷⁷ The degradation of erythrocyte hemoglobin takes place via the endocytosis pathway, which consists of several stages (Figure 1-5). The host erythrocyte hemoglobin is endocytosed at the cytostome. From there, hemoglobin is transferred to the food vacuole, where degradation of hemoglobin takes place. The mechanism of how hemoglobin was transferred from the cytostome to the food vacuole is not clear. Other non-cytostome phagotrophic structures were also

observed,⁷⁸ but it remains unclear whether they are related to hemoglobin endocytosis.⁷⁹

Hemoglobin is metabolized in the parasite food vacuole, which contains a large number of exo- and endopeptidases. These peptidases can catalyze the hydrolysis of α - and β -globin into the corresponding amino acids. *P. falciparum* further uses these amino acids for the synthesis of proteins and other biological activities.

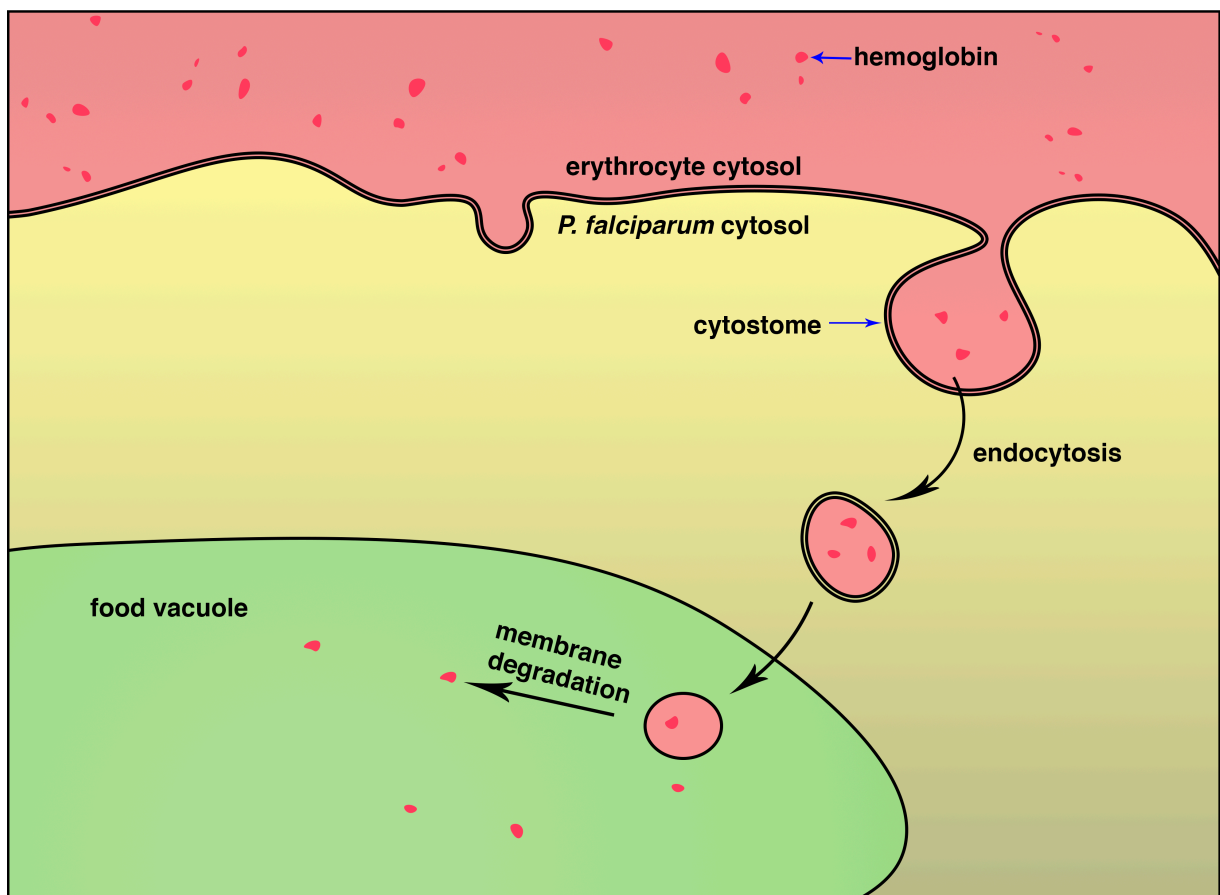


Figure 1-5. Endocytosis as a method to transport hemoglobin through cell membrane into the parasite cytosol

Monitoring hemoglobin catabolism kinetics

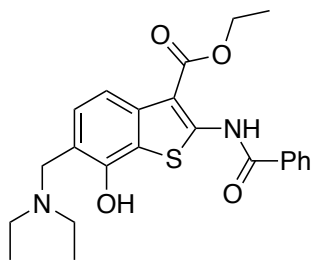
P. falciparum degrades far more hemoglobin than it needs. Only about one fifth of the amino acids from hemoglobin are used by *P. falciparum* for its physiological activities.⁷⁷ A large amount of amino acids is discharged into the medium.⁸⁰ Interestingly, the relative abundance of discharged amino acids was very well correlated to that of host hemoglobin.⁸¹

Dalal and Klemba adapted this concept to develop a very sensitive and rapid UPLC method that could measure the rates of amino acid efflux from parasitized red blood cells.⁷⁹ *P. falciparum*-infected human red blood cells were found to efflux amino acids at a constant rates for up to 8 h, leading to linear plots of concentration vs time for the various amino acids. Thus, the concentrations of amino acids present in the medium at a given time point corresponds to their efflux rates: the higher the concentration, the higher the rate. For nine non-polar amino acids, the observed amino acid abundance shows good correlation ($R^2 = 0.90$) with the amino acid abundances in α - and β -globin. In, contrast, the observed amino acid abundances showed a poor correlation to those of myoglobin and the average amino acid abundances in the UniProt database (a database containing a large amount of protein sequence information). These observations are consistent with the idea that hemoglobin metabolism is a major contributor to the observed amino acid efflux, and that this efflux can serve as a useful tool to monitor the hemoglobin endocytosis process.⁷⁹ As the relative abundance of leucine in hemoglobin is relatively high, it is convenient to follow its efflux from parasitized red blood cells; we will refer to this below as the Leu efflux assay. Note that the Carrier group previously collaborated

with Prof. Klemba to study mefloquine and 19 of its non-piperidine analogs with this Leu efflux assay. Interestingly, an excellent correlation was seen between Leu efflux and *P. falciparum* growth inhibition IC₅₀ values, over 4 orders of magnitude.⁵⁰ As mefloquine and the analogs are not expected to have any protease inhibition activity, the correlation between Leu efflux and growth inhibition potencies could indicate that mefloquine's antimalarial action arises from inhibition of hemoglobin endocytosis or trafficking.

MMV665831

As previously described, amino acid efflux can serve as a powerful tool to monitor the hemoglobin endocytosis process. Our collaborator Prof. Klemba screened the Malaria Box with the Leu efflux assay. The initial threshold was to see which compounds at a concentration of 1 μ M reduced Leu efflux to a similar extent as did 310 μ M of mefloquine. Twenty such compounds (5% of the Malaria Box) met this threshold. These compounds were examined in greater detail and nine were found to have Leu efflux values \leq 400 μ M. The most potent of these compounds was MMV665831 (**1-38**), for which the *P. falciparum* growth inhibition IC₅₀ and the Leu efflux IC₅₀ values are very similar. (Figure 1-6) This compound is classified by MMV as "probe-like," though no reasons for this designation were stated. We believe that the phenolic Mannich base functionality disqualifies it from the "drug-like" subgroup. The hit-to-lead optimization of **1-38** will be discussed in Chapter 4. To close this chapter, I will discuss potential chemical and biological consequences of the Mannich base functional group.



MMV665831 (**1-38**)
Growth $IC_{50} = 11 \pm 2$ nM
Leu Efflux $IC_{50} = 11$ nM

Figure 1-6. *P. falciparum* 3D7 growth inhibition IC_{50} and Leu efflux IC_{50} of MMV665831

Pan Assay Interference Compounds (PAINS) and the reactivity of phenolic Mannich bases

The phenolic Mannich base moiety in **1-38** is a well-known functional group considered to be a PAIN.⁵⁸ HTS is an important technique for pharmaceutical companies. With the aid of HTS, people can screen large numbers of compounds quickly in search of certain biological activity. Inevitably, false positive results will interfere with this process and can dominate the real hits.⁸² This is due to the fact that most compounds being screened are inactive. According to Pfizer's data, approximately 120,000 compounds need to be screened to give 1 lead compound.⁸³ Even if the HTS is 99.9% accurate, the remaining 119,999 compound would randomly give almost 120 false positives. Obviously, it would be very important that these false positive results be excluded from the result database. Usually, a confirmatory re-screen can eliminate most random false positives.

However, there are also compounds that constantly interfere with the screening process. Formation of protein aggregates, covalent reaction with proteins, or direct

interference with HTS readout are all possible reasons for these false positives. By reviewing and analyzing numerous previous HTS data, Baell and Holloway⁵⁸ managed to identify several structural characteristics that emerge frequently as false positives, known as PAINs (Figure 1-7).

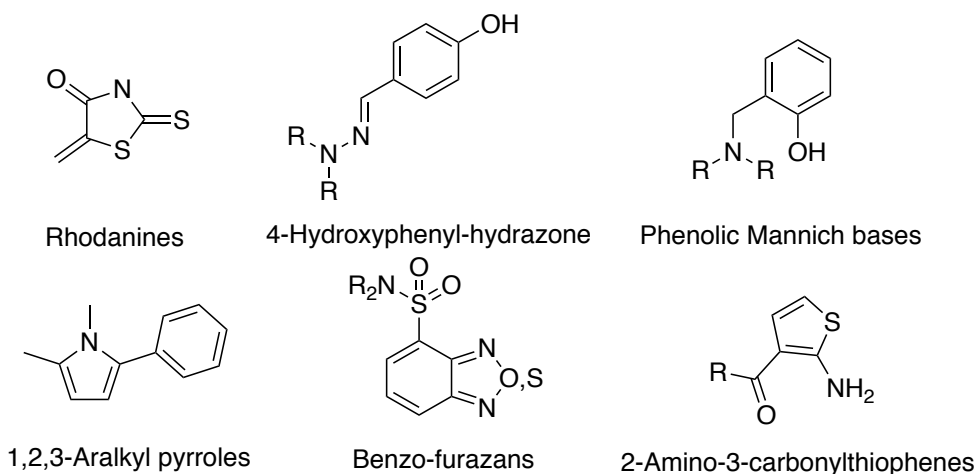


Figure 1-7. Examples of PAINs

Phenolic Mannich base

In 2015 computational tools to identify PAINs and reactive functionality were not widely available. So, at that time, a colleague of Dr. Carlier, Dr. Georgia McGaughy of Vertex Pharmaceuticals, examined **1-38** by using their in-house software (Figure 1-8). Compound **1-38** passed the REOS test with no violations, but the phenolic Mannich base moiety was identified by the software as a PAINs violation. Interestingly, the 2-amino-3-carbonylthiophene in **1-38** was not recognized as PAINs violation.

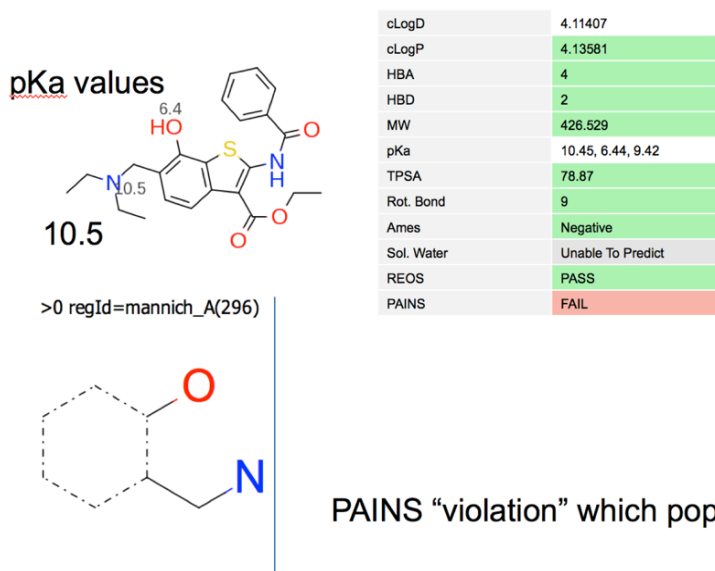
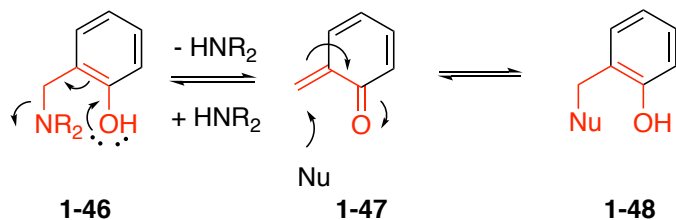


Figure 1-8. Computational analysis of **1-38** (courtesy of Dr. Georgia McGaughey, Vertex Pharmaceuticals)

Dr. Paul Carlier then contacted Dr. Jonathan Baell, the originator of the PAINS classification system regarding the 2-amino-3-carbonylthiophene moiety present in the AD11 molecule. Dr. Baell suggested that the benzothiophene likely exhibits different redox properties than the thiophene analog, and thus may not be problematic.⁸⁴ His comments further confirm the Vertex Pharmaceuticals computational analysis.

The phenolic Mannich base moiety in **1-38** is concerning to us because of its potential reactivity. (Scheme 1-5) Phenolic Mannich bases like **1-46** are unstable and can form quinone methides **1-47**, which can be highly electrophilic⁸⁵⁻⁸⁶ and can bond covalently to biological nucleophiles under physiological conditions.⁸⁷⁻⁸⁹



Scheme 1-5. Unstable phenolic Mannich base is potential toxicophore

Weinert et al.⁸⁵ tested the reactivity of the phenolic Mannich bases **1-49** to **1-53** towards water as a generic nucleophile. The half-life ($t_{1/2}$) for conversion of these compounds into the corresponding benzylic alcohols was found to be quite sensitive to electronic effects. Unsubstituted compound **1-51** had a $t_{1/2}$ value of 115 min at 50 °C, but the presence of electron-withdrawing groups at C4 or C5 slowed the reaction considerably, to the point that **1-49** showed no decomposition over 3 h at 100 °C. In contrast, the addition of electron-donating groups significantly enhanced reactivity, presumably since they can assist ejection of the HNR_2 unit. Both **1-52** and **1-53** had $t_{1/2}$ values of less than 15 min at 22 °C! (Figure 1-9).

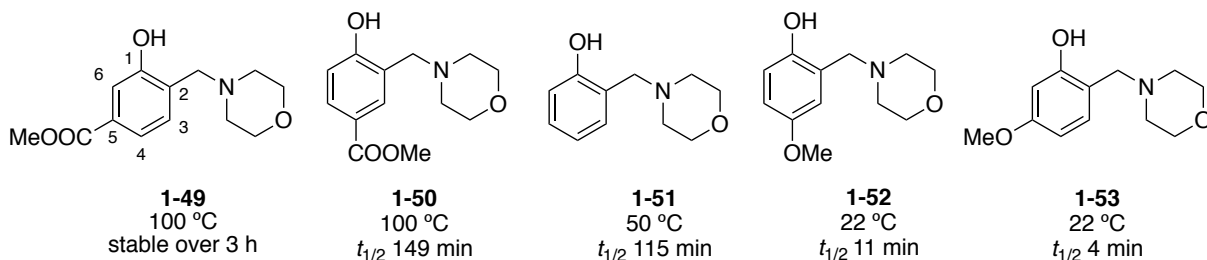


Figure 1-9. Substituent effects on phenolic Mannich base stability in water

The development of the synthetic route to **1-38** and structural analogs will be discussed in Chapter 4. The stability of the phenolic Mannich base moiety, and strategies to prevent the formation of quinone methides will also be included. Lastly, the biological activity of the analogs will be reported and discussed.

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Chapter 2. Probing the B- and C-Rings of Antimalarial MMV008138 for Metabolic Hot Spots, Steric Demand, and Conformational Constraints

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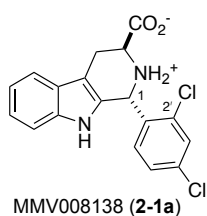
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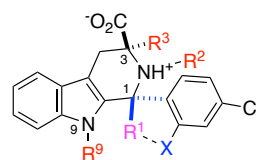
*This chapter has been adapted from a manuscript (submitted to Bioorganic & Medicinal Chemistry Letters) by the authors listed above. P.R.C., S.D., and M.G. designed analogs of **1a**, and S.D. and M.G. synthesized them. J.H.B., E.F.M., and M.B.C. developed and performed the in vitro assays. C.S. performed X-ray crystallography. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.*

Abstract

The antimalarial candidate MMV008138 (**2-1a**) is of particular interest because its target enzyme (IspD) is absent in human. Although **2-1a** is potent against in vitro *Plasmodium falciparum*-infected human erythrocytes, it did not present in vivo therapeutic efficacy in either *P. berghei*-infected mice (murine malaria model) nor in a SCID mouse model of human *P. falciparum* malaria.



Dd2 strain *P. falciparum*
 growth inhibition $EC_{50} = 250 \pm 70$ nM
 Poor stability in mouse liver microsomes



12 analogs explored, including
 C1, N2, C3, and N9 substitution
 and spiro-fusion at C1.

Only D-1 analog **2-2a** retains
 potency
in vitro; microsomal stability
 slightly improved.

To achieve higher potency, and to mitigate perceived metabolic liabilities, a series of analogs of **2-1a** were prepared that featured deuterium or methyl-substitution of the B- and C-rings, as well as ring-chain transformations. X-ray crystallography, NMR spectroscopy and calculation were used to study the effects of these modifications on the conformation of the C-ring and orientation of the D-ring. Unfortunately, with the exception of 1-D analog **2-2a**, all the other analogs explored lost *in vitro* antimalarial activity.

Introduction

Malaria was estimated to be responsible for 435,000 deaths worldwide in 2017.¹ Many prevention methods and drug treatment protocols are available, but emerging resistance to artemisinin and its partner drugs is of great concern. Thus there is a pressing need to develop antimalarials that possess new mechanisms of action.² Malaria is caused by *Plasmodium* parasites, of which *P. falciparum* is the most prevalent, accounting for more than 96% of the malaria cases worldwide.¹ *Plasmodium sp.* contain a relict organelle termed the apicoplast, which is responsible for the biosynthesis of the critical isoprenoid precursors isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP).³ Whereas *Plasmodium sp.* synthesize these compounds via the methylerythritol phosphate (MEP) pathway, the mevalonate pathway is used to synthesize them in humans.³ This biochemical divergence

commends the MEP pathway as a target for antimalarial drug development,⁴ since inhibitors of MEP target enzymes would not adversely affect IPP biosynthesis in humans.

Our initial work in this area⁵ identified MMV008138 as a MEP pathway inhibitor, by performing a phenotypic screen of the 400-compound Malaria Box⁶ with the IPP rescue protocol.³ MMV008138 is a tetrahydro- β -carboline, and differentially-functionalized examples of this scaffold are found in a number of other antimalarials.⁷⁻¹² Subsequent resistance selection studies by Wu et al. demonstrated that 2-C-methyl-D-erythritol-4-phosphate cytidyltransferase (IspD, E.C.2.7.7.60), the third enzyme in the MEP pathway, is the target of MMV008138.¹³ Initially, the absolute configuration of MMV008138 was unknown, since it was not disclosed in the Malaria Box; subsequently three independent investigations¹³⁻¹⁵ demonstrated that the active stereoisomer is (1*R*, 3*S*)-configured, as depicted in **2-1a** in Figure 2-1. Kinetic studies established that **2-1a** competes with cytidine triphosphate (CTP) in its IspD-catalyzed reaction with 2-C-methyl-D-erythritol-4-phosphate.¹⁵

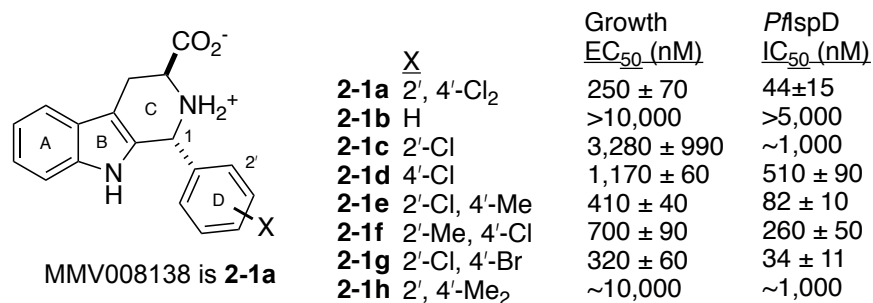


Figure 2-1. Lead compound **2-1a** and tight D-ring SAR. Note that the X= 2'-Br, 4'-Cl and X= 2'-Cl, 4'-F analogs are also potent in both assays¹⁶⁻¹⁷

A collection of D-ring analogs of **2-1a** was prepared by the Pictet–Spengler (PS) reaction of L-Trp-OMe·HCl with various benzaldehydes, separation of diastereomers, and hydrolysis.^{14, 18} Examination of these analogs in both *in vitro* growth inhibition (SYBR Green) and *P. falciparum* IspD (*PfIspD*) inhibition assays show a very close correlation between growth inhibition (EC₅₀) and target engagement (IC₅₀).¹⁸ These data also demonstrate a very tight SAR on the D-ring. At least one halogen is required on the 2'- or 4'- position to retain potency in both assays, as shown in Figure 2-1; substitution at other D-ring positions is not tolerated. It thus appears that the D-ring of **2-1a** binds within a snug, well-defined pocket of *PfIspD*. Note that several species of IspD (including *Escherichia coli* and *Arabidopsis thaliana*) have yielded high resolution X-ray structures. However, *PfIspD* features several long and apparently unstructured insertions not present in such crystallized IspDs, and **1a** does not potently inhibit any of these enzymes.¹³ Therefore, we do not consider it prudent to carry out docking studies of the compounds described in this paper with *PfIspD* homology models based on these crystallized IspDs. In the absence of an X-ray structure for this species of IspD, we have speculated¹⁸ that halogen-bonding¹⁹ contributes to the affinity of **2-1a** for its target.

The *in vivo* activity of **2-1a** was tested in two different types of mouse models—the murine malaria model with *P. berghei* and the humanized mouse model (NODscidIL2R γ ^{null} mice engrafted with human erythrocytes) with *P. falciparum* *Pf3D7*^{0087/N9}. The *P. berghei* test was performed at the Anti-Infectives Core Facility, Department of Microbiology, School of Medicine, New York University. The *P.*

falciparum infected NODscidIL2R γ^{null} mice efficacy was performed by Swiss Tropical and Public Health Institute under Medicines for Malaria Venture's contract.

The *P. falciparum* strain does not infect mice in the erythrocytic stage, and the rodent or avian strains (*P. berghei* and *P. yoelii*, respectively) are often used as alternatives. However, the difference in strains can sometimes give misleading results.²⁰ NODscidIL2R γ^{null} mice were thus developed as a humanized mouse model.²¹ Such SCID (severe compromised immunodeficiency) mice are engrafted with human erythrocytes and thus these mice are susceptible to human malaria parasites such as *P. falciparum*. The chloroquine-sensitive Pf3D7 strain 0087/N9 was selected to induce parasitemia in these mice.²²

Unfortunately, **2-1a** did not provide *in vivo* therapeutic efficacy at 40 mpk po in *P. berghei*-infected mice (murine malaria model), nor at 50 mpk po in the aforementioned SCID mouse model of human *P. falciparum* malaria. (Tables 2-1 and 2-2) The five chloroquine-treated mice survived the 7-day assay and had an average luminescence of $4.7 \pm 0.2 \times 10^3$ (arbitrary units). Two of the five vehicle-treated mice survived, and these two had an average luminescence of 2.4×10^7 . Only one of the **2-1a**-treated mice survived, and it had a luminescence of 1.3×10^6 .

Table 2-1. Effect of **2-1a** on *P. berghei*-infected mice survival

Days post-infection	Number of survived mice		
	Vehicle	2-1a	Chloroquine (control)
1	5	5	5
2	5	5	5
3	5	5	5
4	5	5	5
5	5	5	5
6	5	3	5
7	2	1	5

Table 2-2. Effect of **2-1a** on *P. falciparum* Pf3D7^{0087/N9} in NODscidIL2R γ ^{null} mice engrafted with human erythrocytes

Days post-infection	Parasitemia (%)		
	Vehicle	2-1a	Chloroquine (control)
0	0.01	0.01	0.01
1	-	-	-
2	-	-	-
3	1.02	1.05	0.80
4	2.38	2.63	0.24
5	3.96	3.98	0.05
6	8.79	8.73	0.01
7	9.87	11.50	0.00

Could the lack of efficacy in both mouse models originate from poor pharmacokinetic profile? The pharmacokinetic studies of **2-1a** were thus performed by Pharmaron. In CD1 mice, at 40 mpk po, a C_{max} of 42 μ M was achieved, but at 24 h, the concentration of **2-1a** was < 0.7 μ M. Similarly, pharmacokinetic studies of **2-1a**

in the *P. falciparum*-infected *NODscidIL2R γ ^{null}* mice demonstrated that at 50 mpk po, a C_{max} of 31.8 μM was achieved, but at 24 h, the concentration of **2-1a** was < 0.1 μM . (Figures 2-2 and 2-3)

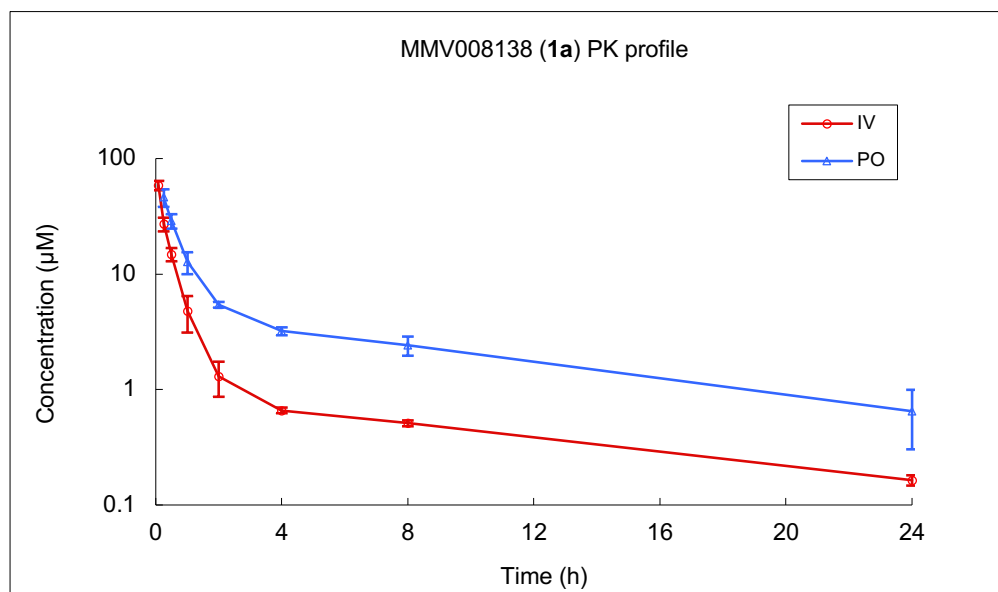


Figure 2-2. PK profile of **2-1a** in uninfected male CD1 mice by IV (10 mpk, n=3) and PO (40 mpk, n=3). Performed by Pharmaron.

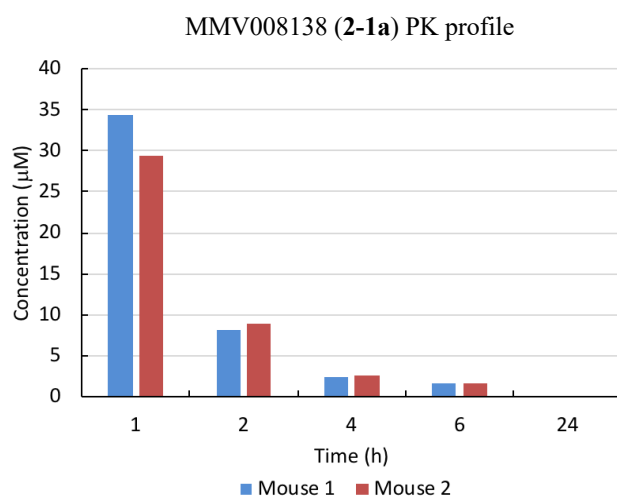


Figure 2-3. PK profile of **2-1a** in *P. falciparum*-infected *NODscidIL2R γ ^{null}* mice. Performed by Swiss Tropical and Public Health Institute.

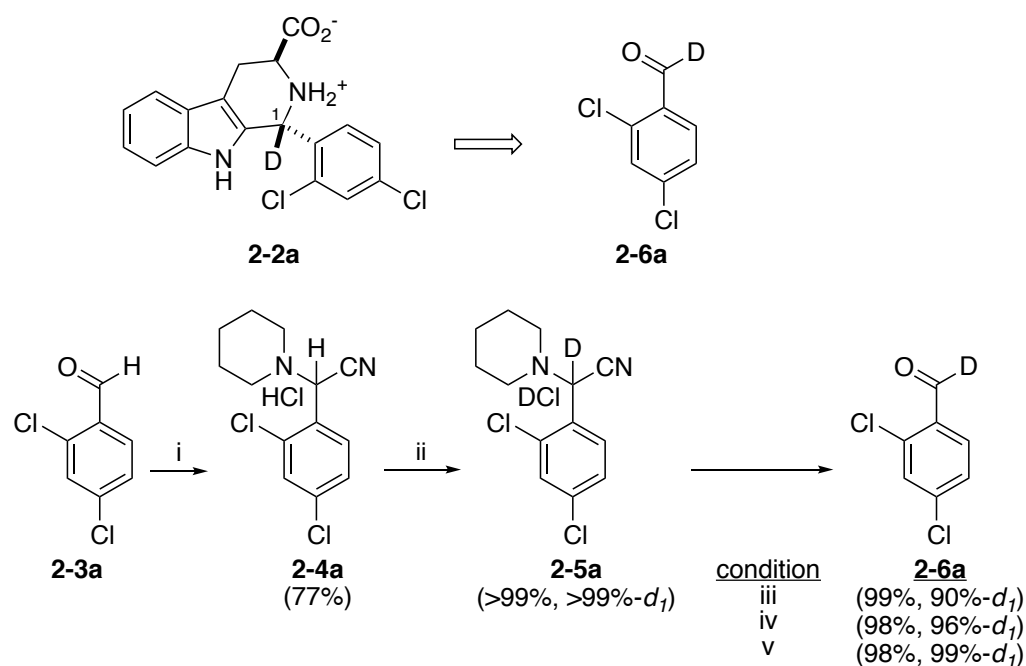
Why is the the plasma exposure so low? We thought that metabolism might be the cause and thus we studied stability in mouse liver microsomes. (Table 2-3) In mouse liver microsomes only 3% of **2-1a** remains after 45 min. We suspected that rapid oxidative metabolism contributed to the low plasma concentrations and low *in vivo* efficacy of **2-1a** in both malaria models in mice. In particular it seemed possible that CYP450 oxidation of **2-1a** might occur at C1 in the C-ring. Tetrahydro- β -carbolines such as **2-1a** can be oxidized to the corresponding β -carbolines,²³⁻²⁴ and the C1-H of **2-1a** is doubly benzylic. As an example, the antidepressant drug amitriptyline undergoes oxidation at both benzylic CH to the hydroxylated analogs.²⁵

Table 2-3. Microsomal stability of **2-1a**

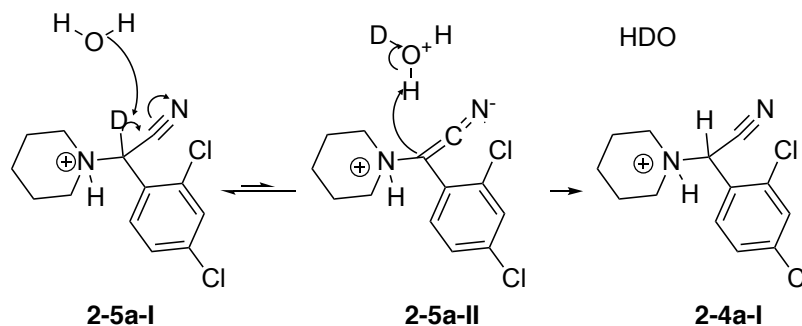
Time (min)	% Remaining	
	Coumarin	2-1a
0	100	100
45	27	3
90	5	1

To tackle the poor PK profile, we proposed to block the C1-H, the potential site of oxidation. Well-known by its low bond dissociation energies, benzylic C-H bonds are labile to oxidation by Cytochrome P450 (CYP450). For example, the antidepressant drug amitriptyline, undergoes oxidation at both benzylic CH to give the hydroxylated analogs.²⁵ CYP450 utilizes molecular oxygen and NADPH. One of the oxygen atoms is inserted into the substrate, and the remaining oxygen is reduced to water by NADPH.²⁶ We undertook the synthesis of the bioisosteric C1-D analog **2-2a** (Scheme 2-2). As a stable isotope of hydrogen, deuterium has been widely incorporated in pharmaceutical discoveries.²⁷ With the extra neutron, deuterium is almost doubly as heavy as hydrogen, making the C-D bond stronger than the C-H bond, known as the kinetic isotope effect (KIE). The C-D bond could be substantially more stable to oxidation, resulting in an increase of stability.²⁸ Apart from the ability to improve ADME, the resemblance between deuterium and hydrogen makes it a great bioisostere. Deuterated drugs have been widely explored to reduce oxidative metabolism by virtue of the kinetic isotope effect,²⁷ and this approach has recently been clinically validated with FDA approval of deutetrabenazine (treatment of chorea associated with Huntington's disease and tardive dyskinesia).²⁹

I started the synthesis of deuterated analog **2-2a** from deuterated benzaldehyde **2-6a**. A protection/H-D exchange/deprotection protocol was chosen for the synthesis of deuterated aldehyde **2-6a**.³⁰ (Scheme 2-1) The benzaldehyde **2-3a** was first converted into aminonitrile derivative **2-4a**, then deprotonated with NaH, followed by deuteration with D₂O quench to give deuterated aminonitrile **2-5a** with >99% deuterium incorporation. However, hydrolysis of **2-5a** with 2M HCl gave the product **2-6a** with only 90% deuterium incorporation.



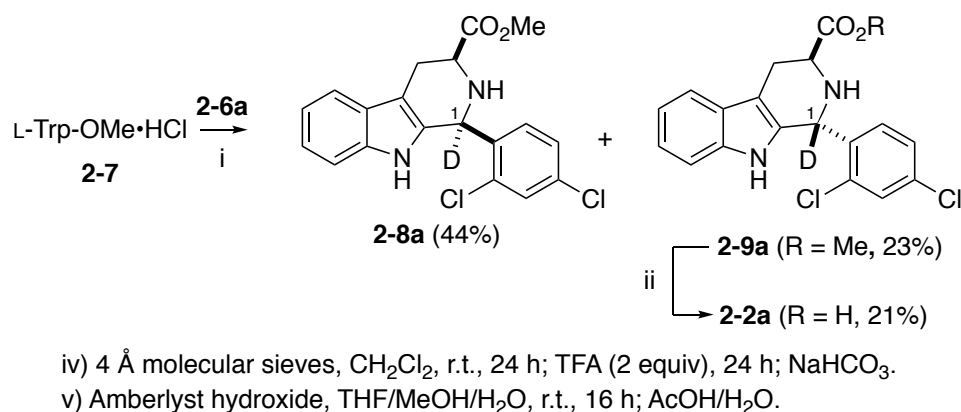
- i) NaCN, piperidine·HCl (1.0 equiv), H₂O, MeOH, r.t., 17 h.
 ii) NaH (2 equiv), 40 °C, 1 h; D₂O, r.t., 30 min; SOCl₂, r.t., 1 min.
 iii) 2 M HCl in H₂O, 97 °C, 1 day.
 iv) 2 M HCl in H₂O/D₂O (1:5 v/v), 97 °C, 1 day.
 v) SOCl₂, D₂O, 97 °C, 1 day.



Scheme 2-1. Synthesis of deuterated benzaldehyde **2-6a**

A possible mechanism of the loss of deuterium was proposed. During hydrolysis of the 1-D aminonitrile DCl salt **2-5a** in aqueous HCl, the protonated 1-D aminonitrile **2-5a-I** was de-deuterated with H₂O to form zwitterionic intermediate **2-5a-II**, which was re-protonated. Suspecting the only source of the “hydrogen leak”

was from the aqueous HCl, I prepared 2M HCl in H₂O/D₂O solution (1:5 v:v) by diluting concentrated HCl (12M in H₂O) with D₂O. And as expected, the hydrolysis of **2-5a** with this 2M HCl in H₂O/D₂O (1:5 v:v) solution results in improved deuterium incorporation in **2-6a**, with 96% deuterium compared to 90% previously. To further eliminate hydrogen in the aqueous HCl solution, a DCl in D₂O solution was prepared by addition of SOCl₂ to D₂O, and hydrolysis with this mixture gave **2-6a** with 99% deuterium incorporation.



Scheme 2-2. Synthesis of C1-D analog **2-2a**

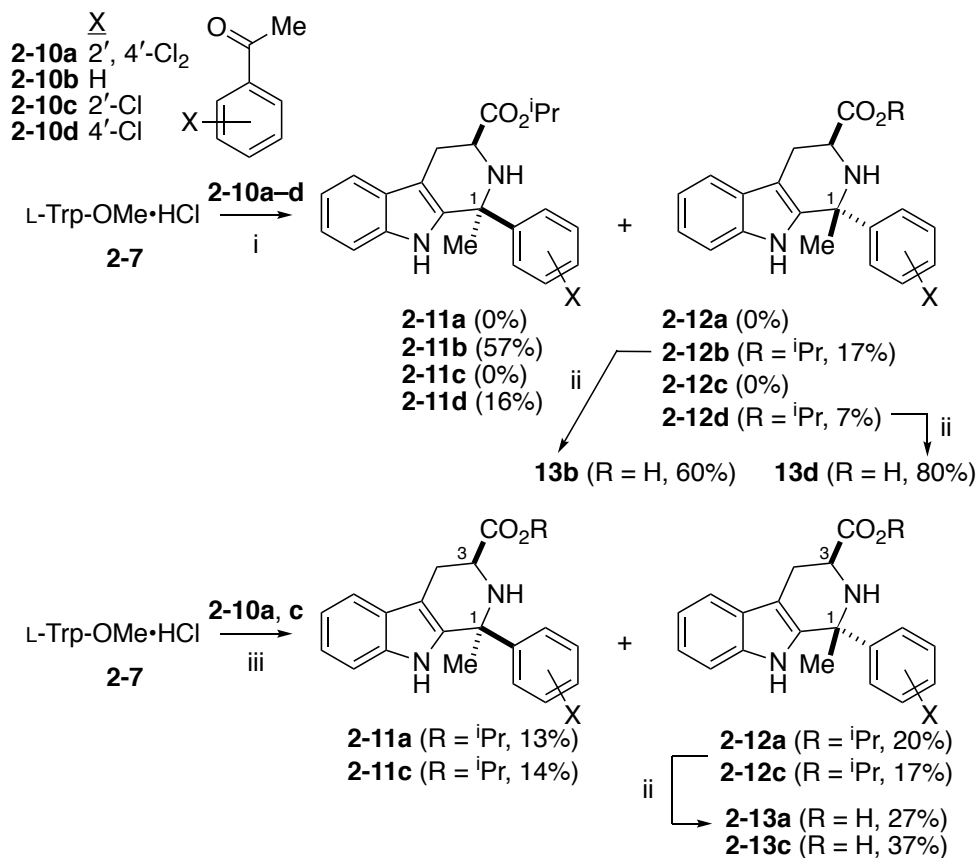
After obtaining **2-6a** with 99% deuterium incorporation, the PS reaction with L-Trp-OMe·HCl **2-7**, separation of diastereomers **2-8a** and **2-9a**, and Amberlyst hydroxide “catch-and-release” hydrolysis³¹ of **2-9a** gave **2-2a** (99%-d₁). As expected, the *in vitro* antimalarial potency of **2-2a** was identical to that of **2-1a** (Table 2-5, cf. entries 1, 6). Unfortunately, the microsomal stability of **2-2a** only improved slightly compared to **2-1a** (14% remains after 45 min, Table 2-4). Thus, deuterium

substitution at C1 provided little protection against oxidative metabolism in mouse liver (est. $k_H/k_D \leq 1.8$, extrapolated from 14% remaining at 45 min).

Table 2-4. Microsomal stability of **2-1a** and **2-2a**

Time (min)	% Remaining		
	Coumarin	2-1a	2-2a
0	100	100	100
45	27	3	14
90	5	1	13

To provide greater protection against oxidative metabolism at C1, and to probe the steric requirements for binding, we envisioned replacement of the C1-H in **2-1a** with a methyl group (i.e. **2-13a**, Scheme 2-3). Previously we disclosed analogs **2-13b** and **2-13d** (synthesized by Dr. Maryam Ghavami),¹⁸ which feature methyl substitution at C1, but non-optimal substitution of the D-ring (X = H (**2-13b**), X = 4'-Cl (**2-13d**)). We attributed the low growth inhibition potency of these compounds to the absence of 2',4'-dichloro substitution. Synthesis of such C1-Me analogs of **2-1a** requires PS reaction of L-Trp-OMe·HCl **2-7** with acetophenones **2-10**, which are significantly less electrophilic than benzaldehydes. Thus, the ester precursors to **2-13b** and **2-13d** were prepared by PS reaction with acetophenones **2-10b** and **2-10d**, according to Horiguchi's protocol:³² ketimine formation in neat Ti(OⁱPr)₄, followed by treatment with TFA and TFAA, all at 70 °C.



- i) free base; $\text{Ti}(\text{O}^i\text{Pr})_4$, 70 °C, 16 h; 0 to 70 °C, TFA/TFAA (100 equiv, 1 equiv); NaHCO_3 .
 ii) Amberlyst hydroxide, THF/MeOH/ H_2O , r.t., 16 h; AcOH/ H_2O .
 iii) free base; $\text{Ti}(\text{O}^i\text{Pr})_4$, 70 °C, 16 h; cool to 0 °C, TFA/TFAA (100 equiv, 1 equiv); NaHCO_3 .

Scheme 2-3. Synthesis of C1-Me analogs of 2-1a

As we noted in our earlier publication,¹⁸ application of the Horiguchi protocol to *ortho*-substituted acetophenones **2-10a** and **2-10c** did not give the expected products. However, I subsequently found that if ketimine formation was followed by treatment with TFA/TFAA at 0 °C to room temperature, the desired *trans*-esters **2-12a** and **2-12c** could be isolated in 20% and 17% yield respectively (isopropyl esters result from $\text{Ti}(\text{O}^i\text{Pr})_4$ -mediated transesterification). As detailed by Horiguchi,³² the *cis*-relative configuration of **2-11a** and **2-11c** was established by the NOE correlation

between H3 and the C1-methyl; this correlation is absent in the corresponding *trans*-isomers **2-12a** and **2-12c**. (Figures 2-4 and 2-5) Hydrolysis of **2-12a** and **2-12c** afforded the desired amino acids **2-13a** and **2-13c**.

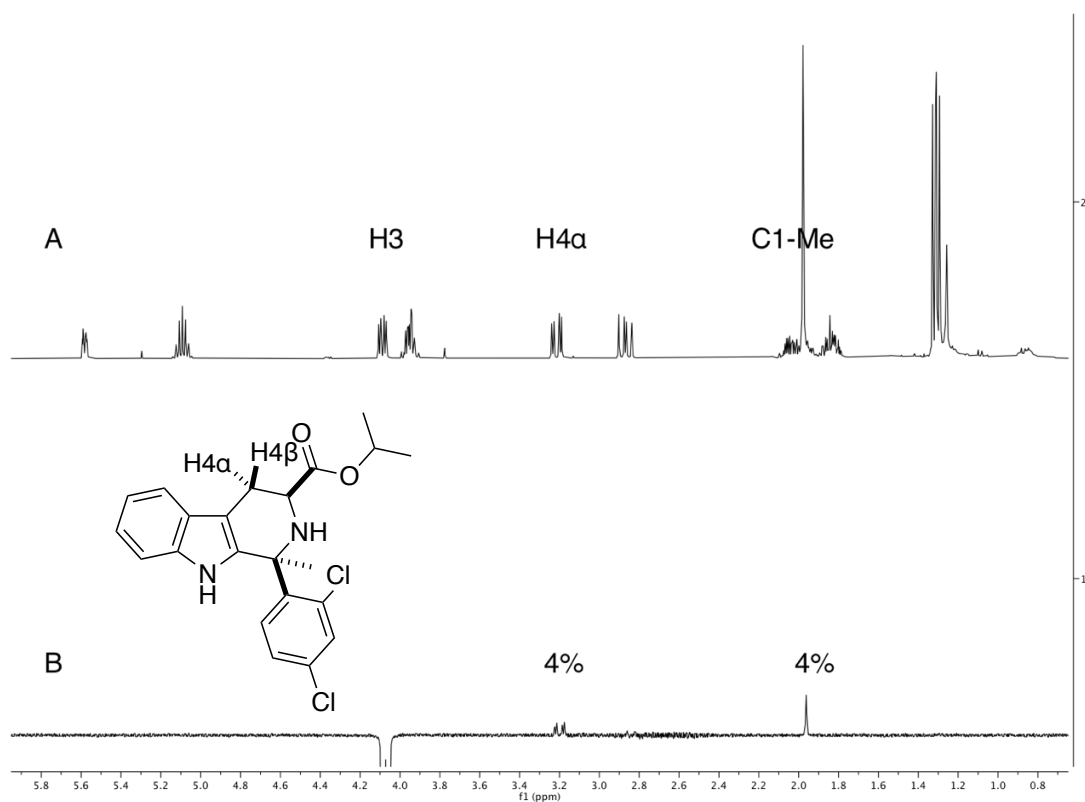


Figure 2-4. A) A portion of the ¹H NMR spectrum of **2-11a** (Chloroform-d); B) 1D NOE ¹H NMR spectrum of **2-11a** resulting from irradiation of H3

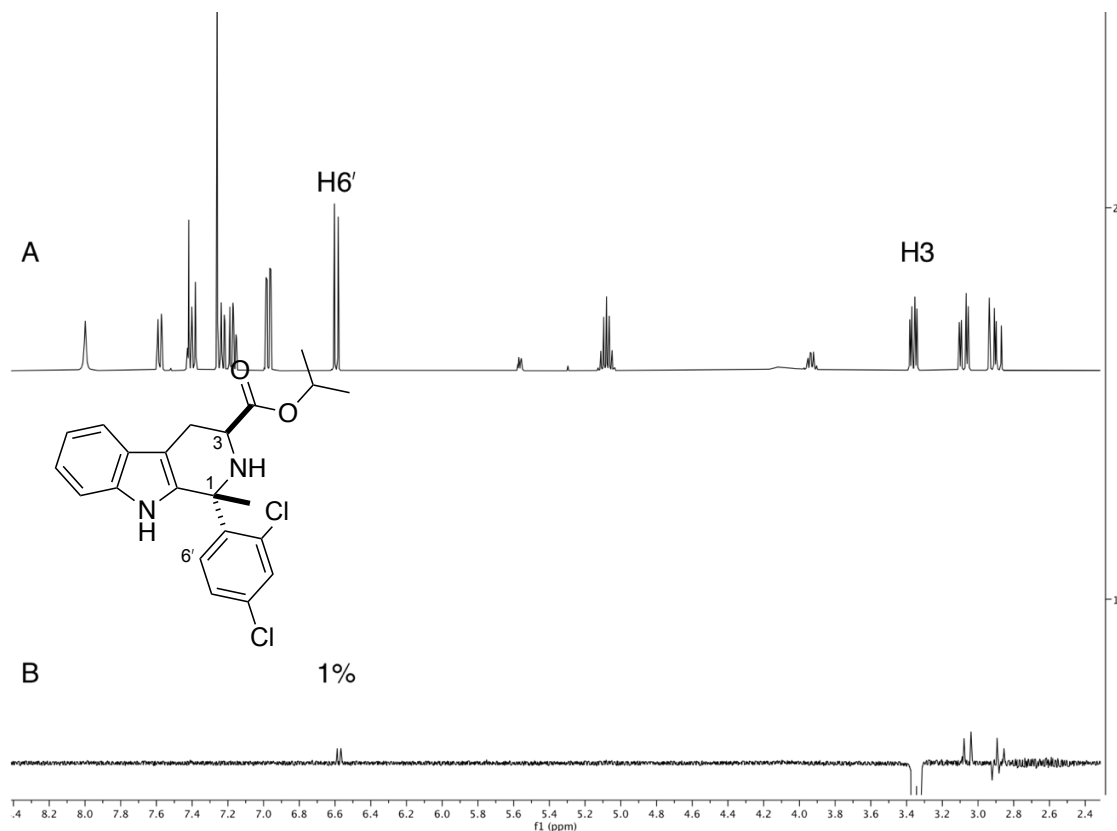


Figure 2-5. A) A portion of the ^1H NMR spectrum of **2-12a** (CDCl_3); B) 1D NOE ^1H NMR spectrum of **2-12a** resulting from irradiation of H3

Unfortunately, the presence of a 2'-Cl substituent in the D-ring of these C1-methyl analogs did not restore antimalarial activity (Table 2-5, entries 7, 9). Compared to our lead **2-1a** ($\text{EC}_{50} = 250 \pm 70$ nM), C1-methyl analog **2-13a** shows no growth inhibition at 10,000 nM. Similarly, the weakly potent 2'-Cl substituted **1c** ($\text{EC}_{50} = 3,280 \pm 990$ nM) loses all growth inhibition potency upon C1-methylation (**2-13c**, no growth inhibition at 10,000 nM). As the mere addition of a methyl group at C1 should not drastically affect permeability or transport of these compounds, we conclude that the loss of growth inhibition potency is due to reduced affinity for

*Pf*IspD, the target of **1a** (and its potent analogues, cf. Figure 1). In particular, it appears that either there is no room in the *Pf*IspD binding pocket for a methyl group at C1, or that the C1-methyl in **2-13** induces a conformational change that disfavors binding.

Table 2-5. *P. falciparum* growth inhibition by **2-1a–d,f**, and indicated B- and C-ring analogs

Entry	Compound #	Dd2 strain <i>P. falciparum</i> Growth EC ₅₀ (nM)
1	2-1a	250 ± 70 ^{a, c}
2	2-1b	>10,000 ^a
3	2-1c	3,280 ± 990 ^{a, d}
4	2-1d	1,170 ± 60 ^{a, c}
5	2-1f	700 ± 90 ^{a, c}
6	2-2a	275 ± 9 ^c
7	2-13a	>10,000
8	2-13b	>10,000 ^b
9	2-13c	>10,000
10	2-13d	>10,000 ^b
11	2-15a	190 ± 30 ^a
12	2-19f	>10,000
13	2-19i	>10,000
14	2-23a	65% inhibition at 10 μM
15	(±)- 2-27a	>10,000
16	2-31a	~8,000
17	2-32a	>10,000
18	2-33a	>10,000

^aReported previously.¹⁴ ^bReported previously.¹⁸ ^c100% rescued by 200 μM IPP @ 10 μM. ^d60% rescued by 200 μM IPP @ 10 μM. ^e50% rescued by 200 μM IPP @ 10 μM. ^f100% rescued by 200 μM IPP @ 2.5 μM.

We were fortunate to obtain a crystal of **2-14a** (Figure 2-6), the methyl amide derivative of **2-13a**, and we compared it to **2-15a**, the methyl amide analog of **2-1a**, which we previously crystallized.¹⁴ As **2-15a** is equipotent (Dd2 strain growth EC₅₀ = 190 ± 30 nM) with **2-1a**, comparison of the conformations of **2-14a** and **2-15a** could be informative.

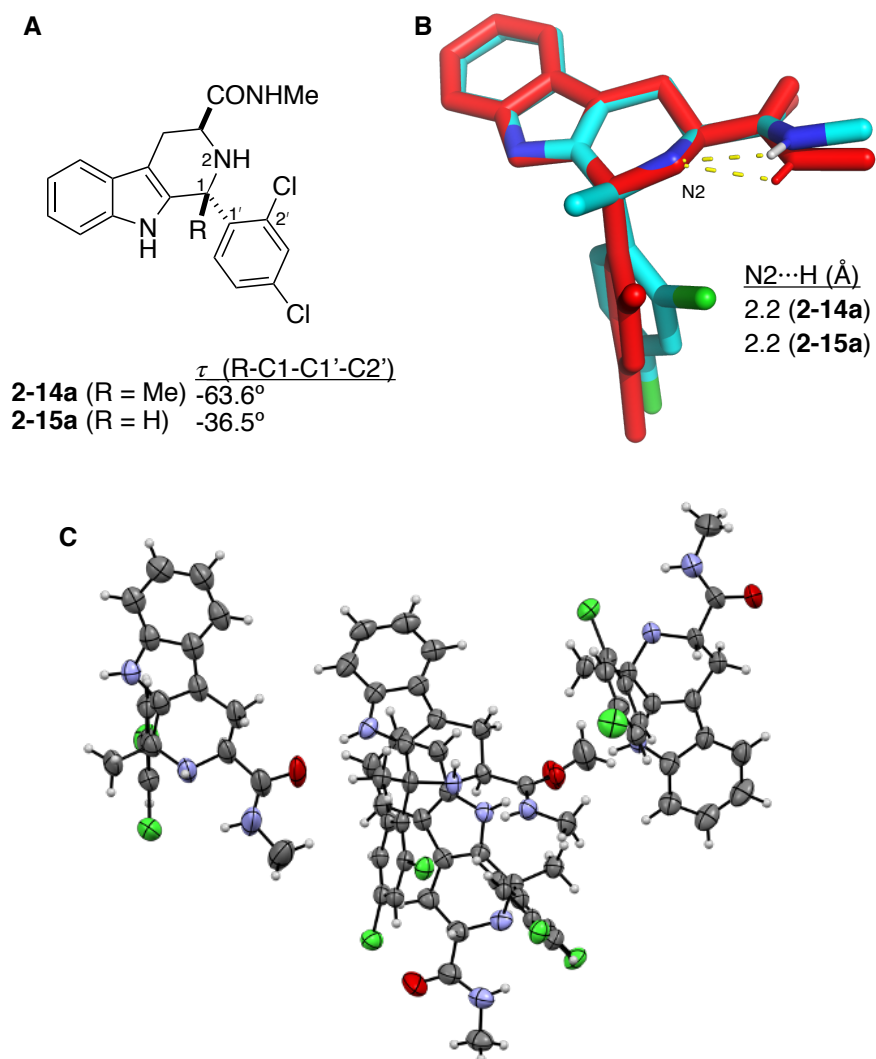
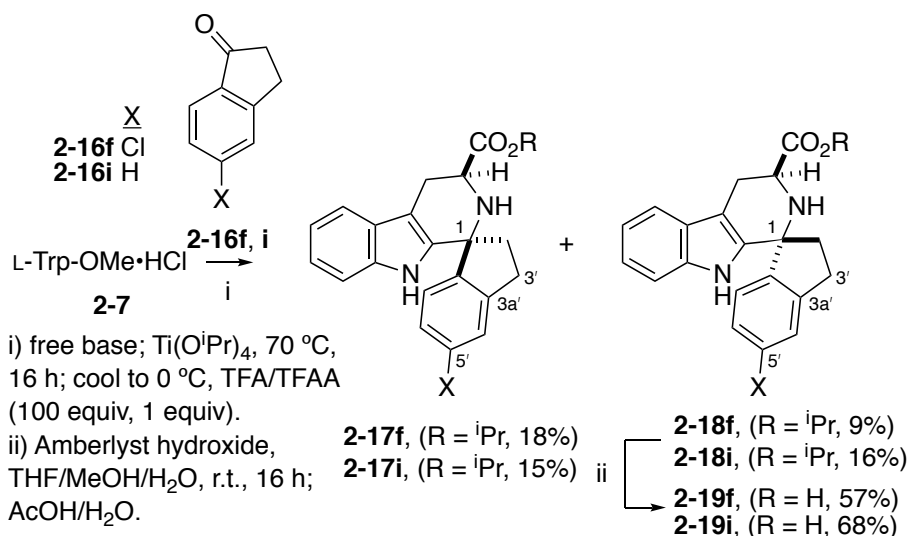


Figure 2-6. A) Comparison of τ (R-C1-C1'-C2') dihedral angles in **2-14a** and **2-15a**.

B) PyMOL³³ overlay of X-ray structures of **2-14a** (cyan: carbon; blue: nitrogen; green: chlorine) and **2-15a** (red). C) A thermal ellipsoid depiction of **2-14a**.

As can be seen in Figure 2-6, the tetrahydropyridine C-rings of **2-14a** and **2-15a** adopt very similar conformations, featuring a pseudoequatorial C(O)NHMe group and an apparent electrostatic interaction between the amide NH and the tetrahydropyridine nitrogen N2 (Figure 2-6). There are 4 molecules of **2-14a** in the

unit cell, and the average RMSD of the 6 C-ring atoms of them from **2-15a** is 0.041 Å (individual values 0.030, 0.033, 0.046, 0.057 respectively). However, steric strain between the C1-Me and the C2'-Cl in **2-14a** causes the D-ring to adopt a different orientation. We define τ as the dihedral angle between the C1 substituent (CH₃ for **2-14a**, H for **2-15a**), C1, C1', and C2'. For **2-14a** (C1-Me), the average τ value is -63.6° (individual values -59.15° , -62.29° , -64.00° , and -68.91° , respectively), whereas the τ value in **2-15a** (C1-H) is nearly 30° smaller, at -36.5° . Given the extreme sensitivity of growth and *PfIspD* inhibition to substitution of the D-ring (see Table 2-5), it is possible that this dihedral angle change alone, apart from the added steric bulk at C1, could be deleterious to potency. To enforce a smaller τ dihedral angle, we thus proposed to connect C1 and C2' with an ethylene bridge as shown in **2-19f** and **2-19i** (Scheme 2-4), imparting a cipargamin⁸-like spiro-fusion. (Figure 2-7)



Scheme 2-4. Synthesis of spiro-fused analogs **2-19f**, **2-19i**

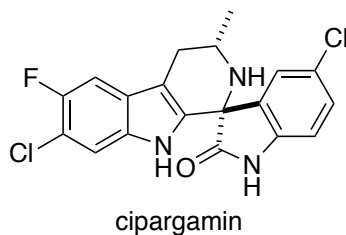


Figure 2-7. Structure of antimalarial spiro-fused tetrahydro- β -carboline cipargamin

Spiro-fused compound **2-19f** would thus be a conformationally-constrained mimic of 2'-Me,4'-Cl-substituted **2-1f**, which has significant potency ($EC_{50} = 700 \pm 90$ nM). The ketone PS reaction between L-Trp-OMe·HCl **2-7** and indanones **2-16f/2-16i** was performed according to the original Horiguchi protocol;³² diastereomer separation gave esters **2-18f** and **2-18i**, which mimic the *trans*-orientation of **2-12a-d**. The *trans*-configuration of **2-18f** and *cis*-configuration of **2-17f** was confirmed via 1D NOE experiments (Figure 2-8).

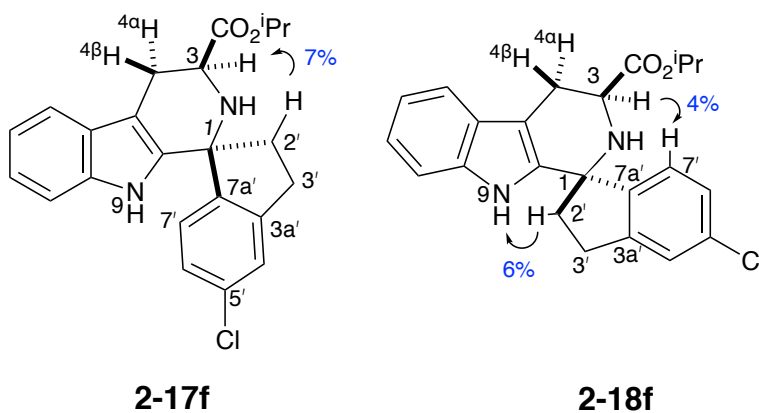


Figure 2-8. 1D NOE observed in **2-17f** and **2-18f**

Irradiating C3-H did not reveal NOE to C7'-H for the *cis*-isomer **2-17f**, but did for the *trans*-isomer **2-18f**. When one of the diastereotopic C2'-H is irradiated in

2-18f, NOE to the N9-H is seen. In contrast, irradiation of one of the diastereotopic C2'-H in the *cis*-isomer **2-17f** transfers NOE to C3-H (Figures 2-9 to 2-12).

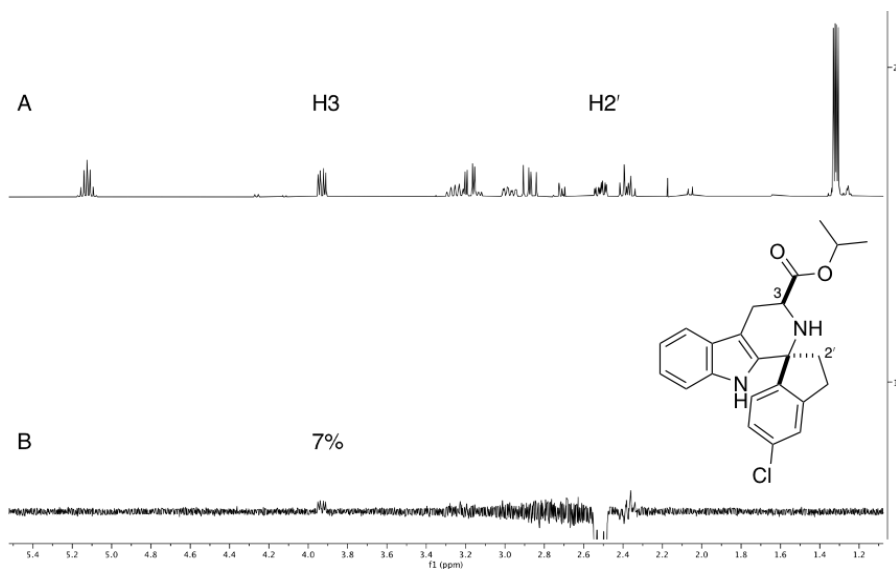


Figure 2-9. A) ¹H NMR spectrum of **2-17f** (Chloroform-d); B) 1D NOE ¹H NMR spectrum of **2-17f** resulting from irradiation of H2'

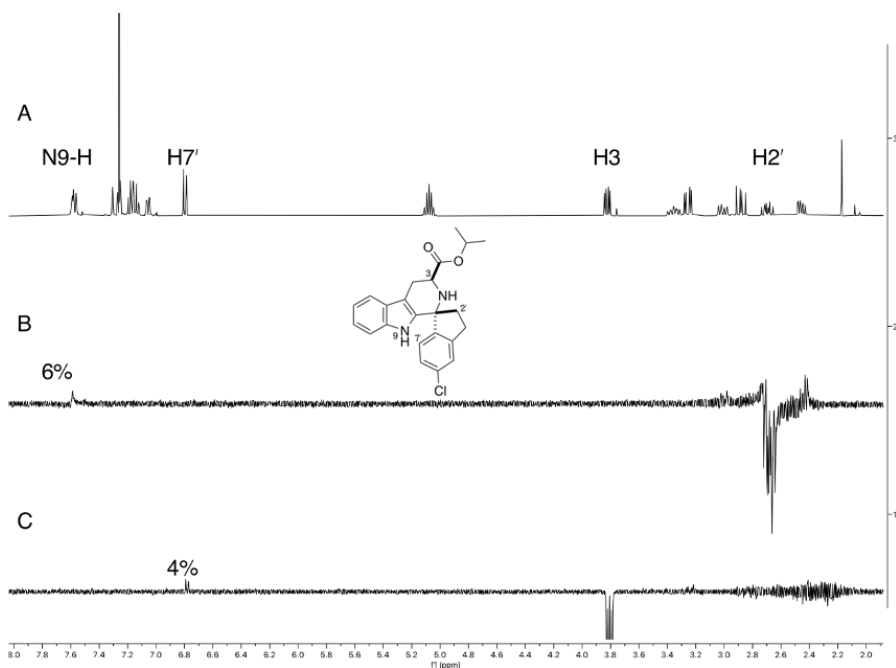


Figure 2-10. A) A portion of the ^1H NMR spectrum of **2-18f** (Chloroform- d); B) 1D NOE ^1H NMR spectrum of **2-18f** resulting from irradiation of H2'; C) 1D NOE ^1H NMR spectrum of **2-18f** resulting from irradiation of H3

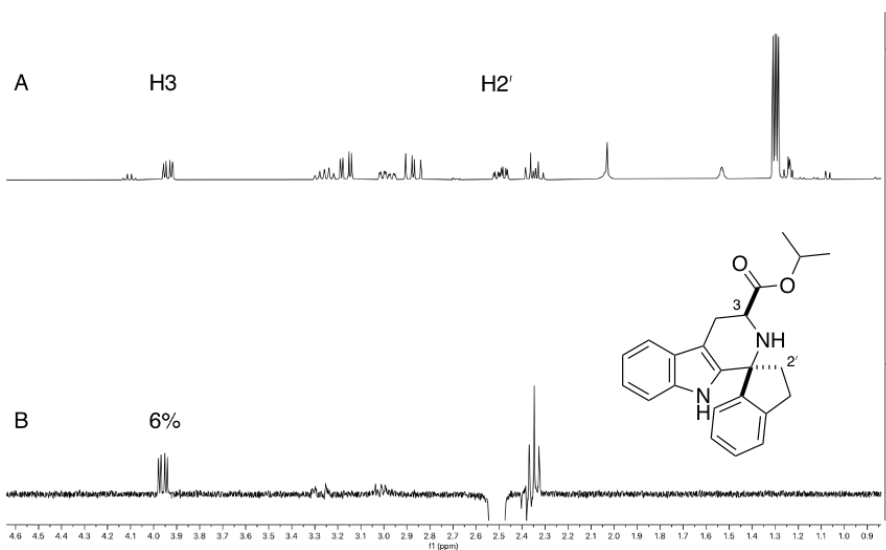


Figure 2-11. A) A portion of the ^1H NMR spectrum of **2-17i** (Chloroform- d); B) 1D NOE ^1H NMR spectrum of **2-17i** resulting from irradiation of H2'

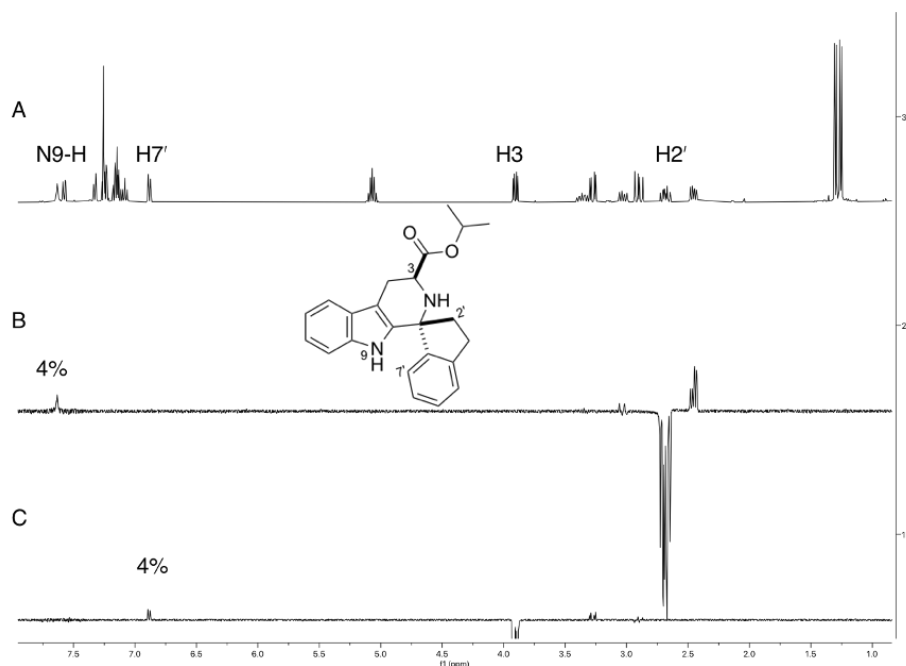


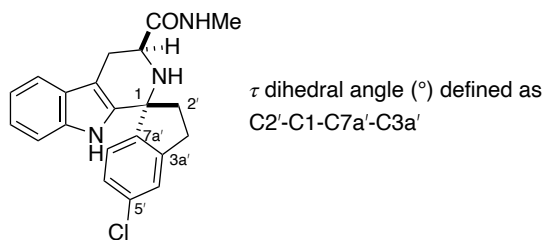
Figure 2-12. A) ^1H NMR spectrum of **2-18i** (Chloroform-d); B) 1D NOE ^1H NMR spectrum of **2-18i** resulting from irradiation of H2'; C) 1D NOE ^1H NMR spectrum of **2-18i** resulting from irradiation of H3

Interestingly, ^1H NMR analysis of **2-18f**, **2-18i** and their *cis*-diastereomers (**2-17f**, **2-17i**) demonstrated one large and one small coupling constant of H3 to the H4 protons, indicating a near antiperiplanar relationship of H3 and H4 β . Thus, regardless of *cis*- or *trans*-orientation, the 3-CO₂¹Pr group is pseudoequatorial, and H3 is pseudoaxial. The *trans*-esters **2-18f** and **2-18i** were then hydrolyzed to give the desired spiro-fused analogs **2-19f** and **2-19i**. Unfortunately, neither compound was potent for growth inhibition (Table 2-5, entries 12 and 13). Compound **2-19f** (EC₅₀ > 10,000 nM) differs from **2-1f** (EC₅₀ = 700 ± 90 nM) by substitution of the C2'-CH₃ group with an ethylene bridge to C1. Molecular mechanics-based conformational analysis^{34-35, 36} of the methyl amide of **2-18f** (**2-18f**NHMe), demonstrates that the spiro-ring fusion generates two conformer ensembles defined by narrow ranges in the

τ dihedral angle (here C2'-C1-C7a'-C3a', Figure 2-8). Ensemble 2 (13 conformers) features average $\tau = -19 \pm 1^\circ$, more similar to that of potent C1-H analog **2-15a** ($\tau = -36.5^\circ$) than of low potency C1-Me analog **2-14a** ($\tau = -63.8^\circ$). Ensemble 1 (16 conformers) features average $\tau = +17 \pm 2^\circ$. Since the lowest energy conformers in each ensemble are similar in energy (Table 2-6), both conformers are expected to be populated, and be available to bind *Pfl*SpD. Thus, unless the -36° τ value exhibited by **2-15a** (and presumably **2-1a**) matches an extremely narrow steric requirement of *Pfl*SpD, it seems most likely that the low potency of spiro-fused analog **2-19f** and C1-Me analogs **2-13a** and **2-13c** is due to steric bulk at the C1 position.

To probe the steric demand of the **2-1a**-binding site in *Pfl*SpD at other positions, we prepared analogs featuring methylation at N2, C3, and N9 (Scheme 2-5). The N2-Me analog **2-23a** was prepared by Dr. Maryam Ghavami from PS reaction of N α -methyl-L-tryptophan methyl ester **2-20** and 2,4-dichlorobenzaldehyde **2-3a**. The PS adduct **2-21a** was isolated as an inseparable mixture of diastereomeric methyl esters, hydrolyzed, and separated by reverse phase prep-HPLC into the *cis*-isomer **2-22a** and the *trans*-isomer **2-23a**. As the coupling constant method³⁷ our group used to assign *trans*-/*cis*-isomers only applies to 1,3-disubstituted tetrahydro- β -carbolines, I assigned the relative configuration of these isomers on the basis of the H3-H4 α and H3-H4 β coupling constants ($^3J_{34\alpha}$ and $^3J_{34\beta}$) of other 1,2,3-trisubstituted PS adducts reported by Van Linn et. al.³⁸ For 1,2,3-trisubstituted PS adducts, 1,3-*trans*-configured compounds have $^3J_{34\alpha} \approx ^3J_{34\beta} = 4.4\text{--}4.9$ Hz. In contrast, 1,3-*cis*-configured-1,2,3-trisubstituted PS adducts have differentiated values for these coupling constants ($^3J_{34\alpha} = 3.8\text{--}5.2$ Hz and $^3J_{34\beta} = 6.5\text{--}8.0$ Hz).

Table 2-6. Conformer energies of **2-18f**NHMe calculated with MMFF

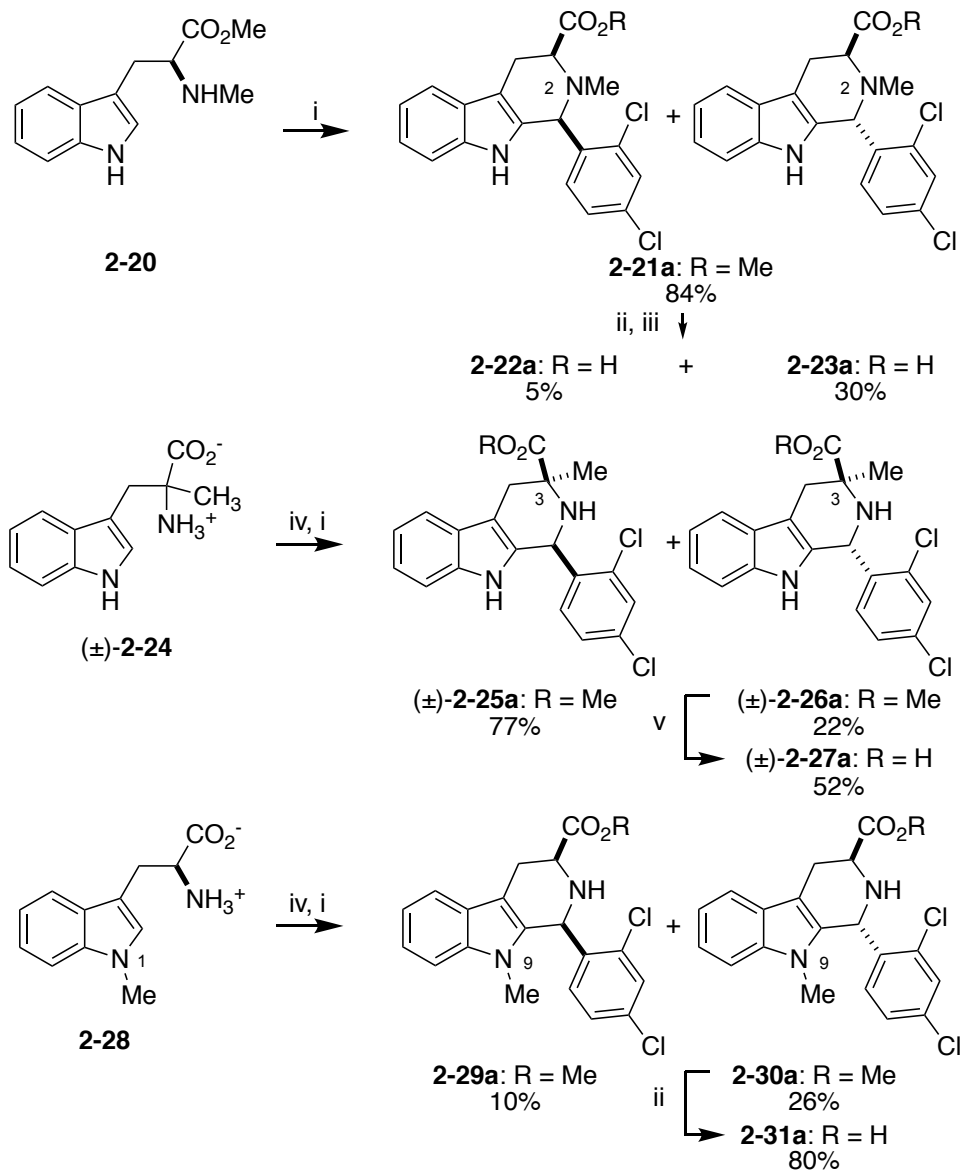


conformer	Ensemble 1		Ensemble 2		
	τ ($^\circ$)	Energy (kcal/mol)	conformer	τ ($^\circ$)	Energy (kcal/mol)
1	17.1	54.1	17	-20.5	52.6
2	18.5	54.2	18	-19.4	54.3
3	16.3	55.4	19	-19.5	54.5
4	17.0	56.8	20	-20.5	54.8
5	17.8	57.7	21	-20.8	57.8
6	16.1	59.5	22	-17.8	57.9
7	16.5	59.8	23	-18.4	59.3
8	17.5	59.9	24	-19.0	60.0
9	17.7	60.1	25	-19.9	60.2
10	16.1	60.4	26	-19.3	60.7
11	16.9	61.6	27	-20.1	60.9
12	17.5	61.7	28	-20.3	60.9
13	17.4	62.3	29	-19.4	61.3
14	16.3	62.4			
15	15.9	62.6			
16	17.4	63.4			
ave	17.0		ave	-19.6	
st dev	0.7		st dev	0.9	

I prepared the racemic C3-Me analog (\pm)-**2-27a** from α -methyl-DL-tryptophan (\pm)-**2-24**. Esterification with $\text{SOCl}_2/\text{MeOH}$ followed by PS reaction with 2,4-dichlorobenzaldehyde **2-3a** gave *cis*-ester (\pm)-**2-25a** and *trans*-ester (\pm)-**2-26a**; the relative configuration of these compounds was established by 1D NOE experiments

(Figure 2-9). Irradiating the C3-Me in (\pm)-**2-25a** shows NOE to H1, but no such NOE is seen on irradiation of the C3-Me in (\pm)-**2-26a**. In addition, irradiation of the C3-Me (\pm)-**2-25a** shows NOE signal to H4 α , but not H4 β . In contrast, irradiation of the C3-Me in (\pm)-**2-26a** shows NOE to both H4 α and H4 β (Figures 2-13 and 2-14). Hydrolysis of the *trans*-ester (\pm)-**2-26a** was again accomplished with the catch and release protocol,³⁹ but required elevated temperature, possibly due to steric hindrance caused by the C3-Me.

Dr. Maryam Ghavami prepared the N9-Me analog **2-31a** by esterification of 1-Me-L-tryptophan **2-28**, PS reaction with 2,4-dichlorobenzaldehyde **2-3a**, separation of diastereomers **2-29a** and **2-30a**, and hydrolysis of **2-30a**. (Scheme 2-5). I determined the relative configuration of the diastereomeric esters **2-29a** and **2-30a** by 1D NOE spectroscopy. (Figures 2-15 and 2-16) Irradiating H3 of the *cis*-isomer **2-29a** shows an NOE signal to H1, but this correlation is not seen in *trans*-isomer **2-30a** (Figure 2-17). In addition, irradiation of H3 in **2-30a** shows NOE signals to both H4 α and H4 β , indicating the 3-CO₂Me group is pseudoaxial orientation. For **2-29a** a strong correlation of H3 to H4 α is observed.



- i) **2-3a**, CH₂Cl₂, 4 Å molecular sieves, 24 h; TFA (2 equiv), r.t., 48 h; NaHCO₃.
 ii) Amberlyst hydroxide, THF/MeOH/H₂O, r.t., 16 h; AcOH/H₂O.
 iii) separate diastereomers.
 iv) SOCl₂, MeOH, reflux.
 v) Amberlyst hydroxide, THF/MeOH/H₂O, microwave, 130 °C, 40 min; AcOH/H₂O.

Scheme 2-5. Synthesis of **2-23a**, **(±)-2-27a**, and **2-31a**. Note: N2- and N9-methyl analogs were prepared by Dr. Maryam Ghavami

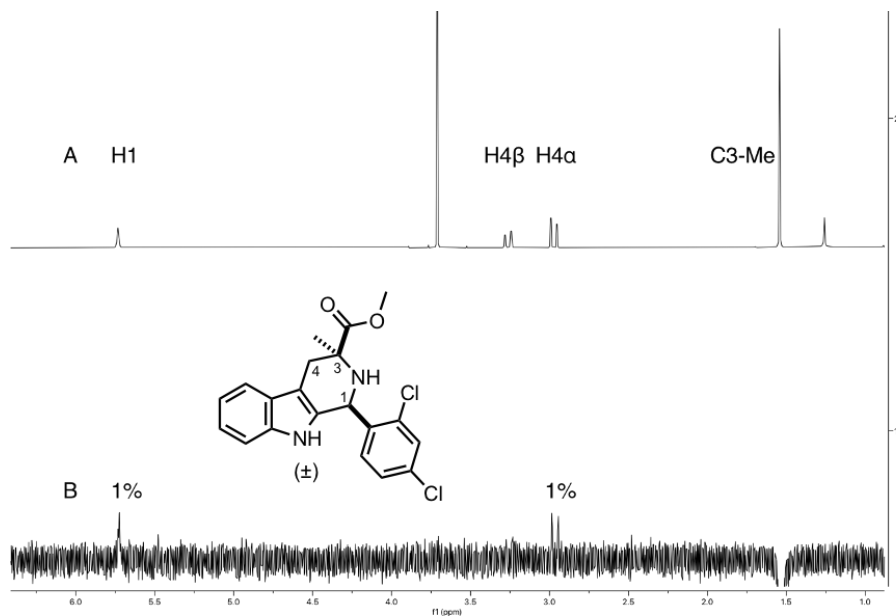


Figure 2-13. A) Portion of the ^1H NMR spectrum of (\pm)-**2-25a** (Chloroform-d); B) 1D NOE ^1H NMR spectrum of (\pm)-**2-25a** resulting from irradiation of C3-Me

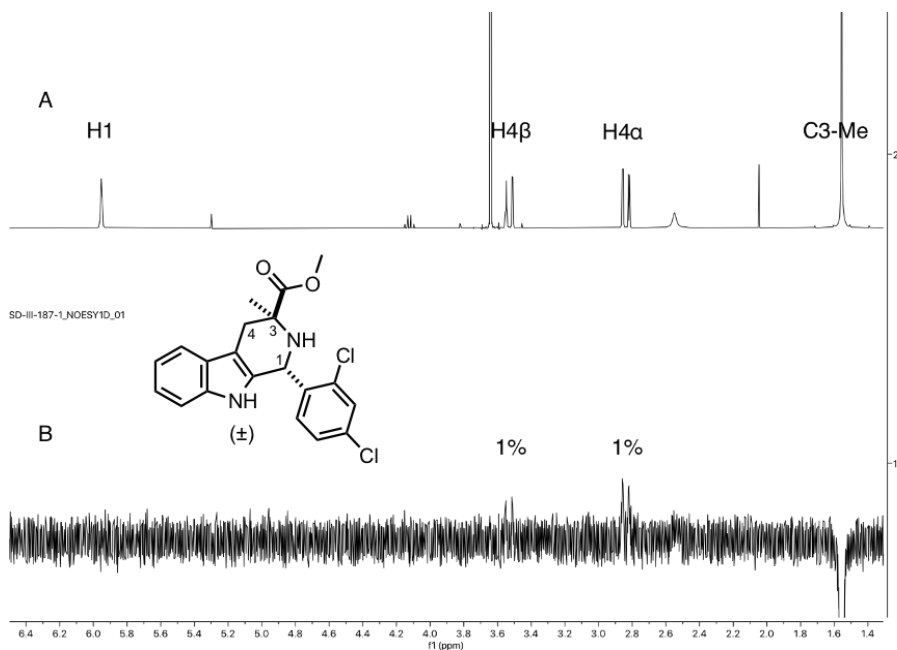


Figure 2-14. A) Portion of ^1H NMR spectrum of (\pm)-**2-26a** (Chloroform-d); B) 1D NOE ^1H NMR spectrum of (\pm)-**2-26a** resulting from irradiation of C3-Me

As can be seen in Table 2-5, methyl substitution at N2, C3 and N9 (compounds **2-23a**, (\pm)-**2-27a** and **2-31a**, respectively) unfortunately abrogates *P. falciparum* growth inhibition ($EC_{50} \geq 8,000$ nM, entries 14–16), as was seen for methylation at C1 (e.g. **2-13a**, entry 7). Thus, at first examination it appeared likely that *PfIspD* has close contact with **2-1a** at all these positions. However, as studies of the stereoisomers¹³⁻¹⁵ and C3-variants^{14, 18} of **2-1a** indicate that interaction of the 3-CO₂⁻ group with *PfIspD* is important for affinity, we thought it important to rule out less direct explanations for the low potency of these compounds. In particular, we sought to determine whether substitution at C1, N2, C3, and N9 could strongly bias a pseudoequatorial- (ψ_{eq-}) or pseudoaxial- (ψ_{ax-}) orientation of the 3-CO₂⁻ group in the tetrahydropyridine ring. To that point, Imlay and co-workers have proposed that **1a** binds to the CTP site of *PfIspD* in the ψ_{eq-} -3-CO₂⁻ conformation, based on docking studies with an *E. coli* IspD-derived homology model.¹⁵

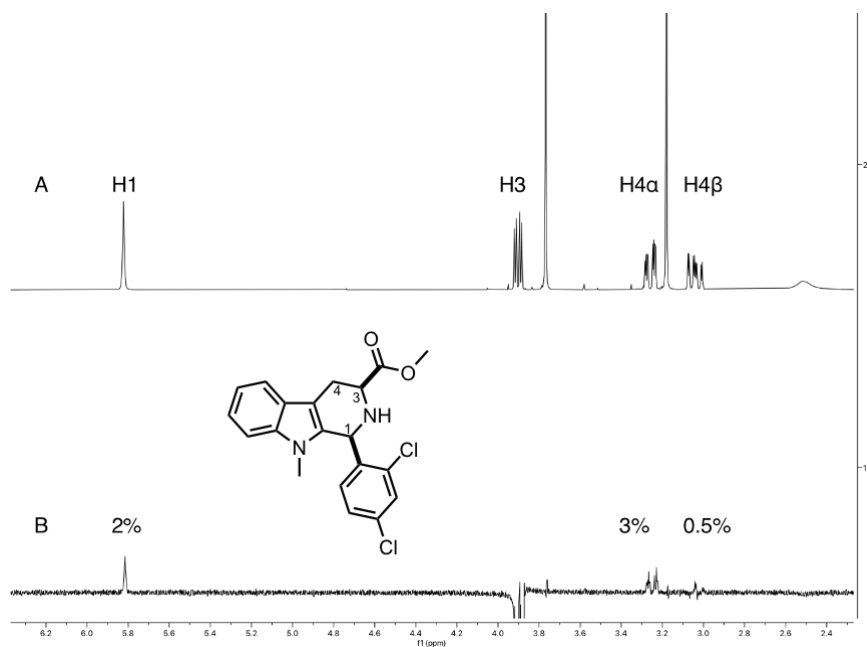


Figure 2-15. A) ^1H NMR spectrum of **2-29a** (Chloroform- d); B) 1D NOE ^1H NMR spectrum of **2-29a** resulting from irradiation of H3

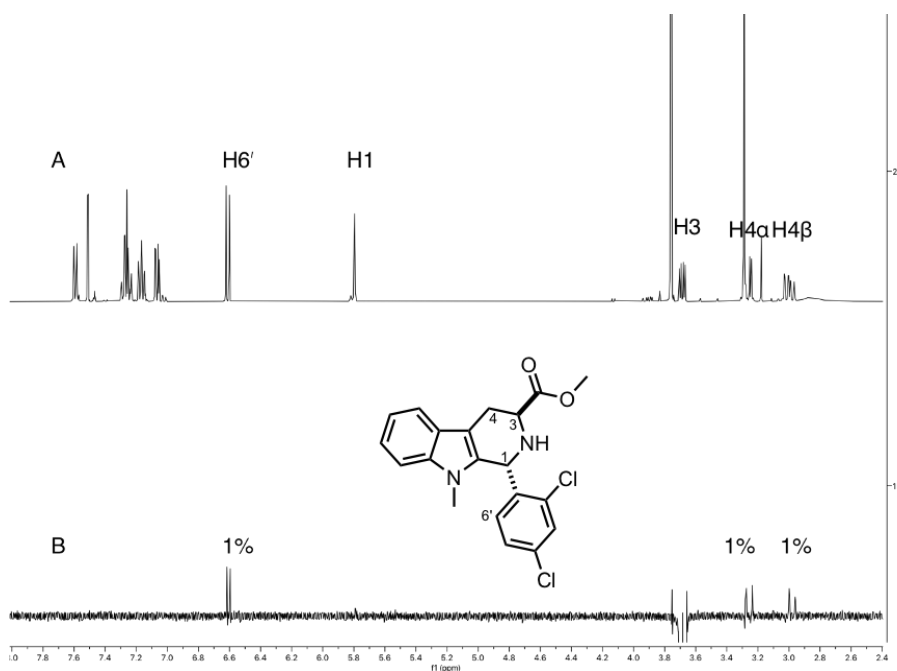


Figure 2-16. A) ^1H NMR spectrum of **2-30a** (Chloroform- d); B) 1D NOE ^1H NMR spectrum of **2-30a** resulting from irradiation of H3

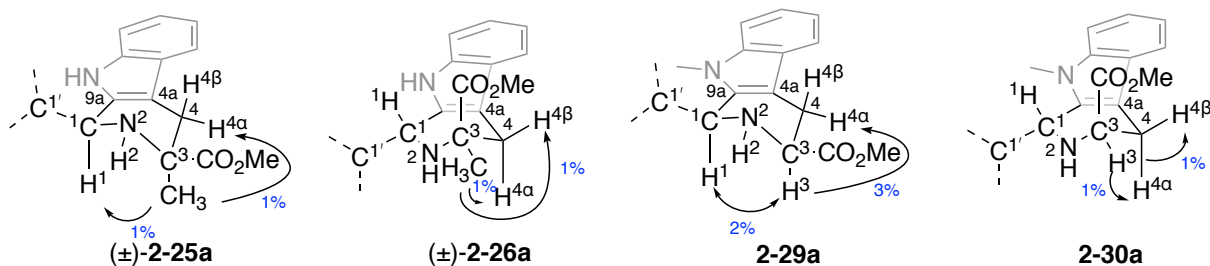


Figure 2-17. Assignment of relative configuration in (±)-**2-25a**/(±)-**2-26a** and **2-29a/30a** by 1D NOE

Thus, for **2-1a**, **2-13a**, **2-19f**, **2-23a** and **2-31a**, we examined ^1H - ^1H coupling constants between H3 and H4 α , and between H3 and H4 β (Table 2-7). As (±)-**2-27a** lacks a proton at C3, we used NOE to deduce the preferred orientation of the 3-CO $_2^-$ group, as was done for the methyl ester precursor (±)-**2-26a** (Figure 2-17). Due to reasons of solubility, these experiments were carried out in CD $_3$ OD; we do recognize that the conformational thermodynamics could vary somewhat in water. However as described below, in large part the conformer preferences seen comport with the principles of maximizing ψ_{eq} -substitution, and relieving torsional strain in the C-ring. These effects are summarized in Figure 2-18.

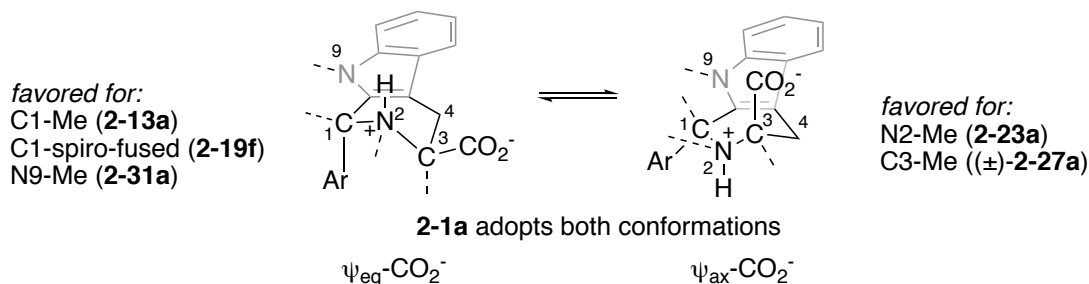
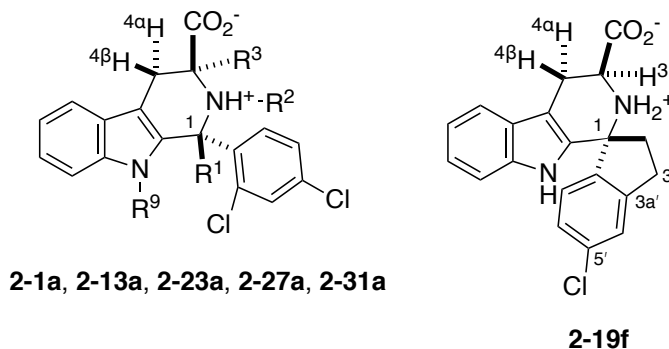


Figure 2-18. Effects of C1-, N2, C3- and N9 substitution on the preferred conformation of the tetrahydropyridine C-ring of **2-1a**

Table 2-7. Predominant orientation of the 3-CO₂⁻ group in **2-1a** and analogs, as judged by ¹H NMR spectroscopic coupling constants ³J₃₄ and NOE



Entry	Compound	R ¹	R ²	R ³	R ⁹	³ J ₃₄ ^a (Hz)	3-CO ₂ ⁻
1	2-1a	H	H	H	H	8.5, 5.5	ψ _{eq} & ψ _{ax}
2	2-13a	CH ₃	H	H	H	12.0, 5.1	ψ _{eq}
3	2-19f	na	na	na	na	11.7, 5.0	ψ _{eq}
4	2-31a	H	H	H	CH ₃	10.3, 4.9	ψ _{eq}
5	2-23a	H	CH ₃	H	H	5.0, 5.0	ψ _{ax}
6	(±)- 2-27a	H	H	CH ₃	H	NOE ^b	ψ _{ax}

^a ¹H NMR spectra measured in CD₃OD. ^b Predominant conformation determined by ¹H-¹H NOE experiments, since R³ = CH₃, see text.

The medium and small ³J₃₄ values seen for **2-1a** (Table 2-7, entry 1, 8.5 & 5.5 Hz) indicates that it exists in solution as a mixture of ψ_{eq}- and ψ_{ax}-3-CO₂⁻ conformers, consistent with our previous observation for the corresponding methyl ester.³⁷ Note that the ψ_{eq}-3-CONHMe conformation seen for methyl amide analog **2-15a** in the solid state (Figure 2-6)¹⁴ may simply reflect better packing of this conformation. In contrast, for C1-methyl analog **2-13a**, spiro-fused analog **2-19f**, and N9-methyl analog **2-31a**, the large coupling constants seen between H3 and H4β (Table 2-7,

entries 2–4, 12.0, 11.7, 10.3 Hz respectively) indicate a preference for the $\psi_{\text{eq}}\text{-3-CO}_2^-$ conformer in solution. For **2-13a** and **2-19f**, this preference is likely a consequence of 1,1-disubstitution of the C-ring and maximization of ψ_{eq} -substitution. For **2-31a**, allylic strain from N9-Me induces the 1-aryl group to be pseudoaxial, and the *trans*-stereochemistry of **2-31a** places its 3-CO₂⁻ group in a ψ_{eq} -position. Interestingly, for N2-methyl analog **2-23a**, the pair of small coupling constants seen (Table 2-7, entry 5, 5.0, 5.0 Hz) indicates a preference for $\psi_{\text{ax}}\text{-3-CO}_2^-$ conformer in solution. Lastly, for (\pm)-**2-27a**, NOE transfer was observed from both H4 α and H4 β to C3-Me, indicating the C3-Me is pseudoequatorial, and the 3-CO₂⁻ group is pseudoaxial (Figure 2-19).

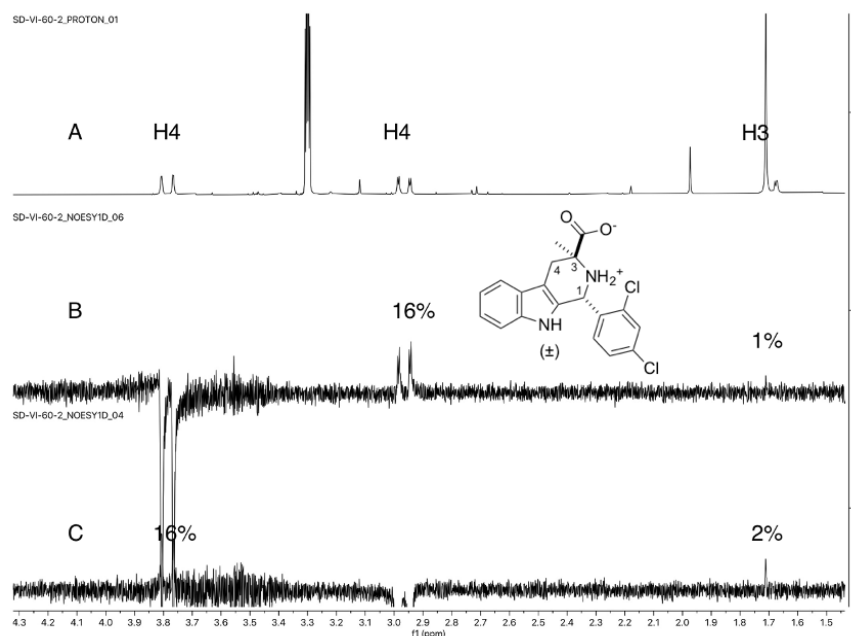


Figure 2-19. A) Portion of ¹H NMR spectrum of (\pm)-**2-27a** (CD₃OD); B) 1D NOE ¹H NMR spectrum of (\pm)-**2-27a** resulting from irradiation of one of the C4-H; C) 1D NOE ¹H NMR spectrum of (\pm)-**2-27a** resulting from irradiation of one of the C4-H

This conformation maximizes pseudoequatorial substitution as the *trans*-configured 1-aryl group is also pseudoequatorial. Thus, as anticipated, substitution at C1, N2, C3, and N9 does affect the preferred conformations of these analogs of **2-1a**. However, since neither enforced $\psi_{\text{eq}}\text{-CO}_2^-$ -orientation (e.g. **2-13a**, **2-19f**, **2-31a**) nor enforced $\psi_{\text{ax}}\text{-3-CO}_2^-$ -orientation (e.g. **2-23a**, (\pm)-**2-27a**) conferred potency, it appears that the low potency of these compounds is indeed steric in origin.

To conclude, this study described the first *in vivo* evaluation of an IspD-targeting antimalarial agent. Despite significant *in vitro* potency, **2-1a** failed to provide therapeutic efficacy in two mouse models. Thinking that the poor *in vivo* performance of **2-1a** was linked to rapid oxidative metabolism and plasma clearance, we prepared a series of analogues that featured substitution at the B- and C-rings. As expected, stereospecific replacement of the C1-H on the D-ring of **2-1a** with deuterium did not affect potency, but this modification reduced the rate of microsomal oxidation only slightly (est. $k_{\text{H}}/k_{\text{D}} \leq 1.8$). We conclude that rate-limiting abstraction of the C1-H is likely not the major pathway for oxidative metabolism of **2-1a** in mouse liver.

