

Design, Synthesis, and Biological Evaluation of Selective Sphingosine Kinase Inhibitors

Mithun Rajendra Raje

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

Doctor of Philosophy

In

Chemistry

Webster L. Santos, Committee Chair

Paul R. Carlier

Felicia A. Etzkorn

James M. Tanko

(April 13, 2012)

(Blacksburg, VA)

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

Copyright 2012, Mithun R. Raje

**ELSEVIER LICENSE
TERMS AND CONDITIONS**

Copyright information for Chapter 2

Apr 27, 2012

This is a License Agreement between Mithun Raje ("You") and Elsevier ("Elsevier") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Elsevier, and the payment terms and conditions.

All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.

Supplier	Elsevier Limited The Boulevard, Langford Lane Kidlington, Oxford, OX5 1GB, UK
Registered Company Number	1982084
Customer name	Mithun Raje
Customer address	1208 Snyder Lane Blacksburg, VA 24060
License number	2892571112630
License date	Apr 19, 2012
Licensed content publisher	Elsevier
Licensed content publication	Bioorganic & Medicinal Chemistry
Licensed content title	Design, synthesis and biological activity of sphingosine kinase 2 selective inhibitors
Licensed content author	Mithun R. Raje, Kenneth Knott, Yugesh Kharel, Philippe Bissel, Kevin R. Lynch, Webster L. Santos
Licensed content date	1 January 2012
Licensed content volume number	20
Licensed content issue number	1
Number of pages	12
Start Page	183
End Page	194
Type of Use	reuse in a thesis/dissertation
Portion	full article
Format	electronic
Are you the author of this Elsevier article?	Yes
Will you be translating?	No
Order reference number	

Title of your thesis/dissertation	Design, synthesis and biological evaluation of selective sphingosine kinase inhibitors
Expected completion date	May 2012
Estimated size (number of pages)	150
Elsevier VAT number	GB 494 6272 12
Permissions price	0.00 USD
VAT/Local Sales Tax	0.0 USD / 0.0 GBP
Total	0.00 USD
Terms and Conditions	

INTRODUCTION

1. The publisher for this copyrighted material is Elsevier. By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the Billing and Payment terms and conditions established by Copyright Clearance Center, Inc. ("CCC"), at the time that you opened your Rightslink account and that are available at any time at <http://myaccount.copyright.com>).

GENERAL TERMS

2. Elsevier hereby grants you permission to reproduce the aforementioned material subject to the terms and conditions indicated.
3. Acknowledgement: If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source, permission must also be sought from that source. If such permission is not obtained then that material may not be included in your publication/copies. Suitable acknowledgement to the source must be made, either as a footnote or in a reference list at the end of your publication, as follows:

 “Reprinted from Publication title, Vol /edition number, Author(s), Title of article / title of chapter, Pages No., Copyright (Year), with permission from Elsevier [OR APPLICABLE SOCIETY COPYRIGHT OWNER].” Also Lancet special credit - “Reprinted from The Lancet, Vol. number, Author(s), Title of article, Pages No., Copyright (Year), with permission from Elsevier.”
4. Reproduction of this material is confined to the purpose and/or media for which permission is hereby given.
5. Altering/Modifying Material: Not Permitted. However figures and illustrations may be altered/adapted minimally to serve your work. Any other abbreviations, additions, deletions and/or any other alterations shall be made only with prior written authorization of Elsevier Ltd. (Please contact Elsevier at permissions@elsevier.com)
6. If the permission fee for the requested use of our material is waived in this instance, please be advised that your future requests for Elsevier materials may attract a fee.
7. Reservation of Rights: Publisher reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii)

these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

8. **License Contingent Upon Payment:** While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by publisher or by CCC) as provided in CCC's Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and publisher reserves the right to take any and all action to protect its copyright in the materials.

9. **Warranties:** Publisher makes no representations or warranties with respect to the licensed material.

10. **Indemnity:** You hereby indemnify and agree to hold harmless publisher and CCC, and their respective officers, directors, employees and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

11. **No Transfer of License:** This license is personal to you and may not be sublicensed, assigned, or transferred by you to any other person without publisher's written permission.

12. **No Amendment Except in Writing:** This license may not be amended except in a writing signed by both parties (or, in the case of publisher, by CCC on publisher's behalf).

13. **Objection to Contrary Terms:** Publisher hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment terms and conditions. These terms and conditions, together with CCC's Billing and Payment terms and conditions (which are incorporated herein), comprise the entire agreement between you and publisher (and CCC) concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall control.

