IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1st Named Inventor:	Mijoon Lee	Examiner:	Jason M. NOLAN
Patent No.:	8,093,287	Art Unit:	1626
Issue Date:	January 10, 2012	Confirmation No:	7167
Customer No.:	119155	Atty. Docket No.:	501.010US1
Title:	INHIBITORS OF MATRIX METALLOPROTEINASES		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR REFUND UNDER 37 CFR § 1.26

Attention: Commissioner for Patents

This is a request for a refund in the amount of $100.00. On May 23, 2016, Applicant's attorney submitted a payment of $100.00 for Fee Code 2811: "Certificate of Correction", electronically via credit card. However, Applicant's Petition for a Certificate of Correction was dismissed by a Decision on Petition mailed March 6, 2017. Accordingly, a refund under 37 CFR § 1.26 is proper.

Applicant respectfully requests a credit of $100.00 be applied to the credit card account to which the fee was charged. For your reference, the payment for which refund is requested was filed via EFS-Web on May 23, 2016, and processed on the USPTO's accounting date of May 24, 2016.

The Commissioner is hereby authorized to apply any necessary debit(s) or credit(s) to Deposit Account No. 50-6273. If a telephone conference would be helpful in facilitating processing of this request, the Office is invited to telephone the undersigned, Applicant's primary attorney of record, at (612) 238-7855.

Respectfully submitted,

Haukaas Fortius PLLC
Customer Number 119155
5100 Eden Avenue, Suite 303
Edina, Minnesota 55436
(612) 238-7855

Dated: March 29, 2017

By: / Michael H. Haukaas /

Michael H. Haukaas
Reg. No. 57,111

MHH/mm

Electronic Acknowledgement Receipt

EFS ID:	28774067
Application Number:	13047605
International Application Number:	
Confirmation Number:	7167
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Customer Number:	119155
Filer:	Michael Hans Haukaas
Filer Authorized By:	
Attorney Docket Number:	501.010US1
Receipt Date:	29-MAR-2017
Filing Date:	14-MAR-2011
Time Stamp:	15:18:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Refund Request	501-010US1_RequestRefund.pdf	82678 168bf161e4fcf4ddff639ac4df3a3e6e3bd8c54d	no	1

Warnings:

Information:	
Total Files Size (in bytes):	82678

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Haukaas Fortius PLLC
5100 Eden Avenue
Suite 303
Edina MN 55436

In re Patent of :
Lee et al. :
Patent No. 8,093,287 :
Issue Date: January 10, 2012 : Decision on Petition
Application No. 13/047,605 :
Filing Date: March 14, 2011 :
Attorney Docket No. 501.010US1 :

This is a decision on the request, filed May 23, 2016, under 37 CFR 3.81(b) to accept the correction of the assignee data and issue a certificate of correction removing Wayne State University as assignee; thereby listing only University of Notre Dame du Lac as assignee.

The request under 37 CFR 3.8(b) is **dismissed**.

Any request for reconsideration of this decision must be submitted within TWO (2) MONTHS from the mail date of this decision. Extensions of time under 37 CFR 1.136(a) are permitted. Petitioner is advised that this is not a final agency decision.

37 CFR 3.81(b) currently states:

> Any request for issuance of an application in the name of the assignee submitted after the date of payment of the issue fee, and any request for a patent to be corrected to state the name of the assignee, must state that the assignment was submitted for recordation as set forth in § 3.11 before issuance of the patent, and must include a request for a certificate of correction under § 1.323 of this chapter (accompanied by the fee set forth in § 1.20(a)) and the processing fee set forth in § 1.17(I) of this chapter.

In other words, the request under 37 CFR 3.81(b) will be granted when:

(1) a request under 37 CFR 3.81 and the fee set forth in 37 CFR 1.17(i) are filed,
(2) the assignment was submitted for recordation prior to issuance of the patent, and
(3) a request for a certificate of correction and the fee set forth in 37 CFR 1.20(a) are submitted.

Petitioner has not met requirement (2) set forth above. When the patent issued, 4 inventors had assigned their rights in the invention to University of Notre Dame du Lac and one inventor had assigned his rights in the invention to Wayne State University. These assignments were recorded in the Office prior to patent issuance. Applicant allowed the patent to issue instead of correcting the inventorship prior to issuance. The assignees listed on the patent were correct based on the record at the time the patent issued.

While 35 USC 256 provides for correction of inventorship, 35 USC 255 and 37 CFR 1.325 do not provide for a correction of this type of error.

As no certificate of correction will be issued, petitioner may request a refund of the $100 certificate of correction fee.

Applicant is encouraged to record a document with Assignments Branch that explains Rafael Fridman is no longer an inventor, and thus Wayne State University does not have an interest in the application/patent.

Further correspondence with respect to this petition decision should be addressed as follows:

By mail:	Mail Stop PETITIONS Commissioner for Patents Post Office Box 1450 Alexandria, VA 22313-1450
By hand:	Customer Service Window Mail Stop Petitions Randolph Building 401 Dulany Street Alexandria, VA 22314
By fax:	(571) 273-8300 ATTN: Office of Petitions
By internet:	EFS-Web

Telephone inquiries concerning this decision should be directed to the undersigned at (571) 272-3230.

Shirene Willis Brantley
Attorney Advisor
Office of Petitions

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1st Named Inventor:	Mijoon Lee	Examiner:	Jason Michael Nolan
Application No.:	13/047,605	Art Unit:	1626
Filing Date:	March 14, 2011	Confirmation No:	7167
Patent No.:	8,093,287	Issue Date:	January 10, 2012
Customer No.:	119155	Docket No.:	501.010US1
Title:	INHIBITORS OF MATRIX METALLOPROTEINASES		

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attention: Commission for Patents

REQUEST TO CORRECT ASSIGNEE UNDER 37 C.F.R. § 3.81(b)

In response to the Decision on Petition mailed January 8, 2016, Applicant hereby submits this Request further to those filed on October 7 and April 29, 2014. In the Decision, the Office of Petitions states that "Assignment information printed on a patent is not updated after a patent is issued, and may not be reflective of the assignment recorded in the Office subsequent to the issuance of the patent." Applicant respectfully points out that the granting of this petition to correct the assignee will not be updating assignment information that changed after the patent was issued, but merely accurately updates for the record the assignment information that was correct before issuance of the patent.

In accordance with 37 CFR 3.81(b), Applicant hereby requests correction of the assignees' names listed on the face page of the printed patent. The correct assignment was submitted for recordation as set forth in 37 CFR 3.11 before issuance of the patent. A Request for Certificate of Correction under 37 CFR 1.323 and Certificate of Correction Form PTO/SB/44 are being submitted herewith.

Please update the name of the assignee as described below, in order to remove the second assignee, which was inadvertently listed on the Issue Fee Transmittal Form PTOL-85B.

- Cover Page, Section (73) Assignee: **University of Notre Dame du Lac**, Notre Dame, IN (US)~~; **Wayne State University**, Detroit, MI (US)~~

The required fee of $70.00 under 37 CFR 1.17(i)(1) (small entity) for entry of this paper is being submitted electronically herewith. If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-6273. The Examiner is invited to telephone Applicant's attorney at (612) 238-7855 to facilitate prosecution of this application.

Respectfully submitted,

Haukaas Fortius PLLC
Customer Number 119155
5100 Eden Avenue, Suite 303
Edina, Minnesota 55436
(612) 238-7855

Dated: May 23, 2016

By: / Michael H. Haukaas /

Michael H. Haukaas
Reg. No. 57,111

MHH/az

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1st Named Inventor:	Mijoon Lee	Examiner:	Jason Michael Nolan
Application No.:	13/047,605	Art Unit:	1626
Filing Date:	March 14, 2011	Confirmation No:	7167
Patent No.:	8,093,287	Issue Date:	January 10, 2012
Customer No.:	119155	Docket No.:	501.010US1
Title:	INHIBITORS OF MATRIX METALLOPROTEINASES		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attention: Commission for Patents

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. §1.323

Applicant requests issuance of a Certificate of Correction in order to correct the error described below. A Certificate of Correction Form PTO/SB/44 is being submitted herewith, as well as a Request to Correct Assignee in an issued patent.

Please correct the following mistakes printed in the issued patent:

Cover Page:

- Section (73) Assignee, at line 2 please delete: "; Wayne State University, Detroit, MI (US)"

The required fee of $100.00 under 37 CFR 1.20(a) is being submitted electronically herewith. If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-6273. Should there be in questions with regard to this communication, the Commissioner is invited to telephone Applicant's attorney at (612) 238-7855 to facilitate processing of this request.

Respectfully submitted,

Haukaas Fortius PLLC
Customer Number 119155
5100 Eden Avenue, Suite 303
Edina, Minnesota 55436
(612) 238-7855

Dated: May 23, 2016 By: / Michael H. Haukaas /

Michael H. Haukaas
Reg. No. 57,111

MHH/az

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,093,287

APPLICATION NO.: 13/047,605

ISSUE DATE : January 10, 2012

INVENTOR(S) : Mijoon Lee et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page, Item (73), delete:

"(73) Assignees: University of Notre Dame du Lac, Notre Dame, IN (US);
Wayne State University, Detroit, MI (US)"

and replace with:

-- (73) Assignee: University of Notre Dame du Lac, Notre Dame, IN (US) --

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Michael H. Haukaas, Ph.D., Haukaas Fortius PLLC
5100 Eden Ave., Suite 303
Edina, MN 55436

Electronic Patent Application Fee Transmittal

Application Number:	13047605
Filing Date:	14-Mar-2011
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Filer:	Michael Hans Haukaas/Angela Zwack
Attorney Docket Number:	501.010US1

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Petition Fee-37CFR 1.17(h) (Group II)	2464	1	70	70
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Certificate of Correction	2811	1	100	100
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**170**

Electronic Acknowledgement Receipt

EFS ID:	25861596
Application Number:	13047605
International Application Number:	
Confirmation Number:	7167
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Customer Number:	119155
Filer:	Michael Hans Haukaas/Angela Zwack
Filer Authorized By:	Michael Hans Haukaas
Attorney Docket Number:	501.010US1
Receipt Date:	23-MAY-2016
Filing Date:	14-MAR-2011
Time Stamp:	20:16:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$170
RAM confirmation Number	6449
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition for review by the Office of Petitions	501-010US1_ReqCorrAssignee.pdf	120620 142cbc67fda39154b03c13c1d8c8b3c072db8fe5	no	2
Warnings:					
Information:					
2	Request for Certificate of Correction	501-010US1_ReqCoC.pdf	190789 0264f1462961cd9b22456b250c197110fd5163b8	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32455 ffecd0f530e001ec4c5b71aa14d6c34c0a231195	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	343864		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,093,287 B2
APPLICATION NO. : 13/047605
DATED : January 10, 2012
INVENTOR(S) : Lee et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page, Item (75) Inventors, should read

-- (75) Inventors: **Mijoon Lee**, Mishawaka, IN (US); **Masahiro Ikejiri**, Osaka (JP); **Mayland Chang**, Granger, IN (US); **Shahriar Mobashery**, Granger, IN (US) --.