Unfortunately, placement of a methyl group on the B-ring (N9, e.g. **2-31a**), C-ring (C1: **2-13a**; N2: **2-23a**; C3: (\pm)-**2-27a**) and installation of a spiro-fusion between the C- and D-rings (e.g. **2-19f**) all drastically reduced *in vitro* antimalarial potency. In addition to the obvious consequence of increased steric bulk at these positions, these modifications also affected the preferred ψ_{eq} - or ψ_{ax} -orientation of the C3-CO₂⁻ group in the tetrahydropyridine C-ring (Table 2-7), and the orientation of the D-ring (Figure 2-6 and text). We conclude that the binding pocket of *Pf*IspD, the antimalarial target

of **2-1a**, features very close contact with the B- and C-rings of **2-1a**, as we had proposed earlier for the D-ring.¹⁸

Acknowledgments

In vivo studies of **2-1a** in *P. berghei*-infected mice were carried out at the New York University Anti-infectives Core Facility. The following collaborators are gratefully acknowledged: Dr. Christoph Siethoff and Dr. Mark Enzler (Swiss BioQuant AG, Reinach, Switzerland) for the drug concentration measurements in animals of the efficacy study; Dr Sergio Wittlin (bioanalytical laboratory of the Swiss Tropical and Public Health Institute, Basel, Switzerland) for efficacy studies using a SCID mouse model of human *P. falciparum* malaria. Pharmacokinetic studies of **2-1a** in CD1 mice were performed by Pharmaron.

Experimental Section

A. Mouse efficacy studies

A.1. Efficacy of **2-1a** (MMV008138) in *P. berghei*-infected mice was performed at the Anti-Infectives Core Facility, Department of Microbiology, School of Medicine, New York University.

Protocol: Three groups of five female Swiss Webster mice weighing 25 to 30 g were used for control (vehicle), **2-1a** treatment (PO, 40 mpk/day) and the positive control chloroquine (PO, 45 mpk/day). The transgenic *P. berghei* line 676m1c11 line (PbGFP-Lucon) was used for infection which expresses a fusion GFP (mutant 3) and firefly luciferase (LucIAV) and has been generated in the reference clone of ANKA strain c115cy1. Parasites of line 676m1c11 contain the PbGFP-Luc gene fusion stably

integrated as a single copy gene by double cross over recombination into the 230p locus and the reporter gene is under control of the constitutive *eef1a* promoter. This line has been selected by FACS-sorting of GFP-expressing parasites and therefore does not contain a drug-selectable marker. Mice were infected via i.p. injection with 10^3 *P. berghei*-Luciferin-infected erythrocytes obtained from another infected mouse. Two days after infection treatment was started once per day orally for five consecutive days. The control group was treated with vehicle (0.5% hydroxymethylcellulose, 0.5% Tween-80) for 5 days (oral gavage). The drug-treated groups were treated by oral gavage with compounds at the determined mpk body weight once a day for 5 days. On day 7 after infection (one day after treatment ended), mice were anesthetized by inhalation of isoflurane and injected (i.p.) with 150 mpk of D-Luciferin Potassium-salt (Goldbio) dissolved in PBS. Mice were imaged 5 to 10 min after injection of luciferin with an IVIS 100 (Xenogen, Alameda, CA) and the data acquisition and analysis were performed with LivingImage (Xenogen) to determine the level of infection.

A.2. Efficacy of **2-1a** (MMV008138) in *P. falciparum*-infected

NODscidIL2R γ^{null} female mice was performed by Swiss Tropical and Public Health Institute under Medicines for Malaria Venture's contract. *P. falciparum* Pf3D7^{0087/N9} strain was used as previously described.²¹

Protocol: The antimalarial efficacy of **2-1a** against *P. falciparum* Pf3D7^{0087/N9} in NODscidIL2R γ^{null} female mice (n=2 per group) engrafted with human erythrocytes was assessed following administration of one oral dose (50 mpk) of **2-1a** per day for four consecutive days on day 3, 4, 5 and 6 post-infection. Three groups of two female

NODscidIL2R γ ^{null} mice weighing 20 to 22 g were used for control (vehicle), **2-1a** treatment (PO, 50 mpk/day) and the positive control chloroquine (PO, 50 mpk/day). Eleven days prior to infection mice were engrafted daily with 0.6 mL of human blood intravenously in the tail. A cryopreserved stock of *P. falciparum* Pf3D7^{0087/N9}-infected erythrocytes from a donor mouse was thawed and parasites were expanded *in vitro*. On the day of infection, *in vitro* cultures with approximately 2-5% parasitemia were diluted in culture medium to 2×10^7 parasitized erythrocytes per 0.1 mL. This suspension was injected intravenously (i.v.) into experimental groups and a control group. Two days after infection treatment was started once per day orally for four consecutive days. The vehicle solution consisted in 70% Tween-80 (d = 1.08 g/mL) and 30% ethanol (d = 0.81 g/mL), followed by a 10-fold dilution in water. The effect on blood parasitemia was assessed by microscopic analysis of Giemsa-stained blood smears on > 10,000 red blood cells on days 3, 4, 5, 6 and 7 post-infection. Mice were euthanized on day 7.

B. Pharmacokinetic studies

B.1. The blood levels of **2-1a** (MMV008138) in uninfected male mice was performed by Pharmaron.

Protocol: Three male CD1 mice per group were used. The test compound **2-1a** was formulated using 20% DMSO, 60% PEG400, and 20% SBE- β -CD (30% w/v in water). Group 1 was dosed intravenously (IV) at 10 mpk, and Group 2 was dosed orally (PO) at 40 mpk. Blood samples (30 μ L) were drawn as follows:

- Group 1 (IV) 0.083 h, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h

- Group 2 (PO) 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h

Drug concentrations were determined by LC-MS.

Raw data

Table S2-1A. Blood levels of **2-1a** in group 1 (IV, 10 mpk)

Time (h)	Blood Conc. (μM)			Mean (μM)	SD (μM)
	Mouse 1	Mouse 2	Mouse 3		
0.083	57.6	64.5	53.7	58.6	5.5
0.25	27.6	30.5	23.2	27.1	3.7
0.5	16.7	15.1	12.8	14.8	1.9
1	6.70	3.68	3.96	4.78	1.67
2	1.80	1.12	0.983	1.30	0.44
4	0.645	0.703	0.634	0.661	0.037
8	0.523	0.532	0.476	0.510	0.030
24	0.161	0.182	0.149	0.164	0.017

Table S2-1B. Blood levels of **2-1a** in group 1 (PO, 40 mpk)

Time (h)	Blood Conc. (μM)			Mean (μM)	SD (μM)
	Mouse 1	Mouse 2	Mouse 3		
0.25	42.1	41.0	55.4	46.1	8.0
0.5	27.4	25.6	33.5	28.8	4.1
1	11.5	10.7	15.8	12.7	2.7
2	5.48	5.70	5.09	5.43	0.31
4	3.49	3.02	3.10	3.20	0.25
8	2.93	2.07	2.25	2.42	0.46
24	1.02	0.335	0.592	0.65	0.35

The blood levels of **2-1a** (MMV008138) in *P. falciparum*-infected

NODscidIL2R γ ^{null} female mice was performed by Swiss Tropical and Public Health

Institute under Medicines for Malaria Venture's contract.

Protocol: The blood levels of the **2-1a** were evaluated in the *P. falciparum*-infected NODscidIL2R γ^{null} female mice used for the efficacy study described in section A.2. Peripheral blood samples (20 μL) were taken at different times (see table below), mixed with 20 μL of H₂O Milli-Q and immediately frozen on dry ice. The frozen samples were stored at $-80\text{ }^{\circ}\text{C}$ until analysis. Blood from control mice was used for calibration and QC purposes. Blood samples were analysed by LC-MS/MS for quantification.

Raw data

Table S2-2. Blood levels of 1a in *P. falciparum*-infected NODscidIL2R γ^{null} female mice (PO, 50 mpk)

Time (h)	Blood Conc. (μM)	
	Mouse 1	Mouse 2
1	34.33	29.34
2	8.14	8.86
4	2.40	2.64
6	1.68	1.63
24	0.07	0.10

C. Microsomal Stability of 2-1a and 2-2a

C.1. Microsomal stability assay: Cytochrome P450 and other NADPH

dependent enzyme assays were performed following manufacture's guidelines. Briefly, pooled female mouse (CD1-) liver microsomes (BD Biosciences, San Jose, CA, catalog# 452702) were rapidly thawed in a water bath at $37\text{ }^{\circ}\text{C}$ and then kept on ice. NADPH Regenerating System Solutions A (BD Biosciences, San Jose, CA, catalog# 451220) and B (BD Biosciences, San Jose, CA, catalog# 451200) were thawed and kept on ice. Reactions were performed at $1\text{ }\mu\text{M}$ final concentration of 2-

1a or **2-2a**. Coumarin (Millipore-Sigma, Burlington, MA, catalog# C4261) was used as a positive control. Reactions were incubated at 37 °C for 5 minutes in a water bath before adding 0.5 mg/mL of mouse liver microsomes. At time 0, 45 and 90 minutes, 50 µL of each sample were transferred into a microcentrifuge tube containing 50 µL of acetonitrile to stop reactions and place on ice. All samples were centrifuged at 14,000 xg at 4 °C for 10 minutes and supernatants were transferred into a 96 well plate (Waters Corporation, Milford, MA, USA) and analyzed by LC-HRMS.

C.2. Ultra-performance liquid chromatography and high-resolution mass spectrometry analysis (LC-HRMS): Compound analysis was performed on an IonKey/MS system composed of an ACQUITY UPLC M-Class, the ionKey source, and an iKey BEH C18, 130 Å 1.7 µm (particle size), 150 µm x 50 mm column coupled to a SYNAPT G2-Si mass spectrometer (Waters Corporation, Milford, MA, USA). Compound separation was accomplished using a binary gradient system consisting of water/0.1% formic acid (mobile phase A) and acetonitrile/0.1% formic acid (mobile phase B). Sample analysis was performed using a linear gradient over a total run time of 9 min. The gradient was programmed as follows: 0.0-1.0 min 1% B, 1-4 min from 1% B to 99% B, 4-5 min from 99% B to 1% B, and re-equilibrated for 4 min. The flow rate was 3 µL/min, the injection volume was 3 µL in partial loop mode, and the iKey temperature was set at 40°C. MS analyses were performed acquiring in MSe mode from 80 to 1200 m/z in positive electrospray ionization mode with a capillary voltage of 3 kV. Data were collected in two channels throughout the entire acquisition: low collision energy (6.0 V) for the molecular ions and high collision energy (15-40 V) for product ions. The source temperature was set at 110°C.

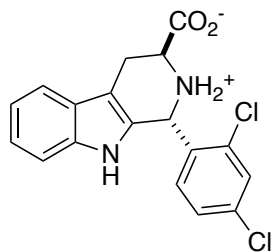
Leucine enkephalin (50 pg/mL) was used as the lock mass (m/z 556.2771) with parameters set to 1 sec scan at 20 sec intervals. Infusion flow rate for lock mass was 1 $\mu\text{L}/\text{min}$. Peak areas were determined using the MassLynx software (Waters Corporation, Milford, MA, USA). Results are reported as a percentage of the area of the corresponding compound at time zero. Values represent the average from two independent assays.

D. Synthesis and analytical characterization of tested compounds

Compounds were purchased from Sigma-Aldrich, Alfa Aesar, and Oakwood Chemical and were used without purification, unless otherwise noted. ^1H NMR spectra were recorded at 400 or 500 MHz; the corresponding ^{13}C NMR resonant frequencies were 101 and 126 MHz respectively. All compounds submitted for bioassay were judged to be $\geq 95\%$ pure by ^1H NMR spectroscopy.

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (2-1a)

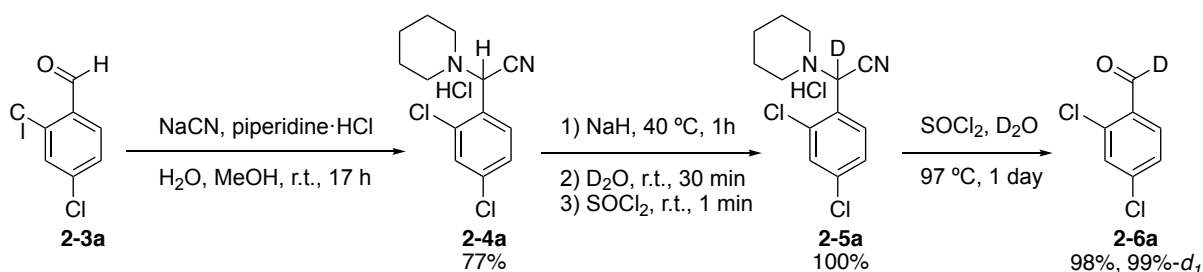
Compound **2-1a** was synthesized according to Yao, 2015¹⁴.



^1H NMR (400 MHz, cd_3od) δ 7.71 (d, $J = 2.1$ Hz, 1H), 7.56 (dt, $J = 7.9, 1.1$ Hz, 1H), 7.36 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.27 (dt, $J = 8.2, 1.0$ Hz, 1H), 7.15 (ddd, $J = 8.2, 7.1, 1.1$ Hz,

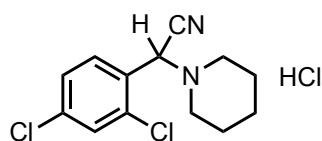
1H), 7.08 (ddd, $J = 7.9, 7.1, 1.1$ Hz, 1H), 7.02 (d, $J = 8.4$ Hz, 1H), 6.38 (s, 1H), 3.95 (dd, $J = 8.5, 5.5$ Hz, 1H), 3.48 (ddd, $J = 16.3, 5.5, 1.0$ Hz, 1H), 3.24 (ddd, $J = 16.3, 8.5, 1.5$ Hz, 1H).

Synthesis of 2,4-Dichlorobenzaldehyde-*formyl-d* (2-6a)



Deuterated aldehyde **2-6a** was synthesized in three steps as shown above, using a modification of the method of Barnett, 2002³⁰ for the synthesis of deuterated benzaldehydes.

2-(2,4-dichlorophenyl)-2-(piperidin-1-yl)acetonitrile hydrochloride (2-4a)



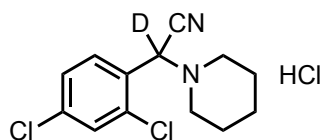
To a 6-dram vial were added piperidine hydrochloride (2.02 g, 16.6 mmol), NaCN (1.22 g, 24.9 mmol) and 10 mL water. 2,4-Dichlorobenzaldehyde **2-3a** (2.91 g, 16.6 mmol) was dissolved in 14 mL MeOH and added to the mixture. The resulting mixture was stirred at room temperature for 17 h. The precipitate formed was filtered and the liquid was poured into 75 mL water to promote further precipitation. The additional precipitate was filtered and washed with water, dried to give the piperidine acetonitrile **2-4** (3.915 g, 77%).

^1H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 2.1 Hz, 1H), 7.30 (dd, J = 8.3, 2.1 Hz, 1H), 4.98 (s, 1H), 2.60 – 2.46 (m, 4H), 1.67 – 1.42 (m, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 135.7, 135.5, 131.0, 130.4, 130.1, 127.0, 115.1, 60.0, 50.9, 25.8, 24.0.

HRMS (ESI+) calculated for $\text{C}_{13}\text{H}_{14}\text{Cl}_2\text{N}_2$ $[\text{M}+\text{H}]^+$: 269.0607, found 269.0607.

2-(2,4-dichlorophenyl)-2-(piperidin-1-yl)acetonitrile-*d* hydrochloride (2-5a)



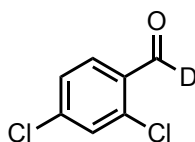
A 100 mL RBF was charged with sodium hydride (1.16 g, 29.1 mmol, 60 w.% suspension in mineral oil) and purged with nitrogen. The mineral oil was removed by repeated washing with anhydrous THF, and then 20 mL of anhydrous THF was added as solvent. The piperidine acetonitrile **2-4** (3.9150 g, 14.5 mmol) was dissolved in 30 mL of THF and added to the RBF via syringe under N_2 atmosphere. The resulting mixture was heated to 40 °C for 1 h, and then cooled in ice/water bath. D_2O (582 mg, 29.1 mmol) was then added dropwise via syringe, and the resulting mixture was stirred at room temperature for 30 min. SOCl_2 was then added until pH 1~2, the mixture was concentrated in vacuo and separate between DCM and water. The DCM layer was washed with brine, dried over Na_2SO_4 , and concentrated in vacuo to give the desired product **2-5** as a light-yellow liquid, which solidified overnight to a light yellow waxy solid (3.9335 g, 100%).

^1H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, $J = 8.3$ Hz, 1H), 7.45 (d, $J = 2.1$ Hz, 1H), 7.30 (dd, $J = 8.3, 2.1$ Hz, 1H), 2.61 – 2.44 (m, 4H), 1.66 – 1.41 (m, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 135.7, 135.5, 131.0, 130.4, 130.1, 127.0, 115.1, 59.8 (t, $^1J_{\text{CD}} = 26.0$ Hz), 50.9, 25.8, 24.0.

HRMS (ESI+) calculated for $\text{C}_{13}\text{H}_{13}\text{DCl}_2\text{N}_2$ $[\text{M}+\text{H}]^+$: 270.0670, found 270.0670.

2,4-Dichlorobenzaldehyde-*formyl-d* (2-6a)



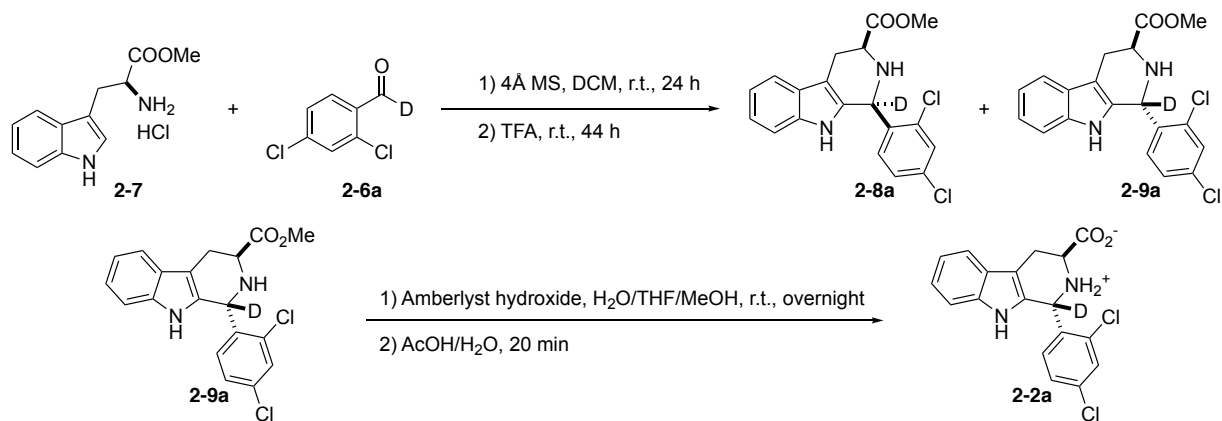
To a 25 mL RBF were added 8 mL D_2O and 0.9 mL SOCl_2 . The resulting mixture was heated to 90 °C under N_2 to generate DCl in D_2O in situ. To an oven-dried sealed tube were added the deuterated piperidine acetonitrile (1.2842 g, 4.17 mmol) and freshly prepared DCl in D_2O . The sealed tube was heated at 97 °C for 1 day and cooled down to room temperature, separated between Et_2O and NaHCO_3 (sat.). The ether layer was washed with brine, dried over Na_2SO_4 and filtered, concentrated in vacuo to give **2-6a** as a white solid (720 mg, 98%, 99%-*d*₁).

^1H NMR (400 MHz, Chloroform-*d*) δ 10.40 (s, 0.01H, residue formyl H), 7.87 (d, $J = 8.4$ Hz, 1H), 7.47 (d, $J = 2.0$ Hz, 1H), 7.37 (dd, $J = 8.4, 2.0$ Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 188.3 (t, $^1J_{\text{CD}} = 28.4$ Hz), 141.2, 138.7, 131.0 (t, $^2J_{\text{CD}} = 3.4$ Hz), 130.6, 130.4, 128.1.

GC/MS (EI) found $m/z = 175.0$, matching the $^{35}\text{Cl}_2$ molecular ion to unit resolution.

Synthesis of (1*R*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic-1-*d* acid (2-2a)

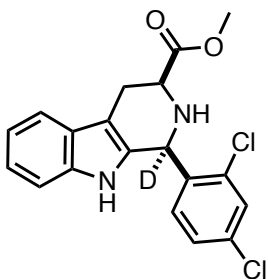


A modified procedure was adapted from Yao, 2015¹⁴ to synthesize **2-2a** over two steps, as shown above.

Synthesis of 2-8a and 2-9a: To an oven-dried 50 mL RBF were added 2.5 g 4Å molecular sieves. The molecular sieves were activated with a heat gun under vacuum for 5 min, then cooled to r.t. under N₂ atmosphere. Then L-Trp-OMe·HCl **7** (1.14 g, 4.5 mmol), 2,4-dichlorobenzaldehyde-*formyl-d* **2-6a** (786.3 mg, 4.5 mmol), and 15 mL DCM were added to the RBF, and the mixture was stirred at r.t. under N₂ for 20 h. Then the reaction was cooled with ice/water bath, and TFA was added dropwise. The resulting mixture was stirred at r.t. for another 44 h until completion was indicated by TLC. After completion, the reaction mixture was basified with aq. sodium bicarbonate. The molecular sieves were removed by filtration, and the remaining mixture was extracted with DCM (35 mL x 3). The organic phase was separated, combined and washed with brine, dried with sodium sulfate, concentrated in vacuo, and purified by flash

chromatography (5:5:1 Hexanes/DCM/EtOAc) to give **2-9a** (386 mg, 23%) and **2-8a** (749 mg, 44%).

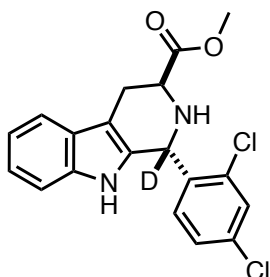
methyl (1*S*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate-1-*d* (2-8a)



^1H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.50 (m, 2H), 7.48 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.25 – 7.23 (m, 1H), 7.21 (dd, J = 8.4, 2.1 Hz, 1H), 7.19 – 7.10 (m, 2H), 4.00 (dd, J = 11.0, 4.1 Hz, 1H), 3.24 (dd, J = 15.1, 4.1 Hz, 1H), 3.01 (dd, J = 15.1, 11.0 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.1, 137.4, 136.3, 134.8, 134.2, 133.3, 131.5, 129.5, 128.2, 127.0, 122.4, 120.0, 118.4, 111.1, 109.6, 56.7, 52.5, 25.5. (C1 triplet not found)

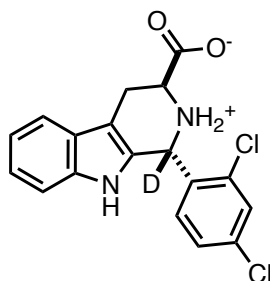
methyl (1*R*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate-1-*d* (2-9a)



^1H NMR (400 MHz, Chloroform-*d*) δ 7.67 (br, 1H), 7.55 (dd, $J = 7.4, 1.6$ Hz, 1H), 7.45 (d, $J = 2.1$ Hz, 1H), 7.27 – 7.24 (m, 1H), 7.21 – 7.11 (m, 2H), 7.09 (dd, $J = 8.4, 2.1$ Hz, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 3.83 (dd, $J = 7.8, 5.0$ Hz, 1H), 3.72 (s, 3H), 3.24 (dd, $J = 15.3, 5.0$ Hz, 1H), 3.08 (dd, $J = 15.3, 7.8$ Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.9, 137.9, 136.4, 134.5, 134.5, 131.6, 131.1, 129.9, 127.3, 126.9, 122.5, 119.9, 118.5, 111.1, 109.8, 52.4, 52.3, 25.0. (C1 triplet not found)

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic-1-*d* acid (2-2a)



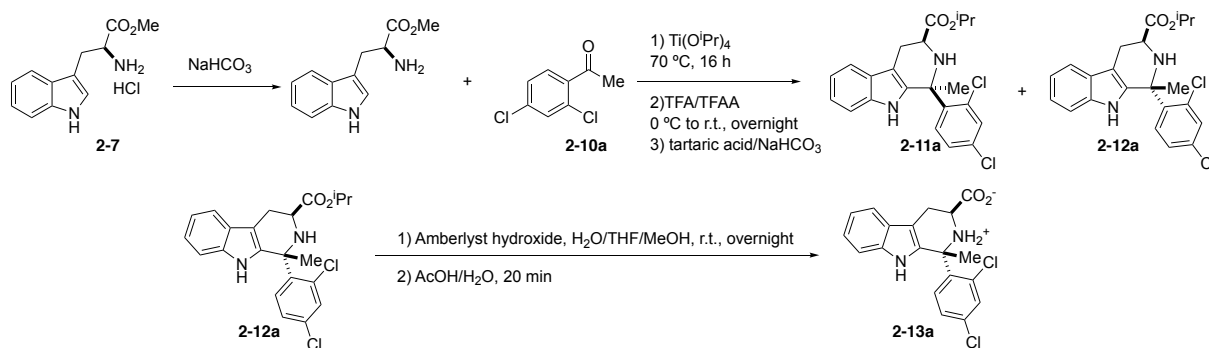
Synthesis of **2-2a**: To a solution of **2-9a** (120 mg, 0.32 mmol) in THF / MeOH / H₂O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.1 g, 0.34 mmol) at room temperature. The reaction mixture was stirred at r.t. overnight. Then the resin was filtered and washed with MeOH and DCM alternatively (2 mL x 4) to remove unreacted ester. The desired carboxylate was freed from the cationic resin by stirring in 50% aqueous AcOH (20 mL) for 20 min, and filtration. This washing step was repeated 3 times. The combined filtrates were concentrated in vacuo. The residue was dissolved in MeOH (0.5 mL) and triturated with diethyl ether repeatedly (2 mL). The precipitate was washed with diethyl ether to afford **2-2a** (80.2 mg, 69 % yield).

¹H NMR (400 MHz, Methanol-*d*₄) δ 7.73 (d, *J* = 2.1 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.38 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.28 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.17 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 7.09 (ddd, *J* = 7.9, 7.1, 1.1 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 4.08 (dd, *J* = 8.3, 5.5 Hz, 1H), 3.52 (dd, *J* = 16.3, 5.5 Hz, 1H), 3.28 (dd, *J* = 16.3, 8.3 Hz, 1H).

¹³C NMR (101 MHz, Methanol-*d*₄) δ 173.0, 138.8, 137.9, 137.3, 133.7, 132.8, 131.1, 129.2, 127.2, 127.1, 123.9, 120.7, 119.3, 112.4, 109.4, 54.8, 23.7.(C1 triplet not found)

HRMS (ESI+) calculated for C₁₈H₁₃DCl₂N₂O₂ [M+H]⁺: 362.0568, found 362.0591.

Synthesis of (1*R*,3*S*)-1-(2,4-dichlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (2-13a**)**



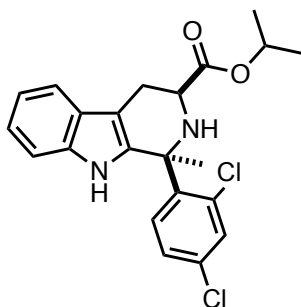
A modified procedure was adapted from Horiguchi, 2003³² to synthesize **2-13a** over two steps, as shown above.

Synthesis of 2-11a and 2-12a: To a 50 mL RBF were added L-tryptophan methyl ester hydrochloride (500 mg, 1.96 mmol), DCM (25 mL), and sat. NaHCO₃ (10 mL). The mixture was stirred for 30 min at r.t. The organic layer was separated, washed with brine and dried over sodium sulfate, concentrated in vacuo gives L-tryptophan methyl ester **2-7** (426 mg, 99%).

To an oven-dried Schlenk flask were added stir bar and **2-7** (426 mg, 1.95 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(O^{*i*}Pr)₄ (2 mL) was added via syringe, followed by 1-(2,4-dichlorophenyl)ethan-1-one **2-10a** (369 mg, 1.95 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (16 mL, 208 mmol) and TFAA (0.27 mL, 1.95 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at r.t. overnight until TLC indicated full conversion, at which point the reaction mixture was

added to 30 mL DCM in a separatory funnel. To the DCM solution were added 10 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (40 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (40 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave **2-12a** (163 mg, 20%) and **2-11a** (114 mg, 14%).

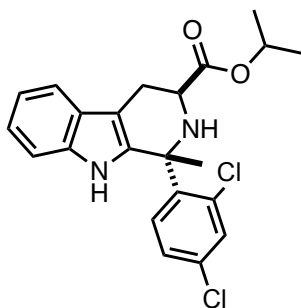
isopropyl (1*S*,3*S*)-1-(2,4-dichlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (2-11a)



^1H NMR (400 MHz, Chloroform-*d*) δ 7.64 (d, $J = 8.6$ Hz, 1H), 7.55 – 7.48 (m, 1H), 7.42 (s, 1H), 7.36 (d, $J = 2.2$ Hz, 1H), 7.29 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.26 – 7.19 (m, 1H), 7.19 – 7.07 (m, 2H), 5.09 (hept, $J = 6.2$ Hz, 1H), 4.09 (dd, $J = 10.8, 4.5$ Hz, 1H), 3.21 (dd, $J = 15.2, 4.5$ Hz, 1H), 2.87 (dd, $J = 15.2, 10.8$ Hz, 1H), 1.98 (s, 3H), 1.32 (d, $J = 6.2$ Hz, 3H), 1.30 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.9, 139.5, 137.1, 135.9, 135.0, 134.8, 131.9, 130.6, 127.2, 126.8, 122.1, 119.8, 118.4, 111.0, 108.1, 68.9, 56.8, 53.4, 27.8, 25.7, 22.0, 21.9.

isopropyl (1*R*,3*S*)-1-(2,4-dichlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (2-12a)

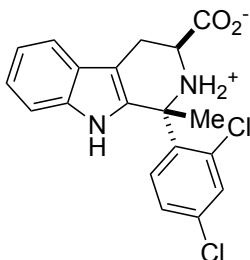


^1H NMR (400 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.58 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.42 (d, $J = 2.2$ Hz, 1H), 7.39 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.24 (ddd, $J = 7.9, 7.1, 1.3$ Hz, 1H), 7.17 (ddd, $J = 8.1, 7.1, 1.0$ Hz, 1H), 6.97 (dd, $J = 8.5, 2.2$ Hz, 1H), 6.59 (d, $J = 8.5$ Hz, 1H), 5.08 (hept, $J = 6.3$ Hz, 1H), 3.36 (dd, $J = 11.4, 4.6$ Hz, 1H), 3.08 (dd, $J = 15.4, 4.6$ Hz, 1H), 2.90 (dd, $J = 15.4, 11.4$ Hz, 1H), 2.07 (s, 3H), 1.29 (d, $J = 6.4$ Hz, 3H), 1.27 (d, $J = 6.4$ Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.3, 140.5, 136.9, 136.2, 133.9, 132.5, 132.2, 131.8, 127.1, 126.6, 122.4, 119.9, 118.8, 111.2, 109.4, 69.0, 59.3, 52.9, 25.7, 25.4, 21.9, 21.8.

HRMS (ESI⁺) calculated for $\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 417.1131, found 417.1139.

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (2-13a)



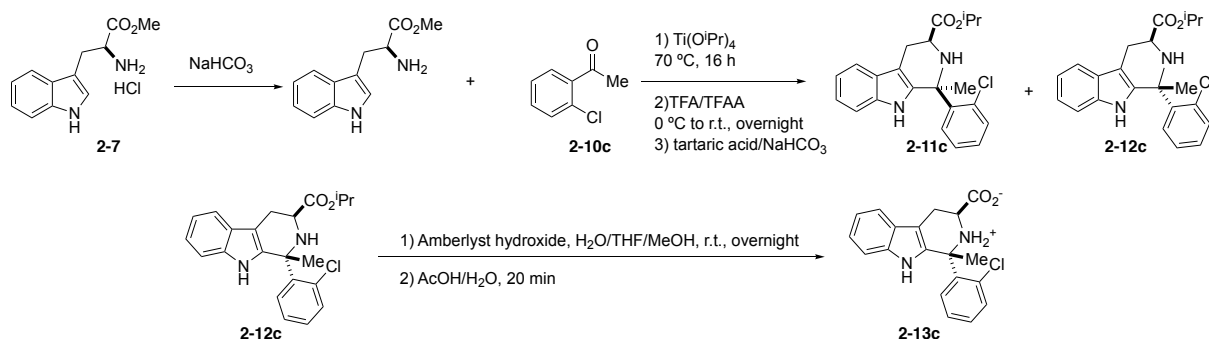
Synthesis of **2-13a**: To a solution of **2-12a** (120 mg, 0.29 mmol) in THF / MeOH / H₂O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.1 g, 0.34 mmol) at room temperature. The reaction mixture was stirred at r.t. overnight. Then the resin was filtered and washed with MeOH and DCM alternatively (2 mL x 4) to remove unreacted ester. The desired carboxylate was freed from the cationic resin by stirring in 50% aqueous AcOH (20 mL) for 20 min, and filtration. This washing step was repeated 3 times. The combined filtrates were concentrated in vacuo. The residue was dissolved in MeOH (0.5 mL) and triturated with diethyl ether repeatedly (2 mL). The precipitate was washed with diethyl ether to afford **2-13a** (29 mg, 27 % yield).

¹H NMR (400 MHz, Methanol-*d*₄) δ 7.63 (d, *J* = 2.2 Hz, 1H), 7.55 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.41 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.24 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.1, 1.0 Hz, 1H), 7.10 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 3.49 (dd, *J* = 11.9, 5.1 Hz, 1H), 3.28 (dd, *J* = 16.1, 5.1 Hz, 1H), 3.02 (dd, *J* = 16.1, 11.9 Hz, 1H), 2.24 (s, 3H).

¹³C NMR (101 MHz, Methanol-*d*₄) δ 173.8, 138.6, 138.0, 136.7, 134.6, 134.4, 132.8, 132.7, 128.9, 127.6, 123.8, 120.8, 119.6, 112.5, 109.7, 62.8, 55.5, 24.7, 24.4.

HRMS (ESI+) calculated for C₁₉H₁₇Cl₂N₂O₂ [M+H]⁺: 375.0662, found 375.0662.

Synthesis of (1*R*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (**2-13c**)



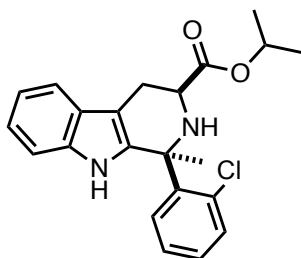
A modified procedure was adapted from Horiguchi, 2003³² for the synthesis of **2-13c**.

Synthesis of **2-11c** and **2-12c**: To a 50 mL RBF were added L-tryptophan methyl ester hydrochloride (510 mg, 2.0 mmol), DCM (25 mL), and sat. NaHCO₃ (10 mL). The mixture was stirred for 30 min at r.t. The aq. layer was separated, extracted with DCM (15 mL x 3), combined with organic layer, washed with brine and dried over sodium sulfate, concentrated in vacuo gives L-tryptophan methyl ester **2-7** (436 mg, 100%).

To an oven-dried Schlenk flask were added stir bar and **2-7** (436 mg, 2.0 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(OⁱPr)₄ (2 mL) was added via syringe, followed by 1-(2-chlorophenyl)ethan-1-one **2-10c** (309 mg, 2.0 mmol). The mixture was heated to 70 °C for 16 h and cooled in ice/water bath. Then TFA (16 mL, 208 mmol) and TFAA (0.28 mL, 2 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at r.t. overnight until TLC indicated full conversion, at which point the reaction mixture was

added to 30 mL DCM in a separatory funnel. To the DCM solution were added 10 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (40 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (40 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave **2-12c** (128 mg, 17%) and **2-11c** (104 mg, 14%).

isopropyl (1*S*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (2-11c)

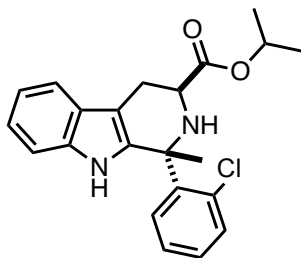


^1H NMR (400 MHz, Chloroform-*d*) δ 7.72 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.56 – 7.49 (m, 1H), 7.42 (s, 1H), 7.35 (dd, $J = 7.4, 1.8$ Hz, 1H), 7.31 (dd, $J = 7.5, 1.9$ Hz, 1H), 7.28 (dd, $J = 7.5, 1.9$ Hz, 1H), 7.25 – 7.18 (m, 1H), 7.18 – 7.06 (m, 2H), 5.10 (hept, $J = 6.3$ Hz, 1H), 4.11 (dd, $J = 10.9, 4.5$ Hz, 1H), 3.22 (dd, $J = 15.1, 4.5$ Hz, 1H), 2.90 (dd, $J = 15.1, 10.9$ Hz, 1H), 1.33 (d, $J = 6.3$ Hz, 3H), 1.31 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.1, 140.8, 137.8, 135.8, 134.1, 132.3, 129.6, 129.6, 127.1, 126.9, 121.9, 119.7, 118.3, 111.0, 108.0, 68.7, 57.0, 53.5, 27.8, 25.8, 22.0, 21.9.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 383.1521, found 383.1525.

isopropyl (1*R*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (2-12c)

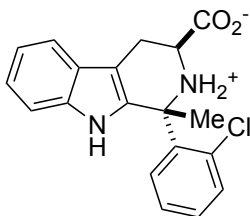


^1H NMR (400 MHz, Chloroform-*d*) δ 7.98 (s, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.44 – 7.37 (m, 2H), 7.24 (m, 1H), 7.20 – 7.14 (m, 2H), 7.00 (ddd, $J = 7.6, 7.4, 1.4$ Hz, 1H), 6.66 (dd, $J = 7.9, 1.7$ Hz, 1H), 5.08 (hept, $J = 6.3$ Hz, 1H), 3.40 (dd, $J = 11.4, 4.6$ Hz, 1H), 3.09 (dd, $J = 15.4, 4.6$ Hz, 1H), 2.92 (dd, $J = 15.4, 11.4$ Hz, 1H), 2.09 (s, 3H), 1.29 (d, $J = 6.2$ Hz, 3H), 1.27 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.4, 141.8, 137.4, 136.2, 132.3, 131.6, 131.6, 128.9, 127.3, 126.5, 122.3, 119.9, 118.9, 111.2, 109.5, 68.9, 59.7, 53.0, 25.9, 25.5, 22.0, 21.9.

HRMS calculated for $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_2$ $[\text{M}+\text{H}^+]$ 383.1521, found 383.1523.

(1*R*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (2-13c)



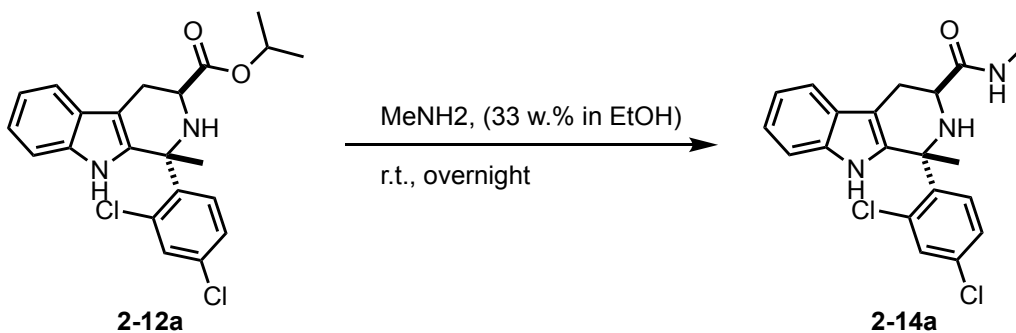
Synthesis of **2-13c**: To a solution of **2-12c** (73.2 mg, 0.19 mmol) in THF / MeOH / H₂O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.1 g, 0.34 mmol) at room temperature. The reaction mixture was stirred at r.t. overnight. Then the resin was filtered and washed with MeOH and DCM alternatively (2 mL x 4) to remove unreacted ester. The desired carboxylate was freed from the cationic resin by stirring in 50% aqueous AcOH (20 mL) for 20 min, and filtration. This washing step was repeated 3 times. The combined filtrates were concentrated in vacuo. The residue was dissolved in MeOH (0.5 mL) and triturated with diethyl ether repeatedly (2 mL). The precipitate was washed with diethyl ether to afford **2-13c** (24 mg, 37 % yield).

¹H NMR (400 MHz, Methanol-*d*₄) δ 7.59 – 7.56 (m, 2H), 7.44 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.40 (ddd, *J* = 8.0, 7.7, 1.6 Hz, 1H), 7.28 – 7.19 (m, 2H), 7.12 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.6 Hz, 1H), 3.52 (dd, *J* = 12.1, 5.3 Hz, 1H), 3.35 (dd, *J* = 16.4, 5.3 Hz, 1H), 3.08 (dd, *J* = 16.4, 12.1 Hz, 1H), 2.32 (s, 3H).

¹³C NMR (101 MHz, Methanol-*d*₄) δ 173.8, 138.6, 138.0, 136.7, 134.6, 134.4, 132.8, 132.7, 128.9, 127.6, 123.8, 120.8, 119.6, 112.5, 109.7, 62.8, 55.5, 24.7, 24.4.

HRMS (ESI⁺) calculated for C₁₉H₁₇ClN₂O₂ [M+H]⁺: 341.1051, found 341.1042

Synthesis of (1*R*,3*S*)-1-(2,4-dichlorophenyl)-*N*,1-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxamide (2-14a)



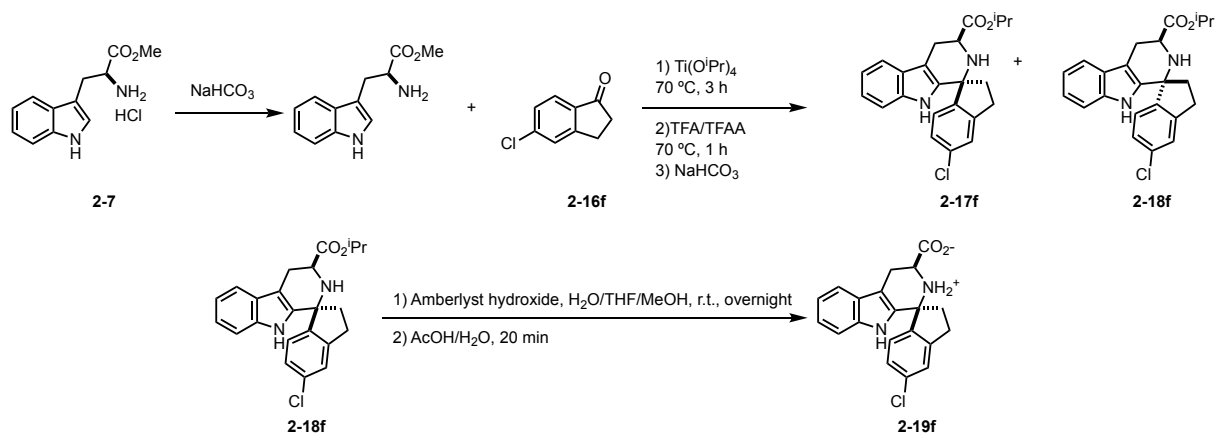
To a 25 mL RBF were added **2-12a** (200 mg, 0.48 mmol), methylamine (33 w.% in EtOH, 15 mL). The resulting mixture was stirred at r.t. overnight. At this point, TLC indicated completion, the mixture was concentrated in vacuo and purified by flash column chromatography (9:1 DCM/EtOAc) and gave **2-14a** (166.4 mg, 89%).

^1H NMR (400 MHz, Chloroform-*d*) δ 8.25 (s, 1H), 7.58 (dd, $J = 8.1, 1.1$ Hz, 1H), 7.42 (d, $J = 2.2$ Hz, 1H), 7.40 (dt, $J = 8.1, 1.1$ Hz, 1H), 7.28 (t, $J = 4.8$ Hz, 1H), 7.25 (ddd, $J = 8.1, 7.1, 1.1$ Hz, 1H), 7.17 (ddd, $J = 8.1, 7.1, 1.1$ Hz, 1H), 6.97 (dd, $J = 8.5, 2.2$ Hz, 1H), 6.68 (d, $J = 8.5$ Hz, 1H), 3.25 (dd, $J = 17.0, 4.8$ Hz, 1H), 3.25 (dd, $J = 12.3, 4.8$ Hz, 1H), 2.84 (d, $J = 4.8$ Hz, 3H), 2.72 (dd, $J = 17.0, 12.3$ Hz, 1H), 2.05 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.6, 139.7, 137.6, 136.2, 134.2, 133.1, 132.7, 132.3, 127.2, 126.7, 122.8, 120.1, 119.1, 111.2, 110.6, 59.6, 54.0, 26.1, 25.7, 25.0.

HRMS (ESI+) calculated for $\text{C}_{20}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 388.0978, found 388.0982.

Synthesis of (1*R*,3'*S*)-5-chloro-2,2',3,3',4',9'-hexahydrospiro[indene-1,1'-pyrido[3,4-*b*]indole]-3'-carboxylic acid (2-19f)



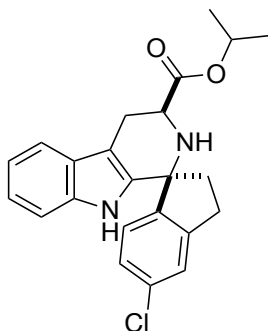
A modified procedure was adapted from Horiguchi, 2003³² for the synthesis of **2-19f**.

Synthesis of 2-17f and 2-18f: To a 50 mL RBF were added L-tryptophan methyl ester hydrochloride (420 mg, 1.64 mmol), DCM (25 mL), and sat. NaHCO₃ (10 mL). The mixture was stirred for 30 min at r.t. The organic layer was separated, washed with brine and dried over sodium sulfate, concentrated in vacuo to give L-tryptophan methyl ester **2-7** (359 mg, 99%).

An oven dried Schlenk flask was charged with **2-7** (359 mg, 1.64 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then 1 mL Ti(O^{*i*}Pr)₄ was added via syringe, followed by 5-chloro-2,3-dihydro-1*H*-inden-1-one **2-16f** (274 mg, 1.64 mmol). The mixture was heated to 70 °C for 3 h and cooled in an ice bath. Then TFA (10 mL, 130 mmol) and TFAA (0.23 mL, 1.64 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at r.t. overnight until TLC indicated full conversion, at which point the reaction mixture was added to 30 mL DCM in a separatory

funnel. To the DCM solution were added 10 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (40 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (40 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (7:3:1 DCM/Hexanes/EtOAc) gave **2-17f** (114.2 mg, 18%) and **2-18f** (59.8 mg, 9%).

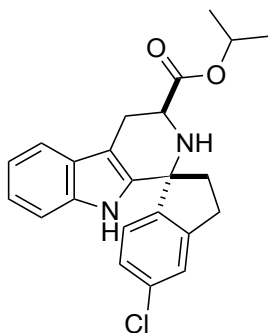
isopropyl (1*S*,3'*S*)-5-chloro-2,2',3,3',4',9'-hexahydrospiro[indene-1,1'-pyrido[3,4-*b*]indole]-3'-carboxylate (2-17f)



^1H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.52 (m, 1H), 7.42 (br, 1H), 7.33 – 7.31 (m, 1H), 7.25 – 7.22 (m, 1H), 7.19 – 7.10 (m, 3H), 6.96 (d, J = 8.1 Hz, 1H), 5.12 (hept, J = 6.3 Hz, 1H), 3.93 (dd, J = 11.1, 4.4 Hz, 1H), 3.30 – 3.21 (m, 1H), 3.18 (dd, J = 15.2, 4.4 Hz, 1H), 2.98 (ddd, J = 16.6, 8.7, 2.1 Hz, 1H), 2.87 (dd, J = 15.2, 11.1 Hz, 1H), 2.51 (ddd, J = 13.3, 7.9, 2.1 Hz, 1H), 2.38 (ddd, J = 13.3, 8.7, 8.7 Hz, 1H), 1.33 (d, J = 3.5 Hz, 3H), 1.31 (d, J = 3.5 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.8, 146.8, 144.3, 137.2, 136.1, 134.6, 127.4, 126.9, 125.6, 125.3, 122.1, 119.7, 118.3, 110.9, 109.1, 68.7, 65.4, 54.2, 40.0, 29.9, 26.1, 21.9, 21.8.

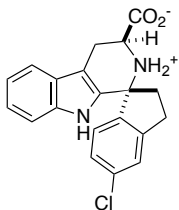
isopropyl (1*R*,3'*S*)-5-chloro-2,2',3,3',4',9'-hexahydrospiro[indene-1,1'-pyrido[3,4-*b*]indole]-3'-carboxylate (2-18f)



^1H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.55 (m, 2H), 7.31 – 7.30 (m, 1H), 7.28 – 7.24 (m, 1H), 7.21 – 7.11 (m, 2H), 7.06 (dd, $J = 8.6, 1.9$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 5.08 (hept, $J = 6.2$ Hz, 1H), 3.82 (dd, $J = 11.1, 4.4$ Hz, 1H), 3.43 – 3.31 (m, 1H), 3.26 (dd, $J = 15.2, 4.4$ Hz, 1H), 3.01 (dd, $J = 16.3, 8.4$ Hz, 1H), 2.88 (dd, $J = 15.2, 11.1$ Hz, 1H), 2.70 (ddd, $J = 13.4, 10.2, 8.4$ Hz, 1H), 2.46 (ddd, $J = 13.4, 7.3, 1.4$ Hz, 1H), 1.30 (d, $J = 6.2$ Hz, 3H), 1.27 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.1, 145.8, 144.7, 139.9, 136.3, 135.1, 127.0, 126.6, 125.6, 125.1, 122.2, 119.7, 118.3, 110.9, 109.1, 68.7, 64.7, 51.8, 41.8, 29.7, 25.9, 21.8, 21.7.

(1*R*,3'*S*)-5-chloro-2,2',3,3',4',9'-hexahydrospiro[indene-1,1'-pyrido[3,4-*b*]indole]-3'-carboxylic acid (2-19f)



Synthesis of **2-19f**: To a solution of **2-18f** (56.0 mg, 0.14 mmol) in THF / MeOH / H₂O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.1 g, 0.34 mmol) at room temperature. The reaction mixture was stirred at r.t. overnight. Then the resin was filtered and washed with MeOH and DCM alternatively (2 mL x 4) to remove unreacted ester. The desired carboxylate was freed from the cationic resin by stirring in 50% aqueous AcOH (20 mL) for 20 min, and filtration. This washing step was repeated 3 times. The combined filtrates were concentrated in vacuo. The residue was dissolved in MeOH (0.5 mL) and triturated with diethyl ether repeatedly (2 mL). The precipitate was washed with diethyl ether to afford **2-19f** (28.7 mg, 57 % yield).

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.48 (s, 1H), 7.47 – 7.42 (m, 2H), 7.23 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.19 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.05 – 6.94 (m, 3H), 3.80 (dd, *J* = 11.2, 4.3 Hz, 1H), 3.17 (ddd, *J* = 16.3, 8.2, 8.0 Hz, 1H), 3.06 (dd, *J* = 15.2, 4.3 Hz, 1H), 2.99 (ddd, *J* = 16.3, 8.5, 2.9 Hz, 1H), 2.79 (dd, *J* = 15.2, 11.2 Hz, 1H), 2.48 – 2.44 (m, 1H), 2.32 (ddd, *J* = 13.1, 8.5, 8.2 Hz, 1H).

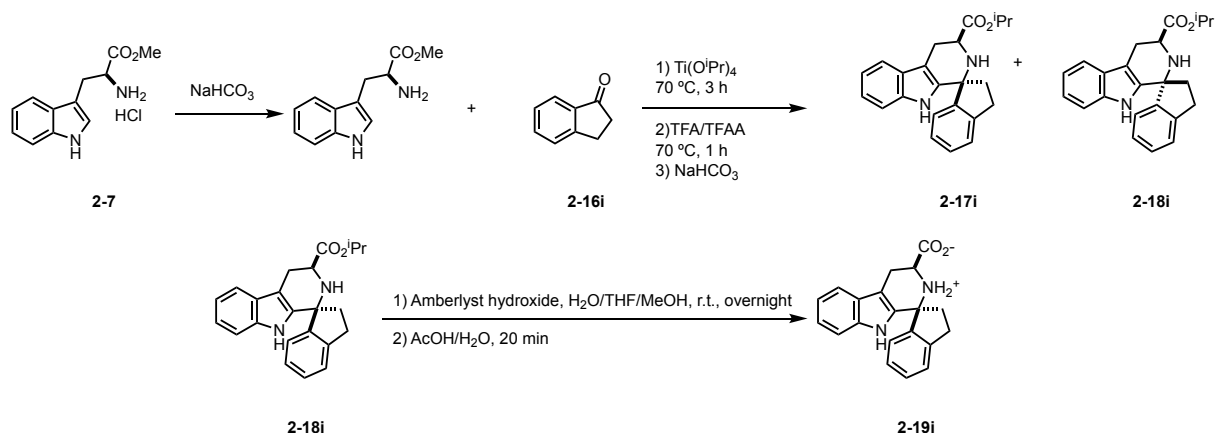
¹H NMR (400 MHz, Methanol-*d*₄) δ 7.53 – 7.50 (m, 1H), 7.49 (br, 1H), 7.33 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.21 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.10 (ddd, *J* = 8.2,

7.0, 1.3 Hz, 1H), 7.07 – 7.02 (m, 1H), 4.22 (dd, $J = 11.7, 5.0$ Hz, 1H), 3.53 – 3.34 (m, 2H), 3.24 – 3.09 (m, 2H), 2.84 (ddd, $J = 14.3, 8.7, 3.5$ Hz, 1H), 2.63 (ddd, $J = 14.3, 9.1, 7.2$ Hz, 1H).

^{13}C NMR (101 MHz, DMSO- d_6) δ 173.6, 147.2, 137.2, 136.4, 132.9, 126.6, 126.3, 126.2, 124.8, 121.0, 118.5, 117.8, 111.2, 109.7, 107.4, 65.6, 53.9, 29.5, 25.4. (missing one peak buried under DMSO signal @ 40 ppm)

HRMS (ESI+) calculated for $\text{C}_{20}\text{H}_{17}\text{ClN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 353.1051, found 353.1049.

Synthesis of (1*R*,3'*S*)-2,2',3,3',4',9'-hexahydrospiro[indene-1,1'-pyrido[3,4-*b*]indole]-3'-carboxylic acid (**2-19i**)

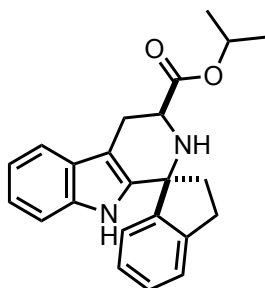


A modified procedure was adapted from Horiguchi, 2003³² for the synthesis of **2-19i**.

Synthesis of **2-17i** and **2-18i**: To a 50 mL RBF were added L-tryptophan methyl ester hydrochloride (395 mg, 1.55 mmol), DCM (25 mL), and sat. NaHCO_3 (10 mL). The mixture was stirred for 30 min at r.t. The organic layer was separated, washed with brine and dried over sodium sulfate, concentrated in vacuo gives L-tryptophan methyl ester **2-7** (337 mg, 99%).

To an oven dried Schlenk flask were added stir bar and **2-7** (337 mg, 1.55 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then 0.9 mL Ti(OⁱPr)₄ was added via syringe, followed by 2,3-dihydro-1*H*-inden-1-one **2-16i** (170 mg, 1.29 mmol). The mixture was heated to 70 °C for 3 h and cooled in ice/water bath. Then TFA (9 mL, 117 mmol) and TFAA (0.22 mL, 1.55 mmol) were added slowly via syringe at 0 °C. The mixture was heated to 70 °C for 1h, at which point the reaction mixture was added to 30 mL DCM in a separatory funnel. To the DCM solution were added 10 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (40 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (40 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (7:3:1 DCM/Hexanes/EtOAc) gave **2-17i** (69.0 mg, 15%) and **2-18i** (73.8 mg, 16%).

isopropyl (1*S*,3'*S*)-2,2',3,3',4',9'-hexahydrospiro[indene-1,1'-pyrido[3,4-*b*]indole]-3'-carboxylate (2-17i)

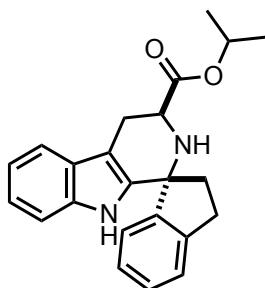


^1H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.49 (m, 1H), 7.42 (s, 1H), 7.32 (ddd, $J = 7.6, 1.6, 0.8$ Hz, 1H), 7.28 (td, $J = 7.3, 1.2$ Hz, 1H), 7.23 – 7.06 (m, 4H), 7.02 (d, $J = 7.8$ Hz, 1H), 5.11 (hept, $J = 6.3$ Hz, 1H), 3.94 (dd, $J = 11.2, 4.4$ Hz, 1H), 3.26 (dt, $J = 16.3, 8.3$ Hz, 1H), 3.16 (dd, $J = 15.2, 4.4$ Hz, 1H), 2.99 (ddd, $J = 16.3, 8.6, 2.5$ Hz, 2H), 2.87 (dd, $J = 15.2, 11.2$ Hz, 1H), 2.49 (ddd, $J = 13.3, 7.9, 2.6$ Hz, 1H), 2.35 (dt, $J = 13.3, 8.7$ Hz, 1H), 1.30 (d, $J = 6.3$ Hz, 3H), 1.29 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.1, 146.1, 145.0, 138.1, 136.3, 128.9, 127.2, 127.1, 125.2, 124.6, 122.1, 119.7, 118.4, 111.0, 109.0, 68.7, 66.1, 54.5, 40.0, 30.2, 26.4, 22.00, 21.96.

HRMS (ESI+) calculated for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 361.1911, found 361.1910.

isopropyl (1*R*,3'*S*)-2,2',3,3',4',9'-hexahydrospiro[indene-1,1'-pyrido[3,4-*b*]indole]-3'-carboxylate (2-18i)

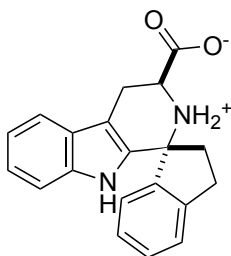


^1H NMR (400 MHz, Chloroform-*d*) δ 7.60 (br, 1H), 7.58 – 7.54 (m, 1H), 7.33 – 7.30 (m, 1H), 7.24 – 7.22 (m, 1H), 7.18 – 7.09 (m, 2H), 7.07 (t, $J = 7.5$ Hz, 1H), 6.87 (d, $J = 7.5$ Hz, 1H), 5.06 (hept, $J = 6.3$ Hz, 1H), 3.89 (dd, $J = 11.1, 4.3$ Hz, 1H), 3.40 – 3.31 (m, 1H), 3.26 (dd, $J = 15.2, 4.3$ Hz, 1H), 3.02 (dd, $J = 16.4, 8.0$ Hz, 1H), 2.89 (dd, $J = 15.2, 11.1$ Hz, 1H), 2.68 (ddd, $J = 13.4, 10.1, 8.6$ Hz, 1H), 2.46 (dd, $J = 13.4, 6.8$ Hz, 1H), 1.29 (d, $J = 6.3$ Hz, 3H), 1.24 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.1, 147.4, 142.9, 136.5, 135.9, 128.5, 127.3, 126.5, 125.5, 124.3, 122.1, 119.7, 118.4, 111.0, 109.6, 68.7, 65.0, 52.6, 41.9, 30.0, 26.1, 22.0, 21.9.

HRMS (ESI+) calculated for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 361.1911, found 361.1907.

(1*R*,3'*S*)-2,2',3,3',4',9'-hexahydrospiro[indene-1,1'-pyrido[3,4-*b*]indole]-3'-carboxylic acid (2-19i)



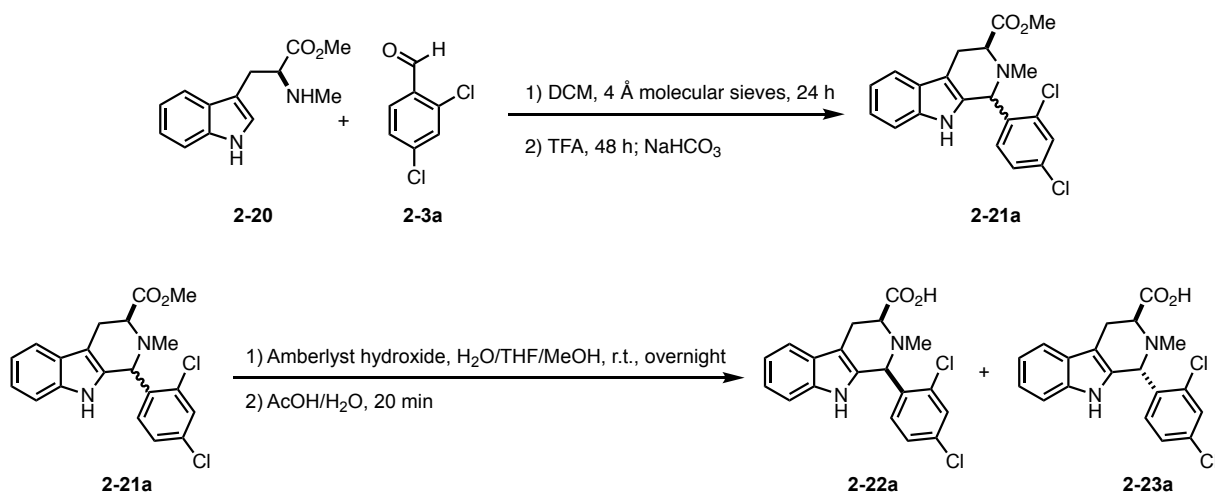
Synthesis of **2-19i**: To a solution of **2-18i** (73.8 mg, 0.20 mmol) in THF / MeOH / H₂O (3 mL / 3 mL / 3 mL) was added Amberlyst hydroxide resin (1.1 g, 0.34 mmol) at room temperature. The reaction mixture was stirred at r.t. overnight. Then the resin was filtered and washed with MeOH and DCM alternatively (2 mL x 4) to remove unreacted ester. The desired carboxylate was freed from the cationic resin by stirring in 50% aqueous AcOH (20 mL) for 20 min, and filtration. This washing step was repeated 3 times. The combined filtrates were concentrated in vacuo. The residue was dissolved in MeOH (0.5 mL) and triturated with diethyl ether repeatedly (2 mL). The precipitate was washed with diethyl ether to afford **2-19i** (44.6 mg, 68 % yield).

¹H NMR (400 MHz, Methanol-*d*₄) δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.41 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.22 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.14 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.08 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 4.13 (dd, *J* = 11.9, 5.1 Hz, 1H), 3.61 (dd, *J* = 16.3, 5.1 Hz, 1H), 3.50 (ddd, *J* = 15.4, 8.5, 8.5 Hz, 1H), 3.26 – 3.03 (m, 3H), 2.85 (dd, *J* = 14.6, 7.3 Hz, 1H).

¹³C NMR (101 MHz, Methanol-*d*₄) δ 173.8, 146.4, 141.6, 138.9, 131.8, 131.6, 128.3, 127.3, 127.1, 126.9, 123.7, 120.6, 119.3, 112.3, 109.0, 70.0, 55.7, 38.4, 30.4, 24.6.

HRMS (ESI+) calculated for C₂₀H₁₈N₂O₂ [M+H]⁺: 319.1441, found 319.1445.

Synthesis of (1*R*,3*S*)-1-(2,4-dichlorophenyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (2-23a)

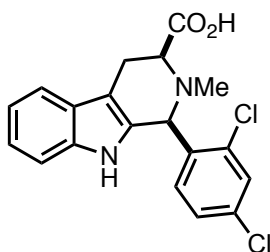


Synthesis of 2-21a: To a mixture of methyl N α -methyl-L-tryptophanate **2-20**, (0.28 g, 1.2 mmol), 4 Å molecular sieves (2.5 g, powder form) and 2,4-dichlorobenzaldehyde **2-3a** (0.21 g, 1.2 mmol), DCM (15 mL) was added under nitrogen. The resulting mixture was stirred for 24 hours at room temperature. TFA (0.2 mL, 2.4 mmol) was then added dropwise. The reaction mixture was stirred at room temperature for an additional 3 days. Aqueous work up followed by silica gel flash chromatography (10% EtOAc in hexanes) afforded **2-21a** as a yellow solid as a mixture of diastereomers (0.4 g, 84% yield).

Synthesis of 2-22a and 2-23a: A solution of **2-21a** (85 mg, 0.22 mmol) in THF / MeOH / H₂O (2.0 mL / 2.0 mL / 2.0 mL) and Amberlyst hydroxide resin (1.1 g, 0.34 mmol, Aldrich, loading: 4.2 mmol/g) were stirred for 7 days at r.t., followed by heating to 40 °C for 24 h. Work up afforded a residue was purified by preparative reverse phase HPLC.

HPLC solvent A is 0.1% formic acid in filtered 17 MΩ H₂O and solvent B is 0.1% formic acid in HPLC grade acetonitrile. A non-linear gradient of 5-95%B over 30 minutes was used. Collected samples were frozen over dry ice and lyophilized to afford **2-23a** (25 mg, 30% yield) as a yellow solid and **2-22a** (4 mg, 5%) as a yellow solid.

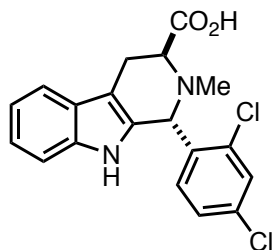
(1*S*,3*S*)-1-(2,4-dichlorophenyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (2-22a)



¹H NMR (400 MHz, Methanol-*d*₄) δ 7.59 (d, *J* = 2.1 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.32 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.19 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.07 – 6.96 (m, 2H), 5.44 (s, 1H), 3.65 (dd, *J* = 9.0, 4.7 Hz, 1H), 3.24 – 3.18 (m, 2H), 2.51 (s, 3H). ¹³C NMR (101 MHz, Methanol-*d*₄) δ 170.4, 138.6, 137.2, 136.9, 136.0, 134.0, 133.9, 130.2, 129.0, 127.4, 122.7, 120.1, 118.8, 112.2, 108.1, 69.0, 63.3, 40.6, 26.6.

HRMS (ESI) calculated for C₁₉H₁₇Cl₂N₂O₂[M+H]⁺: 378.0665, found 378.0639.

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (2-23a)

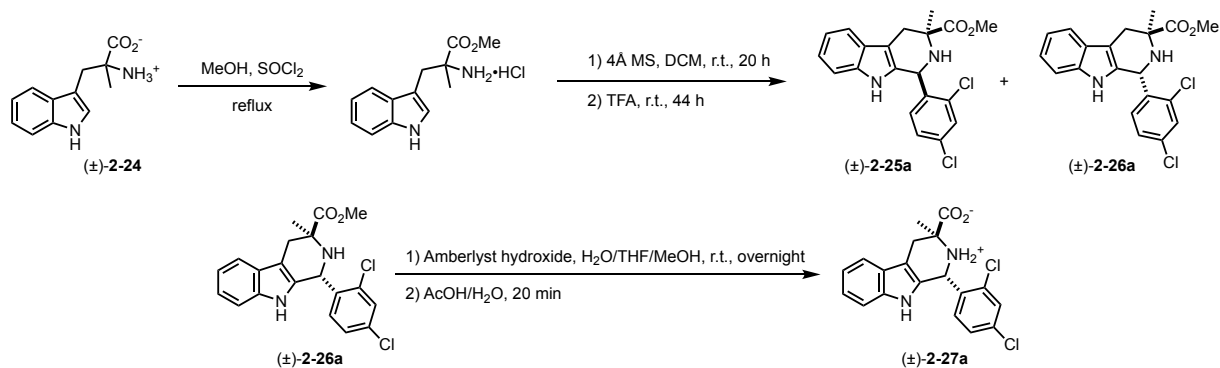


¹H NMR (400 MHz, Methanol-*d*₄) δ 7.58 (d, *J* = 1.7 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.27 (ddd, *J* = 8.5, 2.1, 0.4 Hz, 1H), 7.20 (ddd, *J* = 8.1, 1.2, 0.8 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.08 – 7.02 (m, 1H), 7.02 – 6.97 (m, 1H), 6.13 (s, 1H), 4.03 (t, *J* = 5.0 Hz, 1H), 3.36 – 3.32 (m, 2H), 2.67 (s, 3H).

¹³C NMR (101 MHz Methanol-*d*₄) δ 175.0, 138.7, 137.5, 137.3, 135.9, 133.6, 132.6, 130.3, 128.8, 127.6, 122.7, 120.1, 118.8, 112.1, 107.5, 62.7, 59.4, 39.8, 24.5.

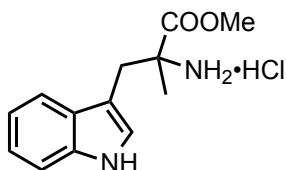
HRMS (ESI⁺) calculated for C₁₉H₁₇Cl₂N₂O₂[M+H]⁺: 375.0662, found 375.0641.

Synthesis of (±)-methyl (1*S*,3*S*)-1-(2,4-dichlorophenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate ((±)-2-27a)



A modified procedure was adapted from Yao, 2015¹⁴ for the synthesis of (±)-2-27a.

(±)-Methyl 2-amino-3-(1*H*-indol-3-yl)-2-methylpropanoate hydrochloride



Synthesis of (±)-Methyl 2-amino-3-(1*H*-indol-3-yl)-2-methylpropanoate hydrochloride:

To a 50 mL RBF were added α -Methyl-D, L-Tryptophan (440 mg, 2 mmol) and 25 mL methanol. The mixture was purged with nitrogen for 10 min and kept under nitrogen atmosphere. To the RBF were added 0.6 mL thionyl chloride (8.3 mmol) and the resulting mixture was heated under reflux for 4 h. The solvent was then concentrated under reduced atmosphere to give a viscous liquid. Diethyl ether (15 mL) was then added to the liquid and stirred for 10 min. The resulting precipitate was filtered to give (±)-**2-24** as a brown powder (535.2 mg, 98%).

^1H NMR (400 MHz, Methanol- d_4) δ 7.52 (dt, $J = 7.9, 1.0$ Hz, 1H), 7.33 (dt, $J = 8.1, 1.0$ Hz, 1H), 7.08 (td, $J = 7.9, 7.0, 1.0$ Hz, 1H), 7.04 (s, 1H), 7.00 (ddd, $J = 8.1, 7.0, 1.0$ Hz, 1H), 4.87 (s, 3H), 3.59 (s, 3H), 3.25 (d, $J = 14.2$ Hz, 1H), 2.97 (d, $J = 14.2$ Hz, 1H), 1.43 (s, 3H).

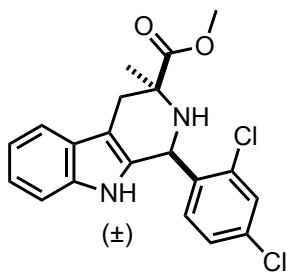
^{13}C NMR (101 MHz, Methanol- d_4) δ 172.7, 138.1, 128.8, 126.2, 122.9, 120.4, 119.1, 112.6, 106.9, 62.1, 53.9, 34.3, 22.5.

HRMS (ESI+) calculated for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 233.1285, found 233.1279.

Synthesis of (±)-**2-25a** and (±)-**2-26a**: To an oven-dried 25 mL RBF were added 0.5 g 4Å molecular sieves. The molecular sieves were activated with a heat gun under vacuum for 5 min, then cooled to r.t. under N_2 atmosphere. Then (±)-**2-24** (200 mg, 0.86 mmol), 2,4-

dichlorobenzaldehyde **2-3a** (150 mg, 0.86 mmol), and 10 mL DCM were added to the RBF, and the mixture was stirred at r.t. under N₂ for 20 h. Then the reaction was cooled with ice/water bath, and TFA (0.15 mL, 1.96 mmol) was added dropwise. The resulting mixture was stirred at r.t. for another 44 h until completion was indicated by TLC. After completion, the reaction mixture was basified with aq. sodium bicarbonate. The molecular sieves were removed by filtration, and the remaining mixture was extracted with DCM (15 mL x 3). The organic phase was separated, combined and washed with brine, dried with sodium sulfate, concentrated in vacuo, and purified by flash chromatography (5:5:1 Hexanes/DCM/EtOAc) to give (±)-**2-26a** (75.5 mg, 22%) and (±)-**2-25a** (259.5 mg, 77%).

(±)-methyl (1S,3S)-1-(2,4-dichlorophenyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate ((±)-2-25a)

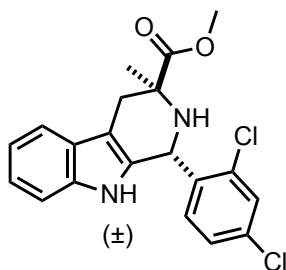


¹H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.52 (m, 2H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.20 – 7.10 (m, 3H), 5.73 (broad s, 1H), 3.71 (s, 3H), 3.26 (dd, *J* = 15.4, 2.3 Hz, 1H), 2.97 (dd, *J* = 15.4, 1.8 Hz, 1H), 1.54 (s, 3H). Note: 5-bond coupling is observed at the diastereotopic H4 (3.26 and 2.97 ppm) to H1, as observed for other tetrahydro-β-carbolines.³⁷

^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.0, 137.4, 136.4, 134.5, 134.3, 131.5, 131.3, 129.4, 127.8, 127.4, 122.2, 119.7, 118.3, 110.9, 108.8, 58.1, 52.3, 50.1, 30.3, 22.7.

HRMS calculated for $\text{C}_{20}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 389.0818, found 389.0814.

(\pm)-methyl (1*R*,3*S*)-1-(2,4-dichlorophenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate ((\pm)-2-26a)



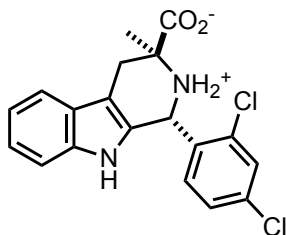
^1H NMR (400 MHz, Chloroform-*d*) δ 7.58 (br, 1H), 7.55 – 7.52 (m, 1H), 7.46 (d, $J = 2.1$ Hz, 1H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.23 – 7.17 (m, 2H), 7.16 – 7.09 (m, 2H), 5.96 (t, $J = 2.1$ Hz, 1H), 3.65 (s, 3H), 3.54 (dd, $J = 15.2, 2.1$ Hz, 1H), 2.85 (dd, $J = 15.2, 2.1$ Hz, 1H).

Note for (\pm)-**2-26a**, 5-bond coupling is observed between the two diastereotopic H4 (3.54 and 2.85 ppm) and H1 (5.96 ppm).³⁷

^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.9, 138.9, 136.5, 134.3, 134.1, 132.5, 131.7, 129.3, 128.1, 126.9, 122.1, 119.6, 118.5, 111.0, 109.1, 60.0, 52.4, 51.3, 30.8, 27.8.

HRMS (ESI+) calculated for $\text{C}_{20}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 389.0818, found 389.0814.

(±)-(1*R*,3*S*)-1-(2,4-dichlorophenyl)-3-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid ((±)-2-27a)



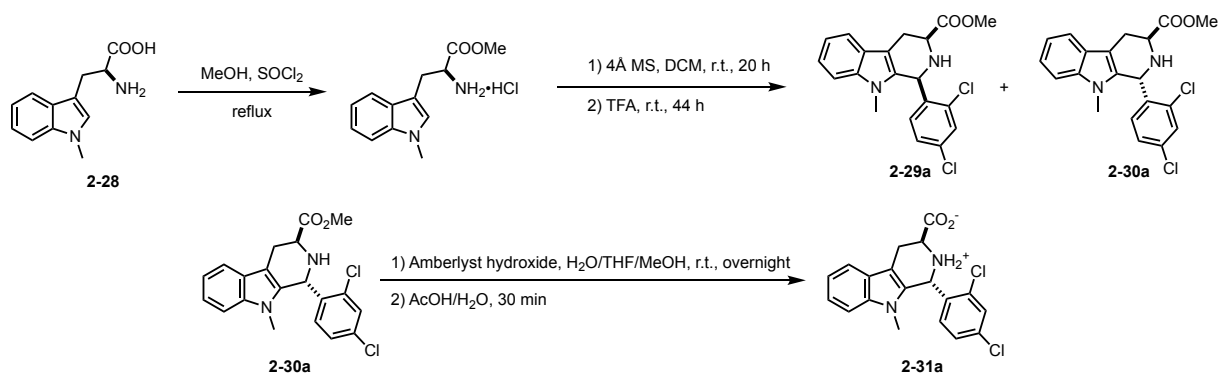
Synthesis of (±)-2-27a: A microwave assisted “catch-and-release” hydrolysis protocol³⁹ was used for the hydrolysis of (±)-2-27a.

To a microwave reaction vial were added (±)-2-26a (62.1 mg, 0.16 mmol), Amberlyst hydroxide (900 mg, 0.28 mmol), methanol (1.9 mL). The vial was sealed and irradiated at 130 °C in a Biotage Initiator microwave reactor for 40 min. Then the resin was filtered and washed with MeOH and DCM alternatively (2 mL x 4) to remove unreacted ester. The desired carboxylate was freed from the cationic resin by stirring in 50% aqueous AcOH (20 mL) for 20 min, and filtration. This washing step was repeated 3 times. The combined filtrates were concentrated in vacuo. The residue was dissolved in MeOH (0.5 mL) and triturated with diethyl ether repeatedly (2 mL). The precipitate was washed with diethyl ether to afford (±)-2-27a (32.2 mg, 54% yield).

¹H NMR (400 MHz, Methanol-*d*₄) δ 7.71 (d, *J* = 2.1 Hz, 1H), 7.51 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.24 – 7.20 (m, 2H), 7.11 (ddd, *J* = 8.0, 7.0, 1.3 Hz, 1H), 7.04 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 6.82 (s, 1H), 3.80 (dd, *J* = 16.1, 1.4 Hz, 1H), 2.98 (dd, *J* = 16.1, 2.4 Hz, 1H), 1.72 (s, 3H).

^{13}C NMR (101 MHz, Methanol- d_4) δ 175.3, 138.8, 137.9, 137.0, 133.7, 133.3, 131.5, 129.1, 128.2, 127.4, 123.5, 119.9, 119.3, 112.2, 110.5, 65.3, 53.7, 30.1, 25.3.
 HRMS (ESI+) calculated for $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 375.0662, found 375.0651.

Synthesis of (1*R*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (2-31a)



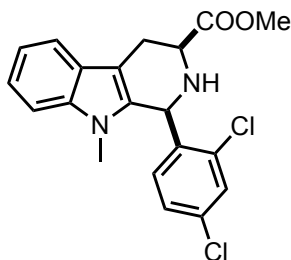
A modified procedure was adapted from Yao, 2015¹⁴ for the synthesis of **2-31a**.

Synthesis of 2-29a and 2-30a: To **2-28** (Sigma Aldrich, 0.6 g, 2.75 mmol) was added dry MeOH (8 mL) under nitrogen atmosphere. SOCl_2 (0.4 mL, 5.5 mmol) was then added dropwise in an ice bath and the solution was stirred at 0 °C for 1 hour and then warmed up to room temperature and continued to stir for 24 hours. After completion of the reaction MeOH was evaporated and Et₂O (15 mL) was added and the mixture was stirred for 20 mins and filtered and washed with cold Et₂O to yield methyl 1-methyl-*L*-tryptophanate hydrochloride (0.7 g, 95%) as a beige solid.

To methyl 1-methyl-*L*-tryptophanate hydrochloride, (0.693 g, 2.98 mmol) 2,4-dichlorobenzaldehyde **2-3a** (0.52 g, 2.6 mmol) and 4Å molecular sieve (1.4 g, powder

form) DCM/MeOH (4:1.5 mL) were added under a nitrogen atmosphere. The resulting reaction mixture was stirred for 32 hours at room temperature. TFA (0.46 mL, 5.97 mmol) was then added dropwise. The reaction mixture was further stirred at room temperature for 72 hours. An aqueous solution of NaHCO₃ (0.75 g, 8.94 mmol, in 6 mL H₂O) was added dropwise at 0 °C, followed by an addition of EtOAc (12 mL). The mixture was stirred for 15 minutes. The phases were separated, and the aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ (1 g), concentrated, then purified by flash chromatography (5 : 5 : 0.1 hexane / DCM / THF) to give **2-30a** (0.27 g, 26 % yield) and **2-29a** (0.107 g, 10 % yield) and 2,4-dichlorobenzaldehyde **2-3a** (0.2 g, 29%) was also recovered.

methyl (1*S*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole- 3-carboxylate (2-29a**)**

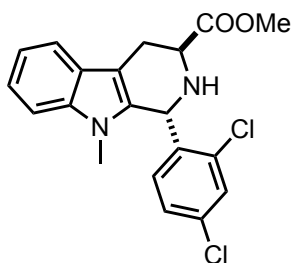


¹H NMR (400 MHz, Chloroform-*d*) δ 7.52 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.24 – 7.13 (m, 3H), 7.09 (ddd, *J* = 8.0, 6.6, 1.5 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 5.77 (broad s, 1H), 3.86 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.72 (s, 3H), 3.21 (ddd, *J* = 15.1, 4.1, 1.8 Hz, 1H), 3.14 (s, 3H), 3.00 (ddd, *J* = 15.1, 10.2, 2.3 Hz, 1H). Note: 5-bond coupling is observed at the diastereotopic H4 (3.21 and 3.00 ppm) to H1.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.6, 138.1, 137.8, 135.2, 134.8, 134.1, 131.6, 130.0, 128.5, 126.7, 122.3, 119.8, 118.6, 109.8, 109.4, 56.4, 53.5, 52.6, 30.6, 25.9.

HRMS (ESI+) calculated for $\text{C}_{20}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 390.0850, found 390.0865.

methyl (1*R*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (2-30a)



^1H NMR (400 MHz, Chloroform-*d*) δ 7.60 (d, $J = 9.5$ Hz, 1H), 7.52 (d, $J = 2.1$ Hz, 1H), 7.27 (m, 2H), 7.17 (ddd, $J = 8.0, 6.5, 1.7$ Hz, 1H), 7.07 (dd, $J = 8.3, 2.1$ Hz, 1H), 6.62 (d, $J = 8.3$ Hz, 1H), 5.80 (s, 1H), 3.76 (s, 3H), 3.70 (dd, $J = 10.2, 4.5$ Hz, 1H), 3.28 (s, 3H), 3.28 (dd, $J = 15.3, 4.5$ Hz, 1H), 3.01 (dd, $J = 15.3, 10.2$ Hz, 1H).

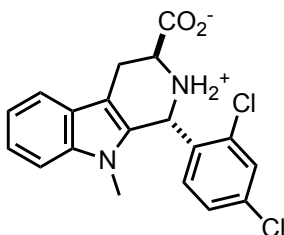
^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.5, 137.5, 136.9, 134.6, 134.4, 132.8, 130.7, 130.2, 127.0, 126.5, 122.0, 119.5, 118.5, 109.2, 109.1, 52.4, 51.2, 51.1, 29.7, 25.5.

HRMS (ESI+) calculated for $\text{C}_{20}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 390.0850, found 390.0875.

(1*R*,3*S*)-1-(2,4-dichlorophenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (2-31a)

Synthesis of **2-31a**: To a solution of **2-30a** (39.0 mg, 0.1 mmol) in THF / MeOH / H₂O (1 mL / 1 mL / 1 mL) was added Amberlyst hydroxide resin (0.63 g, 0.19 mmol) at room temperature. The reaction mixture was stirred at r.t. overnight. Then the resin was filtered and washed with MeOH and DCM alternatively (2 mL x 4) to remove unreacted ester.

The desired carboxylate was freed from the cationic resin by stirring in 50% aqueous AcOH (20 mL) for 20 min, and filtration. This washing step was repeated 3 times. The combined filtrates were concentrated in vacuo. The residue was dissolved in MeOH (0.5 mL) and triturated with diethyl ether repeatedly (2 mL). The precipitate was washed with diethyl ether to afford **2-31a** as an off white solid (30 mg, 80 % yield).



^1H NMR (400 MHz, Methanol- d_4) δ 7.72 (d, $J = 2.1$ Hz, 1H), 7.58 (d, $J = 7.9$ Hz, 1H), 7.35 – 7.28 (m, 2H), 7.23 (ddd, $J = 8.2, 7.0, 1.1$ Hz, 1H), 7.12 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 6.88 (d, $J = 8.4$ Hz, 1H), 6.22 (s, 1H), 3.83 (dd, $J = 10.3, 4.8$ Hz, 1H), 3.47 (dd, $J = 15.7, 4.8$ Hz, 1H), 3.21 (s, 3H), 3.10 (t, $J = 15.7, 10.3$ Hz, 1H).

^{13}C NMR (126 MHz, Methanol- d_4) δ 174.8, 139.4, 137.5, 136.5, 133.8, 133.2, 131.3, 130.0, 129.1, 127.1, 123.8, 120.8, 119.6, 110.3, 109.7, 53.8, 51.8, 29.8, 24.8.

HRMS (ESI+) calculated for $\text{C}_{19}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 375.0662, found 375.0646.

E. X-ray Structure Determination of 2-14a

E.1. Acknowledgements: This material is based upon work supported by the National Science Foundation under CHE-1726077.

E.2. Experimental: A colorless rod (0.05 x 0.06 x 0.21 mm³) was centered on the goniometer of a Rigaku Oxford Diffraction Synergy-S diffractometer equipped with a HyPix6000HE detector and operating with $\text{CuK}\alpha$ radiation. The data

collection routine, unit cell refinement, and data processing were carried out with the program CrysAlisPro.⁴⁰ The Laue symmetry and systematic absences were consistent with the monoclinic space groups $P2_1$ and $P2_1/m$. Only the noncentrosymmetric space group $P2_1$ gave a satisfactory structure solution. The structure was solved using SHELXT⁴¹ and refined using SHELXL⁴² via Olex2⁴³.

The asymmetric unit contains 4 molecules of the main compound, one methanol solvate, and substantial disordered solvent that could not be modeled effectively; therefore, the solvent mask feature of OLEX2 was used. A total of 124.4 e⁻ was subtracted from 1055.2 Å³ total space. Although the disordered solvent likely comprises a mixture of the crystallization solvents (MeOH, EtOH, H₂O), for simplicity the solvent was approximated as 6 CH₃OH molecules, giving a total of 8 CH₃OH / unit cell (this includes the CH₃OH that was located and refined). The final refinement model involved anisotropic displacement parameters for all non-hydrogen atoms. The N-H positions could not be reliably located. Therefore, a riding model was used for all hydrogen atoms except the hydrogens of the secondary amines (N2, N5, N8, N11), for which there was no suitable riding model. For the amine hydrogens, the starting H-atom position were calculated assuming an ammonium (i.e. assigning tetrahedral N-atom with two calculated H-atom positions). For each amine nitrogen, one of the two H-atoms was sterically too close to the amide H-atom and was deleted. For the remaining H-atom on the amine, distance restraints were used to maintain approximately idealized trigonal pyramidal geometry. The absolute configuration of the molecules was known from the synthetic procedure and confirmed from anomalous dispersion effects [Flack $x = 0.012(9)$;⁴⁴ Hooft $P2(\text{true}) =$

1.000, P3(true) = 1.000, P3(rac-twin) = 0.000; P3(false) = 0.000, $y = 0.027(4)$].^{43, 45-46}

The stereochemistry were assigned as S (C9, C29, C49, C69) and R (C10, C30, C50, C70). Olex2⁴³, Mercury⁴⁷ and Pymol⁴⁸ was used for molecular graphics generation.

F. MMFF94 Conformer Energies of 18fNHMe

The methyl amide of **2-18f**, **2-18fNHMe**, was chosen for analysis, to facilitate comparison with the crystallized amides **2-14a** and **2-15a**. Multiple starting geometries of this compound were subjected to an automated conformer distribution search in Spartan '18, using the Conformer Distribution as the job, using the MMFF94 Force Field. In total 29 conformers were located, which were grouped into two conformer ensembles, as defined by the narrow range in τ .

G. Procedures for Biological Assays

G.1. Parasite Culture: *P. falciparum* Dd2 parasites (MRA-150, chloroquine-resistant (intermediate), pyrimethamine-resistant, mefloquine-resistant) were obtained from MR4 Malaria Reagent Repository (ATCC, Manassas, VA), a part of the BEI Resources Repository (NIAID, NIH). Parasites were maintained in O-positive human erythrocytes (Interstate Blood Bank Inc., Memphis, Tennessee) at 5% hematocrit in RPMI 1640 medium supplemented with 5 g/L Albumax I (Gibco Life Technologies), 2 g/liter glucose (Sigma-Aldrich), 2.3 g/L sodium bicarbonate (Sigma-Aldrich), 370 μ M hypoxanthine (Sigma-Aldrich), 25 mM HEPES, and 20 mg/L gentamicin (Gibco Life Technologies). The parasites were kept at 37°C under reduced-oxygen conditions (5% CO₂, 5% O₂, and 90% N₂).

G.2. Growth Inhibition and Rescue by Isopentenyl Diphosphate (IPP)

Supplementation Assays: The effect of MMV008138 analogs was evaluated against asexual blood stages of *P. falciparum* parasites by using the SYBR green assay as described previously.¹⁴ The antimalarial activity of MMV008138 analogs was first evaluated against asexual parasites using four-point dilutions ranging from 10 μM to 1.25 μM . For active compounds, the half maximal effective concentration (EC_{50}) were determined using ten-point dilutions at concentrations ranging from 20 μM to 0.02 μM in constant 0.1% DMSO (vehicle). The percentage of growth was normalized to that of untreated control parasites in the presence of 0.1% DMSO. Background determinations were made using uninfected erythrocytes. Two or more independent experiments were performed. The IC_{50} values were calculated with GraphPad Prism 6 (GraphPad Software Ltd.) using nonlinear regression curve fitting with variable slope (four parameters) and represent the average of two or more independent experiments and their standard deviation (S.D.). To assess whether compounds were specifically targeting the apicoplast, the recovery of growth in the presence of inhibitor and IPP was performed as described previously.¹⁴ Briefly, parasites were grown in the presence or absence of 200 μM IPP along with a serial dilution (10 μM to 0.02 μM) or single concentration (10 or 20 μM) of MMV008138 analogs. All conditions were set in 96-well half area plates using ring-stage parasite cultures (100 μL /well with 1% hematocrit and 1% parasitemia) and incubated for 72 h under normal culture conditions. Parasite growth was measured by a SYBR green assay.

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Chapter 3. Synthesis of fused azepane-indoles from Pictet-Spengler reaction of 2'-substituted acetophenones and tryptophan methyl ester: scope and mechanism

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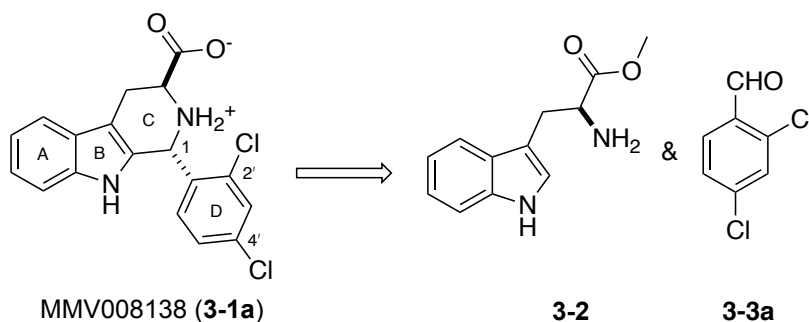
*This chapter has been adapted from a manuscript in preparation by the authors listed above. P.R.C., S.D., and M.G. designed analogues of **3-1a**, and S.D. and M.G. synthesized them. C.S. performed X-ray crystallography. The manuscript was written through contributions of all authors.*

Abstract

The identification of MEP pathway inhibitor MMV008138 sparked our interest in developing structural analogs to improve potency and microsomal stability. During the effort to prepare the C1-Me analog of MMV008138, acetophenones were used as substrates in Pictet–Spengler reactions of tryptophan methyl ester. This reaction required Ti(Oi-Pr)₄ mediated imine formation and acid-mediated cyclization. Acetophenones lacking 2'-substitution proceeded normally to give the desired 1-methyl-1-aryltetrahydro-β-carboline. However, when 2',4'-dichloroacetophenone was used in conjunction with heating in acid, the desired tetrahydro-β-carboline was not isolated. Instead a mixture of diastereomeric fused azepane-indoles was isolated. This ring expansion was observed for a number of other 2'-substituted acetophenones. In this chapter we propose a mechanism for this novel ring expansion, and a range of experiments are presented that support it. DFT calculations suggest that relief of steric strain in 2'-substituted 1-methyl-1-aryltetrahydro-β-carbolines provides the driving force for azepane formation.

Introduction

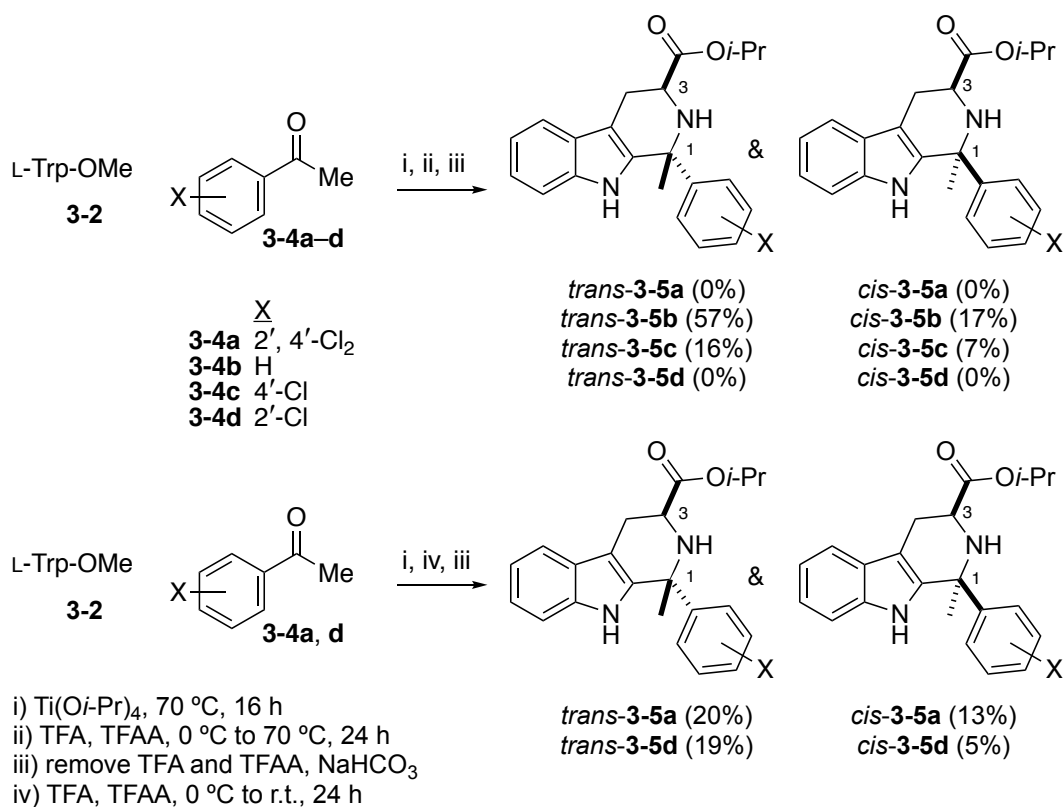
MMV008138 (**3-1a**) has promising antimalarial activity and a novel mechanism of action,¹⁻⁴ and is trivially prepared in a three step sequence of i) Pictet–Spengler (PS) reaction of L-tryptophan methyl ester **3-2** and 2,4-dichlorobenzaldehyde **3-3a**, ii) diastereomer separation, and iii) hydrolysis (Scheme 3-1).²



Scheme 3-1. Antimalarial agent **3-1a** is derived from Pictet–Spengler reaction of **3-2** and **3-3a**

To date a number of D-ring analogs of **3-1a** have been prepared by reaction of various benzaldehydes with **3-2**,^{2,5} and these studies revealed that *P. falciparum* growth inhibition and target enzyme (*Plasmodium falciparum* IspD) engagement require 2',4'-halogen disubstitution of the D-ring, as seen in **3-1a**.⁵ To probe the effect of methyl substitution at C1, we carried out PS reaction of **3-2** with various acetophenones,⁵ according to the published protocol, which involves Ti(Oi-Pr)₄-mediated imine formation at 70 °C, followed by heating with TFA and TFAA to effect cyclization to the desired ketone PS adduct.⁶ (Scheme 3-2) This protocol worked fine for acetophenones lacking 2'-substitution, such as **3-4b** and its 4-chloro analog **3-4c**. However, as we described in Chapter 2, isolation of the

desired ketone PS adduct from acetophenones bearing 2'-substitution (such as **3-4a**, and **3-4d**) could not be achieved, unless the imine intermediates were treated with TFA and TFAA at reduced temperature.⁷

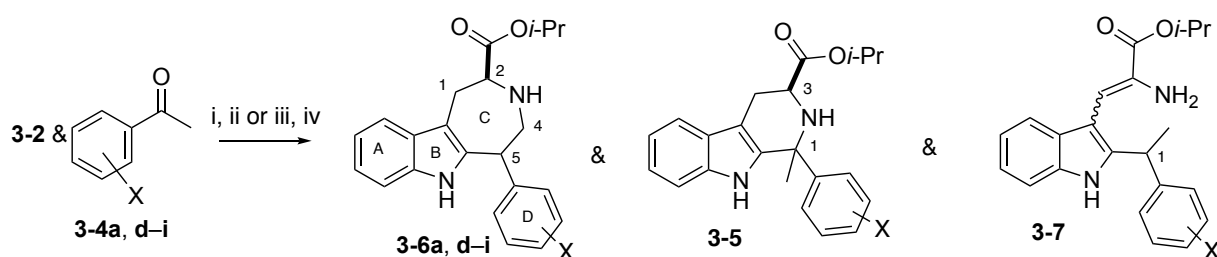


Scheme 3-2. Pictet–Spengler Reaction of **3-2** with acetophenones **3-4a–d**. The number in parenthesis is isolated yield.⁷

Interestingly, when the PS reactions of **3-2** with 2'-substituted acetophenones **3-4a** and **3-4d** were carried out under the original high temperature protocol, my predecessor Dr. Maryam Ghavami found that the expected 1-methyl tetrahydro- β -carbolines **3-5a, d** were not obtained. Instead NMR spectroscopy and X-ray crystallographic analysis indicated the formation of fused azepane-indole products **3-6a** and **3-6d**, as mixtures of diastereomers.⁸

Intrigued by this discovery, she and I carried out PS reactions of **3-2** with additional acetophenones bearing 2'-substituents. (Table 3-1)

Table 3-1. Formation of fused azepane-indole products **3-6** by Pictet-Spengler reaction of 2'-substituted acetophenones with **3-2**. (Note: compounds **3-6a, d, f, g,** and **i** were originally isolated by Dr. Maryam Ghavami; I subsequently repeated those reactions and optimized the yields.)