14. **Revocation:** Elsevier or Copyright Clearance Center may deny the permissions described in this License at their sole discretion, for any reason or no reason, with a full refund payable to you. Notice of such denial will be made using the contact information provided by you. Failure to receive such notice will not alter or invalidate the denial. In no event will Elsevier or Copyright Clearance Center be responsible or liable for any costs, expenses or damage incurred by you as a result of a denial of your permission request, other than a refund of the amount(s) paid by you to Elsevier and/or Copyright Clearance Center for denied permissions.

LIMITED LICENSE

The following terms and conditions apply only to specific license types:

15. **Translation:** This permission is granted for non-exclusive world **English** rights only unless your license was granted for translation rights. If you licensed translation rights you may only translate this content into the languages you requested. A professional translator must perform all translations and reproduce the content word for word preserving the integrity of the article. If this license is to re-use 1 or 2 figures then permission is granted for non-exclusive world rights in all languages.

16. **Website:** The following terms and conditions apply to electronic reserve and author websites:

Electronic reserve: If licensed material is to be posted to website, the web site is to be password-protected and made available only to bona fide students registered on a relevant course if:

This license was made in connection with a course,

This permission is granted for 1 year only. You may obtain a license for future website posting,

All content posted to the web site must maintain the copyright information line on the bottom of each image,

A hyper-text must be included to the Homepage of the journal from which you are licensing at

<http://www.sciencedirect.com/science/journal/xxxxx> or the Elsevier homepage for books at

<http://www.elsevier.com> , and

Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

17. **Author website** for journals with the following additional clauses:

All content posted to the web site must maintain the copyright information line on the bottom of each image, and

the permission granted is limited to the personal version of your paper. You are not allowed to download and post the published electronic version of your article (whether PDF or HTML, proof or final version), nor may you scan the printed edition to create an electronic version,

A hyper-text must be included to the Homepage of the journal from which you are licensing at

<http://www.sciencedirect.com/science/journal/xxxxx> , As part of our normal production process,

you will receive an e-mail notice when your article appears on Elsevier's online service

ScienceDirect (www.sciencedirect.com). That e-mail will include the article's Digital Object

Identifier (DOI). This number provides the electronic link to the published article and should be

included in the posting of your personal version. We ask that you wait until you receive this e-mail and have the DOI to do any posting.

Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

18. **Author website** for books with the following additional clauses:

Authors are permitted to place a brief summary of their work online only.

A hyper-text must be included to the Elsevier homepage at <http://www.elsevier.com>

All content posted to the web site must maintain the copyright information line on the bottom of each image

You are not allowed to download and post the published electronic version of your chapter, nor may you scan the printed edition to create an electronic version.

Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

19. **Website** (regular and for author): A hyper-text must be included to the Homepage of the journal from which you are licensing at <http://www.sciencedirect.com/science/journal/xxxxx>. or for books to the Elsevier homepage at <http://www.elsevier.com>

20. **Thesis/Dissertation**: If your license is for use in a thesis/dissertation your thesis may be submitted to your institution in either print or electronic form. Should your thesis be published commercially, please reapply for permission. These requirements include permission for the Library and Archives of Canada to supply single copies, on demand, of the complete thesis and include permission for UMI to supply single copies, on demand, of the complete thesis. Should your thesis be published commercially, please reapply for permission.

21. **Other Conditions**:

v1.6

If you would like to pay for this license now, please remit this license along with your payment made payable to "COPYRIGHT CLEARANCE CENTER" otherwise you will be invoiced within 48 hours of the license date. Payment should be in the form of a check or money order referencing your account number and this invoice number RLNK500764128. Once you receive your invoice for this order, you may pay your invoice by credit card. Please follow instructions provided at that time.

**Make Payment To:
Copyright Clearance Center
Dept 001
P.O. Box 843006
Boston, MA 02284-3006**

For suggestions or comments regarding this order, contact RightsLink Customer Support: customercare@copyright.com or +1-877-622-5543 (toll free in the US) or +1-978-646-2777.

Gratis licenses (referencing \$0 in the Total field) are free. Please retain this printable license for your reference. No payment is required.



Mithun Raje <mithun.raje@gmail.com>

Copyright permission for Dissertation (Chapter 2)

Jones, Jennifer (ELS-OXF) <J.Jones@elsevier.com>
To: Mithun Raje <mithun.raje@gmail.com>

Fri, Apr 20, 2012 at 10:16 AM

Dear Mithun Raje

Thank you for your email.