Signed and Sealed this
Seventeenth Day of May, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/047,605	03/14/2011	Mijoon Lee	501.010US1	7167

119155 7590 01/08/2016

Haukaas Fortius PLLC
5100 Eden Avenue
Suite 303
Edina, MN 55436

EXAMINER
NOLAN, JASON MICHAEL

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
01/08/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mhaukaas@hfglobalip.com
patents@hfglobalip.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

In re Patent No. 8,093,287	:	
Issue Date: January 10, 2012	:	
Application No. 13/047,605	:	ON PETITION
Filed: March 14, 2011	:	
Attorney Docket No. 501.010US1	:	

This is a decision on the "PETITION UNDER 37 C.F.R. §1.183", filed on October 7, 2014.

The petition is **DISMISSED**.

Any request for reconsideration should be filed within TWO MONTHS of the mailing date of this decision in order to be considered timely. 37 CFR 1.181(f). This time period may not be extended pursuant to 37 CFR 1.136.

Petitioner requests that the Office suspend the rules so that a certificate of correction to correct the assignment to reflect only one assignee on the printed patent can be issued. Petitioner states "Upon review of the issued patent, it was determined by all inventors, assignees, and their legal representative that Rafael Fridman is not an inventor of the claims of U.S. Patent No. 8,093,287. Furthermore, Rafael Fridman was the only assignor conveying rights to assignee Wayne State University in the assignment recorded on October 4, 2011 at Reel 027104, Frame 0235. The correct assignee should be listed as University of Notre Dame du Lac, 203 Main Building, Notre Dame, Indiana 46556. Because it has been determined that Mr. Fridman is not an inventor on this patent, Applicant respectfully requests correction to the assignee portion of the issued patent as outlined in the accompanying Request for Certificate of Correction."

APPLICABLE RULES AND REGULATIONS

37 CFR 1.183 provides that:

> In an extraordinary situation, when justice requires, any requirement of the regulations in this part which is not a requirement of the statutes may be suspended or waived by the Director or the Director's designee, sua sponte, or on petition of the interested party, subject to such other requirements as may be imposed. Any petition under this section must be accompanied by the petition fee set forth in § 1.17(f).

37 CFR 3.81 states in pertinent part:

(b) After payment of the issue fee : Any request for issuance of an application in the name of the assignee submitted after the date of payment of the issue fee, and any request for a patent to be corrected to state the name of the assignee, must state that the assignment was submitted for recordation as set forth in § 3.11 before issuance of the patent, and must include a request for a certificate of correction under § 1.323 of this chapter (accompanied by the fee set forth in § 1.20(a)) and the processing fee set forth in § 1.17(i) of this chapter.

(c) Partial assignees.

(1) If one or more assignee, together with one or more inventor, holds the entire right, title, and interest in the application, the patent may issue in the names of the assignee and the inventor.

(2) If multiple assignees hold the entire right, title, and interest to the exclusion of all the inventors, the patent may issue in the names of the multiple assignees.

DECISION

Petitioner's arguments have been considered but have been determined to not be persuasive. Petitioner has failed to present an argument to establish that justice requires that the Office issue a certificate of correction to correct the assignee. Assignment data printed on the patent will be based solely on the information so supplied. See MPEP 307. Assignment information printed on a patent is not updated after a patent is issued, and may not be reflective of the assignment recorded in the Office subsequent to the issuance of the patent.

As such the request for certificate of correction is DISMISSED.

Petitioner may wish to avail themselves of the provisions of MPEP 323 to correct any errors made in a recorded assignment.

Telephone inquiries regarding this communication should be directed to the undersigned at (571) 272-3215.

/Charlema Grant/
Charlema Grant
Attorney Advisor
Office of Petitions

Office of Petitions: Routing Sheet

Application No. 13047605

This application is being forwarded to your office for further processing. A decision has been rendered on a petition filed in this application, as indicated below. For details of this decision, please see the document PET.OP.DEC filed on the same date as this document.

☐ **GRANTED**

☒ **DISMISSED**

☐ **DENIED**

Office of Petitions: Decision Count Sheet

Mailing Month

Application No. 13047605

13047605

For US serial numbers: enter number only, no slashes or commas. Ex: 10123456
For PCT: enter "51+single digit of year of filing+last 5 numbers", Ex. for PCT/US05/12345, enter 51512345

Deciding Official: GRANT, CHARLEMA

Count (1) - Palm Credit 13/047,605

Decision: DISMISSED

FINANCE WORK NEEDED
☐ Select Check Box for YES

DISMISSED

Decision Type: 503 - 37 CFR 1.183 -SUSPEND/WAIVE EXAMINING-RELA

503

Notes:

Count (2)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Count (3)

Decision: n/a

FINANCE WORK NEEDED
☐ Select Check Box for YES

Decision Type: NONE

Notes:

Initials of Approving Official (if required)

If more than 3 decisions, attach 2nd count sheet & mark this box ☐

Printed on: *1/4/2016*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1st Named Inventor	Mijoon Lee	Atty Docket No.:	501.010US1
Application No.:	13/047,605	U.S. Patent No. :	8,093,287
Filed:	14 March 2011	Issue Date:	10 January 2012
Confirmation No.:	7167		
Title:	INHIBITORS OF MATRIX METALLOPROTEINASES		

PETITION UNDER 37 CFR 1.183 TO SUSPEND RULE

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This is a petition under 37 CFR 1.183 to correct the assignee of the above-referenced patent. Upon review of the issued patent, it was determined by all inventors, assignees, and their legal representative that Rafael Fridman is not an inventor of the claims of U.S. Patent No. 8,093,287. Furthermore, Rafael Fridman was the only assignor conveying rights to assignee Wayne State University in the assignment recorded on October 4, 2011 at Reel 027104, Frame 0235. The correct assignee should be listed as University of Notre Dame du Lac, 203 Main Building, Notre Dame, Indiana 46556. Because it has been determined that Mr. Fridman is not an inventor on this patent, Applicant respectfully requests correction to the assignee portion of the issued patent as outlined in the accompanying Request for Certificate of Correction.

Please let us know if any further documentation is required to make this correction. The Commissioner is invited to telephone Applicants' attorney at (612) 238-7855 to facilitate this correction of the issued patent.

Please charge the $200.00 petition fee and any additional fees required to Deposit Account No. 50-6273.

Respectfully submitted,

Haukaas Fish PLLC
Customer Number 119155
1635 Hennepin Ave., Suite 300
Minneapolis, Minnesota 55403
(612) 238-7855

Dated: October 7, 2014

By: / Michael H. Haukaas /

Michael H. Haukaas
Reg. No. 57,111

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,093,287

APPLICATION NO.: 13/047,605

ISSUE DATE : 10 January 2012

INVENTOR(S) : Lee et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page, Item (73), delete:

"(73) Assignee: University of Notre Dame du Lac, Notre Dame, IN (US);
Wayne State University, Detroit, MI (US)"

and replace with:

-- (73) Assignee: University of Notre Dame du Lac, Notre Dame, IN (US) --

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Michael H. Haukaas, Haukaas Fish PLLC
1635 Hennepin Ave., Suite 300
Minneapolis, MN 55403

Electronic Patent Application Fee Transmittal

Application Number:	13047605
Filing Date:	14-Mar-2011
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Filer:	Michael Hans Haukaas/Brenda Thom
Attorney Docket Number:	501.010US1

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Petition fee- 37 CFR 1.17(g) (Group II)	1463	1	200	200
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**200**

Electronic Acknowledgement Receipt

EFS ID:	20353687
Application Number:	13047605
International Application Number:	
Confirmation Number:	7167
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Customer Number:	119155
Filer:	Michael Hans Haukaas/Brenda Thom
Filer Authorized By:	Michael Hans Haukaas
Attorney Docket Number:	501.010US1
Receipt Date:	07-OCT-2014
Filing Date:	14-MAR-2011
Time Stamp:	17:08:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$200
RAM confirmation Number	3985
Deposit Account	506273
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition for review by the Office of Petitions.	Petition_to_Correct_Assignee.pdf	445739 ee2647f5653243038ea66a34cd2e7bde85addbff	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30289 fe1202f1249bdebeb18c14cc17c8576fedb5bcd8	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	476028		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE
Certificate

Patent No. 8,093,287 B2

Patented: January 10, 2012

On petition requesting issuance of a certificate for correction of inventorship pursuant to 35 U.S.C. 256, it has been found that the above identified patent, through error and without any deceptive intent, improperly sets forth the inventorship.

Accordingly, it is hereby certified that the correct inventorship of this patent is: Mijoon Lee, Mishawaka, IN (US); Masahiro Ikejiri, Osaka (JP); Mayland Chang, Granger, IN (US); and Shahriar Mobashery, Granger, IN (US).

Signed and Sealed this First Day of July 2014.

JOSEPH K. MCKANE
Supervisory Patent Examiner
Art Unit 1626
Technology Center 1600

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

June 20, 2014

Haukaas Fish PLLC
1635 Hennepin Avenue
Suite 300
Minneapolis MN 55403

Patent No.: 8,093,287 B2
Inventor(s): Mijoon Lee, et al.
Issued: January 10, 2012
Title: **INHIBITORS OF MATRIX METALLOPROTEINASES**
Docket No.: **501.010US1**

Re: Request for Certificate of Correction

Consideration has been given your request for the issuance of a Certificate of Correction for the above-identified patent under the provisions of Rule 1.322 and 1.323.