- i) $\text{Ti}(\text{O}i\text{-Pr})_4$, 70 °C, 16 h
 ii) TFA, TFAA, 0 °C to 70 °C, 1-3 h
 iii) TFA, TFAA, 0 °C to 70 °C, 24 h
 iv) remove TFA and TFAA, NaHCO_3

Entry	Ketone	X	Combined % yield of <i>trans</i> - and <i>cis</i> - 3-6 (% isolated <i>trans</i> - 3-6 , <i>cis</i> - 3-6)	Combined % yield of <i>trans</i> - and <i>cis</i> 3-5 (% isolated <i>trans</i> - 3-5 , <i>cis</i> - 3-5)	% Isolated Yield of 3-7	Cyliza- tion condition
1	3-4a	2',4'-Cl ₂	77 (23,17)	0	0	ii
2	3-4d	2'-Cl	89 (57, 12)	0	0	ii
3	3-4e	2'-Br	83 (37, 17)	0	0	ii
4	3-4f	2',4'-F ₂	8 (8,0)	74 (32, 21)	0	ii
5	3-4f	2',4'-F ₂	64 (22, 9)	0	0	iii
6	3-4g	2'-F	17 (17,0)	72 (27, 18)	0	ii
7	3-4g	2'-F	74 (26, 18)	0	0	iii
8	3-4h	2'-OMe	0	54 (5, 13)	0	iii
9	3-4i	2'-Me	54 (0, 0)	0	10	ii

Note that complete separation of the diastereomeric azepane-indoles **3-6** by silica gel chromatography sometimes proved difficult. Thus, the isolated yields reported in Table 3-1 reflects the sum of post-chromatographic yields of *trans*-**3-6**, *cis*-**3-6**, and mixed fractions; isolated yields of diastereomerically pure *trans*- and *cis*-**3-6** are given in parentheses. The same is true for the diastereomeric 1-methyl-tetrahydro- β -carbolines *cis*- and *trans*-**3-5**. Our method to assign *cis*- and *trans*-relative configuration of the fused azepane-indoles is described below; it is worth noting that with a 5:5:1 hexanes/CH₂Cl₂/EtOAc elution system, the *cis*-**3-6** isomer always elutes before the *trans*-**3-6** isomer. Conversely, for the 1-methyl-tetrahydro- β -carbolines **3-5**, the *trans*-isomers always elute before the *cis*-isomers. The relative stereochemistry of *trans*- and *cis*-**3-5** was determined by NOE spectroscopy, as described in Chapter 2.

When 2'-bromoacetophenone **3-4e** was used, the corresponding azepanes **3-6e** were also isolated in 83% total yield (Table 3-1, Entry 3). However, 2'-fluoro-substituted acetophenones **3-4f** and **3-4g** gave a mixture of azepanes **3-6f, g** and 1-methyl tetrahydro- β -carboline **3-5f, g**, with total yields of 82% and 89%, respectively (Table 3-1, Entries 4 and 6). When a longer heating time was used, only azepanes **3-6f, g** were obtained, in 64% and 74% yield (Table 3-1, Entries 5 and 7). The 2'-methoxy acetophenone **3-4h** provides the only example thus far for which the high temperature cyclization protocol of an 2'-substituted acetophenone failed to produce the fused azepane-indole product; even after heating in TFA and TFAA at 70 °C for 24 h, only 1-methyl tetrahydro- β -carbolines *trans*- and *cis*-**3-5h** were isolated. (Table 3-1, Entry 8). Reaction of 2'-Me-acetophenone **3-4i** was remarkable in another way; in addition to the expected azepanes **3-6i** (obtained as a mixture of diastereomers in 54% yield), isopropyl 2-amino-3-(2-(1-arylethyl)-1*H*-indol-3-yl)acrylate **3-**

7i was also obtained in 10% yield (Table 3-1, Entry 9). This observation will inform our discussion of a possible mechanism below.

As mentioned above, the structure of the second-eluting isomer of **3-6a** was confirmed by conversion into the corresponding methyl amide (methanolic MeNH₂, 24 h, 85% yield, Dr. Maryam Ghavami) and X-ray crystallography (Figure 3-1).

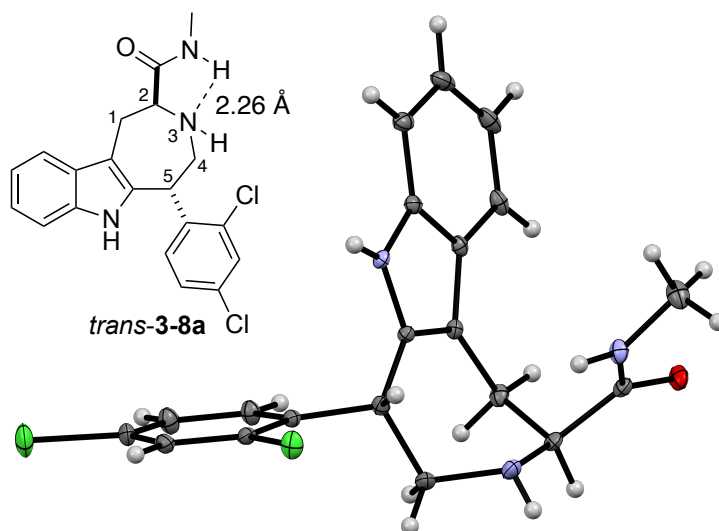
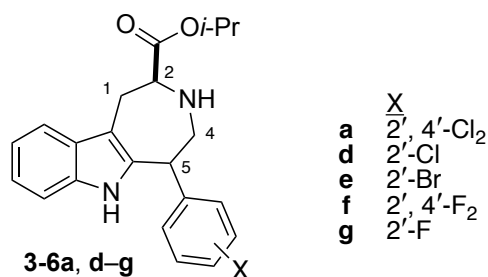


Figure 3-1. Anisotropic displacement ellipsoid drawings (50%) of the X-ray structure of compound **3-8a**; note the azepane ring adopts a distorted half-chair conformation (see Table 3-5 below). Mercury⁹ was used for molecular graphics generation

Since X-ray crystallography of this product **3-8a** unambiguously demonstrated a *trans*-relationship between the C2-carboxy ester and the C5-aryl substituent, we deduced *trans*-relative configuration in its ester precursor **3-6a** (second-eluting diastereomer), and *cis*-relative configuration in the first-eluting diastereomer of **3-6a**. With these assignments in

hand, we examined their ^1H NMR spectra, and found a clear trend that was replicated in the first- and second-eluting diastereomers of **3-6d-g** (Table 3-2).

Table 3-2. ^1H NMR spectroscopic (CDCl_3) characteristics of *trans*- and *cis*- fused azepane-indoles **3-6a, d-g**.^a



	δ H2 (ppm)	$^3J_{12}$ (Hz)	δ H5 (ppm)	$^3J_{45}$ (Hz)
<i>trans</i> - 3-6a	3.90	8.2, 3.5	4.85	9.5, 3.8
<i>cis</i> - 3-6a	3.72	11.1, 3.1	4.70	3.8, 3.8
<i>trans</i> - 3-6d	3.91	8.0, 3.3	4.91	9.5, 3.8
<i>cis</i> - 3-6d	3.75	11.1, 3.1	4.76	4.0, 3.8
<i>trans</i> - 3-6e	3.89	7.9, 3.5	4.87	9.9, 3.9
<i>cis</i> - 3-6e	3.77	11.1, 3.2	4.75	4.1, 3.8
<i>trans</i> - 3-6f	3.85	8.6, 3.1	4.65	9.8, 3.8
<i>cis</i> - 3-6f	3.70	11.1, 2.9	4.57	3.8, 3.5
<i>trans</i> - 3-6g	3.87	8.8, 3.1	4.71	9.9, 3.8
<i>cis</i> - 3-6g	3.73	10.9, 4.2	4.63	3.9, 3.6

^aThe *cis*-fused azepane-indoles uniformly elute first on SiO_2 using 5:5:1 hexanes/ CH_2Cl_2 /EtOAc. Note that the diastereomers of **3-6i** could not be separated by chromatography and thus could not be fully characterized by ^1H NMR spectroscopy.

As can be seen in table 3-2, the diastereomers of **3-6a** can be distinguished on the basis of $^3J_{45}$ values: *trans*-**3-6a** has well-differentiated coupling constants between H5 and the two diastereotopic H4 protons. (9.5, 3.8 Hz). In contrast, in *cis*-**3-6a**, H5 appears as triplet with a

coupling constant of 3.8 Hz. As we will show below in Figure 3-5, these values of $^3J_{45}$ can be attributed to the different orientations of H5 in the minimum energy conformations of *trans*- and *cis*-**3-6**. On this basis the relative configurations of **3-6d–g** were assigned. Following this classification other trends are also apparent: H2 and H5 are uniformly downfield by ~ 0.15 ppm in *trans*-**3-6** relative to *cis*-**3-6**, and greater differentiation of the three-bond coupling constants of H2 to the diastereotopic H1 ($^3J_{12}$) is seen in *cis*-**3-6** relative to *trans*-**3-6**.

To the best of our knowledge, such fused azepane-indoles have never before been isolated from PS reactions of tryptophan or its esters. The fused azepane-indole structure is however embedded in the iboga alkaloids (e.g. **3-9a–c**, Figure 3-2), a family of over 60 analogs, possessing various neurological activities.¹⁰⁻¹¹

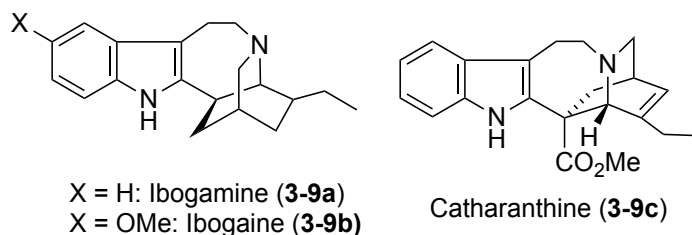
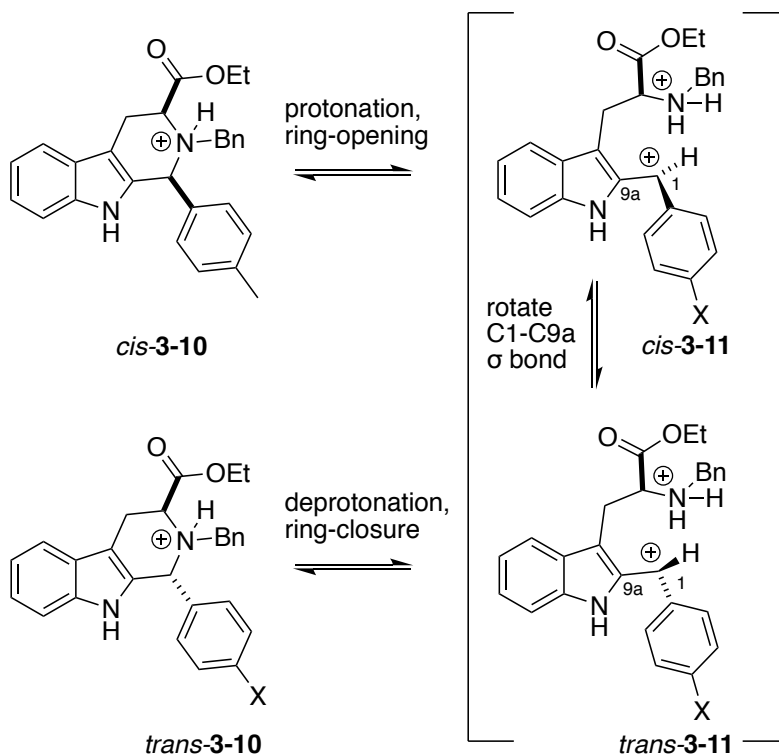


Figure 3-2. Select members of the Iboga alkaloid family

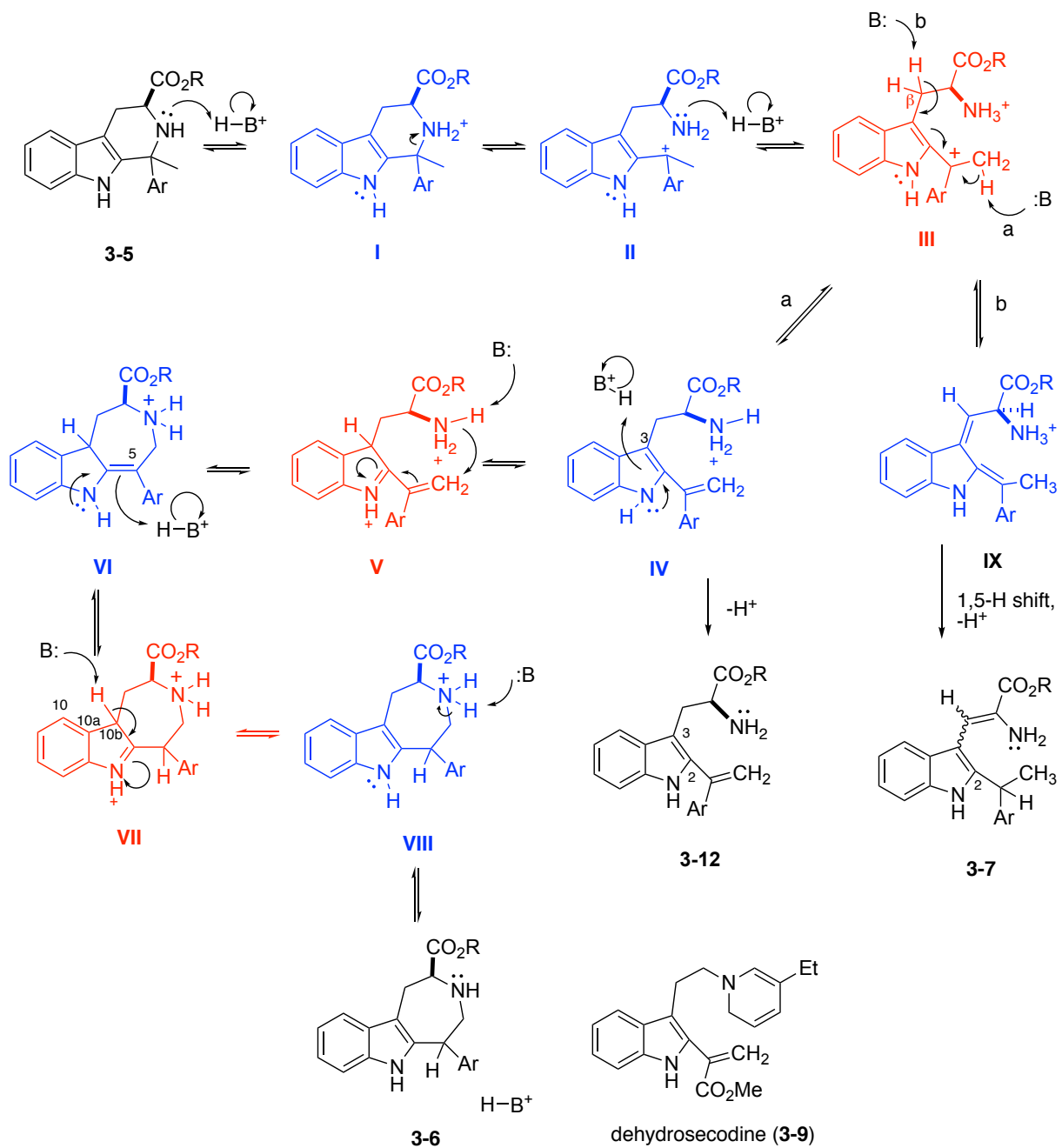
To account for the formation of the fused azepanes **3-6**, we propose that PS reaction of **3-2** with 2'-substituted acetophenones initially produces the expected 1-methyltetrahydro- β -carboline **3-5**, and that in acid with heating, ring expansion to **3-6** occurs via a multistep mechanism involving both cationic and dicationic intermediates. We are aware that dications are rare, but dicationic intermediates have been strongly implicated in the *cis* to *trans* isomerization of *N*2-benzyl-tetrahydro- β -carbolines derived from aldehydes and **3-2** (Scheme 3-3).¹² These authors proposed that formation of the dication was necessary to give sufficient

time for C1-C9a bond-rotation prior to ring-closure. In our proposed mechanism for ring-expansion, formation of a dication intermediate provides the most concise explanation for a number of observations (vide infra).



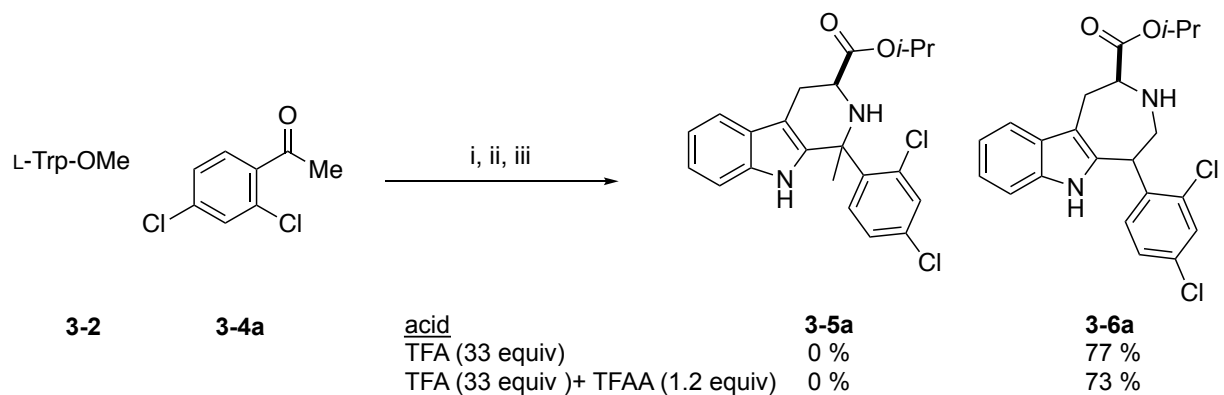
Scheme 3-3. Epimerization of *cis*-N2-benzyl tetrahydro-β-carboline via bond rotation of dicationic intermediate.¹²

The proposed mechanism for ring expansion is shown in Scheme 3-4. Protonated tetrahydro-β-carboline **I** is proposed to undergo ring-opening to the benzylic carbocation **II** which undergoes a second protonation to the dication **III**. Once formed, dication **III** can



Scheme 3-4. Proposed ring-expansion mechanism. Neutral species are in black, cations are in blue, and dicationic intermediates are in red. Note: in each structure, the atoms are numbered according to IUPAC according to the tetra-hydro- β -carboline, indole or fused azepane-indole scaffold they possess. The double bond-geometry in **3-7** is not known.

undergo two divergent deprotonations: removal of a methyl group proton (path a) affords ammonium cation **IV**, which is then protonated at C3 to afford the ammonium α,β -unsaturated iminium dication **V**. Deprotonation at the ammonium group allows cyclization by conjugate addition to afford ammonium cation **VI**. Rearomatization would occur by protonation at C5 to form dication **VII**, followed by aromatizing deprotonation at C10b to form cation **VIII**, which on basic workup would afford the neutral fused indole-azepane **3-6** that we isolated. Alternatively, removal of one of the β -protons of dication **III** (path b) would afford cation **IX**; 1,5-hydride shift and loss of proton would yield 2-(1-arylethyl) dehydrotryptophan ester **3-7** that we observed in reaction of 2'-methoxyacetophenone **3-4h** (Table 3-1, Entry 8). Note that proposed 2-(1-arylvinyl)tryptophan intermediate **3-12** is reminiscent of dehydrosecodine, which has been proposed as an intermediate in the biosynthesis of catharanthine.^{10, 13} The ketone PS reaction protocol reported by Horiguchi et al. calls for the addition of 1 equivalent of TFAA, however the role of TFAA was not discussed in that paper.¹⁴ We were curious if the addition of TFAA is crucial, and conducted control reactions with 2,4-dichloroacetophenone. (Scheme 3-5) When the TFAA was not added, the azepanes **3-6a** were obtained, but at slightly reduced yield. The addition of TFAA slightly improved the reaction rate, but is not required for the ring expansion reaction. Thus we do not include TFAA in the mechanism in Scheme 3-4.



i) $\text{Ti}(\text{O}i\text{-Pr})_4$, 70 °C, 16 h
 ii) add acid, 0 °C to 70 °C, 3 h
 iii) remove acid, NaHCO_3

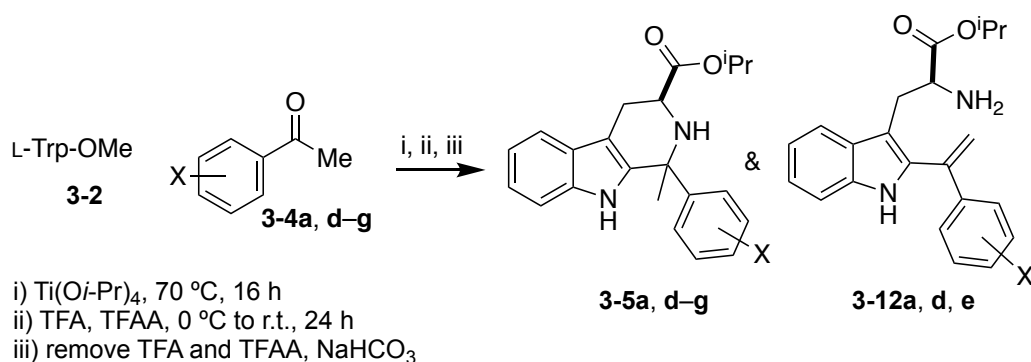
Scheme 3-5. Exploring the effect of TFAA on the reaction, combined yield of *cis*- and *trans*-isomers.

This proposed mechanism is supported by the following observations. First, as previously mentioned, low temperature cyclization of the imine intermediate formed from 2',4'-dichloro- and 2'-chloroacetophenones allowed for the isolation of the tetrahydro- β -carbolines **3-5a, d** (Scheme 3-2). However, when the reaction was carried out at high temperature, the fused azepane-indole isomers **3-6a, d** were obtained, suggesting that **3-5** might be a crucial intermediate on the route to **3-6**. Secondly, the formation of dehydroamino acid **3-7h** can be rationalized by β -deprotonation of dication **III**.

To provide additional evidence for this mechanism, we performed PS reaction of 2'-substituted acetophenones **3-4a, d-g** with **3-2** that featured longer (24 h) acid exposure at 0 to 25 °C (Table 3-3). Under these conditions, not only were the 1-methyl-tetrahydro- β -carbolines **3-5a, d-g** observed in place of the fused azepane-indoles **3-6** (Table 3-3, Entries 1-5), but also, in three cases the 2-(1-arylvinyl)tryptophan esters **3-12** were isolated (Table 3-

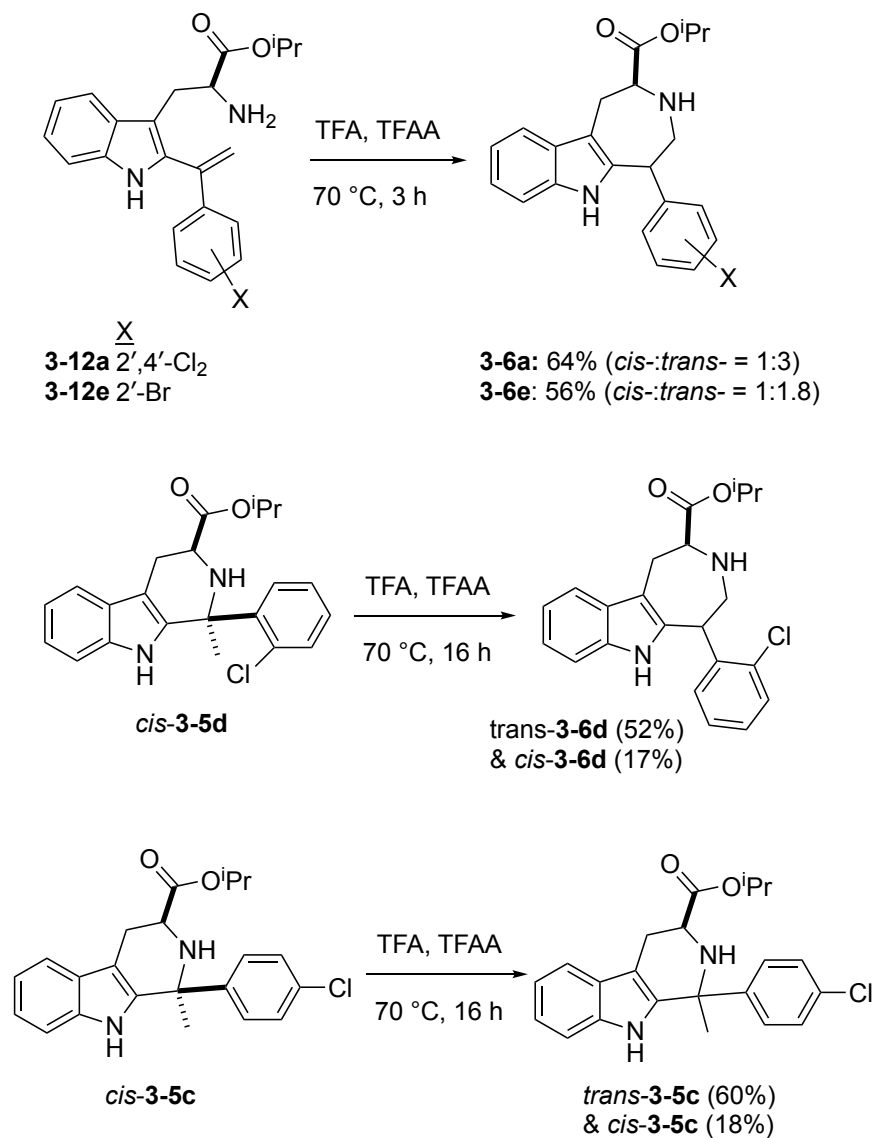
3, Entries 1–3). The formation of these compounds (**3-12a, d, e**) would be expected from deprotonation of cationic intermediate **IV** in Scheme 3-4.

Table 3-3. Low temperature acid treatment allows isolation of 1-methyl-tetrahydro- β -carbolines **3-5a, d–h** and 2-(1-arylvinyl)-tryptophan esters **3-12** from **3-2** and 2'-substituted acetophenones **3-4a, d–g**. Note formation of azepanes **3-6** was not observed with low temperature acid treatment.



Entry	Ketone	X	% Yield of 3-5 (% isolated <i>trans</i> - 3-5 , <i>cis</i> - 3-5)	% Yield of 3-12
1	3-4a	2',4'-Cl ₂	52 (20, 13)	22
2	3-4d	2'-Cl	43 (19, 5)	36
3	3-4e	2'-Br	36 (12, 17)	16
4	3-4f	2',4'-F ₂	56 (34, 2)	0
5	3-4g	2'-F	60 (35, 25)	0

To confirm that **3-12** was on the reaction path to fused azepane-indoles **3-6**, **3-12a** and **3-12e** were both subjected to TFA and TFAA at 70 °C for 3 h. As hoped, the fused azepane-indoles **3-6a** and **3-6e** were isolated in 64 and 56% yield, respectively (Scheme 3-6).



Scheme 3-6. The effect of high-temperature acid treatment of 2-(1-arylvinyl)tryptophan esters **3-12a** and **3-12e**, and 1-methyl-tetrahydro-betacarboline esters *cis-3-5d* and *cis-3-5c*

Similarly, 1-methyl-tetrahydro-betacarbolines *cis-3-5d* and *cis-3-5c* were subjected to TFA and TFAA at 70 °C. The disparate results seen are consistent with the different outcomes of the PS reactions of **3-2** with the corresponding acetophenones **3-4d** and **3-4c**

(Tables 3-1, 3-3). When heated in acid, *cis*-**3-5d** isomerized to the corresponding fused azepane-indoles *trans*- and *cis*-**3-6d**. In contrast, when *cis*-**3-5c**, which has an unsubstituted D-ring, was heated in acid, no ring-expansion to **3-6c** was seen, but only epimerization to a mixture of *trans*- and *cis*-**3-5c**. Thus, these experiments strongly support the proposal that reaction of **3-2** with 2'-substituted acetophenones **3-4a, d-h** initially produces 1-methyl-tetrahydro- β -carbolines **3-5**, which ring-open in acid to **III**. In the case of 1-methyl-tetrahydro- β -carbolines that lack 2'-substitution in the D-ring (e.g. **3-5c**), this intermediate also forms, but it only leads to *cis*/*trans*- isomerization (cf. reaction of *cis*-**3-5c** in Scheme 3-6, and Scheme 3-3). In contrast, when a 2'-substituent is present, **III** can isomerize to 1-arylvinyltryptophans **3-12** at low temperature (Table 3-3), and at high temperature fused azepane-indoles **3-6** are the thermodynamic product (Table 3-1, note 2'-OMe is an exception).

How can the effect of the 2'-substituent be rationalized? The mechanism in Scheme 3-4 suggests that the formation of **3-5** and **3-6** is under thermodynamic control. In the case of 2'-substituted D-rings, steric crowding may make the fused azepane-indoles **3-6** lower in energy than the corresponding 1-methyl-tetrahydro- β -carbolines **3-5**. In the absence of 2'-substitution, we propose the opposite ordering of relative energies. In Chapter 2 I disclosed the X-ray structure of the methyl amide of *trans*-**3-5a** and compared it to the methyl amide of its 1-H analog *trans*-**3-1a**; these structures are reproduced below as Figure 3-3.

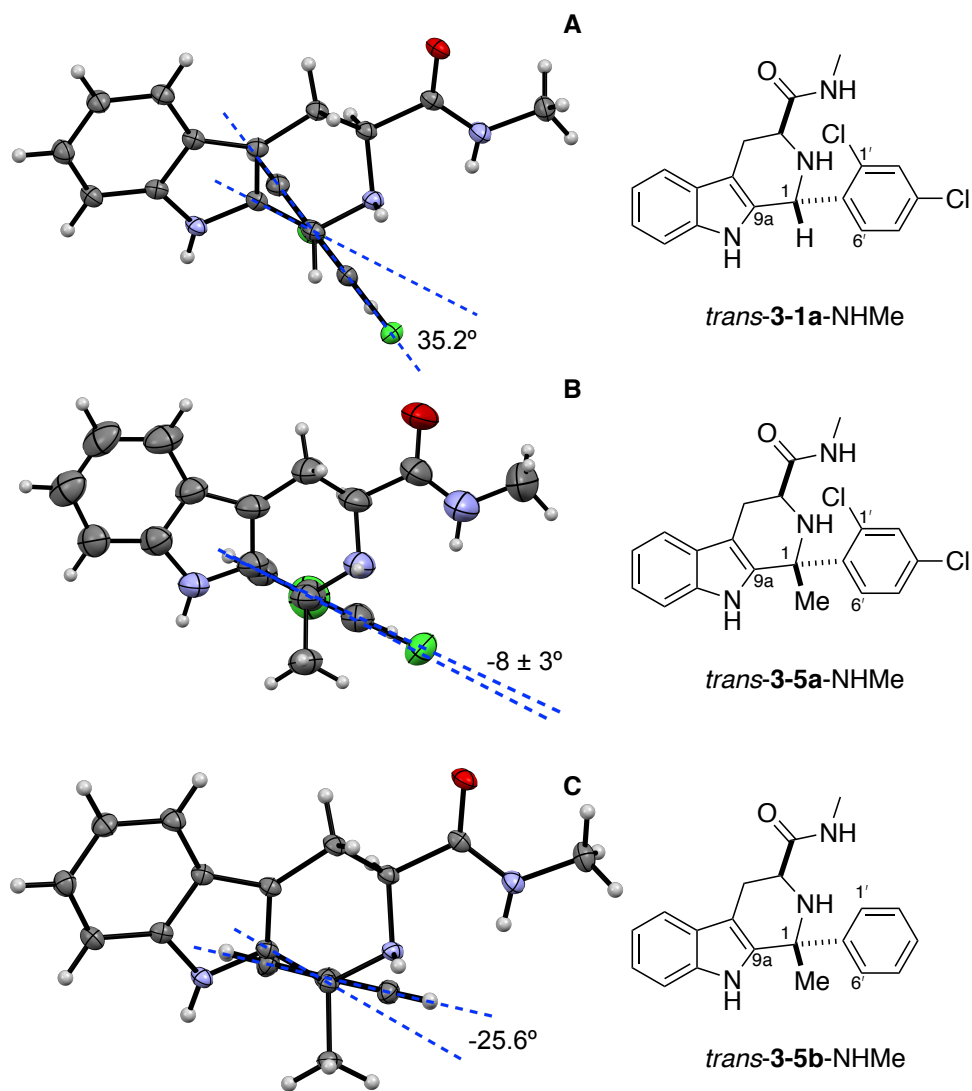


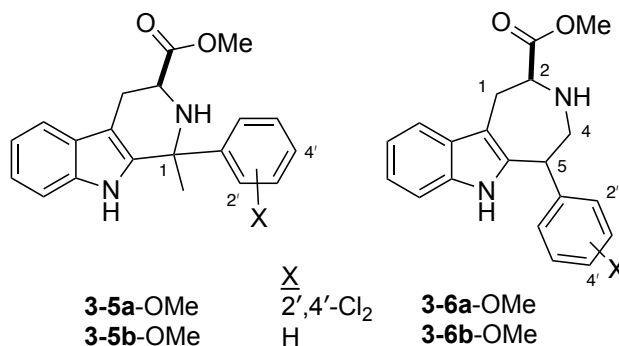
Figure 3-3. Dihedral angle between C9a-C1-C1'-C6' in the crystal structures of A) *trans-3-1a-NHMe*, B) *trans-3-5a-NHMe* (Note there are four molecules in the unit cell; the one depicted has $C9a-C1-C1'-C6' = -8.8^\circ$; the others have -2.8° , -4.8° , -15.4°), and C) *trans-3-5b-NHMe*. Mercury⁹ was used for molecular graphics generation.

As we noted then, the addition of a 1-methyl group caused the 2',4'-dichlorophenyl ring to twist to minimize steric interaction of the 1-methyl group and the 2'-chloro groups.

The roughly equal positioning of C2'-Cl between C1-CH₃ and N2 actually causes a near eclipsing interaction of C6' of the D-ring with C9a of the indole (C9a-C1-C1'-C6' values of -8.0 ± 3 , vs $+35.2$ for *trans*-**3-1a**-NHMe, cf. Figure 3-3B and A). This interaction is avoided in the C1-H analog *trans*-**3-1a**-NHMe, because the C2'-Cl can swing close to the C1-H. I thus prepared the methyl amide of *trans*-**3-5b** and got an X-ray crystal structure of it. As shown in Figure 3-3, in the absence of the 2'-chloro substituent, C2'-H of the D ring swings closer to N2, adopting a significantly less eclipsed conformation of C6' with C9a (Figure 3-3C C9a-C1-C1'-C6' = -25.6°).

To assess the possible energetic effects of 2'-substitution, we performed conformer searches (MMFF94¹⁵) on the methyl ester analogs of *cis*- and *trans*-1-methyl-tetrahydro- β -carbolines **3-5a** and **3-5b**, and on the corresponding methyl ester analogs of *cis*- and *trans*-fused azepane-indoles **3-6a** and **3-6b** (Table 3-4). The choice to calculate the methyl ester analogs **3-5-OMe** and **3-6-OMe** rather than the original isopropyl esters **3-5** and **3-6** was made to reduce conformational complexity; even so, the conformer numbers obtained are quite high. Similarly, although these compounds are formed and interconvert under acidic conditions, we concluded that the effects of steric crowding on conformer energies would also manifest in the corresponding neutral species. In addition, calculations on the neutral species could help confirm ¹H-¹H coupling constant-based deductions of conformational preferences.

Table 3-4. Computational analysis of the isomeric 1-methyl-tetrahydro- β -carboline methyl esters **3-5-OMe** and fused azepane-indole methyl esters **3-6-OMe**.



Compound	Number of conformers examined	ΔG (298 K) of lowest energy conformer (B3LYP/6-31G(d)), kcal/mol
<i>trans</i> - 3-5a-OMe	16	2.8
<i>cis</i> - 3-5a-OMe	16	3.9
<i>trans</i> - 3-6a-OMe	23	0.6
<i>cis</i> - 3-6a-OMe	31	0.0
<i>trans</i> - 3-5b-OMe	8	0.0
<i>cis</i> - 3-5b-OMe	8	0.5
<i>trans</i> - 3-6b-OMe	17	1.0
<i>cis</i> - 3-6b-OMe	16	1.8

As expected, fused azepane-indole methyl esters **3-6-Me** have a larger number of conformers than the 1-methyl-tetrahydro- β -carboline methyl esters **3-5-Me**, due to greater conformational flexibility of the azepane ring (**3-6**) compared to the tetrahydropyridine ring (**3-5**). Note as well that the *o*-chloro substituent of the D-ring of **3-5a-OMe** and **3-6a-OMe** engenders a near doubling of conformations relative to those located for **3-5b-OMe** and **3-6b-OMe**. All conformers were then optimized at B3LYP/6-31G(d),¹⁶⁻¹⁷ and frequencies were calculated to determine that all stationary points were in fact local minima (number of

imaginary frequencies = 0). These frequencies were then used to calculate the relative free energies (ΔG) at 298K of each conformer.

As can be seen in Table 3-4, for compounds bearing 2'-substitution of the D-ring, the lowest energy conformers of the fused azepane-indoles *trans*- and *cis*-**3-6a** are significantly lower in energy than those of the corresponding 1-methyl-tetrahydro- β -carboline *trans*- and *cis*-**3-5a**. In contrast, for compounds lacking 2'-substitution of the D-ring, the lowest energy conformers of 1-methyl-tetrahydro- β -carboline *trans*- and *cis*-**3-5b** are lower in energy than those of the corresponding fused azepane-indoles *trans*- and *cis*-**3-6b**. Thus, density functional calculations are consistent with our proposals that 1) a 2'-substituted D-ring is better accommodated in the more conformationally flexible and spacious fused azepane-indole than in 1-methyl-tetrahydro- β -carboline, and 2) that in the absence of 2'-substitution, the 1-methyl-tetrahydro- β -carboline structure is thermodynamically preferred to the fused azepane-indole isomer.

To identify steric interactions in the tetrahydro- β -carboline **3-5a** that might be alleviated in fused azepane-indole **3-6a**, the DFT-optimized structures of conformers of the corresponding methyl esters **3-5a-OMe** and **3-6a-OMe** were overlapped and aligned. Conformers calculated to contribute less than 1% to the Boltzmann distribution (B3LYP/6-31G(d) free energies at 298 K) were excluded, and Newman-style projections looking down the C1 (C5 for the azepanes) to C1' bond were created and are depicted in Figure 3-4.

As is the case for any sigma bond between sp^3 - and sp^2 -hybridized carbons, complete staggering is impossible. For the 1-methyl-tetrahydro- β -carboline methyl esters *trans*- and *cis*-**3-5b-OMe**, the D-ring adopts two basic orientations, each of which avoid eclipsed interactions with C9a, the C1-Me, or N2 (see Figures 3-4A and 3-4C respectively). In fact,

the most stable conformation of *trans*-**3-5b**-OMe feature a D-ring orientation that is very similar to that seen by X-ray for *trans*-**3-5b**-NHMe (Figure 3-3C). In contrast, when 2',4'-dichloro- substitution is introduced, the steric demand of the 2'-chloro group forces C6'-H of the D-ring to adopt nearly eclipsed interactions with C9a, the C1-Me, or N2 (see Figures 3-4B and 3-4D respectively). Thus, the predicted eclipsed orientation of the D-ring with C9a or N2 in *trans*-**3-5a**-OMe is quite similar to that seen in the the crystal structure of *trans*-**3-5a**-NHMe (cf. Figure 3-4B and Figure 3-3). We propose that these eclipsed interactions, uniquely engendered by the 2'-substituent, could contribute to the driving force for ring expansion to fused azepane-indoles.

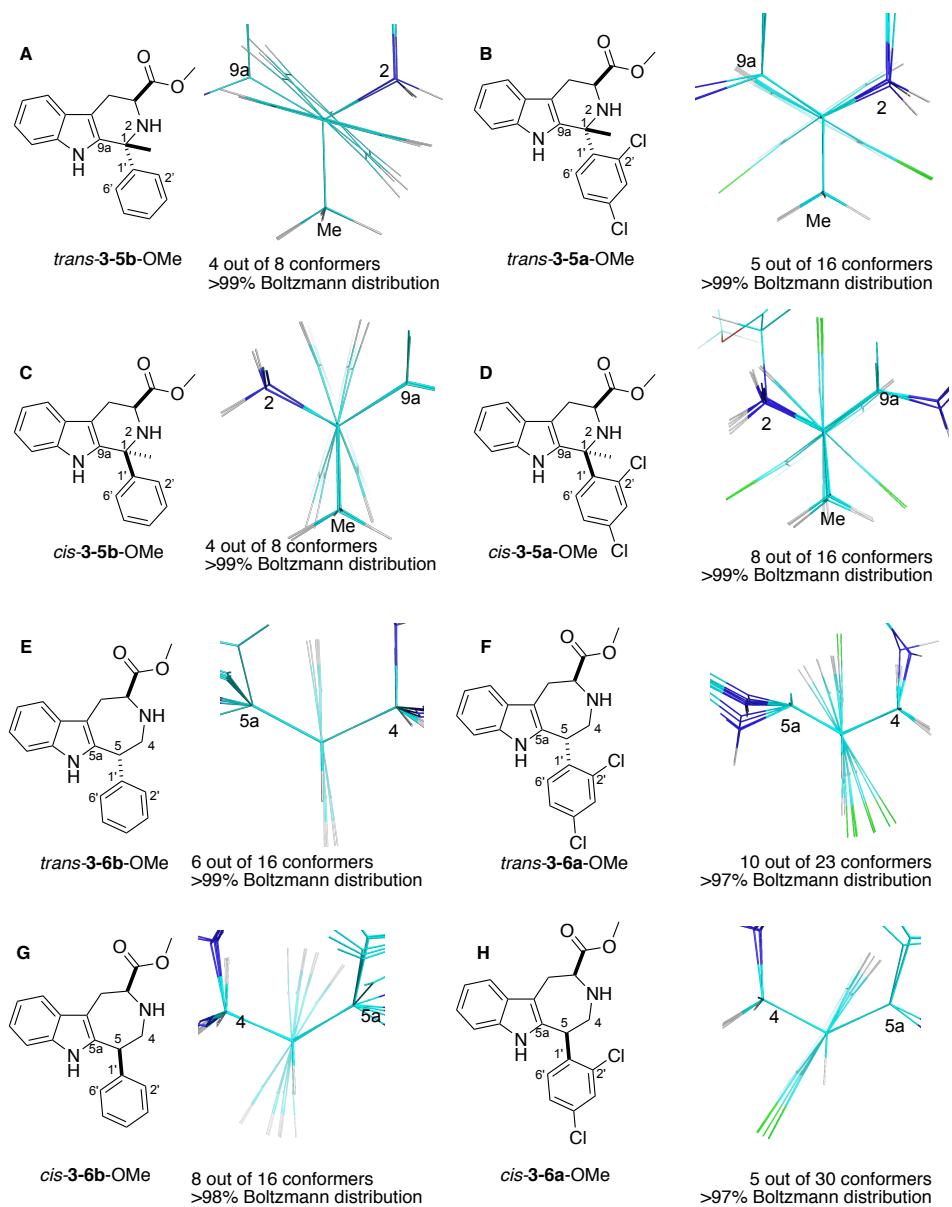
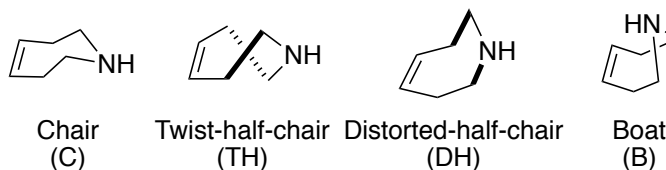


Figure 3-4. Newman projections of the isomeric 1-methyl-tetrahydro- β -carboline methyl esters **3-5-OMe** (viewed down the C1-C1' bond) and fused azepane-indole methyl esters **3-6-OMe** (viewed down the C5- C1' bond). For the diastereomers of **3-5a** and **3-6a** (panels B, D, F, H), the position of the C2'-carbon can be deduced from the light green stick that represents Cl.

Consistent with this idea, examination of D-ring orientations in the corresponding fused azepane-indoles *trans*-**3-6a**-OMe shows a marked preference for near-eclipsing interactions of the D-ring C2'-Cl or C6'-H with the sterically-accommodating azepane C5-H (Figure 3-3F). In *cis*-**3-6a**-OMe the D-ring C2'-Cl is oriented approximately 30° from the C5-H (Figure 3-4H). Lastly, inspection of Figure 3-4 demonstrates that in the fused azepane-indoles, the presence or absence of a C2'-Cl does not significantly affect the orientation of the D-ring (*cf.* Fig 3-4E and F for *trans*- and G and H for *cis*-), consistent with our proposal of reduced steric-strain.

Lastly, to better understand the distinct values of $^3J_{12}$ and $^3J_{45}$ seen by ^1H NMR for the *cis*- and *trans*-diastereomers of **3-6** (Table 3-2) we determined single point energies of the conformers of *cis*- and *trans*-**3-6a**-OMe at B3LYP/6-311+G(2d,p) with PCM¹⁸ (chloroform) solvation. We then classified the conformations of the dehydroazepane ring in each calculated structure, using the terms that Groenewald et al.¹⁹ developed for conformations of cycloheptene and caprolactam. Boltzmann weightings based on B3LYP/6-311+G(2d,p) PCM(CHCl3)//B3LYP/6-31G(d) free energies at 298 K were determined, and a marked preference (>87%) was seen for the chair (C) conformer in both diastereomers. A minor population (10%) of twist half-chair (TH) conformers was seen for *trans*-**3-6**-OMe, followed by distorted-half-chair (DH) conformers (3%); for the *cis*-**3-6**-OMe, the DH conformers are the second most populated (6%), followed by TH and boat (B) conformers (<1%) (Table 3-5). Based on our calculations for *trans*-**3-6a**-OMe, it is surprising that the fused azepane-indole methyl amide *trans*-**3-8a** crystallized in the DH conformation (Figure 3-1). This outcome could be a consequence of improved crystal packing and/or electrostatic interaction between the amide N-H and N3 (non-bonded contact 2.26 Å, Figure 3-1).

Table 3-5. Calculated conformation of dehydroazepane ring found in **3-6a-OMe**.



Compound	Azepane conformation	Conformer numbers ^a	Sum of Boltzmann weighting
<i>trans</i> - 3-6a-OMe	C	4, 5, 6, 7, 8, 10, 11, 15, 23	87%
	TH	1, 2, 3, 13, 14, 16, 19, 20, 21	10%
	DH	9, 12, 17, 18, 22	3%
<i>cis</i> - 3-6a-OMe	C	3, 4, 5, 6, 8, 12, 15, 19, 23, 24, 25, 26, 27, 28	93%
	TH	11, 14, 16, 17, 29, 30, 31	<1%
	DH	1, 2, 7, 9, 10, 13, 18, 21, 22	6%
	B	20	<1%

^aCartesian coordinates, structural drawings and energies for each conformer are given in the Experimental Section. Boltzmann weightings based on B3LYP/6-311+G(d) PCM (CHCl₃)/B3LYP/6-31G(d) free energies (298 K).

Select major chair (C) and minor non-chair (TH or DH) conformers of *trans*- and *cis*-**3-6a-OMe** are shown in Figure 3-5. Regardless of major or minor conformation, the *cis*-isomer exhibits gauche-orientation of H5 with both H4 α & H4 β , consistent with our observation that H5 appears as a triplet with ~ 4 Hz coupling constant (Table 3-2). In contrast in the *trans*-isomer H5 is anti to H4 α and gauche to H4 β for both major and minor conformers, consistent with our observation that H5 in the *trans*-isomers appears as a doublet of doublet with ~10 and 4 Hz coupling constants (Table 3-2)

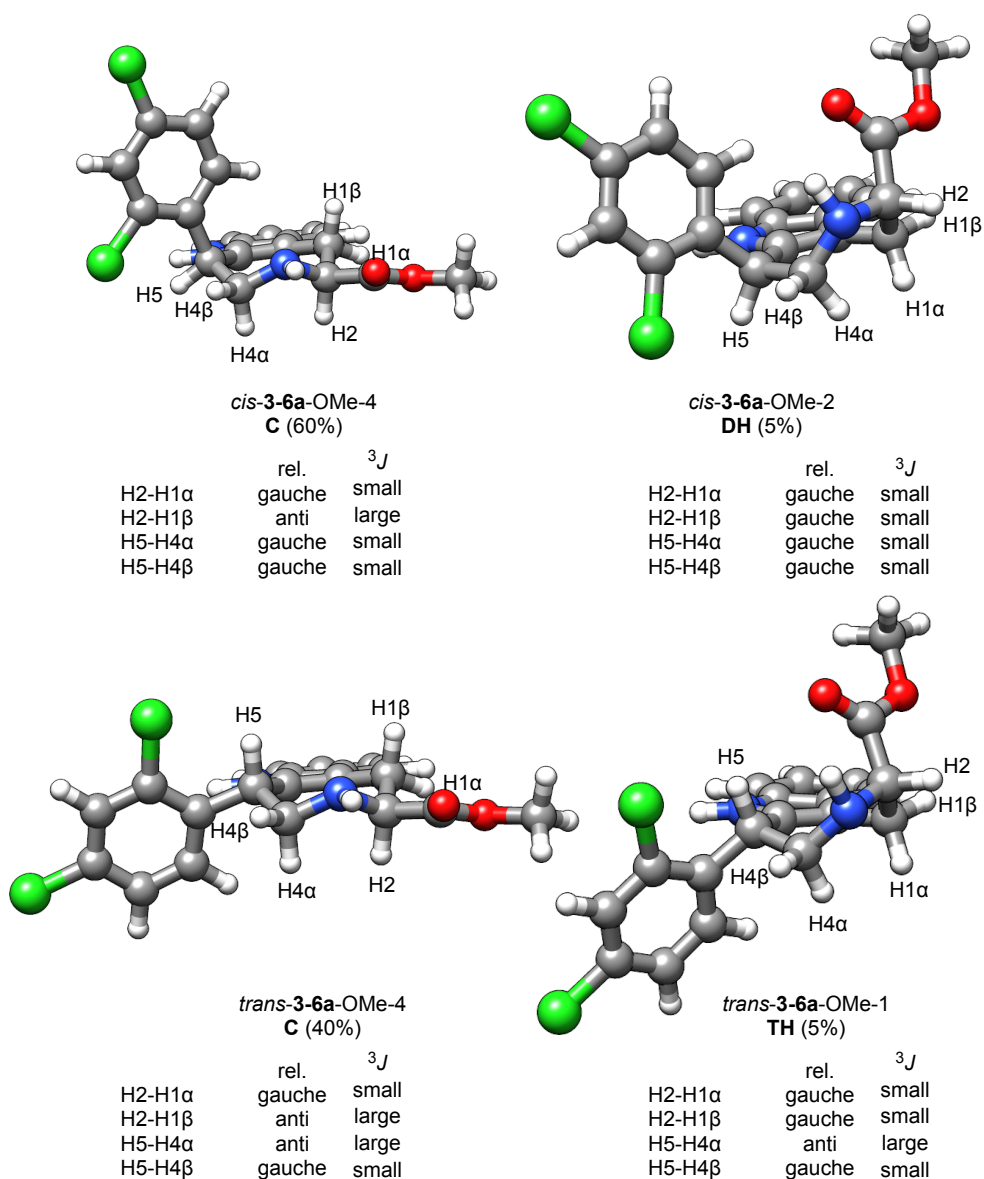


Figure 3-5. Lowest energy conformers of *trans*- and *cis*-3-6a-OMe. **C**: chair; **TH**: twist-half-chair; **DH**: distorted-half-chair. Boltzmann weightings are given in parenthesis (298K, B3LYP/6-311+G(2d,p) SCRF (PCM, CHCl₃)/B3LYP/6-31G(d)).

The divergence in $^3J_{12}$ values seen for *trans*- and *cis*-3-6 is less dramatic than that seen for $^3J_{45}$ values. For *trans*-3-6, one medium (8-9 Hz) and one small (3-4 Hz) value of $^3J_{12}$ is seen; for *cis*-3-6, one large (~11 Hz) and one small (3-4 Hz) value is seen (Table 3-2). A

possible explanation for these observations can again be deduced by inspection of the conformers. For both *trans*- and *cis*-diastereomers, in the major chair conformer, H2 is gauche to H1 α and anti to H1 β , leading to the expectation of widely differentiated $^3J_{1\alpha 2}$ and $^3J_{1\beta 2}$ values. However as we have noted in Table 3-5, for *trans*-**3-6a**-OMe, the sum of Boltzmann weighting of the minor isomers TH and DH is ~13%, whereas it is less than 7% in *cis*-**3-6a**-OMe. As seen in in Figure 3-5, in the minor conformer for *trans*-**3-6**-OMe (TH) H2 is gauche to both H1 α and H1 β ; the same is true for the minor conformer for *cis*-**3-6**-OMe (DH), where H2 is also gauche to both H1 α and H1 β . Consequently, the higher population of the minor conformers in the *trans*-diastereomer will serve to reduce the value of $^3J_{1\beta 2}$ (to 8-9 Hz), compared to its value in the *cis*-diastereomer (~11 Hz, Table 3-2).

In conclusion, we discovered that when carried out at high temperature, Pictet-Spengler reaction of tryptophan methyl ester with 2'-substituted acetophenones in most cases gives fused azepane-indole products rather than the expected 1-methyl-tetrahydro- β -carbolines. This reaction was documented for acetophenones bearing 2'-Cl, Br, F, and Me groups, giving products **3-6a,d-g,i**, as a mixture of *trans*- and *cis*-diastereomers. Interestingly reaction with 2'-OMe substituted acetophenone **3-4h** did not yield the fused azepane-indole, but rather the traditional 1-methyl-tetrahydro- β -carboline **3-5h**. High temperature Pictet-Spengler reactions of acetophenones **3-4b, c** lacking 2'-substitution also gave the traditional 1-methyl-tetrahydro- β -carbolines **3-5b, c**. A mechanism for ring-expansion from an initially formed 1-methyl-tetrahydro- β -carboline **3-5** to fused azepane indoles **3-6** via a dicationic intermediate **III** was proposed (Scheme 3-4). This mechanism accounts for a number of experimental observations: 1) isolation of 2'-substituted 1-methyl-tetrahydro- β -carbolines **3-5** and 1-arylvinyl tryptophan isopropyl esters **3-12** when acid treatment is carried out at low

temperature (Table 3-3); 2) such 2'-substituted 1-methyl-tetrahydro- β -carbolines can be converted to the corresponding fused azepane-indoles at high temperature (Scheme 3-6); 3) when no 2'-substituent is present, high temperature acid treatment causes *cis-trans*-isomerization of a diastereomerically pure 1-methyl-tetrahydro- β -carboline, without ring expansion, (Scheme 3-6); 4) isolation of isopropyl 2-amino-3-(2-(1-(*o*-tolyl)ethyl)-1*H*-indol-3-yl)acrylate **3-7i** as a by-product of high temperature Pictet-Spengler reaction of tryptophan methyl ester with 2'-methyl acetophenone **3-4i**. The driving force for this ring-expansion is proposed to be relief of steric strain in 1-methyl-tetrahydro- β -carbolines that bear 2'-substituents on the 1-aryl ring, and calculations suggest that steric demand of the 2'-substituent forces it away from the C1-CH₃, causing near eclipsing interactions of C6'-H with C9a, C1-Me, or N2 (Figure 3-4B, D). This steric strain is relieved in the corresponding fused azepane-indoles, since they feature hydrogen- rather than methyl-substitution at C5, where the aryl group is attached.

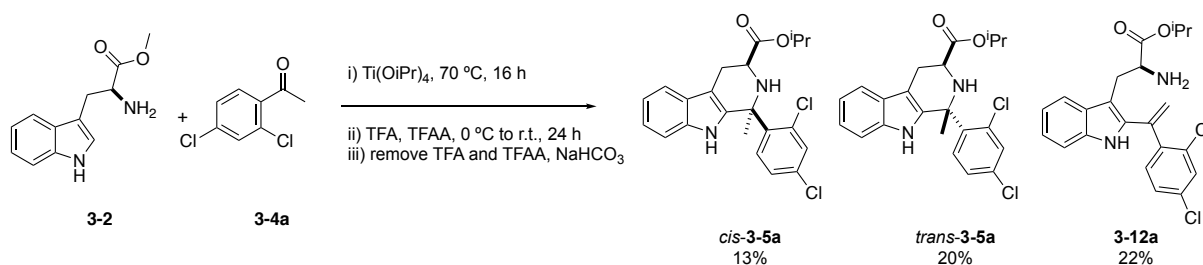
Experimental Section

A. Synthesis and Analytical Characterization of Compounds Synthesized

A.1. Low temperature protocol ketone Pictet-Spengler reactions

The ketone Pictet-Spengler reaction procedure was modified from Horiguchi, 2003¹⁴.

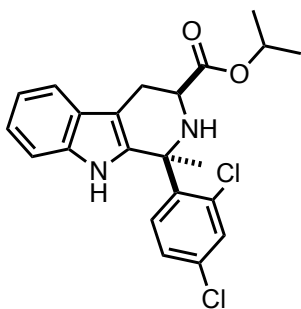
Synthesis of isopropyl (1*R*,3*S*)-1-(2,4-dichlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5a), isopropyl (1*R*,3*S*)-1-(2,4-dichlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5a), and isopropyl 2-amino-3-(2-(1-(2,4-dichlorophenyl)vinyl)-1*H*-indol-3-yl)propanoate (3-12a)



To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(O*i*-Pr)₄ (1.5 mL) was added via syringe, followed by 1-(2,4-dichlorophenyl)ethan-1-one **3-4a** (244.9 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at r.t. overnight until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The

aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave *cis*-**3-5a** (63.9 mg, 13%), mixture of *cis*-**3-5a** and *trans*-**3-5a** (93.6 mg, 19%), *trans*-**3-5a** (98.2 mg, 20%), and **3-12a** (108.0 mg, 22%).

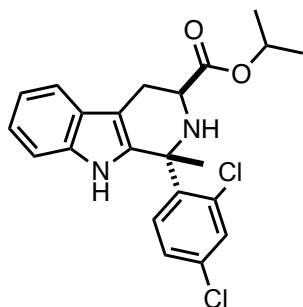
isopropyl (1*S*,3*S*)-1-(2,4-dichlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5a**)**



^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, $J = 8.6$ Hz, 1H), 7.55 – 7.48 (m, 1H), 7.42 (s, 1H), 7.36 (d, $J = 2.2$ Hz, 1H), 7.29 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.26 – 7.19 (m, 1H), 7.19 – 7.07 (m, 2H), 5.09 (hept, $J = 6.2$ Hz, 1H), 4.09 (dd, $J = 10.8, 4.5$ Hz, 1H), 3.21 (dd, $J = 15.2, 4.5$ Hz, 1H), 2.87 (dd, $J = 15.2, 10.8$ Hz, 1H), 1.98 (s, 3H), 1.32 (d, $J = 6.2$ Hz, 3H), 1.30 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.9, 139.5, 137.1, 135.9, 135.0, 134.8, 131.9, 130.6, 127.2, 126.8, 122.1, 119.8, 118.4, 111.0, 108.1, 68.9, 56.8, 53.4, 27.8, 25.7, 22.0, 21.9.

isopropyl (1*R*,3*S*)-1-(2,4-dichlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5a)

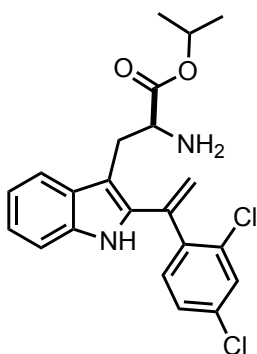


^1H NMR (400 MHz, CDCl_3) δ 8.00 (s, 1H), 7.58 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.42 (d, $J = 2.2$ Hz, 1H), 7.39 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.24 (ddd, $J = 7.9, 7.1, 1.3$ Hz, 1H), 7.17 (ddd, $J = 8.1, 7.1, 1.0$ Hz, 1H), 6.97 (dd, $J = 8.5, 2.2$ Hz, 1H), 6.59 (d, $J = 8.5$ Hz, 1H), 5.08 (hept, $J = 6.3$ Hz, 1H), 3.36 (dd, $J = 11.4, 4.6$ Hz, 1H), 3.08 (dd, $J = 15.4, 4.6$ Hz, 1H), 2.90 (dd, $J = 15.4, 11.4$ Hz, 1H), 2.07 (s, 3H), 1.29 (d, $J = 6.4$ Hz, 3H), 1.27 (d, $J = 6.4$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.3, 140.5, 136.9, 136.2, 133.9, 132.5, 132.2, 131.8, 127.1, 126.6, 122.4, 119.9, 118.8, 111.2, 109.4, 69.0, 59.3, 52.9, 25.7, 25.4, 21.9, 21.8.

HRMS (ESI⁺) calculated for $\text{C}_{22}\text{H}_{23}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 417.1131, found 417.1139.

isopropyl (*S*)-2-amino-3-(2-(1-(2,4-dichlorophenyl)vinyl)-1*H*-indol-3-yl)propanoate (3-12a)

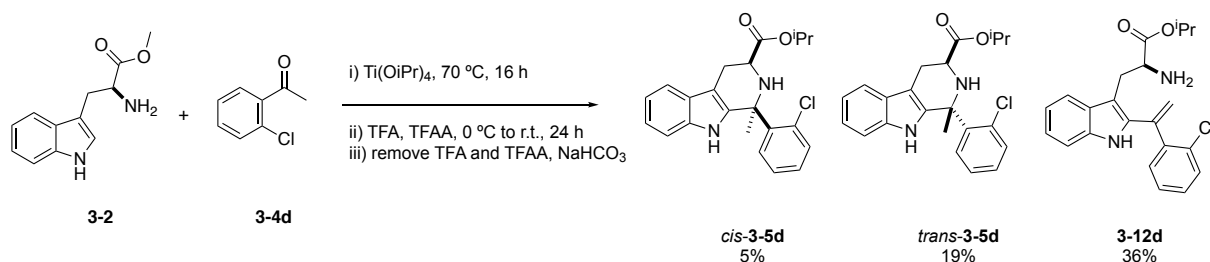


^1H NMR (400 MHz, CDCl_3) δ 8.14 (br, 1H), 7.58 (d, $J = 7.9$ Hz, 1H), 7.41 (d, $J = 2.0$ Hz, 1H), 7.32 (d, $J = 8.2$ Hz, 1H), 7.29 – 7.27 (m, 1H), 7.26 – 7.25 (m, 1H), 7.17 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H), 7.09 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H), 5.86 (d, $J = 0.8$ Hz, 1H), 5.45 (d, $J = 0.8$ Hz, 1H), 4.93 (hept, $J = 6.3$ Hz, 1H), 3.59 (dd, $J = 9.6, 5.0$ Hz, 1H), 2.99 (dd, $J = 14.3, 5.0$ Hz, 1H), 2.71 (dd, $J = 14.3, 9.6$ Hz, 1H), 1.18 (d, $J = 6.3$ Hz, 3H), 1.05 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.6, 138.7, 137.8, 135.5, 134.8, 134.2, 133.9, 132.3, 130.0, 129.4, 127.5, 123.1, 120.0, 119.7, 119.4, 111.0, 110.5, 68.5, 55.5, 30.8, 21.9, 21.6.

HRMS (ESI $^+$) calculated for $\text{C}_{22}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 417.1131, found 417.1139.

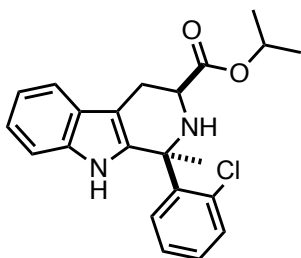
Synthesis of isopropyl (1*R*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5d), isopropyl (1*R*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5d), and isopropyl 2-amino-3-(2-(1-(2-chlorophenyl)vinyl)-1*H*-indol-3-yl)propanoate (3-12d)



To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N_2 three times, then placed under a N_2 atmosphere. Then $\text{Ti}(\text{O}i\text{Pr})_4$ (1.5 mL) was added via syringe, followed by 1-(2-chlorophenyl)ethan-1-one **3-4d** (200.3 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at r.t. overnight until TLC indicated full conversion, at which point the

reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave *cis*-**3-5d** (22.5 mg, 5%), mixture of *cis*-**3-5d** and *trans*-**3-5d** (85.7 mg, 19%), *trans*-**3-5d** (85.5 mg, 19%), and **3-12d** (162.6 mg, 36%).

isopropyl (1*S*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5d**)**

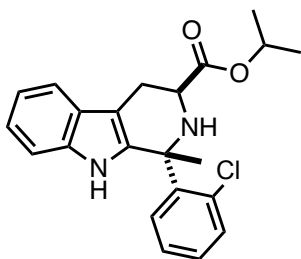


$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.72 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.56 – 7.49 (m, 1H), 7.42 (s, 1H), 7.35 (dd, $J = 7.4, 1.8$ Hz, 1H), 7.31 (dd, $J = 7.5, 1.9$ Hz, 1H), 7.28 (dd, $J = 7.5, 1.9$ Hz, 1H), 7.25 – 7.18 (m, 1H), 7.18 – 7.06 (m, 2H), 5.10 (hept, $J = 6.3$ Hz, 1H), 4.11 (dd, $J = 10.9, 4.5$ Hz, 1H), 3.22 (dd, $J = 15.1, 4.5$ Hz, 1H), 2.90 (dd, $J = 15.1, 10.9$ Hz, 1H), 1.33 (d, $J = 6.3$ Hz, 3H), 1.31 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.1, 140.8, 137.8, 135.8, 134.1, 132.3, 129.6, 129.6, 127.1, 126.9, 121.9, 119.7, 118.3, 111.0, 108.0, 68.7, 57.0, 53.5, 27.8, 25.8, 22.0, 21.9.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 383.1521, found 383.1525.

isopropyl (1*R*,3*S*)-1-(2-chlorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5d)

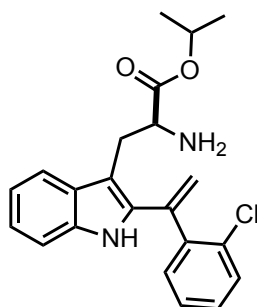


^1H NMR (400 MHz, CDCl_3) δ 7.98 (s, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.44 – 7.37 (m, 2H), 7.24 (m, 1H), 7.20 – 7.14 (m, 2H), 7.00 (ddd, $J = 7.6, 7.4, 1.4$ Hz, 1H), 6.66 (dd, $J = 7.9, 1.7$ Hz, 1H), 5.08 (hept, $J = 6.3$ Hz, 1H), 3.40 (dd, $J = 11.4, 4.6$ Hz, 1H), 3.09 (dd, $J = 15.4, 4.6$ Hz, 1H), 2.92 (dd, $J = 15.4, 11.4$ Hz, 1H), 2.09 (s, 3H), 1.29 (d, $J = 6.2$ Hz, 3H), 1.27 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.4, 141.8, 137.4, 136.2, 132.3, 131.6, 131.6, 128.9, 127.3, 126.5, 122.3, 119.9, 118.9, 111.2, 109.5, 68.9, 59.7, 53.0, 25.9, 25.5, 22.0, 21.9.

HRMS calculated for $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_2$ $[\text{M}+\text{H}^+]$ 383.1521, found 383.1523.

isopropyl (*S*)-2-amino-3-(2-(1-(2-chlorophenyl)viny)-1*H*-indol-3-yl)propanoate (3-12d)

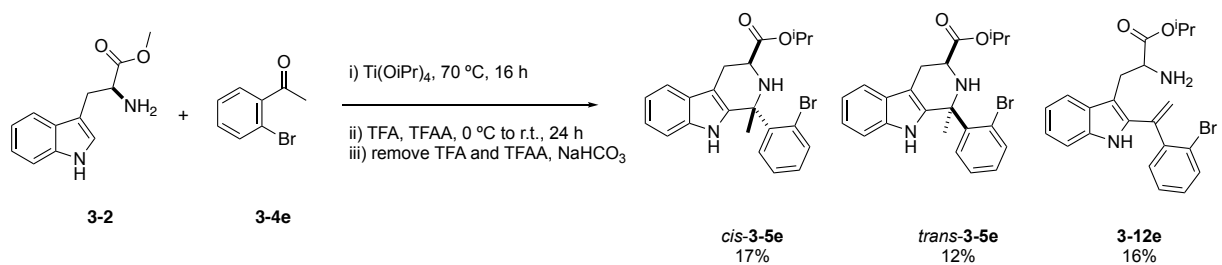


^1H NMR (400 MHz, CDCl_3) δ 7.92 (s, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.44 – 7.39 (m, 2H), 7.36 – 7.31 (m, 2H), 7.28 (dt, $J = 8.1, 1.0$ Hz, 1H), 7.18 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.10 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H), 5.89 (d, $J = 0.9$ Hz, 1H), 5.49 (d, $J = 0.9$ Hz, 1H), 4.93 (hept, $J = 6.3$ Hz, 1H), 3.64 (dd, $J = 9.5, 5.0$ Hz, 1H), 3.06 (dd, $J = 14.2, 5.0$ Hz, 1H), 2.73 (dd, $J = 14.2, 9.5$ Hz, 1H), 1.19 (d, $J = 6.3$ Hz, 3H), 1.04 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 174.9, 139.7, 139.4, 135.5, 134.3, 133.4, 131.6, 130.2, 129.7, 129.5, 127.2, 122.9, 119.9, 119.4, 119.2, 110.9, 110.5, 68.3, 55.5, 31.1, 21.9, 21.7.

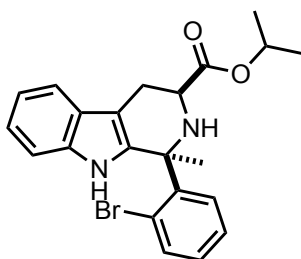
HRMS (ESI⁺) calculated for $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 383.1521, found 383.1568.

Synthesis of isopropyl (1*R*,3*S*)-1-(2-bromophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5e), isopropyl (1*R*,3*S*)-1-(2-bromophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5e), and isopropyl (*S*)-2-amino-3-(2-(1-(2-bromophenyl)viny)-1*H*-indol-3-yl)propanoate (3-12e)



To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(Oi-Pr)₄ (1.5 mL) was added via syringe, followed by 1-(2-bromophenyl)ethan-1-one **3-12e** (257.9 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at r.t. overnight until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave *cis*-**3-5e** (85.8 mg, 17%), mixture of *cis*-**3-5e** and *trans*-**3-5e** (35.3 mg, 7%), *trans*-**3-5e** (60.4 mg, 12%), and **3-12e** (80.7 mg, 16%).

isopropyl (1*S*,3*S*)-1-(2-bromophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5e**)**

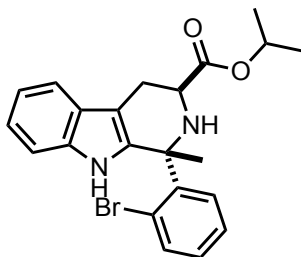


^1H NMR (500 MHz, CDCl_3) δ 7.76 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.58 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.53 – 7.49 (m, 1H), 7.38 (ddd, $J = 7.7, 7.7, 1.4$ Hz, 1H), 7.33 (s, 1H), 7.24 – 7.21 (m, 1H), 7.19 (ddd, $J = 7.7, 7.7, 1.6$ Hz, 1H), 7.15 – 7.08 (m, 2H), 5.11 (hept, $J = 6.3$ Hz, 1H), 4.15 (dd, $J = 11.1, 4.6$ Hz, 1H), 3.21 (dd, $J = 15.1, 4.6$ Hz, 1H), 2.91 (dd, $J = 15.1, 11.1$ Hz, 1H), 2.00 (s, 3H), 1.33 (d, $J = 6.3$ Hz, 3H), 1.31 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.2, 141.9, 137.7, 136.1, 135.8, 129.9, 129.8, 127.7, 126.9, 123.3, 121.9, 119.7, 118.4, 111.0, 108.6, 68.7, 57.6, 53.6, 28.2, 25.8, 22.0, 22.0.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{BrN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 427.1016, found 427.1026.

isopropyl (1*R*,3*S*)-1-(2-bromophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5e)

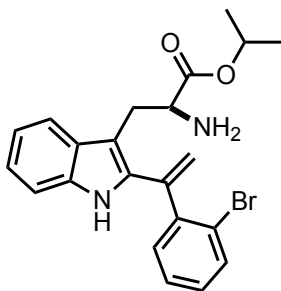


^1H NMR (400 MHz, CDCl_3) δ 8.09 (br, 1H), 7.65 – 7.61 (m, 1H), 7.60 – 7.56 (m, 1H), 7.39 (dt, $J = 8.0, 1.0$ Hz, 1H), 7.23 (ddd, $J = 8.1, 7.1, 1.3$ Hz, 1H), 7.18 – 7.13 (m, 1H), 7.10 – 7.00 (m, 2H), 6.69 – 6.64 (m, 1H), 5.08 (hept, $J = 6.3$ Hz, 1H), 3.38 (dd, $J = 11.4, 4.7$ Hz, 1H), 3.08 (dd, $J = 15.4, 4.7$ Hz, 1H), 2.91 (dd, $J = 15.4, 11.4$ Hz, 1H), 2.11 (s, 3H), 1.29 (d, $J = 6.4$ Hz, 3H), 1.27 (d, $J = 6.4$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 172.2, 142.9, 137.3, 136.0, 135.9, 131.8, 129.0, 127.2, 127.0, 122.2, 120.1, 119.8, 118.8, 111.0, 109.4, 68.8, 60.1, 52.8, 25.7, 25.3, 21.9, 21.8.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{BrN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 427.1016, found 427.1026.

isopropyl (*S*)-2-amino-3-(2-(1-(2-bromophenyl)vinyl)-1*H*-indol-3-yl)propanoate (3-12e)

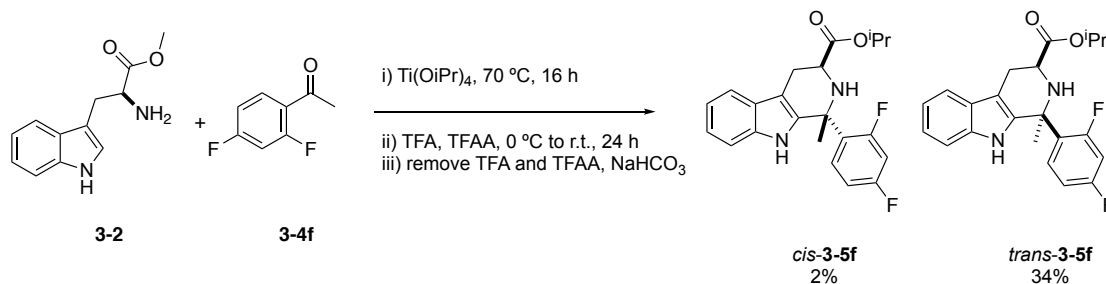


^1H NMR (400 MHz, CDCl_3) δ 7.98 (br, 1H), 7.60 (ddd, $J = 7.9, 2.7, 1.1$ Hz, 2H), 7.43 (dd, $J = 7.6, 1.9$ Hz, 1H), 7.37 (td, $J = 7.4, 1.2$ Hz, 1H), 7.32 – 7.22 (m, 2H), 7.18 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.10 (ddd, $J = 8.1, 7.0, 1.1$ Hz, 1H), 5.88 (d, $J = 0.8$ Hz, 1H), 5.45 (d, $J = 0.8$ Hz, 1H), 4.93 (hept, $J = 6.2$ Hz, 1H), 3.64 (dd, $J = 9.5, 5.0$ Hz, 1H), 3.05 (dd, $J = 14.2, 5.1$ Hz, 1H), 2.71 (dd, $J = 14.2, 9.5$ Hz, 1H), 1.20 (d, $J = 6.2$ Hz, 3H), 1.05 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 174.8, 141.3, 141.3, 135.5, 134.1, 133.4, 131.6, 129.8, 129.5, 127.8, 123.3, 122.9, 119.9, 119.4, 118.8, 110.9, 110.6, 68.3, 55.5, 31.2, 21.9, 21.7.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{BrN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 427.1016, found 427.1016.

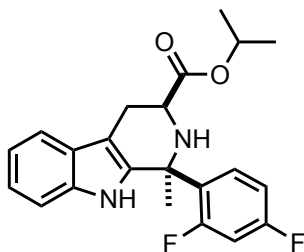
Synthesis of isopropyl (1*R*,3*S*)-1-(2,4-difluorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5f) and isopropyl (1*S*,3*S*)-1-(2,4-difluorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5f)



To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N_2 three times, then placed under a N_2 atmosphere. Then $\text{Ti}(\text{O}i\text{Pr})_4$ (1.5 mL) was added via syringe, followed by 1-(2,4-difluorophenyl)ethan-1-one **3-4f** (202.3 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at r.t. overnight until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave

cis-**3-5f** (8.9 mg, 2%), mixture of *cis*-**3-5f** and *trans*-**3-5f** (90.2 mg, 20%), and *trans*-**3-5f** (154.0 mg, 34%).

isopropyl (1*S*,3*S*)-1-(2,4-difluorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5f**)**



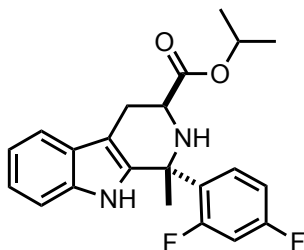
^1H NMR (500 MHz, CDCl_3) δ 7.72 (br, 1H), 7.61 (td, $J = 9.3, 6.5$ Hz, 1H), 7.53 (d, $J = 7.7$ Hz, 1H), 7.27 (d, $J = 8.0$ Hz, 1H), 7.16 (ddd, $J = 8.1, 7.1, 1.4$ Hz, 1H), 7.12 (ddd, $J = 8.2, 7.1, 1.2$ Hz, 1H), 6.87 – 6.79 (m, 2H), 5.11 (hept, $J = 6.3$ Hz, 1H), 4.03 (dd, $J = 10.8, 4.2$ Hz, 1H), 3.18 (dd, $J = 15.0, 4.2$ Hz, 1H), 2.87 (dd, $J = 15.0, 10.8$ Hz, 1H), 1.97 (d, $J = 2.0$ Hz, 3H), 1.33 (d, $J = 6.3$ Hz, 3H), 1.31 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 172.7, 162.5 (dd, $^1J_{\text{CF}} = 249.9$ Hz, $^3J_{\text{CF}} = 12.5$ Hz), 161.2 (dd, $^1J_{\text{CF}} = 250.2$ Hz, $^3J_{\text{CF}} = 11.4$ Hz), 137.5, 135.8, 130.2 (dd, $^3J_{\text{CF}} = 9.4, = 5.6$ Hz), 128.5 (m), 126.7, 122.1, 119.7, 118.4, 111.2 (dd, $J = ^2J_{\text{CF}} = 20.5, ^4J_{\text{CF}} = 3.5$ Hz), 110.9, 107.7, 105.0 (dd, $^2J_{\text{CF}} = 27.9, 25.2$ Hz), 68.8, 55.8, 52.9, 27.0 (d, $^4J_{\text{CF}} = 4.8$ Hz), 25.7, 21.9, 21.8.

^{19}F NMR (376 MHz, CDCl_3) δ -106.22 (app q, $J = 9.7$ Hz), -111.06 (br).

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 385.1722, found 385.1715.

isopropyl (1*R*,3*S*)-1-(2,4-difluorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5f)



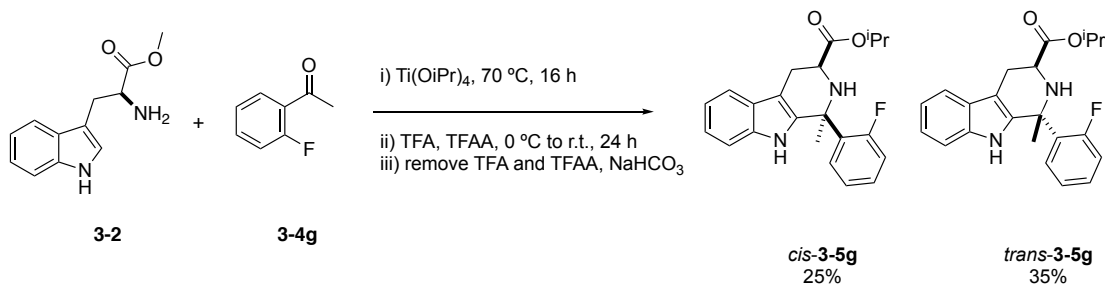
^1H NMR (400 MHz, CDCl_3) δ 8.00 (br, 1H), 7.57 (ddt, $J = 7.8, 1.4, 0.8$ Hz, 1H), 7.39 (dt, $J = 8.1, 1.0$ Hz, 1H), 7.23 (ddd, $J = 8.2, 7.1, 1.3$ Hz, 1H), 7.16 (ddd, $J = 7.8, 7.1, 1.1$ Hz, 1H), 6.89 – 6.81 (m, 1H), 6.72 (td, $J = 9.0, 6.6$ Hz, 1H), 6.65 (dddd, $J = 8.7, 7.7, 2.6, 0.7$ Hz, 1H), 5.10 (hept, $J = 6.3$ Hz, 1H), 3.50 (dd, $J = 11.3, 4.5$ Hz, 1H), 3.10 (dd, $J = 15.3, 4.5$ Hz, 1H), 2.87 (dd, $J = 15.3, 11.3$ Hz, 1H), 1.96 (d, $J = 1.7$ Hz, 3H), 1.30 (d, $J = 6.3$ Hz, 3H), 1.28 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.6, 162.4 (dd, $^1J_{\text{CF}} = 249.3, ^3J_{\text{CF}} = 12.6$ Hz), 160.7 (dd, $^1J_{\text{CF}} = 249.2, ^3J_{\text{CF}} = 11.7$ Hz), 136.5, 136.1, 131.2 (dd, $^3J_{\text{CF}} = 9.2, 5.8$ Hz), 128.7 (dd, $^2J_{\text{CF}} = 11.2, ^4J_{\text{CF}} = 4.0$ Hz), 127.1, 122.5, 120.0, 118.8, 111.2, 110.6 (dd, $^2J_{\text{CF}} = 20.3, ^4J_{\text{CF}} = 3.5$ Hz), 109.4, 105.3 (dd, $^2J_{\text{CF}} = 27.7, 25.2$ Hz), 68.9, 56.9 (d, $^5J_{\text{CF}} = 2.0$ Hz), 52.9, 27.5 (d, $^3J_{\text{CF}} = 5.5$ Hz), 25.7, 22.0, 21.9.

^{19}F NMR (376 MHz, CDCl_3) δ -107.47 (app q, $J = 10.2, 9.8$ Hz), -111.46 (app p, $J = 7.9$ Hz).

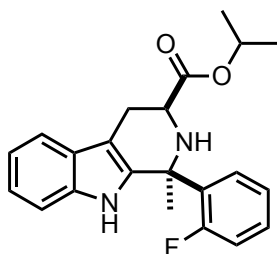
HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 385.1722, found 385.1717.

Synthesis of isopropyl isopropyl (1*S*,3*S*)-1-(2-fluorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5g) and isopropyl (1*R*,3*S*)-1-(2-fluorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5g)



To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(Oi-Pr)₄ (1.5 mL) was added via syringe, followed by 1-(2-fluorophenyl)ethan-1-one **3-4g** (179.0 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at r.t. overnight until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave *cis*-**3-5g** (108.0 mg, 25%), and *trans*-**3-5g** (151.0 mg, 35%).

isopropyl isopropyl (1*S*,3*S*)-1-(2-fluorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5g)



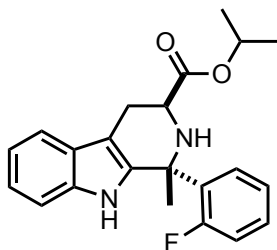
^1H NMR (400 MHz, CDCl_3) δ 7.77 (br, 1H), 7.63 (td, $J = 8.1, 1.8$ Hz, 1H), 7.53 (ddt, $J = 7.5, 1.6, 0.7$ Hz, 1H), 7.32 – 7.25 (m, 2H), 7.18 – 7.03 (m, 4H), 5.11 (hept, $J = 6.3$ Hz, 1H), 4.04 (ddd, $J = 10.8, 4.2, 0.9$ Hz, 1H), 3.18 (dd, $J = 15.0, 4.2$ Hz, 1H), 2.88 (dd, $J = 15.0, 10.8$ Hz, 1H), 1.98 (d, $J = 1.9$ Hz, 3H), 1.33 (d, $J = 6.3$ Hz, 3H), 1.31 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 172.9, 161.3 (d, $^1J_{\text{CF}} = 247.4$ Hz), 137.9, 135.9, 132.3 (d, $J = 10.6$ Hz), 129.7 (d, $J = 9.0$ Hz), 129.1 (d, $J = 4.0$ Hz), 126.9, 124.5 (d, $J = 3.2$ Hz), 122.0, 119.6, 118.4, 116.9 (d, $^2J_{\text{CF}} = 23.7$ Hz), 111.0, 107.6, 68.8, 56.1, 53.1, 27.0 (d, $^4J_{\text{CF}} = 4.5$ Hz), 25.8, 22.0, 21.9.

^{19}F NMR (376 MHz, CDCl_3) δ -110.1 to -110.6 ppm (br m).

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{FN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 367.1816, found 367.1808.

isopropyl (1*R*,3*S*)-1-(2-fluorophenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5g)



^1H NMR (400 MHz, CDCl_3) δ 8.02 (br, 1H), 7.60 – 7.53 (m, 1H), 7.39 (dt, $J = 8.2, 0.9$ Hz, 1H), 7.25 – 7.19 (m, 2H), 7.15 (ddd, $J = 8.0, 7.1, 1.1$ Hz, 1H), 7.09 (ddd, $J = 12.7, 8.2, 1.3$ Hz, 1H), 6.93 (td, $J = 7.6, 1.3$ Hz, 1H), 6.76 (td, $J = 8.2, 1.8$ Hz, 1H), 5.10 (hept, $J = 6.3$ Hz, 1H), 3.54 (dd, $J = 11.3, 4.5$ Hz, 1H), 3.10 (dd, $J = 15.3, 4.5$ Hz, 1H), 2.88 (dd, $J = 15.3, 11.3$ Hz, 1H), 1.98 (d, $J = 1.6$ Hz, 3H), 1.30 (d, $J = 8.5$ Hz, 3H), 1.28 (d, $J = 8.5$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.5, 160.6 (d, $^1J_{\text{CF}} = 245.9$ Hz), 136.6, 136.0, 130.2 (d, $J = 4.3$ Hz), 129.3 (d, $J = 9.0$ Hz), 127.0, 123.7 (d, $J = 3.4$ Hz), 122.2, 119.7, 118.6, 116.8, 116.6, 111.0, 109.1, 68.7, 57.1 (d, $^5J_{\text{CF}} = 1.6$ Hz), 52.9, 27.4 (d, $^4J_{\text{CF}} = 5.7$ Hz), 25.6, 21.9, 21.7.

^{19}F NMR (376 MHz, CDCl_3) δ -111.76 to -111.90 (br m).

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{FN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 367.1816, found 367.1803.

A.2. High temperature protocol ketone Pictet-Spengler reactions

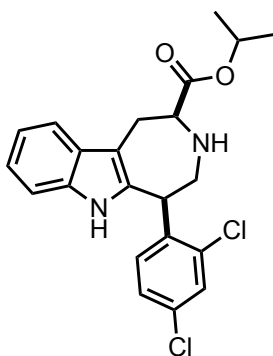
Synthesis of isopropyl (2*S*,5*R*)-5-(2,4-dichlorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*cis*-3-6a) and isopropyl (2*S*,5*S*)-5-(2,4-dichlorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*trans*-3-6a)



To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(Oi-Pr)₄ (1.5 mL) was added via syringe, followed by 1-(2,4-dichlorophenyl)ethan-1-one **3-4a** (244.9 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at 70 °C for 1 h until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave

cis-**3-6a** (83.6 mg, 17%), mixture of *cis*-**3-6a** and *trans*-**3-6a** (181.8 mg, 37%), and *trans*-**3-6a** (112.9 mg, 23%).

isopropyl (2*S*,5*R*)-5-(2,4-dichlorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*cis*-**3-6a**)

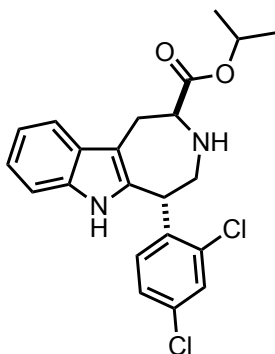


^1H NMR (400 MHz, CDCl_3) δ 7.96 (br, 1H), 7.67 – 7.61 (m, 1H), 7.43 (d, $J = 2.1$ Hz, 1H), 7.21 – 7.15 (m, 3H), 7.05 (dd, $J = 8.4, 2.2$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 5.10 (hept, $J = 6.3$ Hz, 1H), 4.69 (t, $J = 3.6$ Hz, 1H), 3.74 (dd, $J = 11.1, 3.0$ Hz, 1H), 3.66 – 3.54 (m, 2H), 3.35 (dd, $J = 14.0, 3.5$ Hz, 1H), 3.13 (dd, $J = 15.6, 11.1$ Hz, 1H), 2.35 (br, 1H), 1.33 (d, $J = 6.3$ Hz, 3H), 1.32 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.1, 137.2, 135.4, 135.3, 133.3, 133.2, 132.0, 129.4, 128.7, 127.2, 122.1, 119.5, 118.2, 111.7, 110.5, 68.9, 62.5, 51.1, 44.6, 29.4, 21.9, 21.8.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 417.1131, found 417.1128.

isopropyl (2S,5S)-5-(2,4-dichlorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole-2-carboxylate (*trans*-3-6a)

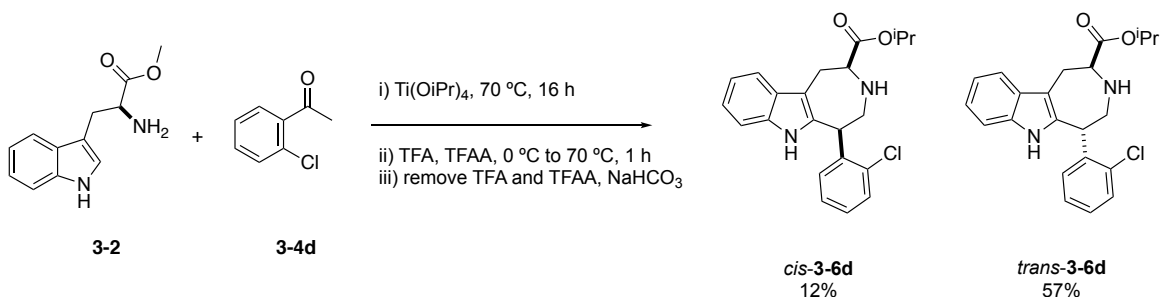


^1H NMR (600 MHz, CDCl_3) δ 7.58 – 7.54 (m, 1H), 7.48 (d, $J = 2.1$ Hz, 1H), 7.45 (br, 1H), 7.20 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.18 – 7.15 (m, 1H), 7.13 – 7.10 (m, 2H), 7.02 (d, $J = 8.4$ Hz, 1H), 4.96 (hept, $J = 6.3$ Hz, 1H), 4.85 (dd, $J = 9.7, 3.8$ Hz, 1H), 3.90 (dd, $J = 8.1, 3.4$ Hz, 1H), 3.51 (dd, $J = 15.7, 3.3$ Hz, 1H), 3.44 (dd, $J = 14.1, 3.9$ Hz, 1H), 3.28 – 3.23 (m, 2H), 1.23 (d, $J = 6.3$ Hz, 3H), 1.05 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.7, 137.2, 135.4, 135.3, 134.6, 133.8, 131.1, 129.9, 128.8, 127.8, 121.9, 119.6, 118.1, 111.2, 110.6, 68.9, 61.2, 50.9, 45.5, 27.1, 21.9, 21.7.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 417.1131, found 417.1127.

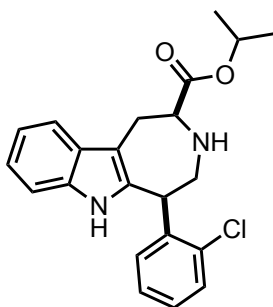
Synthesis of isopropyl (2*S*,5*R*)-5-(2-chlorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*cis*-3-6d) and isopropyl (2*S*,5*S*)-5-(2-chlorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*trans*-3-6d)



To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(Oi-Pr)₄ (1.5 mL) was added via syringe, followed by 1-(2-chlorophenyl)ethan-1-one **3-4d** (200.0 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at 70 °C for 1 h until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave

cis-**3-6d** (54.0 mg, 12%), mixture of *cis*-**3-6d** and *trans*-**3-6d** (90 mg, 20%), and *trans*-**3-6d** (256.6 mg, 57%).

isopropyl (2*S*,5*R*)-5-(2-chlorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*cis*-**3-6d**)

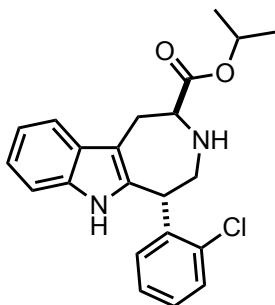


^1H NMR (500 MHz, CDCl_3) δ 7.77 (br, 1H), 7.64 – 7.59 (m, 1H), 7.41 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.22 – 7.13 (m, 4H), 7.11 (td, $J = 7.5, 1.4$ Hz, 1H), 7.02 (dd, $J = 7.7, 1.8$ Hz, 1H), 5.09 (hept, $J = 6.3$ Hz, 1H), 4.76 (t, $J = 3.9$ Hz, 1H), 3.76 (dd, $J = 11.1, 3.1$ Hz, 1H), 3.64 (dd, $J = 14.1, 4.1$ Hz, 1H), 3.57 (dd, $J = 15.6, 3.1$ Hz, 1H), 3.39 (dd, $J = 14.1, 3.7$ Hz, 1H), 3.14 (dd, $J = 15.6, 11.1$ Hz, 1H), 1.30 (d, $J = 6.3$ Hz, 3H) 1.29 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.4, 138.5, 136.1, 135.3, 133.0, 131.1, 129.8, 128.8, 128.3, 127.1, 122.0, 119.5, 118.2, 111.6, 110.6, 68.9, 62.4, 51.0, 45.1, 29.5, 22.0, 21.9.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 383.1521, found 383.1515.

isopropyl (2*S*,5*S*)-5-(2-chlorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*trans*-3-6d)

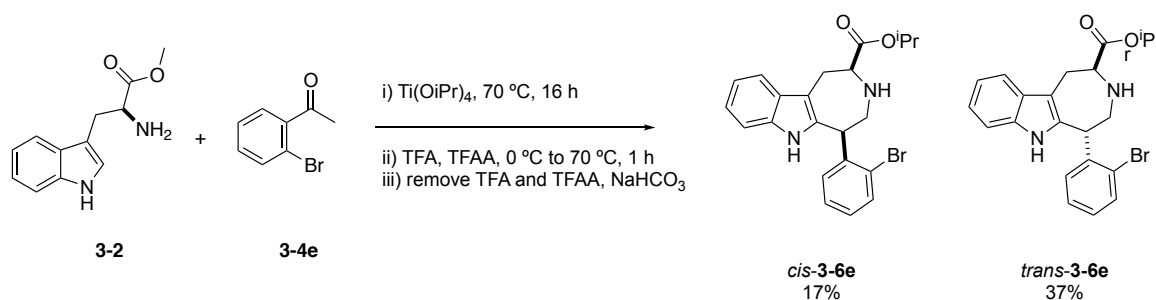


^1H NMR (500 MHz, CDCl_3) δ 7.59 – 7.54 (m, 1H), 7.49 (br, 1H), 7.47 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.28 – 7.20 (m, 2H), 7.17 – 7.08 (m, 4H), 4.99 (hept, $J = 6.3$ Hz, 1H), 4.91 (dd, $J = 9.9, 3.8$ Hz, 1H), 3.90 (dd, $J = 8.3, 3.3$ Hz, 1H), 3.54 (ddd, $J = 15.7, 3.4, 1.0$ Hz, 1H), 3.45 (dd, $J = 14.0, 3.9$ Hz, 1H), 3.29 (dd, $J = 13.3, 9.2$ Hz, 1H), 3.24 (ddd, $J = 15.7, 7.8, 1.1$ Hz, 1H), 2.50 (br, 1H), 1.23 (d, $J = 6.3$ Hz, 3H) 1.07, (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.7, 138.5, 136.1, 135.1, 134.0, 130.20, 130.19, 128.8, 128.7, 127.4, 121.7, 119.4, 118.0, 110.8, 110.5, 68.9, 61.3, 51.2, 45.9, 27.4, 21.9, 21.7.

HRMS (ESI $^+$) calculated for $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 383.1521, found 383.1516.

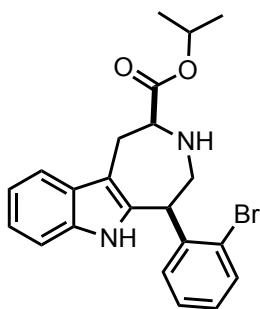
Synthesis of isopropyl (2*S*,5*R*)-5-(2-bromophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*cis*-3-6e) and isopropyl (2*S*,5*S*)-5-(2-bromophenyl)-1,2,3,4,5,6-exahydroazepino[4,5-*b*]indole-2-carboxylate (*trans*-3-6e)



To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(O*i*-Pr)₄ (1.5 mL) was added via syringe, followed by 1-(2-bromophenyl)ethan-1-one **4e** (258 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at 70 °C for 1 h until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave

cis-**3-6e** (85.8 mg, 17%), mixture of *cis*-**3-6e** and *trans*-**3-6e** (145.8 mg, 29%), and *trans*-**3-6e** (186.1 mg, 37%).

isopropyl (2*S*,5*R*)-5-(2-bromophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*cis*-3-6e**)**

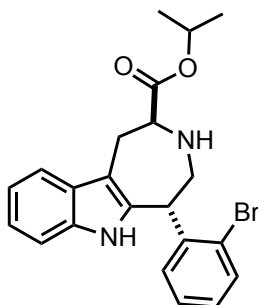


^1H NMR (500 MHz, CDCl_3) δ 7.86 (br, 1H), 7.65 – 7.58 (m, 2H), 7.20 – 7.12 (m, 4H), 7.09 (td, $J = 7.6, 1.9$ Hz, 1H), 7.02 (dd, $J = 7.6, 1.9$ Hz, 1H), 5.09 (hept, $J = 6.3$ Hz, 1H), 4.74 (t, $J = 3.9$ Hz, 1H), 3.78 (dd, $J = 11.1, 3.2$ Hz, 1H), 3.63 (dd, $J = 14.1, 4.3$ Hz, 1H), 3.59 (dd, $J = 15.7, 3.2$ Hz, 1H), 3.38 (dd, $J = 14.1, 3.7$ Hz, 1H), 3.17 (dd, $J = 15.6, 11.0$ Hz, 1H), 2.39 (s, 1H), 1.31 (d, $J = 6.3$ Hz, 3H), 1.30 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.4, 140.1, 136.0, 135.3, 133.2, 131.2, 128.8, 128.6, 127.7, 123.7, 122.0, 119.4, 118.2, 111.4, 110.6, 68.9, 62.3, 50.9, 47.5, 29.3, 22.0, 21.9.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{BrN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 427.1016, found 427.1010.

isopropyl (2*S*,5*S*)-5-(2-bromophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*trans*-3-6e)

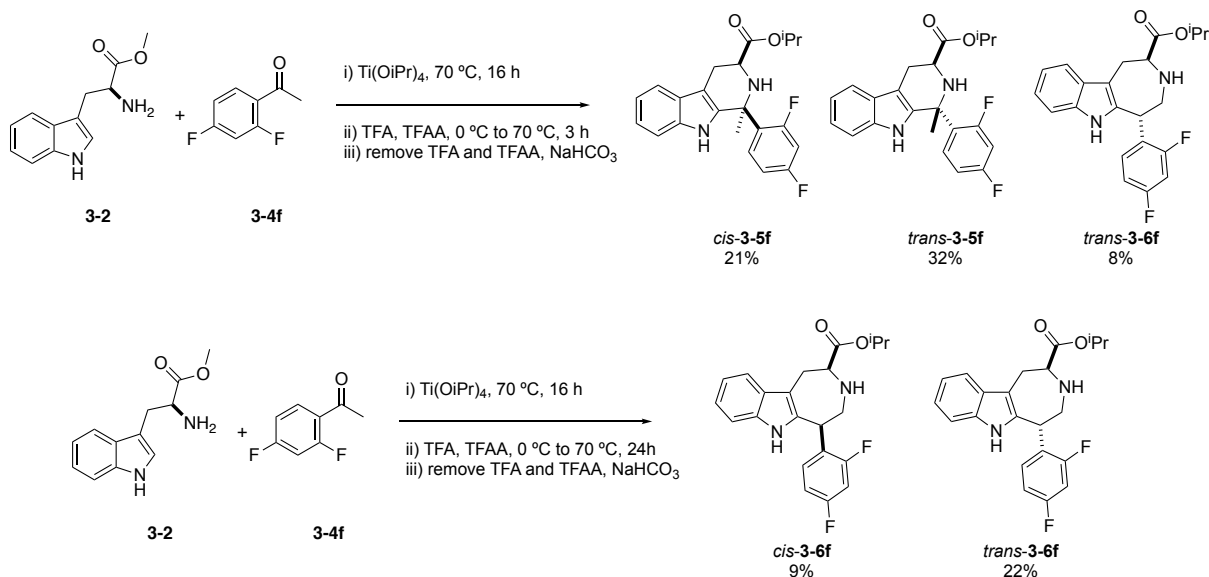


^1H NMR (400 MHz, CDCl_3) δ 7.63 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.56 – 7.50 (m, 1H), 7.39 (br, 1H), 7.29 – 7.20 (m, 1H), 7.17 – 7.03 (m, 3-5h), 4.94 (hept, $J = 6.4$ Hz, 1H), 4.87 (dd, $J = 10.0, 3.9$ Hz, 1H), 3.89 (dd, $J = 8.2, 3.3$ Hz, 1H), 3.51 (ddd, $J = 15.7, 3.3, 1.1$ Hz, 1H), 3.43 (dd, $J = 14.0, 3.9$ Hz, 1H), 1.20 (d, $J = 6.3$ Hz, 3H), 1.02 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.7, 140.3, 136.0, 135.3, 133.4, 130.3, 128.9, 128.7, 128.0, 124.5, 121.6, 119.3, 117.9, 110.6, 110.5, 68.8, 61.0, 50.8, 48.4, 26.8, 21.8, 21.6.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{BrN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 427.1016, found 427.1011.