As author of the requested articles, you do not need to seek Elsevier's permission to include them in your thesis as it is part of the rights you retain as an Elsevier journal author.

If your thesis is being hosted online by your university, then the version you should include in your thesis should **not be Elsevier's PDF version** but the Accepted Author Manuscript ("AAM"), it is the author's version of the manuscript of an article that has been accepted for publication and which may include any author-incorporated changes suggested through the processes of submission processing, peer review, and editor-author communications. AAMs do not include other publisher value added contributions such as copy-editing, formatting, technical enhancements and (if relevant) pagination.

For further information on the rights you retain as an Elsevier journal author, please visit our web page <http://www.elsevier.com/wps/find/authorsview.authors/copyright#rights>

Yours sincerely
Jennifer Jones
Rights Associate
Global Rights Department

Elsevier Ltd
PO Box 800
Oxford OX5 1GB
UK

Elsevier Limited, a company registered in England and Wales with company number 1982084, whose registered office is The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, United Kingdom.

From: Mithun Raje [mailto:mithun.raje@gmail.com]
Sent: 19 April 2012 17:02
To: Rights and Permissions (ELS)
Subject: Copyright permission for Dissertation

[Quoted text hidden]

Elsevier Limited. Registered Office: The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, United Kingdom, Registration No. 1982084 (England and Wales).

Copyright information for Figure 1.5

Draft 09/01/2009

(Questions? Concerns? Contact Gail McMillan, Director of the Digital Library and Archives at Virginia Tech's University Libraries: gailmac@vt.edu)

(Please ensure that Javascript is enabled on your browser before using this tool.)

Virginia Tech ETD Fair Use Analysis Results

This is not a replacement for professional legal advice but an effort to assist you in making a sound decision.

Name: Mithun Raje

Description of item under review for fair use: Figure 1, Trends in Cell Biology, 2012, 22, 50-60

Report generated on: 04-27-2012 at : 13:45:59

Based on the information you provided:

Factor 1

Your consideration of the purpose and character of your use of the copyright work weighs: *in favor of fair use*

Factor 2

Your consideration of the nature of the copyrighted work you used weighs: *in favor of fair use*

Factor 3

Your consideration of the amount and substantiality of your use of the copyrighted work weighs: *in favor of fair use*

Factor 4

Your consideration of the effect or potential effect on the market after your use of the copyrighted work weighs: *in favor of fair use*

Based on the information you provided, your use of the copyrighted work weighs: *in favor of fair use*





Council

Copyright information for Figure 1.10

Lynn Wecker

President
University of South Florida

John S. Lazo

President-Elect
University of Virginia

James R. Halpert

Past-President
University of California, San Diego

Mary E. Vore

Secretary/Treasurer
University of Kentucky

Edward T. Morgan

Secretary/Treasurer-Elect
Emory University

Bryan F. Cox

Past Secretary/Treasurer
Abbott Laboratories

Stephen M. Lanier

Councilor
Medical University of South Carolina

Richard R. Neubig

Councilor
University of Michigan

Kenneth E. Thummel

Councilor
University of Washington

James E. Barrett

Board of Publications Trustees
Drexel University

Brian M. Cox

FASEB Board Representative
Uniformed Services University
of the Health Sciences

Scott A. Waldman

Program Committee
Thomas Jefferson University

Christine K. Carrico

Executive Officer

**9650 Rockville Pike
Bethesda, MD 20814-3995**

**Phone: (301) 634-7060
Fax: (301) 634-7061**

**info@aspēt.org
www.aspēt.org**

April 26, 2012

Mithun Raje
Chemistry
Virginia Tech
3020 Hahn Hall South
Blacksburg, VA 24061

Email: rmithun@vt.edu

Dear Mithun Raje:

This is to grant you permission to reproduce the following figure in your thesis entitled "Design, synthesis, and biological evaluation of selective sphingosine kinase inhibitors" for Virginia Polytechnic Institute and State University:

Figure 5 from Kazuaki Takabe, Steven W. Paugh, Sheldon Milstien, and Sarah Spiegel, "Inside-Out" Signaling of Sphingosine-1-Phosphate: Therapeutic Targets, *Pharmacol Rev* June 2008 60:181-195

Permission to reproduce the figure is granted for worldwide use in all languages, translations, and editions, and in any format or medium including print and electronic. The authors and the source of the materials must be cited in full, including the article title, journal title, volume, year, and page numbers.

Sincerely yours,

Richard Dodenhoff
Journals Director