Granting of a petition under 37 CFR 1.183, requesting the requirements of 37 CFR 3.81 to be waived, is required to correct applicant's error in the Assignee, when the correct name of the assignee was not provided in accordance with either section 3.81(a) or (b) (either no name or an incorrect name was provided in item 5 of the Issue Fee Transmittal, when the assignment had been recorded or submitted for recordation at the time the issue fee was paid, including after issuance of the patent.

A petition to correct the Assignee, under 37 CFR 1.183 should include:

(1) the petition fee set forth in 37 CFR 1.17(i)(1) (currently $140, $70, $35 for large, small, and micro entities, respectively);
(2) the correct name and address of the assignee; and
(3) the reel and frame number where the assignment is recorded or proof of the date the assignment was submitted for recordation.

Any petition under 37 CFR 1.183 should be directed to the attention of the Assistant Commissioner for Patents, using the following mailing address or FAX number.

By Mail: Mail Stop Petitions
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By Fax: (571) 273-8300

Attn.: Office of Petitions

If, the petition under 37 CFR 1.183, is filed and granted, the patentee would be entitled to a Certificate of Correction under 37 CFR 1.323 (required fee currently $100), due to the mistake in not complying with CFR 3.81.

In view of the foregoing, your request is hereby denied. Petition to correct inventorship in patent dated April 29, 2014 has been granted and certificate of correction will be issued.

Antonio Johnson
Office of Data Management
Certificates of Correction Branch
(703) 756-1544

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,093,287

APPLICATION NO.: 13/047,605

ISSUE DATE : 10 January 2012

INVENTOR(S) : Lee et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page, Item (75), delete:

"(75) Inventors: Mijoon Lee, Mishawaka, IN (US);
Masahiro Ikejiri, Osaka (JP);
Rafael Fridman, West Bloomfield, MI (US);
Mayland Chang, Granger, IN (US);
Shahriar Mobashery, Granger, IN (US)"

and replace with:

-- (75) Inventors: Mijoon Lee, Mishawaka, IN (US);
Masahiro Ikejiri, Osaka (JP);
Mayland Chang, Granger, IN (US);
Shahriar Mobashery, Granger, IN (US) --

On the Title Page, Item (73), delete:

"(73) Assignee: University of Notre Dame du Lac, Notre Dame, IN (US);
Wayne State University, Detroit, MI (US)"

and replace with:

-- (73) Assignee: University of Notre Dame du Lac, Notre Dame, IN (US) --

Approved SPE, 1626
/Joseph K. McKane/

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Michael H. Haukaas, Haukaas Fish PLLC
1635 Hennepin Ave., Suite 300
Minneapolis, MN 55403

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/047,605	03/14/2011	Mijoon Lee	501.010US1	7167

119155 7590 06/11/2014

Haukaas Fish PLLC
1635 Hennepin Avenue
Suite 300
Minneapolis, MN 55403

EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
06/11/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jfish@hfglobalip.com
mhaukaas@hfglobalip.com
patents@hfglobalip.com

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address : COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
13/047,605	14 March, 2011	LEE ET AL.	501.010US1

		EXAMINER	
Haukaas Fish PLLC 1635 Hennepin Avenue Suite 300 Minneapolis, MN 55403		MICHAEL BARKER	
		ART UNIT	PAPER
		1626	20140605

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

Please see attached documentation.

/Joseph K. McKane/
Supervisory Patent Examiner, Art Unit 1626

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

MICHAEL H. HAUKAAS
HAUKAAS FISH PLLC
1635 HENNEPIN AVE., SUITE 300
MINNEAPOLIS, MN 55403

In re Patent No. 8,093,287
Issue Date: December 21, 2011
Appl. No: 13/047605
Filed: March 14, 2011
For: Correction of Inventorship

This is a decision on the petition filed April 29, 2014, to correct inventorship under 37 CFR 1.324.

The petition is **GRANTED**.

The patented filed is being forwarded to Certificate of Corrections Branch for issuance of a certificate naming only the actual inventor or inventors.

/Joseph K. McKane/

Joseph K. McKane
Supervisory Patent Examiner Art Unit 1626
Technology Center 1600

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

MICHAEL H. HAUKAAS
HAUKAAS FISH PLLC
1635 HENNEPIN AVE., SUITE 300
MINNEAPOLIS, MN 55403

In re Patent No. 8,093,287
Issue Date: December 21, 2011
Appl. No: 13/047605
Filed: March 14, 2011
For: Correction of Inventorship

This is a decision on the petition filed April 29, 2014, to correct inventorship under 37 CFR 1.324.

The petition is **GRANTED**.

The patented filed is being forwarded to Certificate of Corrections Branch for issuance of a certificate naming only the actual inventor or inventors.

/Joseph K. McKane/

Joseph K. McKane
Supervisory Patent Examiner Art Unit 1626
Technology Center 1600

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/047,605	03/14/2011	Mijoon Lee	5006-004-CON

CONFIRMATION NO. 7167

119155
Haukaas Fish PLLC
1635 Hennepin Avenue
Suite 300
Minneapolis, MN 55403

POA ACCEPTANCE LETTER

OC000000068190062

Date Mailed: 05/06/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/29/2014.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/ddinh/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/047,605	03/14/2011	Mijoon Lee	5006-004-CON

CONFIRMATION NO. 7167

POWER OF ATTORNEY NOTICE

44163
Billion & Armitage
7401 Metro Blvd.
Suite 425
Minneapolis, MN 55439

OC000000068190039

Date Mailed: 05/06/2014

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/29/2014.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/ddinh/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1st Named Inventor	Mijoon Lee	Atty Docket No.:	501.010US1
Application No.:	13/047,605	U.S. Patent No. :	8,093,287
Filed:	14 March 2011	Issue Date:	10 January 2012
Confirmation No.:	7167		
Title:	INHIBITORS OF MATRIX METALLOPROTEINASES		

PETITION UNDER 37 CFR 1.324 TO CORRECT INVENTORSHIP

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attention: Commissioner for Patents:

This is a petition under 37 CFR 1.324 to correct the inventorship of the above-referenced patent. Upon review of the issued patent, it was determined by all inventors, assignees, and their legal representative that Rafael Fridman is not an inventor of the claims of U.S. Patent No. 8,093,287. Attached please find the following documents to effect the removal of Rafael Fridman as a listed inventor:

- Statements by the Inventors;
- Statement by Rafael Fridman;
- Statement by the Assignee, University of Notre Dame du Lac;
- Statement by Wayne State University;
- Request for Certificate of Correction;
- Declarations;
- Statement under 1.373(b); and
- Power of Attorney

Please let us know if any further documentation is required to make this correction. The Commissioner is invited to telephone Applicants' attorney at (612) 238-7855 to facilitate this correction of the issued patent.

Please charge the $130.00 petition fee and any additional fees required to Deposit Account No. 50-6273.

Respectfully submitted,

Haukaas Fish PLLC
Customer Number 119155
1635 Hennepin Ave., Suite 300
Minneapolis, Minnesota 55403
(612) 238-7855

Dated: 29 April 2014 By: / Michael H. Haukaas /

Michael H. Haukaas
Reg. No. 57,111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re. Appln of:	Mijoon Lee et al.
Serial No.:	13/047,605
Filing Date:	March 14, 2011
Title:	Inhibitors of Matrix Metalloproteinases
Attorney Docket No.:	5006-004-CON

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT REGARDING REQUEST TO CORRECT INVENTORSHIP

I hereby declare that the listing of Rafael Fridman as an inventor in the above-identified application was an error that occurred without deceptive intent by me.

Signed: _____ Date: 04/16/14
Mijoon Lee

Current Address: 551 University Park Court
Mishawaka, IN 46545

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re. Appln of:	Mijoon Lee et al.
Serial No.:	13/047,605
Filing Date:	March 14, 2011
Title:	Inhibitors of Matrix Metalloproteinases
Attorney Docket No.:	5006-004-CON

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT REGARDING REQUEST TO CORRECT INVENTORSHIP

I hereby declare that the listing of Rafael Fridman as an inventor in the above-identified application was an error that occurred without deceptive intent by me.

Signed: _____ Date: May 11, 2012
Masahiro Ikejiri

Current Address:

2-16-26-304 Shinke
Tondabayashi
Osaka 584-0085
Japan

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re. Appln of:	Mijoon Lee et al.
Serial No.:	13/047,605
Filing Date:	March 14, 2011
Title:	Inhibitors of Matrix Metalloproteinases
Attorney Docket No.:	5006-004-CON

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT REGARDING REQUEST TO CORRECT INVENTORSHIP

I hereby declare that the listing of Rafael Fridman as an inventor in the above-identified application was an error that occurred without deceptive intent by me.

Signed: Mayland Chang Date: 12/22/11
Mayland Chang

Current Address: 14542 Heatherton Drive
Granger, IN 46530

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re. Appln of:	Mijoon Lee et al.
Serial No.:	13/047,605
Filing Date:	March 14, 2011
Title:	Inhibitors of Matrix Metalloproteinases
Attorney Docket No.:	5006-004-CON

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT REGARDING REQUEST TO CORRECT INVENTORSHIP

I hereby declare that the listing of Rafael Fridman as an inventor in the above-identified application was an error that occurred without deceptive intent by me.

Signed: _____ Date: 12/22/2014
Shahriar Mobashery

Current Address: 14542 Heatherton Drive
Granger, IN 46530

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re. Appln of:	Mijoon Lee et al.
Serial No.:	13/047,605
Filing Date:	March 14, 2011
Title:	Inhibitors of Matrix Metalloproteinases
Attorney Docket No.:	5006-004-CON

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT REGARDING REQUEST TO CORRECT INVENTORSHIP

I hereby declare that the listing of Rafael Fridman as an inventor in the above-identified application was an error that occurred without deceptive intent by me.