Synthesis of isopropyl (2*S*,5*R*)-5-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*cis*-3-6f) and isopropyl (2*S*,5*S*)-5-(2,4-difluorophenyl)-1,2,3,4,5,6-exahydroazepino[4,5-*b*]indole-2-carboxylate (*trans*-3-6f)



The outcome of this reaction was influenced by the heating time.

Heated for 3 h:

To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N_2 three times, then placed under a N_2 atmosphere. Then $\text{Ti}(\text{O}i\text{Pr})_4$ (1.5 mL) was added via syringe, followed by 1-(2,4-difluorophenyl)ethan-1-one **3-4f** (202.3 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at 70 °C for 3 h until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was

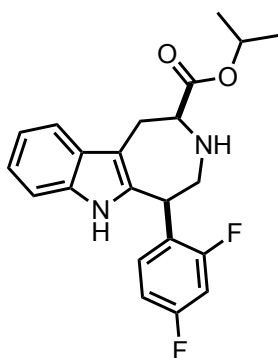
further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave *cis*-**3-5f** (95.2 mg, 21%), mixture of *cis*-**3-5f** and *trans*-**3-5f** (95.0 mg, 21%), *trans*-**3-5f** (145.3 mg, 32%), and *trans*-**3-6f** (36.0 mg, 8%).

Heated for 24 h:

To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(Oi-Pr)₄ (1.5 mL) was added via syringe, followed by 1-(2,4-difluorophenyl)ethan-1-one **3-4f** (202.3 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at 70 °C for 24 h until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave

cis-**3-6f** (41.2 mg, 9%), mixture of *cis*-**3-6f** and *trans*-**3-6f** (149.7 mg, 33%), and *trans*-**3-6f** (99.6 mg, 22%).

isopropyl (2*S*,5*R*)-5-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*cis*-3-6f**)**



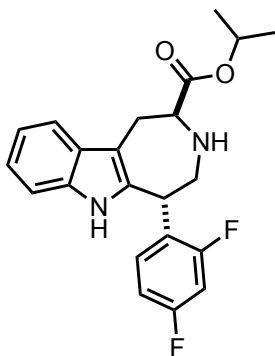
^1H NMR (400 MHz, CDCl_3) δ 7.73 (br, 1H), 7.62 – 7.58 (m, 1H), 7.26 – 7.22 (m, 1H), 7.18 – 7.13 (m, 2H), 6.96 (td, $J = 8.6, 6.5$ Hz, 1H), 6.83 (ddd, $J = 10.4, 8.7, 2.6$ Hz, 1H), 6.75 – 6.68 (m, 1H), 5.08 (hept, $J = 6.3$ Hz, 1H), 4.57 (t, $J = 3.7$ Hz, 1H), 3.70 (dd, $J = 11.1, 2.9$ Hz, 1H), 3.57 (dd, $J = 13.7, 3.8$ Hz, 1H), 3.55 (dd, $J = 15.6, 2.9$ Hz, 1H), 3.37 (dd, $J = 13.9, 3.4$ Hz, 1H), 3.05 (dd, $J = 15.3, 11.1$ Hz, 1H), 1.30 (d, $J = 6.3$ Hz, 3H), 1.29 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 162.1 (dd, $^1J_{\text{CF}} = 205.9, ^3J_{\text{CF}} = 12.1$ Hz), 159.6 (dd, $^1J_{\text{CF}} = 205.5, ^3J_{\text{CF}} = 12.2$ Hz), 135.3, 135.1, 131.6 (dd, $^3J_{\text{CF}} = 9.4, 5.7$ Hz), 128.7, 124.0 (dd, $^2J_{\text{CF}} = 14.5, ^4J_{\text{CF}} = 3.8$ Hz), 122.0, 119.5, 118.1, 111.7, 111.1 (dd, $^2J_{\text{CF}} = 20.7, ^4J_{\text{CF}} = 3.7$ Hz), 110.5, 103.8 (dd, $^2J_{\text{CF}} = 25.9$ Hz), 68.8, 62.3, 51.9, 40.8, 29.6, 21.9, 21.8.

^{19}F NMR (376 MHz, CDCl_3) δ -112.1 to -112.3 (br m), -114.8 to -114.9 (br m).

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 385.1722, found 385.1710.

isopropyl (2S,5S)-5-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole-2-carboxylate (trans-3-6f)



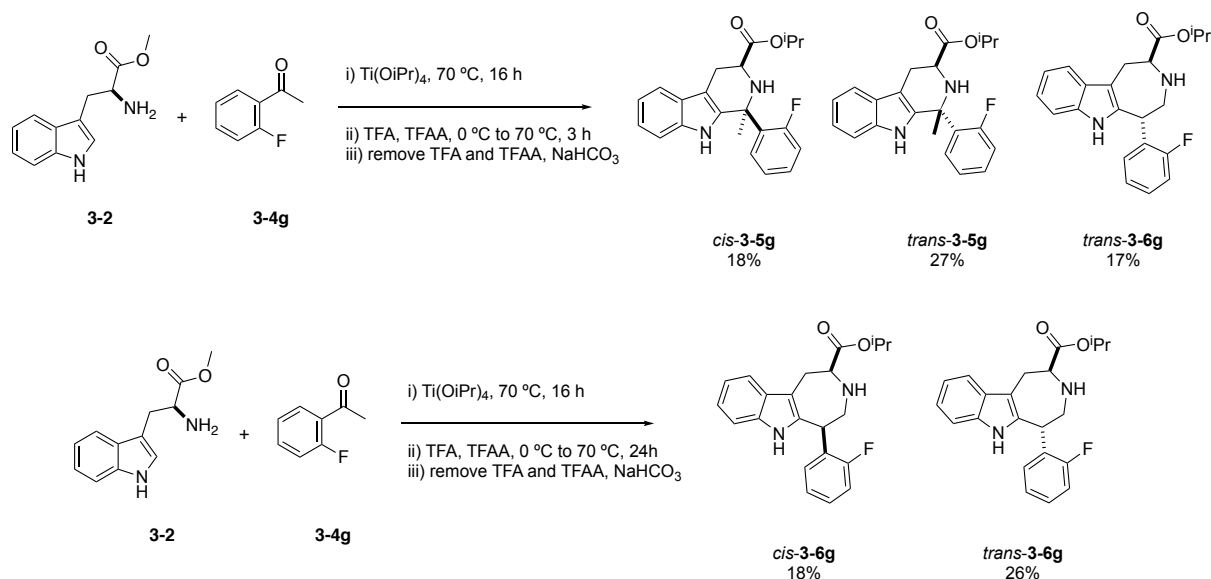
^1H NMR (400 MHz, CDCl_3) δ 7.58 – 7.51 (m, 1H), 7.36 (s, 1H), 7.21 – 7.15 (m, 1H), 7.15 – 7.08 (m, 3H), 6.95 – 6.84 (m, 2H), 5.00 (hept, $J = 6.2$ Hz, 1H), 4.65 (dd, $J = 9.8, 3.7$ Hz, 1H), 3.85 (dd, $J = 8.6, 3.2$ Hz, 1H), 3.52 (ddd, $J = 15.7, 3.1, 0.7$ Hz, 1H), 3.43 (dd, $J = 13.9, 3.8$ Hz, 1H), 3.30 (ddd, $J = 13.9, 9.7, 0.7$ Hz, 1H), 3.18 (ddd, $J = 15.7, 8.7, 1.2$ Hz, 1H), 1.24 (d, $J = 6.2$ Hz, 3H), 1.09 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.5, 162.5 (dd, $^1J_{\text{CF}} = 201.5, ^3J_{\text{CF}} = 11.7$ Hz), 160.5 (dd, $^1J_{\text{CF}} = 201.7, ^3J_{\text{CF}} = 11.9$ Hz), 135.6, 135.0, 131.1 (dd, $^3J_{\text{CF}} = 9.4, 5.8$ Hz), 128.9, 123.6 (dd, $^2J_{\text{CF}} = 14.8, ^4J_{\text{CF}} = 3.8$ Hz), 121.8, 119.5, 118.0, 112.0 (dd, $^2J_{\text{CF}} = 21.0, ^4J_{\text{CF}} = 3.7$ Hz), 110.8, 110.6, 104.5 (dd, $^2J_{\text{CF}} = 25.8$ Hz), 69.0, 61.3, 51.6, 27.6, 21.9, 21.7.

^{19}F NMR (376 MHz, CDCl_3) δ -110.9 (p, $J = 7.6$ Hz), -113.1 (br).

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{22}\text{F}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 385.1722, found 385.1710.

Synthesis of isopropyl (2*S*,5*R*)-5-(2-fluorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*cis*-3-6g) and isopropyl (2*S*,5*S*)-5-(2-fluorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*trans*-3-6g)



The outcome of this reaction was influenced by the heating time.

Heated for 3 h:

To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(Oi-Pr)₄ (1.5 mL) was added via syringe, followed by 1-(2-fluorophenyl)ethan-1-one **3-4g** (179 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at 70 °C for 3 h until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was

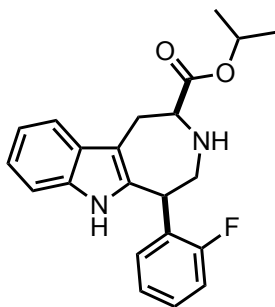
further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave *cis*-**3-5g** (77.8 mg, 18%), mixture of *cis*-**3-5g** and *trans*-**3-5g** (116.7 mg, 27%), *trans*-**3-5g** (116.3 mg, 27%), and *trans*-**3-6g** (73.0 mg, 17%).

Heated for 24 h:

To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N₂ three times, then placed under a N₂ atmosphere. Then Ti(Oi-Pr)₄ (1.5 mL) was added via syringe, followed by 1-(2-fluorophenyl)ethan-1-one **3-4g** (179 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at 70 °C for 24 h until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave

cis-**3-6g** (77.5 mg, 18%), mixture of *cis*-**3-6g** and *trans*-**3-6g** (129.5 mg, 30%), and *trans*-**3-6g** (112.2 mg, 26%).

isopropyl (2*S*,5*R*)-5-(2-fluorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*cis*-**3-6g**)



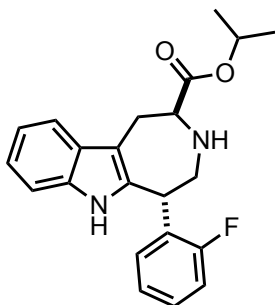
^1H NMR (500 MHz, CDCl_3) δ 7.72 (br, 1H), 7.64 – 7.57 (m, 1H), 7.25 – 7.18 (m, 2H), 7.18 – 7.12 (m, 2H), 7.10 – 7.04 (m, 1H), 7.01 – 6.95 (m, 2H), 5.07 (hept, $J = 6.3$ Hz, 1H), 4.62 (t, $J = 3.8$ Hz, 1H), 3.73 (dd, $J = 11.0, 2.9$ Hz, 1H), 3.62 (dd, $J = 13.9, 4.1$ Hz, 1H), 3.54 (dd, $J = 15.6, 3.0$ Hz, 1H), 3.39 (dd, $J = 14.0, 3.4$ Hz, 1H), 3.08 (dd, $J = 15.6, 11.1$ Hz, 1H), 1.29 (d, $J = 6.3$ Hz, 3H), 1.28 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.3, 160.2 (d, $^1J_{\text{CF}} = 245.2$ Hz), 135.7, 135.3, 130.9 (d, $J = 4.0$ Hz), 128.9, 128.7 (d, $J = 8.2$ Hz), 128.2 (d, $J = 14.0$ Hz), 124.3 (d, $J = 3.5$ Hz), 122.0, 119.6, 118.2, 115.5 (d, $^2J_{\text{CF}} = 22.2$ Hz), 111.8, 110.6, 68.8, 62.4, 51.9, 41.5, 29.8, 22.0, 21.9.

^{19}F NMR (376 MHz, CDCl_3) δ -118.8 to -118.9 (br m).

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{FN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 367.1816, found 367.1840.

isopropyl (2*S*,5*S*)-5-(2-fluorophenyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (*trans*-3-6g)



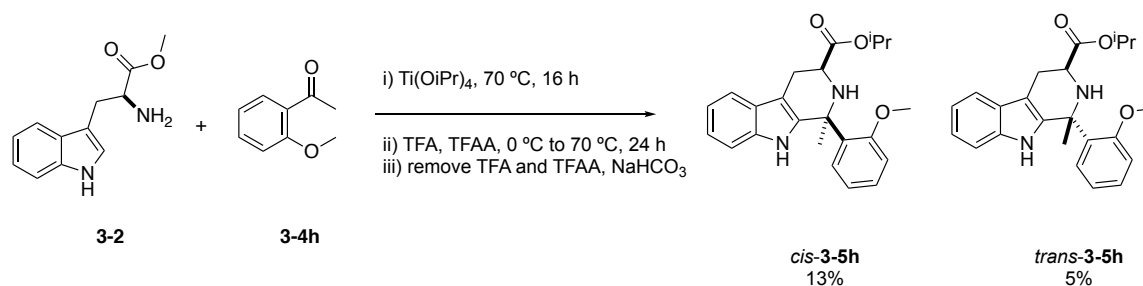
^1H NMR (400 MHz, CDCl_3) δ 7.59 – 7.52 (m, 1H), 7.45 (br, 1H), 7.37 – 7.28 (m, 1H), 7.19 – 7.07 (m, 6H), 5.01 (hept, $J = 6.3$ Hz, 1H), 4.70 (dd, $J = 9.9, 3.8$ Hz, 1H), 3.86 (dd, $J = 8.8, 3.0$ Hz, 1H), 3.54 (ddd, $J = 15.7, 3.1, 0.9$ Hz, 1H), 3.45 (dd, $J = 13.9, 3.8$ Hz, 1H), 3.34 (ddd, $J = 13.9, 9.9, 1.1$ Hz, 1H), 3.18 (ddd, $J = 15.6, 8.8, 1.2$ Hz, 1H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.12 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.6, 160.7 (d, $^1J_{\text{CF}} = 246.9$ Hz), 136.1, 135.0, 130.4 (d, $J = 4.2$ Hz), 129.2 (d, $J = 8.1$ Hz), 128.9, 127.6 (d, $J = 14.6$ Hz), 124.8 (d, $J = 3.6$ Hz), 121.6, 119.4, 118.0, 116.2 (d, $^2J_{\text{CF}} = 22.2$ Hz), 110.6, 110.5, 68.8, 61.4, 51.7 (d, $J = 1.5$ Hz), 42.7, 28.0, 21.9, 21.7.

^{19}F NMR (376 MHz, CDCl_3) δ -117.18.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{23}\text{FN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 367.1816, found 367.1815.

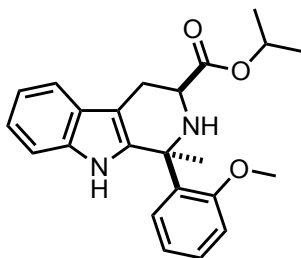
Synthesis of isopropyl (1*S*,3*S*)-1-(2-methoxyphenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5*h*) and isopropyl (1*R*,3*S*)-1-(2-methoxyphenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5*h*)



To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N_2 three times, then placed under a N_2 atmosphere. Then $\text{Ti}(\text{O}i\text{Pr})_4$ (1.5 mL) was added via syringe, followed by 1-(2-methoxyphenyl)ethan-1-one **3-4*h*** (194.7 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at r.t. overnight until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave

cis-**3-5h** (58.0 mg, 13%), mixture of *cis*-**3-5f** and *trans*-**3-5f** (160.5 mg, 36%), and *trans*-**3-5f** (23.4 mg, 5%).

isopropyl (1*S*,3*S*)-1-(2-methoxyphenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*cis*-3-5h**)**

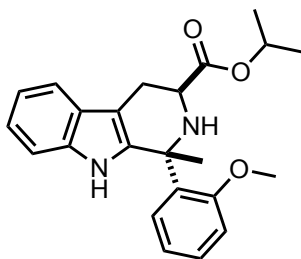


^1H NMR (400 MHz, CDCl_3) δ 7.78 (br, 1H), 7.64 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.52 – 7.48 (m, 1H), 7.28 (ddd, $J = 8.2, 7.4, 1.7$ Hz, 1H), 7.22 – 7.19 (m, 1H), 7.13 – 7.04 (m, 2H), 6.98 (ddd, $J = 7.8, 7.4, 1.2$ Hz, 1H), 6.91 (dd, $J = 8.2, 1.2$ Hz, 1H), 5.09 (hept, $J = 6.3$ Hz, 1H), 4.04 (dd, $J = 10.8, 4.3$ Hz, 1H), 3.68 (s, 3H), 3.16 (dd, $J = 14.9, 4.3$ Hz, 1H), 2.84 (dd, $J = 14.9, 10.8$ Hz, 1H), 1.92 (s, 3H), 1.32 (d, $J = 6.3$ Hz, 3H), 1.30 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 173.2, 157.7, 139.1, 135.4, 132.9, 129.1, 128.0, 127.0, 121.3, 121.0, 119.2, 118.0, 112.6, 110.7, 106.7, 68.4, 56.2, 55.8, 53.2, 26.9, 25.9, 21.9, 21.8.

HRMS (ESI+) calculated for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 379.2016, found 379.2035.

isopropyl (1*R*,3*S*)-1-(2-methoxyphenyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (*trans*-3-5h)

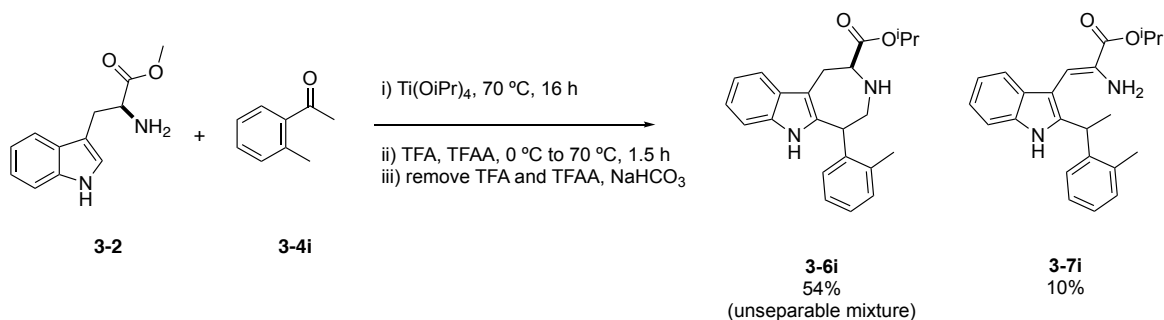


^1H NMR (400 MHz, CDCl_3) δ 8.02 (br, 1H), 7.57 (ddt, $J = 7.8, 1.3, 0.7$ Hz, 1H), 7.43 – 7.34 (m, 1H), 7.25 – 7.18 (m, 2H), 7.15 (ddd, $J = 7.7, 7.1, 1.1$ Hz, 1H), 6.96 (dd, $J = 8.2, 1.1$ Hz, 1H), 6.73 (td, $J = 7.5, 1.2$ Hz, 1H), 6.61 (dd, $J = 7.7, 1.7$ Hz, 1H), 5.07 (hept, $J = 6.2$ Hz, 1H), 3.97 (s, 3H), 3.46 (dd, $J = 11.3, 4.5$ Hz, 1H), 3.07 (dd, $J = 15.2, 4.5$ Hz, 1H), 2.90 (dd, $J = 15.2, 11.3$ Hz, 0H), 1.98 (s, 3H), 1.28 (d, $J = 6.2$ Hz, 3H), 1.27 (d, $J = 6.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.8, 157.0, 137.8, 136.1, 133.3, 130.2, 128.8, 127.4, 121.9, 120.3, 119.6, 118.7, 111.7, 111.0, 109.0, 68.6, 58.7, 55.5, 53.2, 26.6, 25.4, 22.0, 21.9.

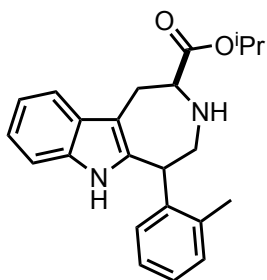
HRMS (ESI+) calculated for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 379.2016, found 379.2029.

Synthesis of isopropyl (2*S*)-5-(*o*-tolyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (3-6i**) and isopropyl (*Z*)-2-amino-3-(2-(1-(*o*-tolyl)ethyl)-1*H*-indol-3-yl)acrylate (**3-7i**)**



To an oven-dried Schlenk flask were added stir bar and **3-2** (257.1 mg, 1.18 mmol), evacuated with vacuum and backfilled with N_2 three times, then placed under a N_2 atmosphere. Then $\text{Ti}(\text{O}i\text{Pr})_4$ (1.5 mL) was added via syringe, followed by 1-(*o*-tolyl)ethan-1-one **3-4i** (173.8 mg, 1.3 mmol). The mixture was heated to 70 °C for 16 h, and then cooled in an ice bath. Then TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol) were added slowly via syringe at 0 °C. The mixture was stirred at 70 °C for 1.5 h until TLC indicated full conversion, at which point the reaction mixture was added to 20 mL DCM in a separatory funnel. To the DCM solution were added 5 mL saturated L-tartaric acid water solution, and the mixture was shaken. Water (15 mL) was then added, the mixture shaken, and the organic layers was separated. The aq. layer was further extracted with DCM (25 mL x 3), and the combined organic layers were concentrated in vacuo to remove most of the residual TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave mixture of *cis*-**3-6i** and *trans*-**3-6i** (232.1 mg, 54%), and **3-7i** (43.3 mg, 10%).

isopropyl (2*S*)-5-(*o*-tolyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxylate (3-6i)

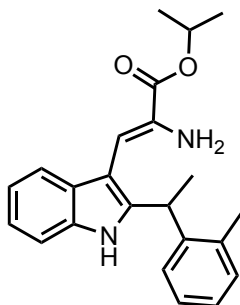


^1H NMR (400 MHz, CDCl_3) δ 7.91 (s, 1H), 7.66 – 7.57 (m, 3.5H), 7.50 (s, 2.5H), 7.35 – 7.05 (m, 20H), 6.96 (dd, $J = 7.7, 1.5$ Hz, 1H), 5.13 – 5.03 (m, 3.5H), 4.61 (dd, $J = 10.4, 3.7$ Hz, 2.5H), 4.57 (dd, $J = 6.1, 3.7$ Hz, 1H), 3.88 (dd, $J = 10.1, 3.6$ Hz, 1H), 3.83 (dd, $J = 9.5, 2.8$ Hz, 2.5H), 3.62 (ddd, $J = 15.5, 2.8, 0.8$ Hz, 2.5H), 3.58 – 3.50 (m, 2H), 3.42 – 3.23 (m, 7H), 3.17 (ddd, $J = 15.6, 9.5, 1.2$ Hz, 2.5H), 2.44 (s, 3H), 2.42 (s, 7.6H) 1.32 (d, $J = 6.3$ Hz, 7.6H), 1.31 (d, $J = 6.3$ Hz, 3H), 1.28 (d, $J = 6.2$ Hz, 3H), 1.21 (d, $J = 6.3$ Hz, 7.6H).

^{13}C NMR (101 MHz, CDCl_3) δ 172.2, 172.1, 138.7, 138.5, 136.3, 136.1, 133.3, 133.2, 130.3, 130.0, 127.9, 127.9, 125.8, 125.7, 125.5, 125.5, 123.4, 123.1, 121.9, 121.8, 119.5, 119.2, 119.2, 119.1, 112.1, 112.1, 111.9, 111.3, 111.0, 111.0, 68.6, 68.3, 66.6, 66.4, 64.9, 59.6, 29.7, 28.9, 22.0, 21.9, 21.9, 21.7, 19.6, 19.0 (note: this is a mixture of diastereomers: 44 out of a possible 46 carbons were found).

HRMS (ESI+) calculated for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 363.2067, found 363.2069.

isopropyl (Z)-2-amino-3-(2-(1-(o-tolyl)ethyl)-1H-indol-3-yl)acrylate (3-7i)

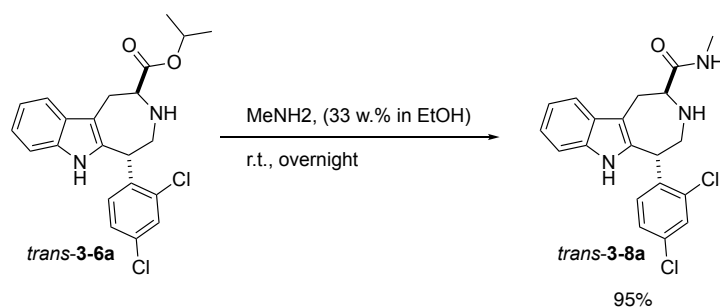


^1H NMR (400 MHz, CDCl_3) δ 8.71 (br, 1H), 7.30 – 7.26 (m, 1H), 7.20 (td, $J = 7.4, 1.8$ Hz, 1H), 7.17 – 7.07 (m, 3H), 6.97 (dd, $J = 7.8, 1.6$ Hz, 1H), 6.89 (d, $J = 2.6$ Hz, 1H), 6.76 – 6.70 (m, 2H), 5.16 (hept, $J = 6.3$ Hz, 1H), 4.37 (q, $J = 7.2$ Hz, 1H), 3.54 (br, 2H), 2.06 (s, 3H), 1.53 (d, $J = 7.2$ Hz, 3H), 1.31 (d, $J = 6.3$ Hz, 3H) 1.30 (d, $J = 6.3$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 160.9, 145.2, 141.5, 138.9, 136.1, 131.2, 130.8, 128.5, 126.9, 126.6, 126.0, 121.5, 121.0, 119.6, 118.2, 116.6, 115.1, 67.8, 33.1, 22.2 (br), 20.5, 19.4.

HRMS (ESI+) calculated for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 363.2067, found 363.2069.

Synthesis of (2*S*,5*S*)-5-(2,4-dichlorophenyl)-*N*-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxamide (*trans*-3-8a)



To a 10 mL RBF were added *trans*-3-6a (100 mg, 0.24 mmol), methylamine (33 w.% in EtOH, 4 mL). The resulting mixture was stirred at r.t. overnight. At this point, TLC indicated completion,

the mixture was concentrated in vacuo and purified by flash column chromatography (9:1 DCM/EtOAc) and gave *trans*-**3-8a** (88.5 mg, 95%).

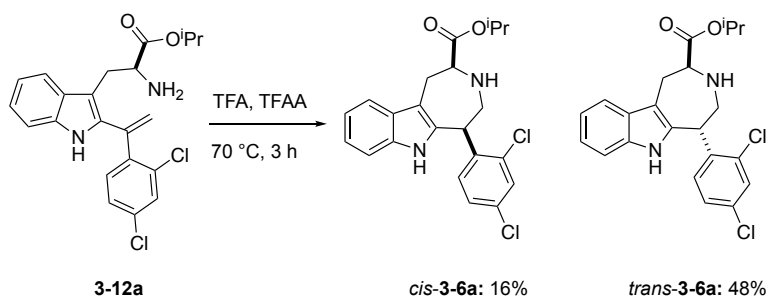
(2*S*,5*S*)-5-(2,4-dichlorophenyl)-*N*-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-2-carboxamide

¹H NMR (400 MHz, CDCl₃) δ 7.65 – 7.59 (m, 1H), 7.58 – 7.49 (m, 2H), 7.48 (d, *J* = 2.2 Hz, 1H), 7.23 – 7.10 (m, 4H), 6.93 (d, *J* = 8.4 Hz, 1H), 4.83 (dd, *J* = 6.3, 3.3 Hz, 1H), 3.84 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.73 (dd, *J* = 16.1, 3.4 Hz, 1H), 3.69 (dd, *J* = 14.7, 3.3 Hz, 1H), 3.37 (dd, *J* = 14.7, 6.3 Hz, 1H), 3.04 (ddd, *J* = 16.1, 10.7, 1.3 Hz, 1H), 2.79 (d, *J* = 5.0 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 174.8, 136.9, 135.6, 134.3, 134.0, 134.0, 131.4, 130.0, 128.4, 127.8, 122.3, 119.8, 118.6, 112.9, 110.5, 62.0, 47.6, 45.3, 26.1, 26.0.

HRMS (ESI⁺) calculated for C₂₀H₁₉Cl₂N₃O [M+H]⁺: 388.0978, found 388.0991.

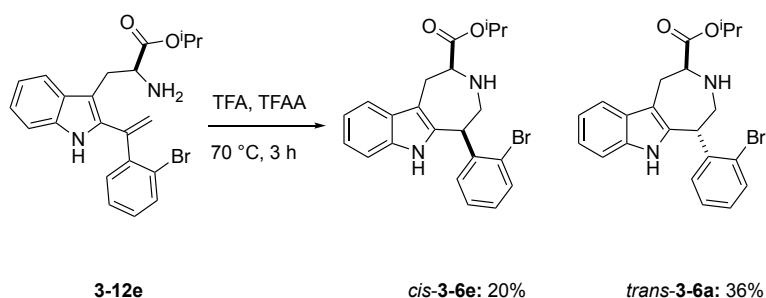
Isomerization of **3-12a**



To a 10 mL round-bottom flask were added stir bar and **3-12a** (100 mg, 0.24 mmol), followed by TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol). The mixture was stirred at 70 °C for 3 h until TLC indicated full conversion, at which point the reaction mixture was concentrated in vacuo to remove most of the TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes

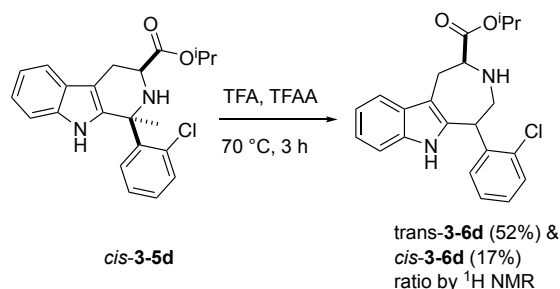
foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave *cis*-**3-6a** (15.8 mg, 16%) and *trans*-**3-6a** (48.4 mg, 48%).

Isomerization of 3-12e



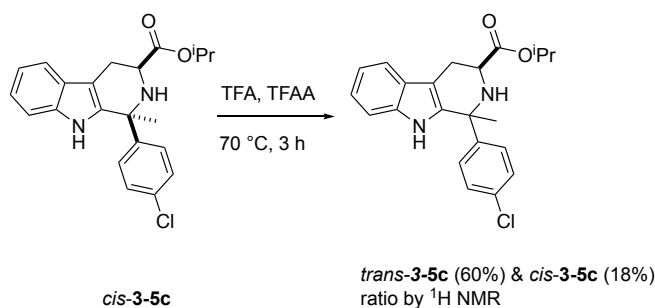
To an oven-dried round-bottom flask were added stir bar and **3-12e** (100 mg, 0.23 mmol), followed by TFA (3 mL, 39.2 mmol) and TFAA (0.2 mL, 1.44 mmol). The mixture was stirred at 70 °C for 3 h until TLC indicated full conversion, at which point the reaction mixture was concentrated in vacuo to remove most of the TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave *cis*-**3-6e** (20.3 mg, 20%) and *trans*-**3-6e** (36.0 mg, 36%).

Isomerization of *cis*-3-5d



To an oven-dried round-bottom flask were added stir bar and *cis*-3-5d (100 mg, 0.26 mmol), followed by TFA (3 mL, 39.2 mmol) and TFAA (# mL, # mmol). The mixture was stirred at 70 °C for 3 h until TLC indicated full conversion, at which point the reaction mixture was concentrated in vacuo to remove most of the TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave a mixture of *cis*-3-6e and *trans*-3-6e (69.3 mg, 52% *trans*- & 17% *cis*- by ¹H NMR).

Isomerization of *cis*-3-5c



To an oven-dried round-bottom flask were added stir bar and *cis*-3-5c (100 mg, 0.26 mmol), followed by TFA (3 mL, 39.2 mmol) and TFAA (# mL, # mmol). The mixture was stirred at 70

°C for 3 h until TLC indicated full conversion, at which point the reaction mixture was concentrated in vacuo to remove most of the TFA, giving a viscous yellow liquid. This residue was diluted with 20 mL of DCM and carefully washed with sat. sodium bicarbonate (caution: residual TFA causes foaming) and brine, dried over sodium sulfate and concentrated in vacuo to give a yellow viscous liquid. Flash column chromatography (5:5:1 DCM/Hexanes/EtOAc) gave a mixture of *cis*-**3-5c** and *trans*-**3-5c** (78.3 mg, 18% *trans*- & 60% *cis*- by ¹H NMR).

B. NOE Spectra of Selected Compounds

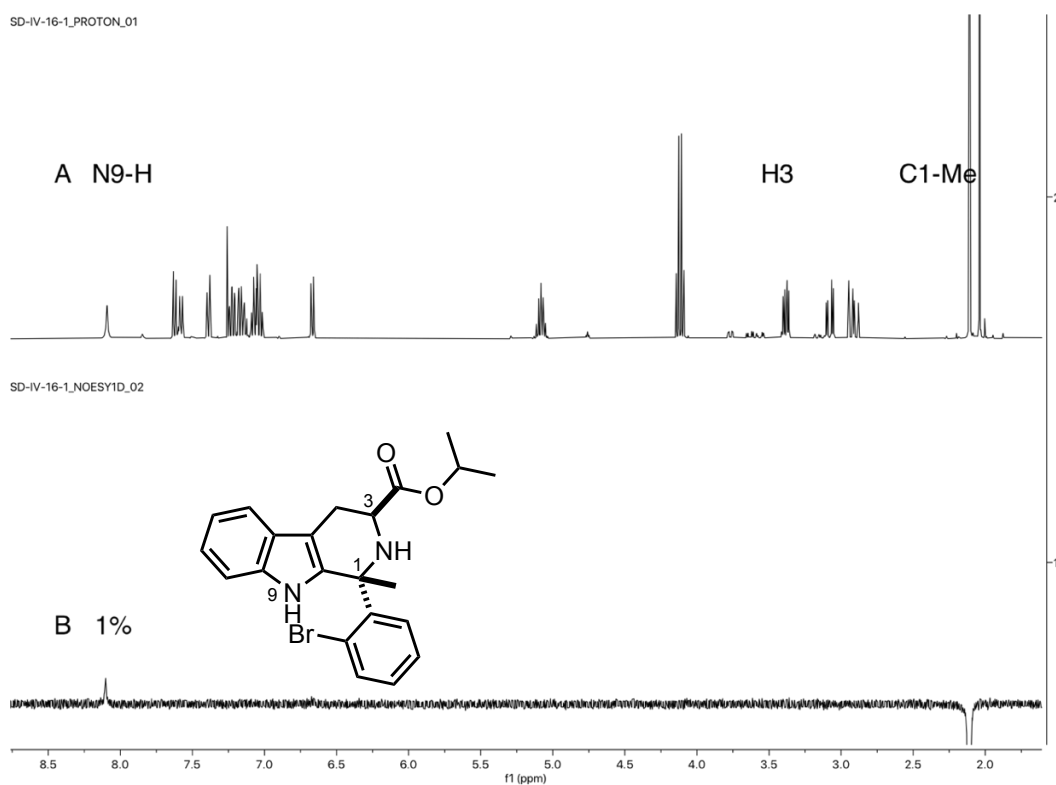
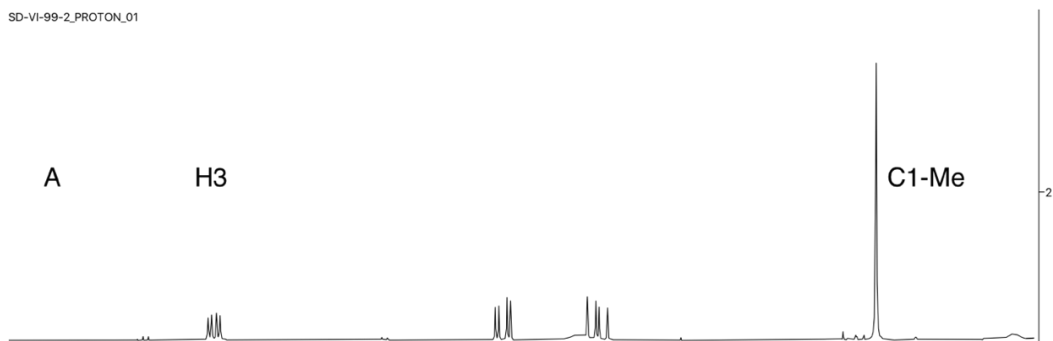


Figure S3-1. A) ¹H NMR spectrum of *trans*-**3-5e** (CDCl₃); B) 1D NOE ¹H NMR spectrum of *trans*-**3-5e** resulting from irradiation of C1-Me. NOE transfer from C1-Me to N9H confirms the depicted *trans*-configuration.

SD-VI-99-2_PROTON_01



SD-VI-99-2_NOESY1D_01

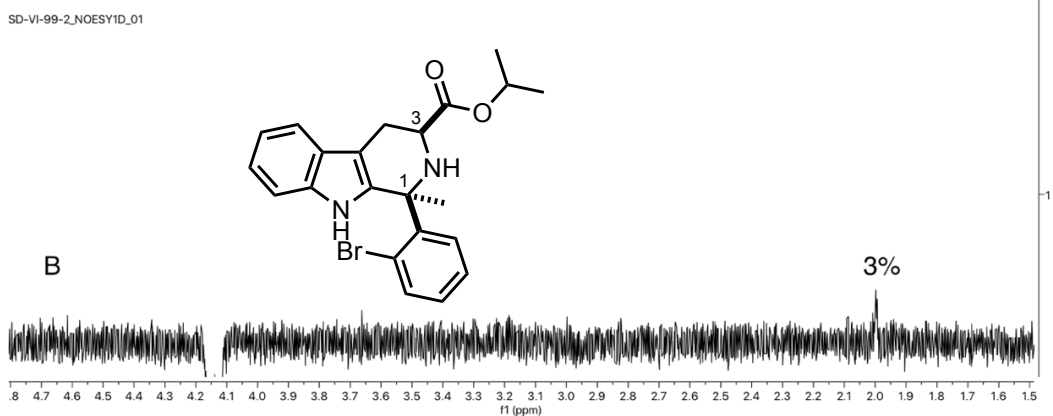
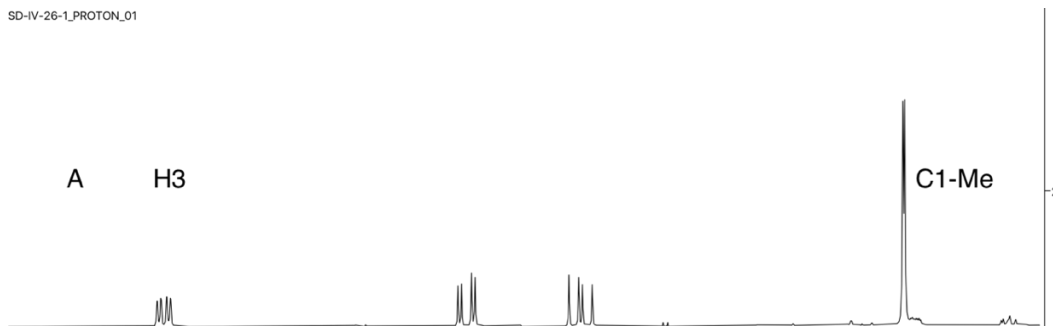


Figure S3-2. A) ^1H NMR spectrum of *cis*-**3-5e** (CDCl_3); B) 1D NOE ^1H NMR spectrum of *cis*-**3-5e** resulting from irradiation of H3. NOE transfer from the H3 to C1-Me confirms the depicted *cis*-configuration.

SD-IV-26-1,PROTON_01



SD-IV-26-1,NOESY1D_01

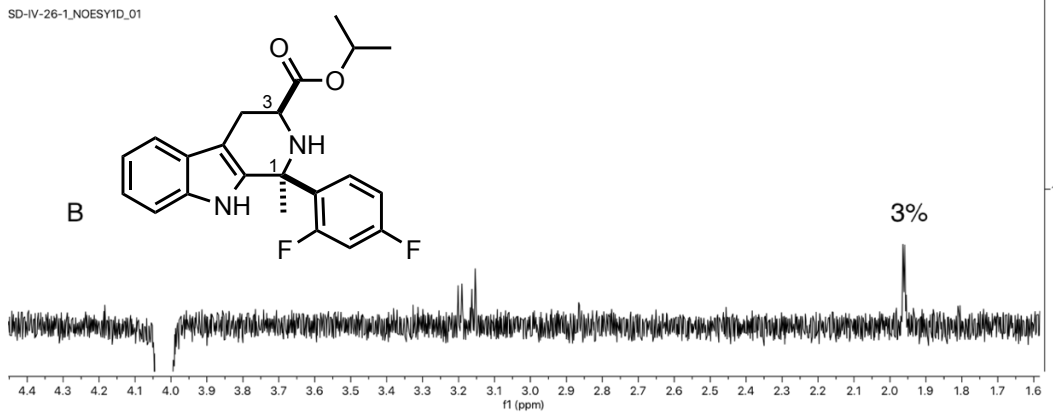


Figure S3-3. A) ^1H NMR spectrum of *cis*-**3-5f** (CDCl_3); B) 1D NOE ^1H NMR spectrum of *cis*-**3-5f** resulting from irradiation of H3. NOE transfer from H3 to C1-Me confirms the depicted *cis*-configuration.

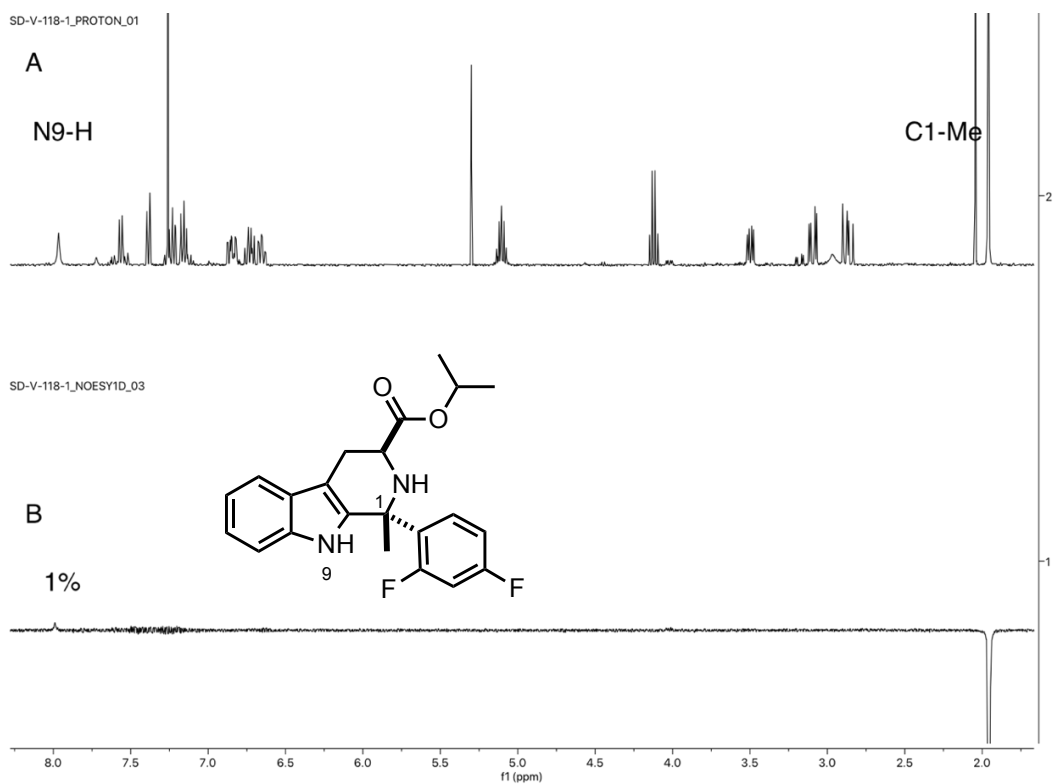


Figure S3-4. A) ^1H NMR spectrum of *trans*-**3-5f** (CDCl_3); B) 1D NOE ^1H NMR spectrum of *trans*-**3-5f** resulting from irradiation of C1-Me. NOE transfer from C1-Me to the N9-H confirms the depicted *trans*-stereochemistry.

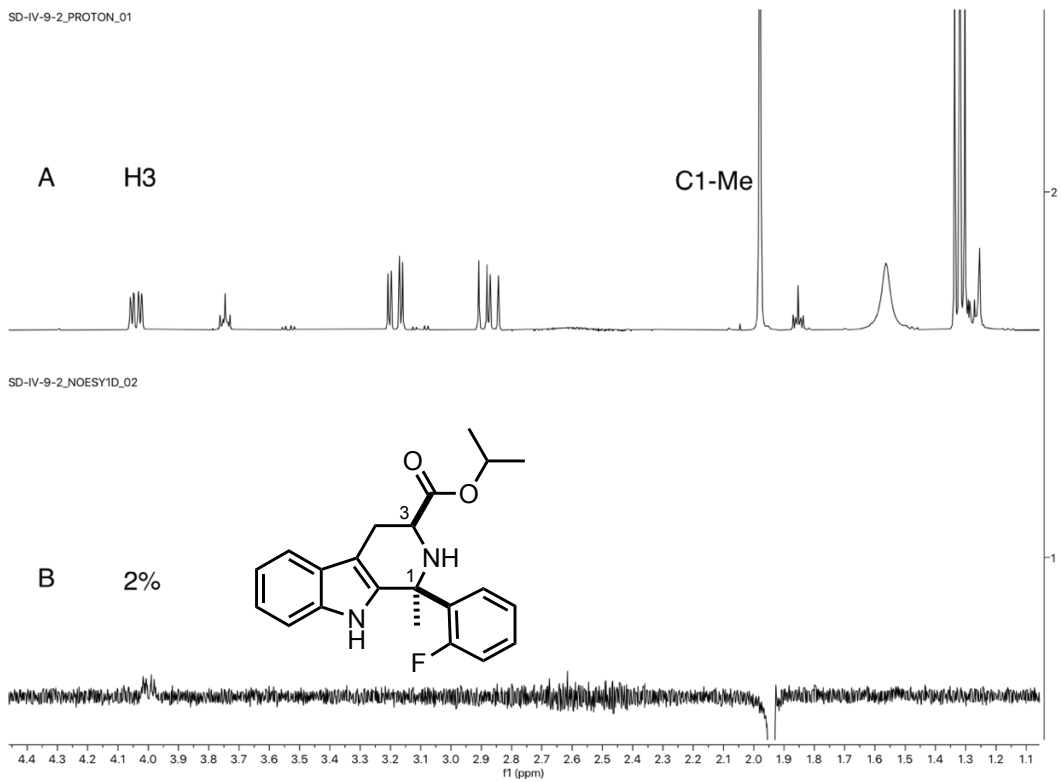


Figure S3-5. A) ^1H NMR spectrum of *cis*-**3-5g** (CDCl_3); B) 1D NOE ^1H NMR spectrum of *cis*-**3-5g** resulting from irradiation of C1-Me. NOE transfer from C1-Me to H3 confirms the depicted *cis*-configuration

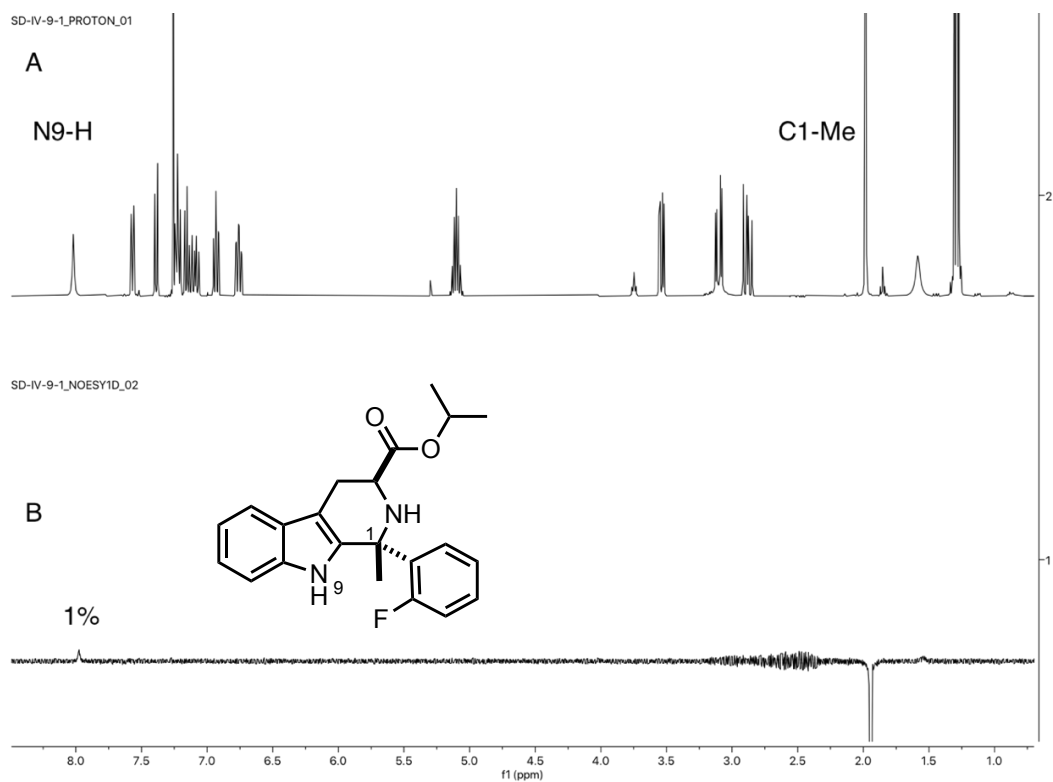


Figure S3-6. A) ^1H NMR spectrum of *trans*-**3-5g** (CDCl_3); B) 1D NOE ^1H NMR spectrum of *trans*-**3-5g** resulting from irradiation of C1-Me. NOE transfer from C1-Me to N9-H confirms the depicted *trans*-configuration.

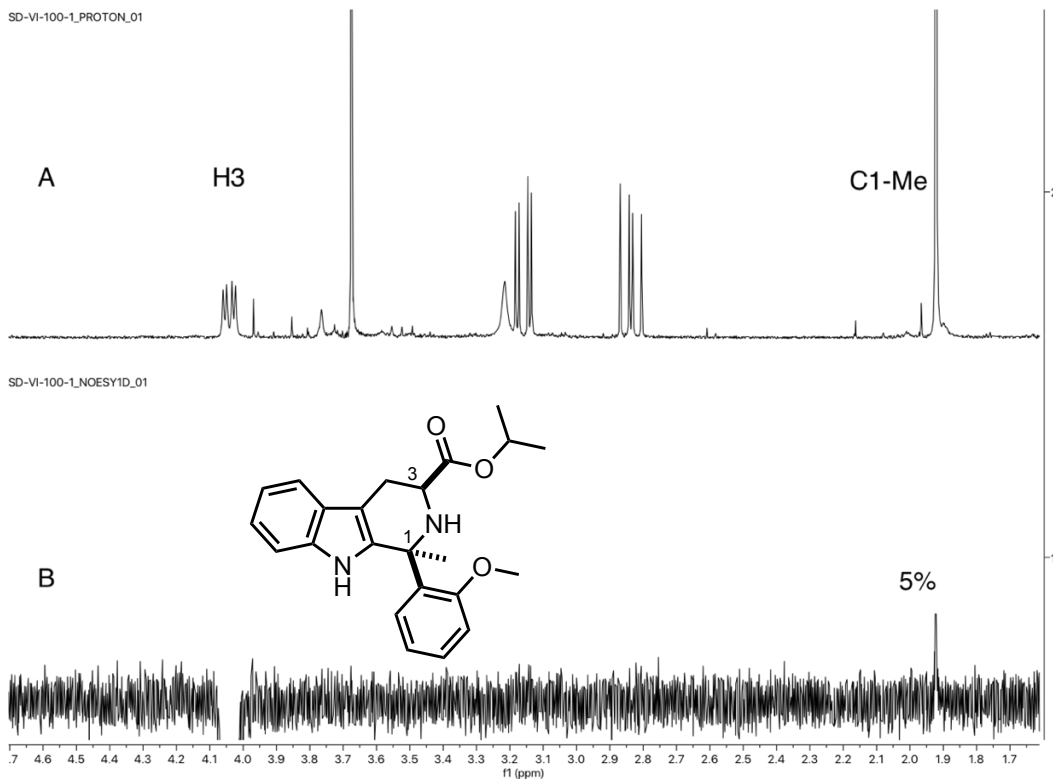


Figure S3-7. A) ^1H NMR spectrum of *cis*-**3-5h** (CDCl_3); B) 1D NOE ^1H NMR spectrum of *cis*-**3-5h** resulting from irradiation of H3. NOE transfer from C3-H to the C1-Me confirms the depicted *cis*-configuration.

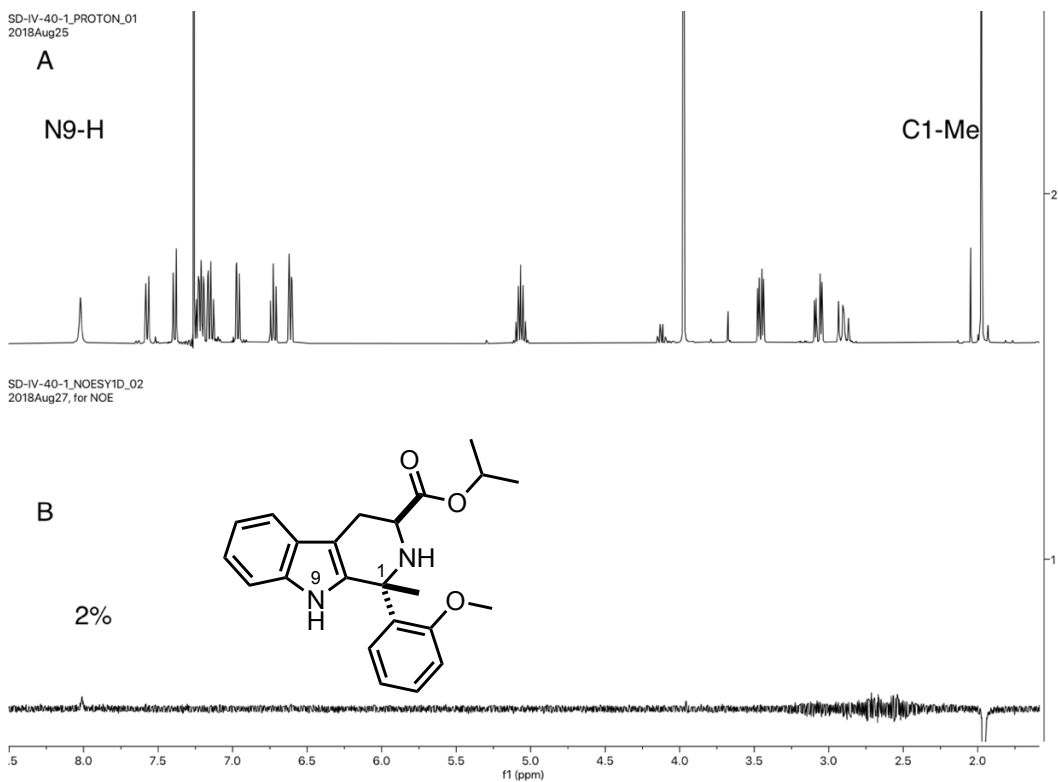


Figure S3-8. A) ^1H NMR spectrum of *trans*-3-5h (CDCl_3); B) 1D NOE ^1H NMR spectrum of *trans*-3-5h resulting from irradiation of C1-Me. NOE transfer from C1-Me to N9-H confirms the depicted *trans*-configuration.

C. Energy, Boltzmann distribution, and dihedral angle of 3-5a,b-OMe and 3-6a,b-OMe

The conformation of the dehydroazepane ring are designated using the terms that Groenewald et al. developed.¹⁹ The numbering of the dehydroazepane ring is given below.

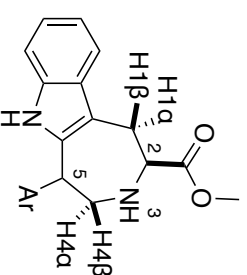
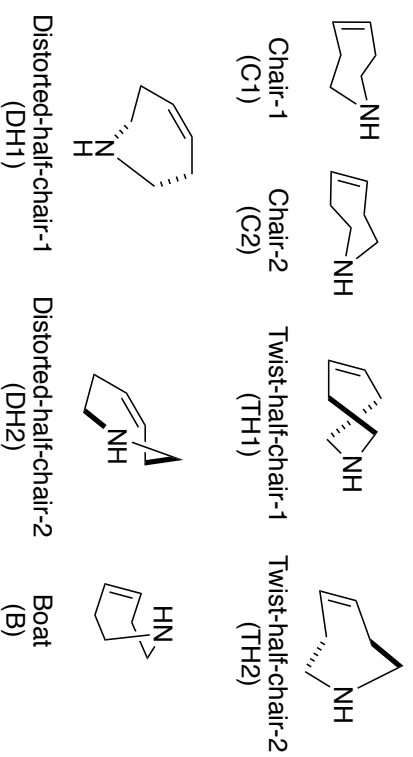


Table S3-1. Calculated energies of *trans*-3-5a-OMe at MMFF94 and B3LYP/6-31G(d) levels of theory.

Conformer #	MMFF94		B3LYP/6-31G(d), vacuum				ΔG (298K) [kcal/mol]	Boltzmann distribution
	e_0 [kcal/mol]	e_0 [Hartree]	ZPVE [Hartree]	G_{corr} (298K) [Hartree]	G (298K) [Hartree]			
<i>trans</i> -3-5a-OMe-1	69.88	-1953.318915	0.344321	0.290812	-1953.028103	0.70	17%	
<i>trans</i> -3-5a-OMe-2	70.17	-1953.320187	0.34426	0.290976	-1953.029211	0.00	55%	
<i>trans</i> -3-5a-OMe-3	70.63	-1953.318479	0.344217	0.290121	-1953.028358	0.54	22%	
<i>trans</i> -3-5a-OMe-4	71.38	-1953.316841	0.34435	0.290325	-1953.026516	1.69	3%	
<i>trans</i> -3-5a-OMe-5	71.56	-1953.316813	0.344708	0.291067	-1953.025746	2.17	1%	
<i>trans</i> -3-5a-OMe-6	72.41	-1953.313043	0.344845	0.291381	-1953.021662	4.74	0%	
<i>trans</i> -3-5a-OMe-7	72.46	-1953.315062	0.34493	0.291114	-1953.023948	3.30	0%	
<i>trans</i> -3-5a-OMe-8	72.78	-1953.315294	0.344983	0.291590	-1953.023704	3.46	0%	
<i>trans</i> -3-5a-OMe-9	72.88	-1953.314307	0.344405	0.290924	-1953.023383	3.66	0%	
<i>trans</i> -3-5a-OMe-10	73.28	-1953.310049	0.344906	0.291635	-1953.018414	6.78	0%	
<i>trans</i> -3-5a-OMe-11	73.62	-1953.312097	0.344247	0.290225	-1953.021872	4.61	0%	
<i>trans</i> -3-5a-OMe-12	74.23	-1953.309202	0.345045	0.291427	-1953.017775	7.18	0%	
<i>trans</i> -3-5a-OMe-13	74.49	-1953.313071	0.344293	0.290004	-1953.023067	3.86	0%	
<i>trans</i> -3-5a-OMe-14	74.8	-1953.311325	0.344268	0.289745	-1953.02158	4.79	0%	
<i>trans</i> -3-5a-OMe-15	76.45	-1953.308187	0.344299	0.290104	-1953.018083	6.98	0%	
<i>trans</i> -3-5a-OMe-16	77.69	-1953.309815	0.344272	0.290678	-1953.019137	6.32	0%	

Table S3-2. Calculated energies of *cis*-3-5a-OMe at MMFF94 and B3LYP/6-31G(d) levels of theory.

Conformer #	MMFF94			B3LYP/6-31G(d), vacuum			ΔG (298K) [kcal/mol]	Boltzmann distribution
	[kcal/mol]	e_0 [Hartree]	ZPVE [Hartree]	G_{corr} (298K) [Hartree]	G (298K) [Hartree]			
<i>cis</i> -3-5a-OMe-1	69.17	-1953.316896	0.3447	0.290868	-1953.026028	0.90	12%	
<i>cis</i> -3-5a-OMe-2	69.63	-1953.315416	0.344864	0.291089	-1953.024327	1.97	2%	
<i>cis</i> -3-5a-OMe-3	70.17	-1953.315827	0.344632	0.291985	-1953.023842	2.28	1%	
<i>cis</i> -3-5a-OMe-4	70.92	-1953.318924	0.34464	0.291455	-1953.027469	0.00	55%	
<i>cis</i> -3-5a-OMe-5	70.97	-1953.314413	0.344466	0.291286	-1953.023127	2.72	1%	
<i>cis</i> -3-5a-OMe-6	71.09	-1953.317089	0.344408	0.290856	-1953.026233	0.78	15%	
<i>cis</i> -3-5a-OMe-7	71.75	-1953.316502	0.344356	0.290867	-1953.025635	1.15	8%	
<i>cis</i> -3-5a-OMe-8	71.87	-1953.315313	0.344499	0.291135	-1953.024178	2.07	2%	
<i>cis</i> -3-5a-OMe-9	72.29	-1953.311546	0.344351	0.291407	-1953.020139	4.60	0%	
<i>cis</i> -3-5a-OMe-10	72.75	-1953.315141	0.344371	0.290214	-1953.024927	1.60	4%	
<i>cis</i> -3-5a-OMe-11	73.68	-1953.313643	0.344433	0.290438	-1953.023205	2.68	1%	
<i>cis</i> -3-5a-OMe-12	74.43	-1953.308702	0.344332	0.291066	-1953.017636	6.17	0%	
<i>cis</i> -3-5a-OMe-13	75.02	-1953.30812	0.344559	0.291528	-1953.016592	6.83	0%	
<i>cis</i> -3-5a-OMe-14	75.95	-1953.307062	0.344631	0.291351	-1953.015711	7.38	0%	
<i>cis</i> -3-5a-OMe-15	76.08	-1953.307503	0.344551	0.291889	-1953.015614	7.44	0%	
<i>cis</i> -3-5a-OMe-16	76.36	-1953.305725	0.344687	0.291345	-1953.01438	8.21	0%	

Table S3-3. Calculated energies of *cis*-3-5b-OMe at MMFF94 and B3LYP/6-31G(d) levels of theory.

Conformer #	MMFF94		B3LYP/6-31G(d), vacuum				
	[kcal/mol]	e0 [Hartree]	ZPVE [Hartree]	G _{corr} (298K) [Hartree]	G (298K) [Hartree]	ΔG (298K) [kcal/mol]	Boltzmann distribution
<i>cis</i> -3-5b-OMe-1	318.11	-1034.134978	0.364007	0.313379	-1033.821599	0.53	24%
<i>cis</i> -3-5b-OMe-2	319.32	-1034.131566	0.364002	0.314769	-1033.816797	3.55	0%
<i>cis</i> -3-5b-OMe-3	320.8	-1034.135079	0.364016	0.314244	-1033.820835	1.01	11%
<i>cis</i> -3-5b-OMe-4	320.88	-1034.133504	0.364041	0.313103	-1033.820401	1.28	7%
<i>cis</i> -3-5b-OMe-5	321.55	-1034.13637	0.363944	0.313923	-1033.822447	0.00	59%
<i>cis</i> -3-5b-OMe-6	325.92	-1034.129876	0.36402	0.314621	-1033.815255	4.51	0%
<i>cis</i> -3-5b-OMe-7	327.52	-1034.129175	0.363892	0.314120	-1033.815055	4.64	0%
<i>cis</i> -3-5b-OMe-8	335.08	-1034.127284	0.364027	0.314852	-1033.812432	6.28	0%

Table S3-4. Calculated energies of *trans*-**3-5b**-OMe at MPMFF94 and B3LYP/6-31G(d) levels of theory.

Conformer #	MPMFF94			B3LYP/6-31G(d), vacuum			
	[kcal/mol]	ϵ_0 [Hartree]	ZPVE [Hartree]	G_{corr} (298K) [Hartree]	G (298K) [Hartree]	ΔG (298K) [kcal/mol]	Boltzmann distribution
<i>trans</i> - 3-5b -OMe-1	317.57	-1034.136946	0.363917	0.313770	-1033.823176	0.00	56%
<i>trans</i> - 3-5b -OMe-2	318.89	-1034.136078	0.363769	0.313561	-1033.822517	0.41	28%
<i>trans</i> - 3-5b -OMe-3	319.05	-1034.135302	0.363961	0.313781	-1033.821521	1.04	10%
<i>trans</i> - 3-5b -OMe-4	322.17	-1034.134577	0.363717	0.313547	-1033.82103	1.35	6%
<i>trans</i> - 3-5b -OMe-5	325.02	-1034.13138	0.364203	0.313896	-1033.817484	3.57	0%
<i>trans</i> - 3-5b -OMe-6	327.45	-1034.131303	0.364182	0.314357	-1033.816946	3.91	0%
<i>trans</i> - 3-5b -OMe-7	347.89	-1034.124268	0.363936	0.313745	-1033.810523	7.94	0%
<i>trans</i> - 3-5b -OMe-8	355.31	-1034.123825	0.363773	0.313652	-1033.810173	8.16	0%

Table S3-5. Calculated energies of *cis-3-6a-OMe* at MMFF94 and B3LYP/6-31G(d) levels of theory.

Conformer #	MMFF94		B3LYP/6-31G(d), vacuum				ΔG (298K) [Kcal/mol]	Boltzmann distribution
	e_0 [Kcal/mol]	e_0 [Hartree]	ZPVE [Hartree]	G_{corr} (298K) [Hartree]	G (298K) [Hartree]			
<i>cis-3-6a-OMe-1</i>	112.22	-1953.324239	0.346388	0.292753	-1953.031486	1.36	7%	
<i>cis-3-6a-OMe-2</i>	112.41	-1953.322453	0.346102	0.291303	-1953.03115	1.57	5%	
<i>cis-3-6a-OMe-3</i>	112.72	-1953.323236	0.345995	0.291605	-1953.031631	1.27	8%	
<i>cis-3-6a-OMe-4</i>	112.84	-1953.325517	0.346116	0.291870	-1953.033647	0.00	67%	
<i>cis-3-6a-OMe-5</i>	112.9	-1953.32348	0.345908	0.291595	-1953.031885	1.11	10%	
<i>cis-3-6a-OMe-6</i>	113.25	-1953.318183	0.346425	0.292565	-1953.025618	5.04	0%	
<i>cis-3-6a-OMe-7</i>	113.6	-1953.318541	0.346207	0.291927	-1953.026614	4.41	0%	
<i>cis-3-6a-OMe-8</i>	113.78	-1953.322234	0.34606	0.292029	-1953.030205	2.16	2%	
<i>cis-3-6a-OMe-9</i>	114.12	-1953.319329	0.346076	0.291838	-1953.027491	3.86	0%	
<i>cis-3-6a-OMe-10</i>	114.13	-1953.320049	0.346	0.291141	-1953.028908	2.97	0%	
<i>cis-3-6a-OMe-11</i>	114.24	-1953.319903	0.345831	0.290850	-1953.029053	2.88	1%	
<i>cis-3-6a-OMe-12</i>	114.87	-1953.319717	0.346262	0.291964	-1953.027753	3.70	0%	
<i>cis-3-6a-OMe-13</i>	115.14	-1953.315796	0.346082	0.291779	-1953.024017	6.04	0%	
<i>cis-3-6a-OMe-14</i>	115.2	-1953.318626	0.345728	0.290808	-1953.027818	3.66	0%	
<i>cis-3-6a-OMe-15</i>	115.36	-1953.316452	0.346232	0.292258	-1953.024194	5.93	0%	
<i>cis-3-6a-OMe-16</i>	116.59	-1953.315563	0.345759	0.291180	-1953.024383	5.81	0%	
<i>cis-3-6a-OMe-17</i>	117.23	-1953.31457	0.345777	0.291393	-1953.023177	6.57	0%	
<i>cis-3-6a-OMe-18</i>	117.28	-1953.319784	0.345708	0.291217	-1953.028567	3.19	0%	
<i>cis-3-6a-OMe-19</i>	117.29	-1953.317181	0.345879	0.290898	-1953.026283	4.62	0%	
<i>cis-3-6a-OMe-20</i>	117.32	-1953.311916	0.345864	0.291590	-1953.020326	8.36	0%	

Table S3-5. Calculated energies of *cis-3-6a-OMe* at MMFF94 and B3LYP/6-31G(d) levels of theory. (continued)

Conformer #	MMFF94		B3LYP/6-31G(d), vacuum				ΔG (298K) [kcal/mol]	Boltzmann distribution
	[kcal/mol]	e_0 [Hartree]	ZPVE [Hartree]	G_{corr} (298K) [Hartree]	G (298K) [Hartree]			
<i>cis</i> -3-6a-OMe-21	117.56	-1953.318306	0.345901	0.290847	-1953.027459	3.88	0%	
<i>cis</i> -3-6a-OMe-22	117.94	-1953.318306	0.345901	0.290846	-1953.02746	3.88	0%	
<i>cis</i> -3-6a-OMe-23	118.54	-1953.314033	0.345811	0.291138	-1953.022895	6.75	0%	
<i>cis</i> -3-6a-OMe-24	118.83	-1953.313194	0.345944	0.291716	-1953.021478	7.64	0%	
<i>cis</i> -3-6a-OMe-25	118.92	-1953.313551	0.345938	0.292039	-1953.021512	7.61	0%	
<i>cis</i> -3-6a-OMe-26	120.18	-1953.314783	0.345852	0.291914	-1953.022869	6.76	0%	
<i>cis</i> -3-6a-OMe-27	120.41	-1953.312322	0.345786	0.291498	-1953.020824	8.05	0%	
<i>cis</i> -3-6a-OMe-28	120.63	-1953.311567	0.346097	0.292645	-1953.018922	9.24	0%	
<i>cis</i> -3-6a-OMe-29	120.8	-1953.30765	0.346141	0.292076	-1953.015574	11.34	0%	
<i>cis</i> -3-6a-OMe-30	121.54	-1953.305269	0.345944	0.291640	-1953.013629	12.56	0%	
<i>cis</i> -3-6a-OMe-31	120.2	-1953.304324	0.346165	0.292598	-1953.011726	13.76	0%	

Table S3-6. Calculated energies of *trans*-**3-6a**-OMe at MMFF94 and B3LYP/6-31G(d) levels of theory.

Conformer #	MMFF94		B3LYP/6-31G(d), vacuum				AG (298K) [kcal/mol]	Boltzmann distribution
	[kcal/mol]	e0 [Hartree]	ZPVE [Hartree]	G _{corr} (298K) [Hartree]	G (298K) [Hartree]			
<i>trans</i> - 3-6a -OMe-1	112.22	-1953.324285	0.346291	0.291945	-1953.03234	0.27	25%	
<i>trans</i> - 3-6a -OMe-2	112.41	-1953.320637	0.346209	0.291981	-1953.028656	2.59	0%	
<i>trans</i> - 3-6a -OMe-3	112.72	-1953.321188	0.34637	0.292814	-1953.028374	2.76	0%	
<i>trans</i> - 3-6a -OMe-4	112.84	-1953.324415	0.346002	0.291637	-1953.032778	0.00	40%	
<i>trans</i> - 3-6a -OMe-5	112.9	-1953.322051	0.345984	0.291602	-1953.030449	1.46	3%	
<i>trans</i> - 3-6a -OMe-6	113.25	-1953.322702	0.345679	0.290684	-1953.032018	0.48	18%	
<i>trans</i> - 3-6a -OMe-7	113.6	-1953.318999	0.346039	0.292004	-1953.026995	3.63	0%	
<i>trans</i> - 3-6a -OMe-8	113.78	-1953.321534	0.346181	0.292527	-1953.029007	2.37	1%	
<i>trans</i> - 3-6a -OMe-9	114.12	-1953.322443	0.346169	0.291396	-1953.031047	1.09	6%	
<i>trans</i> - 3-6a -OMe-10	114.13	-1953.321319	0.345779	0.290847	-1953.030472	1.45	3%	
<i>trans</i> - 3-6a -OMe-11	114.24	-1953.319519	0.345766	0.291490	-1953.028029	2.98	0%	
<i>trans</i> - 3-6a -OMe-12	114.87	-1953.3199	0.346063	0.291172	-1953.028728	2.54	1%	
<i>trans</i> - 3-6a -OMe-13	115.14	-1953.319964	0.345827	0.291288	-1953.028676	2.57	1%	
<i>trans</i> - 3-6a -OMe-14	115.2	-1953.316553	0.346187	0.292511	-1953.024042	5.48	0%	
<i>trans</i> - 3-6a -OMe-15	115.36	-1953.318016	0.345892	0.291672	-1953.026344	4.04	0%	
<i>trans</i> - 3-6a -OMe-16	116.59	-1953.31846	0.345856	0.289920	-1953.02854	2.66	0%	
<i>trans</i> - 3-6a -OMe-17	117.23	-1953.3199	0.346065	0.291206	-1953.028694	2.56	1%	
<i>trans</i> - 3-6a -OMe-18	117.28	-1953.318472	0.345825	0.291253	-1953.027219	3.49	0%	
<i>trans</i> - 3-6a -OMe-19	117.29	-1953.316974	0.345925	0.291849	-1953.025125	4.80	0%	
<i>trans</i> - 3-6a -OMe-20	117.32	-1953.314851	0.34601	0.292462	-1953.022389	6.52	0%	

Table S3-6. Calculated energies of *trans*-**3-6a**-OMe at MMFF94 and B3LYP/6-31G(d) levels of theory. (continued)

Conformer #	MMFF94		B3LYP/6-31G(d), vacuum				Boltzmann distribution
	[kcal/mol]	e0 [Hartree]	ZPVE [Hartree]	G _{corr} (298K) [Hartree]	G (298K) [Hartree]	ΔG (298K) [kcal/mol]	
<i>trans</i> -3-6a-OMe-21	117.56	-1953.312345	0.345928	0.291727	-1953.020618	7.63	0%
<i>trans</i> -3-6a-OMe-22	117.94	-1953.313968	0.346065	0.292424	-1953.021544	7.05	0%
<i>trans</i> -3-6a-OMe-23	118.54	-1953.310171	0.345896	0.291893	-1953.018278	9.10	0%

Table S3-7. Calculated energies of *cis-3-6b*-OMe at MMFF94 and B3LYP/6-31G(d) levels of theory.

Conformer #	MMFF94		B3LYP/6-31G(d), vacuum				ΔG (298K) [kcal/mol]	Boltzmann distribution
	[kcal/mol]	e_0 [Hartree]	ZPVE [Hartree]	G_{corr} (298K) [Hartree]	G (298K) [Hartree]	[kcal/mol]		
<i>cis-3-6b</i> -OMe-1	121.69	-1034.133727	0.36551	0.31457764	-1033.819149	0.68	12%	
<i>cis-3-6b</i> -OMe-2	123.24	-1034.132607	0.365687	0.31565187	-1033.816955	2.06	1%	
<i>cis-3-6b</i> -OMe-3	123.25	-1034.12966	0.365383	0.31387238	-1033.815788	2.79	0%	
<i>cis-3-6b</i> -OMe-4	123.45	-1034.134894	0.365758	0.31593790	-1033.818956	0.80	10%	
<i>cis-3-6b</i> -OMe-5	123.82	-1034.131433	0.36515	0.31441907	-1033.817014	2.02	1%	
<i>cis-3-6b</i> -OMe-6	123.95	-1034.133994	0.365078	0.31375639	-1033.820238	0.00	39%	
<i>cis-3-6b</i> -OMe-7	124.56	-1034.132989	0.365382	0.31497445	-1033.818015	1.39	4%	
<i>cis-3-6b</i> -OMe-8	124.66	-1034.130488	0.365167	0.31475293	-1033.815735	2.83	0%	
<i>cis-3-6b</i> -OMe-9	124.73	-1034.130564	0.365716	0.31586976	-1033.814694	3.48	0%	
<i>cis-3-6b</i> -OMe-10	125.08	-1034.135054	0.365503	0.31510527	-1033.819949	0.18	28%	
<i>cis-3-6b</i> -OMe-11	125.10	-1034.132547	0.365238	0.31450983	-1033.818037	1.38	4%	
<i>cis-3-6b</i> -OMe-12	126.02	-1034.129681	0.365282	0.31479534	-1033.814886	3.36	0%	
<i>cis-3-6b</i> -OMe-13	128.96	-1034.128959	0.365241	0.31414665	-1033.814812	3.40	0%	
<i>cis-3-6b</i> -OMe-14	130.15	-1034.120061	0.365565	0.31567602	-1033.804385	9.95	0%	
<i>cis-3-6b</i> -OMe-15	130.87	-1034.117854	0.365415	0.31554001	-1033.802314	11.25	0%	
<i>cis-3-6b</i> -OMe-16	131.59	-1034.122314	0.365352	0.31546278	-1033.806851	8.40	0%	

Table S3-8. Calculated energies of *trans*-**3-6b**-OMe at M06-3P/6-31G(d) and B3LYP/6-31G(d) levels of theory.

Conformer #	M06-3P/6-31G(d)		B3LYP/6-31G(d), vacuum			Boltzmann distribution	
	[kcal/mol]	e0 [Hartree]	ZPVE [Hartree]	G _{corr} (298K) [Hartree]	G (298K) [Hartree]		ΔG (298K) [kcal/mol]
<i>trans</i> - 3-6b -OMe-1	120.84	-1034.136071	0.365655	0.31554345	-1033.820528	0.66	16%
<i>trans</i> - 3-6b -OMe-2	121.06	-1034.134924	0.365397	0.31516472	-1033.819759	1.14	7%
<i>trans</i> - 3-6b -OMe-3	121.11	-1034.137249	0.365503	0.31567184	-1033.821577	0.00	49%
<i>trans</i> - 3-6b -OMe-4	121.54	-1034.135499	0.365234	0.31471045	-1033.820789	0.49	21%
<i>trans</i> - 3-6b -OMe-5	122.54	-1034.134035	0.365341	0.31498279	-1033.819052	1.58	3%
<i>trans</i> - 3-6b -OMe-6	125.42	-1034.130845	0.365326	0.31475339	-1033.816092	3.44	0%
<i>trans</i> - 3-6b -OMe-7	125.49	-1034.132951	0.365465	0.31423215	-1033.818719	1.79	2%
<i>trans</i> - 3-6b -OMe-8	125.63	-1034.129658	0.365406	0.31554803	-1033.81411	4.69	0%
<i>trans</i> - 3-6b -OMe-9	126.37	-1034.129834	0.365369	0.31464100	-1033.815193	4.01	0%
<i>trans</i> - 3-6b -OMe-10	126.80	-1034.128968	0.365007	0.31369424	-1033.815274	3.96	0%
<i>trans</i> - 3-6b -OMe-11	126.97	-1034.127718	0.3653	0.31478300	-1033.812935	5.42	0%
<i>trans</i> - 3-6b -OMe-12	127.06	-1034.130414	0.365397	0.31443681	-1033.815977	3.51	0%
<i>trans</i> - 3-6b -OMe-13	127.13	-1034.130414	0.365397	0.31443579	-1033.815978	3.51	0%
<i>trans</i> - 3-6b -OMe-14	129.43	-1034.123186	0.365207	0.31525017	-1033.807936	8.56	0%
<i>trans</i> - 3-6b -OMe-15	129.95	-1034.124181	0.365741	0.31549159	-1033.808689	8.09	0%
<i>trans</i> - 3-6b -OMe-16	130.13	-1034.127026	0.365586	0.31403218	-1033.812994	5.39	0%
<i>trans</i> - 3-6b -OMe-17	130.67	-1034.12215	0.365013	0.31482678	-1033.807323	8.94	0%

Table S3-9. Calculated energies and dihedral angles of *cis*-**3-6a**-OMe at B3LYP/6-311+G(2d,p), SCRFF=(PCM, Chloroform)//B3LYP/6-31G(d)

Conformer #	conformation	Dihedral angle						e0	G (298K) [Hartree]	ΔG (298K) [kcal/mol]	Boltzmann distribution
		H5/H4α	H5/H4β	H2/H1α	H2/H1β	[Hartree]	[Hartree]				
<i>cis</i> - 3-6a -OMe-1	DH2	49.6	-64.4	56.5	-56.9	-1953.690691	-1953.397938	3.09	0%		
<i>cis</i> - 3-6a -OMe-2	DH1	-55.7	-170.6	-50.1	-163.9	-1953.691833	-1953.400530	1.47	5%		
<i>cis</i> - 3-6a -OMe-3	C1	52.0	-63.3	-62.4	-176.2	-1953.692846	-1953.401241	1.02	11%		
<i>cis</i> - 3-6a -OMe-4	C1	49.9	-65.5	-60.7	-175.5	-1953.69474	-1953.402869	0.00	60%		
<i>cis</i> - 3-6a -OMe-5	C1	54.0	-60.7	-61.1	-174.8	-1953.693296	-1953.401702	0.73	17%		
<i>cis</i> - 3-6a -OMe-6	C2	-73.8	169.3	58.1	-55.9	-1953.687653	-1953.395088	4.88	0%		
<i>cis</i> - 3-6a -OMe-7	DH1	-60.8	-176.4	-51.2	-165.2	-1953.688728	-1953.396801	3.81	0%		
<i>cis</i> - 3-6a -OMe-8	C1	54.1	-60.9	-62.7	-176.6	-1953.692389	-1953.400360	1.57	4%		
<i>cis</i> - 3-6a -OMe-9	DH2	50.5	-63.6	52.2	-61.1	-1953.687473	-1953.395634	4.54	0%		
<i>cis</i> - 3-6a -OMe-10	DH1	-53.6	-168.6	-48.5	-161.7	-1953.689943	-1953.398802	2.55	1%		
<i>cis</i> - 3-6a -OMe-11	TH1	-71.3	174.3	-74.5	171.7	-1953.689362	-1953.398513	2.73	1%		
<i>cis</i> - 3-6a -OMe-12	C2	-68.3	176.3	54.2	-60.0	-1953.689392	-1953.397428	3.41	0%		
<i>cis</i> - 3-6a -OMe-13	DH1	-58.7	-174.4	-48.7	-162.1	-1953.686794	-1953.395015	4.93	0%		
<i>cis</i> - 3-6a -OMe-14	TH1	-73.5	172.3	-76.1	168.8	-1953.688087	-1953.397279	3.51	0%		
<i>cis</i> - 3-6a -OMe-15	C2	-71.7	171.8	54.2	-59.9	-1953.686805	-1953.394547	5.22	0%		
<i>cis</i> - 3-6a -OMe-16	TH1	-76.4	168.1	-75.2	171.0	-1953.686421	-1953.395241	4.79	0%		
<i>cis</i> - 3-6a -OMe-17	TH1	-77.5	167.1	-76.3	168.6	-1953.685372	-1953.393979	5.58	0%		
<i>cis</i> - 3-6a -OMe-18	DH2	47.1	-67.4	51.1	-62.2	-1953.687569	-1953.396351	4.09	0%		
<i>cis</i> - 3-6a -OMe-19	C2	-68.6	176.0	57.0	-57.1	-1953.687205	-1953.396307	4.12	0%		
<i>cis</i> - 3-6a -OMe-20	B	-2.1	-116.3	40.6	-74.0	-1953.682496	-1953.390907	7.51	0%		

Table S3-9. Calculated energies/dihedral angles of *cis*-**3-6a**-OMe at B3LYP/6-311+G(2,d,p), SCRF=(PCM, Chloroform)/B3LYP/6-31G(d) (cont.)

Conformer #	Conformation	Dihedral angle						e0 [Hartree]	G (298K) [Hartree]	ΔG (298K) [kcal/mol]	Boltzmann distribution
		H5/H4α	H5/H4β	H2/H1α	H2/H1β						
<i>cis</i> - 3-6a -OMe-21	DH2	45.1	-70.0	37.8	-75.8	-1953.68718	-1953.396333	4.10	0%		
<i>cis</i> - 3-6a -OMe-22	DH2	45.1	-70.0	37.8	-75.8	-1953.687181	-1953.396334	4.10	0%		
<i>cis</i> - 3-6a -OMe-23	C1	38.8	-74.7	-59.3	-173.3	-1953.685122	-1953.393984	5.58	0%		
<i>cis</i> - 3-6a -OMe-24	C1	37.7	-75.9	-61.0	-175.1	-1953.684521	-1953.392805	6.32	0%		
<i>cis</i> - 3-6a -OMe-25	C2	-69.4	174.6	55.7	-58.2	-1953.684608	-1953.392568	6.46	0%		
<i>cis</i> - 3-6a -OMe-26	C1	42.6	-72.1	-58.5	-173.4	-1953.685741	-1953.393827	5.67	0%		
<i>cis</i> - 3-6a -OMe-27	C1	44.3	-70.4	-58.9	-172.8	-1953.683791	-1953.392292	6.64	0%		
<i>cis</i> - 3-6a -OMe-28	C1	54.4	-60.8	-64.2	-177.0	-1953.683305	-1953.390660	7.66	0%		
<i>cis</i> - 3-6a -OMe-29	TH1	-71.8	173.6	-73.0	172.5	-1953.679697	-1953.387622	9.57	0%		
<i>cis</i> - 3-6a -OMe-30	TH1	-75.2	169.5	-76.9	168.9	-1953.676873	-1953.385233	11.07	0%		
<i>cis</i> - 3-6a -OMe-31	TH1	-76.9	167.3	-73.2	172.3	-1953.677283	-1953.384686	11.41	0%		

Table S3-10. Calculated energies and dihedral angles of *trans*-3-6a-OMe at B3LYP/6-311+G(2d,p) SCRF=(PCM, Chloroform)//B3LYP/6-31G(d).

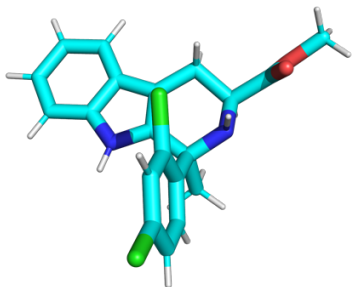
Conformer #	conformation	Dihedral angle						e0	G (298K) [Hartree]	Δ G (298K) [kcal/mol]	Boltzmann distribution
		H5/H4 α	H5/H4 β	H2/H1 α	H2/H1 β	[Hartree]	[Hartree]				
<i>trans</i> -3-6a-OMe-1	TH2	-174.6	71.0	67.8	-46.3	-1953.691825	-1953.399880	1.17	5%		
<i>trans</i> -3-6a-OMe-2	TH2	-174.9	70.7	65.0	-49.0	-1953.689279	-1953.397298	2.79	0%		
<i>trans</i> -3-6a-OMe-3	TH2	-168.9	75.7	68.1	-45.9	-1953.689383	-1953.396569	3.25	0%		
<i>trans</i> -3-6a-OMe-4	C1	177.5	62.1	-62.8	-178.0	-1953.693382	-1953.401745	0.00	40%		
<i>trans</i> -3-6a-OMe-5	C1	179.6	64.1	-64.3	-178.4	-1953.691408	-1953.399806	1.22	5%		
<i>trans</i> -3-6a-OMe-6	C1	-176.2	68.6	-64.4	-178.6	-1953.692149	-1953.401465	0.18	29%		
<i>trans</i> -3-6a-OMe-7	C1	-177.2	66.3	-64.4	-178.4	-1953.689202	-1953.397199	2.85	0%		
<i>trans</i> -3-6a-OMe-8	C1	178.7	62.5	-62.2	-177.2	-1953.691425	-1953.398899	1.79	2%		
<i>trans</i> -3-6a-OMe-9	DH1	67.3	-47.4	-49.9	-163.6	-1953.690364	-1953.398968	1.74	2%		
<i>trans</i> -3-6a-OMe-10	C1	179.9	64.8	-64.9	-179.0	-1953.691216	-1953.400369	0.86	9%		
<i>trans</i> -3-6a-OMe-11	C1	-176.9	67.5	-62.8	-176.6	-1953.68998	-1953.398489	2.04	1%		
<i>trans</i> -3-6a-OMe-12	DH1	68.9	-46.1	-48.5	-161.5	-1953.688311	-1953.397139	2.89	0%		
<i>trans</i> -3-6a-OMe-13	TH1	53.8	-60.5	-71.8	174.8	-1953.689654	-1953.398365	2.12	1%		
<i>trans</i> -3-6a-OMe-14	TH2	-170.8	74.0	64.8	-49.1	-1953.686348	-1953.393837	4.96	0%		
<i>trans</i> -3-6a-OMe-15	C1	-179.4	64.9	-63.9	-177.8	-1953.688946	-1953.397274	2.81	0%		
<i>trans</i> -3-6a-OMe-16	TH1	55.6	-58.9	-66.9	179.3	-1953.689159	-1953.399238	1.57	3%		
<i>trans</i> -3-6a-OMe-17	DH1	68.8	-46.1	-48.5	-161.5	-1953.688311	-1953.397105	2.91	0%		

Table S3-10. Calculated energies/dihedral angles of *trans*-3-6a-OMe at B3LYP/6-311+G(2,d,p) SCRF=(PCM, Chloroform)//B3LYP/6-31G(d) (cont.)