Signed: _____ Date: 12/12/11
Rafael Fridman

Current Address:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re. Appln of:	Mijoon Lee et al.
Serial No.:	13/047,605
Filing Date:	March 14, 2011
Title:	Inhibitors of Matrix Metalloproteinases
Attorney Docket No.:	5006-004-CON

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT REGARDING REQUEST TO CORRECT INVENTORSHIP

I hereby declare that the listing of Rafael Fridman as an inventor in the above-identified application was an error that occurred without deceptive intent by the University of Notre Dame.

Signed: _____ Date: 12/15/11

Dick Cox
Director, Office of Technology Transfer
University of Notre Dame
203 Main Building
Office of the General Counsel
Notre Dame, Indiana 46556

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re. Appln of:	Mijoon Lee et al.
Serial No.:	13/047,605
Filing Date:	March 14, 2011
Title:	Inhibitors of Matrix Metalloproteinases
Attorney Docket No.:	5006-004-CON

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT REGARDING REQUEST TO CORRECT INVENTORSHIP

I hereby declare that the listing of Rafael Fridman as an inventor in the above-identified application was an error that occurred without deceptive intent by Wayne State University.

Signed: Hilary R Ratner Date: Feb 16, 2012

Hilary Ratner
Vice President for Research
Wayne State University
5057 Woodward Avenue – 6th Floor
Detroit, Michigan 48202

PTO/SB/44 (09-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8,093,287

APPLICATION NO.: 13/047,605

ISSUE DATE : 10 January 2012

INVENTOR(S) : Lee et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page, Item (75), delete:

"(75) Inventors: Mijoon Lee, Mishawaka, IN (US);
Masahiro Ikejiri, Osaka (JP);
Rafael Fridman, West Bloomfield, MI (US);
Mayland Chang, Granger, IN (US);
Shahriar Mobashery, Granger, IN (US)"

and replace with:

-- (75) Inventors: Mijoon Lee, Mishawaka, IN (US);
Masahiro Ikejiri, Osaka (JP);
Mayland Chang, Granger, IN (US);
Shahriar Mobashery, Granger, IN (US) --

On the Title Page, Item (73), delete:

"(73) Assignee: University of Notre Dame du Lac, Notre Dame, IN (US);
Wayne State University, Detroit, MI (US)"

and replace with:

-- (73) Assignee: University of Notre Dame du Lac, Notre Dame, IN (US) --

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Michael H. Haukaas, Haukaas Fish PLLC
1635 Hennepin Ave., Suite 300
Minneapolis, MN 55403

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/01A (01-09) MODIFIED CBC 09-10
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	INHIBITORS OF MATRIX METALLOPROTEINASES

As the below named inventor(s), I/we declare that:

This declaration is directed to:

☐ The attached application, or

☒ Application No. 13/047,605 filed on March 14, 2011

☐ As amended on _____ (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

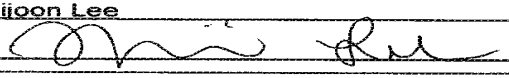
WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

All statements made herein of my/our own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

Inventor one: Mijoon Lee — Date: 04/16/12

Signature:  — Citizen of: KR

Inventor two: Masahiro Ikejiri — Date: _____

Signature: _____ — Citizen of: JP

Inventor three: Mayland Chang — Date: _____

Signature: _____ — Citizen of: US

Inventor four: Shahriar Mobashery — Date: _____

Signature: _____ — Citizen of: US

☐ Additional inventors or a legal representative are being named on __ additional form(s) attached hereto.

PTO/SB/01A (01-09) MODIFIED CBC 09-10
Approved for use through 08/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	INHIBITORS OF MATRIX METALLOPROTEINASES

As the below named inventor(s), I/we declare that:

This declaration is directed to:

☐ The attached application, or

☒ Application No. 13/047,805 filed on March 14, 2011

☐ As amended on _____ (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

All statements made herein of my/our own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

Inventor one: Miloon Lee — Date: _____

Signature: _____ — Citizen of: KR

Inventor two: Masahiro Ikejiri — Date: May 11, 2012

Signature: [signature] — Citizen of: JP

Inventor three: Mayland Chang — Date: _____

Signature: _____ — Citizen of: US

Inventor four: Shahriar Mobashery — Date: _____

Signature: _____ — Citizen of: US

☐ Additional inventors or a legal representative are being named on __ additional form(s) attached hereto.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/SB/01A (01-09) MODIFIED CBC 09-10
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	INHIBITORS OF MATRIX METALLOPROTEINASES

As the below named inventor(s), I/we declare that:

This declaration is directed to:

☐ The attached application, or

☒ Application No. 13/047,605 filed on March 14, 2011

☐ As amended on _____ (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

All statements made herein of my/our own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

Inventor one: Mijoon Lee — Date: _____

Signature: _____ — Citizen of: KR

Inventor two: Masahiro Ikejiri — Date: _____

Signature: _____ — Citizen of: JP

Inventor three: Mayland Chang — Date: 12/22/11

Signature: Mayland Chang — Citizen of: US

Inventor four: Shahriar Mobashery — Date: December 23, 2011

Signature: Shahriar Mobashery — Citizen of: US

☐ Additional inventors or a legal representative are being named on ___ additional form(s) attached hereto.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Mijoon Lee et al.

Application No./Patent No.: 13/047,605 Filed/Issue Date: March 14, 2011

Titled: INHIBITORS OF MATRIX METALLOPROTEINASES

University of Notre Dame Du Lac , a university

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☐ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Lee, Ikejiri, Chang and Mobashery To: University of Notre Dame

The document was recorded in the United States Patent and Trademark Office at
Reel 027014 , Frame 0351 , or for which a copy thereof is attached.

2. From: Fridman To: Wayne State University

The document was recorded in the United States Patent and Trademark Office at
Reel 027014 , Frame 0235 , or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/ Michael Haukaas / April 24, 2014

Signature Date

Michael Haukaas Attorney of Record, # 57,111

Printed or Typed Name Title

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

☒ Practitioners associated with Customer Number: 119155

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

☒ The address associated with Customer Number: 119155

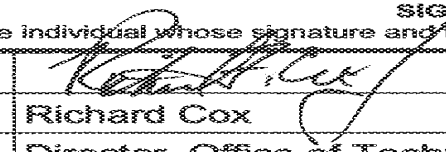
OR

☐	Firm or Individual Name			
	Address			
	City		State	Zip
	Country			
	Telephone		Email	

Assignee Name and Address: University of Notre Dame Du Lac
Office of Technology Transfer, 940 Grace Hall
Notre Dame, IN 46556-5812

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	11/12/2013
Name	Richard Cox	Telephone	(574) 631-4551
Title	Director, Office of Technology Transfer		

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	13047605
Filing Date:	14-Mar-2011
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Filer:	Michael Hans Haukaas/Janice Messer
Attorney Docket Number:	5006-004-CON

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Processing Fee Correcting Inventorship	1816	1	130	130
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	18897541
Application Number:	13047605
International Application Number:	
Confirmation Number:	7167
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Customer Number:	44163
Filer:	Michael Hans Haukaas/Janice Messer
Filer Authorized By:	Michael Hans Haukaas
Attorney Docket Number:	5006-004-CON
Receipt Date:	29-APR-2014
Filing Date:	14-MAR-2011
Time Stamp:	22:26:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$130
RAM confirmation Number	7476
Deposit Account	506273
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition for review by the Office of Petitions.	Petition_to_Correct_Inventorship.pdf	125035 96d129a821b030162c94d989a69c5265c00a99d9	no	2
Warnings:					
Information:					
2	Miscellaneous Incoming Letter	A_Statements_by_Inventors.pdf	1222775 4c8156ad86a5dfa8746b339aeece6d26c33377fd	no	4
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	B_Statement_by_Fridman.pdf	126069 02e1a15e08815eecfc7a359d28d5c0503c116b57	no	1
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	C_Statement_by_NotreDame.pdf	42975 60526ef9b2b23849c4fb178973a143ea57cfa1ad	no	1
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	D_Statement_by_WayneState.pdf	137830 ae20da2b9a004163443b4c538dcf28b481e19471	no	1
Warnings:					
Information:					
6	Request for Certificate of Correction	E_Certificate_of_Correction.pdf	164845 96c342a6c7ab55058967f6faae8bd75b405e3038	no	2
Warnings:					
Information:					
7	Oath or Declaration filed	F_Declarations.pdf	460007 c4c8ce82f7b00c39ee9c81166951d8f692165e57	no	3
Warnings:					
Information:					
8	Assignee showing of ownership per 37 CFR 3.73.	2_501-010us1_373b.pdf	427688 5662e59453b7c843dc325ae99469a5895624a1ad	no	2
Warnings:					
Information:					

9	Power of Attorney	1_SignedGeneralPOA-UND.pdf	110979 6a2e2af1bed9db04f11aac0d0ff3a00ec11ec9e8	no	1
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	30119 faedacde03258f844f9692834be824d9bf88b571	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2848322	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/047,605	01/10/2012	8093287	5006-004-CON	7167

44163 7590 12/21/2011

Clise, Billion & Cyr, P.A.
605 U.S. Highway 169
Suite 300
Plymouth, MN 55441

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Mijoon Lee, Mishawaka, IN;
Masahiro Ikejiri, Osaka, JAPAN;
Mayland Chang, Granger, IN;
Rafael Fridman, West Bloomfield, MI;
Shahriar Mobashery, Granger, IN;

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

44163 7590 09/01/2011

Clise, Billion & Cyr, P.A.
605 U.S. Highway 169
Suite 300
Plymouth, MN 55441

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Angela Zwack	(Depositor's name)
	(Signature)
December 1, 2011	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/047,605	03/14/2011	Mijoon Lee	5006-004-CON	7167

TITLE OF INVENTION: INHIBITORS OF MATRIX METALLOPROTEINASES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	12/01/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
NOLAN, JASON MICHAEL	1626	514-430000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Clise, Billion & Cyr, P.A.
2 Michael Haukaas
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE	(B) RESIDENCE: (CITY and STATE OR COUNTRY)
University of Notre Dame du Lac	Notre Dame, Indiana
Wayne State University	Detroit, Michigan

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 50-3141 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date December 1, 2011

Typed or printed name Michael Haukaas Registration No. 57,111

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal

Application Number:	13047605
Filing Date:	14-Mar-2011
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Filer:	Michael Hans Haukaas/Angela Zwack
Attorney Docket Number:	5006-004-CON

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	2501	1	870	870
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1170**

Electronic Acknowledgement Receipt

EFS ID:	11520786
Application Number:	13047605
International Application Number:	
Confirmation Number:	7167
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Customer Number:	44163
Filer:	Michael Hans Haukaas/Angela Zwack
Filer Authorized By:	Michael Hans Haukaas
Attorney Docket Number:	5006-004-CON
Receipt Date:	01-DEC-2011
Filing Date:	14-MAR-2011
Time Stamp:	13:38:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1170
RAM confirmation Number	12939
Deposit Account	503141
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Issue Fee Payment (PTO-85B)	IssueFeeTransmittal.pdf	54801 61a4c464e4a2483c67002f8762cf65059288ac2f	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31977 33114e2fe3fb10c5cd8dcf6d154db6fe34c9a8ff	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	86778	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/047,605	03/14/2011	Mijoon Lee	5006-004-CON

CONFIRMATION NO. 7167

44163
Clise, Billion & Cyr, P.A.
605 U.S. Highway 169
Suite 300
Plymouth, MN 55441

PUBLICATION NOTICE

Title:INHIBITORS OF MATRIX METALLOPROTEINASES

Publication No.US-2011-0224275-A1
Publication Date:09/15/2011

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

44163 7590 09/01/2011

Clise, Billion & Cyr, P.A.
605 U.S. Highway 169
Suite 300
Plymouth, MN 55441

EXAMINER
NOLAN, JASON MICHAEL

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 09/01/2011

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/047,605	03/14/2011	Mijoon Lee	5006-004-CON	7167

TITLE OF INVENTION: INHIBITORS OF MATRIX METALLOPROTEINASES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	12/01/2011

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

44163 7590 09/01/2011

Clise, Billion & Cyr, P.A.
605 U.S. Highway 169
Suite 300
Plymouth, MN 55441

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/047,605	03/14/2011	Mijoon Lee	5006-004-CON	7167

TITLE OF INVENTION: INHIBITORS OF MATRIX METALLOPROTEINASES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$755	$300	$0	$1055	12/01/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
NOLAN, JASON MICHAEL	1626	514-430000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/047,605	03/14/2011	Mijoon Lee	5006-004-CON	7167

44163 7590 09/01/2011

Clise, Billion & Cyr, P.A.
605 U.S. Highway 169
Suite 300
Plymouth, MN 55441

EXAMINER	
NOLAN, JASON MICHAEL	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 09/01/2011

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	13/047,605	LEE ET AL.	
	Examiner	Art Unit	
	JASON M. NOLAN	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *06/08/2011*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *2-21 (now 1-20)*.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 07/15/2011
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Preliminary Amendment, filed June 8, 2011. As filed, New Claims 2-21 are pending. Claim 1 is cancelled.

Information Disclosure Statement

Applicant's information disclosure statement (IDS), filed on July 15, 2011 has been considered. Please refer to Applicant's copy of the 1449 submitted herein.

Statement of Reasons for Allowance

The present invention pertains to compounds and compositions according to Formula (30). The Examiner finds that the compounds according to Formula (30) are free of the prior art; i.e., nothing known in the art anticipates or renders the compounds of the instant application obvious. The closest prior art is Lim *et al.*, *J. Organic Chem.* 2004 *69*, 3572-73 (IDS). The instant invention is distinct from the prior art because the prior art does not disclose an amino substituent on the benzene ring.

Conclusion

Claims 2-21 are allowed and have been renumbered Claims 1-20.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason M. Nolan whose telephone number is (571) 272-4356 and e-mail is Jason.Nolan@uspto.gov. The examiner can normally be reached Monday - Friday (9:00AM - 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph M^{c}Kane, may be contacted at Joseph.McKane@uspto.gov or (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system, (Private PAIR or Public PAIR). Status information for unpublished applications is available through Private PAIR only. For information about the PAIR system, see http://pair-direct.uspto.gov. For questions on Private PAIR system, contact the Electronic Business Center at (866) 217-9197.

/Jason M. Nolan/

Examiner, Art Unit 1626

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13047605	LEE ET AL.
	Examiner	Art Unit
	JASON M NOLAN	1626

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	08/29/2011								
	1	-								
1	2	=								
2	3	=								
3	4	=								
4	5	=								
5	6	=								
6	7	=								
7	8	=								
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19	20	=								
20	21	=								

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BIB DATA SHEET

CONFIRMATION NO. 7167

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/047,605	03/14/2011 RULE	548	1626	5006-004-CON

APPLICANTS

Mijoon Lee, Mishawaka, IN;
Masahiro Ikejiri, Osaka, JAPAN;
Mayland Chang, Granger, IN;
Rafael Fridman, West Bloomfield, MI;
Shahriar Mobashery, Granger, IN;

**** CONTINUING DATA **************************

This application is a CON of 11/914,933 07/31/2008 PAT 7,928,127
which is a 371 of PCT/US06/19656 05/19/2006 *
which claims benefit of 60/682,385 05/19/2005
and claims benefit of 60/743,467 03/13/2006
(*)Data provided by applicant is not consistent with PTO records.

**** FOREIGN APPLICATIONS **************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
03/23/2011

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /JASON M. NOLAN/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		IN	12	1	1

ADDRESS

Clise, Billion & Cyr, P.A.
605 U.S. Highway 169
Suite 300
Plymouth, MN 55441
UNITED STATES

TITLE

INHIBITORS OF MATRIX METALLOPROTEINASES

FILING FEE RECEIVED		
597	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13047605	LEE ET AL.
	Examiner	Art Unit
	JASON M NOLAN	1626

SEARCHED

Class	Subclass	Date	Examiner
514	430	8/29/11	JMN
549	90	8/29/11	JMN

SEARCH NOTES

Search Notes	Date	Examiner
Abstract; Preliminary Amendment; ADS; Bib Data Sheet; Drawings; Oath; and Specification reviewed	8/29/11	JMN
STN Structure Search (Registry/Caplus) - attached	8/29/11	JMN
IDS considered	8/29/11	JMN
EAST Class/Subclass Search - attached	8/29/11	JMN
Inventor Search (STN; eDAN) - reviewed for double patenting	8/29/11	JMN

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner
514	430	8/29/11	JMN
549	90	8/29/11	JMN

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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	NOV 22	Higher System Limits Increase the Power of STN Substance-Based Searching
NEWS 3	NOV 24	Search an additional 46,850 records with MEDLINE backfile extension to 1946
NEWS 4	DEC 14	New PNK Field Allows More Precise Crossover among STN Patent Databases
NEWS 5	DEC 18	ReaxysFile available on STN
NEWS 6	DEC 21	CAS Learning Solutions -- a new online training experience
NEWS 7	DEC 22	Value-Added Indexing Improves Access to World Traditional Medicine Patents in CAplus
NEWS 8	JAN 24	The new and enhanced DPCI file on STN has been released
NEWS 9	JAN 26	Improved Timeliness of CAS Indexing Adds Value to USPATFULL and USPAT2 Chemistry Patents
NEWS 10	JAN 26	Updated MeSH vocabulary, new structured abstracts, and other enhancements improve searching in STN reload of MEDLINE
NEWS 11	JAN 28	CABA will be updated weekly
NEWS 12	FEB 23	PCTFULL file on STN completely reloaded
NEWS 13	FEB 23	STN AnaVist Test Projects Now Available for Qualified Customers
NEWS 14	FEB 25	LPCI will be replaced by LDPCI
NEWS 15	MAR 07	Pricing for SELECTing Patent, Application, and Priority Numbers in the USPAT and IFI Database Families is Now Consistent with Similar Patent Databases on STN
NEWS 16	APR 26	Expanded Swedish Patent Application Coverage in CA/CAplus Provides More Current and Complete Information
NEWS 17	APR 28	The DWPI (files WPINDEX, WPIDS and WPIX) on STN have been enhanced with thesauri for the European Patent Classifications
NEWS 18	MAY 02	MEDLINE Improvements Provide Fast and Simple Access to DOI and Chemical Name Information
NEWS 19	MAY 12	European Patent Classification thesauri added to the INPADOC files, PCTFULL, GBFULL and FRFULL
NEWS 20	MAY 23	Enhanced performance of STN biosequence searches
NEWS 21	MAY 23	Free Trial of the Numeric Property Search Feature in PCTFULL on STN
NEWS 22	JUN 20	STN on the Web Enhanced with New Patent Family Assistant and Updated Structure Plug-In
NEWS 23	JUN 20	INPADOC databases enhanced with first page images
NEWS 24	JUN 20	PATDPA database updates to end in June 2011
NEWS 25	JUN 26	MARPAT Enhancements Save Time and Increase Usability

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 NEWS 26  JUL 25  STN adds Australian patent full-text database,
                  AUPATFULL, including the new numeric search feature.
 NEWS 27  AUG 01  CA Sections Added to ACS Publications Web Editions
                  Platform
 NEWS 28  AUG 16  INPADOC: Coverage of German Patent Data resumed,
                  enhanced legal status
 NEWS 29  AUG 18  Upgrade now to STN Express, Version 8.5

 NEWS EXPRESS 18 AUGUST 2011 CURRENT WINDOWS VERSION IS V8.5,
              AND CURRENT DISCOVER FILE IS DATED 24 JANUARY 2011.

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 NEWS LOGIN    Welcome Banner and News Items

Enter NEWS followed by the item number or name to see news on that
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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:27:43 ON 29 AUG 2011

=> FIL REG
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.23       0.23

FILE 'REGISTRY' ENTERED AT 13:27:49 ON 29 AUG 2011
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provided by InfoChem.

STRUCTURE FILE UPDATES:   28 AUG 2011  HIGHEST RN 1324845-09-1
DICTIONARY FILE UPDATES:  28 AUG 2011  HIGHEST RN 1324845-09-1

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TSCA INFORMATION NOW CURRENT THROUGH June 24, 2011.