Conformer #	conformation	Dihedral angle					e0 [Hartree]	G (298K) [Hartree]	ΔG (298K) [kcal/mol]	Boltzmann distribution
		H5/H4α	H5/H4β	H2/H1α	H2/H1β					
<i>trans</i> -3-6a-OMe-18	DH2	-167.0	51.9	38.6	-75.2	-1953.688736	-1953.397483	2.67	0%	
<i>trans</i> -3-6a-OMe-19	TH2	-171.6	73.6	65.8	-48.5	-1953.687099	-1953.395250	4.08	0%	
<i>trans</i> -3-6a-OMe-20	TH2	-163.9	79.9	65.8	-48.4	-1953.685051	-1953.392589	5.75	0%	
<i>trans</i> -3-6a-OMe-21	TH2	-169.4	74.8	61.8	-52.2	-1953.683934	-1953.392208	5.98	0%	
<i>trans</i> -3-6a-OMe-22	DH1	63.4	-50.6	-60.0	-174.2	-1953.684311	-1953.391887	6.19	0%	
<i>trans</i> -3-6a-OMe-23	C1	-179.6	65.1	-67.0	180.0	-1953.681903	-1953.390010	7.36	0%	

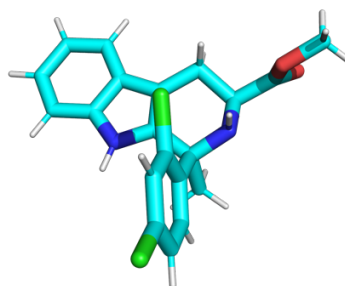
D. Conformation and coordinate of 3-5a,b-OMe and 3-6a,b-OMe

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cis-3-5a-OMe-



1

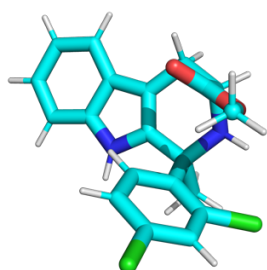
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C	1.28537800	3.47898100	0.69308400
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C	0.64302500	-1.16197400	0.81612000
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2

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cis-3-5a-OMe-

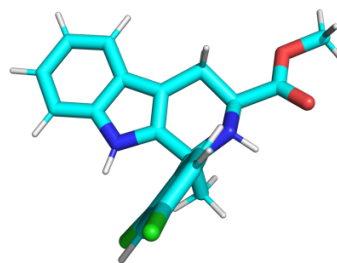


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 H -0.59773200 -0.76232400 0.51758700

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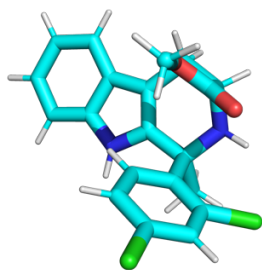


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 N 2.40131900 2.54658400 1.15197600
 C 1.95595200 1.24570200 0.98847800
 C 2.68087900 0.01462300 1.50126800
 N 1.94117300 -1.14381200 0.95389000

C 0.48493800 -1.07305900 0.98805500
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 C -0.05128200 -2.47403300 0.71701700
 O 0.59567200 -3.49272100 0.84394000
 O -1.35173700 -2.45037200 0.37272700
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 H -1.90093700 -4.34241400 1.06874000
 H -1.45719500 -4.26685800 -0.65358800
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 C 6.51695900 0.52574000 0.74923300
 C 6.66105900 -0.30397700 -0.35575200
 C 5.56482300 -0.99461300 -0.86061200
 C 4.33304900 -0.85206300 -0.23116100
 H 3.47125300 -1.38480400 -0.61339400
 H 5.66880800 -1.63418900 -1.73032200
 Cl 8.23610700 -0.46470500 -1.11282200
 H 7.36314700 1.07818300 1.13888600
 Cl 5.25255000 1.79516800 2.71615300
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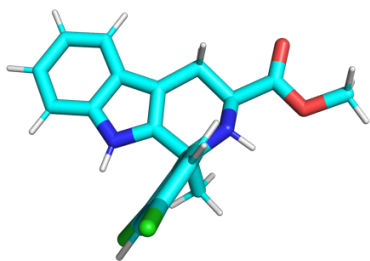


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 C 3.58252900 3.12737100 -0.04749000

C 3.33707500 4.19353500 -0.93619300
 C 2.15676200 4.26489100 -1.66882800
 C 1.22424900 3.23846700 -1.49222400
 N -0.01492100 3.04342500 -2.07244700
 C -0.57327400 1.87340500 -1.57294000
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 N -1.92520900 -0.09454900 -1.54454400
 C -1.48300400 -0.37080600 -0.17051400
 H -1.58302200 -1.45725800 -0.05070000
 C -2.45106900 0.19538100 0.88965000
 O -3.64582100 -0.01276700 0.84887500
 O -1.85208300 0.90328300 1.86683600
 C -2.73294500 1.42351300 2.87949700
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 H -3.44895800 2.12003900 2.43618500
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 H -2.85214900 -0.48594900 -1.68477700
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 H -2.78197100 0.74767400 -3.95390800
 H -1.01130400 0.75827000 -3.90982500
 H -1.92281200 2.28910400 -3.98383200
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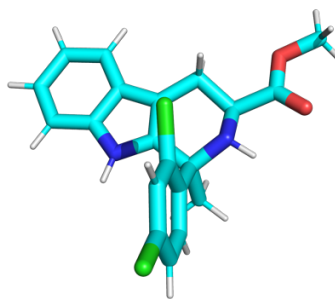


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C	1.18476800	-4.57366000	-0.55289900
C	0.24839900	-5.43508500	0.05494200
C	-0.87096500	-4.93577500	0.71184500
C	-1.03433000	-3.54733100	0.74577900
N	-2.02812200	-2.77831300	1.31772600
C	-1.75607800	-1.43969500	1.08623800
C	-2.62804400	-0.29263400	1.55671000
N	-2.06101400	0.93940500	0.94953500
C	-0.59770800	1.05127000	0.94044300
H	-0.15783900	0.89640700	1.94630700
C	-0.19085200	2.46493800	0.53472200
O	0.73116100	2.74012700	-0.19844600
O	-0.96160600	3.39455200	1.14644700
C	-0.62851700	4.76385400	0.85517400
H	-0.72081300	4.95905800	-0.21611900
H	0.39490300	4.98183600	1.17066900
H	-1.34184800	5.36504800	1.41929600
H	-2.45426000	1.74744900	1.42695800
C	-2.59820000	-0.14889800	3.10247000
H	-3.35271900	0.57385600	3.43468600
H	-1.61071200	0.21855700	3.39966300
H	-2.76845400	-1.08533800	3.63147300
C	-4.07545500	-0.45419400	0.98298900
C	-5.11041200	-1.25548000	1.50006500
C	-6.37524600	-1.33175100	0.91120400
C	-6.63432600	-0.60463400	-0.24385400
C	-5.63887600	0.18113900	-0.81483200
C	-4.39315100	0.23898400	-0.19976000
H	-3.60953100	0.84883100	-0.63176200
H	-5.83124600	0.73927300	-1.72466900
Cl	-8.22473800	-0.69366900	-0.97993000
H	-7.14051500	-1.95824300	1.35270900
Cl	-4.93687100	-2.29771000	2.93116700

H	-2.83008200	-3.13300100	1.81686000
H	-1.59188300	-5.60108200	1.17999100
H	0.40353300	-6.50960600	0.00942600
H	2.04791800	-4.99876400	-1.05788300
H	-0.22315400	0.27326900	-1.03970400
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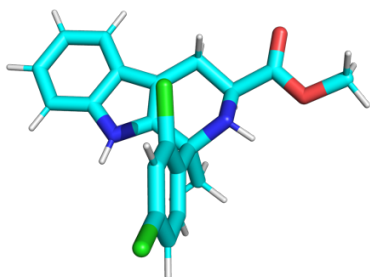


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C	-1.07526200	4.63302300	-0.36928400
C	-0.06181500	5.44975500	0.17111500
C	1.07961400	4.89778900	0.74392700
C	1.18503800	3.50456300	0.76137800
N	2.18078900	2.68755700	1.26693600
C	1.84508700	1.36678000	1.01889700
C	2.67646100	0.18429200	1.46453600
N	2.09443400	-1.00277500	0.81524000
C	0.63885400	-1.11309700	0.85176400
H	0.22301500	-1.01376000	1.87571100
C	0.27608000	-2.53169200	0.42710400
O	1.02334200	-3.48296900	0.51978400
O	-0.99625400	-2.61899600	-0.00308500
C	-1.43837100	-3.94133700	-0.35857200
H	-1.37161300	-4.61138600	0.50255000
H	-0.82686100	-4.34249400	-1.17059200
H	-2.47440600	-3.82574100	-0.67735400
H	2.51690300	-1.85913100	1.16505500
C	2.58704400	0.08484800	3.01296900
H	3.13215400	-0.78893400	3.38745000
H	1.53825800	-0.01958200	3.30257200
H	2.96979300	0.97989300	3.51490300
C	4.14238400	0.31325100	0.97810900
C	4.50632300	0.42590500	-0.38213500
C	5.84020300	0.51882300	-0.78452000
C	6.85100300	0.50660300	0.17130500

C	6.54332000	0.40641200	1.52222300
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H	6.07873300	0.60229500	-1.83791100
Cl	3.33703100	0.48445200	-1.68798200
H	3.08343400	3.00235300	1.58893500
H	1.85975400	5.52891600	1.16208200
H	-0.17336100	6.53018200	0.14132000
H	-1.95444600	5.09741700	-0.80768600
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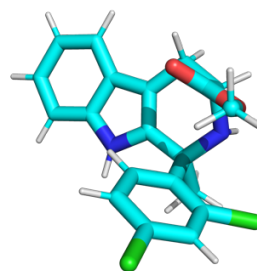


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H	2.17490600	-2.31151400	-0.70131900
C	1.84415600	-4.39135700	-0.24176200
C	0.98103900	-5.35232600	0.32188100
C	-0.23813700	-4.98550700	0.88285500
C	-0.57614600	-3.62975900	0.86420700
N	-1.69628400	-2.97889600	1.35043200
C	-1.58621300	-1.62741500	1.06428800
C	-2.60179900	-0.59106000	1.48506400
N	-2.24849400	0.66571000	0.78928400
C	-0.82385900	1.02670800	0.79250200
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C	-0.65292800	2.43128800	0.22029900
O	0.22087900	2.77334700	-0.54323500
O	-1.58034600	3.28056500	0.72149500
C	-1.48870900	4.63907300	0.25740700
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H	-0.52037500	5.06909700	0.52570500
H	-2.29874600	5.17366800	0.75410900
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C	-2.50806400	-0.42098400	3.02640700

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H	-2.71562600	-1.35145300	3.56519500
C	-4.02889100	-0.98801800	1.03278100
C	-4.38551800	-1.20693400	-0.31651100
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C	-6.66978900	-1.68771700	0.28482900
C	-6.36646800	-1.49024900	1.62604100
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H	-2.53577900	-3.43242700	1.67757200
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H	1.27257600	-6.39909600	0.31996600
H	2.78973900	-4.71281800	-0.66989600
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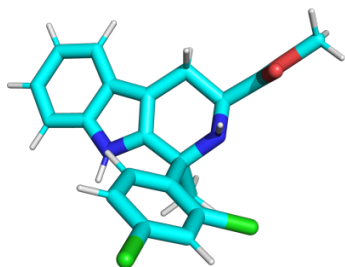


9

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H	-2.89141500	1.03940600	-0.97023900
C	-3.70764500	2.94235600	-0.37184100
C	-3.51433400	4.13128500	0.36023600
C	-2.34477500	4.35320700	1.07978000
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N	-0.13077800	3.28899900	1.66092700
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C	1.82106000	1.61774900	1.86693700
N	2.00024100	0.18091200	1.55372500
C	1.49411000	-0.29663800	0.25675400
H	1.64913500	-1.38268700	0.27368000
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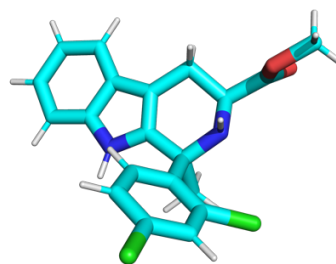


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 C 1.70886200 -5.08979600 0.86442800
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 H 2.15673900 -6.07197700 0.98821400
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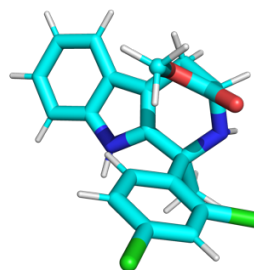


11

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C	3.03880100	-3.65172400	-0.09657500
C	2.52754600	-4.77968100	0.57665000
C	1.26052500	-4.76430100	1.15037800
C	0.51443900	-3.58758900	1.03564400
N	-0.74802100	-3.27660000	1.50506800
C	-1.07757200	-1.98093300	1.12165900
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N	-2.30388200	0.14442400	1.01400700
C	-0.98398600	0.77810400	0.91372900
H	-0.55145700	0.84451100	1.91551100
C	-1.14670600	2.21461400	0.43438300
O	-0.59158100	3.17606700	0.91579800
O	-1.95859700	2.27962100	-0.64611900
C	-2.16985100	3.59625500	-1.18403600
H	-1.22270700	4.03099200	-1.51395100
H	-2.61793600	4.24809900	-0.42991600
H	-2.84694800	3.46287300	-2.02809300
H	-2.73066800	0.15221200	0.09032900
C	-2.31222800	-1.19806200	3.11036200
H	-3.14667800	-0.62279700	3.50693700
H	-1.37974600	-0.74030100	3.45421600
H	-2.35488600	-2.21170700	3.52357900
C	-3.62997100	-1.89120400	1.02228700
C	-4.93261100	-1.41973000	1.29660800
C	-6.07102300	-2.04761600	0.78421300
C	-5.93337200	-3.15886300	-0.03996800
C	-4.67138700	-3.63794600	-0.37030100
C	-3.55314000	-2.99735400	0.15824800
H	-2.57588100	-3.36971900	-0.12371100
H	-4.55902900	-4.49017500	-1.03141000
Cl	-7.36870500	-3.94305500	-0.67538300
H	-7.05305700	-1.65908900	1.02498100
Cl	-5.27164200	0.01214100	2.26617700
H	-1.35382900	-3.90813000	2.00564300
H	0.86933000	-5.63394600	1.67229000
H	3.13435600	-5.67791200	0.65085800
H	4.03334100	-3.69832800	-0.53157000
H	-0.30228900	0.12292000	-1.04990900
H	1.00925900	0.42248400	0.09013900

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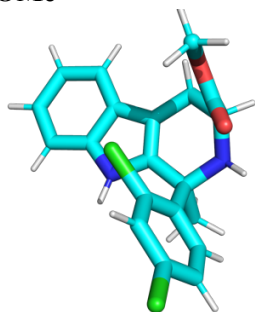


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C	2.68975200	2.05088800	0.00998200
H	2.87594000	1.25755400	0.72944900
C	3.63896600	3.04243500	-0.20690400
C	3.40968400	4.07758000	-1.13575000
C	2.22752000	4.14280200	-1.86599800
C	1.27607200	3.14253000	-1.64523400
N	0.03093600	2.94758000	-2.21272800
C	-0.55054600	1.80868700	-1.66467400
C	-1.88824500	1.22610100	-2.08078800
N	-2.01933000	-0.13838900	-1.52255100
C	-1.49198200	-0.37226900	-0.16881400
H	-1.60955300	-1.44942400	-0.00294200
C	-2.44871600	0.24596600	0.86951400
O	-3.60371400	-0.09026800	0.99389500
O	-1.85349000	1.17107600	1.65302400
C	-2.69923700	1.75423300	2.65881300
H	-3.10080900	0.97964800	3.31719900
H	-3.52882100	2.29083600	2.19170800
H	-2.06016800	2.44096400	3.21465300
H	-1.58345900	-0.80013900	-2.15960800
C	-1.89814200	1.11068300	-3.62602500
H	-2.77712300	0.57003600	-3.97761600
H	-0.99759900	0.58403100	-3.96151500
H	-1.90293700	2.10209000	-4.09032700
C	-3.08848500	2.08844900	-1.59860400
C	-4.44180600	1.74844900	-1.80722900
C	-5.48582200	2.56531800	-1.36882300
C	-5.19753900	3.74935200	-0.69855000
C	-3.88071000	4.11932800	-0.45320100
C	-2.85778800	3.28513900	-0.90154000
H	-1.83622100	3.57429200	-0.68648600
H	-3.65392300	5.03676300	0.07889000
Cl	-6.51581600	4.77465500	-0.15475600
H	-6.51224800	2.26832500	-1.54624700
Cl	-4.96125500	0.27606100	-2.61856900

H -0.38784100 3.54079100 -2.91169400
H 2.05288800 4.94221800 -2.58172200
H 4.16961000 4.83986800 -1.28437300
H 4.57376800 3.02280400 0.34661200
H 0.25106400 0.09212300 1.06218300
H 0.60926700 -0.83012900 -0.38973100

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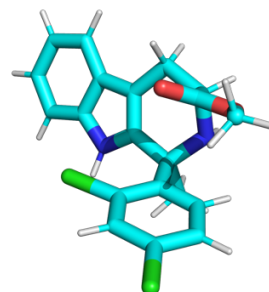


13

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C 2.37297500 -1.85030300 -1.58066500
H 2.76940600 -0.84453600 -1.46629500
C 3.12550200 -2.83750900 -2.20623300
C 2.62355100 -4.14493500 -2.36280400
C 1.36120400 -4.49350800 -1.89286100
C 0.60924800 -3.49916500 -1.26187600
N -0.64739600 -3.55734400 -0.68609000
C -0.99174600 -2.29132500 -0.23712900
C -2.26367800 -1.99126500 0.50751300
N -2.20478900 -0.57589000 0.97937800
C -1.45983700 0.43300800 0.22504600
H -1.44063700 1.32500800 0.87003000
C -2.21376200 0.92100500 -1.02655200
O -3.42138000 0.86310900 -1.13325100
O -1.41248600 1.51444400 -1.93031900
C -2.07973200 2.06572700 -3.08060600
H -2.81252100 2.81653000 -2.77380100
H -2.58740200 1.27438800 -3.63716600
H -1.29300300 2.51802500 -3.68491300
H -3.15630400 -0.24258800 1.11196400
C -2.22272500 -2.85268300 1.80362200
H -2.96837100 -2.52213500 2.53167500
H -1.24138900 -2.72481500 2.26533900
H -2.38137600 -3.91656500 1.59415300
C -3.57332400 -2.28362400 -0.29338700
C -3.75122200 -2.27548800 -1.69241000
C -4.99278600 -2.51322400 -2.29005400
C -6.10744100 -2.75092800 -1.49744400

C -5.99371600 -2.75283000 -0.11187200
C -4.74362700 -2.52556500 0.45302800
H -4.68225500 -2.53697000 1.53432800
H -6.86020800 -2.93287700 0.51474000
Cl -7.66176700 -3.04811300 -2.25624500
H -5.07796400 -2.50164900 -3.36968600
Cl -2.45661600 -1.96547900 -2.84990700
H -1.29898300 -4.31705700 -0.81275300
H 0.97638500 -5.50317900 -2.01185600
H 3.23302200 -4.89553500 -2.85865100
H 4.11697300 -2.60043300 -2.58255500
H 0.46748600 0.66469100 -0.73212900
H 0.54488100 0.13235000 0.94507000

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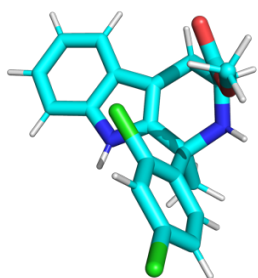


14

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H 2.90683000 -0.51816200 -1.22681100
C 3.98646600 -2.36046600 -0.93189900
C 3.97961200 -3.65514300 -0.37531100
C 2.88654300 -4.12420400 0.34653700
C 1.79380100 -3.26544900 0.49542000
N 0.60490700 -3.44232000 1.18054100
C -0.20096500 -2.32468800 0.97667800
C -1.53112600 -2.07898500 1.65548400
N -1.70662200 -0.60656500 1.81104400
C -1.39740500 0.23189600 0.63312400
H -1.45706500 1.26062500 1.00464700
C -2.51203000 0.12640300 -0.41959800
O -2.39969800 -0.37681000 -1.51546600
O -3.63901300 0.72650900 0.01554800
C -4.74486100 0.69409000 -0.90277800
H -5.06869400 -0.33572800 -1.07258500
H -4.46300900 1.14356300 -1.85839600
H -5.53770600 1.27047700 -0.42488000
H -1.08502700 -0.31054300 2.56165200
C -1.48371600 -2.66443200 3.09059200

H	-2.36714400	-2.35517400	3.65550300
H	-0.58470000	-2.32019600	3.61395200
H	-1.46512900	-3.75836300	3.06726600
C	-2.82399900	-2.63439400	0.98170000
C	-2.95304200	-3.63020000	0.00006500
C	-4.20271500	-4.08224300	-0.44228500
C	-5.35996300	-3.54357800	0.10087900
C	-5.28616900	-2.55066900	1.07521500
C	-4.03284100	-2.11811000	1.48962800
H	-3.96431700	-1.32119900	2.22063100
H	-6.18893100	-2.12478700	1.49955700
Cl	-6.92464500	-4.11805800	-0.45286000
H	-4.25536200	-4.84696400	-1.20739900
Cl	-1.58858900	-4.41901000	-0.78838700
H	0.24752600	-4.35033500	1.43636400
H	2.88565200	-5.12087400	0.78055100
H	4.84414300	-4.29931500	-0.51099300
H	4.85829800	-2.02536400	-1.48723500
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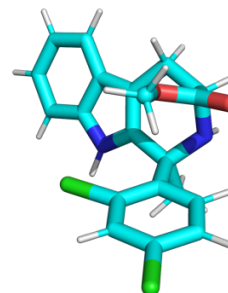


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C	2.40040600	-1.96901000	-1.37618300
H	2.77323000	-0.94799300	-1.38197800
C	3.17091200	-3.00417000	-1.89249700
C	2.69751900	-4.33147700	-1.89619500
C	1.44598200	-4.65192200	-1.37965400
C	0.67600500	-3.60889100	-0.85845600
N	-0.57664200	-3.62791600	-0.27042400
C	-0.94326400	-2.32668400	0.03873800
C	-2.21106700	-1.97130800	0.76557500
N	-2.20872600	-0.50365700	1.01751700
C	-1.46845200	0.42821100	0.16527500
H	-1.47635600	1.38369900	0.71207700
C	-2.10687100	0.80103700	-1.18772600
O	-1.50691000	1.23580700	-2.14535200

O	-3.45491800	0.70240600	-1.13359900
C	-4.15155800	1.13836000	-2.31385000
H	-3.86075800	0.52755400	-3.17157500
H	-3.92329500	2.18616100	-2.52627300
H	-5.21161300	1.01143700	-2.09235000
H	-3.16363900	-0.18124100	1.13704000
C	-2.10301400	-2.62721800	2.17403300
H	-2.84929400	-2.22486300	2.86491900
H	-1.12035900	-2.38349700	2.58279100
H	-2.20901500	-3.71721300	2.13110500
C	-3.51933400	-2.43568300	0.05006600
C	-3.73161400	-2.56799100	-1.33886800
C	-4.96568700	-2.95285400	-1.87347600
C	-6.03917800	-3.19962900	-1.02738700
C	-5.89074500	-3.06728600	0.34861800
C	-4.64774700	-2.69698300	0.85207500
H	-4.55800900	-2.61033400	1.92767300
H	-6.72445500	-3.25594500	1.01594200
Cl	-7.58464100	-3.67771600	-1.70715800
H	-5.07662000	-3.05266800	-2.94646700
Cl	-2.49286900	-2.26001700	-2.55221500
H	-1.21163600	-4.41119800	-0.30044400
H	1.08300500	-5.67661400	-1.38095300
H	3.32073700	-5.11993200	-2.30930800
H	4.15401600	-2.78957600	-2.30265200
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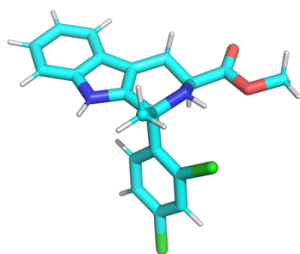


16

C	0.00000000	0.00000000	0.00000000
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H	2.86207100	-0.59506200	-1.28549900
C	3.84310300	-2.50643800	-1.11188300
C	3.76640200	-3.83311300	-0.64235200
C	2.64661600	-4.29191100	0.04409000
C	1.59878500	-3.38917700	0.24750400
N	0.39912300	-3.54802800	0.91604100

C -0.34963300 -2.38112300 0.78701800
 C -1.66085900 -2.10604400 1.49784800
 N -1.74869400 -0.63982000 1.74407300
 C -1.39758800 0.25874700 0.62278100
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 O -3.56036500 0.95189300 -0.22726400
 O -2.30859400 -0.43650800 -1.49226900
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 H -2.49960100 -2.45592500 3.48140200
 H -0.71683400 -2.51904200 3.43071000
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 C -2.99668300 -2.54817300 0.81854800
 C -3.21151900 -3.56230300 -0.12915400
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 C -5.60051400 -3.25097900 -0.06357500
 C -5.44269400 -2.23604600 0.87588700
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 H 4.59778500 -4.51045700 -0.81775300
 H 4.73485300 -2.18044100 -1.64033800
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 H 0.73775900 0.63214900 0.51714300

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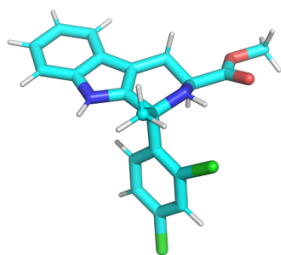


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 C 0.30224600 -2.01815300 1.47252600
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 C 2.01047300 1.51926000 -0.12643500
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 C 3.79177500 3.04987100 0.11272500
 H 3.14303800 3.84819300 0.48200300
 H 3.92096200 3.16568400 -0.96639000
 H 4.75598400 3.07074200 0.62087700
 O 1.42323700 2.30699200 -0.83360500
 H 2.79220200 0.08663000 1.82095100
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 H 0.92531800 -1.20975800 3.91477900
 H 2.68504800 -1.41703100 3.88947500
 H 1.64528300 -2.83723800 3.79114800
 C 2.77714000 -2.56063900 1.26505900
 C 4.16658800 -2.42792200 1.45957900
 C 5.10151800 -3.25359000 0.83428900
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 H -0.08150000 -3.81626400 2.56300800
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 H -4.87611900 -2.45387500 -0.70221400
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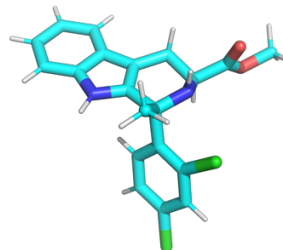


2

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C	-2.68089700	-2.02852800	-0.45879800
H	-2.88047700	-1.09648700	-0.98140400
C	-3.61835200	-3.05423000	-0.46380500
C	-3.37314000	-4.26740300	0.21076000
C	-2.18526100	-4.48055500	0.90249400
C	-1.24523100	-3.44594000	0.90527200
N	0.00440700	-3.37152800	1.49266700
C	0.56336200	-2.13042500	1.21973100
C	1.90692500	-1.65695400	1.73727000
N	1.87724500	-0.19584600	1.56224800
C	1.50326800	0.25669500	0.22619300
H	2.05527600	-0.27926000	-0.57201400
C	1.90445500	1.71859200	0.08580800
O	1.31678200	2.29205200	-0.98244800
C	1.68103400	3.66237300	-1.22536100
H	2.75738900	3.74780400	-1.39587400
H	1.40478600	4.28833600	-0.37303700
H	1.12563800	3.95785000	-2.11570700
O	2.68689100	2.29187000	0.81342400
H	2.74539200	0.24453500	1.85222700
C	1.98389900	-1.96085900	3.25235000
H	1.10522200	-1.53534900	3.74399100
H	2.87691900	-1.52713700	3.70389700
H	2.01214200	-3.04095500	3.43801000
C	3.08720800	-2.34240400	0.96970800
C	4.44992400	-2.05329600	1.18266200
C	5.47540300	-2.68159000	0.47487200
C	5.15372400	-3.62889900	-0.49161000
C	3.82539900	-3.93930600	-0.75758400
C	2.82604600	-3.29498400	-0.03086700
H	1.79549300	-3.54282500	-0.25486100
H	3.57140000	-4.66747200	-1.52008300
Cl	6.44137400	-4.42211800	-1.38197900
H	6.50863600	-2.42560800	0.67590400
Cl	5.00294600	-0.83870600	2.34668600

H	0.41590400	-4.08167900	2.07760100
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H	-4.12493400	-5.05158000	0.18999200
H	-4.55699400	-2.92225600	-0.99501400
H	-0.58697300	0.72873300	0.57611600
H	-0.24844700	0.15186700	-1.05624600

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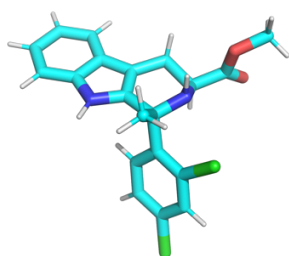


3

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C	-1.50032100	-2.18128500	0.27982400
C	-2.70029800	-1.99641400	-0.42760600
H	-2.87973700	-1.07617300	-0.97768400
C	-3.65424200	-3.00673200	-0.41405300
C	-3.43496000	-4.20491200	0.29529300
C	-2.25781800	-4.41765800	1.00513000
C	-1.30104500	-3.39849400	0.98918700
N	-0.05867500	-3.32488900	1.59132400
C	0.52776800	-2.10236800	1.28729000
C	1.87166400	-1.62110000	1.80467700
N	1.98071300	-0.16964600	1.57568300
C	1.50220300	0.30125700	0.27862500
H	2.10434300	-0.17489800	-0.50164200
C	1.72132300	1.80537400	0.22338700
O	2.00679300	2.21927200	-1.02655500
C	2.15490000	3.64173300	-1.18632200
H	2.97652800	4.01094200	-0.56737700
H	1.23432300	4.15772000	-0.90098900
H	2.37085900	3.79558500	-2.24373900
O	1.59531700	2.54833800	1.17329100
H	1.51782700	0.35356200	2.31614600
C	1.93098900	-1.87797200	3.32958400
H	1.04287400	-1.45169700	3.80901100
H	2.81979900	-1.42688300	3.77097600
H	1.95308400	-2.95126500	3.54581100
C	3.05821400	-2.31915700	1.08033100
C	4.41643200	-2.01026600	1.30522800
C	5.44716200	-2.66474400	0.62683200
C	5.13984200	-3.64872500	-0.30695800

C 3.81705100 -3.97971800 -0.57334500
 C 2.80876100 -3.31113800 0.11822400
 H 1.78089600 -3.56713600 -0.10960900
 H 3.57420000 -4.73772400 -1.30982600
 Cl 6.44146500 -4.46685700 -1.15526200
 H 6.47783300 -2.39943900 0.82867100
 Cl 4.96048700 -0.77892400 2.44205600
 H 0.34805000 -4.03845800 2.17547000
 H -2.09078600 -5.34216100 1.55206600
 H -4.19884900 -4.97753100 0.28768900
 H -4.58551100 -2.87435900 -0.95790100
 H -0.62604000 0.74471100 0.51438300
 H -0.20182300 0.11038500 -1.07349000

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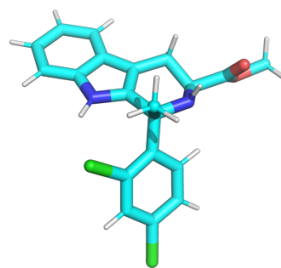


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 H -2.85847500 -1.26648600 -0.79926500
 C -3.57288100 -3.13233600 0.00870900
 C -3.31398000 -4.22597300 0.85953700
 C -2.12638500 -4.31563900 1.57797100
 C -1.19984000 -3.27987100 1.42542600
 N 0.04456800 -3.09782000 1.99967700
 C 0.59359300 -1.90695200 1.53937200
 C 1.92174500 -1.32199500 1.98802200
 N 1.97647900 0.09635000 1.57917600
 C 1.49668000 0.35644700 0.21768600
 H 2.10159500 -0.24345300 -0.46830700
 C 1.74915700 1.80902100 -0.16079000
 O 1.39528100 2.64603700 0.84154600
 C 1.58056600 4.04588300 0.57101900
 H 0.97691200 4.35321400 -0.28697000
 H 2.63203000 4.25704100 0.36055000
 H 1.25790100 4.56444700 1.47421700
 O 2.16065900 2.18449000 -1.23516700
 H 1.44586200 0.66334200 2.23757300
 C 1.98659400 -1.38498300 3.53321500

H 1.08631900 -0.92869400 3.95989000
 H 2.86236700 -0.85866000 3.91288600
 H 2.03776600 -2.42269900 3.87901300
 C 3.13440000 -2.06193600 1.35926100
 C 4.47950400 -1.67681900 1.54131000
 C 5.53646200 -2.37912200 0.95816900
 C 5.26950600 -3.49123300 0.16656000
 C 3.96069100 -3.90225900 -0.05388400
 C 2.92532900 -3.18300200 0.53960900
 H 1.90848400 -3.50464000 0.34741700
 H 3.74910500 -4.76098000 -0.68138200
 Cl 6.60391700 -4.37058300 -0.55979200
 H 6.55586100 -2.05157300 1.12217500
 Cl 4.97443300 -0.28553000 2.50336300
 H 0.47572300 -3.72262500 2.66265800
 H -1.92858100 -5.16007600 2.23336300
 H -4.05504900 -5.01469500 0.95592200
 H -4.51096900 -3.09544000 -0.53822900
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 H -0.21382500 -0.03571100 -1.07633900

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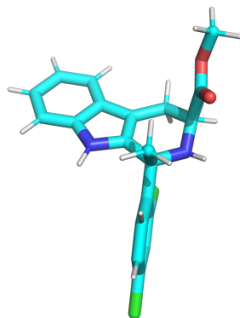


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 H -2.12866200 -2.03880900 -1.26929300
 C -1.79794400 -4.16685200 -1.34188900
 C -0.93730400 -5.23937500 -1.02811300
 C 0.28039300 -5.02498700 -0.39242700
 C 0.61987500 -3.70542800 -0.07499000
 N 1.74224800 -3.19654200 0.54316700
 C 1.63572100 -1.81729600 0.63818000
 C 2.65037800 -0.88914100 1.29665200
 N 2.16662200 0.50353500 1.19057400
 C 1.26630300 0.88480400 0.10604800
 H 1.79783200 0.82477200 -0.84974500
 C 0.85359700 2.32914500 0.34970900
 O 0.56249400 2.95991200 -0.80315600

C	0.07224200	4.30652500	-0.66523600
H	0.81921400	4.93568000	-0.17470200
H	-0.84817600	4.32021400	-0.07580700
H	-0.11586000	4.65330900	-1.68137100
O	0.74275000	2.83340000	1.44770200
H	1.77508300	0.82611600	2.07032500
C	2.75299000	-1.16352500	2.81749200
H	1.75696100	-1.07534800	3.26447300
H	3.41728700	-0.42337600	3.27722000
H	3.13666800	-2.15682800	3.04264500
C	4.06814200	-0.98025300	0.61857900
C	4.98056100	-2.05216900	0.66383200
C	6.21155100	-2.03379000	0.00249700
C	6.57578600	-0.91230000	-0.73131300
C	5.72975600	0.18917500	-0.78625300
C	4.51378700	0.13489000	-0.11350600
H	3.87919700	1.01047100	-0.11223200
H	6.01624000	1.07843200	-1.33705300
Cl	8.11833000	-0.89032700	-1.56700200
H	6.87605800	-2.88612100	0.07272200
Cl	4.72967100	-3.54857800	1.60023400
H	2.52252700	-3.74249500	0.87378300
H	0.94331400	-5.85234400	-0.15271900
H	-1.23073900	-6.25264100	-1.28876700
H	-2.74201400	-4.37156000	-1.83947900
H	-0.69568200	0.25821400	0.81293200
H	-0.52131500	0.20876100	-0.94279900

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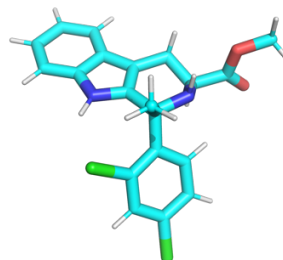


6

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C	-1.19974300	3.11127900	-0.67744200
H	-1.83703800	2.68032900	0.09066100
C	-1.42615900	4.40310500	-1.13773100
C	-0.60544000	4.97610800	-2.12974300
C	0.45659300	4.26853900	-2.68395100
C	0.67992300	2.96960400	-2.21972800
N	1.63664400	2.03994100	-2.58391100

C	1.46347800	0.89469800	-1.82364200
C	2.28734500	-0.35564100	-1.99917600
N	1.90723500	-1.31428400	-0.93274100
C	0.53354900	-1.38165700	-0.43543700
H	0.57594100	-2.00815200	0.46909200
C	-0.42135100	-2.17016000	-1.35537600
O	-1.71260800	-2.03019300	-0.99350500
C	-2.65521600	-2.82946600	-1.73044200
H	-2.42161100	-3.89191200	-1.62344000
H	-2.63348700	-2.56481300	-2.79063600
H	-3.63023900	-2.60326700	-1.29838400
O	-0.05728500	-2.91866100	-2.23932500
H	2.20916000	-2.24384100	-1.21193400
C	1.99328400	-0.90874900	-3.42062900
H	0.92315700	-1.08094300	-3.52495600
H	2.49775400	-1.86579800	-3.59045100
H	2.30094200	-0.20602500	-4.20276300
C	3.80300500	-0.06156500	-1.81126000
C	4.35394400	0.47763400	-0.62872700
C	5.72280300	0.71033100	-0.48541300
C	6.58545700	0.40516000	-1.53339500
C	6.09357700	-0.12687800	-2.71825700
C	4.72171800	-0.34861800	-2.83361000
H	4.36445500	-0.77108300	-3.76397300
H	6.76348600	-0.36867500	-3.53601900
Cl	8.30620100	0.70004800	-1.34656700
H	6.10383100	1.12739200	0.43887400
Cl	3.38271200	0.92154100	0.76453100
H	2.41178100	2.21220700	-3.20543500
H	1.08813100	4.71158500	-3.44986500
H	-0.80525300	5.98873600	-2.46936100
H	-2.24726300	4.98421100	-0.72674600
H	-1.08380100	-0.05821600	0.13056400
H	0.42795800	0.23672500	0.98344400

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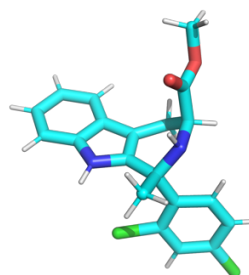


7

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C -1.93758100 -2.64725100 -0.73082100
 H -2.41984700 -1.76015000 -1.13388900
 C -2.51878400 -3.89866000 -0.89011000
 C -1.90380400 -5.05792400 -0.37265500
 C -0.69705600 -4.98917200 0.31401900
 C -0.11550000 -3.72651500 0.47292500
 N 1.05400100 -3.35490900 1.10097500
 C 1.22804400 -1.98311700 0.99006900
 C 2.35893300 -1.16790200 1.61690900
 N 2.06123300 0.27154600 1.41395500
 C 1.38594400 0.65206700 0.16102400
 H 2.01368800 0.33933100 -0.67695100
 C 1.33202300 2.17296400 0.09917600
 O 0.69004800 2.67940200 1.17765400
 C 0.60195500 4.11430600 1.22934600
 H 0.05992500 4.49463100 0.35988800
 H 1.60106300 4.55716100 1.24822400
 H 0.06256700 4.34199100 2.14900200
 O 1.79071400 2.85418900 -0.78996900
 H 1.49817400 0.60444600 2.19251800
 C 2.39456700 -1.35424300 3.15356400
 H 1.40612800 -1.13076500 3.57072600
 H 3.12865000 -0.66567600 3.58503500
 H 2.65915000 -2.36974900 3.44509500
 C 3.77290500 -1.47137800 1.00609500
 C 4.50212700 -2.67345200 1.09377200
 C 5.75177800 -2.85281700 0.49538300
 C 6.32958800 -1.80360100 -0.20775000
 C 5.67863700 -0.57861300 -0.28853800
 C 4.43480600 -0.43688800 0.31821900
 H 3.95810500 0.53300400 0.29200500
 H 6.13353300 0.25623100 -0.81022200
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 H -2.38191700 -6.02347500 -0.51361100
 H -3.46209400 -3.99024400 -1.42162200
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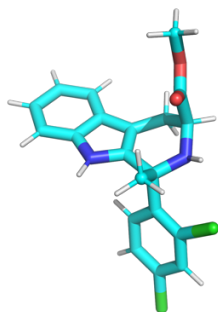


8

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 C -2.36471600 -2.44755300 -0.60193300
 H -2.44768300 -1.74140800 -1.42460300
 C -3.21327600 -3.54516600 -0.52798500
 C -3.11104100 -4.47494100 0.52674500
 C -2.16352700 -4.32071200 1.53325000
 C -1.31543800 -3.21199200 1.46050100
 N -0.31448000 -2.79584800 2.32081000
 C 0.28095600 -1.66028500 1.79882200
 C 1.31443200 -0.76292200 2.45133100
 N 0.80604000 0.63488500 2.36401800
 C 0.18637000 1.09482200 1.11004600
 H 0.79317700 1.89697000 0.66740300
 C -1.16158900 1.73057700 1.45974200
 O -1.68924100 2.37451000 0.40374300
 C -2.96629100 2.99831000 0.63143800
 H -2.88859700 3.74821300 1.42271800
 H -3.70996900 2.25066400 0.91827800
 H -3.23499000 3.46498200 -0.31634200
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 H 0.09862000 0.74262900 3.09025100
 C 1.48896500 -1.06666500 3.95358600
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 H 2.13145400 -0.30572400 4.40495900
 H 1.95201000 -2.04444500 4.11175700
 C 2.70698100 -0.82728100 1.76759100
 C 3.40835800 -2.00623500 1.46175800
 C 4.67225500 -1.99644000 0.86918700
 C 5.27640200 -0.77755500 0.58059100
 C 4.63868800 0.41853100 0.89268600
 C 3.37723500 0.37334400 1.48055700
 H 2.87859700 1.29617600 1.75191600
 H 5.11838900 1.36861400 0.68385000
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 H 5.17348100 -2.93019400 0.64492500
 Cl 2.77321400 -3.61290200 1.83146500

H	0.07562500	-3.36126100	3.05867800
H	-2.08927100	-5.03575400	2.34872200
H	-3.78469000	-5.32699300	0.55520600
H	-3.96669500	-3.69472200	-1.29670000
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H	0.94721300	-0.07937700	-0.54849800

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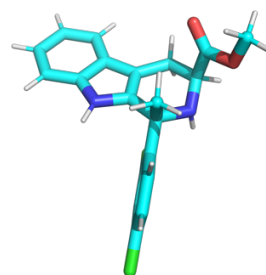


9

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C	1.84913900	2.81131800	0.63601800
H	2.19586600	2.41314300	-0.31418800
C	2.43762600	3.94475900	1.18300300
C	1.99604900	4.47271100	2.41347500
C	0.95728100	3.87851600	3.12203600
C	0.36726200	2.73850600	2.56809900
N	-0.66415500	1.94632400	3.03711200
C	-0.89140300	0.91348600	2.13861900
C	-1.94241500	-0.15668300	2.31485500
N	-1.67223200	-1.24319100	1.33073900
C	-0.39509500	-1.34510100	0.63793700
H	-0.53668600	-2.08041700	-0.16791400
C	0.73387700	-1.92644900	1.51280200
O	1.91499900	-1.93398500	0.86027300
C	3.01645500	-2.52018900	1.57613300
H	2.80265400	-3.56434400	1.81906900
H	3.20569600	-1.97019600	2.50145700
H	3.87279900	-2.44849500	0.90512300
O	0.58396800	-2.39385100	2.62228500
H	-1.90631000	-2.13569200	1.75052700
C	-1.89300700	-0.65744700	3.78391100
H	-0.88390000	-0.99822000	4.02261500
H	-2.58329800	-1.48804300	3.94134600
H	-2.18581200	0.13877400	4.47949800
C	-3.36707900	0.40161300	1.99675500
C	-4.53418600	-0.38659800	1.97490800
C	-5.79417500	0.14079200	1.69046600
C	-5.91678300	1.49772800	1.40996700

C	-4.79619100	2.31864300	1.40532300
C	-3.55246600	1.76035200	1.69612700
H	-2.68851300	2.41355600	1.67607200
H	-4.88663600	3.37462500	1.17537600
Cl	-7.50220800	2.16361200	1.05254200
H	-6.66351800	-0.50547600	1.68426200
Cl	-4.52696200	-2.12962500	2.28312700
H	-1.13602800	2.06753700	3.91938100
H	0.61906600	4.28649300	4.07116400
H	2.47565000	5.36046200	2.81645600
H	3.25119600	4.43573900	0.65605700
H	0.98870200	-0.08518700	-0.45818200
H	-0.71678000	0.22768800	-0.80002600

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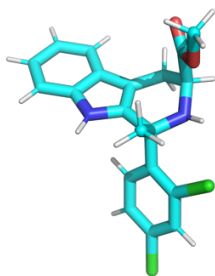


10

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C	1.26247400	-3.02560800	-0.86554600
H	1.93214900	-2.58903200	-0.12894300
C	1.52016900	-4.28567900	-1.39249500
C	0.66172900	-4.86384900	-2.34894200
C	-0.46964100	-4.19201600	-2.80096300
C	-0.72348300	-2.92428800	-2.27078900
N	-1.74734900	-2.03207200	-2.53216400
C	-1.58530900	-0.91317100	-1.72900300
C	-2.45694400	0.32333300	-1.79151100
N	-2.14204000	1.24123900	-0.66166500
C	-0.72860300	1.34403800	-0.24691800
H	-0.76262500	1.90383000	0.69648300
C	0.07179300	2.25597700	-1.19150400
O	-0.52049000	3.45938800	-1.32428300
C	0.17911700	4.39790300	-2.15632900
H	0.26027500	4.02019900	-3.17947600
H	1.18445700	4.58357400	-1.76862700
H	-0.41731900	5.31042900	-2.13184200
O	1.12678700	1.97095100	-1.71781700
H	-2.67241800	0.95011800	0.15351700
C	-2.12460900	1.05883500	-3.11403400

H -1.04558800 1.21200000 -3.17708200
H -2.61864900 2.03336100 -3.15359100
H -2.40931300 0.46103200 -3.98593800
C -3.96127800 -0.03359200 -1.70200800
C -4.52630500 -0.80613100 -0.66551800
C -5.88567200 -1.11836900 -0.61549500
C -6.72891200 -0.65248200 -1.61853900
C -6.22587000 0.12143100 -2.65808700
C -4.86427800 0.41526500 -2.68004400
H -4.49826500 1.02405300 -3.49645600
H -6.88292500 0.49196600 -3.43711900
Cl -8.43676500 -1.04645800 -1.55931700
H -6.27344000 -1.71671200 0.19995900
Cl -3.57080700 -1.43711400 0.67673700
H -2.55531000 -2.22349700 -3.10433900
H -1.12952600 -4.63787400 -3.54105800
H 0.88783600 -5.85098400 -2.74293500
H 2.39726000 -4.83665200 -1.06385700
H 1.08137300 0.16139800 -0.06160800
H -0.21417900 -0.32895800 1.02781800

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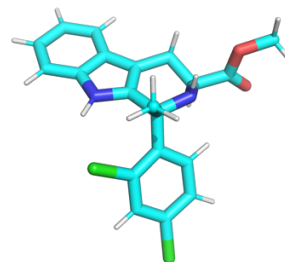


11

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C 0.77826800 -2.10166300 -1.45603100
C 1.87545700 -2.71911600 -0.83248600
H 2.25680700 -2.34011800 0.11202000
C 2.46487900 -3.82000200 -1.44130000
C 1.98074000 -4.31953300 -2.66753900
C 0.89954600 -3.72753000 -3.31158500
C 0.30990300 -2.61959400 -2.69542400
N -0.75494100 -1.83354300 -3.09479400
C -0.97584000 -0.84556800 -2.14268900
C -2.04511100 0.21443900 -2.25703700
N -1.83867500 1.18521300 -1.15213700
C -0.53868800 1.34618000 -0.50630000
H -0.72276900 1.99627800 0.36245300
C 0.55301100 2.09523500 -1.30140900
O 0.01516100 2.98435400 -2.16945500

C 0.96333800 3.80523900 -2.87351400
H 1.64161900 3.18511000 -3.46499000
H 1.55103400 4.39980000 -2.16913000
H 0.36884000 4.45115900 -3.52025800
O 1.74594600 1.98432200 -1.12274200
H -2.21847900 2.08700900 -1.41413800
C -1.93707900 0.84636200 -3.67490700
H -0.91481300 1.18648600 -3.85365900
H -2.60867900 1.69828600 -3.78808800
H -2.20200200 0.11620800 -4.44918000
C -3.47126800 -0.39004200 -2.05342500
C -4.65913200 0.36649100 -2.05825800
C -5.91908200 -0.20398500 -1.87546200
C -6.02068700 -1.57561600 -1.66790900
C -4.87918600 -2.36663100 -1.63025300
C -3.63650200 -1.76504000 -1.82061000
H -2.75689900 -2.39536100 -1.77361900
H -4.95333200 -3.43371100 -1.45156200
Cl -7.60494800 -2.29754500 -1.44169700
H -6.80435200 0.42013400 -1.88816600
Cl -4.68082400 2.12723800 -2.25900400
H -1.28788400 -1.96243500 -3.94038700
H 0.53001600 -4.11224100 -4.25879100
H 2.46200700 -5.18237200 -3.11977400
H 3.31335400 -4.30621600 -0.96781300
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H -0.61103600 -0.32708800 0.85124500

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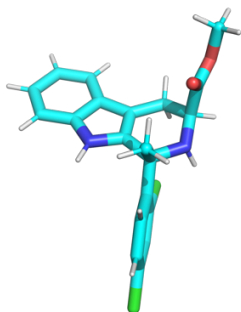


12

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C -1.93640100 -2.64804700 -0.73090900
H -2.41901800 -1.76113700 -1.13397500
C -2.51713300 -3.89968300 -0.89012900
C -1.90168100 -5.05869700 -0.37267300
C -0.69492100 -4.98947000 0.31393200
C -0.11385100 -3.72658000 0.47277500
N 1.05559600 -3.35453400 1.10066500

C 1.22900100 -1.98264000 0.98990100
 C 2.35957600 -1.16693900 1.61669800
 N 2.06142500 0.27237300 1.41352600
 C 1.38570400 0.65264200 0.16074300
 H 2.01337000 0.34023300 -0.67741100
 C 1.33104200 2.17351900 0.09896400
 O 0.68938400 2.67961300 1.17777900
 C 0.60060600 4.11450400 1.22953700
 H 0.05760500 4.49452000 0.36055600
 H 1.59950800 4.55784600 1.24753800
 H 0.06190800 4.34190600 2.14966700
 O 1.78888200 2.85498000 -0.79044000
 H 1.49856100 0.60533600 2.19219800
 C 2.39515100 -1.35306800 3.15337700
 H 1.40659200 -1.12987400 3.57040000
 H 3.12895400 -0.66418100 3.58481900
 H 2.66007200 -2.36843300 3.44509300
 C 3.77364800 -1.47010300 1.00595900
 C 4.50328300 -2.67191500 1.09396800
 C 5.75294600 -2.85103200 0.49553400
 C 6.33034000 -1.80183900 -0.20798100
 C 5.67897000 -0.57711200 -0.28913300
 C 4.43513200 -0.43562400 0.31769500
 H 3.95811700 0.53410300 0.29120300
 H 6.13351200 0.25771800 -0.81114300
 Cl 7.89565000 -2.02855100 -0.96619200
 H 6.26820900 -3.79860500 0.59328800
 Cl 3.98622800 -4.09694300 2.03001700
 H 1.71893800 -3.98865100 1.51650200
 H -0.22173000 -5.88354500 0.71163900
 H -2.37942700 -6.02443600 -0.51359300
 H -3.46044300 -3.99163900 -1.42157600
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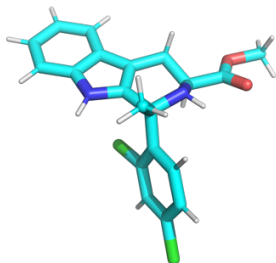


13

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 C -0.05132600 2.41853100 -1.11099800

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 H -1.73457100 2.72107900 0.22284600
 C -1.29030500 4.47795500 -0.94418100
 C -0.46314400 5.06684200 -1.92153000
 C 0.57630400 4.35417800 -2.51091300
 C 0.76974200 3.03302100 -2.09822400
 N 1.70074900 2.09433200 -2.50093200
 C 1.50545700 0.92268000 -1.78535300
 C 2.28956500 -0.34976000 -2.02064400
 N 1.82039100 -1.43264900 -1.10736600
 C 0.47703700 -1.39177500 -0.51637800
 H 0.52119000 -2.06305000 0.34877200
 C -0.58899500 -2.02402800 -1.42233900
 O -1.70327900 -2.27133500 -0.69101000
 C -2.79898100 -2.85533400 -1.41379600
 H -2.51135700 -3.82487400 -1.82914700
 H -3.11457000 -2.19959200 -2.22960200
 H -3.60078100 -2.97340900 -0.68424800
 O -0.50463900 -2.29511300 -2.59823900
 H 2.48522800 -1.54624100 -0.35250600
 C 2.03420600 -0.80265400 -3.47921100
 H 0.96637600 -0.96674500 -3.60990800
 H 2.53440100 -1.75484600 -3.67661300
 H 2.36829800 -0.05347200 -4.20605100
 C 3.80453500 -0.11249200 -1.76276700
 C 4.34333400 0.35454400 -0.54491400
 C 5.70913700 0.57495800 -0.35981900
 C 6.58844000 0.32860300 -1.40844500
 C 6.11328400 -0.13952000 -2.62770700
 C 4.74471400 -0.35089900 -2.78009300
 H 4.40189000 -0.72267100 -3.73634000
 H 6.79650500 -0.34054200 -3.44546500
 Cl 8.30451500 0.60981900 -1.17872300
 H 6.07354000 0.93570000 0.59433400
 Cl 3.34798000 0.69210000 0.87150100
 H 2.45445000 2.26074400 -3.14945600
 H 1.21281500 4.80984100 -3.26525200
 H -0.64006900 6.09611000 -2.22158700
 H -2.09293800 5.06376600 -0.50437000
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 H 0.42923100 0.16509500 0.99845300

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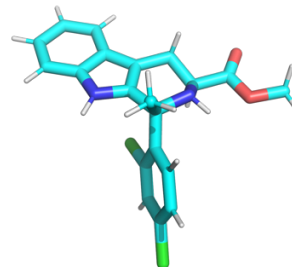


14

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C	-2.55795200	-2.15127000	-0.60409300
H	-2.84718400	-1.18038100	-0.99843700
C	-3.40735000	-3.24393800	-0.72922600
C	-3.04492800	-4.50897300	-0.22398200
C	-1.82776500	-4.70594200	0.41994700
C	-0.97692100	-3.60421700	0.54529400
N	0.26486800	-3.49645400	1.14299200
C	0.73523700	-2.20415300	0.97112500
C	2.03391300	-1.69183200	1.54510000
N	1.95819600	-0.22092600	1.44401700
C	1.50193700	0.30018000	0.15775000
H	2.02782900	-0.16355800	-0.70037800
C	1.86213900	1.77821400	0.09699800
O	1.15983900	2.42597800	-0.85052500
C	1.48537400	3.81721000	-1.01959900
H	2.53649200	3.93299600	-1.29631400
H	1.29718400	4.36855400	-0.09490900
H	0.83524300	4.17291600	-1.81904800
O	2.71452800	2.30346200	0.78305900
H	2.84439400	0.21359400	1.69098700
C	2.03011300	-2.02873700	3.05951600
H	1.06763300	-1.72837300	3.47871500
H	2.80873200	-1.48424200	3.60080900
H	2.18009800	-3.09965600	3.23562500
C	3.34321000	-2.22980100	0.87185100
C	3.49916200	-2.85100600	-0.38323000
C	4.75466500	-3.22169800	-0.88352200
C	5.89818800	-2.96465500	-0.14205500
C	5.80411300	-2.33457400	1.09590000
C	4.54570900	-1.98525400	1.56823700
H	4.49962000	-1.49028500	2.53167500
H	6.69403100	-2.12217400	1.67803200
Cl	7.46578800	-3.43244200	-0.77581200
H	4.82301800	-3.70379300	-1.85106900
Cl	2.16516100	-3.23916700	-1.47193900

H	0.82124300	-4.27806000	1.45325000
H	-1.55041500	-5.68161300	0.81098100
H	-3.72829100	-5.34597300	-0.33852700
H	-4.36690700	-3.12507000	-1.22516400
H	-0.57495300	0.64990700	0.67417500
H	-0.32030600	0.23193100	-1.02175400

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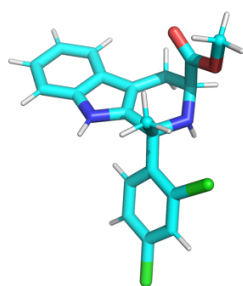


15

C	0.00000000	0.00000000	0.00000000
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C	-2.59824500	-2.15202100	-0.43075300
H	-2.89550800	-1.19450800	-0.85076000
C	-3.45540800	-3.24431200	-0.48941200
C	-3.08302500	-4.49156800	0.05129700
C	-1.84709700	-4.67144400	0.66395100
C	-0.98838100	-3.57042200	0.72192000
N	0.27509500	-3.44850200	1.27030500
C	0.73863200	-2.16200700	1.04528600
C	2.05488300	-1.64274800	1.56131100
N	2.08456600	-0.18469500	1.28466600
C	1.51109500	0.27242600	0.01150800
H	1.96315300	-0.23524000	-0.86053700
C	1.80675800	1.75592100	-0.18284100
O	3.08304500	2.05291500	0.15861400
C	3.46793100	3.42637100	-0.02620000
H	2.83902800	4.08368800	0.57958100
H	3.37217500	3.71093300	-1.07710000
H	4.50816700	3.48503000	0.29504600
O	1.03097200	2.56944300	-0.63059400
H	3.03810000	0.15571700	1.37129900
C	2.01228900	-1.76687400	3.10917200
H	1.05503300	-1.37112200	3.45359600
H	2.79820800	-1.17297900	3.58508600
H	2.10923300	-2.80627500	3.44239000
C	3.31714000	-2.35893300	0.97847200
C	3.46225400	-2.93157600	-0.30367400
C	4.67116400	-3.48113600	-0.74536900
C	5.78387100	-3.46304400	0.08482700

C 5.70035100 -2.90210600 1.35470300
 C 4.48403100 -2.37090000 1.76962900
 H 4.44680900 -1.94555600 2.76491100
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 H 4.73072000 -3.91585500 -1.73572900
 Cl 2.16275900 -3.03415200 -1.49222400
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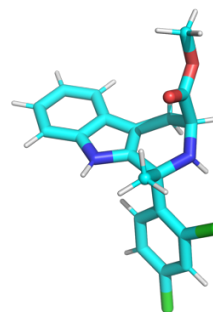


16

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 C 2.53060800 -3.74678800 -1.44812500
 C 1.94466600 -4.38078000 -2.56225600
 C 0.75076100 -3.92110000 -3.10848600
 C 0.15487500 -2.80650700 -2.51115600
 N -1.00927300 -2.13298300 -2.82993500
 C -1.20460400 -1.09659200 -1.92207700
 C -2.30725100 -0.05956800 -2.02203000
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 H -0.99774900 1.86785700 0.47092000
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 O -0.77359900 3.22392900 -1.72156000
 C -0.11322000 4.14883100 -2.59978000
 H 0.12515300 3.67068200 -3.55401100
 H 0.81245400 4.51630800 -2.14847700
 H -0.82028400 4.96552600 -2.74769500
 O 1.07836500 1.93721000 -1.77149100
 H -2.72669200 0.58992900 -0.12320100
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 C -6.25157600 -1.92212100 -1.57139200
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 H -5.14618500 -3.73027000 -1.18019500
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 H -1.63829900 -2.37957300 -3.57805800
 H 0.30236600 -4.40934300 -3.97012100
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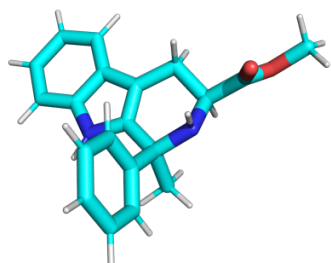


17

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 C -1.82334800 2.81611800 -0.61749900
 H -2.17496800 2.40847700 0.32700400
 C -2.41326200 3.95156200 -1.15894100
 C -1.96469600 4.49235800 -2.38125400
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 C -0.32771200 2.76584000 -2.53961200
 N 0.71075200 1.98277600 -3.00620300
 C 0.93897600 0.94309700 -2.11536700
 C 1.97866800 -0.13727100 -2.31298000
 N 1.67045900 -1.28759900 -1.40431100
 C 0.41403400 -1.34470600 -0.66048300
 H 0.56370700 -2.09157000 0.12778300
 C -0.73198800 -1.88160700 -1.52541800
 O -1.78153200 -2.21296300 -0.73597500

C -2.93957100 -2.70961300 -1.42692500
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 H -3.32268000 -1.95828800 -2.12250900
 H -3.67437800 -2.92394900 -0.65025700
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 H 2.43123400 -1.41068700 -0.74738000
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 H 2.21959500 0.21161100 -4.47186200
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 C 4.82817600 2.28104200 -1.28286500
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 H 4.91622500 3.32430900 -1.00025900
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 H 6.70573200 -0.51483700 -1.72686300
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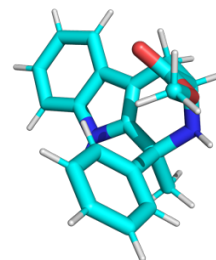
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1
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 C -3.23951000 -0.98695400 -0.26790100
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 C -4.62447300 -1.10706200 -0.25752700
 C -5.44140500 -0.06149000 0.21670400
 C -4.89031800 1.12313300 0.69552200
 C -3.49768800 1.23886600 0.68701700
 N -2.68065000 2.27291200 1.10663200

C -1.35805500 1.93434600 0.86528300
 C -0.17196200 2.81011800 1.21763400
 N 1.07788700 2.19425200 0.70428800
 C 1.14965300 0.73337800 0.75261700
 H 1.13288500 0.41302000 1.79884000
 C 2.48038800 0.32137700 0.14187500
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 O 2.97819400 -0.78216500 0.73554200
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 H 4.99411600 -0.54474700 0.24458100
 H 4.05363500 -1.54759600 -0.88523900
 H 4.44482800 -2.17748800 0.75059200
 H 1.26812800 2.49966900 -0.24750600
 C -0.05763000 2.90965300 2.75636900
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 H 0.00780600 1.90694100 3.18835700
 H -0.93171500 3.40195800 3.19615700
 C -0.31198300 4.19098700 0.54590200
 C -0.04564200 5.39205500 1.21329300
 C -0.15517800 6.61871200 0.55248500
 C -0.52857900 6.66584400 -0.78946400
 C -0.79552100 5.47490100 -1.46851800
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 H -0.91451300 3.33273900 -1.33809100
 H -1.09082000 5.49592000 -2.51423600
 H -0.61254400 7.62017100 -1.30237700
 H 0.05649200 7.53789300 1.09257100
 H 0.25326000 5.38467000 2.25551200
 H -2.99611500 3.19686000 1.36063500
 H -5.52164300 1.92760700 1.06441000
 H -6.52128600 -0.18220700 0.21068400
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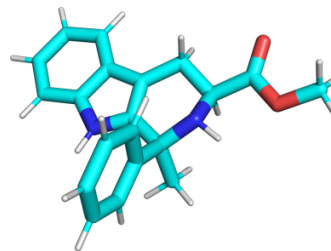
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2
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 C 1.86417700 -1.68503600 -0.89459400

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H	2.99318600	0.13510700	-1.23111800
C	4.08949000	-1.62653900	-1.81545100
C	4.09377400	-3.03172300	-1.92185200
C	2.99771100	-3.78863300	-1.51992300
C	1.89270100	-3.10389000	-1.00658600
N	0.68605700	-3.57974700	-0.52853300
C	-0.10357700	-2.50549600	-0.14379100
C	-1.48050800	-2.65006800	0.44662100
N	-1.87726600	-1.30490300	0.95404500
C	-1.52311200	-0.11219800	0.16985800
H	-1.87498500	0.73894800	0.76812300
C	-2.26323100	0.02218400	-1.17566500
O	-1.76324900	0.21885200	-2.26120600
O	-3.59861800	-0.06564800	-0.97257800
C	-4.41426100	0.02810500	-2.15231600
H	-4.21123100	-0.81366500	-2.81862800
H	-4.21703600	0.96439000	-2.68094900
H	-5.44542600	-0.00519900	-1.79908500
H	-2.88083500	-1.30649100	1.12047000
C	-1.39529300	-3.55570600	1.69945600
H	-2.33846800	-3.55175200	2.25470800
H	-0.61568100	-3.17454900	2.36311700
H	-1.16635300	-4.59390000	1.43311600
C	-2.48764000	-3.22536300	-0.58380100
C	-3.71587500	-3.75895000	-0.15953300
C	-4.64838900	-4.24628800	-1.07491900
C	-4.37353900	-4.21421100	-2.44337900
C	-3.16163000	-3.68125900	-2.88217000
C	-2.23022600	-3.19155000	-1.96266000
H	-1.29973000	-2.76801000	-2.32570400
H	-2.93215500	-3.64649900	-3.94415900
H	-5.09566000	-4.60075300	-3.15767400
H	-5.58879800	-4.65709800	-0.71626800
H	-3.95640700	-3.80020200	0.89890400
H	0.37849600	-4.53875500	-0.57297500
H	3.00323400	-4.87273400	-1.60134400
H	4.96872600	-3.53450200	-2.32497100
H	4.96285400	-1.06652700	-2.13862400
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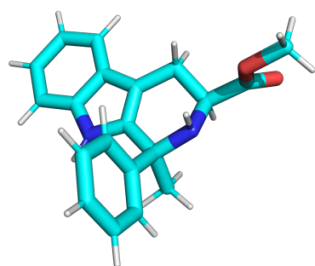


3

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H	-2.88708500	-1.36748500	-0.58564200
C	-4.75006100	-0.34264400	-0.22987000
C	-5.38185500	0.83499800	0.21656800
C	-4.64161000	1.92155900	0.67272500
C	-3.24939500	1.80365100	0.66782900
N	-2.27311000	2.69681000	1.07410100
C	-1.02837400	2.13441100	0.83979000
C	0.27871100	2.82612900	1.15363100
N	1.33557200	2.00913600	0.51156600
C	1.23792900	0.55816700	0.71800300
H	1.15967900	0.28920700	1.79063500
C	2.51407900	-0.11997900	0.22894500
O	2.56074500	-1.15080200	-0.40306500
O	3.61517100	0.55310100	0.63865800
C	4.87330100	-0.02377100	0.24798700
H	4.94651100	-0.07779900	-0.84115700
H	4.97673400	-1.02993700	0.66229100
H	5.63803900	0.63969600	0.65255800
H	2.24674100	2.33821600	0.82118300
C	0.47596800	2.91030200	2.68901800
H	1.38295000	3.47570700	2.93321200
H	0.56813500	1.90370700	3.10705000
H	-0.37218600	3.38552500	3.19194600
C	0.28891000	4.22208300	0.49261400
C	0.04517300	5.39736200	1.21565500
C	0.00840600	6.64008700	0.57449300
C	0.21583000	6.72706400	-0.80025900
C	0.45923500	5.56090400	-1.53117900
C	0.49249900	4.32345800	-0.89256200
H	0.68967700	3.41736400	-1.45453700
H	0.62348800	5.61578100	-2.60435300
H	0.19089500	7.69238500	-1.29885700
H	-0.17683100	7.53846900	1.15780300
H	-0.10591200	5.36155600	2.28982400

H -2.42457500 3.67872700 1.25268100
H -5.13048600 2.82790000 1.02113000
H -6.46675000 0.89611000 0.20718300
H -5.35864500 -1.17383600 -0.57579200
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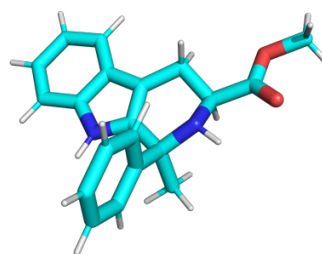


4

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C -4.70721800 0.49708600 -0.52914000
C -5.14743700 1.77658100 -0.13561100
C -4.25480400 2.72979000 0.34461900
C -2.90580300 2.37256300 0.42040600
N -1.81066200 3.09220900 0.86258800
C -0.66869500 2.31992900 0.71535600
C 0.72361200 2.76190400 1.12004600
N 1.71603800 1.73575100 0.69554700
C 1.27212200 0.34012500 0.82460100
H 1.06219000 0.14269800 1.87913900
C 2.41394300 -0.59557300 0.45236300
O 2.74413700 -1.57582500 1.08112100
O 2.99324800 -0.22395200 -0.71317300
C 4.07687900 -1.05691900 -1.15773000
H 3.73030900 -2.08051400 -1.32249500
H 4.87870200 -1.06809000 -0.41501600
H 4.42414500 -0.61326800 -2.09124000
H 1.98206100 1.90394400 -0.27233500
C 0.78843200 2.88835900 2.65939400
H 1.81336600 3.08524400 2.98373000
H 0.46163300 1.95486400 3.12582800
H 0.13323000 3.68684700 3.02370900
C 1.10434800 4.07503600 0.40671200
C 1.82541700 5.09647100 1.03719300
C 2.18755600 6.25294800 0.34195400
C 1.84024000 6.40749900 -0.99943100

C 1.12556900 5.39510600 -1.64257400
C 0.76140500 4.24427500 -0.94490600
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H 0.84538500 5.50219600 -2.68724500
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H 2.74532500 7.03253900 0.85427300
H 2.11446300 4.99996200 2.07770100
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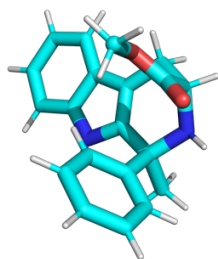


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H -1.81454500 -2.62132800 -0.62892300
C -3.94440000 -2.66443100 -0.29960700
C -5.08506900 -1.96171900 0.13656600
C -4.99140100 -0.65310300 0.60077400
C -3.72635600 -0.06035800 0.61427500
N -3.33129500 1.19855300 1.03198500
C -1.97005600 1.33509300 0.81665100
C -1.18773100 2.59074400 1.13800200
N 0.13751600 2.39733200 0.51829300
C 0.77075200 1.10300500 0.75097100
H 0.78440000 0.81355700 1.82169400
C 2.23916300 1.22269500 0.36239800
O 2.84515200 2.27076000 0.28396500
O 2.80621700 0.01573100 0.17297800
C 4.21183600 0.03523800 -0.13176800
H 4.77341800 0.50123000 0.68217300
H 4.39512000 0.59123900 -1.05466100
H 4.49900200 -1.00993100 -0.24849200
H 0.77565200 3.14812700 0.77177800
C -1.08651000 2.77551900 2.67463300

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H	-0.50743700	1.95599600	3.11031900
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C	-2.69576000	4.68715000	1.15610300
C	-3.34263300	5.73673600	0.49549300
C	-3.17136900	5.91514800	-0.87553600
C	-2.34792200	5.03490500	-1.58267700
C	-1.70678600	3.98770300	-0.92488400
H	-1.05934200	3.30808500	-1.46773000
H	-2.20380300	5.16512900	-2.65224100
H	-3.67038000	6.73271900	-1.38900800
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H	-2.83544100	4.58275600	2.22741900
H	-3.95441400	1.97237000	1.21099700
H	-5.87156800	-0.11344700	0.94116500
H	-6.05545700	-2.45013400	0.11266600
H	-4.05262100	-3.68663300	-0.65224800
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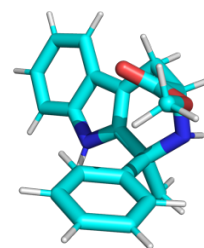


6

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H	2.99454900	0.26733900	-1.21423700
C	4.05149600	-1.40342500	-2.07295300
C	4.02503700	-2.77405900	-2.39958100
C	2.91162900	-3.56043100	-2.12050300
C	1.82065400	-2.94106700	-1.50432900
N	0.60265300	-3.45895900	-1.10569200
C	-0.16297700	-2.44341400	-0.55134500
C	-1.54985000	-2.64240700	-0.00033000
N	-1.89172400	-1.40546400	0.76125600
C	-1.52356800	-0.10287000	0.18559200
H	-1.82704100	0.63695400	0.93818300
C	-2.39249600	0.26121500	-1.03482000
O	-3.60454600	0.21594100	-0.99277100

O	-1.69852400	0.66201700	-2.11761000
C	-2.49740300	1.01958500	-3.26004500
H	-3.18042600	1.83511300	-3.00872900
H	-3.07811800	0.15754800	-3.59742700
H	-1.78723100	1.33255700	-4.02598600
H	-2.89628800	-1.40149700	0.92927000
C	-1.51865000	-3.77921100	1.05016900
H	-2.47335200	-3.85104200	1.58044700
H	-0.73989300	-3.56764300	1.78683700
H	-1.32239800	-4.75235500	0.58574300
C	-2.57041900	-2.96699600	-1.12263600
C	-3.85872400	-3.41944600	-0.79533600
C	-4.80491300	-3.68500200	-1.78363600
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H	-2.94343100	-2.91577000	-4.51782500
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H	-4.13837700	-3.56381800	0.24468900
H	0.28076200	-4.39747400	-1.28389500
H	2.89383600	-4.61811300	-2.37123600
H	4.88973400	-3.22631500	-2.87765600
H	4.93830100	-0.81924000	-2.30355700
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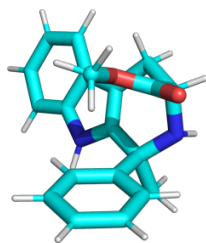


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C	4.23649100	-1.52329200	-1.50446800
C	4.34561600	-2.92716400	-1.44534400
C	3.29023100	-3.71376200	-0.99475900
C	2.11884300	-3.06004200	-0.60206700
N	0.92953400	-3.56667800	-0.11261600

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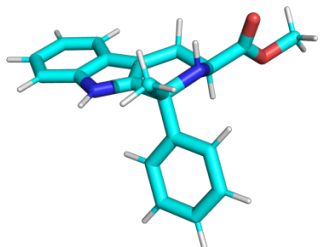


8

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 C 4.15840900 -1.59595600 -1.63573100
 C 4.21656100 -3.00401100 -1.65063900
 C 3.13502700 -3.77416500 -1.23481400
 C 1.99037800 -3.09977300 -0.80069100
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 H -3.20197700 0.75926300 -3.24119500
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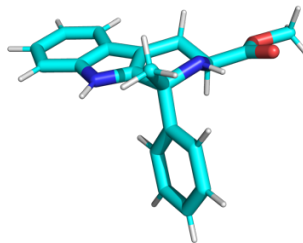


1

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C	2.46718400	0.99894400	0.02645500
C	3.34150500	0.05703200	-0.54167900
H	2.96303500	-0.89122800	-0.91503900
C	4.69683000	0.35450000	-0.62034200
C	5.20172400	1.57975000	-0.14055800
C	4.36171700	2.53252200	0.42704800
C	2.99952200	2.22925500	0.50421400
N	1.94328600	2.96519600	1.00900400
C	0.76773200	2.23952800	0.86775800
C	-0.60336600	2.68153300	1.33679400
N	-1.49596000	1.50403400	1.39374200
C	-1.40995800	0.62238700	0.22918900
H	-1.68228700	1.20655500	-0.65510800
C	-2.41894900	-0.50000600	0.41146200
O	-2.72101100	-0.98567800	1.48065000
O	-2.88944100	-0.93750100	-0.77445400
C	-3.79048700	-2.05632800	-0.70553200
H	-3.30348400	-2.91344500	-0.23294500
H	-4.05300100	-2.28411000	-1.73890900
H	-4.68241400	-1.79337400	-0.13091300
H	-1.30549100	0.95660400	2.23184000
C	-0.52414400	3.25704700	2.76970300
H	-0.03955300	2.54431400	3.44741100
H	-1.53114700	3.46869100	3.14026800
H	0.04322100	4.19333600	2.79023500
C	-1.24902300	3.73918600	0.41036100
C	-2.62203000	4.00024700	0.53769800
C	-3.23924900	4.97782600	-0.24049400
C	-2.49592900	5.71386500	-1.16657200
C	-1.13352200	5.45652100	-1.30810700
C	-0.51560000	4.47542600	-0.52733000
H	0.54285100	4.27947200	-0.66543000
H	-0.54512400	6.01256400	-2.03359500
H	-2.97689800	6.47460300	-1.77581200
H	-4.30478600	5.16165200	-0.12756300
H	-3.20329100	3.41025100	1.23903300

H	2.01832400	3.87797800	1.42955200
H	4.75277500	3.47700300	0.79713800
H	6.26612000	1.78511700	-0.21510200
H	5.38127400	-0.36710700	-1.05806900
H	0.13327500	-0.86551200	0.66709200
H	0.06260300	-0.38600400	-1.02578400

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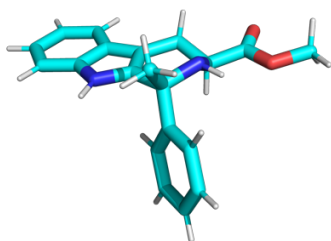


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C	-2.41554600	-1.13888900	-0.08358300
C	-3.34411700	-0.21156300	-0.58566000
H	-3.02805500	0.79289700	-0.85592500
C	-4.67185400	-0.59563800	-0.73194200
C	-5.09596600	-1.89415500	-0.38490500
C	-4.20152700	-2.83457300	0.11615700
C	-2.86747400	-2.44414000	0.26281100
N	-1.77304400	-3.14854600	0.72864600
C	-0.65241100	-2.33450600	0.67783800
C	0.72706700	-2.75396900	1.12611200
N	1.51222700	-1.50040400	1.20540700
C	1.40411300	-0.63342900	0.03452900
H	1.54067500	-1.18869600	-0.91566300
C	2.54811100	0.36937400	0.08001400
O	3.57235300	0.21398400	0.71175300
O	2.31473100	1.43242300	-0.71413400
C	3.37801800	2.39849500	-0.78027500
H	3.57606300	2.81780300	0.20947600
H	3.02622400	3.17267500	-1.46253400
H	4.29266700	1.93575300	-1.16015800
H	2.49418900	-1.70410300	1.38013400
C	0.65154200	-3.31850400	2.56254000
H	0.14707700	-2.59603700	3.20883400
H	1.65228400	-3.49448200	2.96954700
H	0.11108700	-4.27139100	2.59329600
C	1.37256100	-3.77862500	0.15753900
C	2.57690200	-4.41158300	0.50941200
C	3.21094900	-5.29502400	-0.36213100
C	2.65568600	-5.56727800	-1.61465700

C 1.46604600 -4.94241800 -1.98293700
 C 0.83233300 -4.05700900 -1.10610800
 H -0.09315800 -3.57967700 -1.41187100
 H 1.02415200 -5.13965700 -2.95635000
 H 3.14828000 -6.25713400 -2.29461300
 H 4.14059700 -5.77168200 -0.06198600
 H 3.03445700 -4.21261500 1.47479400
 H -1.77760200 -4.11673500 1.00894800
 H -4.53035400 -3.83549600 0.38436900
 H -6.14041300 -2.16661300 -0.50996200
 H -5.39749300 0.11436000 -1.11951500
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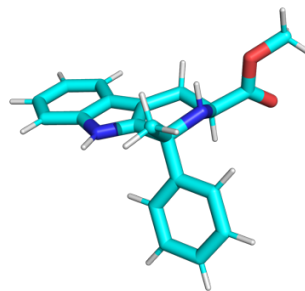


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 H 3.06628000 -0.68680700 -0.81887100
 C 4.68734800 0.70106100 -0.51458800
 C 5.08288300 1.96745000 -0.03892900
 C 4.16014900 2.85093200 0.51192200
 C 2.82689500 2.43612900 0.57595700
 N 1.70880300 3.08511200 1.06578200
 C 0.60103600 2.26807100 0.90012600
 C -0.79593400 2.63954700 1.32853600
 N -1.59692400 1.38674700 1.25298400
 C -1.41205400 0.60446000 0.02304500
 H -1.53732400 1.22854100 -0.88476200
 C -2.47774300 -0.48037600 -0.07929800
 O -2.28968800 -1.60719900 -0.47956300
 O -3.69554000 -0.01377100 0.28409800
 C -4.77395000 -0.95919300 0.18394000
 H -4.88518700 -1.30354200 -0.84745600
 H -5.66567400 -0.42224400 0.50849800
 H -4.58691400 -1.82163400 0.82883200
 H -2.58141100 1.62780000 1.34293900
 C -0.78201100 3.05340200 2.81708600

H -0.28826900 2.27365200 3.40186800
 H -1.79855900 3.17038100 3.20572000
 H -0.25765200 4.00399000 2.96700300
 C -1.39978000 3.75153600 0.43371500
 C -2.56024200 4.43457900 0.83580900
 C -3.15864600 5.38902800 0.01455700
 C -2.61089400 5.68450300 -1.23555900
 C -1.46283100 5.01318600 -1.65225200
 C -0.86454400 4.05770500 -0.82648900
 H 0.03096900 3.54732300 -1.16650300
 H -1.02538100 5.23047700 -2.62333900
 H -3.07527400 6.42981600 -1.87564500
 H -4.05360800 5.90442300 0.35379100
 H -3.00961500 4.22356200 1.80211100
 H 1.68889200 4.03001300 1.41610000
 H 4.46685600 3.82687000 0.87988300
 H 6.12751200 2.25982300 -0.10253400
 H 5.43483600 0.03526900 -0.93745000
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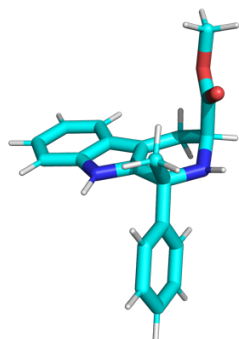


4

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 C 2.467377 0.998822 0.026797
 C 3.341526 0.057029 -0.541868
 H 2.962619 -0.890629 -0.916263
 C 4.696802 0.354486 -0.620510
 C 5.201664 1.579622 -0.140334
 C 4.361719 2.532558 0.427043
 C 2.999394 2.229485 0.504009
 N 1.942680 2.966112 1.007090
 C 0.767429 2.239334 0.866621
 C -0.603701 2.680090 1.337721
 N -1.486384 1.491445 1.408505
 C -1.405705 0.626238 0.223017
 H -1.663628 1.236678 -0.646581
 C -2.457604 -0.470627 0.299710
 O -3.149128 -0.839033 -0.622831

O -2.488759 -1.035450 1.530066
 C -3.435610 -2.103893 1.694867
 H -4.451263 -1.746896 1.505619
 H -3.330709 -2.432268 2.729373
 H -3.213034 -2.923099 1.006060
 H -1.235185 0.940810 2.228624
 C -0.521427 3.265363 2.766318
 H -0.034172 2.558606 3.448652
 H -1.527357 3.479997 3.137846
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 C -1.259376 3.726791 0.408362
 C -2.634100 3.978856 0.534400
 C -3.257403 4.949146 -0.248252
 C -2.518243 5.687104 -1.175878
 C -1.153986 5.438570 -1.315789
 C -0.530132 4.464216 -0.531513
 H 0.529600 4.274241 -0.668365
 H -0.569047 5.995748 -2.043135
 H -3.004175 6.441817 -1.788596
 H -4.324525 5.124820 -0.138112
 H -3.212429 3.387776 1.237198
 H 2.018084 3.875962 1.433921
 H 4.752794 3.477444 0.796067
 H 6.265991 1.785199 -0.215292
 H 5.381094 -0.366663 -1.059173
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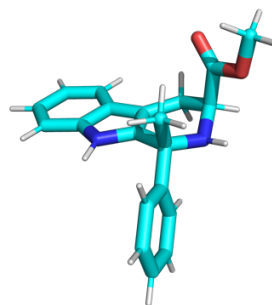


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 H -1.71003600 2.76180000 0.14051100
 C -1.22355200 4.48499700 -1.05998600
 C -0.37546800 5.03862100 -2.03948000
 C 0.65823000 4.29538300 -2.60140100
 C 0.82726000 2.98212200 -2.15541900
 N 1.74191900 2.01700700 -2.53644400

C 1.52696200 0.87186200 -1.78695900
 C 2.35868200 -0.37973900 -1.92598400
 N 1.89582900 -1.33467300 -0.88405700
 C 0.49198800 -1.38022400 -0.47790000
 H 0.45724900 -2.05707500 0.39004600
 C -0.43799200 -2.07797000 -1.49263200
 O -0.05484400 -2.86488500 -2.33399700
 O -1.74149800 -1.81235700 -1.27241800
 C -2.66913500 -2.51860800 -2.11558300
 H -3.65938800 -2.18877600 -1.80067900
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 H -2.49583900 -2.26919400 -3.16541900
 H 2.20810500 -2.26841600 -1.13687500
 C 2.20962500 -0.94333600 -3.36141600
 H 1.17474100 -1.22547800 -3.54999000
 H 2.83422100 -1.83432200 -3.49168000
 H 2.50208100 -0.20795700 -4.11832700
 C 3.83562100 -0.02929800 -1.60384800
 C 4.82075900 0.09021800 -2.59225100
 C 6.12964100 0.45990300 -2.26271000
 C 6.47454600 0.71868200 -0.93879500
 C 5.49994300 0.60179300 0.05667200
 C 4.19901400 0.23202300 -0.27333400
 H 3.44699600 0.12410100 0.50042200
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 H 7.49109400 1.00440900 -0.68159000
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 H 4.58801800 -0.11750700 -3.63130400
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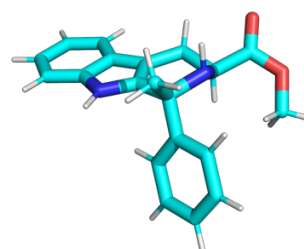


6

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 H 3.22958100 -0.20526600 -0.04285700
 C 4.28630200 -1.66082000 -1.23096100
 C 4.19344300 -2.72288500 -2.15205800
 C 2.95973100 -3.16591700 -2.61936600
 C 1.81674300 -2.52191400 -2.13878900
 N 0.48056900 -2.73132100 -2.43059200
 C -0.28427300 -1.86235300 -1.66854500
 C -1.79024900 -1.79273400 -1.73680600
 N -2.21763000 -0.96675500 -0.58028500
 C -1.48955800 0.27382600 -0.27943500
 H -1.95030100 0.66044100 0.63989800
 C -1.68581300 1.40792600 -1.30512300
 O -0.82129100 2.07751500 -1.82528500
 O -3.00982400 1.60164700 -1.53006400
 C -3.33219900 2.65176900 -2.45611600
 H -2.93523000 2.42328400 -3.44927600
 H -2.91385500 3.60344100 -2.11846500
 H -4.42143000 2.69747900 -2.48168800
 H -3.21263300 -0.77307700 -0.65833200
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 H -3.29170500 -1.08236100 -3.17618400
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 H -3.17303700 -3.48748400 -3.51635500
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 H 5.10105400 -3.20365800 -2.50696400
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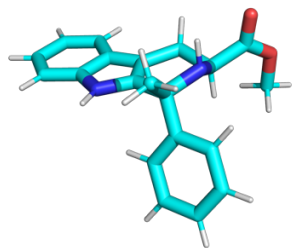
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7
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 C -4.79796400 -2.56549000 -0.06680200
 C -3.79478800 -3.31019900 0.54479500
 C -2.51982000 -2.74121500 0.61580100
 N -1.34639500 -3.23376800 1.15602300
 C -0.33421500 -2.29841800 0.98057100
 C 1.09133000 -2.45717700 1.46333300
 N 1.77399100 -1.13578600 1.40222600
 C 1.48902000 -0.36218300 0.17446700
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 H 5.26766400 -0.09682000 -0.84940000
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 C 1.09697200 -2.89515600 2.94641400
 H 0.48390100 -2.21447500 3.54795700
 H 2.11572300 -2.89284800 3.34347800
 H 0.69503000 -3.90704400 3.05986600
 C 1.90460800 -3.46526800 0.62092100
 C 3.25898300 -3.67720300 0.92767900
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 C 3.45369700 -5.30598000 -0.85113400
 C 2.11415000 -5.09771600 -1.17196700
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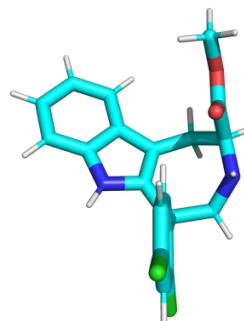


8

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C -4.57727100 -1.02724400 -0.76472900
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C -3.95616300 -3.14753000 0.26986500
C -2.65549100 -2.64998900 0.38870500
N -1.51685800 -3.23290300 0.91429100
C -0.45737700 -2.34109600 0.81717700
C 0.95095300 -2.58706100 1.31724200
N 1.65903500 -1.29381500 1.41588200
C 1.47999300 -0.41514600 0.25730400
H 1.84477500 -0.96472600 -0.61435900
C 2.30506900 0.84622600 0.52262000
O 2.33019300 1.35821800 1.61780800
O 2.97077200 1.44560100 -0.49406700
C 3.03653400 0.86276500 -1.79996500
H 3.56513600 -0.09601400 -1.78568600
H 3.60128800 1.57457800 -2.40415000
H 2.04191300 0.73208800 -2.23913800
H 1.36800800 -0.78735600 2.25070700
C 0.92198700 -3.19570600 2.73820200
H 0.32739100 -2.57087100 3.41484500
H 1.94007400 -3.27156300 3.13041100
H 0.49096000 -4.20225600 2.72872800
C 1.76686200 -3.51993600 0.39055400
C 3.15991600 -3.58298200 0.55151700
C 3.93198900 -4.44130000 -0.22963700
C 3.32689400 -5.25348600 -1.19209500

C 1.94547700 -5.19243600 -1.36669300
C 1.17219600 -4.33073700 -0.58313000
H 0.10005800 -4.28788500 -0.74555000
H 1.46227600 -5.81046800 -2.11918200
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H 5.00953800 -4.47330700 -0.08886400
H 3.63149600 -2.93498200 1.28345600
H -1.47353500 -4.14449000 1.34201700
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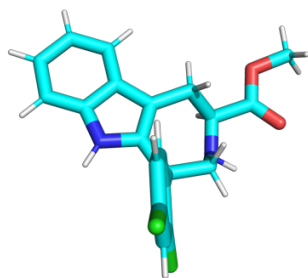


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H 2.43822400 -1.24027000 -1.52208000
C 2.29450200 -2.96955900 -2.79707400
C 1.46234700 -3.96476200 -3.34897300
C 0.10410200 -4.01126100 -3.05483400
C -0.40345600 -3.03467800 -2.19233500
N -1.68241800 -2.83053000 -1.72028300
C -1.71075700 -1.71385200 -0.89624900
C -2.99189600 -1.30596900 -0.22045300
C -2.79513800 -0.04192800 0.68394100
N -2.26921200 1.15749100 0.06183100
C -0.84426600 1.27906700 -0.23213300
H -0.39672500 2.06047300 0.40458900
C -0.65988200 1.77576200 -1.66823800
O 0.62415000 2.08658800 -1.91819200
C 0.90498200 2.55281000 -3.25040900
H 0.33551800 3.46061100 -3.46507100
H 0.64789100 1.78496700 -3.98428300
H 1.97565100 2.75682200 -3.26734200
O -1.55094500 1.90150300 -2.48495200
H -2.81539300 1.44062400 -0.74686600

H -3.77248000 0.20260800 1.11499300
H -2.15451400 -0.31845800 1.52694900
H -3.28619100 -2.11684200 0.45946000
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C -3.92943000 -0.48212000 -2.44340900
C -4.96423400 -0.24010400 -3.34416900
C -6.25689300 -0.63388200 -3.00801500
C -6.52258100 -1.25136200 -1.78879400
C -5.46607100 -1.47091200 -0.90497600
Cl -5.87187900 -2.24151100 0.63242800
H -7.52892100 -1.55520300 -1.52718900
Cl -7.57817900 -0.35409600 -4.13094700
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H -2.50113500 -3.34601900 -2.00608900
H -0.53740600 -4.77977300 -3.47839200
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H 3.35244400 -2.96412200 -3.04511000
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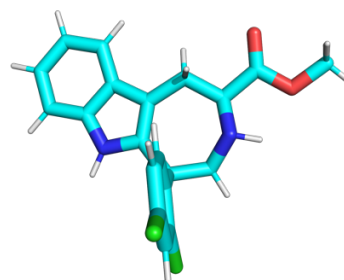


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C -0.89500000 4.59857000 0.14625400
C 0.13380300 5.34148600 0.76033000
C 1.27525200 4.71842700 1.25275300
C 1.36216400 3.32952300 1.11712300
N 2.35088000 2.44968900 1.50312500
C 1.99700200 1.15563500 1.14885100
C 2.89599500 0.00126900 1.49884000
C 2.23029500 -1.36582400 1.17821300
N 0.92542900 -1.48464200 1.82397100
C -0.25878800 -1.10553600 1.05383600
H -1.00918700 -0.71253500 1.75646000
C -0.90477800 -2.33401800 0.39655100

O -2.02153300 -2.00692300 -0.28548600
C -2.72024700 -3.10560600 -0.89808700
H -3.58673600 -2.66304000 -1.38998100
H -3.03425600 -3.82855700 -0.14078500
H -2.07907600 -3.60886100 -1.62634200
O -0.49211500 -3.47053600 0.50153100
H 0.79656100 -2.44229400 2.13783100
H 2.21024200 -1.52008600 0.08866300
H 2.87933200 -2.14704000 1.58434700
H 3.03946300 0.01429300 2.58608200
C 4.26671600 0.09165000 0.83350800
C 4.39281200 0.58649100 -0.47389400
C 5.61473300 0.64315400 -1.13835100
C 6.75794700 0.19324800 -0.48069900
C 6.68732800 -0.30911700 0.81537300
C 5.44517500 -0.35669700 1.44957500
Cl 5.41484800 -1.01598900 3.08661600
H 7.57710900 -0.65873000 1.32491400
Cl 8.31522700 0.25994500 -1.28939400
H 5.68097400 1.03283600 -2.14819700
H 3.49876400 0.94707900 -0.97491300
H 3.21645700 2.70253500 1.95511100
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H -1.77381600 5.11671900 -0.22782900
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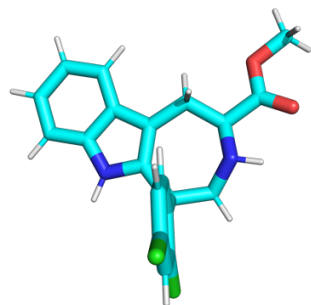


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C 2.24271600 -4.03796200 -0.45397000
C 1.60720700 -5.11459600 0.19814900
C 0.42665300 -4.92973300 0.90860500
C -0.10548600 -3.63689100 0.94905700
N -1.23753900 -3.15000700 1.56297500

C -1.35588300 -1.78405900 1.33350700
 C -2.54339500 -1.05857600 1.91109600
 C -2.20985000 0.39479400 2.33310700
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 C -0.34082600 1.17165900 0.93065800
 H 0.25407100 1.05207100 1.86038000
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 H -2.01070200 2.21117700 1.44161400
 H -3.11901100 0.83322100 2.75632800
 H -1.46125500 0.34316200 3.14508100
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 C -3.67769000 -1.08541700 -0.37961500
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 C -6.06166300 -1.14304000 -0.64147200
 C -6.22281000 -1.16973900 0.74036800
 C -5.08328800 -1.14950500 1.54482500
 Cl -5.35223300 -1.17663100 3.29356900
 H -7.20972700 -1.20710100 1.18533100
 Cl -7.48569700 -1.16915500 -1.67021200
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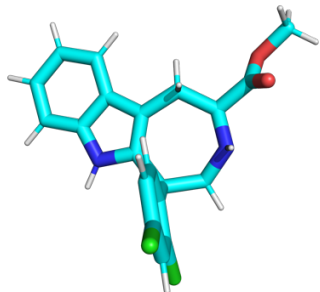
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 C -1.68088700 4.26853800 -0.64169100
 C -0.88997000 5.28388400 -0.06596700
 C 0.27432000 4.98077600 0.63073700
 C 0.63044100 3.63236900 0.73530200
 N 1.70310200 3.03150700 1.35369000
 C 1.63670200 1.65142900 1.19855400
 C 2.75073400 0.82094100 1.78521000
 C 2.28234100 -0.58100400 2.25281600
 N 1.69206500 -1.37735600 1.19031900
 C 0.26847000 -1.16126600 0.97380300
 H -0.25441000 -0.92397700 1.92295400
 C -0.34422500 -2.47732000 0.49214500
 O -1.60459700 -2.31765800 0.04968100
 C -2.27030200 -3.52218600 -0.37163100
 H -3.26466000 -3.20853800 -0.68954800
 H -2.33537100 -4.23187800 0.45702600
 H -1.72904500 -3.98803500 -1.19886400
 O 0.21900000 -3.55163400 0.53932400
 H 1.85323100 -2.37037900 1.33378800
 H 3.15826000 -1.11363200 2.63614400
 H 1.58872300 -0.43653900 3.10183400
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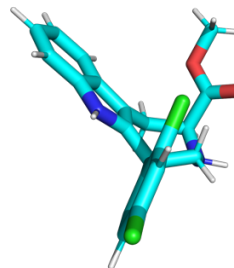


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H	2.21942300	-1.88230000	-1.05329400
C	2.25452200	-4.00736700	-0.71404400
C	1.62324000	-5.12086800	-0.12240900
C	0.44715000	-4.97840900	0.60465600
C	-0.08512300	-3.69048700	0.72400500
N	-1.21602900	-3.24230900	1.36936200
C	-1.33725500	-1.86638300	1.22239900
C	-2.51715000	-1.16829900	1.84519200
C	-2.13957100	0.23177700	2.43395000
N	-1.62024700	1.24729000	1.54529500
C	-0.25903600	1.11113400	1.05244400
H	0.39620700	0.93312400	1.91209500
C	0.12279600	2.44289300	0.41268900
O	1.40895800	2.76617200	0.65721700
C	1.87041100	3.97607200	0.02962900
H	2.91645900	4.07518100	0.32037800
H	1.28999700	4.83305300	0.38077600
H	1.77674200	3.90454500	-1.05721600
O	-0.62207100	3.10419400	-0.27871600
H	-2.25942900	1.51200400	0.80116900
H	-3.03496500	0.63619700	2.91893600
H	-1.39642000	0.06515200	3.22359200
H	-2.81928800	-1.76275200	2.71733500
C	-3.73522700	-1.07760500	0.92624900
C	-3.59862000	-0.97973700	-0.46640700
C	-4.69189800	-0.84704200	-1.31992400
C	-5.97216600	-0.81573300	-0.77408800
C	-6.16479800	-0.91883700	0.60107700
C	-5.04813600	-1.04465400	1.42637800
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H	-7.16159300	-0.90389100	1.02495400
Cl	-7.36936400	-0.65399300	-1.82462400
H	-4.55121700	-0.77418900	-2.39274100
H	-2.60234900	-1.03572700	-0.89161700

H	-1.85943400	-3.81772500	1.89137300
H	-0.04074700	-5.83629900	1.06019900
H	2.06301700	-6.10776700	-0.23696000
H	3.17232800	-4.15415900	-1.27677800
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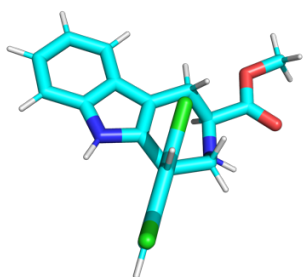


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H	1.84782600	2.42348400	0.77766700
C	1.10724200	4.24448900	1.65615800
C	-0.00981100	4.95258600	2.14547400
C	-1.28005500	4.38737100	2.13300900
C	-1.40562000	3.09364900	1.61748900
N	-2.51871900	2.29355100	1.46810900
C	-2.14797400	1.07071500	0.93399300
C	-3.13928100	-0.02491200	0.60979100
C	-2.65172600	-1.41675700	1.09567500
N	-1.55408000	-1.94706900	0.27031600
C	-0.20453200	-1.43652400	0.51712900
H	0.46247300	-2.07122600	-0.08580800
C	0.27194500	-1.65155500	1.96644500
O	1.37417600	-0.92995100	2.25245700
C	1.90954200	-1.11199900	3.57506100
H	2.77790200	-0.45532700	3.63150600
H	2.20154800	-2.15400900	3.73067200
H	1.16730200	-0.83306700	4.32701300
O	-0.23785900	-2.43044100	2.74496700
H	-1.53072600	-2.95223300	0.42306700
H	-2.40368900	-1.38081500	2.16094200
H	-3.48439300	-2.11825500	0.97476000
H	-3.17107000	-0.11235400	-0.48525000
C	-4.57366000	0.27077600	1.04152900
C	-5.54305500	0.43983800	0.03802200
C	-6.88647800	0.68147000	0.30992300
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H	-6.69498800	0.67322200	3.70790000
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H	-3.44249500	2.51175200	1.80785500
H	-2.14267100	4.93210600	2.50839600
H	0.12359500	5.95692600	2.53819200
H	2.08600500	4.71634000	1.67872400
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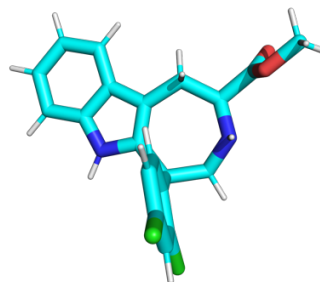


7

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H	1.31772200	2.78611000	0.60314800
C	0.35639200	4.66912100	0.19708400
C	-0.78107400	5.33073100	-0.30866100
C	-1.86116600	4.61692100	-0.81643100
C	-1.77496100	3.22167400	-0.80731300
N	-2.66722800	2.26405000	-1.24085000
C	-2.14776400	0.99850800	-1.00988600
C	-2.90309200	-0.22406400	-1.46088700
C	-2.12786000	-1.53570800	-1.17092800
N	-0.83000600	-1.52343100	-1.84742300
C	0.33303800	-1.02670400	-1.10958500
H	0.99929500	-0.52125100	-1.82549900
C	1.15079100	-2.19402900	-0.53778800
O	2.24786600	-1.76542300	0.11824000
C	3.09775300	-2.79785400	0.64911700
H	3.92702000	-2.27625200	1.12752100
H	3.46054200	-3.44464000	-0.15388600
H	2.55344900	-3.40500900	1.37701800
O	0.87527800	-3.36707300	-0.68676500
H	-0.61283800	-2.46770100	-2.15445300

H	-2.07307100	-1.72167000	-0.09073300
H	-2.71264500	-2.35698400	-1.59716600
H	-2.95248200	-0.17349700	-2.55833500
C	-4.35346200	-0.27435100	-0.98142800
C	-5.37059200	-0.36743600	-1.94558600
C	-6.72286500	-0.43720100	-1.61903700
C	-7.08456900	-0.41224000	-0.27519200
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C	-4.77108600	-0.25636100	0.36120700
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H	-6.40173800	-0.30399500	1.76763500
Cl	-8.77847500	-0.49417500	0.17744700
H	-7.48001200	-0.50875000	-2.39205800
H	-5.08520400	-0.38924500	-2.99453600
H	-3.59137900	2.44528500	-1.60194800
H	-2.73877900	5.12618900	-1.20662600
H	-0.81517600	6.41676300	-0.30207000
H	1.18312700	5.25673400	0.58707600
H	-0.43565800	-0.52275000	0.86195400
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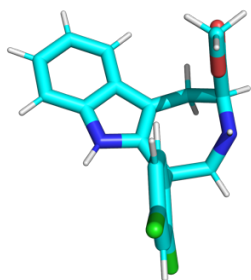


8

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H	2.43547800	-1.52166700	-1.14988400
C	2.74426500	-3.64039300	-0.92945100
C	2.26253400	-4.85702800	-0.40380200
C	1.07928500	-4.90801700	0.32379400
C	0.38622200	-3.70776400	0.51175800
N	-0.79003900	-3.44481900	1.17768600
C	-1.08642000	-2.08936100	1.10876900
C	-2.34779400	-1.58934600	1.76239900
C	-2.16829500	-0.18137100	2.41923900
N	-1.79130800	0.93384100	1.57371100
C	-0.40675400	0.99601300	1.11422600
H	0.23664600	0.82843100	1.98369200
C	-0.10695600	2.41856000	0.64579100

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 H -2.56463000 -2.26234100 2.60228900
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 C -3.44698400 -1.44856700 -0.54529600
 C -4.54902900 -1.42569000 -1.39781300
 C -5.82201400 -1.58547000 -0.85748200
 C -5.99811500 -1.77046200 0.51133000
 C -4.87407400 -1.78249500 1.33617600
 Cl -5.16395100 -2.03314700 3.06060400
 H -6.98772300 -1.90546300 0.93086200
 Cl -7.22885800 -1.56538000 -1.90722300
 H -4.41972900 -1.29266300 -2.46633200
 H -2.45216000 -1.35717300 -0.96838300
 H -1.35152400 -4.12594600 1.66588400
 H 0.70725000 -5.84548000 0.72907500
 H 2.82584200 -5.77106800 -0.57023400
 H 3.67275800 -3.63638200 -1.49372600
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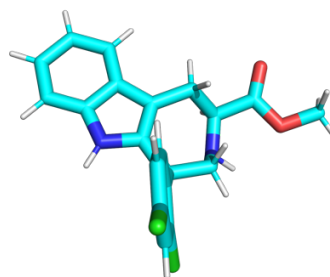


9

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 C 1.84839200 -1.82778800 -2.04391500
 H 2.45419700 -1.01727500 -1.64730000
 C 2.40044100 -2.75137500 -2.92280400
 C 1.62840900 -3.80605000 -3.45139700
 C 0.28880400 -3.95784000 -3.11145400
 C -0.26091900 -3.02581700 -2.22549500
 N -1.53574000 -2.91977700 -1.71122700

C -1.61909400 -1.81263700 -0.87653400
 C -2.90978800 -1.49642500 -0.17095700
 C -2.77742200 -0.23071500 0.74238900
 N -2.34463200 1.00060500 0.11321600
 C -0.92669800 1.23355500 -0.15715400
 H -0.53950000 1.98594400 0.54985300
 C -0.65401000 1.87005400 -1.52370500
 O -1.75120300 1.97105700 -2.30849700
 C -1.53812500 2.60669900 -3.58277100
 H -2.51403900 2.62115600 -4.06855300
 H -0.81699700 2.03805900 -4.17467900
 H -1.16208100 3.62278000 -3.44125700
 O 0.44006600 2.26345300 -1.86278100
 H -2.92524900 1.25609300 -0.67624100
 H -3.75805000 -0.05558600 1.19934600
 H -2.09812200 -0.46868200 1.56638300
 H -3.14645200 -2.33196900 0.50196800
 C -4.08552800 -1.34724600 -1.13300200
 C -3.91238000 -0.75465400 -2.39432300
 C -4.96905600 -0.56267000 -3.28165000
 C -6.24574500 -0.97541400 -2.90850900
 C -6.47199500 -1.56557900 -1.66794500
 C -5.39348900 -1.73762700 -0.80020400
 Cl -5.74707400 -2.47985500 0.76197200
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 Cl -7.59358600 -0.75651200 -4.01218300
 H -4.80368600 -0.10415300 -4.25044800
 H -2.91522800 -0.43791500 -2.68186500
 H -2.31919600 -3.50217900 -1.96510700
 H -0.30680200 -4.77118600 -3.51813100
 H 2.08774700 -4.51317900 -4.13670800
 H 3.44451600 -2.66167200 -3.20991800
 H 1.00721400 0.33035900 -0.27083300
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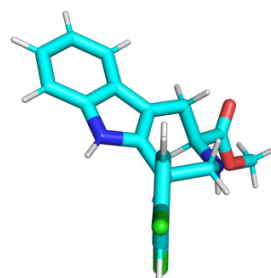


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C	-1.09953500	4.55281800	0.19129900
C	-0.12793500	5.32693000	0.85800900
C	1.01842800	4.74346300	1.38622300
C	1.16879800	3.36178100	1.23277700
N	2.17741900	2.51664600	1.64442900
C	1.89092400	1.21501100	1.25714300
C	2.82204800	0.09373000	1.63241000
C	2.20402500	-1.29921500	1.31735900
N	0.86623500	-1.41801600	1.88697800
C	-0.27150200	-1.14059900	1.01429900
H	-1.10521300	-0.81747600	1.65577600
C	-0.82577900	-2.34674200	0.23668900
O	-0.24552000	-3.51423500	0.59946500
C	-0.75424000	-4.68493600	-0.06425800
H	-0.18812100	-5.52266900	0.34375300
H	-0.60383800	-4.60674700	-1.14395800
H	-1.82184700	-4.80464500	0.13718400
O	-1.70848700	-2.27187100	-0.59087800
H	0.74500000	-2.32580000	2.32096100
H	2.24069300	-1.48187000	0.23290000
H	2.84800900	-2.05498200	1.77666700
H	2.94450500	0.12410900	2.72201900
C	4.20259900	0.22065600	0.99414500
C	4.34189000	0.71994100	-0.31023600
C	5.57520600	0.80933600	-0.94960400
C	6.71647300	0.38904500	-0.26932600
C	6.63309800	-0.11611900	1.02496700
C	5.37990900	-0.19681900	1.63337500
Cl	5.33364400	-0.85776300	3.27031200
H	7.52137800	-0.44210800	1.55248400
Cl	8.28724000	0.49672200	-1.04676400
H	5.65151600	1.20208500	-1.95754200
H	3.44907400	1.05795800	-0.82886600
H	3.01040300	2.79665100	2.13949900
H	1.76755800	5.33985600	1.90082700
H	-0.27680300	6.39828600	0.96129600
H	-1.98368800	5.04059800	-0.21000500
H	0.57850100	-0.40153600	-0.84179100
H	-0.96424700	0.28530700	-0.42749500

cis-**3-6a-OMe**-

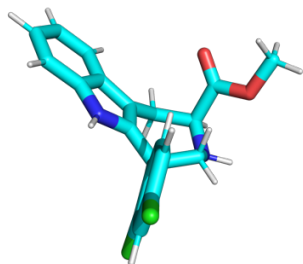


11

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H	-1.11521800	2.91174500	-0.01086300
C	-0.09577900	4.58758300	0.87864700
C	1.05207700	5.04829800	1.55556700
C	2.08949700	4.18312200	1.88513600
C	1.95012500	2.84054800	1.51933900
N	2.79002400	1.76497000	1.71502000
C	2.23111700	0.62248000	1.15504600
C	2.94004800	-0.70600100	1.23732000
C	2.30466900	-1.73885300	0.24728300
N	0.97325300	-2.24372300	0.53347800
C	-0.12931900	-1.30508400	0.79482900
H	-0.19551100	-1.03504700	1.86362400
C	-1.42870100	-2.03937800	0.44987600
O	-1.53794000	-3.16602700	1.19024500
C	-2.70055600	-3.96897700	0.92635200
H	-2.62931400	-4.82035000	1.60391600
H	-2.70513300	-4.30491500	-0.11392100
H	-3.61262200	-3.39823000	1.11979500
O	-2.26101700	-1.68466200	-0.35470500
H	0.99602000	-2.95158400	1.26026600
H	2.31861600	-1.29046000	-0.75297200
H	2.96138700	-2.61335300	0.20103200
H	2.83233300	-1.11069500	2.25147300
C	4.42904900	-0.59381000	0.93190000
C	4.87458300	0.20319900	-0.13614700
C	6.21607100	0.28881100	-0.49785600
C	7.15539300	-0.44294600	0.22632400
C	6.76584700	-1.25334100	1.28879100
C	5.41214600	-1.32207000	1.62065900
Cl	4.97978300	-2.38657400	2.96076100
H	7.49695300	-1.82360200	1.84896800
Cl	8.85541800	-0.34663200	-0.19898900
H	6.52884700	0.91415800	-1.32679200
H	4.13984400	0.77829300	-0.69252500

H	3.71526200	1.80924100	2.11386500
H	2.97294700	4.53762700	2.41002200
H	1.12745300	6.09797800	1.82602800
H	-0.88835600	5.29074900	0.63779900
H	0.21606600	-0.23733600	-1.05014700
H	-0.98316400	0.47899200	-0.00843300

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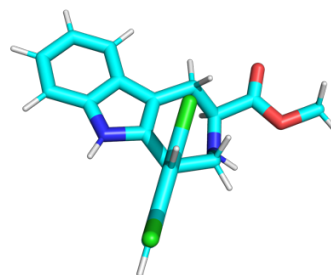


12

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C	-0.97480800	2.90972300	-1.18857400
H	-1.84711200	2.34270500	-0.87457700
C	-1.11888500	4.19771900	-1.68838500
C	-0.00032800	4.94745500	-2.10735200
C	1.28461100	4.42208300	-2.03440400
C	1.42267100	3.12623100	-1.52654900
N	2.54843600	2.35510400	-1.33512700
C	2.19178700	1.11758600	-0.81533600
C	3.22966700	0.08037200	-0.44496700
C	2.78911900	-1.35604700	-0.83330600
N	1.67215900	-1.86457000	-0.03734700
C	0.31759000	-1.44888700	-0.40046500
H	-0.34879600	-2.08450000	0.20209600
C	-0.11817600	-1.73273500	-1.85240000
O	0.51997100	-2.81640300	-2.35953900
C	0.10317700	-3.20920000	-3.67858900
H	0.71240400	-4.07702900	-3.93313600
H	0.27069200	-2.39718500	-4.39079500
H	-0.95874500	-3.46908200	-3.68311500
O	-0.97824800	-1.12960200	-2.45375000
H	1.71086300	-2.87914000	-0.05703600
H	2.60168500	-1.39264100	-1.91882800
H	3.63626500	-2.02094400	-0.63400500
H	3.33672000	0.07919000	0.64499800
C	4.59406600	0.35147800	-1.06500600
C	4.72377200	0.44920600	-2.46232700
C	5.95047700	0.64269500	-3.09185100
C	7.09779300	0.74326300	-2.30734000

C	7.02513100	0.65264900	-0.92090400
C	5.77970700	0.45700500	-0.31971900
Cl	5.76734100	0.34254200	1.43833100
H	7.91820400	0.73211500	-0.31302800
Cl	8.65863400	0.99031400	-3.07039500
H	6.01603200	0.71351400	-4.17194600
H	3.82777000	0.37532000	-3.07198300
H	3.49011600	2.62141600	-1.57684000
H	2.14846000	4.99844900	-2.35605400
H	-0.14471900	5.95256800	-2.49424000
H	-2.10988100	4.63764400	-1.76091200
H	-1.05482800	0.17726100	-0.22785600
H	0.10425300	0.05190000	1.09250700

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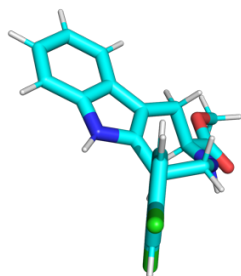


13

C	0.00000000	0.00000000	0.00000000
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H	1.33292700	2.77380800	0.61897700
C	0.39854900	4.66474600	0.18603700
C	-0.71961200	5.33523600	-0.35040200
C	-1.79169900	4.63007600	-0.88637300
C	-1.71704400	3.23411300	-0.87407700
N	-2.60569000	2.28317400	-1.32954500
C	-2.10279100	1.01330500	-1.08325500
C	-2.85756700	-0.20068700	-1.56037900
C	-2.08120800	-1.51964000	-1.29910400
N	-0.75698200	-1.45204500	-1.91530100
C	0.37213500	-1.04781900	-1.08078600
H	1.12007900	-0.58456500	-1.74075200
C	1.12634700	-2.19015700	-0.38135900
O	0.60035500	-3.40922500	-0.64684800
C	1.28065500	-4.51665400	-0.03005100
H	0.73351400	-5.40711600	-0.34088200
H	1.26613400	-4.41466700	1.05798500
H	2.31924400	-4.56343200	-0.36758500
O	2.10017500	-2.02506900	0.32124600
H	-0.53864600	-2.33322300	-2.36631500

H	-2.06025100	-1.75308900	-0.22744500
H	-2.64204000	-2.32697300	-1.78094800
H	-2.90174000	-0.12385400	-2.65663900
C	-4.31098500	-0.26205700	-1.09156700
C	-5.32283500	-0.32711400	-2.06350000
C	-6.67714300	-0.40216500	-1.74656300
C	-7.04641900	-0.41242900	-0.40458400
C	-6.08488800	-0.35160400	0.60039500
C	-4.73620500	-0.27967200	0.24861600
Cl	-3.58950800	-0.20755000	1.58163200
H	-6.37482200	-0.36067600	1.64423300
Cl	-8.74302500	-0.50259900	0.03609000
H	-7.43013400	-0.45069400	-2.52541500
H	-5.03175600	-0.32093100	-3.11116100
H	-3.51720200	2.47237800	-1.71754400
H	-2.65452100	5.14628000	-1.29984200
H	-0.74495000	6.42153900	-0.34526900
H	1.21926000	5.24586600	0.59780400
H	-0.48255400	-0.51110500	0.84375200
H	0.93997200	0.39097400	0.39750500

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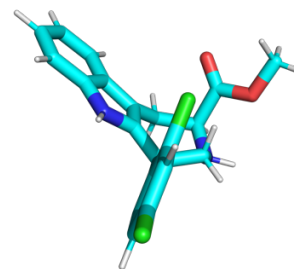


14

C	0.00000000	0.00000000	0.00000000
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C	-0.35354700	3.24438600	0.48971700
H	-1.24863200	2.85488400	0.01110800
C	-0.27032400	4.58737400	0.83596000
C	0.88514800	5.11024200	1.45199500
C	1.97811700	4.29945400	1.73765300
C	1.88707900	2.94806500	1.38972100
N	2.78710600	1.91687200	1.55230700
C	2.25985400	0.74287000	1.02885000
C	3.03548100	-0.55228200	1.08095800
C	2.48118100	-1.56389600	0.02086900
N	1.18486400	-2.17000900	0.25775600
C	0.07820500	-1.35031400	0.73537000
H	0.15966400	-1.10560700	1.81430300
C	-1.18114900	-2.22036500	0.65200000

O	-2.31288200	-1.49727200	0.52999600
C	-3.53312300	-2.25889900	0.54219900
H	-4.33468300	-1.52720600	0.43849000
H	-3.63100800	-2.80889600	1.48177500
H	-3.54806700	-2.96892600	-0.28847100
O	-1.16842500	-3.42760000	0.76044300
H	1.24804800	-3.01703600	0.81166100
H	2.47533800	-1.04327000	-0.94569800
H	3.19600700	-2.38650800	-0.07721900
H	2.91719300	-1.00752000	2.07150200
C	4.52390900	-0.35297400	0.82896700
C	4.95823700	0.45945700	-0.23268100
C	6.30404200	0.62453700	-0.54802400
C	7.25989400	-0.03994800	0.21806800
C	6.88277400	-0.86137500	1.27641800
C	5.52486800	-1.01087900	1.56218000
Cl	5.11379900	-2.08478800	2.90036100
H	7.62711300	-1.37897800	1.86936700
Cl	8.96501400	0.15701300	-0.14823900
H	6.60717500	1.25916700	-1.37347100
H	4.21066600	0.98219800	-0.82249200
H	3.72674900	2.00916700	1.90658900
H	2.86746800	4.70163900	2.21615100
H	0.92232200	6.16510200	1.70990900
H	-1.10711300	5.24884500	0.62866800
H	0.12113700	-0.17576300	-1.07832700
H	-1.00605800	0.40461800	0.13364100

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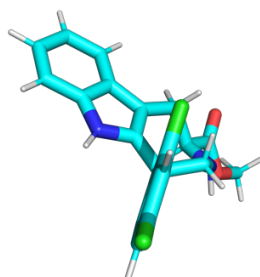


15

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H	1.72161200	2.38680000	1.03036200
C	0.88924900	4.15140300	1.94046400
C	-0.27091000	4.81571700	2.38899400
C	-1.52598300	4.23019500	2.26721500
C	-1.59122200	2.96152500	1.68280500
N	-2.67556000	2.15115800	1.42246900

C -2.24598500 0.95943100 0.85839300
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 C -2.71226600 -1.54318500 0.75908000
 N -1.57193200 -1.95332200 -0.06918800
 C -0.24062700 -1.48420800 0.32077700
 H 0.45876200 -2.04879600 -0.31445900
 C 0.21412700 -1.82006200 1.75555500
 O -0.37947000 -2.94846200 2.21540100
 C 0.05053700 -3.37761000 3.51893400
 H -0.52693900 -4.27638400 3.73752300
 H -0.14838600 -2.60088300 4.26153600
 H 1.12130400 -3.59834800 3.51550600
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 C -7.38544500 0.45930400 1.51311700
 C -6.45821700 0.25844700 2.53078000
 C -5.11141900 0.08397900 2.20221200
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 H -6.77158400 0.23429700 3.56753800
 Cl -9.07728700 0.67565700 1.92417300
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 H -5.31980800 0.34324500 -1.15326500
 H -3.62027800 2.32988800 1.72552000
 H -2.42186400 4.74057700 2.61185300
 H -0.18313100 5.80141400 2.83791600
 H 1.85522800 4.63670000 2.05156700
 H 1.04476000 0.21830000 0.23820700
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cis-3-6a-OMe-

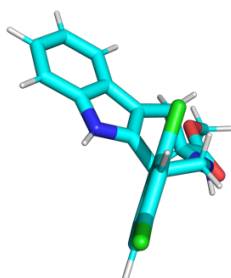


16

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 H 0.90368900 2.98949500 0.08432700
 C -0.29585700 4.62310000 -0.64469000
 C -1.51594200 5.02595600 -1.22519700
 C -2.50092700 4.09828700 -1.54605800
 C -2.23565000 2.75370500 -1.26922500
 N -2.99935200 1.62572900 -1.48417400
 C -2.32365800 0.50774600 -1.01523200
 C -2.92264600 -0.87319100 -1.12975300
 C -2.22977800 -1.86075500 -0.13337600
 N -0.88118900 -2.29928200 -0.46428500
 C 0.13959600 -1.29586400 -0.80882000
 H 0.10467000 -1.02042000 -1.87860400
 C 1.50356100 -1.95331600 -0.57880100
 O 1.60752500 -3.08237100 -1.31809400
 C 2.83454200 -3.81375000 -1.15886100
 H 2.74877500 -4.67837000 -1.81781600
 H 2.95779300 -4.13250600 -0.12050700
 H 3.68949500 -3.19534100 -1.44473600
 O 2.38680100 -1.54300300 0.13993600
 H -0.89485700 -3.01823500 -1.18099900
 H -2.22677800 -1.40566600 0.85974900
 H -2.84033100 -2.76693300 -0.06202600
 H -2.71468400 -1.25976100 -2.13957600
 C -4.44410000 -0.89841600 -0.99780000
 C -5.19850000 -1.43279300 -2.05569300
 C -6.58694200 -1.53499000 -2.02351900
 C -7.26192300 -1.08481800 -0.89219300
 C -6.56517200 -0.54301100 0.18422700
 C -5.17305000 -0.45646800 0.12241300
 Cl -4.37708800 0.24526000 1.52560500
 H -7.09179200 -0.19242800 1.06367900
 Cl -9.01129100 -1.19405800 -0.81428200
 H -7.13398000 -1.95376500 -2.86093700
 H -4.67100000 -1.78299600 -2.93934300
 H -3.95749200 1.62002700 -1.79902500
 H -3.44102800 4.40821500 -1.99544200
 H -1.69004400 6.07950300 -1.42631300
 H 0.45299400 5.37396300 -0.40757700
 H -0.13097300 -0.25148800 1.06132700
 H 0.95641000 0.52783500 -0.05779600

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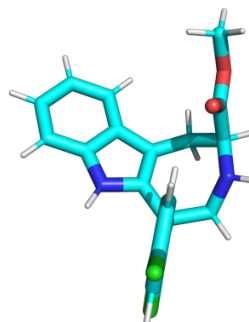


17

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H	1.09169800	2.92229800	0.10681800
C	-0.01749100	4.64079500	-0.56852600
C	-1.22475300	5.13061000	-1.10740100
C	-2.27838300	4.27408300	-1.40743600
C	-2.09517500	2.91165100	-1.15241400
N	-2.93696400	1.83918600	-1.35841100
C	-2.32433000	0.67301000	-0.92298600
C	-3.01414700	-0.66680400	-1.03333000
C	-2.40723600	-1.67884300	-0.00422700
N	-1.09015100	-2.21762400	-0.30428700
C	-0.04162800	-1.32308500	-0.78526100
H	-0.17403200	-1.04024600	-1.85016000
C	1.25696700	-2.13739800	-0.78496400
O	2.35874400	-1.37900500	-0.61799300
C	3.60943100	-2.08506000	-0.69870700
H	4.38076600	-1.33054300	-0.54264000
H	3.72077500	-2.55451200	-1.67961100
H	3.66203800	-2.85713000	0.07294000
O	1.29335000	-3.33243600	-0.98730800
H	-1.13316400	-3.03791600	-0.89949600
H	-2.38613900	-1.19265000	0.97489100
H	-3.08245700	-2.53578500	0.08455900
H	-2.81016500	-1.08177300	-2.03204600
C	-4.53566900	-0.59172700	-0.93370700
C	-5.30035100	-1.09600200	-1.99928400
C	-6.69260900	-1.11192000	-1.99520100
C	-7.36167500	-0.60160200	-0.88603300
C	-6.65493000	-0.08575400	0.19646300
C	-5.25900400	-0.08711400	0.16361600
Cl	-4.45077800	0.58673000	1.57413400
H	-7.17665000	0.31122800	1.05892700
Cl	-9.11570700	-0.60115000	-0.84447900
H	-7.24707200	-1.51075500	-2.83744400
H	-4.77771400	-1.49343400	-2.86555100

H	-3.90139800	1.89982400	-1.64716500
H	-3.20843400	4.65087700	-1.82551400
H	-1.33416200	6.19568000	-1.29275800
H	0.78652000	5.33755500	-0.34723600
H	-0.07504600	-0.22153400	1.07415700
H	0.98166700	0.45588800	-0.15070500

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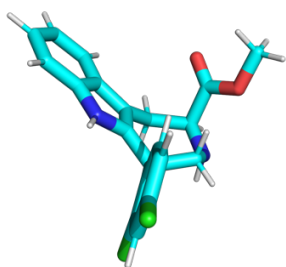


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H	2.30266900	-1.38825900	-1.60449200
C	2.00376700	-3.09240000	-2.88597200
C	1.09031000	-4.02453100	-3.41890700
C	-0.25833300	-3.98282400	-3.08247600
C	-0.67269900	-2.98234600	-2.19818400
N	-1.91953300	-2.69974200	-1.68245800
C	-1.84755400	-1.59277900	-0.85077500
C	-3.08154900	-1.09656200	-0.14315000
C	-2.76333200	0.15613500	0.72596700
N	-2.17493200	1.23755300	-0.04115800
C	-0.73768600	1.34528900	-0.21542600
H	-0.27893200	2.06192600	0.48798100
C	-0.42777400	1.88731500	-1.62204200
O	0.87095900	2.25759100	-1.70043700
C	1.29932900	2.74332500	-2.98381900
H	0.72709500	3.63032700	-3.26821700
H	1.16609000	1.97336200	-3.74818900
H	2.35515000	2.98928900	-2.86657200
O	-1.20476500	1.98757200	-2.54489000
H	-2.60897500	2.13373700	0.13188900
H	-3.70656900	0.51499900	1.14827200
H	-2.14531000	-0.16403200	1.57858000
H	-3.40697600	-1.87794500	0.55475600
C	-4.23352300	-0.82681400	-1.10653900
C	-4.03010900	-0.02681800	-2.24523600
C	-5.06162100	0.27275800	-3.13106400
C	-6.33451400	-0.23936500	-2.88776600

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 C -5.53416900 -1.31156000 -0.90055100
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 Cl -7.64935300 0.11657600 -3.99931000
 H -4.87787500 0.89658000 -3.99893200
 H -3.04258800 0.38605300 -2.42214600
 H -2.78111000 -3.14869500 -1.95455800
 H -0.96285200 -4.70275400 -3.49098000
 H 1.44566600 -4.79020000 -4.10307500
 H 3.05163000 -3.15524700 -3.16689000
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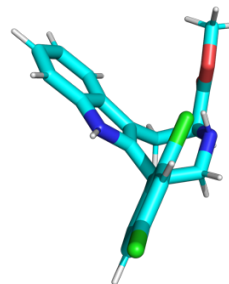


19

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 H -1.91805500 2.33011800 -0.80809200
 C -1.24329800 4.18225300 -1.67419900
 C -0.15108900 4.93616800 -2.15167100
 C 1.14051400 4.42276700 -2.13011400
 C 1.31270900 3.13478000 -1.61266000
 N 2.45284600 2.37420000 -1.46542000
 C 2.13186900 1.14308500 -0.91070900
 C 3.18692300 0.11200800 -0.57373000
 C 2.76379800 -1.33330500 -1.00460100
 N 1.63125600 -1.94877600 -0.33326400
 C 0.27889900 -1.43080000 -0.51475200
 H -0.36367000 -2.10164600 0.07607300
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 O 0.46280200 -2.40556500 -2.72100600
 C -0.06952700 -2.62171400 -4.03946300
 H 0.63677700 -3.29063400 -4.53198100
 H -0.15121900 -1.67584500 -4.58139900
 H -1.05932100 -3.08197000 -3.98145600
 O -1.29719300 -1.05979200 -2.30850000
 H 1.81906600 -2.05889800 0.65973400

H 2.57078000 -1.34439600 -2.08074100
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 H 3.29912600 0.09231000 0.51731200
 C 4.54874800 0.41725900 -1.17814400
 C 4.68648300 0.53228200 -2.57371400
 C 5.91337700 0.75518700 -3.19277400
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 C 5.72929900 0.52991100 -0.42552600
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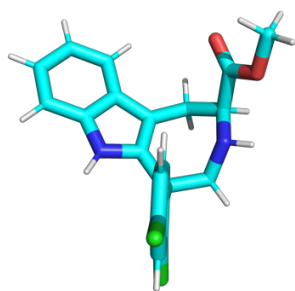


20

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 C -2.52573700 -1.39028300 0.81666700
 N -1.28985100 -1.58326400 1.54712300
 C -0.03871900 -1.31937200 0.84465100
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 O 2.30018800 -1.41143300 1.43572800
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 C -5.45956000 0.65443400 0.11157300
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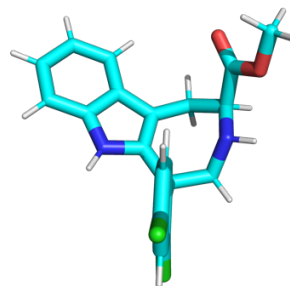


21

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 C 1.91162100 -3.31316400 -2.68676800
 C 0.99447100 -4.31060400 -3.07646200
 C -0.33972700 -4.25125800 -2.68955500
 C -0.73397700 -3.16690200 -1.89950500
 N -1.96515000 -2.84409500 -1.36907400

C -1.87781900 -1.65004000 -0.66548000
 C -3.10225300 -1.07961600 0.00271300
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 C -0.71682600 1.34562200 -0.24267700
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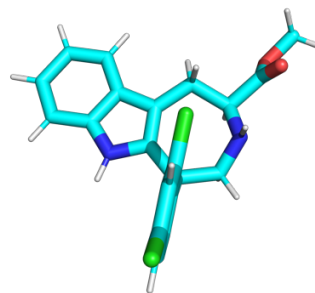


22

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 C 1.91100800 -3.31349800 -2.68689400
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 C -0.73461200 -3.16658100 -1.89983700
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 C -1.87813600 -1.64953900 -0.66573800
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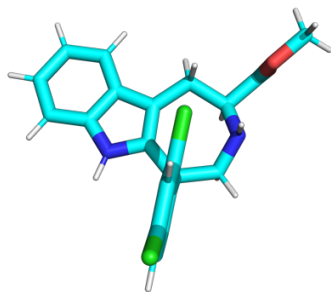


23

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 C 0.34697800 5.33650000 -0.09250600
 C 1.43321400 4.77678600 0.57078900
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 C 1.99711400 1.22479400 1.15651500
 C 2.88544200 0.18072100 1.78702200
 C 2.17259500 -1.17244800 2.13288700
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 C 0.02149500 -1.25264300 0.91090600
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 O -2.11758600 -2.27413900 0.67049100
 C -3.01381900 -3.20385100 0.03676100
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 H -3.05408800 -3.02466800 -1.04099400
 H -3.98841600 -3.02766800 0.49272400
 O -0.44012900 -3.08438300 -0.61209700
 H 1.78848800 -2.12112200 0.32214300
 H 2.95698100 -1.87301500 2.44533500
 H 1.55670000 -0.97635700 3.02005700
 H 3.12993200 0.57850700 2.78347900
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 C 5.39231700 0.17192400 1.95216700
 C 6.70022400 0.04466300 1.49281800
 C 6.90649400 -0.23937800 0.14618700
 C 5.82775900 -0.40005800 -0.71738000
 C 4.52840100 -0.27248200 -0.22182600
 Cl 3.24136800 -0.51435400 -1.39591900
 H 5.98769000 -0.62508200 -1.76495800
 Cl 8.53892300 -0.39768400 -0.47741300
 H 7.54158000 0.16757900 2.16586800
 H 5.23490000 0.39582600 3.00466300

H	3.24719100	2.85443700	1.72513800
H	2.22662200	5.39915600	0.97681700
H	0.29019200	6.41563500	-0.20625600
H	-1.51498400	4.99820000	-1.13414600
H	0.34639600	-0.30586000	-0.99836000
H	-1.04717000	0.30670900	-0.12402700

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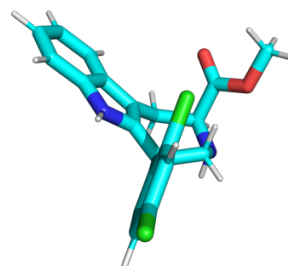


24

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C	-0.67889500	3.10511500	-0.66385600
H	-1.47943200	2.46510100	-1.02583200
C	-0.73471900	4.47849000	-0.86731500
C	0.29565400	5.32439900	-0.40879800
C	1.40103800	4.81353400	0.26215900
C	1.45062800	3.43028300	0.46234000
N	2.39465600	2.64528500	1.08276700
C	2.01344400	1.30562500	1.03638600
C	2.93492300	0.30985400	1.69828300
C	2.26980300	-1.04934200	2.10848600
N	1.40286400	-1.76533600	1.19773500
C	0.07691500	-1.19386600	0.97746000
H	-0.31076200	-0.87933600	1.95161400
C	-0.86545600	-2.29840700	0.50141700
O	-0.35357700	-2.94449500	-0.57179200
C	-1.16232500	-4.01138800	-1.09372200
H	-0.60431000	-4.41678800	-1.93828000
H	-2.13410500	-3.63175700	-1.42047500
H	-1.31920600	-4.77957300	-0.33197800
O	-1.94415000	-2.55679700	0.98684200
H	1.85303200	-1.99856100	0.31806800
H	3.08180900	-1.72257100	2.41016400
H	1.67919100	-0.84862500	3.01081900
H	3.18643500	0.75536700	2.67243900
C	4.30453600	0.16178400	1.01717700
C	5.44486700	0.37545900	1.81225100
C	6.74652500	0.26584100	1.33093600
C	6.93426400	-0.06725700	-0.00711600

C	5.84352700	-0.29356700	-0.84062400
C	4.55157300	-0.18193000	-0.32307700
Cl	3.24800800	-0.50898700	-1.46036300
H	5.98927900	-0.55671700	-1.88134300
Cl	8.55748800	-0.20544100	-0.65825900
H	7.59711400	0.43964400	1.98074400
H	5.30190200	0.63793500	2.85784000
H	3.25754700	2.97696100	1.48576100
H	2.19604500	5.46528800	0.61551500
H	0.22534900	6.39471300	-0.58250700
H	-1.58438700	4.91050200	-1.38886900
H	0.30790300	-0.35308200	-0.99491700
H	-1.05518800	0.28980100	-0.09694000

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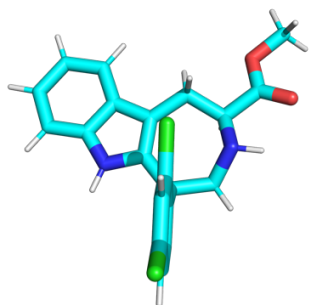


25

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C	0.88407700	2.85918100	1.38469400
H	1.77531900	2.34022800	1.04213300
C	0.98505900	4.11289600	1.97424100
C	-0.15868000	4.79711300	2.43524200
C	-1.42662900	4.24041300	2.31276900
C	-1.52163000	2.98033300	1.71376900
N	-2.62390200	2.19660000	1.44837400
C	-2.22401200	1.00193200	0.86855300
C	-3.22480700	-0.03416900	0.40695900
C	-2.77764200	-1.50130700	0.71429400
N	-1.59994100	-2.00269100	0.02263400
C	-0.27518200	-1.48098500	0.34586100
H	0.42112800	-2.07291900	-0.26869500
C	0.18433700	-1.77800000	1.78042900
O	-0.53484100	-2.73791400	2.39295000
C	-0.08338900	-3.08467000	3.71366300
H	-0.77489100	-3.85093600	4.06489300
H	-0.10712400	-2.21086800	4.36985200
H	0.93780800	-3.47329800	3.67872100
O	1.14692500	-1.24140000	2.28606900
H	-1.73215900	-1.97692600	-0.98547300

H	-2.61742400	-1.62438600	1.78508400
H	-3.61132900	-2.15802600	0.43641900
H	-3.26734500	0.03135200	-0.69208700
C	-4.65665500	0.21244500	0.87598400
C	-5.64505400	0.45460300	-0.09348200
C	-6.98854300	0.64193700	0.21853700
C	-7.37650300	0.59044300	1.55481200
C	-6.44063900	0.35982100	2.55825900
C	-5.10020800	0.17341300	2.21169800
Cl	-3.99044900	-0.10003700	3.55350300
H	-6.74286200	0.32085900	3.59788900
Cl	-9.06052900	0.82124800	1.98836700
H	-7.72015200	0.82592800	-0.56037300
H	-5.34286000	0.49660700	-1.13653800
H	-3.56428100	2.39423900	1.75329500
H	-2.30976400	4.76589300	2.66737500
H	-0.04756000	5.77549400	2.89482200
H	1.96175000	4.57575500	2.08708400
H	1.05300800	0.20032700	0.21799800
H	-0.11411400	0.10185600	-1.09130100

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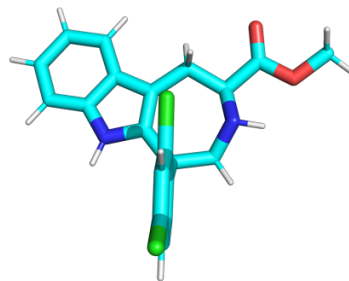


26

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C	-0.98329500	3.05440000	-0.46637300
H	-1.71910600	2.36114900	-0.86595600
C	-1.17302400	4.42529700	-0.59089800
C	-0.22760700	5.33969300	-0.08336800
C	0.92531800	4.90069800	0.55807800
C	1.11004000	3.51975400	0.67842700
N	2.12806900	2.79556100	1.25449500
C	1.87814900	1.43114200	1.12946600
C	2.88236100	0.48685300	1.74180600
C	2.29468300	-0.89920600	2.11511100
N	1.61713100	-1.58633200	1.03359300
C	0.21091700	-1.23938800	0.88573000
H	-0.25508100	-1.02684800	1.87113200
C	-0.52625400	-2.46874400	0.35243600

O	-1.77448600	-2.17666700	-0.05527300
C	-2.54966000	-3.29436800	-0.52473800
H	-3.51520200	-2.87797000	-0.81220300
H	-2.66997300	-4.03632100	0.26891500
H	-2.06111900	-3.76465400	-1.38172700
O	-0.06156800	-3.59029800	0.33671500
H	1.69589700	-2.59545000	1.12440800
H	3.12488900	-1.52611400	2.45714000
H	1.62604800	-0.74099700	2.98329100
H	3.12891600	0.92899800	2.71910600
C	4.24322700	0.38863800	1.03338300
C	5.37867800	0.44008800	1.86277100
C	6.68211200	0.32641400	1.39040800
C	6.87610300	0.16104600	0.02217900
C	5.79193600	0.11001200	-0.84584900
C	4.49212900	0.22038500	-0.34036800
Cl	3.21698100	0.15085500	-1.54240900
H	5.94463800	-0.01553300	-1.91093300
Cl	8.50380000	0.02232600	-0.62216500
H	7.52771700	0.37086500	2.06784800
H	5.22858700	0.57167900	2.93203700
H	2.95683500	3.18527200	1.67681000
H	1.65542600	5.60528600	0.94831000
H	-0.40190900	6.40636500	-0.19567100
H	-2.06256300	4.80202800	-1.08847400
H	0.35217900	-0.24457700	-1.01217200
H	-1.07617200	0.18358700	-0.07826100

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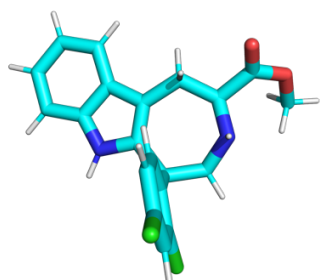


27

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C	-0.02007200	-2.57919800	0.25192900
C	1.15124000	-3.00753000	-0.39673800
H	1.84331000	-2.28541700	-0.82219200
C	1.41268200	-4.36898100	-0.49082600
C	0.52353700	-5.31987700	0.05034900
C	-0.64408400	-4.92788400	0.69564400
C	-0.90122600	-3.55620100	0.78557300
N	-1.95117800	-2.87378800	1.35615600

C -1.77406200 -1.50170400 1.19558600
 C -2.80864400 -0.58952800 1.80240700
 C -2.26842800 0.82127000 2.14588100
 N -1.66485000 1.54687500 1.03865000
 C -0.24290500 1.25733600 0.84438700
 H 0.26128500 1.11449200 1.82416800
 C 0.47975800 2.44597700 0.20365600
 O -0.04293800 3.62914500 0.60528300
 C 0.60136600 4.80125300 0.07549000
 H 0.05790200 5.64840900 0.49449700
 H 0.54372900 4.80695200 -1.01577200
 H 1.65138400 4.82768100 0.37739100
 O 1.43605700 2.36294600 -0.53329900
 H -1.77765100 2.54399600 1.18712000
 H -3.11225200 1.41109000 2.51954300
 H -1.55863900 0.69679400 2.98583600
 H -3.02178200 -1.02098800 2.79237400
 C -4.18469100 -0.55480100 1.11797500
 C -5.30230300 -0.62489800 1.96987400
 C -6.61723800 -0.56807400 1.51974600
 C -6.84171800 -0.44411200 0.15171500
 C -5.77596800 -0.37765800 -0.73782400
 C -4.46419300 -0.43008500 -0.25429400
 Cl -3.21312100 -0.34601600 -1.47981100
 H -5.95208600 -0.28503400 -1.80269100
 Cl -8.48472300 -0.37759800 -0.46474300
 H -7.44840500 -0.62511500 2.21394600
 H -5.12844300 -0.72553900 3.03894000
 H -2.74882600 -3.29692900 1.80522600
 H -1.33080200 -5.66089300 1.11152700
 H 0.75366800 -6.37816000 -0.03869000
 H 2.31529000 -4.70974700 -0.99073300
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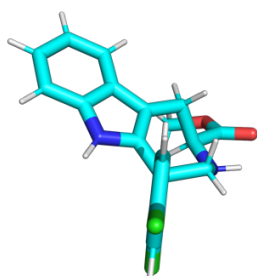


28

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 C 0.76416600 -2.41627900 0.62910000

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 H 2.31859800 -1.88192800 -0.79031000
 C 2.56669400 -3.87710100 -0.02159800
 C 2.07026400 -4.88681200 0.82859900
 C 0.92340200 -4.68824900 1.58831800
 C 0.28185600 -3.45045100 1.47487700
 N -0.85214600 -2.96743200 2.08892300
 C -1.10474600 -1.66710500 1.66884600
 C -2.31813500 -0.95441800 2.20369000
 C -2.05884300 0.56297100 2.45826100
 N -1.68020800 1.39879100 1.32905000
 C -0.31344700 1.26870900 0.81035000
 H 0.35284000 1.29658500 1.68106200
 C -0.06922200 2.51485600 -0.06380600
 O 0.16349600 3.70493500 0.53600000
 C 0.18934200 3.84331300 1.96159400
 H 0.27766500 4.91557400 2.14484400
 H 1.06000700 3.33776000 2.39548600
 H -0.73178800 3.45934200 2.40554700
 O -0.11171700 2.47275000 -1.27241900
 H -2.35750700 1.33740700 0.57090900
 H -2.96840000 0.98640200 2.89806500
 H -1.26747100 0.64608800 3.21264000
 H -2.52493600 -1.36965200 3.19875900
 C -3.57851900 -1.16946200 1.36296800
 C -3.51000200 -1.38080100 -0.02218000
 C -4.64643100 -1.53644600 -0.81361100
 C -5.89992700 -1.48761200 -0.20975100
 C -6.02360400 -1.28947800 1.16316900
 C -4.86639200 -1.13123500 1.92422400
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 Cl -7.34867500 -1.68685100 -1.17938000
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 H -2.53188400 -1.45068500 -0.48654600
 H -1.41691000 -3.47160500 2.75550100
 H 0.53936600 -5.46677100 2.24249300
 H 2.59249900 -5.83757500 0.89035200
 H 3.46444000 -4.06672600 -0.60346100
 H -0.63306600 0.00637700 -0.89783200
 H 1.02510300 0.08611200 -0.37983200

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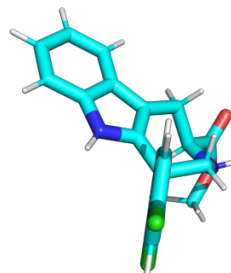


29

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H	-1.46082300	2.77361600	-0.09547500
C	-0.67211700	4.56321800	0.80491200
C	0.39544500	5.16305900	1.50351500
C	1.52021900	4.43037900	1.86640800
C	1.55078200	3.07772700	1.51356300
N	2.50811300	2.11201400	1.74136700
C	2.10433000	0.90597500	1.18649100
C	2.96185500	-0.32986900	1.31245100
C	2.47943200	-1.45151700	0.35837000
N	1.24221900	-2.09725000	0.78044700
C	0.01448900	-1.30245900	0.85800500
H	-0.14346500	-0.99612300	1.89847500
C	-1.14702700	-2.19629700	0.40593600
O	-2.39656600	-1.92813800	0.85194300
C	-2.64393500	-1.03926400	1.94927700
H	-3.72769900	-1.03863800	2.07538300
H	-2.30630800	-0.01948100	1.74217200
H	-2.17497600	-1.40451800	2.86862600
O	-0.99515300	-3.09592600	-0.38979600
H	1.05492300	-2.88155200	0.15796800
H	2.44768800	-1.03189500	-0.66340500
H	3.24342800	-2.23580200	0.34940200
H	2.87786400	-0.72366900	2.33213100
C	4.43234600	-0.03281800	1.03077300
C	4.79171600	0.73160200	-0.09181800
C	6.11720500	0.99112300	-0.42806900
C	7.12771300	0.47669200	0.38229100
C	6.82503000	-0.28706500	1.50544900
C	5.48539600	-0.53483800	1.81152500
Cl	5.17058100	-1.52332600	3.23661400
H	7.61231600	-0.68647000	2.13325600
Cl	8.80854700	0.79543200	-0.00902800
H	6.36324200	1.58465300	-1.30164000
H	3.99996900	1.14050500	-0.71325600

H	3.41305000	2.27084800	2.15777500
H	2.34252100	4.89226200	2.40671700
H	0.33902000	6.21649000	1.76333200
H	-1.53574300	5.16514400	0.53580100
H	0.28888500	-0.25627500	-1.02778700
H	-1.02775700	0.37495600	-0.06948200

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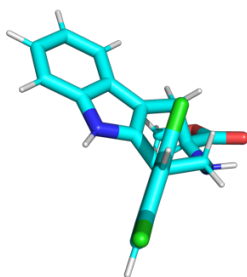


30

C	0.00000000	0.00000000	0.00000000
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H	-1.24623900	2.86006500	0.18736800
C	-0.28039300	4.52256900	1.15844700
C	0.86364600	4.99340900	1.83503900
C	1.94789400	4.15913700	2.08331300
C	1.85958400	2.83725100	1.63544400
N	2.75365500	1.79281600	1.74113600
C	2.23297800	0.66429700	1.12077800
C	3.00377200	-0.63700000	1.09415500
C	2.49966800	-1.56009000	-0.04207900
N	1.23083600	-2.23829900	0.24915000
C	0.08251400	-1.39658300	0.65230000
H	0.15610300	-1.23864200	1.73545500
C	-1.18174600	-2.21889900	0.35720700
O	-1.50525200	-3.23690700	1.18623500
C	-0.72483100	-3.53691300	2.35491500
H	-1.07535900	-4.51422800	2.69087800
H	-0.91078900	-2.80069200	3.14498700
H	0.34005300	-3.57970500	2.11449800
O	-1.87544300	-2.01021500	-0.61177000
H	0.97490600	-2.75365900	-0.59210600
H	2.46785200	-0.96065200	-0.96722400
H	3.23977000	-2.35196800	-0.19979400
H	2.85527200	-1.17221200	2.03944300
C	4.50259800	-0.41268400	0.91050200
C	4.96446800	0.44043600	-0.10594100
C	6.31876500	0.64434700	-0.35408200
C	7.25362800	-0.01949900	0.43857000

C	6.84789600	-0.87539800	1.45800000
C	5.48175900	-1.06370000	1.67714000
Cl	5.03692400	-2.17475900	2.97184800
H	7.57634400	-1.39020900	2.07270200
Cl	8.96788000	0.22454000	0.15658100
H	6.64456800	1.30873100	-1.14676900
H	4.23214400	0.96453400	-0.71362300
H	3.68965000	1.85884000	2.11061300
H	2.82826300	4.52115100	2.60818700
H	0.89868200	6.02643700	2.17000600
H	-1.11031100	5.20145200	0.98263400
H	0.12455000	-0.09426200	-1.08668500
H	-1.01570000	0.38504200	0.14120900

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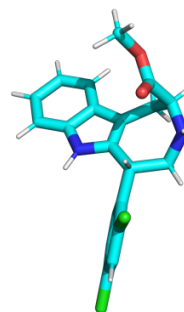


31

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C	-0.94457500	1.06002300	-0.49749600
C	-0.66876900	2.47237900	-0.58973900
C	0.42095500	3.28157000	-0.22303500
H	1.30057500	2.84716900	0.24618900
C	0.35583400	4.64977900	-0.45661300
C	-0.78158000	5.23387200	-1.05033200
C	-1.87429600	4.46013300	-1.42617500
C	-1.80139300	3.08363800	-1.19328600
N	-2.70460900	2.07794400	-1.46742400
C	-2.20011900	0.86269100	-1.03145600
C	-2.96879000	-0.42184800	-1.23294700
C	-2.43346200	-1.54829500	-0.31368400
N	-1.18438700	-2.12715700	-0.80803900
C	-0.00547900	-1.26250000	-0.91701100
H	0.07362500	-0.90268100	-1.94934500
C	1.22348100	-2.11494300	-0.57850100
O	2.42888600	-1.76567500	-1.08650700
C	2.56633300	-0.81221800	-2.14780100
H	2.19557800	0.17812900	-1.86735300
H	2.05885500	-1.15365000	-3.05587900
H	3.63900800	-0.75171500	-2.33816600
O	1.16534000	-3.05484700	0.18222700
H	-0.92629800	-2.90635600	-0.20409500

H	-2.37396500	-1.16620300	0.71590500
H	-3.16516000	-2.36326000	-0.31001900
H	-2.78726800	-0.77548400	-2.25866200
C	-4.48350200	-0.24854800	-1.12328100
C	-5.27613100	-0.60780700	-2.22576000
C	-6.66544200	-0.51079900	-2.22506200
C	-7.29946600	-0.03248200	-1.08168400
C	-6.56228300	0.34148000	0.03840900
C	-5.17094800	0.22983300	0.00741300
Cl	-4.32023900	0.72713400	1.46488200
H	-7.05724200	0.71344900	0.92738300
Cl	-9.04778400	0.10776000	-1.04338000
H	-7.24395600	-0.80000400	-3.09543200
H	-4.77972400	-0.98261000	-3.11703400
H	-3.64425300	2.21261000	-1.80877500
H	-2.75102100	4.91006100	-1.88497600
H	-0.80577800	6.30723800	-1.21699800
H	1.19193100	5.28350300	-0.17366700
H	-0.21683800	-0.31615400	1.02914400
H	1.01306900	0.41861700	0.02965000

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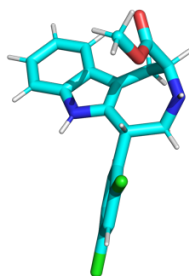


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C	0.68216300	4.57447400	2.77225900
C	-0.49047200	3.92089400	3.13489000
C	-0.79364300	2.72595500	2.47510400
N	-1.86074700	1.86601400	2.62182000
C	-1.74153300	0.80731300	1.73262400
C	-2.76761300	-0.29496300	1.70358500
C	-2.58135800	-1.20704700	0.44508500
N	-1.40465400	-2.05928400	0.38154200
C	-0.06660700	-1.47636500	0.44575800
H	0.58871400	-2.04805700	-0.23063400
C	0.54356700	-1.64549700	1.84554000

O	-0.01742900	-2.17395500	2.78395100
O	1.80593200	-1.18243400	1.89282100
C	2.46603900	-1.30061400	3.16574000
H	2.52523100	-2.34880700	3.47007200
H	1.92450800	-0.73516900	3.92808400
H	3.46296300	-0.88533900	3.01709900
H	-1.47183600	-2.77902300	1.09736300
H	-3.44713900	-1.87471000	0.38899900
H	-2.62554700	-0.57299100	-0.44784300
H	-2.62315600	-0.93158100	2.58443800
C	-4.19464800	0.23997600	1.71853500
C	-5.23568600	-0.36596500	2.44008100
C	-6.54973500	0.10271400	2.39447600
C	-6.84223900	1.20367700	1.59511700
C	-5.84642100	1.83268600	0.85021200
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H	-7.32544800	-0.38619000	2.97128800
Cl	-4.93337300	-1.77679800	3.45411300
H	-2.65018500	2.00853700	3.23313800
H	-1.14440400	4.32347300	3.90425200
H	0.94826500	5.50519100	3.26578400
H	2.44068700	4.58544300	1.51789000
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H	-0.47905700	0.08158900	-0.98476300

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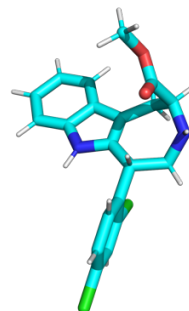


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C	0.64760900	4.42933700	2.99878900
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C	-0.81647100	2.58907500	2.61087000
N	-1.87938900	1.71691000	2.71406000

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C	-2.58684800	-1.23405200	0.37540300
N	-1.40639700	-2.07262300	0.26689600
C	-0.06273200	-1.50425600	0.34352200
H	0.56801000	-2.02291300	-0.39484000
C	0.68000900	-1.72198000	1.67193300
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C	0.56951500	-2.51813700	3.88722300
H	0.91832700	-1.57409700	4.31284000
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H	-0.17975700	-2.97911500	4.53130800
H	-1.48208900	-2.86784600	0.89203500
H	-3.44962800	-1.90093900	0.27772700
H	-2.63062300	-0.54969500	-0.47968700
H	-2.64335300	-1.07589000	2.52617300
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C	-5.25298000	-0.51096500	2.39528100
C	-6.56777800	-0.04376400	2.37103600
C	-6.85824400	1.10296800	1.63772800
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H	-3.77384500	1.81478500	0.45120000
H	-6.09633000	2.66782500	0.36610200
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Cl	-4.95403300	-1.98109100	3.32577200
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H	-1.18233500	4.11761500	4.11038300
H	0.90695500	5.33780000	3.53553800
H	2.41366700	4.50376400	1.75747800
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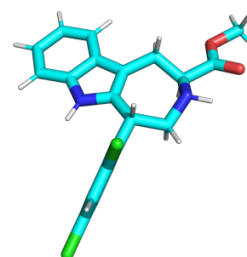


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 C 0.87635600 4.13899400 -2.74824400
 C 1.07297500 2.87397600 -2.18671700
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 C 1.86699000 0.84584000 -1.57403600
 C 2.81490800 -0.32585900 -1.59480800
 C 2.57384600 -1.26843000 -0.36898200
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 O 0.15088400 -2.01481200 -2.89396300
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 C 4.28214600 0.07145300 -1.73524500
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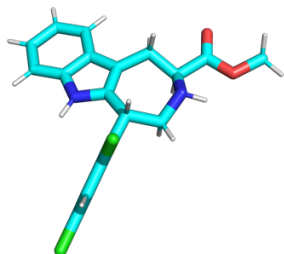
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 C -0.04232700 4.61957000 -0.28587100
 C -1.33616000 5.17932100 -0.25283500
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H	-1.45306500	6.25861700	-0.29907000
H	0.81931600	5.27797000	-0.35631700
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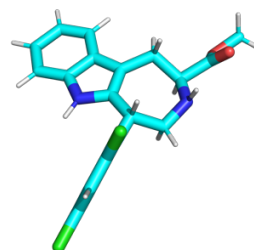


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C	-0.28873200	4.61342800	-0.35453600
C	-1.61140300	5.10139800	-0.32329100
C	-2.69442600	4.23606100	-0.21795800
C	-2.41970900	2.86672900	-0.14220400
N	-3.26711500	1.78730900	-0.03105800
C	-2.53524600	0.60502500	-0.01264800
C	-3.23115900	-0.72410000	0.19399800
C	-2.55023200	-1.89728500	-0.55966100
N	-1.19563400	-2.18081400	-0.10468600
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O	1.03994600	-3.41803100	-0.89128400
C	2.25915900	-4.18007200	-0.94373600
H	2.81886800	-4.06706500	-0.01203900
H	2.88179800	-3.84472600	-1.77696900
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H	-2.59760800	-1.69534100	-1.64626700
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H	-3.71452000	4.61079800	-0.19027600
H	-1.78764600	6.17209400	-0.38054100
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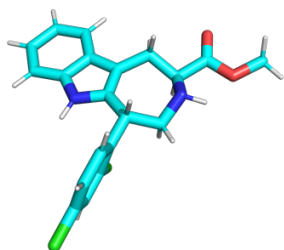


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C	-2.41672300	4.40323900	-0.35358400
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N	-3.12906500	1.98572700	-0.26733500
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C	-2.57975900	-1.65733300	-1.01465400
N	-1.24741900	-2.12222000	-0.70115300
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H	-0.14166700	-0.89824200	-1.96546900
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O	1.26399700	-2.93726400	0.12930700
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H	3.24444600	-3.48636600	-1.55308800
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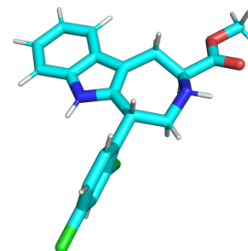


7

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C 2.89525800 4.08547600 0.44368600
C 2.55370600 2.73776500 0.29387000
N 3.34732600 1.62672900 0.11302700
C 2.55802200 0.48579500 0.04802400
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C 4.68750000 -0.92288900 0.01205300
C 5.32895900 -0.73323400 1.25083200
C 6.71424400 -0.84036800 1.39647500
C 7.49277600 -1.14671000 0.28458500
C 6.90657300 -1.34089800 -0.96339800
C 5.52392400 -1.22420700 -1.07615500
H 5.06586700 -1.37407700 -2.05010600
H 7.51749800 -1.57574500 -1.82792800
Cl 9.23225400 -1.28346800 0.46677500
H 7.17123900 -0.68809100 2.36681800
Cl 4.43002500 -0.33279300 2.71222700
H 4.35415700 1.61693300 0.16492300
H 3.93283600 4.40991900 0.43860200
H 2.08550400 6.05268400 0.71198900
H -0.27737900 5.31336000 0.71457500
H -0.25165500 -0.14020300 -1.06112300
H -0.85186200 0.51961200 0.44869300

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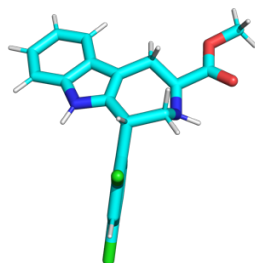


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C 1.09701700 2.33748800 0.26439100
C 0.01971700 3.22500100 0.43384500
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C 0.27798800 4.58330500 0.57259000
C 1.59681100 5.08092200 0.54408100
C 2.68234100 4.22915400 0.37214700
C 2.41440000 2.86428500 0.22850100
N 3.26441500 1.79929500 0.03319000

C 2.54161100 0.61338600 -0.01693900
 C 3.25890800 -0.68658000 -0.32037600
 C 2.59804300 -1.94385700 0.30309200
 N 1.23787300 -2.14454700 -0.17417600
 C 0.21299200 -1.41589400 0.56252400
 H 0.47736400 -1.31305400 1.63454800
 C -1.06764000 -2.25114700 0.54220900
 O -1.12117000 -3.41402400 0.19651600
 O -2.12931900 -1.56395800 1.00081300
 C -3.36275100 -2.30189000 1.06793600
 H -3.25650400 -3.16371200 1.73180200
 H -3.65376300 -2.65100000 0.07404500
 H -4.09943200 -1.60120400 1.46114600
 H 0.99409200 -3.13169800 -0.17001700
 H 3.19365700 -2.80702400 -0.01343700
 H 2.65613400 -1.88785900 1.40166000
 H 3.17449300 -0.84384900 -1.40514000
 C 4.75609000 -0.65617700 -0.01713000
 C 5.33142100 -0.44938700 1.25092200
 C 6.71309600 -0.47500900 1.45490100
 C 7.55500100 -0.71585600 0.37334400
 C 7.03516500 -0.92593700 -0.90116000
 C 5.65391900 -0.89041900 -1.07223000
 H 5.24715200 -1.05231400 -2.06688900
 H 7.69535500 -1.11045200 -1.74129000
 Cl 9.29065900 -0.74901600 0.62811200
 H 7.11863400 -0.31152900 2.44606700
 Cl 4.34668600 -0.12999300 2.67610500
 H 4.27122300 1.84566600 0.06193600
 H 3.69973500 4.61126800 0.34691200
 H 1.76833100 6.14799900 0.65666500
 H -0.54843500 5.27641600 0.70530100
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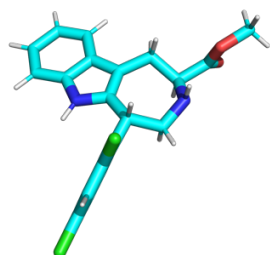


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 H 1.60178200 2.54809200 -0.84593500
 C 0.76192100 4.53010100 -0.87662900
 C -0.37364000 5.33611400 -0.65692700
 C -1.57562200 4.78359400 -0.22841400
 C -1.61440800 3.40076600 -0.02542600
 N -2.64150200 2.58383400 0.39689200
 C -2.21251800 1.26463300 0.43205300
 C -3.14814000 0.17449900 0.88375200
 C -2.46150000 -1.21905400 0.81816400
 N -1.95668900 -1.52004400 -0.51870000
 C -0.56575800 -1.18177500 -0.82376400
 H -0.50978100 -0.89165500 -1.88446400
 C 0.33695400 -2.41698600 -0.68595500
 O -0.05409500 -3.52520800 -0.38262400
 O 1.62054900 -2.13550000 -0.98606100
 C 2.53169600 -3.24806200 -0.92737700
 H 2.22825400 -4.02753000 -1.63099800
 H 2.55760200 -3.66871100 0.08107000
 H 3.50609200 -2.84198300 -1.19965600
 H -2.08556800 -2.50858300 -0.71376700
 H -1.69330700 -1.26896200 1.60401500
 H -3.21162500 -1.97261500 1.07465800
 H -3.39094500 0.35009500 1.93933400
 C -4.45937600 0.17470200 0.10332300
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 C -6.89910100 -0.06434600 -0.02087500
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 C -5.62389000 0.30766500 -2.04828600
 C -4.45622400 0.33886500 -1.29155800
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 H -5.59140600 0.43645900 -3.12461500
 Cl -8.33193400 0.07486200 -2.32976100
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 Cl -5.84626700 -0.27918600 2.45243800
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 H -2.45084600 5.40470100 -0.05582200
 H -0.30886800 6.40785500 -0.82347300
 H 1.68672500 4.99422500 -1.20838800
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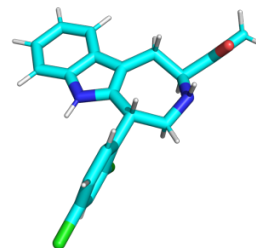


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H	1.06280500	2.90084300	-0.08376100
C	-0.19684100	4.64300700	0.01605400
C	-1.51004700	5.15017800	0.10017300
C	-2.60741800	4.29841200	0.15021500
C	-2.35695300	2.92275000	0.11711500
N	-3.22353700	1.85342200	0.15400900
C	-2.51534700	0.66049700	0.07571700
C	-3.23012900	-0.66967700	0.19432600
C	-2.61459400	-1.79184400	-0.70602900
N	-1.23977700	-2.18233900	-0.46779200
C	-0.18751900	-1.25797400	-0.88118200
H	-0.40764000	-0.94100500	-1.90538700
C	1.13416900	-2.01939200	-0.95794500
O	1.90178700	-1.99878700	-1.89346800
O	1.36937100	-2.69945000	0.18896700
C	2.59524600	-3.44958100	0.22191500
H	2.60410900	-4.20097500	-0.57184800
H	2.62154600	-3.92636900	1.20219200
H	3.45425700	-2.78592000	0.09289100
H	-1.08757300	-2.49938100	0.48645500
H	-3.23960600	-2.68372800	-0.57603100
H	-2.70332500	-1.49240700	-1.75726300
H	-3.12047600	-1.01296800	1.23067200
C	-4.71878200	-0.58193600	-0.11122300
C	-5.72021300	-1.06153100	0.74862200
C	-7.07530800	-1.02129800	0.41420500
C	-7.45004400	-0.49250800	-0.81707900
C	-6.49389400	-0.01028100	-1.70924600
C	-5.15133200	-0.06402300	-1.34553300
H	-4.40504400	0.31495000	-2.03818500
H	-6.79406900	0.39666900	-2.66855600
Cl	-9.15069300	-0.43376300	-1.24302400
H	-7.82006400	-1.39680100	1.10540800
Cl	-5.31970300	-1.75327600	2.32026800

H	-4.22941800	1.91412200	0.18316600
H	-3.62024100	4.68741300	0.21729400
H	-1.66715000	6.22494500	0.12740400
H	0.63875100	5.33667200	-0.02008600
H	0.23853100	-0.33442200	1.02133000
H	0.88929700	0.53682400	-0.35555300

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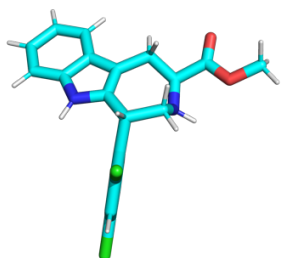


11

C	0.00000000	0.00000000	0.00000000
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H	-1.04435000	2.88812300	0.40152400
C	0.23459100	4.61126100	0.56702500
C	1.55473200	5.10566200	0.60037700
C	2.64497400	4.25022500	0.48925400
C	2.38083100	2.88478200	0.34351200
N	3.23862900	1.81711000	0.19847400
C	2.51662200	0.63462900	0.12223200
C	3.21308100	-0.68782700	-0.11596300
C	2.55825300	-1.88937600	0.64376700
N	1.19874600	-2.24043400	0.29443800
C	0.11906100	-1.36573900	0.72615400
H	0.23690600	-1.18394000	1.79965300
C	-1.18545300	-2.12249500	0.49419000
O	-1.41340500	-2.80053000	-0.48523500
O	-2.07879900	-1.89872700	1.47908100
C	-3.36341000	-2.52099300	1.29889300
H	-3.25679700	-3.60749700	1.24643300
H	-3.83641100	-2.16537500	0.37967400
H	-3.95186300	-2.23396600	2.17065200
H	1.08160500	-2.50147500	-0.68123500
H	3.18578800	-2.76840800	0.45120400
H	2.59152400	-1.70056000	1.72010700
H	3.08979400	-0.92427900	-1.18464300
C	4.72127700	-0.65719100	0.11741600
C	5.35244200	-0.41074800	1.35179500
C	6.74089100	-0.44840600	1.49956400
C	7.53410200	-0.74316200	0.39487700

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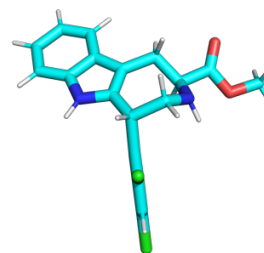


12

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 H 1.59990400 2.56426800 -0.79700600
 C 0.77844100 4.55332400 -0.72592400
 C -0.34344100 5.35936200 -0.44410600
 C -1.53896200 4.80030100 -0.00620400
 C -1.58532600 3.41069100 0.14187100
 N -2.60837000 2.58597400 0.55924100
 C -2.19123000 1.26243300 0.52778300
 C -3.12956300 0.16285700 0.95333500
 C -2.47634000 -1.23797100 0.76892600
 N -1.98724700 -1.42830700 -0.59277800
 C -0.57694300 -1.15204700 -0.85966900
 H -0.49503900 -0.84642000 -1.91395200
 C 0.37068200 -2.35738700 -0.73594800
 O 1.57454200 -2.28589900 -0.85692300
 O -0.28584000 -3.51894700 -0.51180500
 C 0.54769200 -4.68902500 -0.42896200
 H 1.25941600 -4.59198100 0.39467500
 H 1.10081700 -4.83030100 -1.36098800
 H -0.13323100 -5.52228300 -0.25378800
 H -2.22140800 -2.35403900 -0.93138100

H -1.69692500 -1.36844500 1.53350000
 H -3.23948700 -1.99385100 0.97582600
 H -3.33079000 0.27699000 2.02596700
 C -4.46750600 0.23145600 0.22210100
 C -5.69852900 0.00345700 0.85532500
 C -6.91311700 0.03037200 0.16756600
 C -6.89913800 0.28343000 -1.20052100
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 H -5.70297600 0.69937000 -2.94420100
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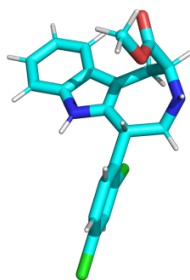


13

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 C -2.68518600 -3.50403600 -1.53097400
 C -2.05597700 -4.76330900 -1.45271000
 C -0.76545200 -4.89373300 -0.95181200
 C -0.11732600 -3.72915900 -0.52838000
 N 1.14090200 -3.54437000 0.00389600
 C 1.34674900 -2.19627800 0.26986900
 C 2.62743800 -1.73415900 0.90860100
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 N 2.29596700 0.82479500 0.59667400
 C 1.22897700 0.81560400 -0.41726500
 H 1.58470100 0.41033400 -1.37999300
 C 0.85485300 2.27914900 -0.67437500

O -0.23384800 2.78178300 -0.50633500
 O 1.93045100 2.95997500 -1.13103800
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 H 1.43659400 4.86214500 -0.42582900
 H 0.93779400 4.52197900 -2.10001400
 H 2.67752600 4.74784500 -1.71791000
 H 3.17621700 1.08807400 0.16684300
 H 1.59964000 -0.33585300 2.18428500
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 H 2.81250300 -2.38230600 1.77691100
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 C 5.14823900 -2.02759600 0.50698000
 C 6.27350200 -2.09196500 -0.31447400
 C 6.10574900 -1.96247000 -1.69061200
 C 4.84003700 -1.77805000 -2.24174200
 C 3.73773700 -1.72270200 -1.39188400
 H 2.74706200 -1.59954500 -1.81912800
 H 4.71793800 -1.68462300 -3.31531900
 Cl 7.51340000 -2.04170000 -2.73635000
 H 7.25735000 -2.24161800 0.11363700
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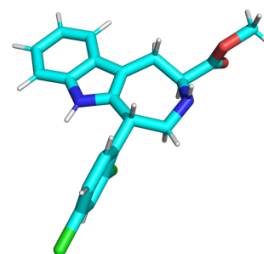


14

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 H -1.72446700 2.56427900 -0.44548700
 C -1.18756200 4.14659200 -1.80334000
 C -0.25198800 4.63572300 -2.73754500
 C 0.89306000 3.91296200 -3.05409700
 C 1.08020400 2.68665800 -2.40929500
 N 2.09265500 1.75725600 -2.52518700

C 1.85960700 0.69847800 -1.66006700
 C 2.80247800 -0.47490500 -1.60328300
 C 2.54153700 -1.34686400 -0.33143300
 N 1.31660600 -2.13094000 -0.30299800
 C 0.00512800 -1.49240700 -0.39818500
 H -0.67370500 -2.00601900 0.30006200
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 O -1.85517600 -1.29147200 -1.93794700
 O 0.06537000 -2.19052200 -2.71490400
 C -0.57521300 -2.34557300 -3.99420800
 H 0.16201800 -2.83047200 -4.63500600
 H -0.85621500 -1.36961600 -4.39755200
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 H 1.37381000 -2.89827200 -0.96395900
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 C 4.27466900 -0.09384200 -1.74228300
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 C 6.33407900 1.05425300 -1.06121200
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 C 6.38008200 -0.43876700 -2.96608100
 C 5.02314200 -0.68577100 -2.77340700
 H 4.51659700 -1.36995800 -3.44949800
 H 6.92405100 -0.91545000 -3.77401000
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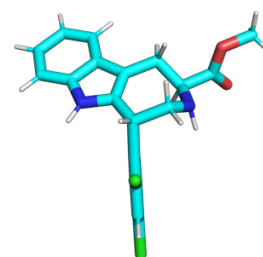


15

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H	-0.92076200	2.92895900	0.29771300
C	0.41379400	4.61728500	0.25807700
C	1.74548600	5.07001300	0.15891100
C	2.79978700	4.17523000	0.01556900
C	2.48744500	2.81282000	-0.02699000
N	3.30078000	1.71126400	-0.17281400
C	2.54286600	0.54903800	-0.11900600
C	3.19716500	-0.79835700	-0.34163200
C	2.55176600	-1.96904300	0.46843300
N	1.15572900	-2.26651600	0.21226300
C	0.15877800	-1.34362700	0.74997700
H	0.42479300	-1.13866500	1.79137800
C	-1.19274100	-2.05338700	0.79800800
O	-1.92759000	-2.10043100	1.75846800
O	-1.49654700	-2.59962100	-0.40385300
C	-2.75576900	-3.28957200	-0.46701400
H	-2.77135300	-4.12205600	0.24126300
H	-2.83937800	-3.65558900	-1.49082300
H	-3.57823900	-2.60861000	-0.23281300
H	0.97262900	-2.46270000	-0.76895700
H	3.13216500	-2.87140100	0.23879800
H	2.66291000	-1.78026500	1.53920100
H	3.03442300	-1.05842400	-1.39991100
C	4.71323600	-0.79624200	-0.15868000
C	5.38801400	-0.51725700	1.04535700
C	6.77902000	-0.58437500	1.15191700
C	7.52981700	-0.94207400	0.03606400
C	6.90990400	-1.22627900	-1.17798000
C	5.52203600	-1.14703200	-1.25288400
H	5.03843900	-1.36668000	-2.20110000
H	7.49925500	-1.50092100	-2.04578100
Cl	9.27650500	-1.02893600	0.16947600
H	7.26226300	-0.36267400	2.09582300
Cl	4.52340000	-0.04844600	2.50657000
H	4.30895300	1.72885400	-0.17280400
H	3.82680800	4.52267400	-0.06296900
H	1.95164600	6.13625800	0.19424100
H	-0.38723900	5.34339900	0.36708100
H	-0.30569700	-0.22404700	-1.03385500
H	-0.84192100	0.54321200	0.44926500

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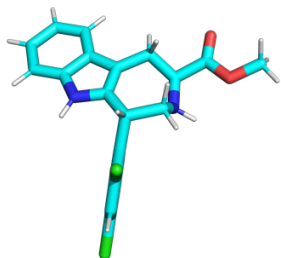


16

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C	-0.10649300	-2.60597100	-0.28355100
C	-1.37913600	-2.88884700	-0.80923200
H	-2.08967000	-2.08861500	-1.00069100
C	-1.72082800	-4.20794000	-1.08035600
C	-0.81505300	-5.25983800	-0.83421200
C	0.44983300	-5.01322100	-0.31226000
C	0.78785700	-3.68361900	-0.04143100
N	1.94554500	-3.13814400	0.47080300
C	1.82057800	-1.75736200	0.55394200
C	2.94037000	-0.92880500	1.11951100
C	2.46139900	0.53104700	1.40951800
N	2.10395300	1.36841800	0.28113000
C	0.97770700	1.02234100	-0.60221100
H	1.33599500	0.61961500	-1.55969500
C	0.29626800	2.34807800	-0.95962100
O	0.51815300	2.97175100	-1.97573400
O	-0.54705600	2.76772600	0.00646600
C	-1.15224700	4.05061200	-0.22031100
H	-1.72564700	4.04800100	-1.15114200
H	-0.38638500	4.82881700	-0.27778100
H	-1.80744900	4.22093100	0.63459700
H	2.91831000	1.61389900	-0.27151900
H	1.61200500	0.47151500	2.09737000
H	3.26154400	1.04754200	1.94960600
H	3.20688300	-1.35198300	2.09773500
C	4.20163900	-0.94063900	0.26076600
C	5.49070900	-0.83292400	0.80833000
C	6.64115400	-0.80191200	0.02048300
C	6.50686000	-0.87188700	-1.36371500
C	5.25029300	-0.97460400	-1.95592200
C	4.12248600	-1.00910100	-1.13892100
H	3.14250100	-1.11062200	-1.59609100
H	5.15551700	-1.03033200	-3.03482800
Cl	7.94680800	-0.83462700	-2.36629000
H	7.61900700	-0.72436700	0.48026600
Cl	5.72437400	-0.73248600	2.55577800

H	2.78079100	-3.65202000	0.70695500
H	1.14799200	-5.82421700	-0.12152400
H	-1.11022600	-6.28177500	-1.05569500
H	-2.70202600	-4.43604200	-1.48750800
H	-0.36537800	0.37143300	0.96512300
H	-0.88133800	-0.03085900	-0.65111800

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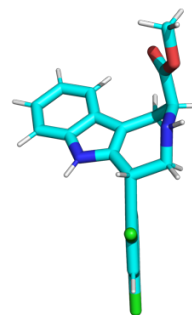


17

C	0.00000000	0.00000000	0.00000000
C	-0.87916000	1.21557300	0.10513800
C	-0.46950500	2.57674600	-0.14316900
C	0.72701100	3.17249000	-0.57839900
H	1.60070500	2.56361200	-0.79748600
C	0.78005900	4.55298100	-0.72624700
C	-0.34140300	5.35949600	-0.44413200
C	-1.53702200	4.80093600	-0.00585900
C	-1.58392600	3.41134700	0.14222600
N	-2.60720300	2.58708100	0.55995000
C	-2.19066700	1.26334500	0.52824900
C	-3.12946000	0.16419300	0.95392900
C	-2.47658400	-1.23687900	0.76979500
N	-1.98771800	-1.42769600	-0.59179800
C	-0.57760500	-1.15187700	-0.85941000
H	-0.49607300	-0.84636800	-1.91378700
C	0.36985800	-2.35748600	-0.73620000
O	1.57372200	-2.28639500	-0.85785900
O	-0.28687400	-3.51888400	-0.51161000
C	0.54637600	-4.68920300	-0.42950600
H	1.25658700	-4.59379700	0.39565300
H	1.10122800	-4.82878100	-1.36074300
H	-0.13492800	-5.52271600	-0.25704800
H	-2.22272300	-2.35306200	-0.93072600
H	-1.69714200	-1.36726700	1.53437400
H	-3.23987600	-1.99251700	0.97704900
H	-3.33077100	0.27856700	2.02651700
C	-4.46722100	0.23306500	0.22245400
C	-5.69841000	0.00470900	0.85526400
C	-6.91279100	0.03170300	0.16715300
C	-6.89846900	0.28523300	-1.20084800

C	-5.70032900	0.50864900	-1.87690300
C	-4.50771000	0.48074900	-1.15972300
H	-3.56801200	0.64734800	-1.67423000
H	-5.70185900	0.70197100	-2.94403200
Cl	-8.41923500	0.32509600	-2.07956900
H	-7.84480400	-0.14258100	0.69096800
Cl	-5.78143300	-0.34593300	2.58578900
H	-3.55393600	2.88015900	0.74820700
H	-2.40110000	5.42231100	0.21532800
H	-0.27042800	6.43650100	-0.56922900
H	1.70038200	5.02199200	-1.06348000
H	0.24145900	-0.38535300	0.99966000
H	0.96293600	0.27011500	-0.44015600

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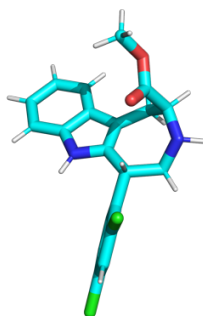


18

C	0.00000000	0.00000000	0.00000000
C	-0.47143100	0.91665300	1.09661000
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C	1.21982500	2.91769700	1.00698600
H	1.85090100	2.52611800	0.21383900
C	1.50688900	4.14311400	1.59505700
C	0.70791100	4.65729100	2.63695900
C	-0.39105700	3.95261000	3.11541700
C	-0.67353900	2.71842200	2.52175000
N	-1.67298800	1.80491900	2.78228800
C	-1.55560300	0.71964200	1.92441300
C	-2.49940800	-0.44516500	2.05629100
C	-2.03686600	-1.66288300	1.20243700
N	-0.62848600	-1.95691800	1.42908300
C	0.32144100	-1.44426500	0.44269800
H	0.33637300	-2.05890100	-0.48140600
C	1.74788200	-1.54569100	0.99637800
O	2.63818000	-0.75023300	0.79319000
O	1.91968000	-2.69243200	1.68929000
C	3.23886300	-2.90024200	2.22181000
H	3.49849700	-2.09978500	2.91917500
H	3.97805900	-2.92465700	1.41678200
H	3.19878100	-3.86029200	2.73721800
H	-0.46376900	-2.94299400	1.59167800

H -2.63539000 -2.52573900 1.51048900
H -2.27682900 -1.48108100 0.14368400
H -2.45327500 -0.78053200 3.09986900
C -3.94898000 -0.09020200 1.73669100
C -5.04164200 -0.69986600 2.37178900
C -6.36407700 -0.39977000 2.04292000
C -6.60765300 0.53434100 1.04019900
C -5.55656600 1.16272100 0.37515000
C -4.24963900 0.84303700 0.73243600
H -3.42404900 1.33865600 0.22933300
H -5.75788200 1.89037600 -0.40332000
Cl -8.26688900 0.92314900 0.61694400
H -7.18250600 -0.88640300 2.55956300
Cl -4.79294100 -1.89829700 3.64520100
H -2.39216000 1.90720000 3.48194300
H -1.00425900 4.34558100 3.92253100
H 0.95714200 5.61912000 3.07696200
H 2.36332400 4.71630700 1.25042100
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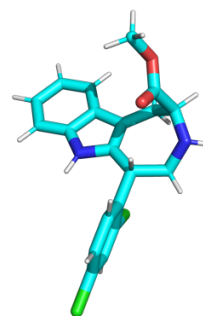


19

C 0.00000000 0.00000000 0.00000000
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C -1.13575200 2.90458700 -1.11390100
H -1.83244400 2.51316100 -0.37663300
C -1.40285300 4.10371200 -1.76344900
C -0.50883000 4.62996500 -2.71802900
C 0.66876500 3.96559100 -3.04333100
C 0.93018900 2.75794000 -2.38913600
N 1.99301600 1.88790000 -2.50254900
C 1.82467500 0.81860300 -1.63607500
C 2.82979100 -0.30572700 -1.58940800
C 2.64828300 -1.16969300 -0.31480700
N 1.48624600 -2.04835500 -0.35531700
C 0.14305800 -1.48141900 -0.44644800
H -0.51569800 -2.07986500 0.19425900
C -0.40994600 -1.63142900 -1.87425100

O 0.22488800 -1.86616400 -2.87572900
O -1.75165300 -1.44471000 -1.86609200
C -2.38718300 -1.48901000 -3.15403500
H -1.98277200 -0.71050100 -3.80616500
H -3.44737100 -1.31753300 -2.96461200
H -2.23329500 -2.46367200 -3.62486400
H 1.53503000 -2.69548400 0.42337600
H 3.52212600 -1.82339900 -0.22536100
H 2.66968300 -0.49002400 0.55718200
H 2.65584900 -0.96661600 -2.44547200
C 4.26644300 0.20655300 -1.63028400
C 5.27776400 -0.39957000 -2.39296500
C 6.59832600 0.05416900 -2.37568200
C 6.92668400 1.13791400 -1.56710900
C 5.96014800 1.76770600 -0.78546700
C 4.65127600 1.29557000 -0.83035300
H 3.89152100 1.79029200 -0.23184000
H 6.22607000 2.61098500 -0.15760900
Cl 8.58457500 1.71593000 -1.53987500
H 7.35160300 -0.43414300 -2.98195200
Cl 4.93180400 -1.78825700 -3.41881600
H 2.80012000 2.02031100 -3.09261400
H 1.35766800 4.36947000 -3.78085700
H -0.74354800 5.57047200 -3.20893900
H -2.31448800 4.64829700 -1.53275500
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H 0.39963200 0.09049000 1.02000400

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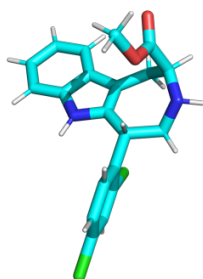


20

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C 0.23417300 2.29894100 -1.25071900
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H -1.71050800 2.60574700 -0.33613500
C -1.10511200 4.28100400 -1.54670400
C -0.11510800 4.84048500 -2.37975200
C 1.05744700 4.14955500 -2.66638800
C 1.21542600 2.88231900 -2.09805300
N 2.24577700 1.97239300 -2.20634400

C 1.96575400 0.85155700 -1.44310400
 C 2.89840600 -0.33544300 -1.41381000
 C 2.66424400 -1.19747700 -0.14682300
 N 1.49327600 -2.06854800 -0.27161200
 C 0.17375900 -1.46999000 -0.47534100
 H -0.54898100 -2.07713200 0.08280900
 C -0.25002300 -1.57917100 -1.95042400
 O 0.46349800 -1.81828100 -2.89816400
 O -1.58064100 -1.35816200 -2.05933600
 C -2.10160700 -1.36757500 -3.39839800
 H -1.62388500 -0.58921600 -3.99907000
 H -3.16993200 -1.17288200 -3.29891800
 H -1.92984500 -2.33860900 -3.87050900
 H 1.46098400 -2.67689900 0.53979200
 H 3.52585600 -1.86147100 -0.01753700
 H 2.62960000 -0.53623300 0.73175500
 H 2.63296400 -0.98596700 -2.25734600
 C 4.36823600 0.03157100 -1.60321700
 C 5.11966400 0.87368500 -0.76351400
 C 6.47015500 1.14280600 -0.99429500
 C 7.09960000 0.56028400 -2.09074100
 C 6.39928400 -0.27873100 -2.95305700
 C 5.05269300 -0.52520100 -2.69651200
 H 4.50271300 -1.18031900 -3.36669200
 H 6.89461700 -0.72841800 -3.80644200
 Cl 8.79751900 0.89702300 -2.38291300
 H 7.01679700 1.79584500 -0.32463300
 Cl 4.40205400 1.65452600 0.64206000
 H 3.11188900 2.12219000 -2.70083500
 H 1.82118900 4.57946600 -3.30950600
 H -0.26997000 5.82815700 -2.80547300
 H -2.00975100 4.84760800 -1.34268200
 H -1.07038000 0.22908100 -0.02423400
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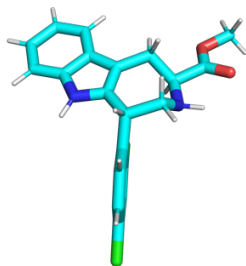


21

C 0.00000000 0.00000000 0.00000000
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 H -1.73290500 2.57715000 -0.40118400
 C -1.18311500 4.19283300 -1.71420800
 C -0.23561100 4.70783100 -2.62213700
 C 0.91790800 3.99783800 -2.93712200
 C 1.10073700 2.75746500 -2.31875500
 N 2.12021600 1.83626800 -2.43958500
 C 1.87788600 0.75629300 -1.60514700
 C 2.81362900 -0.42540100 -1.57497500
 C 2.55889500 -1.32330200 -0.33729500
 N 1.34631400 -2.12709000 -0.47011500
 C 0.02818300 -1.48577400 -0.44662300
 H -0.60768600 -2.03610900 0.25767800
 C -0.73560600 -1.58683000 -1.77761400
 O -1.93463700 -1.41005500 -1.84714400
 O 0.03760100 -1.86107100 -2.84447500
 C -0.66044300 -1.90030100 -4.10019000
 H -1.11925500 -0.93131600 -4.31405700
 H -1.44063500 -2.66566600 -4.08192600
 H 0.09613800 -2.14163900 -4.84775900
 H 1.37192400 -2.87494000 0.21342600
 H 3.38850500 -2.03458600 -0.26415600
 H 2.58843600 -0.70138300 0.56969000
 H 2.58039200 -1.05956300 -2.44106700
 C 4.28716700 -0.04515500 -1.71355100
 C 4.99705800 0.81137200 -0.85225700
 C 6.35294300 1.09103300 -1.03339700
 C 7.03111800 0.50460300 -2.09821800
 C 6.37339500 -0.34984900 -2.97871600
 C 5.02008900 -0.60627800 -2.77236100
 H 4.50424500 -1.27427400 -3.45718200
 H 6.90624800 -0.80315600 -3.80721300
 Cl 8.73542900 0.85540200 -2.32712000
 H 6.86649900 1.75596000 -0.34941000
 Cl 4.21993600 1.59816300 0.51669500
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 H 1.64837100 4.39280100 -3.63873800
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 H 0.42150600 0.06468700 1.01266000

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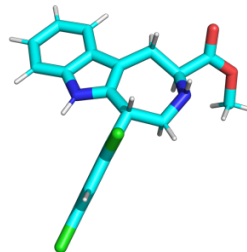


22

C	0.00000000	0.00000000	0.00000000
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C	1.08655300	2.98812000	-0.90099100
H	1.90194100	2.27383600	-0.98494700
C	1.28445600	4.31970800	-1.24520300
C	0.24080100	5.26151700	-1.14120800
C	-1.02051100	4.88968600	-0.68873300
C	-1.21313900	3.54903800	-0.34281200
N	-2.32843700	2.89844000	0.14153100
C	-2.04548300	1.55187000	0.31771200
C	-3.07850300	0.62699600	0.89846400
C	-2.49134000	-0.78619800	1.15535500
N	-2.07793100	-1.48719500	-0.04685700
C	-0.78997600	-1.15617600	-0.66549800
H	-0.95982400	-0.85219100	-1.70894300
C	0.07172200	-2.42065900	-0.73475700
O	-0.22800100	-3.49264000	-0.24852400
O	1.20445700	-2.21294500	-1.43315700
C	2.06399400	-3.35717300	-1.57865200
H	2.38941600	-3.71938800	-0.60005300
H	2.91617400	-3.00898500	-2.16265800
H	1.54171200	-4.16259600	-2.10138900
H	-2.09624500	-2.49008900	0.11789700
H	-1.69763400	-0.67418000	1.91366700
H	-3.27965600	-1.38837700	1.61874000
H	-3.30484600	1.01423000	1.90461100
C	-4.43673600	0.57770700	0.19076700
C	-4.68051200	0.53142500	-1.19346800
C	-5.97586500	0.43364500	-1.71178900
C	-7.06049900	0.37514500	-0.84448100
C	-6.87151600	0.42168300	0.53400800
C	-5.57213400	0.52574600	1.01915200
H	-5.42383100	0.56442100	2.09596200
H	-7.71875600	0.38324300	1.20971900
Cl	-8.68387800	0.25222300	-1.50271600
H	-6.12518300	0.40282900	-2.78428000
Cl	-3.39966400	0.62730600	-2.39097300

H	-3.24992000	3.30118700	0.22116700
H	-1.82553400	5.61555400	-0.60657900
H	0.42442100	6.29601800	-1.41821300
H	2.25898200	4.64366800	-1.60042100
H	0.29114200	-0.28996700	1.01940300
H	0.93428600	0.10715700	-0.55803500

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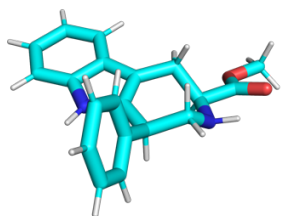


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C	0.29807400	3.22427000	-0.48809500
H	1.28583400	2.77473800	-0.42521200
C	0.16247700	4.59549000	-0.66343000
C	-1.11012100	5.19844300	-0.74175800
C	-2.27172000	4.44120000	-0.64478000
C	-2.12774700	3.06155500	-0.46456700
N	-3.07582500	2.07124400	-0.33622000
C	-2.45739800	0.83445900	-0.19628000
C	-3.27217800	-0.41638800	0.05695100
C	-2.69700300	-1.68401900	-0.65143900
N	-1.36702700	-2.13617300	-0.27577200
C	-0.21565600	-1.34073400	-0.71910000
H	-0.36519600	-1.14383100	-1.78760500
C	1.02031800	-2.24187800	-0.52877400
O	1.77986700	-2.10657400	0.40301700
O	1.24670900	-3.24363400	-1.41039600
C	0.37158600	-3.49106000	-2.51689400
H	0.42755100	-2.68484300	-3.25770000
H	-0.65807100	-3.62165000	-2.17628500
H	0.73708700	-4.41315200	-2.97227500
H	-1.30388000	-2.31440400	0.72533200
H	-3.39164300	-2.50851300	-0.45069300
H	-2.70215200	-1.51947700	-1.73578400
H	-3.24020600	-0.62314700	1.13410900
C	-4.73448300	-0.27882000	-0.34556500
C	-5.80717900	-0.59478900	0.50433200
C	-7.13788600	-0.51737300	0.08845400
C	-7.41448400	-0.11968800	-1.21600200

C -6.38489700 0.19675600 -2.10057700
 C -5.06885700 0.11069700 -1.65503700
 H -4.26575300 0.36194400 -2.34211400
 H -6.60895000 0.50238800 -3.11664600
 Cl -9.08310200 -0.01658600 -1.74576800
 H -7.93956800 -0.76419100 0.77390100
 Cl -5.53265400 -1.11833600 2.16479200
 H -4.07408200 2.20689800 -0.37046500
 H -3.25313400 4.90513200 -0.70198000
 H -1.18445000 6.27381900 -0.87821800
 H 1.05015700 5.21738900 -0.74004800
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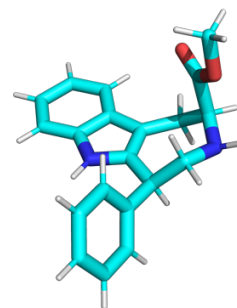


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 H 0.62819500 3.04245000 0.33826800
 C -0.72832000 4.61308500 -0.23527500
 C -1.98891700 4.94902100 -0.76913900
 C -2.88905000 3.96427700 -1.16203900
 C -2.49719400 2.63115300 -1.00644100
 N -3.15712300 1.45984000 -1.31029900
 C -2.37518000 0.37081500 -0.95226600
 C -2.86729800 -1.03509200 -1.18601400
 C -1.98237000 -2.06498100 -0.44415500
 N -0.66738200 -2.24404300 -1.04880100
 C 0.31693800 -1.16020300 -0.98364900
 H 0.42943700 -0.69767000 -1.97462200
 C 1.67606300 -1.77175100 -0.64098800
 O 1.84597700 -2.89349000 -0.20765100
 O 2.67976200 -0.90573500 -0.87695800
 C 3.99988500 -1.38719700 -0.57038900
 H 4.22905500 -2.27612100 -1.16367000
 H 4.08091900 -1.63648400 0.49088000
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H -1.96133000 -1.79264400 0.62611900
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 H -2.78253200 -1.27019000 -2.25736400
 C -4.32999700 -1.21017900 -0.78671400
 C -4.79089800 -0.80735900 0.47631100
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 C -6.56609000 -2.02741400 -1.29291400
 C -5.23620900 -1.81902300 -1.66451000
 H -4.89474900 -2.13589900 -2.64769600
 H -7.25338100 -2.49970700 -1.99002100
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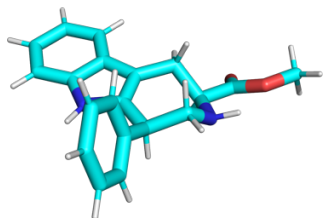


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 H 2.01544700 2.23067200 0.86548000
 C 1.42202700 4.06314900 1.82738200
 C 0.36583400 4.83107400 2.36003200
 C -0.94316400 4.36313700 2.34054000
 C -1.17070600 3.10646000 1.77019700
 N -2.33957100 2.39561100 1.60691600
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 C -3.16822300 0.19597500 0.65494400
 C -2.77120100 -1.25608000 1.02270600
 N -1.72363100 -1.81549900 0.16317600
 C -0.33262800 -1.44111400 0.42093300
 H 0.26469000 -2.09529500 -0.23260600
 C 0.20917200 -1.74172800 1.83310800

O 1.15902700 -1.19374700 2.34590100
O -0.45219700 -2.77400300 2.41281700
C 0.04970600 -3.17527400 3.69886400
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H 1.08918400 -3.50464600 3.61915800
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H -1.79086600 -2.82785300 0.21317700
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H -3.30299800 0.20269400 -0.43632800
C -4.50985000 0.54279600 1.28853000
C -4.67404900 0.57626200 2.68376200
C -5.91687600 0.86137300 3.25176900
C -7.02010000 1.11990000 2.43587200
C -6.87045400 1.09188700 1.04884100
C -5.62608600 0.80673100 0.48386500
H -5.51755700 0.78728700 -0.59808900
H -7.72155400 1.29384700 0.40380000
H -7.98728500 1.34283600 2.87817600
H -6.02232300 0.88076200 4.33341500
H -3.82219500 0.37997500 3.33000100
H -3.25125800 2.67016800 1.93949400
H -1.75881000 4.95367000 2.75042100
H 0.57823000 5.80465100 2.79364400
H 2.43425500 4.45726500 1.86109000
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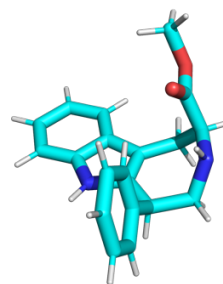


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C -1.00235100 3.14950700 0.00065300
H 0.01693600 3.10161200 0.37581900
C -1.64976400 4.37355100 -0.11629600
C -2.97239900 4.45488300 -0.59729200
C -3.67126800 3.31389400 -0.97642900
C -3.01356000 2.08545100 -0.86042300
N -3.43651900 0.80878400 -1.16325500

C -2.43885800 -0.10421000 -0.85249900
C -2.64567400 -1.58005400 -1.08752700
C -1.58532200 -2.41299000 -0.32820000
N -0.26158200 -2.37684600 -0.94261700
C 0.47246200 -1.10548800 -0.98744900
H 0.38232900 -0.66916800 -1.99103200
C 1.97783700 -1.29931500 -0.79781500
O 2.80284100 -0.46912600 -1.10958600
O 2.29861900 -2.47446500 -0.20731600
C 3.70372000 -2.69179000 0.01012900
H 4.24372900 -2.66783100 -0.93956500
H 3.77994800 -3.67586900 0.47318600
H 4.10977200 -1.92099100 0.66999200
H 0.32148100 -3.07972000 -0.50115000
H -1.60235100 -2.10052500 0.73125900
H -1.90271300 -3.46078200 -0.35128000
H -2.50844200 -1.80050900 -2.15663300
C -4.04884200 -2.03841700 -0.69868000
C -4.58876500 -1.73587200 0.56095600
C -5.85161000 -2.20230200 0.92665700
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C -6.07774700 -3.27719900 -1.22126600
C -4.81203000 -2.81147400 -1.58328000
H -4.40856100 -3.05261500 -2.56447600
H -6.65411300 -3.87354000 -1.92382300
H -7.58621400 -3.33508700 0.32012500
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H -4.01762000 -1.12310300 1.25386000
H -4.37468300 0.54707700 -1.42621800
H -4.68973900 3.37597100 -1.35139800
H -3.45406800 5.42581000 -0.67532700
H -1.13080400 5.28499600 0.16796900
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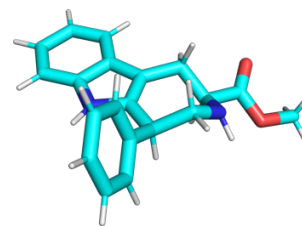


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C	-2.76784200	-3.19548800	2.02079800
C	-2.06386200	-4.33287600	2.46555100
C	-0.68944200	-4.44427900	2.28388300
C	-0.03387000	-3.38685000	1.64611200
N	1.29608900	-3.21744700	1.32493600
C	1.48249300	-1.98389600	0.71721500
C	2.85463000	-1.57057700	0.25681900
C	2.84827100	-0.13840400	-0.37428000
N	2.32705700	0.95423800	0.42525300
C	0.88562900	1.13791400	0.57223400
H	0.57129800	2.05983100	0.05447400
C	0.55314300	1.37066200	2.04771700
O	1.34085900	1.27226400	2.96720200
O	-0.73360800	1.72987700	2.20937000
C	-1.14955700	1.95712200	3.56764500
H	-1.03140100	1.04583900	4.15916200
H	-2.20018400	2.24162400	3.50654600
H	-0.55843600	2.75786500	4.01929900
H	2.77715500	1.00588500	1.33490200
H	3.88633200	0.10128700	-0.63380000
H	2.30047000	-0.17725600	-1.32136500
H	3.15873100	-2.24957100	-0.55708500
C	3.91612400	-1.70288600	1.34707400
C	3.68952200	-1.25637400	2.65835000
C	4.69781900	-1.33972500	3.62064300
C	5.94466500	-1.87558400	3.29421500
C	6.17932900	-2.32847900	1.99480500
C	5.17214100	-2.24202900	1.03296400
H	5.36216200	-2.59824800	0.02217300
H	7.14434900	-2.75286700	1.72966100
H	6.72602900	-1.94304200	4.04658900
H	4.50429100	-0.98397700	4.62925600
H	2.72447400	-0.83831800	2.92782200
H	2.05267200	-3.81139700	1.62996400
H	-0.14616400	-5.32195800	2.62479200
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H	-3.84225000	-3.14167600	2.17501500
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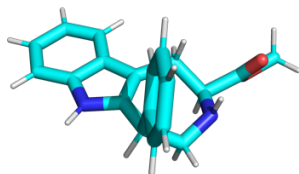


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H	-0.11156100	3.11711700	0.14972600
C	-1.78261300	4.28918200	-0.53842100
C	-3.07388800	4.28668000	-1.10442800
C	-3.71075300	3.09650100	-1.43895200
C	-3.02314400	1.90423200	-1.19132000
N	-3.38422000	0.59456400	-1.42430300
C	-2.37802800	-0.25597700	-0.98471300
C	-2.51797900	-1.75370300	-1.11402900
C	-1.53653300	-2.47785500	-0.13759600
N	-0.11290300	-2.45784700	-0.44961800
C	0.52090000	-1.18411200	-0.82364100
H	0.36302100	-0.93775400	-1.88975600
C	2.03024900	-1.36816500	-0.64421800
O	2.76165200	-0.68597800	0.03769000
O	2.46401100	-2.41569300	-1.38398300
C	3.86594700	-2.71173100	-1.27331400
H	4.12386800	-2.96228400	-0.24094300
H	4.46524300	-1.85455800	-1.59138400
H	4.03858600	-3.56548200	-1.92944400
H	0.11178500	-3.15516800	-1.15261000
H	-1.69439000	-2.06143500	0.86424600
H	-1.82394500	-3.53266000	-0.08129700
H	-2.24763800	-2.05795300	-2.13771300
C	-3.94271000	-2.23478100	-0.86195200
C	-4.63956000	-1.85949300	0.29792000
C	-5.92087100	-2.34954400	0.55088800
C	-6.53167500	-3.22211400	-0.35277100
C	-5.85146700	-3.59966500	-1.51109000
C	-4.56836300	-3.10896300	-1.76065800
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H	-6.31905800	-4.27405000	-2.22378600
H	-7.53110000	-3.60094900	-0.15677700
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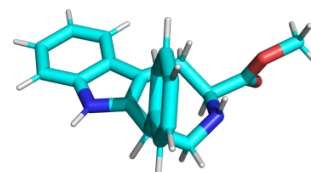


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H -2.96339500 -0.26979600 0.85696100
C -4.17598700 -2.00397700 0.46197100
C -4.25027800 -3.28787300 -0.11586000
C -3.15508800 -3.84917700 -0.76292000
C -1.97975100 -3.09331400 -0.81563700
N -0.75496600 -3.37440300 -1.37902600
C 0.11677000 -2.31024000 -1.18692200
C 1.52637600 -2.41476900 -1.70526900
C 2.04867900 -1.05962000 -2.28017000
N 2.14972700 0.08001800 -1.39303700
C 0.91896900 0.75065300 -0.99983500
H 0.34508500 0.96168000 -1.90855600
C 1.31500600 2.07442100 -0.35266900
O 2.23021100 2.20315100 0.43202000
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C 0.75310200 4.34742900 -0.09224600
H 0.67705100 4.26742600 0.99545400
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C 3.33892600 -3.40998500 1.54549600
C 4.45981400 -4.07060800 1.04350200

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C 3.65272100 -3.68748200 -1.20283900
H 3.77921800 -3.80403700 -2.27777000
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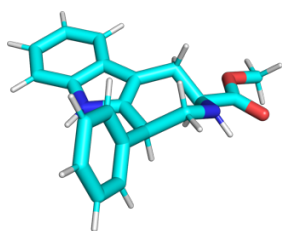