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  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:
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http://www.cas.org/support/stngen/stndoc/properties.html

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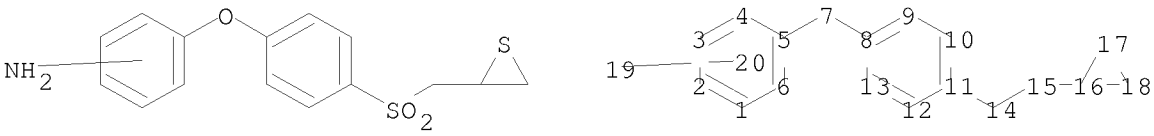
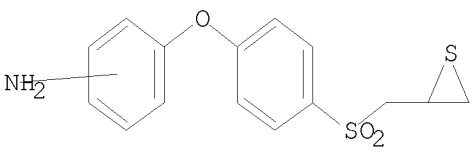


chain nodes :
14 19
ring nodes :
1 2 3 4 5 6 8 9 10 11 12 13 16 17 18
ring/chain nodes :
7 15
chain bonds :
5-7 7-8 11-14 14-15 15-16
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13 16-17 16-18 17-18
exact/norm bonds :
5-7 7-8 16-17 16-18 17-18
exact bonds :
11-14 14-15 15-16
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:Atom 17:Atom 18:Atom 19:CLASS 20:CLASS

L1 STRUCTURE UPLOADED

=> D
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> S L1
SAMPLE SEARCH INITIATED 13:28:36 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 9 TO ITERATE

100.0% PROCESSED 9 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 9 TO 360
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> S L1 FULL
FULL SEARCH INITIATED 13:28:43 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 151 TO ITERATE

100.0% PROCESSED 151 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L3 0 SEA SSS FUL L1

=>
Uploading C:\Users\jnolan\Documents\STN Express 8.4\Queries\13047605\2.str

chain nodes :
14
ring nodes :
1 2 3 4 5 6 8 9 10 11 12 13 16 17 18
ring/chain nodes :
7 15
chain bonds :
5-7 7-8 11-14 14-15 15-16
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13 16-17 16-18
17-18
exact/norm bonds :
5-7 7-8 16-17 16-18 17-18
exact bonds :
11-14 14-15 15-16
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:Atom 17:Atom 18:Atom

L4 STRUCTURE UPLOADED

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=> D
L4 HAS NO ANSWERS
L4                STR
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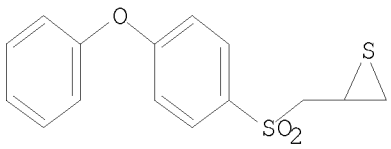

Structure attributes must be viewed using STN Express query preparation.

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=> S L4 FULL
FULL SEARCH INITIATED 13:29:21 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      151 TO ITERATE

100.0% PROCESSED      151 ITERATIONS                                87 ANSWERS
SEARCH TIME: 00.00.01

L5            87 SEA SSS FUL L4

=> D SCAN
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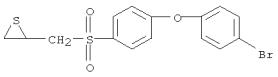
L5 87 ANSWERS REGISTRY COPYRIGHT 2011 ACS on STN
IN Thiirane, 2-[[[4-(4-bromophenoxy)phenyl]sulfonyl]methyl]-
MF C15 H13 Br O3 S2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> FIL CAPLUS
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	394.23	394.46

FILE 'CAPLUS' ENTERED AT 13:29:30 ON 29 AUG 2011
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 29 Aug 2011 VOL 155 ISS 10
FILE LAST UPDATED: 28 Aug 2011 (20110828/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2011
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2011

CAplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2011.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> S L5
L6 44 L5

=> FIL REG
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.52	394.98

FILE 'REGISTRY' ENTERED AT 13:30:12 ON 29 AUG 2011
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 28 AUG 2011 HIGHEST RN 1324845-09-1
DICTIONARY FILE UPDATES: 28 AUG 2011 HIGHEST RN 1324845-09-1

CAS Information Use Policies apply and are available at:

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TSCA INFORMATION NOW CURRENT THROUGH June 24, 2011.

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

```
=> D HIS

     (FILE 'HOME' ENTERED AT 13:27:43 ON 29 AUG 2011)

     FILE 'REGISTRY' ENTERED AT 13:27:49 ON 29 AUG 2011
L1             STRUCTURE UPLOADED
L2           0 S L1
L3           0 S L1 FULL
L4             STRUCTURE UPLOADED
L5          87 S L4 FULL

     FILE 'CAPLUS' ENTERED AT 13:29:30 ON 29 AUG 2011
L6          44 S L5
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     FILE 'REGISTRY' ENTERED AT 13:30:12 ON 29 AUG 2011

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Uploading C:\Users\jnolan\Documents\STN Express 8.4\Queries\13047605\3.str
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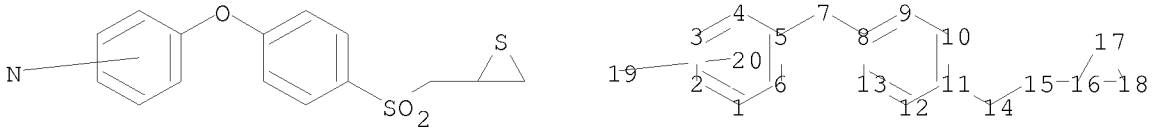


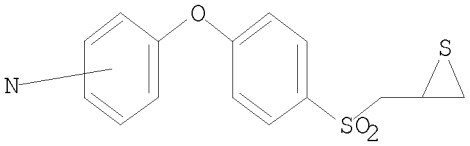

```
chain nodes :
14
ring nodes :
1  2  3  4  5  6  8  9  10  11  12  13  16  17  18
ring/chain nodes :
7  15  19
chain bonds :
5-7  7-8  11-14  14-15  15-16
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  8-9  8-13  9-10  10-11  11-12  12-13  16-17  16-18
17-18
exact/norm bonds :
```

5-7 7-8 16-17 16-18 17-18
exact bonds :
11-14 14-15 15-16
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:Atom 17:Atom 18:Atom 19:CLASS
20:CLASS

L7 STRUCTURE UPLOADED

=> D
L7 HAS NO ANSWERS
L7 STR



Structure attributes must be viewed using STN Express query preparation.

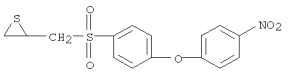
=> S L7 FULL SUB=L5
FULL SUBSET SEARCH INITIATED 13:30:38 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED - 87 TO ITERATE

100.0% PROCESSED 87 ITERATIONS 4 ANSWERS
SEARCH TIME: 00.00.01

L8 4 SEA SUB=L5 SSS FUL L7

=> D SCAN TOT
'TOT' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

L8 4 ANSWERS REGISTRY COPYRIGHT 2011 ACS on STN
IN Thiirane, 2-[[[4-(4-nitrophenoxy)phenyl]sulfonyl]methyl]-
MF C15 H13 N O5 S2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

The following are valid formats:

Substance information can be displayed by requesting individual fields or predefined formats. The predefined substance formats are: (RN = CAS Registry Number)

REG - RN
SAM - Index Name, MF, and structure - no RN
FIDE - All substance data, except sequence data
IDE - FIDE, but only 50 names
SQIDE - IDE, plus sequence data
SQIDE3 - Same as SQIDE, but 3-letter amino acid codes are used
SQD - Protein sequence data, includes RN
SQD3 - Same as SQD, but 3-letter amino acid codes are used
SQN - Protein sequence name information, includes RN

EPROP - Table of experimental properties
PPROP - Table of predicted properties
PROP - EPROP, ETAG, PPROP

Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

ABS -- Abstract
APPS -- Application and Priority Information
BIB -- CA Accession Number, plus Bibliographic Data
CAN -- CA Accession Number
CBIB -- CA Accession Number, plus Bibliographic Data (compressed)
IND -- Index Data
IPC -- International Patent Classification
PATS -- PI, SO
STD -- BIB, IPC, and NCL

IABS -- ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

L8 4 ANSWERS REGISTRY COPYRIGHT 2011 ACS on STN (Continued)
OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

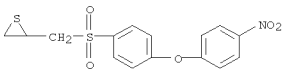
SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.
The MAX format is the same as ALL plus SPEC.
The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

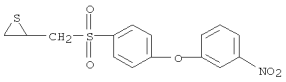
L8 4 ANSWERS REGISTRY COPYRIGHT 2011 ACS on STN
IN Thiirane, 2-[[[4-(4-nitrophenoxy)phenyl]sulfonyl]methyl]-
MF C15 H13 N O5 S2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):3

L8 4 ANSWERS REGISTRY COPYRIGHT 2011 ACS on STN
IN Thiirane, 2-[[[4-(3-nitrophenoxy)phenyl]sulfonyl]methyl]-
MF C15 H13 N O5 S2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L8 4 ANSWERS REGISTRY COPYRIGHT 2011 ACS on STN
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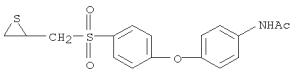
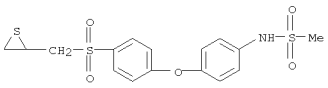
MF C17 H17 N O4 S2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L8 4 ANSWERS REGISTRY COPYRIGHT 2011 ACS on STN
IN Methanesulfonamide, N-[4-[4-[(2-thiiranylmethyl)sulfonyl]phenoxy]phenyl]-
MF C16 H17 N O5 S3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

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=> FIL CAPLUS
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                47.36     442.34

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FILE COVERS 1907 - 29 Aug 2011  VOL 155 ISS 10
FILE LAST UPDATED: 28 Aug 2011  (20110828/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Jun 2011
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Jun 2011

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2011.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> S L8
L9            3 L8

=> D IBIB TOT
```