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H -2.79673500 0.92939900 0.95168700
C -4.60001500 -0.21455300 0.68276600
C -5.18965600 -1.38986300 0.17409300
C -4.42668800 -2.35379300 -0.47531800
C -3.05467500 -2.11393400 -0.60057400
N -2.06013600 -2.86786000 -1.18278200
C -0.83760600 -2.21836300 -1.06938600
C 0.39798200 -2.88857700 -1.60955400
C 1.39541200 -1.87580400 -2.25555500
N 1.96280700 -0.83923400 -1.41453800
C 1.09361500 0.28053900 -1.05947500
H 0.61068000 0.62698600 -1.97855000
C 1.96397000 1.44316000 -0.58701300
O 1.90412000 2.57970700 -0.99952000
O 2.80398400 1.04897600 0.39926700
C 3.67456400 2.06994400 0.91358000
H 3.09261900 2.89505300 1.33273000
H 4.31942300 2.45740700 0.12045500
H 4.26921700 1.58578600 1.68885300
H 2.41835200 -1.22345000 -0.59005800

H 2.22500100 -2.45928800 -2.67405300
H 0.89018500 -1.38482500 -3.09614800
H 0.07837800 -3.53322500 -2.44316600
C 1.10946100 -3.79673500 -0.60211000
C 1.05392200 -3.58101200 0.78052300
C 1.76102000 -4.40375300 1.66130000
C 2.53400000 -5.45751900 1.17487400
C 2.59344000 -5.68669200 -0.20175900
C 1.88770800 -4.86347000 -1.07782000
H 1.93750800 -5.05305300 -2.14860000
H 3.18482400 -6.51045400 -0.59317300
H 3.08061600 -6.09912900 1.86070900
H 1.70063400 -4.22064700 2.73103400
H 0.43392800 -2.77997000 1.17149100
H -2.18735700 -3.76760700 -1.62034700
H -4.88031500 -3.26042300 -0.86775100
H -6.25862300 -1.54554400 0.29118400
H -5.22498000 0.51890500 1.18493300
H 0.50104000 -0.29285700 0.93481700
H -0.51178600 0.94663200 0.21863000

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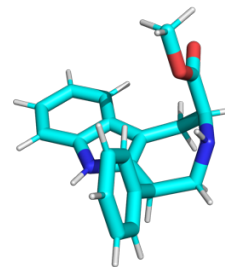


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C -0.42224600 3.26832100 -0.21300600
H 0.56179800 3.06149400 0.20043800
C -0.83187400 4.57867800 -0.42778000
C -2.10684700 4.86529500 -0.95701000
C -2.99456300 3.84684700 -1.28688200
C -2.57585800 2.53002000 -1.07181100
N -3.21789000 1.33387700 -1.30793900
C -2.40958500 0.27771100 -0.90873500
C -2.87610800 -1.15302800 -1.04804000
C -2.10605600 -2.07109000 -0.04496200
N -0.70665400 -2.36355200 -0.31463000
C 0.16887300 -1.30469700 -0.80031600
H -0.02252200 -1.03770900 -1.86074100
C 1.58757500 -1.88311100 -0.82312800

O 1.82950700 -3.06167400 -0.97383400
O 2.54294100 -0.93416500 -0.74601200
C 3.89439700 -1.41155000 -0.86236200
H 4.04303200 -1.90833500 -1.82473300
H 4.12076600 -2.11772600 -0.05950900
H 4.52454800 -0.52519400 -0.78484100
H -0.59007100 -3.18905200 -0.89216800
H -2.20109100 -1.61687100 0.94976800
H -2.62203700 -3.03483500 0.00662900
H -2.65378800 -1.51248600 -2.06468800
C -4.37734000 -1.30480700 -0.83344000
C -4.99811200 -0.81180700 0.32601500
C -6.36252300 -1.00548400 0.54274400
C -7.13407400 -1.69198500 -0.39759300
C -6.53065100 -2.18195900 -1.55634900
C -5.16442600 -1.98871700 -1.76959300
H -4.70090400 -2.37468500 -2.67512600
H -7.12208300 -2.71340500 -2.29736800
H -8.19739500 -1.83994800 -0.22956300
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H -3.97629900 4.06742800 -1.69838200
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H -0.16179300 5.39845800 -0.18303200
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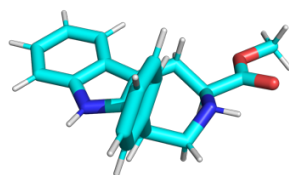


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C -2.27506800 -1.84633500 1.54626200
H -2.73392800 -0.91271900 1.23105300
C -3.02426300 -2.80424900 2.21861800
C -2.44503900 -4.01841500 2.64015700
C -1.10508600 -4.29906000 2.39583200
C -0.35647800 -3.33230300 1.71741300
N 0.96762700 -3.32902600 1.33302300

C 1.27350900 -2.13116800 0.70072000
 C 2.66366200 -1.89229700 0.17566100
 C 2.80707900 -0.47118300 -0.46307800
 N 2.44270100 0.66655300 0.35966300
 C 1.03728400 1.05394500 0.47716300
 H 0.85310000 1.95020000 -0.13728700
 C 0.64427600 1.50697900 1.88566900
 O -0.41921300 2.02890600 2.13905200
 O 1.59520300 1.27799700 2.81931400
 C 1.26314800 1.70787300 4.15215800
 H 1.05492800 2.78041500 4.16425400
 H 2.13838300 1.47758400 4.76005500
 H 0.38513100 1.16886400 4.51605100
 H 2.89970700 0.64192800 1.26333500
 H 3.85661900 -0.35761300 -0.76085800
 H 2.22294700 -0.43987300 -1.38806500
 H 2.85255600 -2.60841400 -0.64109200
 C 3.74599600 -2.13711500 1.22535400
 C 3.60473600 -1.69453900 2.54961700
 C 4.63271100 -1.87978200 3.47625600
 C 5.81707300 -2.51461100 3.09897800
 C 5.96731200 -2.96427700 1.78589800
 C 4.93976100 -2.77635900 0.86097400
 H 5.06403300 -3.13176900 -0.16015600
 H 6.88237700 -3.46590300 1.48175700
 H 6.61396600 -2.66266200 3.82281600
 H 4.50446100 -1.53073700 4.49778100
 H 2.68264200 -1.20863100 2.85472800
 H 1.65642700 -4.01557100 1.60167400
 H -0.65803400 -5.23588100 2.71882800
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 H -4.07455800 -2.61680400 2.42488100
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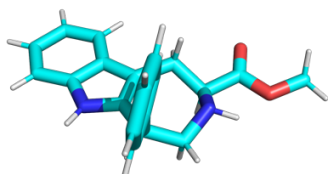


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 C -1.39750700 2.17639000 -0.21830000

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 H 0.37456000 2.92832400 0.78564300
 C -1.08806900 4.47208300 0.44956400
 C -2.35605100 4.80572100 -0.06760300
 C -3.16310100 3.84489600 -0.66735000
 C -2.67049400 2.53804300 -0.73295700
 N -3.22148200 1.39502400 -1.26555100
 C -2.35824700 0.31788300 -1.09392600
 C -2.83050900 -1.03495400 -1.57130800
 C -1.67658900 -1.98324300 -1.97843200
 N -0.68861600 -2.19778000 -0.93327400
 C 0.37344100 -1.20281600 -0.88257400
 H 0.60845400 -0.81118400 -1.89380700
 C 1.65307100 -1.89498000 -0.41119200
 O 1.79483300 -3.09883700 -0.34160800
 O 2.62940100 -1.01505600 -0.12285600
 C 3.88455400 -1.59289300 0.27841300
 H 3.75586300 -2.19804800 1.17925100
 H 4.54471500 -0.74750300 0.47281800
 H 4.28771200 -2.22207700 -0.51935300
 H -0.26751200 -3.11999600 -1.00438200
 H -2.12218400 -2.95113600 -2.23066800
 H -1.21789900 -1.58116500 -2.90182400
 H -3.38839300 -0.85893800 -2.50381500
 C -3.81279600 -1.69107500 -0.59982600
 C -3.49664300 -1.88981500 0.75177500
 C -4.40348500 -2.51427300 1.60762000
 C -5.64370700 -2.94722100 1.13202000
 C -5.97010200 -2.75310300 -0.20983700
 C -5.05909900 -2.12975500 -1.06540900
 H -5.32086200 -1.98477700 -2.11233100
 H -6.93272500 -3.08261700 -0.59267400
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 H -4.14100400 -2.66158400 2.65219400
 H -2.53454900 -1.55935600 1.12627200
 H -4.15308900 1.31575100 -1.64380300
 H -4.14095400 4.10114000 -1.06728400
 H -2.70965200 5.83081000 0.00288700
 H -0.48193000 5.24666400 0.91169200
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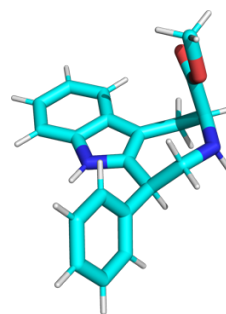


11

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C	3.00269100	-1.22413800	0.31641700
H	2.27857300	-1.90200100	0.76120100
C	4.35921800	-1.52402800	0.35417700
C	5.31287000	-0.65491000	-0.21349200
C	4.92822900	0.52999600	-0.83162800
C	3.56212800	0.82654600	-0.86410000
N	2.88708100	1.89937800	-1.40117200
C	1.51987200	1.76213800	-1.18698600
C	0.61185400	2.86628600	-1.66655700
C	-0.79255000	2.36080400	-2.07537100
N	-1.52939200	1.68905800	-1.01074800
C	-1.23411600	0.26201100	-0.87281600
H	-1.05384600	-0.19947900	-1.86673000
C	-2.43477900	-0.49669300	-0.29946800
O	-2.36546400	-1.47811700	0.40559100
O	-3.61028700	0.02758000	-0.72095100
C	-4.79118500	-0.65050100	-0.25745900
H	-4.83504100	-0.63620900	0.83440400
H	-4.79375100	-1.68808500	-0.60072800
H	-5.63054500	-0.10092500	-0.68412900
H	-2.52482100	1.80432700	-1.16757900
H	-1.37543400	3.23515400	-2.38390700
H	-0.67252500	1.71233000	-2.96364700
H	1.04862700	3.24662200	-2.60288600
C	0.54302600	4.05544500	-0.70724900
C	0.34412000	3.88817800	0.66962600
C	0.25040900	4.99495500	1.51333300
C	0.35598200	6.28865500	0.99755200
C	0.55709400	6.46776400	-0.37114000
C	0.65005700	5.35770300	-1.21288400
H	0.80808900	5.50643500	-2.27991400
H	0.64723400	7.46897200	-0.78498000
H	0.28668600	7.14891800	1.65813400
H	0.09687900	4.84564500	2.57908200
H	0.26700200	2.88692700	1.07842300

H	3.31515900	2.70718100	-1.82699700
H	5.66311300	1.20058800	-1.26994900
H	6.36708700	-0.91458400	-0.16782600
H	4.69357000	-2.44217200	0.82965400
H	-0.21931500	0.37827400	1.00879500
H	0.10845000	-1.08410900	0.10470800

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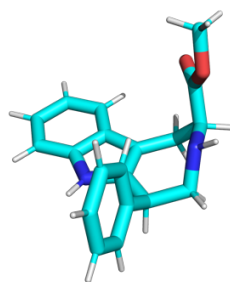


12

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H	2.07640200	2.19362300	0.83887700
C	1.53516400	4.02485800	1.83413700
C	0.50394400	4.80385800	2.39897800
C	-0.81282900	4.35806900	2.40338500
C	-1.07395100	3.11257500	1.82289100
N	-2.25802900	2.42305800	1.67759600
C	-2.02457300	1.21128700	1.04565300
C	-3.14763800	0.25494400	0.71028300
C	-2.78829100	-1.21925700	1.08292100
N	-1.71610700	-1.87586600	0.34733200
C	-0.33156800	-1.43240800	0.48175900
H	0.24818200	-2.11465100	-0.15917400
C	0.27097100	-1.66190300	1.87466900
O	1.34777900	-1.21249400	2.20499900
O	-0.47328900	-2.45595000	2.66924000
C	0.10296100	-2.73606900	3.95634800
H	0.26499700	-1.81056900	4.51518200
H	1.05984700	-3.25238300	3.84320300
H	-0.61985600	-3.37406400	4.46577900
H	-1.94963600	-1.93646500	-0.64052400
H	-2.55278700	-1.27357700	2.14911300
H	-3.68985500	-1.82387600	0.92622800
H	-3.29056500	0.27440500	-0.38240200
C	-4.48032400	0.63465400	1.34148000
C	-4.64285400	0.66463000	2.73717000
C	-5.87788800	0.97591400	3.30806400
C	-6.97646500	1.26153500	2.49494600

C	-6.82954700	1.23460500	1.10762200
C	-5.59242700	0.92486300	0.53991000
H	-5.48663800	0.90843700	-0.54252300
H	-7.67706200	1.45686900	0.46455300
H	-7.93793100	1.50360800	2.93953100
H	-5.98138200	0.99270600	4.38990500
H	-3.79580300	0.44451300	3.38212100
H	-3.15938300	2.71283300	2.02525200
H	-1.60901700	4.95684900	2.83871800
H	0.74235400	5.76835800	2.83922300
H	2.55447500	4.40132800	1.85090900
H	1.08440200	0.12969600	0.06105400
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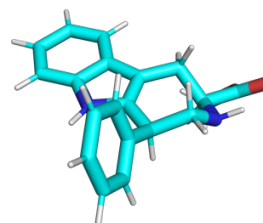


13

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C	1.79515400	2.28793400	1.59101800
H	2.45081000	1.47881000	1.27993600
C	2.30725200	3.38497000	2.27302200
C	1.46918500	4.43656400	2.69671000
C	0.10151300	4.41131000	2.44561100
C	-0.40827200	3.30593900	1.75767800
N	-1.69658100	3.00901800	1.36543400
C	-1.72245300	1.77689500	0.72766500
C	-3.02734600	1.22323700	0.21232800
C	-2.85887600	-0.24291400	-0.28598000
N	-2.15477800	-1.07460300	0.68240700
C	-0.72425200	-1.27957600	0.47586000
H	-0.51854900	-2.05363200	-0.29259500
C	-0.06551600	-1.83315100	1.74638900
O	1.10882500	-1.71525200	2.02098800
O	-0.93282800	-2.54972000	2.49286600
C	-0.37392100	-3.15617600	3.67040600
H	0.42670800	-3.85059500	3.40184600
H	-1.19960700	-3.68574000	4.14672200
H	0.02942900	-2.39091700	4.33826300
H	-2.62202500	-1.95715500	0.84842800

H	-3.85946300	-0.65690400	-0.44484400
H	-2.36675400	-0.23200000	-1.27058200
H	-3.33779800	1.81545400	-0.66351000
C	-4.14851300	1.34399500	1.24299600
C	-4.02285600	0.78836800	2.52690100
C	-5.06966600	0.88170200	3.44361800
C	-6.25566200	1.53676500	3.10078200
C	-6.38884300	2.09753000	1.83082800
C	-5.34125400	1.99982000	0.91147900
H	-5.45304400	2.43733300	-0.07892600
H	-7.30496900	2.61258400	1.55314600
H	-7.06703500	1.61198200	3.82002800
H	-4.95782200	0.44413900	4.43255100
H	-3.10404300	0.27447000	2.78938700
H	-2.52522900	3.50760300	1.65349000
H	-0.54609300	5.22133600	2.77181400
H	1.89821200	5.28109400	3.22934300
H	3.37149100	3.43472200	2.48740200
H	1.06723100	-0.16055400	0.17208400
H	-0.12312300	0.07816600	-1.08757300

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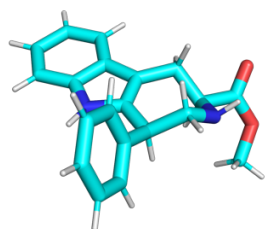


14

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H	-1.05958000	2.93549300	-0.32083900
C	0.02012100	4.67012900	0.35956100
C	1.19492300	5.17183000	0.95581900
C	2.21767700	4.32000100	1.35892500
C	2.03665100	2.94922900	1.15093800
N	2.85206200	1.87963000	1.45388200
C	2.25628100	0.69880100	1.03604400
C	2.93528900	-0.63218600	1.25827100
C	2.31471000	-1.72778900	0.35771900
N	1.01439700	-2.20363100	0.82289900
C	-0.08633200	-1.24584600	0.93583100
H	-0.12090300	-0.86733200	1.96368000
C	-1.38524100	-1.99710700	0.62272100

O -1.41738000 -2.94188100 -0.13348500
 O -2.54984000 -1.54685200 1.14742100
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 H -2.14191500 0.37935500 1.89983200
 H -2.09761200 -0.94538400 3.10298100
 H -3.65032900 -0.42081000 2.40457900
 H 0.69829500 -2.95518700 0.21204000
 H 2.31163300 -1.34988100 -0.68050900
 H 2.98107400 -2.59650100 0.37247500
 H 2.77223500 -0.95142100 2.29871100
 C 4.44327500 -0.55902500 1.03372000
 C 4.97640500 -0.02895100 -0.15164700
 C 6.35434000 -0.01203600 -0.36862400
 C 7.22490900 -0.51992300 0.59841200
 C 6.70734900 -1.04394500 1.78342000
 C 5.32751300 -1.06193600 1.99683100
 H 4.93001400 -1.47568700 2.92111200
 H 7.37582900 -1.43825200 2.54428500
 H 8.29833100 -0.50366300 0.43017000
 H 6.74852300 0.40082000 -1.29354800
 H 4.30664600 0.37800600 -0.90506400
 H 3.80334900 1.94059100 1.78475700
 H 3.12248800 4.70645400 1.82106300
 H 1.30370700 6.24277300 1.10365400
 H -0.75956300 5.36355300 0.05619000
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 H -0.97751200 0.49612600 -0.03374100

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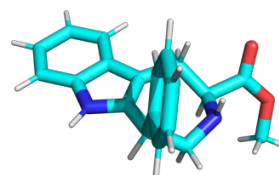


15

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 C 1.48475000 2.04319800 0.72482900
 C 0.73491200 3.19783400 0.44076100
 H -0.24199500 3.12017000 -0.02991900
 C 1.26247500 4.44201800 0.76389900
 C 2.53104200 4.56073000 1.36782500
 C 3.29437800 3.43725500 1.66576600
 C 2.75670700 2.18744500 1.34248700
 N 3.26264800 0.91845000 1.52768200

C 2.37375300 -0.01962700 1.02003700
 C 2.68421400 -1.49844400 1.09067600
 C 1.87895000 -2.28177500 0.02795800
 N 0.46643000 -2.49642300 0.37763700
 C -0.33296100 -1.30740700 0.74871200
 H -0.16054800 -1.11718200 1.81531900
 C -1.80513900 -1.69952000 0.54756800
 O -2.44238800 -1.34604000 -0.41813600
 O -2.39688300 -2.50271300 1.46155200
 C -1.69450000 -2.96420900 2.62618500
 H -1.59753300 -2.16085800 3.36530300
 H -0.71149100 -3.35907300 2.35871100
 H -2.31880100 -3.75628800 3.04335300
 H 0.02852300 -2.93805300 -0.43008300
 H 2.00908800 -1.76646500 -0.93778800
 H 2.32221100 -3.27766800 -0.07866000
 H 2.38797800 -1.89106300 2.07544600
 C 4.17396800 -1.78899800 0.91892200
 C 4.88675900 -1.29022500 -0.18279300
 C 6.23580500 -1.59931300 -0.35790700
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 C 6.20126000 -2.90537900 1.67048700
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 H 4.31237600 -2.98891000 2.70233100
 H 6.70782300 -3.53233100 2.39950800
 H 7.94927900 -2.64661800 0.43311200
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 H 4.38170200 -0.65007700 -0.90172900
 H 4.19990700 0.69833500 1.82907500
 H 4.27066100 3.52826000 2.13517700
 H 2.91893700 5.54731500 1.60642800
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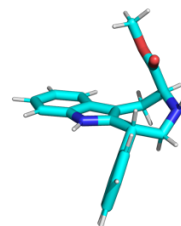


16

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 C -2.33228900 -1.02578900 -0.57591100

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H	-2.94537200	0.59902500	0.72755700
C	-4.61866100	-0.56104200	0.02902600
C	-5.05858300	-1.65213700	-0.74813500
C	-4.15716500	-2.44577300	-1.44848700
C	-2.80035300	-2.12136600	-1.34999300
N	-1.69256600	-2.70768700	-1.92091900
C	-0.54243400	-2.02897500	-1.53776300
C	0.79489700	-2.51974300	-2.02491900
C	1.76520300	-1.34959800	-2.36944600
N	2.16103600	-0.44873100	-1.29674400
C	1.17096200	0.53558300	-0.84081100
H	0.76285900	1.00583000	-1.74388600
C	1.95391900	1.58497400	-0.02721300
O	1.93780900	1.60955100	1.18241900
O	2.71580400	2.49221600	-0.68240100
C	2.81639600	2.50740900	-2.11095100
H	1.87035900	2.81148900	-2.57420000
H	3.12568700	1.53040200	-2.48879100
H	3.57598600	3.25770100	-2.33789900
H	2.53751600	-0.96577300	-0.50344500
H	2.67889600	-1.79248300	-2.78471700
H	1.30849000	-0.74342800	-3.16118900
H	0.62379000	-3.02852400	-2.98630800
C	1.46851000	-3.54063900	-1.10289800
C	1.26507800	-3.55475200	0.28272100
C	1.94013900	-4.47048600	1.09403200
C	2.82711500	-5.38910900	0.53351800
C	3.03467300	-5.38857200	-0.84777800
C	2.36112600	-4.47253400	-1.65443000
H	2.52644300	-4.48302900	-2.73042500
H	3.71669200	-6.10522800	-1.29799700
H	3.34852300	-6.10323800	1.16503100
H	1.76563900	-4.46574000	2.16673300
H	0.55664200	-2.86207000	0.72641400
H	-1.70147100	-3.52519100	-2.51147500
H	-4.49528400	-3.28786900	-2.04709600
H	-6.12020400	-1.87770800	-0.80031500
H	-5.34954700	0.03802600	0.56529900
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H	-0.60089000	0.85727100	0.32668400

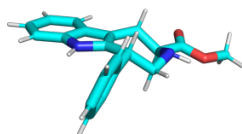
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H	1.98015300	2.41720700	0.03903400
C	1.67508900	4.19407900	1.21683000
C	0.84009200	4.88495300	2.11834000
C	-0.35573700	4.32954700	2.56095900
C	-0.69798400	3.06278800	2.07776300
N	-1.79232400	2.26690300	2.33942600
C	-1.70874000	1.09152100	1.60788500
C	-2.77764800	0.03443200	1.71847900
C	-2.67897700	-0.97202100	0.52791800
N	-1.56231000	-1.91012600	0.50925100
C	-0.18970400	-1.41718900	0.58052200
H	0.44376900	-2.09503500	-0.01372800
C	0.36610900	-1.49782400	2.01095800
O	-0.25334900	-1.90325900	2.97411900
O	1.65703200	-1.11996000	2.05990800
C	2.27178700	-1.16560400	3.35923100
H	2.24082200	-2.18114000	3.76260000
H	1.75637300	-0.49030000	4.04678000
H	3.30180000	-0.84267500	3.20654200
H	-1.68917700	-2.59239000	1.25313600
H	-3.58831000	-1.58182600	0.52758500
H	-2.69224500	-0.40303400	-0.40897200
H	-2.60802000	-0.54346200	2.63848800
C	-4.18094100	0.62499600	1.79141200
C	-5.07587400	0.20472300	2.78459200
C	-6.38144500	0.69758900	2.83108500
C	-6.81440900	1.62244700	1.88024600
C	-5.93235000	2.05182600	0.88580900
C	-4.62823300	1.55874500	0.84312200
H	-3.94489900	1.90700500	0.07249600
H	-6.25944500	2.77419400	0.14235600
H	-7.82944700	2.00898600	1.91504000
H	-7.05789000	0.36007900	3.61210200
H	-4.74470300	-0.51655500	3.52876300

H	-2.60020700	2.53371800	2.88149900
H	-0.99862500	4.86039100	3.25855700
H	1.13567600	5.86795000	2.47493700
H	2.60364300	4.65592600	0.89206200
H	1.07443800	0.15340100	-0.13696500
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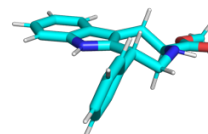


2

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C	1.21789400	3.00938800	0.49290400
H	0.13442700	3.06650800	0.42471100
C	1.97020800	4.16242300	0.67949700
C	3.37669900	4.10934900	0.76764200
C	4.05760200	2.90119900	0.66826500
C	3.29501800	1.74444100	0.47650400
N	3.67974800	0.42991600	0.33787400
C	2.56168200	-0.37983700	0.18903200
C	2.70706200	-1.86758200	-0.05066500
C	1.62318800	-2.69764300	0.68355800
N	0.27011500	-2.47184000	0.18339200
C	-0.41130400	-1.29147800	0.72118000
H	-0.19383800	-1.16332200	1.80246400
C	-1.93131000	-1.46546400	0.64108900
O	-2.72768400	-0.57426500	0.45022600
O	-2.30238100	-2.74813200	0.87101500
C	-3.71937700	-2.99378800	0.85452200
H	-4.13994300	-2.73487800	-0.12039900
H	-4.21752700	-2.40120600	1.62599900
H	-3.83422200	-4.05970100	1.05297200
H	-0.29433100	-3.28935600	0.39187400
H	1.85639900	-3.75441400	0.51428500
H	1.70918100	-2.51357800	1.77061400
H	2.54348900	-2.05315900	-1.12209700
C	4.08795800	-2.40627200	0.30513300
C	4.86250500	-3.06049800	-0.66199500
C	6.11003100	-3.59947100	-0.34225200
C	6.60755600	-3.49071800	0.95686700

C	5.84926500	-2.83882000	1.93146600
C	4.60218300	-2.30143900	1.60853600
H	4.02328200	-1.79154200	2.37445500
H	6.22795400	-2.74767500	2.94620200
H	7.57895000	-3.90788500	1.20813300
H	6.69287600	-4.10183600	-1.10981100
H	4.48169100	-3.14927600	-1.67689200
H	4.62164200	0.07803100	0.41617200
H	5.14203800	2.85880200	0.73270500
H	3.93837500	5.02809700	0.91364400
H	1.46917700	5.12355700	0.75849000
H	-0.21686400	-0.13683200	-1.06901700
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trans-**3-6b-OMe**-

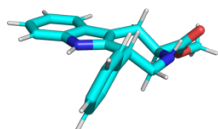


3

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H	-0.48689400	3.01572000	0.38170700
C	1.08352600	4.47143300	0.60199300
C	2.47115000	4.71264000	0.67123000
C	3.38690400	3.67107000	0.57291100
C	2.87926700	2.37908300	0.40139100
N	3.52582900	1.17181800	0.26966800
C	2.60055500	0.14298400	0.14561000
C	3.07595400	-1.27601400	-0.09456600
C	2.17350800	-2.34161500	0.57851200
N	0.81305200	-2.34623100	0.06412100
C	-0.09283700	-1.38189700	0.67250800
H	0.12500900	-1.23948000	1.75140900
C	-1.50467700	-1.96773900	0.62206800
O	-1.75560100	-3.12965300	0.37402000
O	-2.44513800	-1.05798400	0.93671600
C	-3.79624100	-1.55087100	0.96822500
H	-3.89566300	-2.34640400	1.71128800
H	-4.08387000	-1.94051000	-0.01149800
H	-4.41254400	-0.69299900	1.23770500
H	0.39715800	-3.27057400	0.14262700

H	2.61403500	-3.32063400	0.36175100
H	2.21291000	-2.20226400	1.67520200
H	3.00281200	-1.47111900	-1.17428100
C	4.52600100	-1.50071200	0.31865600
C	5.46790600	-1.95309700	-0.61478300
C	6.78945900	-2.20450800	-0.24058700
C	7.19301800	-2.00446900	1.07997600
C	6.26682200	-1.55079100	2.02156000
C	4.94670000	-1.30088400	1.64429100
H	4.23573100	-0.94199100	2.38435300
H	6.57155700	-1.39080600	3.05255500
H	8.22122600	-2.19781800	1.37363600
H	7.50252900	-2.55437400	-0.98243600
H	5.16042600	-2.11094600	-1.64612600
H	4.52027600	1.02250400	0.34694600
H	4.45712300	3.85533600	0.62320800
H	2.83132800	5.72956100	0.80162000
H	0.39451900	5.30832300	0.67932700
H	-0.23365600	-0.13401200	-1.06624400
H	-0.78242500	0.64108900	0.41719900

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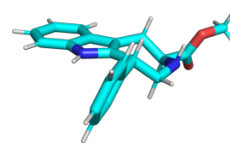


4

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C	1.02412900	4.51403800	0.61405300
C	2.40681600	4.75736200	0.74774700
C	3.32649900	3.71564300	0.70624300
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N	3.48325300	1.21297100	0.44128100
C	2.56623400	0.18525200	0.27823800
C	3.01350200	-1.24997900	0.10400200
C	2.13208300	-2.24770700	0.92497700
N	0.73538200	-2.38726800	0.56657600
C	-0.18305600	-1.29283000	0.84200100
H	-0.09751300	-1.03095800	1.90224200
C	-1.58974800	-1.81988800	0.57765300

O	-1.88287800	-2.54693900	-0.34792200
O	-2.48369400	-1.33096200	1.46135500
C	-3.84899600	-1.72562000	1.23887100
H	-3.94738800	-2.81227500	1.30422600
H	-4.18858500	-1.39698100	0.25303700
H	-4.42558800	-1.23961100	2.02629500
H	0.59754200	-2.73621700	-0.37844900
H	2.59214500	-3.23877100	0.83023600
H	2.18554900	-1.97322000	1.98593600
H	2.87418200	-1.51895100	-0.95512600
C	4.48283400	-1.47544400	0.43431200
C	5.36053500	-1.98432900	-0.53240400
C	6.69880400	-2.23950000	-0.22779200
C	7.18563700	-1.98729700	1.05532900
C	6.32436700	-1.47938700	2.02991800
C	4.98647500	-1.22706200	1.72264900
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H	6.69260800	-1.28068000	3.03302600
H	8.22721900	-2.18382800	1.29439500
H	7.36030800	-2.63334000	-0.99491900
H	4.98983400	-2.18236600	-1.53568100
H	4.47609700	1.06835200	0.54459100
H	4.39290300	3.90142000	0.80656600
H	2.75974900	5.77598100	0.88403100
H	0.33193100	5.35106400	0.64927800
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H	-0.83248600	0.67808200	0.22722000

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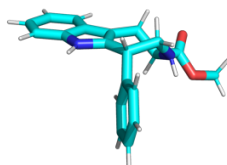


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C	1.58377800	4.36987600	0.35242700
C	2.99148600	4.45485100	0.36121500
C	3.78059100	3.31318900	0.28094100
C	3.12526900	2.08084000	0.18959100
N	3.62901500	0.80315500	0.09448800

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 O -2.10169700 -2.16894400 -0.30275800
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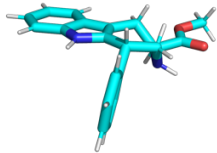
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6
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 C -4.45616900 -0.32257600 -1.38300700
 C -4.94684800 -1.64401300 -1.37378400
 C -4.14697100 -2.70570300 -0.96498200
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 H 1.82931300 -5.46814800 1.30720200
 H -1.87402000 -4.24470900 -0.07043500
 H -4.52568100 -3.72468200 -0.95581700
 H -5.96834000 -1.83724400 -1.69001400
 H -5.10870100 0.48433100 -1.70528700
 H 0.09638800 0.36952600 1.02935000
 H -0.39612000 0.84623800 -0.56968100

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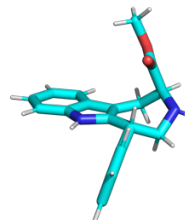


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C	-1.51719500	-2.12075000	0.33047500
C	-0.66178100	-3.17846600	0.68439100
H	0.41008200	-3.01772900	0.77266100
C	-1.20260500	-4.43621600	0.92288500
C	-2.58904400	-4.66562200	0.81245400
C	-3.46067500	-3.64175900	0.45702000
C	-2.91107900	-2.37906600	0.21639300
N	-3.51120800	-1.19505800	-0.15628000
C	-2.55760400	-0.19247200	-0.25099000
C	-2.96223400	1.20285300	-0.65248400
C	-1.76870800	2.19287300	-0.53528600
N	-1.11562100	2.13006600	0.77227900
C	0.05074600	1.25687600	0.90375700
H	0.09469100	0.90615800	1.94598600
C	1.35314000	2.03608000	0.66905700
O	1.41316000	3.22074000	0.41163900
O	2.43993600	1.25167100	0.82287800
C	3.70918600	1.90940100	0.66138100
H	3.81586700	2.71871400	1.38836400
H	3.80124500	2.32236400	-0.34652500
H	4.46150400	1.13864200	0.83060600
H	-0.83718600	3.06591600	1.05239800
H	-1.07775900	2.02039500	-1.37413800
H	-2.16391500	3.20425200	-0.66778400
H	-3.23922200	1.18469900	-1.71884100
C	-4.19335000	1.69059600	0.10872400
C	-5.31353200	2.15393400	-0.59392900
C	-6.44125000	2.62855000	0.08033000
C	-6.46360800	2.64443600	1.47470200
C	-5.35372400	2.18174900	2.18664800
C	-4.22965600	1.70554000	1.51227900
H	-3.36543900	1.35313500	2.06489000
H	-5.36419400	2.18965000	3.27370100
H	-7.33937500	3.01091700	2.00385900
H	-7.29953300	2.98254300	-0.48508800
H	-5.30222200	2.14627700	-1.68235000

H	-4.50557200	-1.02526200	-0.18579100
H	-4.52966900	-3.81818300	0.36821500
H	-2.98385900	-5.65931700	1.00600600
H	-0.54821100	-5.25881100	1.19879200
H	0.26325200	0.28180700	-1.02835700
H	0.79839900	-0.66897800	0.33143800

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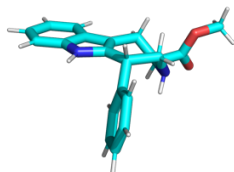


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C	1.25521800	2.97394700	0.73860400
H	1.94160500	2.45629500	0.07284400
C	1.56340300	4.24268700	1.21503000
C	0.68326600	4.93141200	2.07423300
C	-0.52032500	4.36233200	2.47692000
C	-0.82345100	3.08428900	1.99779100
N	-1.91659700	2.27606600	2.22419700
C	-1.78627900	1.09352800	1.51379200
C	-2.83610000	0.01190200	1.60719700
C	-2.74533700	-0.94938300	0.39714900
N	-1.64178000	-1.90406200	0.48468700
C	-0.26666200	-1.41890900	0.57462600
H	0.36331800	-2.11935600	0.01289400
C	0.23963100	-1.48464000	2.02611800
O	-0.42660200	-1.63527300	3.02417200
O	1.58668400	-1.34334500	2.04484000
C	2.18683000	-1.32850800	3.34976300
H	1.99170600	-2.26840400	3.87329500
H	1.78978000	-0.50108100	3.94354200
H	3.25626500	-1.19918600	3.17975000
H	-1.71824700	-2.55943700	-0.28573900
H	-3.66315500	-1.54626100	0.36912700
H	-2.73468700	-0.33899300	-0.52428800
H	-2.63426200	-0.59412600	2.50030400
C	-4.24799300	0.57750500	1.72145500
C	-5.09743600	0.14805100	2.74966800
C	-6.40691300	0.62358400	2.84515500
C	-6.88869600	1.54018100	1.90994500

C	-6.05131700	1.97976100	0.88197400
C	-4.74272600	1.50476600	0.79060300
H	-4.09413400	1.86215100	-0.00548000
H	-6.41628400	2.69667300	0.15092000
H	-7.90686500	1.91300900	1.98299100
H	-7.04822900	0.27833000	3.65197500
H	-4.72761600	-0.56800100	3.48008200
H	-2.74366400	2.53147200	2.74218400
H	-1.19831700	4.89145200	3.14185900
H	0.94951000	5.92325700	2.42943200
H	2.49667400	4.71524700	0.92044800
H	1.08471300	0.13670000	-0.05783200
H	-0.36694600	0.01896000	-1.03658200

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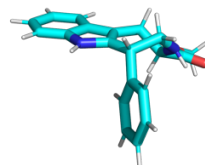


9

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C	2.19716700	1.42682900	0.14767900
C	1.80967500	2.70337700	0.59006800
H	0.76593600	2.92369700	0.80025100
C	2.77907800	3.68470500	0.75815900
C	4.13718200	3.42009200	0.48876800
C	4.55146800	2.16961800	0.04316600
C	3.57136700	1.18661100	-0.12459700
N	3.67404000	-0.11981200	-0.55258100
C	2.42263900	-0.72289300	-0.53693000
C	2.27945400	-2.15797600	-0.96486400
C	0.78751600	-2.62257600	-0.92936000
N	0.11835000	-2.52905900	0.35244400
C	-0.41352000	-1.24262000	0.82261600
H	-0.09462900	-1.08987600	1.85855800
C	-1.94216100	-1.34487900	0.89196700
O	-2.59597800	-1.32224500	1.91236100
O	-2.48618500	-1.47704700	-0.33943000
C	-3.91221500	-1.64006900	-0.36735800
H	-4.20438700	-2.54802300	0.16730400
H	-4.17925000	-1.71510500	-1.42214900
H	-4.40804600	-0.78222900	0.09504500
H	0.64625600	-2.99718800	1.07988000

H	0.21387000	-2.05725800	-1.66896100
H	0.76370900	-3.66971700	-1.25484400
H	2.60017800	-2.24113700	-2.01623200
C	3.15940900	-3.11034400	-0.15665700
C	3.73323200	-4.22915300	-0.77790100
C	4.48399300	-5.15084700	-0.04816700
C	4.67585100	-4.96875600	1.32309300
C	4.11532500	-3.85740700	1.95374000
C	3.36563500	-2.93509600	1.22014000
H	2.95331200	-2.05916700	1.71430700
H	4.26474200	-3.70228700	3.01911700
H	5.26270700	-5.68376300	1.89323300
H	4.92240500	-6.00875400	-0.55135300
H	3.58914100	-4.37819600	-1.84634600
H	4.53771800	-0.61724400	-0.70904900
H	5.59814700	1.96562900	-0.16795800
H	4.87335400	4.20674400	0.62993300
H	2.48832700	4.67366000	1.10191600
H	-0.47696300	-0.05096200	-0.98604800
H	-0.44263300	0.87495200	0.49179400

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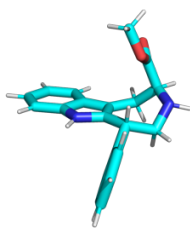


10

C	0.00000000	0.00000000	0.00000000
C	0.49064800	-1.41849900	0.14884000
C	1.80993500	-1.81013900	0.58376300
C	2.97062000	-1.10055100	0.93681100
H	2.98593000	-0.01406100	0.90123600
C	4.10149200	-1.80572100	1.33071100
C	4.10042700	-3.21451700	1.37886000
C	2.96866700	-3.94548100	1.03377300
C	1.83409600	-3.23065800	0.63779400
N	0.58811800	-3.66888400	0.24305700
C	-0.22551800	-2.58094400	-0.04656900
C	-1.62786300	-2.78949600	-0.54987000
C	-2.13518400	-1.50228600	-1.27362300
N	-2.42568700	-0.31529800	-0.49153600
C	-1.45358800	0.17702300	0.47790800
H	-1.51797700	-0.35038700	1.44928600
C	-1.84572500	1.62031300	0.82097600

O -2.96617700 2.06561600 0.70760500
O -0.82032500 2.32095600 1.35576600
C -1.14899200 3.64951500 1.79474500
H -1.92131200 3.61754800 2.56794200
H -1.51138100 4.25114400 0.95722200
H -0.22232600 4.06361100 2.19336000
H -3.34816100 -0.34866400 -0.07249900
H -1.39006700 -1.25636500 -2.04041000
H -3.05827500 -1.75146000 -1.80748900
H -1.57307400 -3.55248800 -1.34374400
C -2.62216900 -3.30789000 0.48905800
C -3.76862000 -3.99123100 0.05577800
C -4.72284200 -4.44616600 0.96496100
C -4.54441500 -4.23021400 2.33335200
C -3.40492000 -3.56008500 2.77850700
C -2.45248200 -3.10405300 1.86406300
H -1.56132100 -2.59654400 2.22279600
H -3.25165700 -3.39255500 3.84152500
H -5.28441800 -4.58626600 3.04497400
H -5.60232000 -4.97428500 0.60562200
H -3.91263800 -4.17154200 -1.00805400
H 0.28068000 -4.62945900 0.23167900
H 2.96797200 -5.03198700 1.07019400
H 4.99944000 -3.73944800 1.69027600
H 5.00336700 -1.26540200 1.60551500
H 0.08284500 0.36385000 -1.03436000
H 0.63415800 0.65329400 0.60387300

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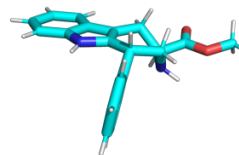


11

C 0.00000000 0.00000000 0.00000000
C -0.52496500 1.06896800 0.92204500
C 0.15180700 2.29819900 1.25936800
C 1.36390900 2.88672200 0.85990900
H 2.01370700 2.38476200 0.14752200
C 1.72296100 4.12087100 1.38815200
C 0.89292600 4.78643000 2.31296700
C -0.30973700 4.22762100 2.73199000
C -0.66393300 2.98393900 2.19998100
N -1.76758800 2.18997100 2.42979900

C -1.69697400 1.04599500 1.64863200
C -2.77828100 -0.00218600 1.72320600
C -2.67891100 -0.98858200 0.53458300
N -1.56249800 -1.92178200 0.63846700
C -0.18189300 -1.44468800 0.53552700
H 0.35623800 -2.10535900 -0.15533400
C 0.61903300 -1.56096600 1.84343900
O 1.83199100 -1.50766300 1.86223500
O -0.13560800 -1.70282500 2.94779900
C 0.60223100 -1.75449000 4.17981200
H 1.16643100 -0.82974700 4.32727800
H 1.29825200 -2.59740400 4.17558000
H -0.14606100 -1.87843800 4.96347100
H -1.70871300 -2.68656900 -0.01015400
H -3.58773300 -1.59943600 0.53298100
H -2.69257600 -0.40110200 -0.40118500
H -2.62975400 -0.59947500 2.63343200
C -4.17634100 0.60721900 1.77951300
C -5.09740400 0.17564100 2.74306700
C -6.39439600 0.69165800 2.77868200
C -6.79107900 1.65151200 1.84679400
C -5.88181200 2.09290500 0.88273900
C -4.58597800 1.57711600 0.85144200
H -3.87923300 1.93572700 0.10732800
H -6.18046700 2.84328700 0.15528000
H -7.79917800 2.05643100 1.87357300
H -7.09241600 0.34503800 3.53635500
H -4.79430200 -0.57383100 3.47110000
H -2.57908900 2.45264800 2.96849000
H -0.94834900 4.73822600 3.44843800
H 1.19854300 5.75164100 2.70769400
H 2.65857000 4.58309400 1.08514500
H 1.07502100 0.15000200 -0.14026800
H -0.45255100 0.05643700 -0.99983200

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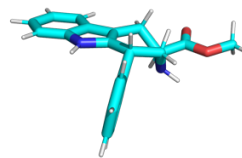


12

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C 2.39809600 1.04169300 0.25725500

C	2.21581000	2.38667700	0.62283800
H	1.21607500	2.79506600	0.74955800
C	3.33135600	3.19079400	0.82289000
C	4.63555000	2.68029700	0.66247900
C	4.84873700	1.35624200	0.29400700
C	3.72292300	0.55231800	0.09184900
N	3.62002300	-0.77049600	-0.28299000
C	2.28491400	-1.14474500	-0.33029100
C	1.90819300	-2.55158400	-0.72070200
C	0.38273900	-2.80012100	-0.53435700
N	-0.08437600	-2.38811500	0.78706300
C	-0.67336000	-1.05697900	0.91332900
H	-0.52865000	-0.73022200	1.95379700
C	-2.19232800	-0.97531100	0.68917800
O	-2.82875800	0.05515700	0.74065700
O	-2.75482600	-2.18368700	0.45166500
C	-4.18075000	-2.16842700	0.26313600
H	-4.44534900	-1.54485700	-0.59460500
H	-4.67984800	-1.77648600	1.15309500
H	-4.46467700	-3.20636500	0.08716200
H	-0.72077200	-3.07765500	1.16976800
H	-0.16391300	-2.31036900	-1.35410200
H	0.20557900	-3.87397000	-0.64597400
H	2.11210200	-2.67820900	-1.79615400
C	2.74650500	-3.59857300	0.00974700
C	3.41645700	-4.59238100	-0.71586700
C	4.16345700	-5.57830000	-0.06666200
C	4.25172000	-5.58186700	1.32532200
C	3.59075200	-4.59381800	2.05990000
C	2.84736500	-3.60857700	1.41022000
H	2.33015200	-2.84392600	1.98004800
H	3.65694900	-4.58846000	3.14501500
H	4.83400300	-6.34514100	1.83485800
H	4.67664100	-6.33880500	-0.64969900
H	3.35149500	-4.59616100	-1.80242600
H	4.38703800	-1.42330900	-0.34460900
H	5.85394000	0.96239500	0.16636000
H	5.48912500	3.33224700	0.82733400
H	3.19923700	4.23122400	1.10751400
H	-0.39758100	-0.10170200	-1.01854000
H	-0.34036300	0.98003500	0.34357900

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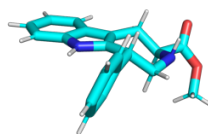


13

C	0.00000000	0.00000000	0.00000000
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C	-2.21616700	-2.38636200	0.62303100
H	-1.21649200	-2.79490700	0.74973100
C	-3.33183100	-3.19030200	0.82310000
C	-4.63595500	-2.67960600	0.66270400
C	-4.84893800	-1.35552000	0.29423300
C	-3.72300500	-0.55177000	0.09205900
N	-3.61989500	0.77103600	-0.28274600
C	-2.28473500	1.14505700	-0.33016600
C	-1.90778700	2.55184700	-0.72051000
C	-0.38232400	2.80023500	-0.53400800
N	0.08460800	2.38799500	0.78745600
C	0.67355300	1.05678600	0.91343600
H	0.52890700	0.72990000	1.95387100
C	2.19247600	0.97508700	0.68912700
O	2.82884400	-0.05543900	0.74003100
O	2.75504400	2.18356900	0.45223500
C	4.18094600	2.16834900	0.26367800
H	4.46498400	3.20643100	0.08874000
H	4.44548300	1.54561700	-0.59469900
H	4.68003200	1.77543700	1.15321700
H	0.72117800	3.07738600	1.17016700
H	0.16439400	2.31054200	-1.35373700
H	-0.20507700	3.87408600	-0.64543800
H	-2.11158500	2.67856600	-1.79597300
C	-2.74604400	3.59894100	0.00989200
C	-3.41582000	4.59282100	-0.71578100
C	-4.16275000	5.57884100	-0.06664300
C	-4.25112700	5.58242300	1.32533200
C	-3.59034400	4.59429100	2.05996700
C	-2.84702400	3.60895600	1.41036100
H	-2.32994000	2.84424400	1.98022000
H	-3.65664200	4.58894300	3.14507600
H	-4.83335800	6.34576900	1.83481900
H	-4.67578600	6.33940900	-0.64972800
H	-3.35076900	4.59658600	-1.80233500

H -4.38682800 1.42392200 -0.34459300
H -5.85408100 -0.96150800 0.16660800
H -5.48962200 -3.33143200 0.82757600
H -3.19988200 -4.23075400 1.10772600
H 0.39751800 0.10183100 -1.01854700
H 0.34028700 -0.98013100 0.34338500

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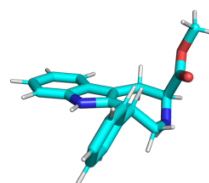


14

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C 1.58743700 1.99373800 0.58354700
C 0.76018100 3.12613800 0.69175200
H -0.31454500 3.04223600 0.55102100
C 1.33460300 4.35804200 0.97794200
C 2.72718100 4.48902600 1.15949700
C 3.57176800 3.38979900 1.05629000
C 2.98772700 2.15255600 0.76485400
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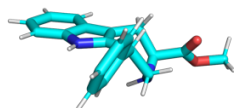


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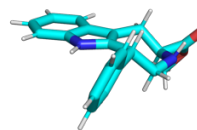


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17

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E. X-ray Structure Determination of 3-5b-NHMe

E.1. Acknowledgements: This material is based upon work supported by the National Science Foundation under CHE-1726077.

E.2. Experimental: A large colorless plate was cut into a prism (0.10 x 0.12 x 16 mm³) was centered on the goniometer of a Rigaku Oxford Diffraction Synergy-S diffractometer equipped with a HyPix6000HE detector and operating with CuK α radiation. The data collection routine, unit cell refinement, and data processing were carried out with the program CrysAlisPro.²⁰ The Laue symmetry and systematic absences were consistent with the orthorhombic space group $P2_12_12_1$. The structure was solved using SHELXT²¹ and refined using SHELXL²² via Olex2.²³ The final refinement model involved anisotropic displacement parameters for non-hydrogen atoms. A riding model was used for all C-H hydrogens. The N-H hydrogens were located from the residual electron density map and refined independently. The absolute configuration (C9=S, C10=R) was established from anomalous dispersion effects [Flack $x = -0.07(11)$;²⁴ Hooft $P2(\text{true}) = 1.000$, $P3(\text{true}) = 1.000$, $P3(\text{rac-twin}) = 5.059\text{e-}06$; $P3(\text{false}) = 2.409\text{e-}22$, $y = 0.01(10)$].²⁵⁻²⁶ Mercury⁹ was used for molecular graphics generation.

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Chapter 4. *In vitro* and *in vivo* evaluation of the antimalarial MMV665831 and structural analogs

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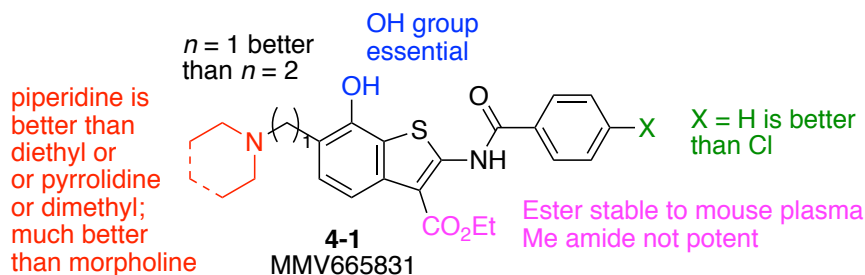
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This chapter has been adapted from a paper currently in press at Bioorganic & Medicinal Chemistry Letters, by the authors listed above. P.R.C. and S.D. designed analogs of MMV665831, and S.D. synthesized them. K.R.F and M.K. developed and performed the in vitro assays. The manuscript was written through contributions of all authors.

Abstract

Antimalarial candidates possessing novel mechanisms of action are needed to control drug resistant *Plasmodium falciparum*. We were drawn to Malaria Box compound **4-1** (MMV665831) by virtue of its excellent in vitro potency, and twelve analogs were prepared to probe its structure-activity relationship. Modulation of the diethyl amino group was fruitful, producing compound **4-25**, which was twice as potent as **4-1** against cultured parasites. Efforts were made to modify the phenolic Mannich base functionality of **4-1**, to prevent formation of a reactive quinone methide. Homologated analog **4-28** had reduced potency relative to **4-1**, but still inhibited growth with $EC_{50} \leq 200$ nM. Thus, the antimalarial activity of **4-1** does not derive from quinone methide formation. Chemical stability studies on dimethyl analog **4-2** showed remarkable hydrolytic stability of both the phenolic Mannich base and ethyl ester moieties, and **4-1** was evaluated for *in vivo* efficacy in *P. berghei*-infected mice (40 mg/kg, oral). Unfortunately, no reduction in parasitemia was seen relative

to control. These results are discussed in the context of measured plasma and hepatocyte stabilities, with reference to structurally-related, orally-efficacious antimalarials.



Introduction

Malaria remains a deadly disease, leading to approximately 228 million malaria cases worldwide and killing over 400,000 in 2018.¹ Artemisinin combination therapies have contributed in large part to a decline in malaria mortality over the last 15 years; however, resistance to these treatments is emerging, and the estimated malaria caseload has been on the rise in the last two years. Thus, the need for novel antimalarial compounds remains urgent.^{1,2} Malaria symptoms in humans are caused by the blood-stage growth of *Plasmodium spp.*, of which *P. falciparum* is responsible for ~96% of malaria cases worldwide. To accelerate the development of novel antimalarial drugs, a collection known as the “Malaria Box” was assembled from over 20,000 compounds with confirmed *in vitro* activity against blood-stage *P. falciparum*.³ Out of the 20,000 hits, 400 compounds were selected by using several criteria, including commercial availability, oral bioavailability, and chemical diversity. This final set contained 200 “drug-like” and 200 “probe-like” compounds, classified according to their perceived druglikeness.

One of us (Klemba) identified compound **4-1** (Figure 4-1, MMV665831) as having excellent *in vitro* growth inhibition of asexual blood-stage *P. falciparum*, and similar high

potency in inhibiting amino acid efflux⁴ from parasitized erythrocytes.⁵ We have previously observed such behavior in a study of mefloquine (MQ) and its non-piperidine analogs, and suggested that the antimalarial action of MQ may stem from inhibition of hemoglobin endocytosis.² Repeat assay with purchased authentic samples of **4-1** and its *N,N*-dimethyl analog **4-2** (ChemDiv) confirmed these activities. Thus, we sought to explore the structural determinants of antimalarial action of **4-1** and **4-2**. In particular, we wanted to establish whether potency could be sustained when the phenolic Mannich base functionality (a likely trigger of the probe-like designation⁶) and C3-carboxylic ester were converted into less-reactive moieties (Figure 4-1).

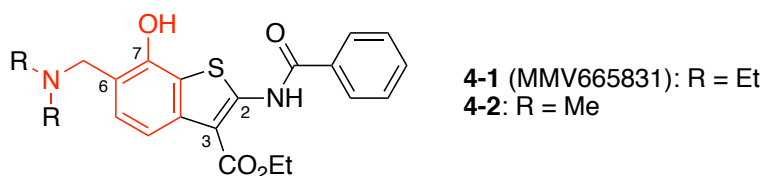
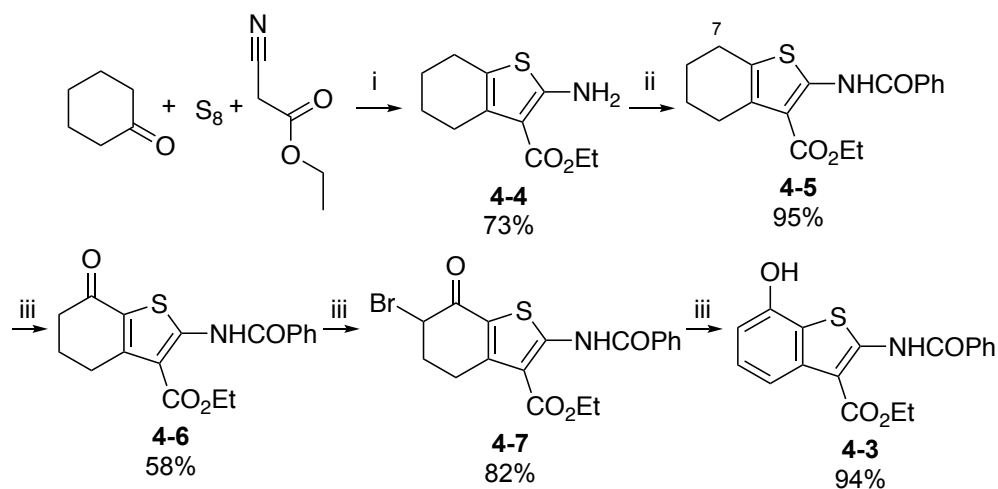


Figure 4-1. Structure of MMV665831 (**4-1**) and its *N,N*-dimethyl analog (**4-2**), with their phenolic Mannich base functionality highlighted in red. The carboxylic ester at C3 is also a potential metabolic liability

To enable the synthesis of such analogs of **4-1/4-2**, we developed a gram-scale synthesis of the core 7-hydroxybenzothiophene **4-3**, which serves as a Mannich reaction precursor for **4-1** and its analogs. (Scheme 4-1) A facile Gewald reaction from cyclohexanone, sulfur, and ethyl cyanoacetate⁷ constructed the known thiophene **4-4** in 73% yield, which was benzoylated to give **4-5** in 95% yield. Regioselective oxidation at C7 was achieved with CuSO₄/potassium persulfate⁸ to give **4-6** with 58% yield.

To achieve the conversion of ketone **4-6** to the desired phenol **4-3**, we employed an α -halogenation/dehydrohalogenation sequence. Whereas bromination of **4-6** with Br₂ or NBS

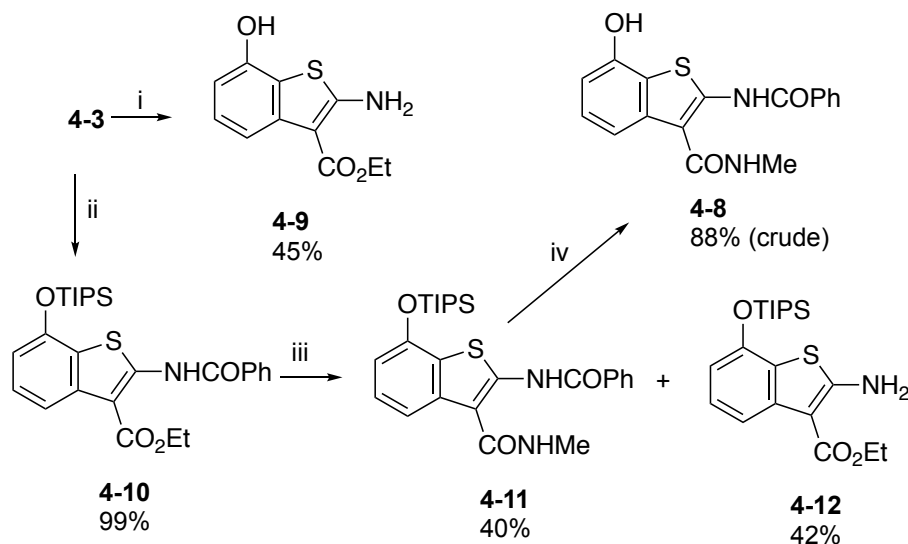
resulted in a mixture of mono- and di-brominated product, regioselective mono-bromination was achieved with Bu_4NBr_3 ⁹ affording **4-7** in 82% yield. Treatment of **4-7** with lithium carbonate in DMF at 120 °C for 2 h cleanly eliminated HBr;¹⁰ addition of water precipitated phenol **4-3** in 94% yield, which was sufficiently pure for further steps.



Scheme 4-1. Synthesis of benzothiophene **4-3**. Reagents and conditions: (i) piperidine, r.t., 6 h. (ii) PhCOCl , TEA, DCM, r.t., 1 day. (iii) $\text{K}_2\text{S}_2\text{O}_8$, CuSO_4 , $\text{H}_2\text{O}/\text{MeCN}$, 80 °C, overnight. (iv) Bu_4NBr_3 , DCM, MeOH, r.t., 18 h. (v) Li_2CO_3 , LiBr, DMF, 120 °C, 2 h.

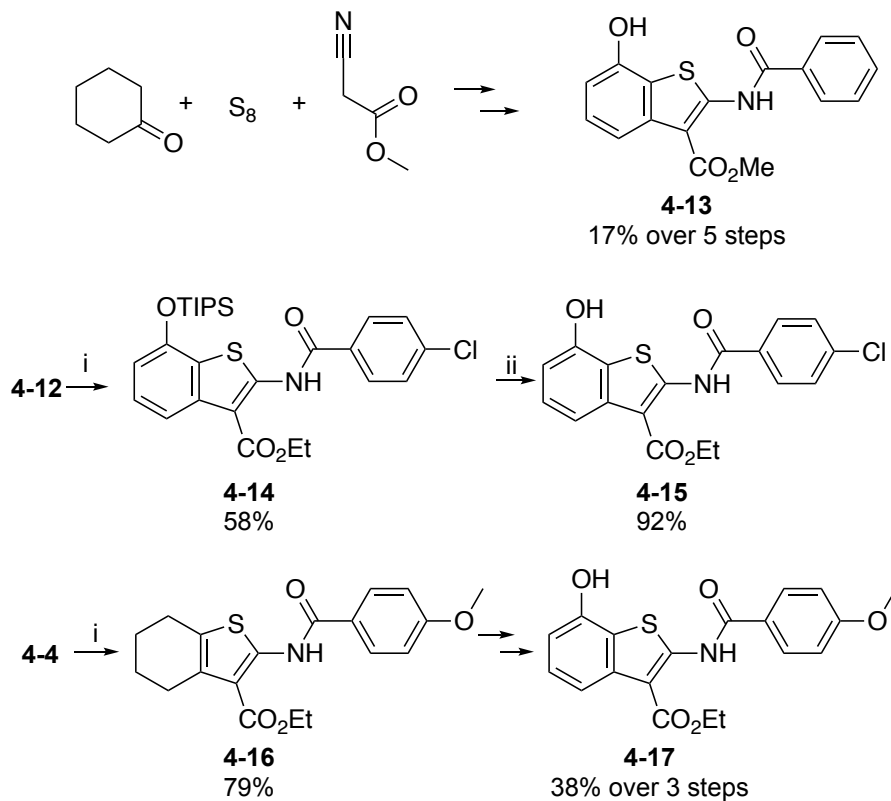
As the 2-ethyl ester in **4-1** was viewed as a potential hydrolytic liability *in vivo*, we desired to prepare and evaluate amide analogs. Compound **4-3** dissolved poorly in ethanolic methylamine (33 wt%) at 25 °C, and no conversion was observed after 24 h; the mixture was heated to 60 °C in a sealed tube overnight, but instead of the ethyl ester **4-8**, amine **4-9** was isolated in 45% yield due to aminolysis of the benzamide (Scheme 4-2). The silyl ether **4-10** was prepared to improve substrate solubility, and subsequent aminolysis at 35 °C gave full conversion. Under these conditions the desired methyl amide **4-11** was isolated in 40% yield, together with 42% of debenzoylated byproduct **4-12**. The factors contributing to the stability of the ester group towards aminolysis remain unclear, but byproduct **4-12** proved useful as

shown below. Silyl ether **4-11** was easily deprotected with TBAF to give phenol Mannich precursor **4-8** in 88% yield.



Scheme 4-2. Synthesis of amide derivative **4-8**. Reagents and conditions: (i) MeNH₂, EtOH, sealed tube, 60 °C 16 h. (ii) TIPSCl, TEA, DCM, 0 °C to r.t., 1 h. Material used directly for Mannich reaction (Table 1) (iii) MeNH₂, EtOH, sealed tube, 35 °C, 16 h. (iv) TBAF, THF, 0 °C to r.t., 30 min.

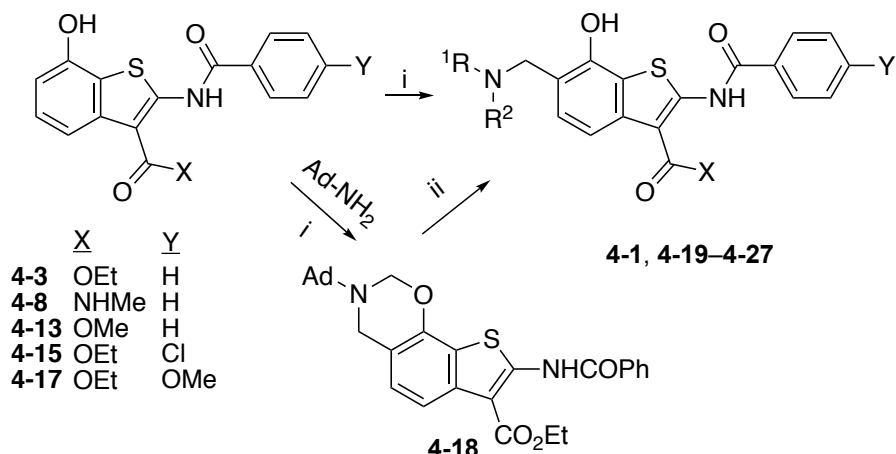
To provide isosteric comparison with the methyl amide **4-8**, the methyl ester **4-13** was prepared from methyl cyanoacetate, by using the method for **4-3** (Scheme 4-3). The byproduct 2-aminobenzothiophene **4-12** obtained from the aminolysis of **4-10** was acetylated with 4-chlorobenzoyl chloride to give **4-14**, which was desilylated to give phenol Mannich precursor **4-15**. Curiously, the reaction of **4-12** with 4-methoxybenzoyl chloride, even with 4-DMAP catalysis, did not give any conversion. Fortunately, thiophene **4-4** could be benzoylated with the 4-methoxybenzoyl chloride to give **4-16**, which was converted into precursor **4-17** (Scheme 4-3).



Scheme 4-3. Synthesis of **4-13**, **4-15**, and **4-17**. Reagents and conditions: (i) 4-Cl-benzoyl chloride or 4-OMe-benzoyl chloride, TEA, DCM, r.t., overnight. (ii) TBAF, THF, 0 °C to r.t., 30 min.

Phenols **4-3**, **4-8**, **4-13**, **4-15**, and **4-17** readily underwent Mannich reaction with a series of secondary amines in the presence of formalin, giving the desired products **4-1**, **4-19–4-26** in 44–92% yield. (Table 4-2) Reaction of **4-3** with the primary amine 1-adamantylamine and formalin initially gave hemiaminal ether **4-18**; treatment with aqueous acid gave the desired product **4-27**.

Table 4-1. Mannich reaction of **4-3**, **4-8**, **4-13**, **4-15**, and **4-17**.



i) R^1R^2NH , formalin, EtOH/H₂O, 60 °C, 4 h. ii) HCl, H₂O, r.t., overnight

Entry	Product (starting phenol)	X	Y	NR ¹ R ²	Yield
1	4-1 (4-3)	OEt	H	NEt ₂	72%
2	4-19 (4-15)	OEt	Cl	NEt ₂	48%
3	4-20 (4-17)	OEt	OMe	NEt ₂	90%
4	4-21 (4-13)	OMe	H	NEt ₂	82%
5	4-22 (4-8)	NHMe	H	NEt ₂	44%
6	4-23 (4-3)	OEt	H	NPr ₂	92%
7	4-24 (4-3)	OEt	H	N(CH ₂) ₄	81%
8	4-25 (4-3)	OEt	H	N(CH ₂) ₅	80%
9	4-26 (4-3)	OEt	H	N(CH ₂ CH ₂) ₂ O	60%
10	4-27 (4-3)	OEt	H	NHAd ^a	45%

^aAd designates 1-adamantyl; isolated as HCl salt.

The *P. falciparum* growth inhibition potencies of compound **4-1**, **4-19–4-27** were tested in a 48-hour growth assay; MQ was used as positive control. Within error compound **4-1** is equipotent with MQ, with a *P. falciparum* growth inhibition EC₅₀ values of 27 ± 8 and 16 ± 6 nM, respectively. (Entries 1 and 2, Table 4-2). Our limited series modifying the *para*-position of the benzamide (Y, Table 4-2, entries 2, 4, 5) shows Y = H (**4-1**, 27 ± 8 nM) is favorable to Y = Cl (**4-19**, 70 ± 18 nM), although Y = OCH₃ (**20**, 66 ± 35 nM) is indistinguishable from Y = H (**4-1**). Similarly, our limited modification of the 3-carboxy

substituent (X) indicates that an amide is not tolerated (**4-22**, Table 4-2, Entry 7, > 1,000 nM). Methyl ester **4-21** is equipotent with **4-1**, within error (Entry 6, Table 4-2, 53 ± 25 nM). Thus, the poor potency of the methyl amide **4-22** is not steric in origin.

To our delight, varying the NR^1R^2 moiety is well-tolerated, and can result in improved potency. Whereas dimethylamine analog **4-2** is equipotent to **4-1** (Entry 3, Table 4-2, 24 ± 8 nM); dipropylamine analog **4-23** and pyrrolidine analog **4-24** appear slightly more potent than **4-1** (Entries 8 and 9, Table 4-2, 16 ± 2 , 16 ± 5 nM, respectively); piperidine analog **4-25** is the most potent in this series (Entry 10, Table 4-2, 13 ± 2 nM). Interestingly, the isosteric morpholine analog **4-26** is 7- to 8-fold less potent than piperidine analog **4-25** (Entry 11, Table 4-2, 100 ± 50 nM). It is tempting to speculate that the reduced basicity of morpholine related to piperidine may drive this reduced potency.¹¹ Compound **4-27** with its 1-adamantyl (1-Ad) group was assessed to probe the effect of increased lipophilicity in the high potency of **4-25**. The significant (14-fold) loss of potency compared to **4-1** (Entry 12, Table 4-2, 388 ± 116 nM), may well be a consequence of the significant steric bulk of the 1-Ad group.

Compound **4-1** is classified as a “probe-like” member of the Malaria Box, but no explanation for this designation was given in the original publication.³ As alluded to above, we suspected the phenolic Mannich base functionality of **4-1** was to blame, and application of the PAINs (Pan Assay Interference Compounds) filter⁶ in SwissADME¹² did generate an alert for this functionality.

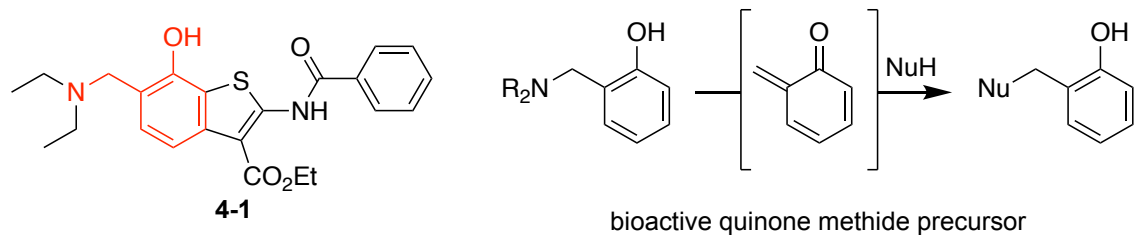
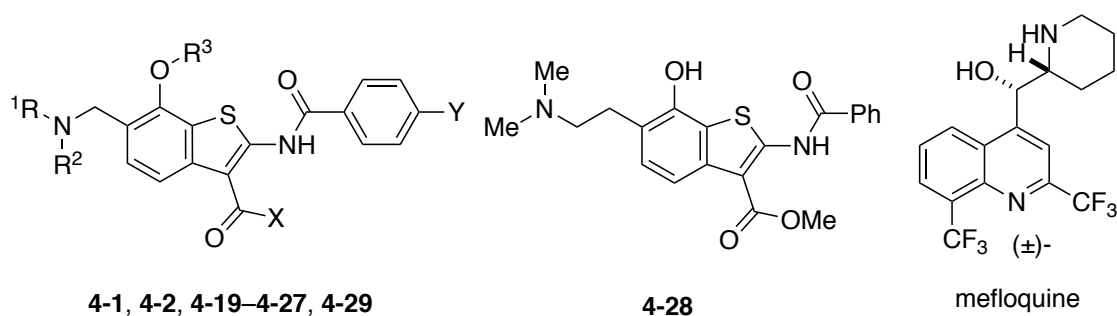


Figure 4-2. Phenolic Mannich base moiety in **4-1** is a quinone methide precursor

Table 4-2. *P. falciparum* growth inhibitory activity

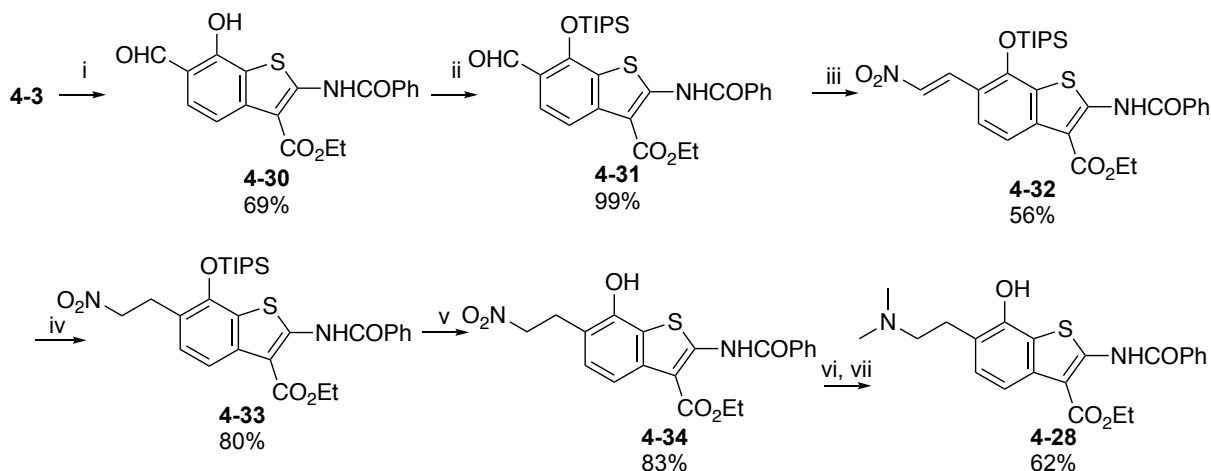


Entry	Compound	X	Y	NR ¹ R ²	R ³	<i>P. falciparum</i> 3D7 strain ^a Growth inhibition EC ₅₀ (nM)
1	Mefloquine (MQ)	NA	NA	NA	NA	16 ± 6
2	4-1	OEt	H	NEt ₂	H	27 ± 8
3	4-2^b	OEt	H	NMe ₂	H	24 ± 8
4	4-19	OEt	Cl	NEt ₂	H	70 ± 18
5	4-20	OEt	OMe	NEt ₂	H	66 ± 35
6	4-21^b	OMe	H	NEt ₂	H	53 ± 25
7	4-22^b	NHMe	H	NEt ₂	H	>1000
8	4-23^b	OEt	H	N ⁿ Pr ₂	H	16 ± 2
9	4-24^b	OEt	H	N(CH ₂) ₄	H	16 ± 5
10	4-25^b	OEt	H	N(CH ₂) ₅	H	13 ± 2
11	4-26^b	OEt	H	N(CH ₂ CH ₂) ₂ O	H	100 ± 50
12	4-27^b	OEt	H	NHAd ^c	H	388 ± 116
13	4-28	na	na	na	na	182 ± 72
14	4-29^b	OEt	H	NEt ₂	Me	> 1,000

^aThis strain is sensitive to chloroquine, pyrimethamine, and mefloquine. ^bTested as HCl salt. ^cAd designates 1-adamantyl.

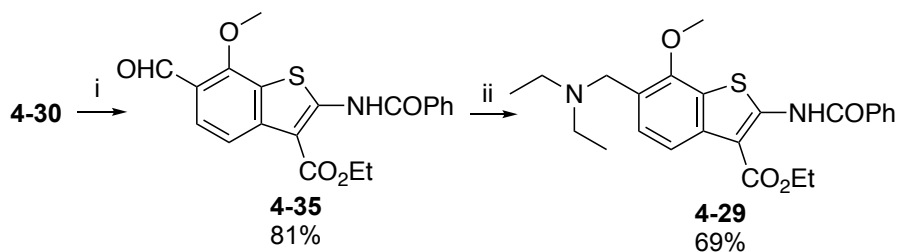
Elimination of the phenolic Mannich base moiety to a highly electrophilic quinone methide¹³⁻¹⁴ and subsequent reaction with biological nucleophiles¹⁵⁻¹⁷ may be responsible for promiscuous binding sometimes exhibited by this class of compounds (Figure 4-2). More importantly, formation of this electrophile *in vivo* could lead to idiosyncratic toxicity. To block this potential reactivity, we proposed two different analogs: a) one resulting from insertion of an additional methylene i.e., compound **4-28**, and b) the other resulting from methylating the phenol, i.e., compound **4-29**.

To synthesize the desired homologated analog, phenol **4-3** was formylated selectively at the *ortho*- position with paraformaldehyde and MgCl₂.¹⁸⁻¹⁹ (Scheme 4-4) However, attempted Henry reaction of **4-30** was unsuccessful, presumably due to its poor solubility in nitromethane. We thus prepared the silyl ether **4-31** to improve solubility as well as reduce polarity. Henry reaction of silyl ether **4-31** catalyzed by AcOH and pyridine²⁰ was successful, affording the desired product **4-32** in 56% yield.²¹ The nitrostyrene **4-32** was reduced with sodium borohydride at 0 °C to give **4-33**,²² and the silyl ether was deprotected with TBAF to give nitro alkane **4-34** in 83% yield. The nitro alkane **4-34** was reduced under catalytic hydrogenation conditions, and a subsequent Eschweiler-Clarke reaction gave the homolog **4-28**. Unfortunately, insertion of the additional methylene in **4-28** caused an approximate 7-fold loss of potency compared to **2** (Entry 13, Table 4-2, 182 ± 72 nM). However, the fact that **4-28** retained significant growth inhibition potency strongly suggests that quinone methide formation is **not** the basis of the antimalarial activity of this compound class.



Scheme 4-4. Synthesis of homolog **4-28**. Reagents and conditions: (i) paraformaldehyde, MgCl_2 , TEA, MeCN, 80 °C, overnight. (ii) TIPSCl, TEA, DCM, 0 °C to r.t., 1 h. (iii) MeNO_2 , HOAc, pyridine, DCM, 0 °C to r.t., overnight. (iv) NaBH_4 , MeOH/THF, 0 °C, 30 min. (v) TBAF, THF, 0 °C to r.t., 30 min (vi) Pd/C, H_2 , MeOH, r.t. overnight. (vii) HCHO, NaBH_3CN , HOAc, MeCN, 1 h.

The *o*-formyl phenol **4-30** was readily methylated using methyl iodide/ K_2CO_3 , giving **4-35** in 81% yield (Scheme 4-5). Interestingly, the standard reductive amination protocol (sodium triacetoxyborohydride in DCE²³) was not effective for reaction of **4-35** with diethylamine. Fortunately the alternative $\text{Ti}(\text{O}^i\text{Pr})_4/\text{NaBH}_3\text{CN}$ protocol²⁴ recommended by Abdel-Magid et al.²³ did afford **4-29** in 69% yield, with 25% recovered starting material **4-35**. Unfortunately, methylation of the phenol completely abrogated potency (Entry 14, Table 4-2, $\text{EC}_{50} > 1,000$ nM).



Scheme 4-5. Synthesis of 7-methoxy analog **4-29**. Reagents and conditions: (i) K_2CO_3 , MeI, DMF/THF, r.t., overnight. (ii) Et_2NH , $Ti(O^iPr)_4$; $NaBH_3CN$, EtOH, 16 h.

As structural modifications to prevent quinone methide formation from **4-1** or **4-2** significantly reduced potency, we thought it would be worthwhile to investigate the thermal stability of these compounds. After all, two WHO-approved and several investigational antimalarials²⁵⁻²⁹ contain the phenolic Mannich base functionality (Figure 4-3).

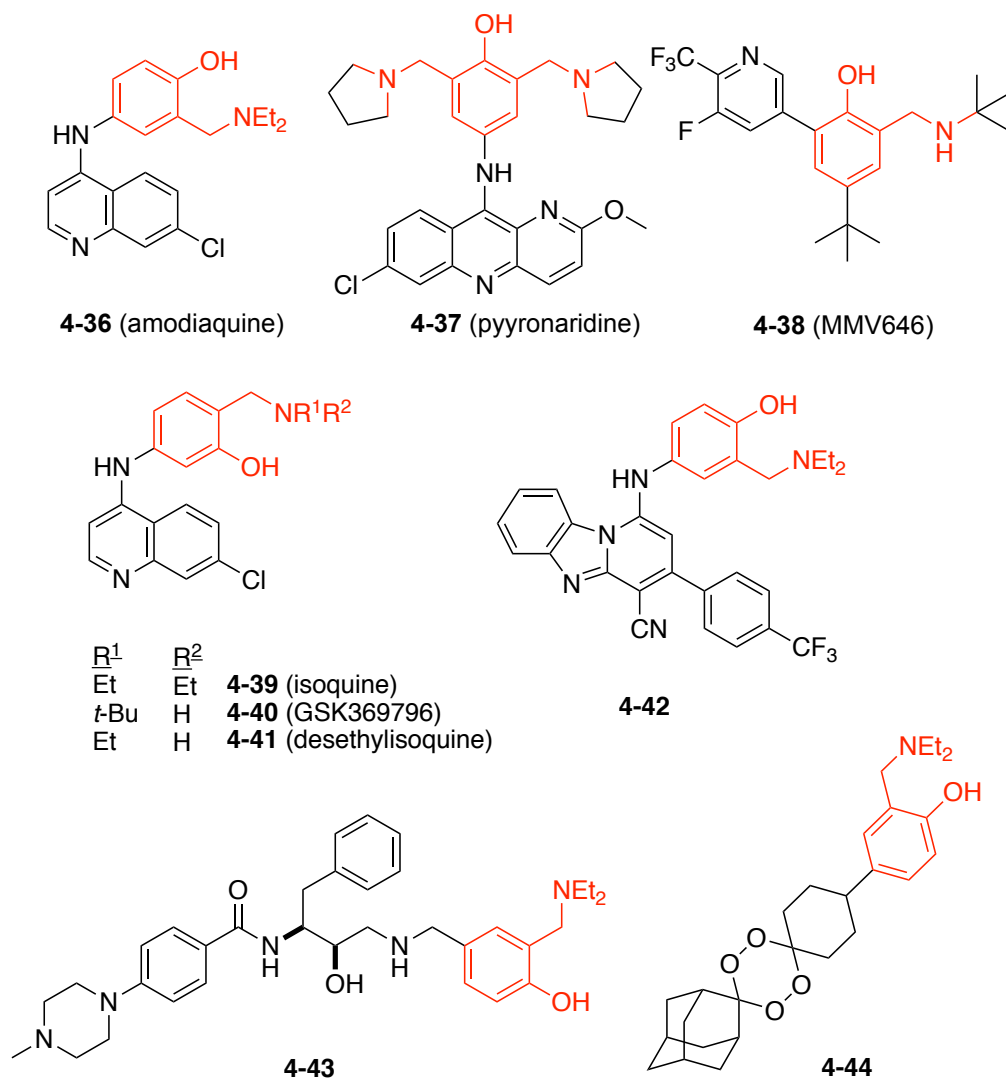
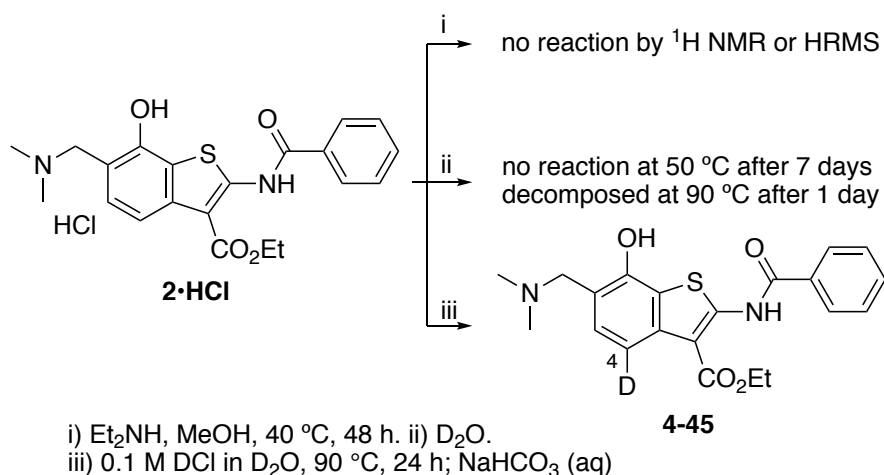


Figure 4-3. WHO-approved and orally-active investigational antimalarial drugs containing the phenolic Mannich base moiety.²⁵⁻²⁹

To our knowledge, formation of quinone methide intermediates has not been implicated for any of the phenolic Mannich base antimalarials in Figure 4-3, or others reported to have *in vitro* activity.³⁰⁻³¹ But studies of phenolic Mannich bases directed at other diseases/targets have demonstrated quinone methide formation in compounds ranging from quite reactive¹⁴⁻¹⁷ to fairly robust.^{13, 32} Thus we subjected **4-2** to a series of tests (Scheme 4-6). Heating **4-2**•HCl in methanolic diethylamine at 40 °C for 2 days did not result in any

observable change by ^1H NMR or HRMS. Not only did the dimethylamino group remain intact, so did the ethyl ester, consistent with our observation of the low reactivity of **4-3** towards amidation (Scheme 4-2). Compound **4-2**•HCl also proved stable in D_2O at $50\text{ }^\circ\text{C}$ after 7 days, but heating at $90\text{ }^\circ\text{C}$ overnight resulted in the formation of a precipitate, which was insoluble in D_2O or CDCl_3 . This result suggests the quinone methide intermediate did form under neutral conditions at $90\text{ }^\circ\text{C}$, and subsequently polymerized. However under acidic conditions (0.1 M DCl in D_2O), **4-2**•HCl was quite stable after 1 day at $90\text{ }^\circ\text{C}$, only undergoing H-D exchange selectively at C4, forming **4-45**.



Scheme 4-6. Stability test of **2**•HCl

Thus, the ethyl ester moiety of **4-2** (and by extension **4-1**) is remarkably stable to acidic hydrolysis. Together these experiments indicated that **4-1** might be stable enough to exert antimalarial activity *in vivo*, and thus we tested **4-1** (40 mg/kg po) in a mouse model of blood-stage malaria (*P. berghei*). Unfortunately, compound **4-1** did not reduce parasitemia *in vivo* compared to vehicle control. (Figures 4-4 and 4-5)

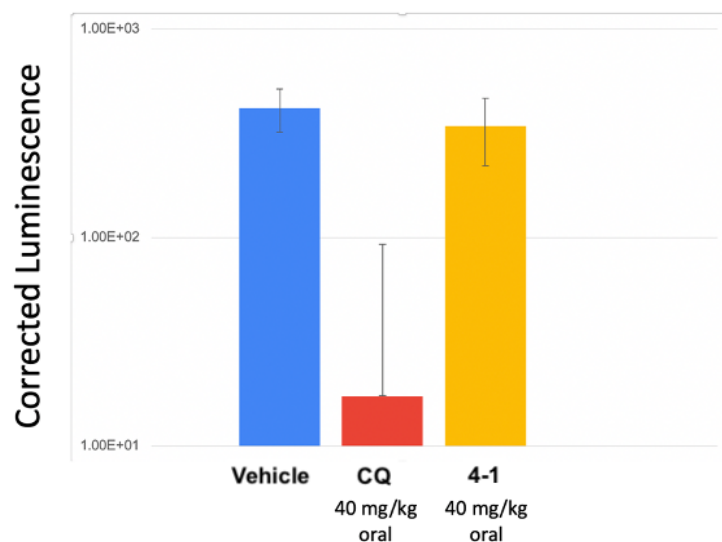


Figure 4-4. Average parasitemia in treated and untreated *P. berghei*-infected mice (five per group, CQ is chloroquine), infected Day 0, dosed daily on Days 2-6, imaged Day 7.



Figure 4-5. IVIS imaging of individual treated and untreated *P. berghei*-infected mice, infected Day 0, dosed daily on Days 2-6, imaged Day 7.

Plasma (mouse) stability studies of **4-1** showed no loss of parent over 120 minutes, indicating that the ethyl ester moiety was quite stable towards plasma carboxylesterases. Mouse hepatocyte stability experiments showed rapid loss of parent with a $t_{1/2}$ of 11 min. However, a number of other phenolic Mannich Base antimalarials have similar rates of liver metabolism, and yet retain *in vivo* efficacy (e.g. **4-36**, **4-39**–**4-44**, see Experimental Section,

Table S4-3).²⁶⁻²⁹ Without performing oral pharmacokinetics and identifying metabolites (and their antimalarial efficacy), it is impossible to know whether the failed efficacy of **4-1** is due to poor plasma exposure, or to a (rare) species difference (*P. berghei* vs *P. falciparum*) in drug sensitivity.³³⁻³⁴

In conclusion, we prepared a series of analogs of **4-1** featuring modifications at the C2-benzamide, C3-ester, C6-Mannich base, and C7-phenol moieties. *In vitro* *P. falciparum* growth inhibition potencies revealed that neither an electron-withdrawing group or electron-donating group on the C2-benzamide improved potency (cf. **4-19**, **4-20** with **4-1**), that an amide cannot substitute for an ester at the C3 position (cf. **4-22** with **4-1**, **4-21**), and that the C7-phenol is essential for potency (cf. **4-29**, **4-1**). Increasing lipophilicity of the NR₂ unit of the C6 Mannich base can double potency (cf. **4-23–4-25** with **4-1**, **4-2**), but steric constraints eventually limit this effect (cf. **4-27** with **4-1**, **4-2**). Attempts to block quinone methide formation by homologation of **4-1** to **4-28** reduced, but did not eliminate antimalarial potency (cf. Table 4-2). Thus, antimalarial action of **1** does not appear to require formation of the quinone methide. In fact, the Mannich base and ester functionalities of **4-2** (and by extension **4-1**) were found to be quite stable under neutral and acidic conditions, and no loss of **4-1** was seen in mouse plasma after 2 h. Unfortunately, **4-1** was rapidly consumed in mouse hepatocytes, and it failed to show oral efficacy at 40 mg/kg in a mouse model of malaria.

Acknowledgments

We acknowledge the National Institutes of Health (AI0128362 to PRC) and the Virginia Tech Center for Drug Discovery for financial support. *In vivo* studies of **4-1** in *P. berghei*-infected mice were carried out at the New York University Anti-infectives Core Facility. Plasma and microsomal stability studies of **4-1** were performed by Pharmaron.

Experimental Section

A. Parasite culture and antimalarial assay procedure

A.1. Parasite culture

P. falciparum clone 3D7 was cultured in human O⁺ erythrocytes (Interstate Blood Bank) at 2% hematocrit in RPMI medium (Gibco) supplemented with 27 mM sodium bicarbonate, 11 mM glucose, 0.37 mM hypoxanthine, 10 µg/mL gentamicin and 5 g/liter Albumax I (Invitrogen) at 37 °C in a 5% CO₂ incubator. Parasites were synchronized by treatment with 5% sorbitol³⁵.

A.2. Parasite growth assays

Compounds were assayed over the concentration range 10 µM to 0.15 nM (10 concentrations). Assays were generated in 96 well plates to contain synchronized ring-stage parasites at 3% parasitemia and 1% hematocrit in a volume of 200 µL with a final DMSO concentration of 0.1-0.2%. Parasites were incubated for 48 hours at 37 °C in a 5% CO₂, 5% O₂, 90% N₂ environment. Parasite growth was quantified using a well-established SYBR Green I assay³⁶⁻³⁷ that reports on the amount of parasite DNA. SYBR Green I fluorescence values were plotted against drug concentration and EC₅₀ values were determined by non-linear regression fit to a four-parameter sigmoidal curve using Kaleidagraph 4.5 (Synergy Software). Parasite growth EC₅₀ values are reported as the mean and standard deviations of at least three independent experiments.

B. Mouse efficacy studies of 4-1 (MMV665831)

Efficacy evaluation of 4-1 (MMV665831) in *P. berghei*-infected mice was performed at the Anti-Infectives Core Facility, Department of Microbiology, School of Medicine, New York University.

Protocol

Three groups of five female Swiss Webster mice weighing 25 to 30 g were used for vehicle control, 4-1 treatment (PO, 40 mg/kg/d) and the positive control chloroquine (PO, 40 mg/kg/d). Note that all five mice in each infected group survived to day 7, and were dosed and imaged as described below. The transgenic *P. berghei* line 676m1c11 line (PbGFP-Luccon) was used for infection, which expresses a fusion GFP (mutant 3) and firefly luciferase (LucIAV) and has been generated in the reference clone of ANKA strain c115cy1. Parasites of line 676m1c11 contain the PbGFP-Luc gene fusion stably integrated as a single copy gene by double cross over recombination into the 230p locus and the reporter gene is under control of the constitutive *eef1aα* promoter. This line has been selected by FACS-sorting of GFP-expressing parasites and therefore does not contain a drug-selectable marker. Mice were infected via i.p. injection with 10^3 *P. berghei*-Luccon infected erythrocytes obtained from another infected mouse. Two days after infection treatment was started once per day orally for five consecutive days. The control group was treated with vehicle (0.5% (hydroxypropyl)methyl cellulose, 0.5% Tween-80) for 5 days (oral gavage). The drug-treated groups were treated by oral gavage with compounds at the determined mpk body weight once a day for 5 days. On day 7 after infection (one day after treatment ended), mice were anesthetized by inhalation of isoflurane and injected (i.p.) with 150 mpk of D-Luciferin Potassium-salt (Goldbio) dissolved in PBS. An uninfected group of 4 mice were also injected

with this reagent. Mice were imaged 5 to 10 min after injection of luciferin with a Bruker In-Vivo Xtreme IVIS and the data acquisition and analysis were performed with LivingImage (Xenogen) to determine the level of infection. The average luminescence of the four uninfected mice was subtracted from the luminescence of each infected mouse.

C. Metabolic stability studies of 4-1 (MMV665831)

Metabolic stability tests of **4-1** were performed by Pharmaron.

Protocol

C.1. Mouse hepatocyte stability

Incubation medium (William's E Medium supplemented with GlutaMAX) and hepatocyte thawing medium was thawed in 37 °C water bath for 15 min prior to use. Cryopreserved hepatocytes from male CD-1 mouse (BioreclamationIVT, Cat. # M00505) was thawed in 37 °C water bath for 2 min. and transferred to 50 mL conical tube containing thawing medium. The conical tube was centrifuged at 100 g for 10 min. Upon completion of spin, aspirate thawing medium and resuspended hepatocytes in enough incubation medium to yield $\sim 1.5 \times 10^6$ cells/mL. The viable cell density was determined with AOPI staining solution, and diluted with incubation medium to a working cell density of 0.5×10^6 viable cells/mL. A portion of this hepatocytes were boiled for 5 min for negative control.

Compound **4-1** was reacted with hepatocytes at 1 μ M, and was sampled at 0, 15, 30, 60, and 120 mins. The aliquots are quenched with acetonitrile containing internal standards (100 nM alprazolam, 200 nM labetalol, 200 nM caffeine and 2 μ M ketoprofen), centrifuged at 3220 g for 20 min to precipitate proteins. The supernatant was diluted with ultra-pure H₂O

and analyzed with LC-MS. All incubations were performed in duplicate. Verapamil was used as positive control.

Table S4-1. Metabolic Stability of **4-1** and control compound Verapamil in Mouse Hepatocytes

Compound	Assay Format	Remaining Percentage (%)					
		0 min	15 min	30 min	60 min	90 min	120 min
Verapamil	Hepatocytes	100.00	30.63	10.10	2.49	0.52	0.14
	Boiled hepatocytes	100.00	97.18	97.95	95.03	95.10	94.83
4-1	Hepatocytes	100.00	40.26	11.39	2.10	0.53	0.29
	Boiled hepatocytes	100.00	104.61	96.94	98.65	87.25	86.99

C.2. Mouse plasma stability

Compound **4-1** was reacted with pooled CD-1 mouse plasma (gender mixed, BioIVT, Lot # MSE336029) at 37 °C at 5 µM. The assays were quenched with acetonitrile containing internal standards (100 nM Alprazolam, 500 nM Labetalol and 2 µM Ketoprofen) at 15, 30, 60 and 120 minutes, centrifuged at 3220 g for 30 min at 4 °C to precipitate proteins. The supernatant was diluted with ultra-pure H₂O and analyzed with LC-MS. All incubations were performed in duplicate. Propantheline was used as positive control.

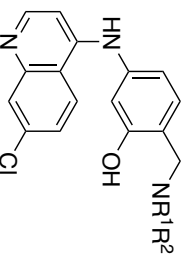
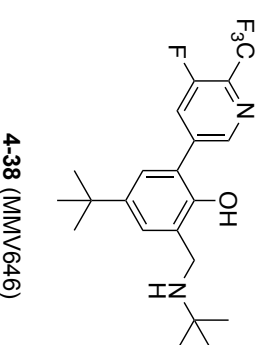
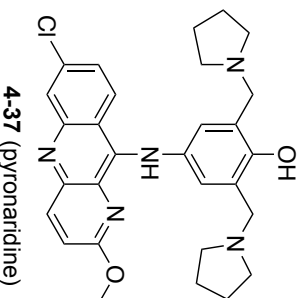
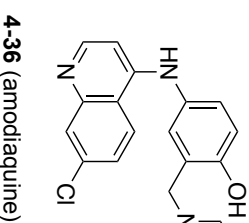
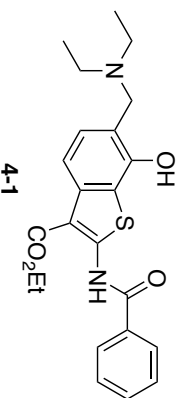
Table S4-2. The stability results of **4-1** and control compound propantheline in mouse plasma

Compound	Percent remaining (%)				
	0 min	15 min	30 min	60 min	120 min
Propantheline	100.00	79.68	57.99	26.86	5.96
4-1*	100.00	108.87	104.44	102.02	114.92

*Percent remaining values greater than 100%, but less than 120%, are considered to be within acceptable bioanalysis variance of > 99%.

D. Comparison of ADME Characteristics and *P. berghei*-infected mouse efficacy of Phenolic Mannich Base

Antimalarials



R^1	R^2	
Et	Et	4-39 (isoquine)
<i>t</i> -Bu	H	4-40 (GSK369796)
Et	H	4-41 (desethylisoquine)

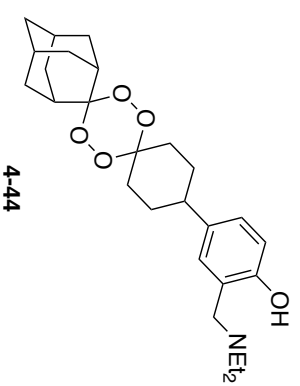
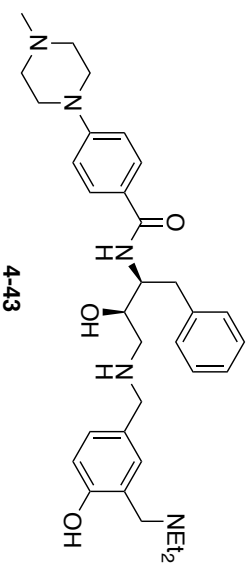
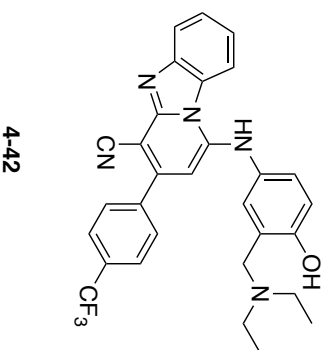


Table S4-3. Comparison of ADME Characteristics and *P. berghei*-infected mouse efficacy of Phenolic Mannich Base Antimalarials

	4-1	4-36	4-37	4-38	4-39	4-40	4-41	4-42	4-43	4-44
		Amodiaquine	Pyronaridine	MMV646 (JPC-3210)	Isoquine	GSK369746	Desethyl isoquine			
MW (g/mol) ^a	426.5	355.9	518.1	398.5	355.9	355.9	327.8	529.56	573.77	457.6
H-bond acceptor ^b	5	3	6	7	3	3	3	7	6	6
H-bond donor ^b	2	2	2	2	2	3	3	2	4	1
tPSA (Å ²) ^b	107.11	48.39	73.75	45.15	48.39	57.18	57.18	76.59	91.31	60.39
Consensus Log P ^b	4.26	4.22	4.65	5.3	4.18	4.33	3.74	5.9	3.47	4.78
GI absorption ^b	High	High	High	Low	High	High	High	Low	High	High
Ro5 violations ^b	0	0	1	0	0	0	0	2	1	1
Structure alerts ^b	Mannich	Mannich, hydroquinone	Mannich, hydroquinone, polycyclic aromatic	Mannich	Mannich	Mannich	Mannich	Mannich, hydroquinone	Mannich	Mannich, peroxide

^aFree base.

^bAs calculated or indicated by SwissADME¹² at <http://www.swissadme.ch>

Table S4-3. continued

	4-1	4-36 Amodiaquine	4-37 Pyronaridine	4-38 MMV646 (JPC-3210)	4-39 Isoquine	4-40 GSK369 746	4-41 Desethyl isoquine	4-42	4-43	4-44
Hepatocyte stability	$t_{1/2} = 11$ min		Mouse microsomal $t_{1/2} = 173$ min ³⁸	> 54 h, based on <5% conversion at 10 μ M after 4 h. ³⁹ Mouse elimination $t_{1/2}$ in plasma is 50 h (PK). ⁴⁰				~20 min, based on 35% remaining after 30 min in mouse microsomes ²⁷		
Mouse Hepatocyte Cl_{int} (μ L/min/ 10^6 cells) ^e	130.4	> 416 (but metabolite is active)			342	53.5	91.7			Microsome 90 μ L/min/mg
Mouse Hepatocyte Cl_{int} (mL/min/g liver)		>50 ⁴¹			41 \pm 7 ⁴¹	6.4 \pm 1.0 ⁴¹	11 \pm 2 ⁴¹			
Effective oral dose in <i>P. berghei</i> -infected mice	Not effective at 40 mg/kg/day (5 days) ^d	ED ₉₀ = 3.2 mg/kg ^e	ED ₅₀ = 6.8 \pm 1.4 mg/kg (oral) ⁴²	100% Effective at 32 mg/kg ^f	ED ₉₀ = 5.3 mg/kg ^e	ED ₉₀ = 4.7 mg/kg ^e	ED ₉₀ = 7.3 mg/kg ^e	ED ₉₅ = 50 mg/kg ^e	ED ₉₀ = 100 mg/kg ^h	ED ₉₀ = 10 mg/kg ⁱ

^eExcept for **1**, calculated from reported mL/min/g liver Cl_{int} values, based on a mouse hepatocellularity of 120×10^6 cell/g liver.⁴¹

^dMice were infected with 10^3 infected red blood cells, and then dosed on Days 2-6.

^eMice were infected with 1×10^7 parasites, and dosed at Day 0 (1 h post-infection) and on days 1-3.²⁶

^fTested prophylactically, administered 11 days before being infected with 5×10^5 parasitized erythrocytes, 7/7 mice alive with no parasites seen at 31 days post-inoculation.⁴³

^gDosed four times, at 4, 24, 48 and 72 h post infection.²⁷

^hA single oral dose, mice survived to 7 days.²⁸

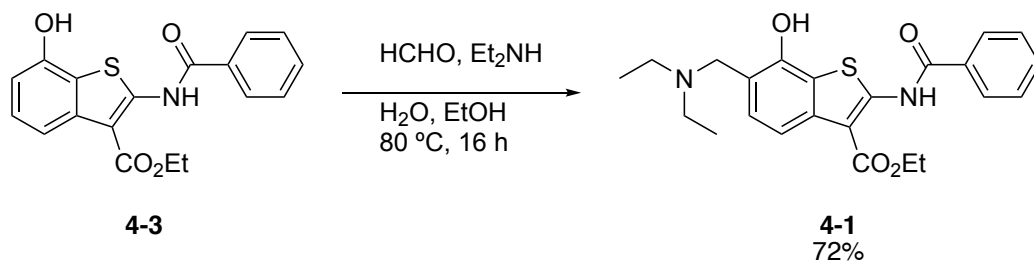
ⁱThree oral doses (10 mg/kg), survival to 27 days.²⁹

E. Synthesis and analytical characterization of tested compounds

General

Compounds were purchased from Sigma-Aldrich, Alfa Aesar, and Oakwood Chemical and were used without purification, unless otherwise noted. ^1H NMR spectra were recorded at 400 or 500 MHz; the corresponding ^{13}C NMR resonant frequencies were 101 and 126 MHz respectively; the corresponding ^{19}F NMR resonant frequencies were 376 and 470 MHz. Compound **4-2** was purchased from ChemDiv and its purity and identity were confirmed by ^1H and ^{13}C NMR spectroscopy.

Ethyl 2-benzamido-6-((diethylamino)methyl)-7-hydroxybenzo[*b*]thiophene-3-carboxylate (**4-1**)



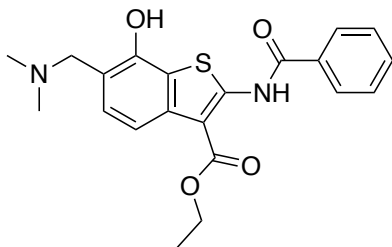
To a 25 mL RBF were added **4-3** (1.15 g, 3.35 mmol, 1 equiv), water (10 mL), EtOH (10 mL), formalin (37 w.% in water, 440 mg, 1.6 equiv), and diethylamine (523 mg, 2.1 equiv). The mixture was heated to 80 °C for 16 h, then the solvent was removed in vacuo, and purified by flash column chromatography (80:20:1 DCM/acetone/TEA) to give **4-1** as a grey powder (1.04 g, 2.43 mmol, 72%).

^1H NMR (400 MHz, CDCl_3) δ 12.77 (s, 1H), 8.13 – 8.06 (m, 2H), 7.72 (d, $J = 8.2$ Hz, 1H), 7.64 – 7.59 (m, 1H), 7.58 – 7.52 (m, 2H), 7.03 (d, $J = 8.2$ Hz, 1H), 4.52 (q, $J = 7.1$ Hz, 2H), 3.91 (s, 2H), 2.68 (q, $J = 7.2$ Hz, 4H), 1.52 (t, $J = 7.1$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 167.5, 164.4, 153.7, 153.1, 134.9, 133.0, 132.4, 129.2, 127.9, 126.5, 121.8, 115.4, 113.8, 107.1, 61.2, 56.9, 46.6, 14.6, 11.3.

HRMS (ESI+) calculated for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 427.1686, found 427.1680.

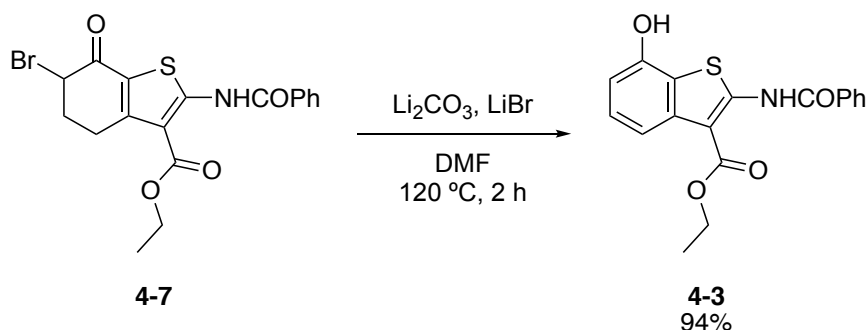
Ethyl 2-benzamido-6-((dimethylamino)methyl)-7-hydroxybenzo[*b*]thiophene-3-carboxylate (4-2)



^1H NMR (400 MHz, CD_3OD) δ 8.09 – 8.03 (m, 1H), 7.97 (d, $J = 8.3$ Hz, 1H), 7.74 – 7.68 (m, 1H), 7.67 – 7.60 (m, 2H), 7.40 (d, $J = 8.3$ Hz, 1H), 4.56 (q, $J = 7.1$ Hz, 2H), 4.43 (s, 2H), 2.89 (s, 6H), 1.52 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD) δ 167.9, 165.9, 154.5, 152.0, 139.3, 134.6, 133.0, 131.0, 130.4, 128.6, 124.1, 117.2, 113.1, 108.5, 62.7, 57.8, 43.1, 14.7.

Ethyl 2-benzamido-7-hydroxybenzo[*b*]thiophene-3-carboxylate (**4-3**)



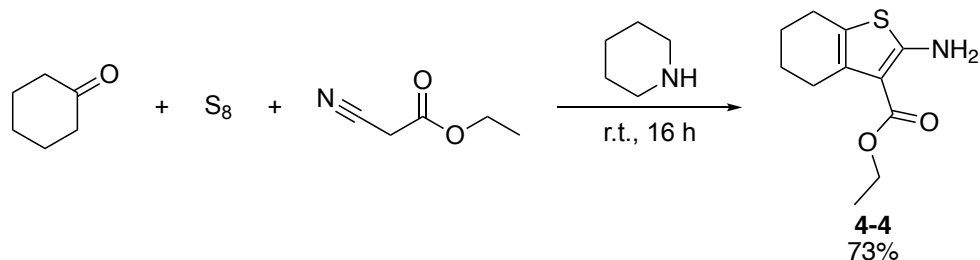
Prepared using a modification of a procedure from Samanta.¹⁰ To a 50 mL RBF were added **4-7** (1.14 g, 2.69 mmol, 1 equiv), lithium carbonate (397 mg, 5.38 mmol, 2 equiv), lithium bromide (525 mg, 6.05 mmol, 2.25 equiv), and DMF (15 mL). The mixture was capped with a rubber septum and heated to 120 °C for 2 h until full conversion was indicated by TLC. The mixture was poured to 120 mL cold water, cooled for 16 h in the fridge to promote precipitation, and filtered to give **4-3** as an off-white powder (864.6 mg, 94%). This material was used without further purification.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.53 (s, 1H), 10.49 (s, 1H), 8.05 – 7.97 (m, 2H), 7.79 – 7.71 (m, 2H), 7.71 – 7.64 (m, 2H), 7.30 (dd, *J* = 8.0, 7.9 Hz, 1H), 6.79 (dd, *J* = 7.9, 0.9 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.0, 163.7, 151.9, 151.7, 135.3, 133.3, 131.6, 129.4, 127.3, 127.3, 120.4, 114.2, 108.7, 106.9, 61.1, 14.2.

HRMS (ESI⁺) calculated for C₁₈H₁₅NO₄S [M+H]⁺: 342.0795, found 342.0788.

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4-4)

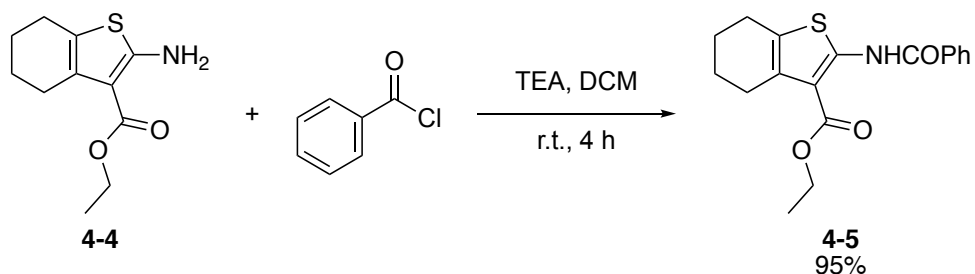


Prepared using a modification of the literature procedure.⁷ To a 250 mL round-bottomed flask (RBF) were added S₈ (3.21 g 12.5 mmol, 0.125 equiv), 11.31 g ethyl cyanoacetate (100 mmol, 1 equiv), 31 mL cyclohexanone (300 mmol, 3 equiv); the mixture was cooled in ice/water bath and 4.95 mL piperidine (50 mmol, 0.5 equiv) was slowly added dropwise over 2 min period. The mixture was stirred at r.t. overnight; the precipitation was filtered and recrystallized from 1:1 ethanol/water (v:v, 250 mL) to give **4-4** as yellow crystals (15.89 g, 73%).

¹H NMR (400 MHz, CDCl₃) δ 5.93 (br, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.72 – 2.67 (m, 2H), 2.52 – 2.47 (m, 2H), 1.82 – 1.69 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 166.3, 161.8, 132.6, 117.8, 105.9, 59.5, 27.1, 24.7, 23.4, 23.0, 14.6.

Ethyl 2-benzamido-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**4-5**)



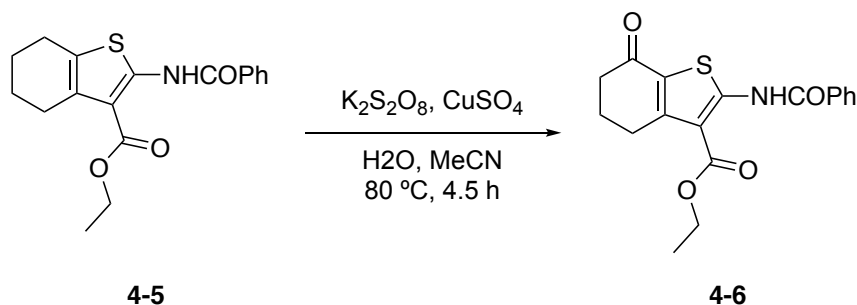
To a 250 mL RBF were added **4-4** (6.08 g, 27.0 mmol), DCM (60 mL), benzoyl chloride (4.18 g, 29.7 mmol), the RBF was capped with a septum and purged with N₂ flow for 5 min. The mixture was cooled in ice/water bath and triethylamine (3.28 g, 32.4 mmol) was added dropwise. The mixture was stirred at r.t. for 4 h until TLC indicated full conversion. N,N-Dimethylethylenediamine (0.3 mL, 2.7 mmol) was added to scavenge residual benzoyl chloride, and the mixture was stirred at r.t. for an additional 20 min. The mixture was then washed with sat. ammonium chloride, water, and then brine. The organic layer was separated, dried over sodium sulfate, and concentrated in vacuo to give **4-5** as a yellow powder (8.4732 g, 95%).

¹H NMR (400 MHz, CDCl₃) δ 12.31 (s, 1H), 8.04 – 7.98 (m, 2H), 7.61 – 7.52 (m, 1H), 7.53 – 7.47 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.82 – 2.77 (m, 2H), 2.71 – 2.64 (m, 2H), 1.87 – 1.75 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 167.2, 163.6, 148.2, 132.7, 132.5, 131.2, 129.0, 127.6, 127.2, 112.1, 60.7, 26.6, 24.6, 23.1, 23.0, 14.5.

HRMS (ESI⁺) calculated for C₁₈H₁₉NO₃S [M+H]⁺: 330.1158, found 330.1156.

Ethyl 2-benzamido-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (4-6)



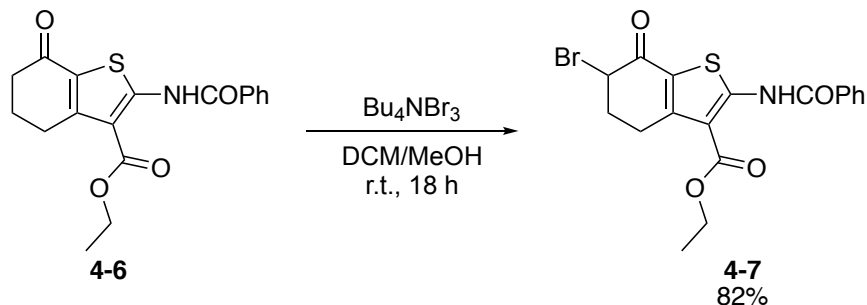
Prepared using a modification of the procedure from Lilienkamp⁸. To a 250 mL RBF were added **4-5** (2.00 g, 6.07 mmol), CuSO₄ (2.91 g, 18.21 mmol), K₂S₂O₈ (4.92 g, 18.21 mmol), water (50 mL), and MeCN (50 mL). The flask was equipped with a condenser and the mixture was refluxed at 80 °C for 4.5 h until TLC indicated full conversion. The mixture was diluted with water (50 mL) and EtOAc (50 mL), the aq. layer was separated and washed with DCM (50 mL x 3), and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc in DCM) gave **4-6** as an off-white powder (1.15 g, 58%).

¹H NMR (400 MHz, CDCl₃) δ 12.59 (s, 1H), 8.06 – 8.00 (m, 2H), 7.65 – 7.59 (m, 1H), 7.58 – 7.51 (m, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 3.11 (t, *J* = 6.1 Hz, 2H), 2.59 (m, 2H), 2.19 (p, *J* = 6.3 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.6, 166.7, 164.3, 156.8, 150.2, 133.3, 131.9, 129.2, 127.9, 127.8, 112.6, 61.5, 37.8, 26.7, 24.0, 14.5.

HRMS (ESI⁺) calculated for C₁₈H₁₇NO₄S [M+H]⁺: 344.0951, found 344.0947.

Ethyl 2-benzamido-6-bromo-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4-7)



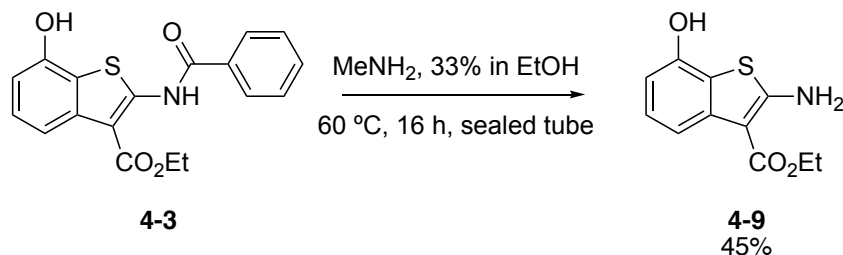
Prepared using a modification of the procedure from Voet.⁹ To a 50 mL RBF were added **4-6** (1.15 g, 3.35 mmol, 1 equiv), tetrabutylammonium tribromide (1.78 g, 3.68 mmol, 1.1 equiv), DCM (25 mL) and MeOH (10 mL). The resulting mixture was capped with a septum and stirred at r.t. for 18 h; washed with water (50 mL x 3), then brine (50 mL x 1); dried over Na_2SO_4 , concentrated in vacuo and purified by flash column chromatography (100:3 DCM/EtOAc) to give **4-7** as a yellow powder (1.15 g, 82%).

^1H NMR (500 MHz, CDCl_3) δ 12.65 (s, 1H), 8.06 – 7.99 (m, 2H), 7.67 – 7.60 (m, 1H), 7.57 – 7.53 (m, 2H), 4.65 (t, $J = 4.0$ Hz, 1H), 4.46 (q, $J = 7.1$ Hz, 2H), 3.31 (dt, $J = 18.4$, 4.2 Hz, 1H), 3.16 (ddd, $J = 18.4$, 9.1, 5.3 Hz, 1H), 2.60 – 2.46 (m, 2H), 1.47 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 185.2, 166.4, 164.3, 157.9, 149.6, 133.4, 131.6, 129.3, 127.8, 124.9, 112.5, 61.8, 49.1, 32.9, 24.0, 14.5.

HRMS (ESI+) calculated for $\text{C}_{18}\text{H}_{16}\text{BrNO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 422.0056, found 422.0062.

Ethyl 2-amino-7-hydroxybenzo[*b*]thiophene-3-carboxylate (**4-9**)



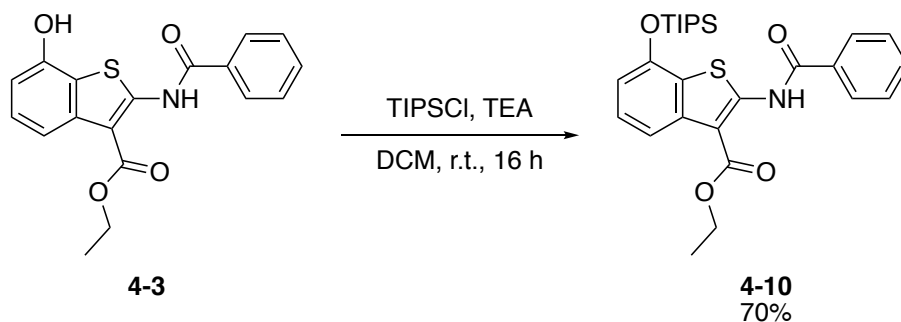
To a 10 mL thick-walled pressure tube equipped with a threaded teflon cap was added **4-3** (22.4 mg, 0.07 mmol, 1 equiv) and methylamine (33 w.% in ethanol, 3 mL, 24 mmol, 191 equiv). The tube was sealed and heated to 60 °C for 16 h. The mixture was concentrated in vacuo and purified by flash column chromatography (100:6 DCM/EtOAc) to give **4-9** as a sticky solid (7.0 mg, 0.03 mmol, 45%).

¹H NMR (500 MHz, CD₃OD) δ 7.54 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.50 (dd, *J* = 8.0, 0.9 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CD₃OD) δ 167.81, 167.79, 152.3, 140.8, 127.4, 116.6, 114.9, 108.2, 99.4, 60.6, 14.9.

HRMS (ESI+) calculated for C₁₁H₁₁NO₃S [M+H]⁺: 238.0532, found 238.0550.

Ethyl 2-benzamido-7-((triisopropylsilyl)oxy)benzo[*b*]thiophene-3-carboxylate (**4-10**)



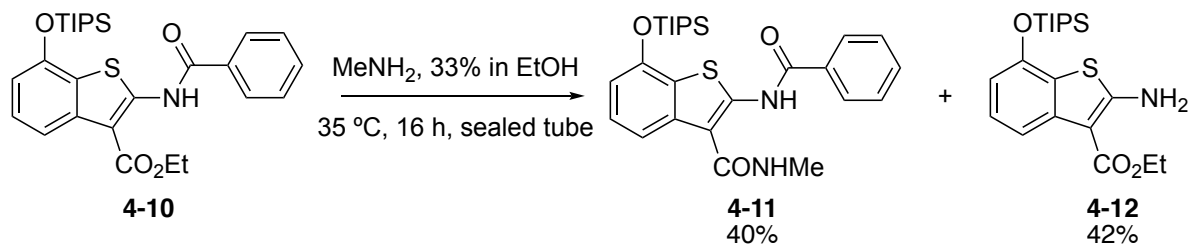
To a 25 mL RBF were added **4-3** (223.8 mg, 0.66 mmol, 1 equiv), DCM (2 mL), and triisopropylsilyl chloride (TIPSCl) (139.0 mg, 0.72 mmol, 1.1 equiv). The mixture was capped with a septum and purged with N₂ flow for 5 min. cooled in ice/water bath, and TEA (79.6 mg, 0.79 mmol, 1.2 equiv) was added dropwise via syringe. The mixture was stirred at r.t. for 16 h, the mixture was concentrated in vacuo, and purified by gradient flash column chromatography (0-3% EtOAc in DCM) to give **4-10** as a white powder (227.6 mg, 0.46 mmol, 70%).

¹H NMR (500 MHz, CDCl₃) δ 12.83 (s, 1H), 8.15 – 8.07 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.59 (m, 1H), 7.59 – 7.53 (m, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 1.54 (t, *J* = 7.1 Hz, 3H), 1.40 (hept, *J* = 7.4 Hz, 3H), 1.17 (d, *J* = 7.4 Hz, 18H).

¹³C NMR (126 MHz, CDCl₃) δ 167.5, 164.6, 153.7, 150.8, 136.0, 133.1, 132.2, 129.2, 127.8, 127.0, 125.9, 116.3, 112.1, 107.5, 61.3, 18.2, 14.6, 13.1.

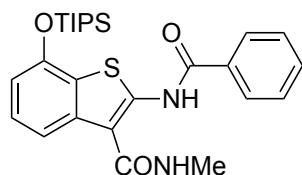
HRMS calculated for C₂₇H₃₅NO₄SSi [M+H⁺] 498.2129, found 498.2128.

2-Benzamido-*N*-methyl-7-((triisopropylsilyl)oxy)benzo[*b*]thiophene-3-carboxamide (4-11) & ethyl 2-amino-7-((triisopropylsilyl)oxy)benzo[*b*]thiophene-3-carboxylate (4-12)



To a sealed tube were added **4-10** (64.4 mg, 0.16 mmol, 1 equiv), methylamine (33 w.% in ethanol, 3 mL, 24 mmol, 191 equiv). The tube was sealed and heated to 35 °C for 16 h. The mixture was concentrated in vacuo, and purified by flash column chromatography (2:1 DCM/Hexanes) to give **4-11** (24.1 mg, 0.06 mmol, 40%) and **4-12** (21.0 mg, 0.07 mmol, 42%) as off-white powders.

2-Benzamido-*N*-methyl-7-((triisopropylsilyl)oxy)benzo[*b*]thiophene-3-carboxamide (4-11)

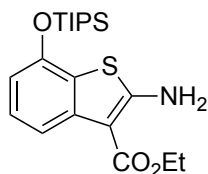


$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 13.27 (s, 1H), 8.12 – 8.08 (m, 2H), 7.62 – 7.57 (m, 1H), 7.56 – 7.52 (m, 2H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.30 (t, $J = 8.0$ Hz, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.39 (q, $J = 4.8$ Hz, 1H), 3.12 (d, $J = 4.8$ Hz, 3H), 1.40 (hept, $J = 7.5$ Hz, 3H), 1.16 (d, $J = 7.5$ Hz, 18H).

^{13}C NMR (126 MHz, CDCl_3) δ 167.6, 164.5, 151.7, 150.0, 135.2, 132.8, 132.4, 129.1, 127.9, 127.2, 126.8, 112.7, 111.8, 110.1, 26.8, 18.2, 13.1.

HRMS calculated for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_3\text{SSi}$ $[\text{M}+\text{H}^+]$ 483.2132, found 483.2117

Ethyl 2-amino-7-((triisopropylsilyloxy)benzo[*b*]thiophene-3-carboxylate (4-12)

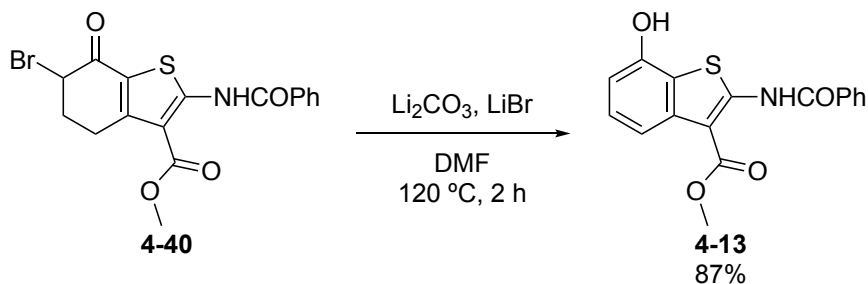


^1H NMR (500 MHz, CDCl_3) δ 7.69 (dd, $J = 8.0, 0.9$ Hz, 1H), 7.17 (t, $J = 8.0$ Hz, 1H), 6.61 (dd, $J = 8.0, 0.9$ Hz, 1H), 6.52 (br, 2H), 4.40 (q, $J = 7.1$ Hz, 2H), 1.45 (t, $J = 7.1$ Hz, 3H), 1.33 (hept, $J = 7.4$ Hz, 3H), 1.12 (d, $J = 7.4$ Hz, 18H).

^{13}C NMR (126 MHz, CDCl_3) δ 166.6, 164.9, 149.9, 139.3, 126.8, 120.2, 115.6, 111.2, 100.6, 60.0, 18.1, 14.7, 13.0.

HRMS calculated for $\text{C}_{20}\text{H}_{31}\text{NO}_3\text{SSi}$ $[\text{M}+\text{H}^+]$ 394.1867, found 394.1855.

Methyl 2-benzamido-7-hydroxybenzo[*b*]thiophene-3-carboxylate (4-13)

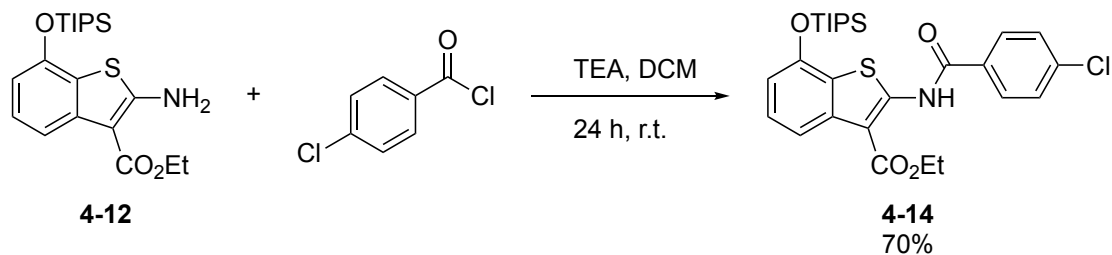


Prepared according to a modified procedure from Samanta, 1997.¹⁰ To a 50 mL RBF were added **4-40** (1.32 g, 3.22 mmol, 1 equiv), lithium carbonate (475 mg, 6.43 mmol, 2 equiv), lithium bromide (559 mg, 6.43 mmol, 2 equiv), and DMF (15 mL). The mixture was heated to 120 °C for 2 h until full conversion indicated by TLC. The mixture was poured to 125 mL cold water, cooled in fridge to promote precipitation, and filtered to give **4-13** as a grey powder (922 mg, 87%) and used without further purification.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.45 (br, 1H), 10.51 (br, 1H), 8.04 – 7.97 (m, 2H), 7.75 – 7.62 (m, 4H), 7.27 (dd, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 4.01 (s, 3H).
¹³C NMR (101 MHz, dms) δ 166.5, 163.7, 151.9, 151.8, 135.2, 133.3, 131.6, 129.4, 127.3, 127.2, 120.4, 114.2, 108.7, 106.9, 52.2.

HRMS (ESI⁺) calculated for C₁₇H₁₃NO₄S [M+H]⁺: 328.0638, found 328.0641.

Ethyl 2-(4-chlorobenzamido)-7-((triisopropylsilyl)oxy)benzo[*b*]thiophene-3-carboxylate (**4-14**)



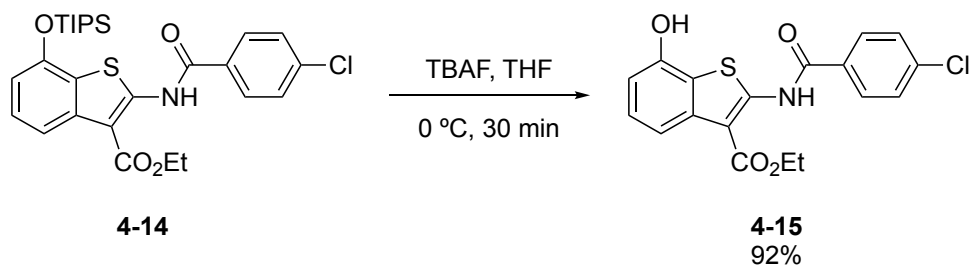
To a 10 mL RBF were added **4-12** (72 mg, 0.18 mmol, 1 equiv), DCM (5 mL), benzoyl chloride (35 mg, 0.20 mmol, 1.1 equiv). The mixture was cooled in ice/water bath and triethylamine (21.8 mg, 0.22 mmol, 1.2 equiv) was added dropwise. The mixture was

stirred at r.t. for 24 h until TLC indicated full conversion. N,N-Dimethylethylenediamine (0.01 mL, 0.09 mmol) was added and the mixture was stirred at r.t. for an additional 20 min. The mixture was then washed with sat. ammonium chloride, water, and then brine; the organic layer was separated, dried over sodium sulfate, and concentrated in vacuo, and recrystallized from EtOH to give **4-14** as a light yellow powder (68.2 mg, 0.13 mmol, 70%).

^1H NMR (400 MHz, CDCl_3) δ 12.84 (s, 1H), 8.07 – 8.00 (m, 2H), 7.90 (dd, $J = 8.1, 0.8$ Hz, 1H), 7.56 – 7.49 (m, 2H), 7.29 (t, $J = 8.1$ Hz, 1H), 6.78 (dd, $J = 8.1, 0.8$ Hz, 1H), 4.53 (q, $J = 7.1$ Hz, 2H), 1.53 (t, $J = 7.1$ Hz, 3H), 1.39 (hept, $J = 7.4$ Hz, 3H), 1.16 (d, $J = 7.4$ Hz, 18H).

^{13}C NMR (101 MHz, CDCl_3) δ 167.4, 163.3, 153.3, 150.6, 139.4, 135.8, 130.5, 129.9, 129.4, 129.1, 126.9, 116.2, 112.0, 107.5, 61.2, 18.0, 14.4, 13.0.

Ethyl 2-(4-chlorobenzamido)-7-hydroxybenzo[*b*]thiophene-3-carboxylate (**4-15**)



To a 10 mL RBF were added **4-14** (68.2 mg, 0.13 mmol, 1 equiv) and THF (3 mL), the mixture was cooled in ice/water bath, and TBAF (1 M in THF, 1.5 equiv). The resulting mixture was stirred at 0 °C for 30 min until full conversion indicated by TLC. The solvent

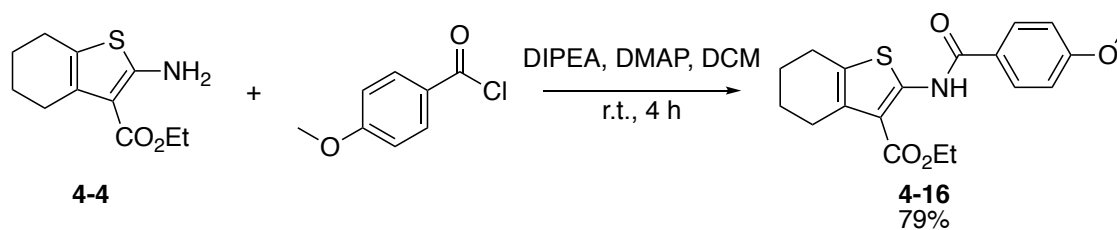
was removed in vacuo, and the resulting crude was washed with water, then brine, dried over Na₂SO₄, then concentrated in vacuo to give **4-15** (44.3 mg, 92%) as a light yellow powder.

¹H NMR (400 MHz, CDCl₃) δ 7.88 – 7.80 (m, 2H), 7.70 – 7.63 (m, 1H), 7.38 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.11 (ddd, *J* = 8.1, 8.0, 1.9 Hz, 1H), 6.63 – 6.55 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 167.2, 163.4, 152.5, 151.6, 139.3, 135.6, 130.3, 129.3, 128.9, 126.9, 121.4, 114.8, 108.6, 107.5, 61.1, 14.0.

HRMS (ESI⁺) calculated for C₁₈H₁₄ClNO₄S [M+H]⁺: 376.0405, found 376.0399.

Ethyl 2-(4-methoxybenzamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (4-16)



To a 250 mL RBF were added **4-4** (3.27 g, 14.5 mmol, 1 equiv), DCM (50 mL), benzoyl chloride (2.6 g, 15.24 mmol, 1.05 equiv). The mixture was cooled in ice/water bath and DIPEA (1.97 g, 15.24 mmol, 1.05 equiv) was added dropwise, followed by DMAP (88 mg, 0.73 mmol, 0.05 equiv). The mixture was stirred at r.t. for 4 h until TLC shows full conversion. N,N-Dimethylethylenediamine (0.3 mL, 2.7 mmol) was added and the mixture is stirred at r.t. for an additional 20 min. The mixture was then washed with sat.

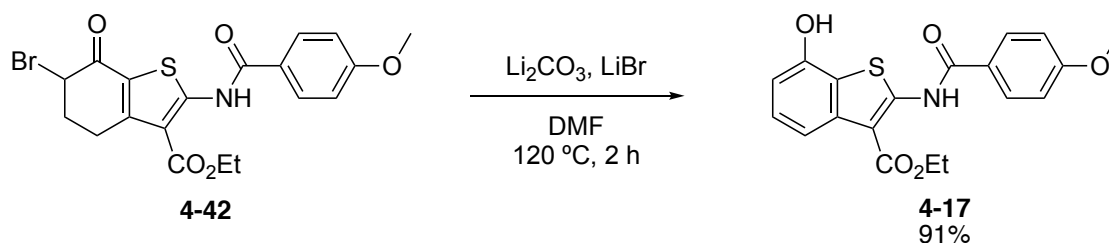
ammonium chloride, water, and then brine; the organic layer was separated, dried over sodium sulfate, and concentrated in vacuo, and recrystallized from EtOH to give **4-16** as a yellow crystal (4.13 g, 79%).

^1H NMR (400 MHz, CDCl_3) δ 12.20 (s, 1H), 7.94 (d, $J = 8.8$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 4.33 (q, $J = 7.1$ Hz, 2H), 3.83 (s, 3H), 2.81 – 2.59 (m, 4H), 1.84 – 1.71 (m, 4H), 1.37 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 167.1, 163.0, 163.0, 148.5, 130.9, 129.4, 126.7, 124.8, 114.1, 111.6, 60.6, 55.5, 26.5, 24.4, 23.0, 22.9, 14.4.

HRMS (ESI+) calculated for $\text{C}_{19}\text{H}_{21}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 360.1264, found 360.1260.

Ethyl 7-hydroxy-2-(4-methoxybenzamido)benzo[*b*]thiophene-3-carboxylate (**4-17**)



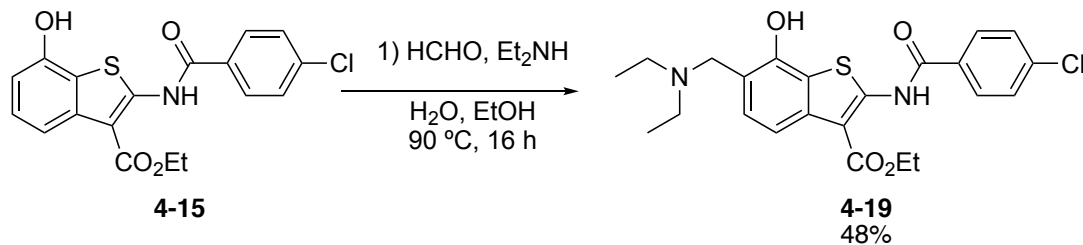
Prepared according to a modified procedure from Samanta, 1997.¹⁰ To a 25 mL RBF were added **4-42** (1.33 g, 2.94 mmol, 1 equiv), lithium carbonate (434 mg, 5.88 mmol, 2 equiv), lithium bromide (511 mg, 5.88 mmol, 2 equiv), and DMF (15 mL). The mixture was heated to $120\text{ }^\circ\text{C}$ for 2 h until full conversion was indicated by TLC. The mixture was poured to 125 mL cold water, cooled in fridge to promote precipitation, and filtered to give **4-17** as a brown powder (993 mg, 91%) and used without further purification.

^1H NMR (400 MHz, dms o) δ 12.45 (s, 1H), 10.43 (s, 1H), 8.00 – 7.91 (m, 2H), 7.73 (dd, J = 8.0, 0.8 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.22 – 7.17 (m, 2H), 6.77 (dd, J = 8.0, 0.8 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, dms o) δ 166.1, 163.2, 163.1, 152.1, 151.8, 135.3, 129.4, 127.2, 123.6, 120.3, 114.7, 114.1, 108.6, 106.4, 61.1, 55.7, 14.2.

HRMS ESI $^+$ calculated for $\text{C}_{19}\text{H}_{17}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 372.0900, found 372.0893.

Ethyl 2-(4-chlorobenzamido)-6-((diethylamino)methyl)-7-hydroxybenzo[*b*]thiophene-3-carboxylate (4-19)



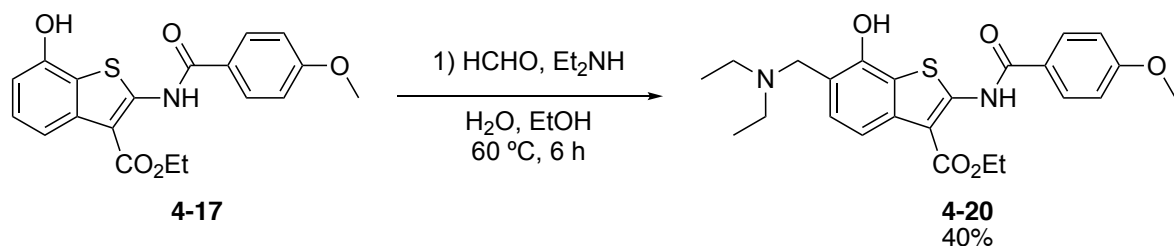
To a 1-dram vial were added **4-15** (10 mg, 0.027 mmol, 1 equiv), water (0.3 mL), EtOH (0.3 mL), formalin (37 w.% in water, 3 μL , 1.6 equiv), and diethylamine (6 μL , 2.1 equiv). The mixture was heated to 90 °C for 16 h, then the solvent was removed in vacuo, and purified by flash column chromatography (80:20:1 DCM/acetone/TEA) to give **4-19** as a brown powder (5.9 mg, 0.013 mmol, 48%).

^1H NMR (400 MHz, CDCl_3) δ 12.79 (s, 1H), 8.05 – 8.01 (m, 2H), 7.72 (d, $J = 8.2$ Hz, 1H), 7.55 – 7.50 (m, 2H), 7.04 (d, $J = 8.2$ Hz, 1H), 4.52 (q, $J = 7.1$ Hz, 2H), 3.91 (s, 2H), 2.68 (q, $J = 7.2$ Hz, 4H), 1.52 (t, $J = 7.1$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 167.6, 163.3, 153.4, 153.2, 139.4, 134.8, 130.8, 129.5, 129.3, 126.5, 121.8, 115.5, 113.9, 107.3, 61.3, 56.9, 46.6, 14.6, 11.3.

HRMS (ESI+) calculated for $\text{C}_{23}\text{H}_{25}\text{ClN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 461.1296, found 461.1284.

Ethyl 6-((diethylamino)methyl)-7-hydroxy-2-(4-methoxybenzamido)benzo[*b*]thiophene-3-carboxylate hydrochloride (4-20•HCl)



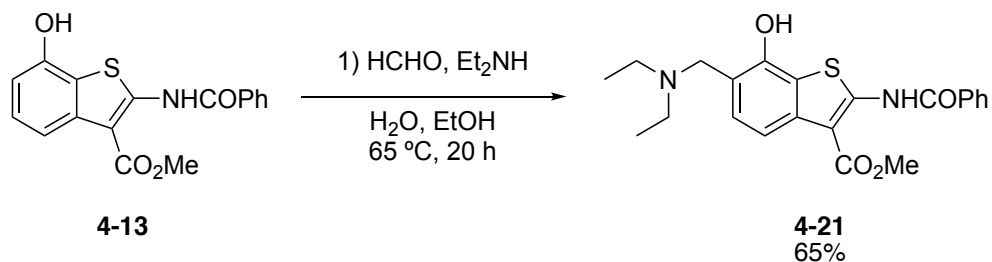
To a 25 mL RBF were added **4-17** (141.7 mg, 0.38 mmol, 1 equiv), water (3 mL), EtOH (3 mL), formalin (37 w.% in water, 43 μL , 1.6 equiv), and diethylamine (79 μL , 2 equiv). The mixture was heated to 60°C for 6 h, then the solvent was removed in vacuo, and purified by flash column chromatography (80:20:1 DCM/acetone/TEA) to give **4-20** (69 mg, 0.15 mmol, 40%). The free base was dissolved in methanol, HCl (1 M in EtOAc, 1.1 equiv) was added at 0°C , the mixture was stirred at r.t. for 30 min and concentrated in vacuo to give **4-20•HCl** as a yellow powder (67.2 mg, 0.14 mmol, 90%).

^1H NMR (400 MHz, cd_3od) δ 8.00 – 7.95 (m, 2H), 7.93 (d, $J = 8.3$ Hz, 1H), 7.38 (d, $J = 8.3$ Hz, 1H), 7.12 – 7.08 (m, 2H), 4.53 (q, $J = 7.1$ Hz, 2H), 4.42 (s, 2H), 3.25 (q, $J = 7.3$ Hz, 4H), 1.51 (t, $J = 7.1$ Hz, 3H), 1.39 (t, $J = 7.3$ Hz, 6H).

^{13}C NMR (126 MHz, CD_3OD) δ 167.9, 165.44, 165.38, 154.8, 151.9, 139.2, 130.9, 130.7, 124.8, 124.0, 117.2, 115.6, 113.0, 108.0, 62.6, 56.2, 52.4, 48.5, 14.7, 9.2.

HRMS (ESI+) calculated for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 457.1792, found 457.1786.

Methyl 2-benzamido-6-((diethylamino)methyl)-7-hydroxybenzo[*b*]thiophene-3-carboxylate hydrochloride (4-21)



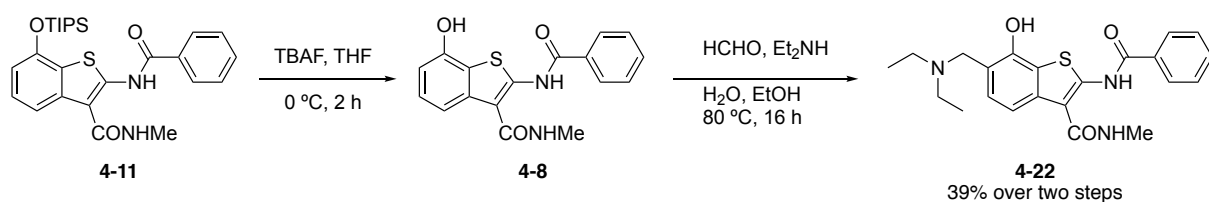
To a 1-dram vial were added **4-13** (100 mg, 0.31 mmol, 1 equiv), water (1 mL), EtOH (1 mL), formalin (37 w.% in water, 46 μL , 2 equiv), and diethylamine (95 μL , 3 equiv). The mixture was heated to 65°C for 20 h, then the solvent was removed in vacuo, and purified by flash column chromatography (80:20:1 DCM/acetone/TEA) to give **4-21** (82 mg, 0.2 mmol, 65%). The free base was dissolved in methanol, HCl (1 M in EtOAc, 1.1 equiv) was added at 0°C , the mixture was stirred at r.t. for 30 min and concentrated in vacuo to give **4-21**•HCl as an off-white powder (79 mg, 0.17 mmol, 88%).

^1H NMR (400 MHz, cd_3od) δ 8.07 – 8.03 (m, 2H), 7.93 (d, $J = 8.3$ Hz, 1H), 7.75 – 7.68 (m, 1H), 7.66 – 7.59 (m, 2H), 7.42 (d, $J = 8.3$ Hz, 1H), 4.44 (s, 2H), 4.08 (s, 3H), 3.29 – 3.19 (m, 4H), 1.40 (t, $J = 7.3$ Hz, 6H).

^{13}C NMR (101 MHz, cd_3od) δ 168.3, 165.9, 154.5, 152.0, 139.0, 134.6, 132.9, 131.0, 130.4, 128.6, 124.1, 117.3, 113.2, 108.4, 52.7, 52.5, 48.5, 9.2.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 413.1530, found 413.1532.

2-Benzamido-6-((diethylamino)methyl)-7-hydroxy-*N*-methylbenzo[*b*]thiophene-3-carboxamide (4-22)



To a 1-dram vial were added **4-11** (243 mg, 0.50 mmol, 1 equiv) and THF (1 mL). The mixture was cooled in ice/water bath, and TBAF (1 M in THF, 1.5 equiv) was added dropwise. The resulting mixture was capped with a septum and stirred at 0 °C for 2 h until full conversion indicated by TLC. Solvent was removed in vacuo, and the resulting crude residue was washed with water, dried in air, then triturated with hexanes, dried to give **4-8** as a yellow powder, which was used for next step without further purification.

To a 2-dram vial were added **4-8**, water (1 mL), EtOH (1 mL), formalin (37 w.% in water, 67 μL , 1.6 equiv), and diethylamine (123 μL , 2.1 equiv). The vial was capped and heated to 80 °C for 16 h, then the solvent was removed in vacuo, and purified by flash

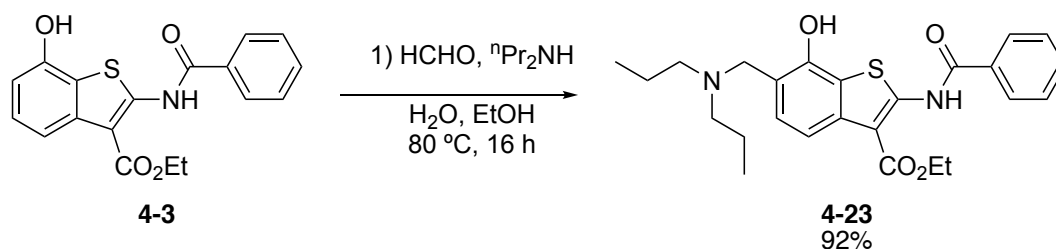
column chromatography (80:20:1 DCM/acetone/TEA) to give **4-22** as a yellow powder (80.1 mg, 39% over two steps)

^1H NMR (500 MHz, CDCl_3) δ 13.22 (s, 1H), 8.13 – 8.06 (m, 2H), 7.61 – 7.57 (m, 1H), 7.56 – 7.51 (m, 2H), 7.19 (d, $J = 8.1$ Hz, 1H), 7.04 (d, $J = 8.1$ Hz, 1H), 6.37 (br, 1H), 3.93 – 3.88 (m, 2H), 3.12 (d, $J = 4.8$ Hz, 3H), 2.68 (q, $J = 7.2$ Hz, 4H), 1.15 (t, $J = 7.2$ Hz, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 167.7, 164.4, 154.2, 150.1, 134.1, 132.7, 132.6, 129.1, 127.9, 126.5, 122.6, 115.2, 110.2, 109.7, 56.9, 46.6, 26.7, 11.3.

HRMS calculated for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$ [$\text{M}+\text{H}^+$] 412.1689, found 412.1680.

Ethyl 2-benzamido-6-((dipropylamino)methyl)-7-hydroxybenzo[*b*]thiophene-3-carboxylate hydrochloride (4-23•HCl)



To a 1-dram vial were added **4-3** (100 mg, 0.29 mmol, 1 equiv), water (1 mL), EtOH (1 mL), formalin (37 w.% in water, 35 μL , 1.6 equiv), and dipropylamine (86 μL , 2.1 equiv). The mixture was heated to 80 $^\circ\text{C}$ for 48 h, then the solvent was removed in vacuo, and purified by flash column chromatography (80:20:1 DCM/acetone/TEA) to give **4-23** (122.4 mg, 0.27 mmol, 92%) as a beige powder. The free base was dissolved in

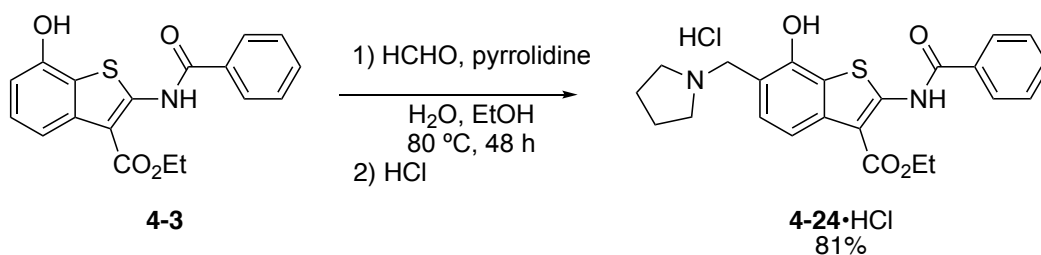
methanol, HCl (1 M in EtOAc, 1.1 equiv) was added at 0 °C, the mixture was stirred at r.t. for 30 min and concentrated in vacuo to give **4-23**•HCl.

¹H NMR (500 MHz, CD₃OD) δ 8.11 – 8.05 (m, 2H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.65 (t, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 4.57 (q, *J* = 7.1 Hz, 2H), 4.49 (s, 2H), 3.21 – 3.08 (m, 4H), 1.95 – 1.78 (m, 4H), 1.54 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 6H).

¹³C NMR (126 MHz, CD₃OD) δ 167.9, 165.9, 154.5, 152.0, 139.2, 134.6, 133.0, 131.1, 130.4, 128.6, 124.1, 117.3, 113.1, 108.5, 62.7, 55.8, 53.4, 18.3, 14.7, 11.3.

HRMS (ESI⁺) calculated for C₂₅H₃₀N₂O₄S [M+H]⁺: 455.1999, found 455.2008.

Ethyl 2-benzamido-7-hydroxy-6-(pyrrolidin-1-ylmethyl)benzo[*b*]thiophene-3-carboxylate hydrochloride (4-24)



To a 1-dram vial were added **4-3** (100 mg, 0.29 mmol, 1 equiv), water (1 mL), EtOH (1 mL), formalin (37 w.% in water, 35 μL, 1.6 equiv), and pyrrolidine (52 μL, 2.1 equiv). The mixture was heated to 80 °C for 48 h, then the solvent was removed in vacuo, and purified by flash column chromatography (80:20:1 DCM/acetone/TEA) to give **4-24** (100.3 mg, 0.24 mmol, 81%). The free base was dissolved in methanol, HCl (1 M in

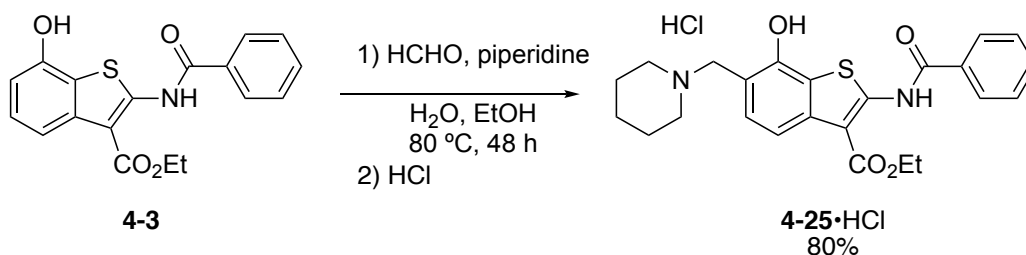
EtOAc, 1.1 equiv) was added at 0 °C, the mixture was stirred at r.t. for 30 min and concentrated in vacuo to give **4-24**•HCl as a brown powder.

¹H NMR (500 MHz, CD₃OD) δ 8.10 – 8.05 (m, 2H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.68 – 7.60 (m, 2H), 7.45 (d, *J* = 8.3 Hz, 1H), 4.57 (q, *J* = 7.1 Hz, 2H), 4.51 (s, 2H), 3.57 – 3.48 (m, 2H), 3.33 – 3.25 (m, 2H), 2.26 – 2.13 (m, 2H), 2.09 – 1.98 (m, 2H), 1.53 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CD₃OD) δ 167.9, 166.0, 154.5, 151.8, 139.1, 134.6, 133.0, 130.7, 130.4, 128.6, 124.2, 117.3, 114.1, 108.5, 62.7, 54.9, 54.5, 23.8, 14.7.

HRMS (ESI+) calculated for C₂₃H₂₄N₂O₄S [M+H]⁺: 425.1530, found 425.1536.

Ethyl 2-benzamido-7-hydroxy-6-(piperidin-1-ylmethyl)benzo[*b*]thiophene-3-carboxylate hydrochloride (**4-25**•HCl)



To a 1-dram vial were added **4-3** (100 mg, 0.29 mmol, 1 equiv), water (1 mL), EtOH (1 mL), formalin (37 w.% in water, 35 μL, 1.6 equiv), and piperidine (62 μL, 2.1 equiv). The mixture was heated to 80 °C for 48 h, then the solvent was removed in vacuo, and purified by flash column chromatography (80:20:1 DCM/acetone/TEA) to give **4-25** (102.6 mg, 0.23 mmol, 80%). The free base was dissolved in methanol, HCl (1 M in

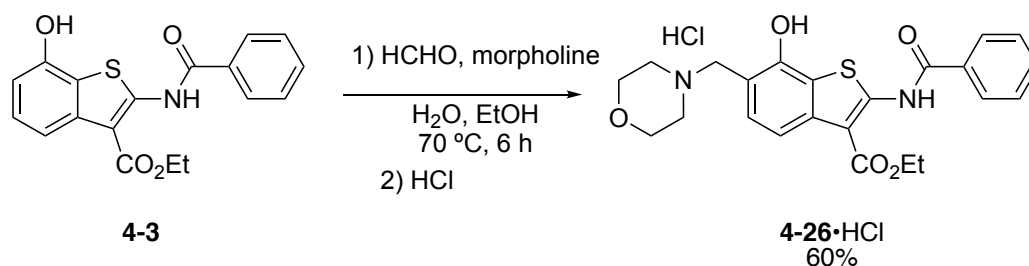
EtOAc, 1.1 equiv) was added at 0 °C, the mixture was stirred at r.t. for 30 min and concentrated in vacuo to give **4-25**•HCl as a brown powder.

¹H NMR (500 MHz, CD₃OD) δ 8.09 – 8.04 (m, 2H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.75 – 7.69 (m, 1H), 7.67 – 7.60 (m, 2H), 7.44 (d, *J* = 8.3 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 4.43 (s, 2H), 3.55 – 3.48 (m, 2H), 3.09 – 3.01 (m, 2H), 2.00 – 1.91 (m, 2H), 1.87 – 1.70 (m, 3H), 1.59 – 1.51 (m, 1H), 1.52 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CD₃OD) δ 167.9, 165.9, 154.6, 152.2, 139.2, 134.6, 133.0, 131.4, 130.4, 128.6, 124.3, 117.2, 112.5, 108.5, 62.7, 56.6, 54.0, 24.0, 22.7, 14.7.

HRMS (ESI+) calculated for C₂₄H₂₆N₂O₄S [M+H]⁺: 439.1686, found 439.1693.

Ethyl 2-benzamido-7-hydroxy-6-(morpholinomethyl)benzo[*b*]thiophene-3-carboxylate hydrochloride (**4-26**•HCl)



To a 2-dram vial were added **4-3** (108 mg, 0.32 mmol, 1 equiv), water (1 mL), EtOH (1 mL), formalin (37 w.% in water, 37 μL, 1.6 equiv), and morpholine (58 mg, 2.1 equiv). The mixture was heated to 70 °C for 6 h, then the solvent was removed in vacuo, and purified by flash column chromatography (80:20:1 DCM/acetone/TEA) to give **4-26**. The free base was dissolved in methanol, HCl (1 M in EtOAc, 1.1 equiv) was added at 0 °C,

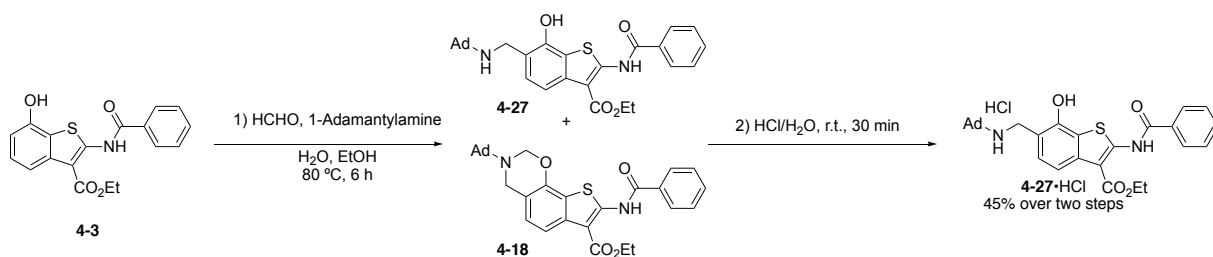
the mixture was stirred at r.t. for 30 min and concentrated in vacuo to give **4-26•HCl** as a brown powder (89.4 mg, 0.19 mmol, 60%).

^1H NMR (500 MHz, Methanol- d_4) δ 7.97 – 7.93 (m, 2H), 7.86 (d, $J = 8.3$ Hz, 1H), 7.63 – 7.59 (m, 1H), 7.55 – 7.50 (m, 2H), 7.34 (d, $J = 8.3$ Hz, 1H), 4.44 (q, $J = 7.1$ Hz, 2H), 4.40 (s, 2H), 3.95 (br, 2H), 3.68 (br, 2H), 3.34 (br, 2H), 3.21 (br, 2H), 1.41 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 167.9, 165.9, 154.6, 152.3, 139.3, 134.6, 133.0, 131.5, 130.4, 128.6, 124.2, 117.2, 111.8, 108.5, 64.9, 62.7, 56.9, 52.8, 14.7.

HRMS (ESI+) calculated for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 441.1479 found 441.1480.

Ethyl 6-(((adamantan-1-yl)amino)methyl)-2-benzamido-7-hydroxybenzo[*b*]thiophene-3-carboxylate hydrochloride (4-27•HCl**)**



To a 2-dram vial were added **4-3** (108 mg, 0.32 mmol, 1 equiv), water (1 mL), EtOH (1 mL), formalin (37 w.% in water, 37 μL , 1.6 equiv), and 1-adamantylamine (93 mg, 2.1 equiv). The mixture was heated to 80 $^\circ\text{C}$ for 6 h, then the solvent was removed in vacuo, and purified by flash column chromatography (80:20:1 DCM/acetone/TEA), which contains a mixture of **4-18** and **4-27** according to ^1H NMR. The separated spot was

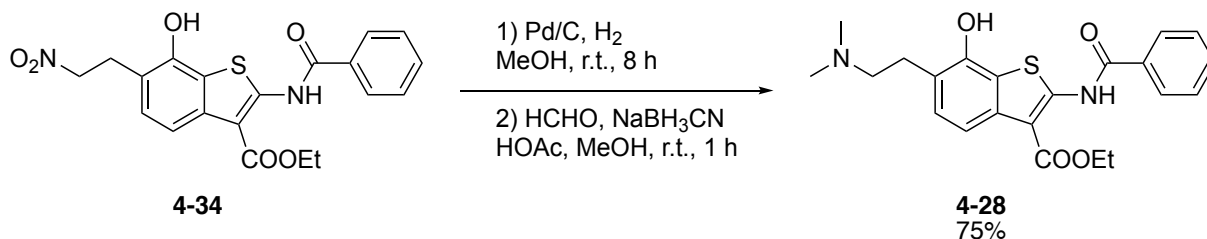
concentrated in vacuo and stirred in HCl (1 M in H₂O) at r.t. for 30 min, concentrated in vacuo gives **4-27**•HCl as a light yellow powder (67.2 mg, 0.13 mmol, 45%).

¹H NMR (400 MHz, cd₃od) δ 8.08 – 8.04 (m, 2H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.74 – 7.69 (m, 1H), 7.66 – 7.60 (m, 2H), 7.41 (d, *J* = 8.3 Hz, 1H), 4.55 (q, *J* = 7.1 Hz, 2H), 4.27 (s, 2H), 2.26 (br, 3H), 2.06 (d, *J* = 2.9 Hz, 6H), 1.90 – 1.71 (m, 6H), 1.52 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, cd₃od) δ 167.9, 165.9, 154.2, 151.5, 138.7, 134.5, 133.0, 130.4, 130.3, 128.6, 124.0, 117.2, 115.2, 108.5, 62.6, 59.0, 41.5, 39.4, 36.6, 30.6, 14.7.

HRMS (ESI+) calculated for C₂₉H₃₂N₂O₄S [M+H]⁺: 505.2156 found: 505.2153.

Ethyl 2-benzamido-6-(2-(dimethylamino)ethyl)-7-hydroxybenzo[*b*]thiophene-3-carboxylate (4-28)



To a 1-dram vial were added **4-34** (12.9 mg, 0.03 mmol, 1 equiv), Pd/C (10 w.%, 3.3 mg, 0.1 equiv), and MeOH (1 mL). The vial was evacuated with a water respirator until bubble start to form and back filled with H₂. The mixture was stirred under H₂ atmosphere for 8 h, then the Pd/C was removed by filtration and the solvent was removed in vacuo to give a yellow powder.

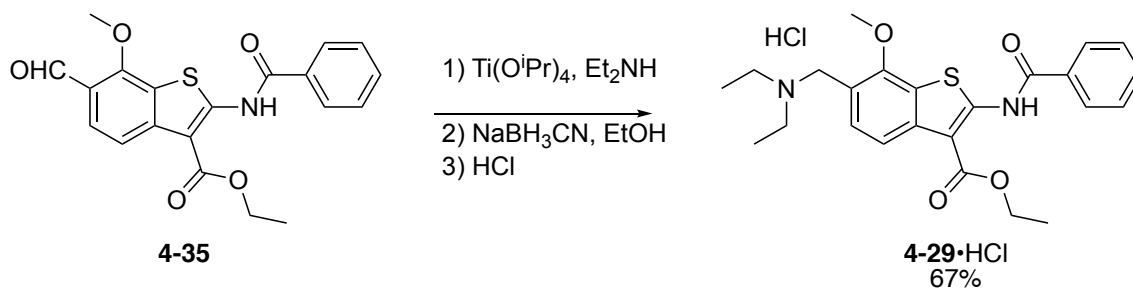
To the yellow powder was added 2 mL MeCN, formalin (37 w.% in water, 20 μL, 0.27 mmol, 8.6 equiv), and NaBH₃CN (8 mg, 0.18 mmol, 4 equiv). The resulting mixture was

stirred at r.t. for 15 min, and then acetic acid (1 equiv) was added and the mixture was stirred for an additional 1 h at r.t., then 1 equiv ammonia was added, and the mixture was extracted with DCM, concentrated in vacuo and purified with flash column chromatography (50:50:2 DCM/EtOAc/TEA) to give **4-28** as a yellow solid (9.6 mg, 0.02mmol, 75%).

^1H NMR (500 MHz, CDCl_3) δ 12.74 (s, 1H), 8.12 – 8.06 (m, 2H), 7.65 (d, $J = 8.2$ Hz, 1H), 7.64 – 7.57 (m, 1H), 7.58 – 7.51 (m, 2H), 7.06 (d, $J = 8.2$ Hz, 2H), 4.51 (q, $J = 7.1$ Hz, 2H), 2.98 – 2.92 (m, 2H), 2.78 – 2.72 (m, 2H), 2.48 (s, 6H), 1.52 (t, $J = 7.1$ Hz, 3H).
 ^{13}C NMR (126 MHz, CDCl_3) δ 167.5, 164.3, 153.6, 152.4, 134.6, 132.8, 132.5, 129.5, 129.1, 127.8, 123.9, 120.6, 113.4, 107.2, 61.1, 60.3, 44.7, 31.5, 14.6.

HRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 413.1530, found 413.1525.

Ethyl 2-benzamido-6-((diethylamino)methyl)-7-methoxybenzofuran-3-carboxylate hydrochloride (**4-29**•HCl)



To a 10 mL RBF was added **4-35** (110 mg, 0.3 mmol, 1 equiv), capped with a septum and purged with N_2 for 10 min. Titanium isopropoxide (3 mL) was added followed by diethylamine (0.15 mL, 1.45 mmol, 4.8 equiv). The mixture was stirred at r.t. for 2 h.

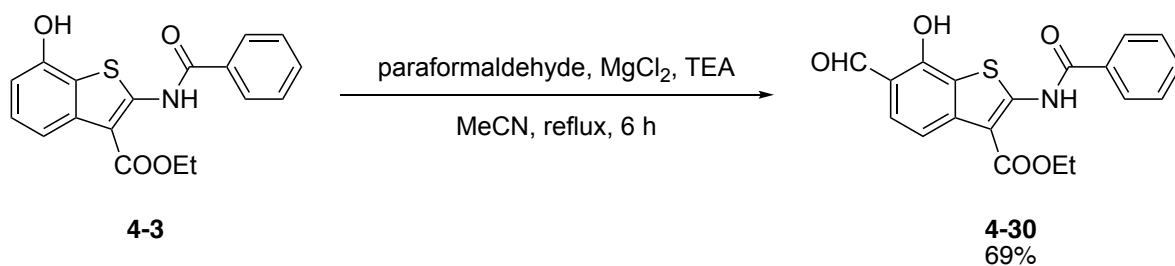
Then NaBH₃CN (80 mg, 2.11 mmol, 7 equiv, dissolved in 3 mL EtOH) was added dropwise, and the reaction was stirred for 16 h at r.t. Then the mixture was diluted with DCM, washed with sodium sulfate, brine, and dried over sodium sulfate. The solvent was removed in vacuo, and the crude was purified with gradient flash column chromatography (100% DCM to 100:5:1 DCM/MeOH/TEA) to give **4-29**. The free base was dissolved in methanol, and HCl (1 M in EtOAc, 1.1 equiv) was added at 0 °C, the mixture was stirred at r.t. for 30 min and concentrated in vacuo to give **4-29**•HCl as a yellow powder (92 mg, 0.2 mmol, 67%).

¹H NMR (500 MHz, CDCl₃) δ 12.83 (s, 1H), 11.96 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.10 – 8.05 (m, 2H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.60 – 7.54 (m, 2H), 4.53 (q, *J* = 7.2 Hz, 2H), 4.36 (d, *J* = 5.2 Hz, 2H), 4.06 (s, 3H), 3.25 – 3.12 (m, 2H), 3.08 – 2.95 (m, 2H), 1.53 (t, *J* = 7.2 Hz, 3H), 1.45 (t, *J* = 7.2 Hz, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 166.8, 164.6, 154.0, 153.6, 138.1, 133.4, 131.5, 130.4, 129.2, 127.7, 126.0, 120.3, 115.7, 107.2, 61.7, 61.6, 49.2, 46.0, 14.4, 8.9.

HRMS (ESI+) calculated for C₂₄H₂₈N₂O₄S [M+H]⁺: 441.1843, found 441.1840.

Ethyl 2-benzamido-6-formyl-7-hydroxybenzo[*b*]thiophene-3-carboxylate (**4-30**)



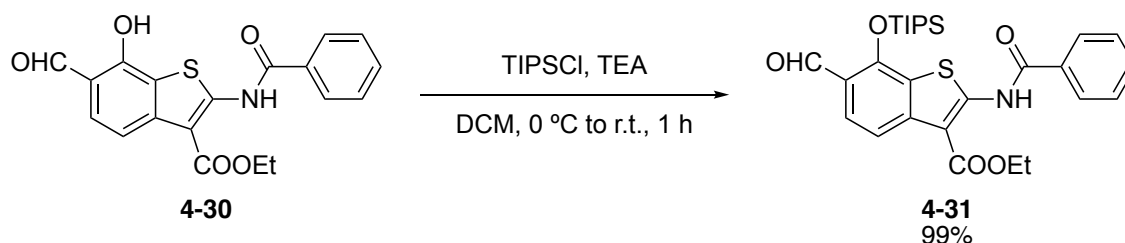
Prepared according to a modified procedure from Doshi, 2006.¹⁹ To a 2-dram vial were added **4-3** (205 mg, 0.6 mmol, 1 equiv), MgCl₂ (86 mg, 0.9 mmol, 1.5 equiv) paraformaldehyde (123 mg, 4.0 mmol, 6.8 equiv), and MeCN (4.5 mL), and TEA (0.3 mL, 2.28 mmol, 3.8 equiv). The mixture was heated to 81 °C for 6 h. DCM (50 mL) and HCl (1 M in H₂O, 50 mL) was added, the organic layer was separated, washed with brine, and dried over Na₂SO₄, purified with flash column chromatography (100% DCM) to give **4-30** as a white powder (155.5 mg, 0.41 mmol, 69%).

¹H NMR (500 MHz, CDCl₃) δ 12.82 (s, 1H), 11.82 (s, 1H), 9.86 (s, 1H), 8.05 (d, *J* = 7.5 Hz, 2H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 1.54 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 195.6, 166.9, 164.5, 157.7, 157.4, 141.8, 133.4, 131.6, 130.0, 129.3, 127.9, 120.9, 115.3, 115.1, 107.3, 61.7, 14.5.

HRMS (ESI+) calculated for C₁₉H₁₅NO₅S [M+H]⁺: 370.0744, found 370.0737.

Ethyl 2-benzamido-6-formyl-7-((triisopropylsilyl)oxy)benzo[*b*]thiophene-3-carboxylate (4-31)



To a 2-dram vial were added **4-30** (83.9 mg, 0.23 mmol, 1 equiv), DCM (3 mL), TIPSCl (53 μL, 0.25 mmol, 1.1 equiv). The mixture was cooled in ice/water bath, and TEA (38

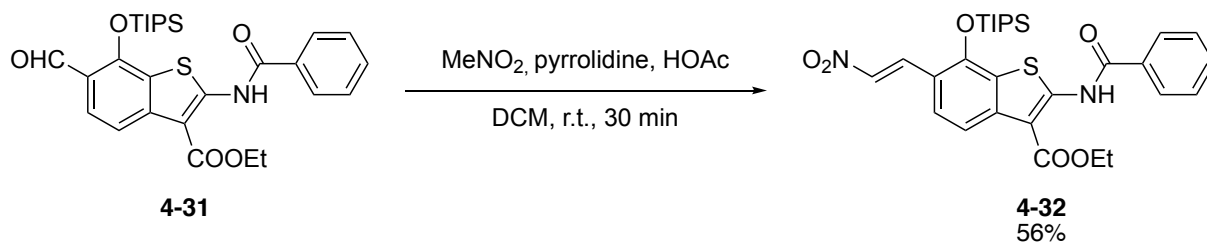
μL , 0.27 mmol, 1.2 equiv) was added. The mixture was stirred at r.t. for 1 h, the solvent was removed in vacuo and the crude was purified by gradient flash column chromatography (70-30% hexanes in DCM) to give **4-31** as a white powder (119 mg, 0.23 mmol, 99%).

^1H NMR (500 MHz, CDCl_3) δ 12.89 (s, 1H), 10.43 (d, $J = 0.8$ Hz, 1H), 8.11 – 8.07 (m, 2H), 8.00 (d, $J = 8.5$ Hz, 1H), 7.86 (d, $J = 8.5$ Hz, 1H), 7.69 – 7.62 (m, 1H), 7.61 – 7.55 (m, 2H), 4.55 (q, $J = 7.1$ Hz, 2H), 1.55 (t, $J = 7.1$ Hz, 3H), 1.49 (hept, $J = 7.5$ Hz, 3H), 1.17 (d, $J = 7.5$ Hz, 16H).

^{13}C NMR (126 MHz, CDCl_3) δ 188.9, 167.0, 164.8, 155.9, 155.5, 141.3, 133.4, 131.8, 129.3, 127.9, 126.5, 125.7, 122.5, 117.2, 107.8, 61.7, 18.1, 17.8, 14.6.

HRMS (ESI+) calculated for $\text{C}_{28}\text{H}_{35}\text{NO}_5\text{SSi}$ $[\text{M}+\text{H}]^+$: 526.2078, found 526.2063.

Ethyl (*E*)-2-benzamido-6-(2-nitrovinyl)-7-((triisopropylsilyl)oxy)benzo[*b*]thiophene-3-carboxylate (**4-32**)



Prepared according to a modified procedure from Pérez-Caaveiro, 2014.⁴⁴ To a 2-dram vial were added **4-31** (119.3 mg, 0.23 mmol, 1 equiv), DCM (1 mL), nitromethane (97 mg, 1.59 mmol, 7 equiv), pyrrolidine (3.2 mg, 0.05 mmol, 0.2 equiv), and acetic acid (3 mg, 0.05 mmol, 0.22 equiv). The mixture was stirred at r.t. for 30 min. Then the solvent

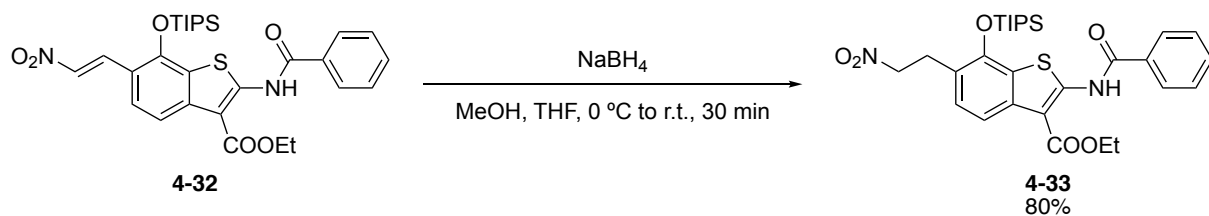
was removed in vacuo, the crude was purified with flash column chromatography (2:1 DCM/hexanes) to give **4-32** as a light yellow powder (72.1 mg, 0.13 mmol, 56%).

^1H NMR (500 MHz, CDCl_3) δ 12.83 (s, 1H), 8.50 (d, $J = 13.6$ Hz, 1H), 8.13 – 8.06 (m, 2H), 7.96 (d, $J = 8.6$ Hz, 1H), 7.67 – 7.63 (m, 1H), 7.62 – 7.56 (m, 3H), 7.52 (d, $J = 8.6$ Hz, 1H), 4.55 (q, $J = 7.2$ Hz, 2H), 1.57 – 1.46 (m, 6H), 1.18 (d, $J = 7.6$ Hz, 18H).

^{13}C NMR (126 MHz, CDCl_3) δ 166.9, 164.8, 155.2, 152.4, 139.6, 135.5, 134.8, 133.4, 131.8, 129.3, 127.9, 127.0, 124.7, 117.7, 116.0, 107.8, 61.7, 18.1, 17.9, 14.6.

HRMS (ESI $^+$) calculated for $\text{C}_{29}\text{H}_{36}\text{N}_2\text{O}_6\text{SSi}$ $[\text{M}+\text{H}]^+$: 569.2136, found 569.2124.

Ethyl 2-benzamido-6-(2-nitroethyl)-7-((triisopropylsilyl)oxy)benzo[b]thiophene-3-carboxylate (**4-33**)



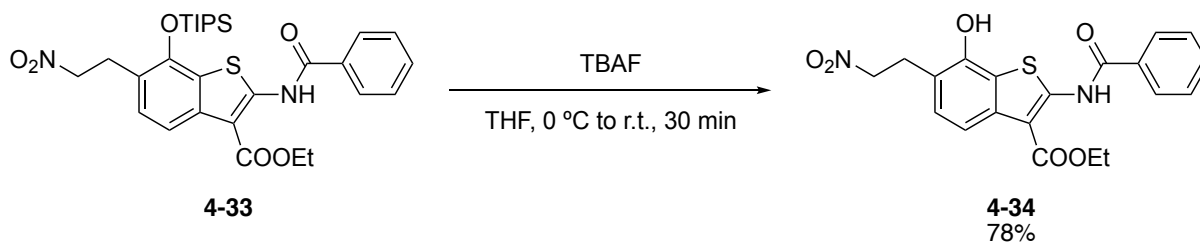
To a 10 mL RBF were added **4-32** (63.1 mg, 0.11 mmol, 1 equiv), THF (3 mL) and MeOH (3 mL), and NaBH_4 (8.4 mg, 0.22 mmol, 2 equiv). The mixture was stirred at r.t. for 30 min and separated between DCM (5 mL) and H_2O (5 mL). The organic layer was separated, washed with brine, and dried over Na_2SO_4 . The crude was purified with flash column chromatography (2:1 DCM/hexanes) to give **4-33** as a light yellow powder (50.5 mg, 0.09 mmol, 80%).

^1H NMR (400 MHz, CDCl_3) δ 12.75 (s, 1H), 8.11 – 8.05 (m, 2H), 7.90 (d, $J = 8.3$ Hz, 1H), 7.65 – 7.59 (m, 1H), 7.59 – 7.52 (m, 2H), 7.18 (d, $J = 8.3$ Hz, 1H), 4.63 – 4.57 (m, 2H), 4.52 (q, $J = 7.1$ Hz, 2H), 3.50 – 3.42 (m, 2H), 1.56 – 1.43 (m, 6H), 1.16 (d, $J = 7.5$ Hz, 18H).

^{13}C NMR (101 MHz, CDCl_3) δ 167.0, 164.5, 152.9, 149.0, 135.5, 133.0, 132.0, 129.0, 128.2, 127.7, 126.5, 120.1, 117.2, 107.1, 75.0, 61.2, 28.8, 18.1, 17.7, 14.4.

HRMS (ESI+) calculated for $\text{C}_{29}\text{H}_{38}\text{N}_2\text{O}_6\text{SSi}$ $[\text{M}+\text{H}]^+$: 571.2293, found 571.2272.

Ethyl 2-benzamido-7-hydroxy-6-(2-nitroethyl)benzo[*b*]thiophene-3-carboxylate (4-34)



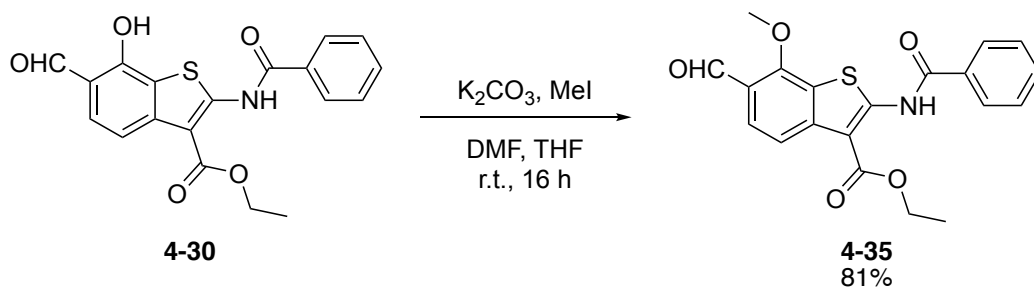
To a 1-dram vial were added **4-33** (32.7 mg, 0.06 mmol, 1 equiv). The vial was cooled in ice/water bath and TBAF (1 M in THF, 1 mL, 1 mmol, 17.5 equiv) was added. The mixture was stirred at r.t. for 30 min, separated between DCM (3 mL) and NH_4Cl (sat., 3 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude was purified with gradient flash column chromatography (0-10% EtOAc in DCM) to give **4-34** as a sticky yellow solid (18.4 mg, 0.04 mmol, 78%).

^1H NMR (400 MHz, CDCl_3) δ 12.79 (s, 1H), 8.09 (d, $J = 7.5$ Hz, 2H), 7.89 (d, $J = 8.3$ Hz, 1H), 7.69 – 7.61 (m, 1H), 7.58 (t, $J = 7.5$ Hz, 2H), 7.21 (d, $J = 8.3$ Hz, 1H), 5.92 (s, 1H), 4.71 (d, $J = 6.9$ Hz, 2H), 4.54 (d, $J = 7.3$ Hz, 2H), 3.45 (d, $J = 6.9$ Hz, 2H), 1.53 (d, $J = 7.3$ Hz, 3H).

^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 165.9, 163.8, 151.5, 149.1, 134.4, 133.3, 131.6, 129.4, 128.9, 127.4, 122.7, 117.9, 115.1, 106.8, 75.0, 61.2, 27.4, 14.2.

HRMS (ESI+) calculated for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$: 415.0958, found 415.0947.

Ethyl 2-benzamido-6-formyl-7-methoxybenzo[*b*]thiophene-3-carboxylate (**4-35**)



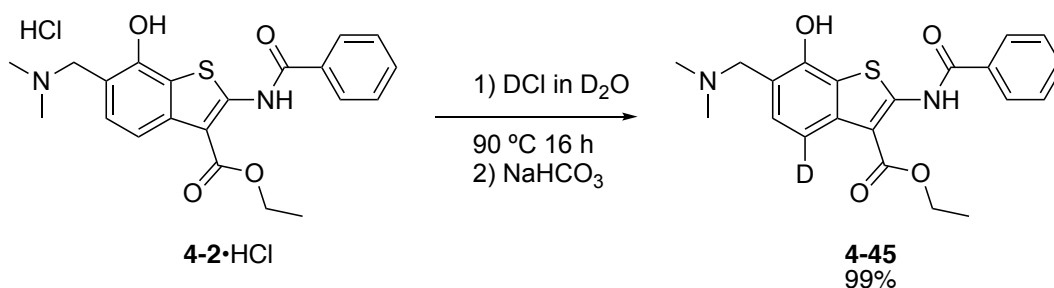
To a 1-dram vial were added **4-30** (237 mg, 0.64 mmol, 1 equiv), THF (1 mL), potassium carbonate (133 mg, 0.96 mmol, 1.5 equiv), MeI (40 μL , 0.64 mmol, 1 equiv), and DMF (1 mL). The mixture was stirred at r.t. for 16 h, separated between DCM (5 mL) and water (5 mL). The organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The crude was purified with gradient flash column chromatography (10-0% hexanes in DCM) to give **4-35** as an off-white powder (199.3 mg, 0.52 mmol, 81%).

^1H NMR (400 MHz, CDCl_3) δ 12.89 (s, 1H), 10.44 (d, $J = 0.8$ Hz, 1H), 8.14 – 8.07 (m, 3H), 7.88 (d, $J = 8.6$ Hz, 1H), 7.69 – 7.63 (m, 1H), 7.62 – 7.56 (m, 2H), 4.56 (q, $J = 7.1$ Hz, 2H), 4.19 (s, 3H), 1.55 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 188.6, 166.8, 164.7, 158.7, 156.2, 141.6, 133.5, 131.6, 129.3, 127.9, 126.8, 126.2, 123.7, 119.4, 107.6, 63.7, 61.8, 14.5.

HRMS (ESI+) calculated for $\text{C}_{20}\text{H}_{17}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 384.0900, found 384.0898.

Ethyl 2-benzamido-6-((dimethylamino)methyl)-7-hydroxybenzo[*b*]thiophene-3-carboxylate-4-*d* (4-45)

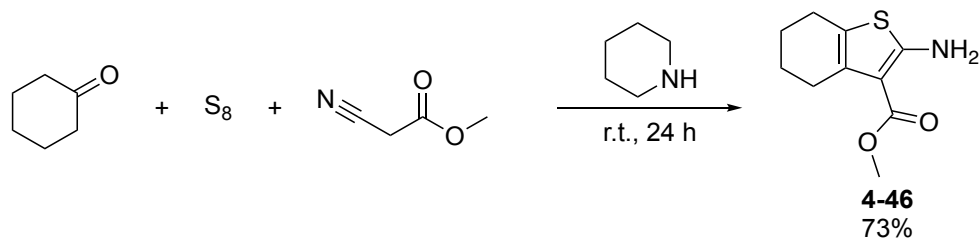


To an NMR tube was added **4-2**·HCl (5 mg), DCl (0.1 M in D_2O , 0.7 mL). The sample was heated to 90 °C for 16 h, after which ^1H NMR confirmed quantitative conversion of **4-2** to **4-45**. The sample was basified with NaHCO_3 , and extracted with DCM. The organic layer was washed with brine, concentrated in vacuo to give **4-45** as an off-white powder (5 mg, 99%).

^1H NMR (400 MHz, CDCl_3) δ 12.78 (s, 1H), 8.14 – 8.06 (m, 2H), 7.66 – 7.57 (m, 1H), 7.60 – 7.51 (m, 2H), 7.03 (q, $J = 1.1$ Hz, 1H), 4.52 (q, $J = 7.1$ Hz, 2H), 3.79 (d, $J = 0.8$ Hz, 2H), 2.38 (s, 6H), 1.53 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 167.5, 164.4, 153.7, 152.8, 135.0, 133.0, 132.4, 129.2, 127.9, 126.4, 121.7, 115.3, 107.1, 62.8, 61.2, 44.7, 14.6. (C4 D-coupled triplet not found)
HRMS (ESI+) calculated for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 400.1436, found 400.1428.

Methyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (4-46)



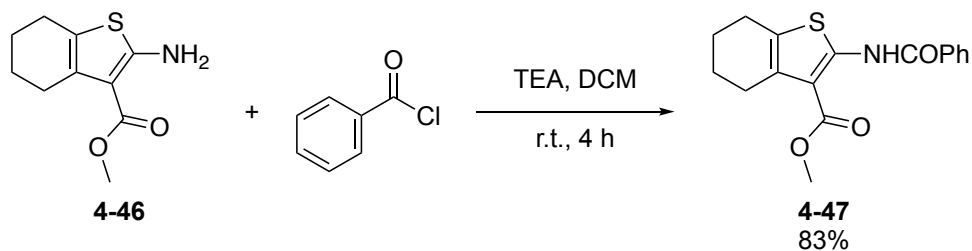
Prepared according to the modified procedure from Fondjo⁷ that was used for compound 4-4. To a 25 mL RBF were added 970 mg S_8 (3.78 mmol, 0.125 equiv), 3 g methyl cyanoacetate (30 mmol, 1 equiv), 8.91 g cyclohexanone (90.8 mmol, 3 equiv); the mixture was cooled in ice/water bath and 1.29 g piperidine (15.1 mmol, 0.5 equiv) was slowly added dropwise over 2 min period. The mixture was stirred at r.t. for 24 h; the precipitation was filtered and recrystallized from 1:1 ethanol/water (v:v, 250 mL) to give 4-46 as a yellow crystal (4.6455 g, 73%).

^1H NMR (400 MHz, Chloroform-*d*) δ 5.95 (br, 2H), 3.77 (s, 3H), 2.70 – 2.64 (m, 2H), 2.52 – 2.45 (m, 2H), 1.81 – 1.68 (m, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 166.6, 162.0, 132.5, 117.7, 105.7, 50.7, 27.0, 24.6, 23.4, 22.9.

HRMS calculated for $\text{C}_{10}\text{H}_{13}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 212.0740, found 212.0737.

Methyl 2-benzamido-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4-47)



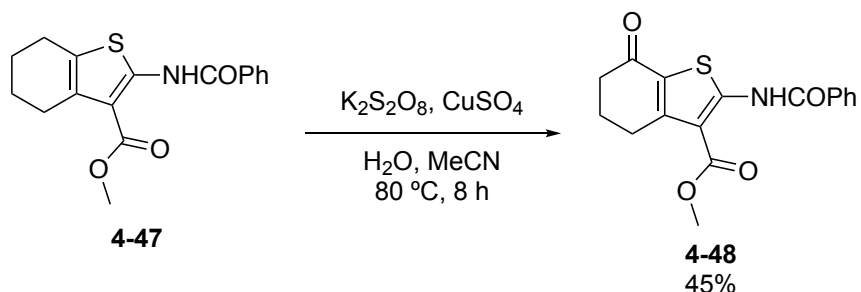
To a 250 mL RBF were added **4-46** (4.65 g, 22 mmol, 1 equiv), DCM (50 mL), benzoyl chloride (3.4 g, 24.2 mmol, 1.1 equiv). The mixture was cooled in ice/water bath and triethylamine (2.67 g, 26.4 mmol, 1.2 equiv) was added dropwise. The mixture was stirred at r.t. for 4 h until TLC shows full conversion. N,N-Dimethylethylenediamine (0.3 mL, 2.7 mmol) was added and the mixture was stirred at r.t. for an additional 20 min. The mixture was then washed with sat. ammonium chloride, water, and then brine; the organic layer was separated, dried over sodium sulfate, and concentrated in vacuo, and recrystallized from EtOH to give **4-47** as a yellow powder (5.75 g, 83%).

^1H NMR (400 MHz, CDCl_3) δ 12.29 (s, 1H), 8.04 – 7.99 (m, 2H), 7.60 – 7.55 (m, 1H), 7.54 – 7.49 (m, 2H), 3.90 (s, 3H), 2.81 – 2.75 (m, 2H), 2.71 – 2.65 (m, 2H), 1.86 – 1.74 (m, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 167.6, 163.5, 148.4, 132.6, 132.6, 131.1, 129.0, 127.6, 127.2, 111.9, 51.7, 26.5, 24.5, 23.1, 22.9.

HRMS calculated for $\text{C}_{17}\text{H}_{17}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 316.1002, found 316.1006.

Methyl 2-benzamido-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4-48)



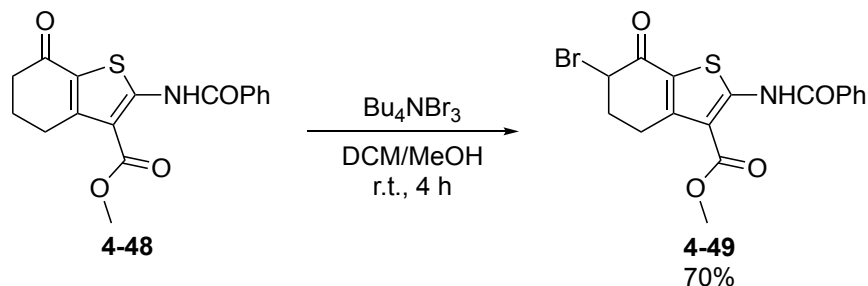
Prepared according to the modified procedure from Lilienkampf⁸ used for compound 4-6. To a 250 mL RBF were added **4-47** (3.47 g, 10.92 mmol, 1 equiv), CuSO₄ (5.23 g, 32.76 mmol, 3 equiv), K₂S₂O₈ (8.86 g, 32.76 mmol, 3 equiv), water (50 mL), and MeCN (50 mL). The mixture was refluxed at 90 °C for 8 h until TLC shows full conversion. The mixture was diluted with water (50 mL) and EtOAc (50 mL), the aq. layer was separated and washed with DCM (50 mL *3), and all organic layer was concentrated in vacuo, purified with gradient flash column chromatography (3-5% EtOAc in DCM) to give **4-48** as a light brown powder (1.62 g, 4.92 mmol, 45%).

¹H NMR (400 MHz, CDCl₃) δ 12.51 (s, 1H), 8.01 – 7.96 (m, 2H), 7.63 – 7.57 (m, 1H), 7.55 – 7.49 (m, 2H), 3.93 (s, 3H), 3.04 (t, *J* = 6.1 Hz, 2H), 2.57 – 2.53 (m, 1H), 2.14 (p, *J* = 6.3 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 192.6, 167.0, 164.1, 156.7, 150.2, 133.2, 131.6, 130.2, 129.2, 128.5, 127.7, 52.2, 37.7, 26.6, 23.9.

HMRS (ESI⁺) calculated for C₁₇H₁₅NO₄S [M+H]⁺: 330.0795, found 330.0800.

Methyl 2-benzamido-6-bromo-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4-49)



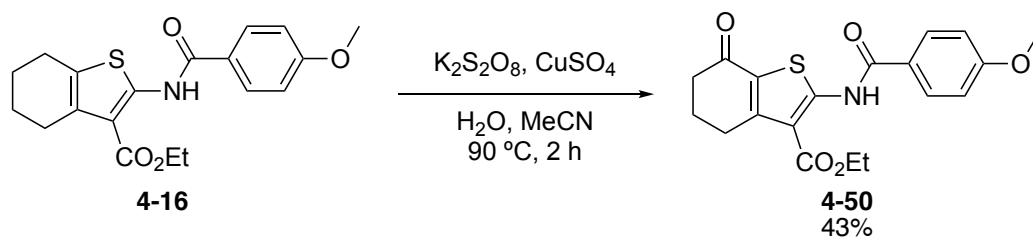
Prepared according to a modified procedure from Voet, 2006.⁹ To a 50 mL RBF were added **4-48** (1.56 g, 4.70 mmol, 1 equiv), tetrabutylammonium tribromide (2.49 g, 5.16 mmol, 1.1 equiv), DCM (28 mL) and MeOH (12 mL). The resulting mixture was stirred at r.t. for 4 h; washed with water (50 mL x 3), then brine (50 mL x 1); dried over Na_2SO_4 , concentrated in vacuo and purified by flash column chromatography (100:3 DCM/EtOAc) to give **4-49** as a yellow powder (1.34 g, 3.27 mmol, 70%).

^1H NMR (400 MHz, CDCl_3) δ 12.56 (s, 1H), 8.02 – 7.95 (m, 2H), 7.66 – 7.57 (m, 1H), 7.57 – 7.48 (m, 2H), 4.62 (t, $J = 4.1$ Hz, 1H), 3.97 (s, 3H), 3.26 (dt, $J = 18.5, 4.4$ Hz, 1H), 3.13 (ddd, $J = 18.5, 9.0, 5.1$ Hz, 1H), 2.58 – 2.43 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 185.1, 166.8, 164.2, 157.8, 149.6, 133.4, 131.4, 129.3, 127.7, 124.8, 112.3, 52.4, 49.1, 32.8, 24.0.

HRMS (ESI+) calculated for $\text{C}_{17}\text{H}_{14}\text{BrNO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 407.9900, found 407.9904.

Ethyl 2-(4-methoxybenzamido)-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4-50)



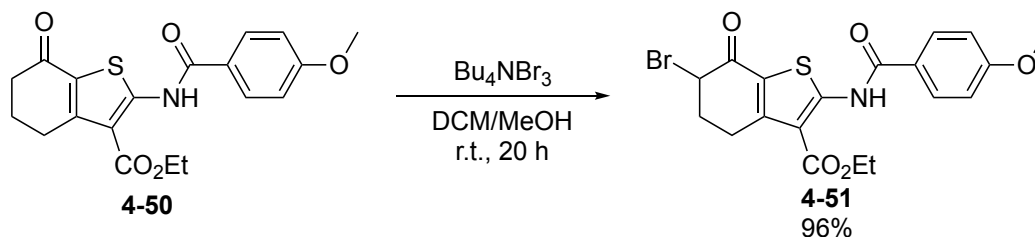
Prepared according a modified procedure from Lilienkampff, 2009.⁸ To a 250 mL RBF were added **4-16** (2.55 g, 7.08 mmol, 1 equiv), CuSO₄ (2.83 g, 17.71 mmol, 2.5 equiv), K₂S₂O₈ (4.79 g, 17.71 mmol, 2.5 equiv), water (20 mL), and MeCN (20 mL). The mixture was refluxed at 90 °C for 2 h until TLC shows full conversion. The mixture was diluted with water (20 mL) and EtOAc (40 mL), the aq. layer was separated and washed with DCM (40 mL *3), and all organic layer was concentrated in vacuo, purified with gradient flash column chromatography (3-5% EtOAc in DCM) to give **4-50** as a dark yellow powder (1.15 g, 3.07 mmol, 43%).

¹H NMR (400 MHz, CDCl₃) δ 12.49 (s, 1H), 8.00 – 7.95 (m, 2H), 7.03 – 6.98 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.09 (t, *J* = 6.1 Hz, 1H), 2.57 (dd, *J* = 7.6, 5.5 Hz, 2H), 2.21 – 2.13 (m, 2H), 1.44 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.6, 166.7, 163.7, 163.6, 157.1, 150.2, 129.8, 127.7, 124.1, 114.5, 112.2, 61.5, 55.7, 37.8, 26.7, 24.0, 14.5.

HRMS (ESI+) calculated for C₁₉H₁₉NO₅S [M+H]⁺: 374.1057, found 374.1054.

Ethyl 6-bromo-2-(4-methoxybenzamido)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (4-51)



Prepared according to a modified procedure from Voet, 2006.⁹ To a 50 mL RBF were added **4-50** (1.14 g, 3.04 mmol, 1 equiv), tetrabutylammonium tribromide (1.54 g, 3.19 mmol, 1.05 equiv), DCM (15 mL) and MeOH (6 mL). The resulting mixture was stirred at r.t. for 20 h; washed with water (25 mL x 3), then brine (25 mL x 1); dried over Na_2SO_4 , concentrated in vacuo and purified by flash column chromatography (100:3 DCM/EtOAc) to give **4-51** as a dark yellow powder (1.33 g, 2.94 mmol, 96%).

^1H NMR (400 MHz, CDCl_3) δ 12.56 (s, 1H), 8.01 – 7.96 (m, 2H), 7.05 – 7.00 (m, 2H), 4.64 (t, $J = 4.0$ Hz, 1H), 4.45 (q, $J = 7.1$ Hz, 2H), 3.30 (dt, $J = 18.4, 4.3$ Hz, 1H), 3.16 (ddd, $J = 18.4, 8.8, 5.5$ Hz, 1H), 2.60 – 2.45 (m, 2H), 1.47 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 185.2, 166.5, 163.8, 163.8, 158.3, 149.7, 129.9, 124.7, 123.8, 114.5, 112.2, 61.7, 55.7, 49.2, 32.9, 24.0, 14.5.

HRMS (ESI+) calculated for $\text{C}_{19}\text{H}_{18}\text{BrNO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 452.0162, found 452.0154

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