L9 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2011:516147 CAPLUS
DOCUMENT NUMBER: 155:40719
TITLE: Exploration of mild copper-mediated coupling of organotrifluoroborates in the synthesis of thiirane-based inhibitors of matrix metalloproteinases
AUTHOR(S): Testero, Sebastian A.; Bouley, Renee; Fisher, Jed F.; Chang, Mayland; Mobashery, Shahriar
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, 46556, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2011), 21(9), 2675-2678
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 155:40719
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2006:1229166 CAPLUS
DOCUMENT NUMBER: 146:7815
TITLE: Preparation of thioepoxides as inhibitors of matrix metalloproteinases
INVENTOR(S): Lee, Mijoon; Ikejiri, Masahiro; Chang, Mayland; Fridman, Rafael; Mobashery, Shahriar
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 175pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006125208	A1	20061123	WO 2006-US19656	20060519
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20090005420	A1	20090101	US 2008-914933	20080731
US 7928127	B2	20110419		
PRIORITY APPLN. INFO.:			US 2005-682385P	P 20050519
			US 2006-743467P	P 20060313
			WO 2006-US19656	W 20060519

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 146:7815; MARPAT 146:7815
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:1061383 CAPLUS
DOCUMENT NUMBER: 143:474182
TITLE: Potent Mechanism-based Inhibitors for Matrix Metalloproteinases
AUTHOR(S): Ikejiri, Masahiro; Bernardo, M. Margarida; Bonfil, R. Daniel; Toth, Marta; Chang, Mayland; Fridman, Rafael; Mobashery, Shahriar
CORPORATE SOURCE: Department of Pathology, Wayne State University School of Medicine, and Proteases and Cancer Program, Karmanos Cancer Institute, Detroit, MI, 48201, USA
SOURCE: Journal of Biological Chemistry (2005), 280(40), 33992-34002
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:474182
OS.CITING REF COUNT: 54 THERE ARE 54 CAPLUS RECORDS THAT CITE THIS RECORD (55 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> D HIS

     (FILE 'HOME' ENTERED AT 13:27:43 ON 29 AUG 2011)

     FILE 'REGISTRY' ENTERED AT 13:27:49 ON 29 AUG 2011
L1              STRUCTURE UPLOADED
L2            0 S L1
L3            0 S L1 FULL
L4              STRUCTURE UPLOADED
L5           87 S L4 FULL

     FILE 'CAPLUS' ENTERED AT 13:29:30 ON 29 AUG 2011
L6           44 S L5

     FILE 'REGISTRY' ENTERED AT 13:30:12 ON 29 AUG 2011
L7              STRUCTURE UPLOADED
L8            4 S L7 FULL  SUB=L5

     FILE 'CAPLUS' ENTERED AT 13:31:00 ON 29 AUG 2011
L9            3 S L8

=> D IBIB ABS HITSTR TOT L9
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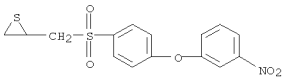
L9 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2011:516147 CAPLUS
DOCUMENT NUMBER: 155:40719
TITLE: Exploration of mild copper-mediated coupling of organotrifluoroborates in the synthesis of thiirane-based inhibitors of matrix metalloproteinases
AUTHOR(S): Testero, Sebastian A.; Bouley, Renee; Fisher, Jed F.; Chang, Mayland; Mobashery, Shahriar
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, 46556, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2011), 21(9), 2675-2678
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 155:40719
AB The copper-mediated and non-basic oxidative cross-coupling of organotrifluoroborates with phenols was applied to elaboration of the structures of thiirane-based inhibitors of matrix metalloproteinases. By revision of the synthetic sequence to allow this cross-coupling as the final step, and taking advantage of the neutral nature of organotrifluoroborate cross-coupling, a focussed series of inhibitors showing aryloxy and alkenyloxy replacement of the phenoxy substituent was prepared This reaction shows exceptional promise as an alternative to the classic copper-mediated but strongly basic Ullmann reaction, for the diversification of ether segments within base-labile lead structures.
IT 1310415-76-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of phenoxyphenylsulfonylmethylthiiranes via Cu-mediated coupling of aryltrifluoroborates with thiiranylmethylsulfonylphenol)
RN 1310415-76-9 CAPLUS
CN Thiirane, 2-[[[4-(3-nitrophenoxy)phenyl]sulfonyl]methyl]- (CA INDEX NAME)



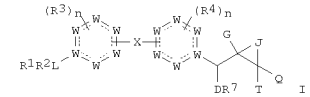
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2006:1229166 CAPLUS
DOCUMENT NUMBER: 146:7815
TITLE: Preparation of thioepoxides as inhibitors of matrix metalloproteinases
INVENTOR(S): Lee, Mijoon; Ikejiri, Masahiro; Chang, Mayland; Fridman, Rafael; Mobashery, Shahriar
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 175pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006125208	A1	20061123	WO 2006-US19656	20060519
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20090005420	A1	20090101	US 2008-214933	20080731
US 7928127	B2	20110419		
PRIORITY APPLN. INFO.:			US 2005-682385P	P 20050519
			US 2006-743467P	P 20060313
			WO 2006-US19656	W 20060519

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 146:7815; MARPAT 146:7815
GI

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)



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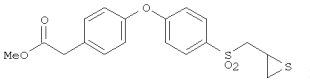
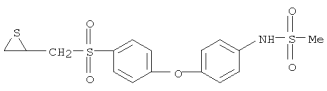


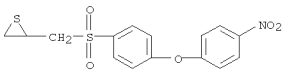
II

AB Title compds. e.g. [I; R1 = alkyl, haloalkyl, alkoxy, aralkyl, heteroarylalkyl, aralkoxy, heteroaralkoxy, aryl, heteroaryl, OH, SR5, N(R5)2, null; R2 = CH2, CO, SO2, OH; L = CH2, NR5, OH; W = independently C, N, O, S, null, and form 5-6 membered rings; dotted lines = optional double bonds; R3, R4 = OH, alkyl, alkoxy, alkanoyl, alkanoyloxy, aryl, heteroaryl, CO2H, cyano, NO2, halo, CF3, OCF3, SR5, N(R5)2, CO2R5; n = 0-4; R5 = H, alkyl, alkanoyl, aroyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, protecting group; X = O, S, SO, SO2, CH2O, CH2S, NR5, CO, bond, etc.; D = S, SO, SO2, P(O)OH, C:NOH, CO, etc.; E = bond, alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl; J = S, O, NR5; G, T, Q = H, alkyl, cyano; any alkyl, amino, aryl, heteroaryl, cycloalkyl is optionally substituted; with provisos], were prepared Thus, title compound (II) (multistep preparation given) inhibited matrix metalloproteinase-2 with Ki = 50 nM.
IT 869577-53-7P 869577-57-1P 869577-61-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of thioepoxides as inhibitors of matrix metalloproteinases)
RN 869577-53-7 CAPLUS
CN Methanesulfonamide, N-[4-[4-[(2-thiiranylmethyl)sulfonyl]phenoxy]phenyl]- (CA INDEX NAME)

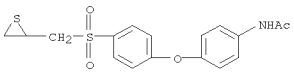


RN 869577-57-1 CAPLUS
CN Thiirane, 2-[[[4-(4-nitrophenoxy)phenyl]sulfonyl]methyl]- (CA INDEX NAME)

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)



RN 869577-61-7 CAPLUS
CN Acetamide, N-[4-[4-[(2-thiiranylmethyl)sulfonyl]phenoxy]phenyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

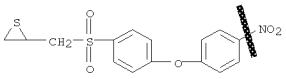
L9 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:1061383 CAPLUS
DOCUMENT NUMBER: 143:474182
TITLE: Potent Mechanism-based Inhibitors for Matrix Metalloproteinases
AUTHOR(S): Ikejiri, Masahiro; Bernardo, M. Margarida; Bonfil, R. Daniel; Toth, Marta; Chang, Mayland; Fridman, Rafael; Mobashery, Shahriar
CORPORATE SOURCE: Department of Pathology, Wayne State University School of Medicine, and Proteases and Cancer Program, Karmanos Cancer Institute, Detroit, MI, 48201, USA
SOURCE: Journal of Biological Chemistry (2005), 280(40), OCT. 7TH 33992-34002
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:474182

July 26

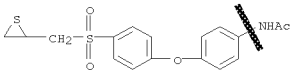
AB Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that play important roles in physiol. and pathol. conditions. Both gelatinases (MMP-2 and -9) and membrane-type 1 MMP (MMP-14) are important targets for inhibition, since their roles in various diseases, including cancer, have been well established. We describe herein a set of mechanism-based inhibitors that show high selectivity to gelatinases and MMP-14 (inhibitor 3) and to only MMP-2 (inhibitors 5 and 7). These mols. bind to the active sites of these enzymes, initiating a slow binding profile for the onset of inhibition, which leads to covalent enzyme modification. The full kinetic anal. for the inhibitors is reported. These are nanomolar inhibitors (Ki) for the formation of the noncovalent enzyme-inhibitor complexes. The onset of slow binding inhibition is rapid (kon of 102 to 104 M-1 s-1) and the reversal of the process is slow (koff of 10-3 to 10-4 s-1). However, with the onset of covalent chemical with the best of these inhibitors (e.g. inhibitor 3), very little recovery of activity (<10%) was seen over 48 h of dialysis. We previously reported that broad spectrum MMP inhibitors like GM6001 enhance MT1-MMP-dependent activation of pro-MMP-2 in the presence of tissue inhibitor of metalloproteinases-2. Herein, we show that inhibitor 3, in contrast to GM6001, had no effect on pro-MMP-2 activation by MT1-MMP. Furthermore, inhibitor 3 reduced tumor cell migration and invasion in vitro. These results show that these new inhibitors are promising candidates for selective inhibition of MMPs in animal models of relevant human diseases.

IT 869577-57-1P 869577-61-7P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(potent mechanism-based inhibitors for matrix metalloproteinases)

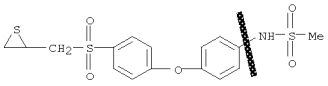
L9 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)
RN 869577-57-1 CAPLUS
CN Thiirane, 2-[[[4-(4-nitrophenoxy)phenyl]sulfonyl]methyl]- (CA INDEX NAME)



RN 869577-61-7 CAPLUS
CN Acetamide, N-[4-[4-[(2-thiiranylmethyl)sulfonyl]phenoxy]phenyl]- (CA INDEX NAME)



IT 869577-53-7P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(potent mechanism-based inhibitors for matrix metalloproteinases)
RN 869577-53-7 CAPLUS
CN Methanesulfonamide, N-[4-[4-[(2-thiiranylmethyl)sulfonyl]phenoxy]phenyl]- (CA INDEX NAME)



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REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	2	of	5

Complete if Known	
Application Number	13/047,605
Filing Date	November 19, 2007
First Named Inventor	Mijoon Lee
Art Unit	1626
Examiner Name	~~Joseph K. McKane~~ Jason Nolan
Attorney Docket Number	5006-004-CON

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No [1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/JN/		US-2,949,474	08/16/1960	Murdoch, Guy C., et al.	
		US-2,965,651	12/20/1960	Kosmin, Milton, et al.	
		US-3,222,326	12/07/1965	Brodoway, Nicolas	
		US-4,797,218	01/10/1989	Steinberg, David H., et al.	
		US-5,288,722	02/22/1994	Kishimoto, Shoji, et al.	
		US-5,981,763	11/09/1999	Garapon, Jacques, et al.	
		US-6,703,415	03/09/2004	Mobashery, S., et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document Country Code[3]-Number [4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T [6]
/JN/		WO-2006125208A1	11/23/2006	Lee, M., et al.		☐
		WO-95/35275	12/28/1995	Miller, Andrew, et al.		☐
		WO-97/18231	05/22/1997	Collins, Douglas A., et al.		☐
		WO-98/33788	08/06/1998	Alpegiani, Marco, et al.		☐

Examiner Signature	/Jason M. Nolan/	Date Considered	08/29/2011

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 5

Complete if Known	
Application Number	13/047,605
Filing Date	November 19, 2007
First Named Inventor	Mijoon Lee
Art Unit	1626
Examiner Name	~~Joseph K. McKane~~ Jason Nolan
Attorney Docket Number	5006-004-CON

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No [1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/JN/		"International Application Serial No. PCT/US06/19656 (Atty Ref 1319.018WO1), International Search Report mailed 10-02-06", 6 pgs	
		"International Application Serial No. PCT/US06/19656 (Atty Ref 1319.018WO1), Written Opinion mailed 10-02-06", 5 pgs	
		BECKETT, R. PAUL, et al., "Recent Advances in Matrix Metalloproteinase Inhibitor Research", Drug Discovery Today, 1(1), (January 1996), 16-26	
		BREW, K., et al., "Tissue Inhibitors of Metalloproteinases: Evolution, Structure and Function", Biochimica et Biophysica Acta, 1477(1-2), (March 7, 2000), 267-283	
		BROWN, STEPHEN, et al., "Potent and Selective Mechanism-Based Inhibition of Gelatinases", Journal of the American Chemical Society, 122(28), (July 19, 2000), 6799-6800	
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		DEMEDTS, INGEL K, et al., "Matrix metalloproteinases in asthma and COPD", Current Opinion in Pharmacology, (2005), 257-263	
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		FRIDMAN, R., et al., "Domain structure of human 72-kDa gelatinase/type IV collagenase. Characterization of proteolytic activity and identification of the tissue inhibitor of metalloproteinase-2 (TIMP-2) binding regions", Journal of Biological Chemistry, 267(22), (August 5, 1992), 15398-15405	

Examiner Signature	/Jason M. Nolan/	Date Considered	08/29/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 4 of 5

Complete if Known	
Application Number	13/047,605
Filing Date	November 19, 2007
First Named Inventor	Mijoon Lee
Art Unit	1626
Examiner Name	~~Joseph K. McKane~~ Jason Nolan
Attorney Docket Number	5006-004-CON

NON-PATENT LITERATURE DOCUMENTS

/JN/		FRIDMAN, R., et al., "Expression of human recombinant 72 kDa gelatinase and tissue inhibitor of metalloproteinase-2 (TIMP-2): characterization of complex and free enzyme", Biochemical Journal, 289(Pt 2), (January 15, 1993), 411-416	
		GREENWALD, R A., et al., "Thirty-six Years in the Clinic without an MMP Inhibitor: What Hath Collagenase Wrought?", Annals of the New York Academy of Sciences, 878, (June 1999), 412-419	
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Examiner Signature	/Jason M. Nolan/	Date Considered	08/29/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**

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Sheet	5	of	5

Complete if Known	
Application Number	13/047,605
Filing Date	November 19, 2007
First Named Inventor	Mijoon Lee
Art Unit	1626
Examiner Name	~~Joseph K. McKane~~ Jason Nolan
Attorney Docket Number	5006-004-CON

NON-PATENT LITERATURE DOCUMENTS

/JN/		MORGUNOVA, EKATERINA, et al., "Structure of Human Pro-Matrix Metalloproteinase-2: Activation Mechanism Revealed", Science, 284(5420), (June 4, 1999), 1667-1670	
		NELSON, AMY R., et al., "Matrix Metalloproteinases: Biologic Activity and Clinical Implications", Journal of Clinical Oncology, 18(5), (March 1, 2000), 1135-1149	
		OLSON, MATTHEW W, "Characterization of the monomeric and dimeric forms of latent and active matrix metalloproteinase-9. Differential rates for activation by stromelysin 1", Journal of Biological Chemistry, 275(4), (January 28, 2000), 2661-2668	
		PYKE, C., et al., "Localization of messenger RNA for Mr 72,000 and 92,000 type IV collagenases in human skin cancers by in situ hybridization", Cancer Research, 52(5), (March 1, 1992), 1336-1341	
		SALO, TUULA, et al., "Purification and Characterization of a Murine Basement Membrane Collagen-degrading Enzyme Secreted by Metastatic Tumor Cells", Journal of Biological Chemistry, 258(5), (March 10, 1983), 3058-3063	
		SURYADEVARA, RADHIKA, et al., "Regulation fo Tissue Inhibitor of Metalloproteinase-1 by Astrocytes", GLIA 44, (2003), 47-56	
		TAMURA, Y., "Highly Selective and Orally Active Inhibitors of Type IV Collagenase (MMP-9 and MMP-2): N-Sulfonylamino Acid Derivatives", Journal of Medicinal Chemistry, 41(4), (February 12, 1998), 640-649	
		TOFT-HANSEN, HENRIK, et al., "Key Metalloproteinases Are Expressed by Specific Cell Types in Experimental Autoimmune Encephalomyelitis", The Journal of Immunology, (2004), 5209-5218	
		VERMAELEN, KARIM Y, et al., "Matrix Metalloproteinase-9-Mediated Dendritic Cell Recruitment into the Airways Is a Critical Step in a Mouse Model of Asthma", The Journal of Immunology, (2003), 1016-1022	
		WESTERMARCK, JUKKA, et al., "Regulation of Matrix Metalloproteinase Expression in Tumor Invasion", FASEB Journal, 13(8), (May 1999), 781-792	
		ZHANG, KUNYAN, et al., "HIV-induced metalloproteinase processing of the chemokine stromal cell derived factor-1 causes neurodegeneration", Nature Neuroscience Vol 6, No. 10, (21 September 2003), 1064-1071	
		Application Serial No. PCT/US2006/019656, Int'l Preliminary Examination Report Mailed 02-20-09, 6 pgs.	

Examiner Signature	/Jason M. Nolan/	Date Considered	08/29/2011

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	548/90.CCLS.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/08/29 14:14
L2	144	549/90.CCLS.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/08/29 14:14
L3	172	514/430.CCLS.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/08/29 14:14
L4	295	L2 OR L3	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2011/08/29 14:14

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	123	549/90.CCLS.	USPAT; UPAD	OR	OFF	2011/08/29 14:17
L6	133	514/430.CCLS.	USPAT; UPAD	OR	OFF	2011/08/29 14:17
L7	242	L5 OR L6	USPAT; UPAD	OR	OFF	2011/08/29 14:17

8/ 29/ 2011 2:17:55 PM
C:\ Users\ jnolan\ Documents\ EAST\ Workspaces\ 13047605.wsp

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
13047605	LEE ET AL.
Examiner	**Art Unit**
JASON M NOLAN	1626

ORIGINAL		INTERNATIONAL CLASSIFICATION														
CLASS	SUBCLASS	CLAIMED									NON-CLAIMED					
514	430	A	6	1	K	31 / 38 (2006.0)										
CROSS REFERENCE(S)		C	0	7	D	331 / 02 (2006.01.01)										
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)															
549	90															

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	2	17	18												
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NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	20	
/JASON M NOLAN/ Primary Examiner.Art Unit 1626	08/29/2011	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	2	of	5

Complete if Known	
Application Number	13/047,605
Filing Date	November 19, 2007
First Named Inventor	Mijoon Lee
Art Unit	1626
Examiner Name	Joseph K. McKane
Attorney Docket Number	5006-004-CON

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No [1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-2,949,474	08/16/1960	Murdoch, Guy C., et al.	
		US-2,965,651	12/20/1960	Kosmin, Milton, et al.	
		US-3,222,326	12/07/1965	Brodoway, Nicolas	
		US-4,797,218	01/10/1989	Steinberg, David H., et al.	
		US-5,288,722	02/22/1994	Kishimoto, Shoji, et al.	
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		US-6,703,415	03/09/2004	Mobashery, S., et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document Country Code[3]-Number [4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T 6
		WO-2006125208A1	11/23/2006	Lee, M., et al.		☐
		WO-95/35275	12/28/1995	Miller, Andrew, et al.		☐
		WO-97/18231	05/22/1997	Collins, Douglas A., et al.		☐
		WO-98/33788	08/06/1998	Alpegiani, Marco, et al.		☐

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	3	of	5

Complete if Known	
Application Number	13/047,605
Filing Date	November 19, 2007
First Named Inventor	Mijoon Lee
Art Unit	1626
Examiner Name	Joseph K. McKane
Attorney Docket Number	5006-004-CON

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No [1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		"International Application Serial No. PCT/US06/19656 (Atty Ref 1319.018WO1), International Search Report mailed 10-02-06", 6 pgs	
		"International Application Serial No. PCT/US06/19656 (Atty Ref 1319.018WO1), Written Opinion mailed 10-02-06", 5 pgs	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	4	of	5

Complete if Known	
Application Number	13/047,605
Filing Date	November 19, 2007
First Named Inventor	Mijoon Lee
Art Unit	1626
Examiner Name	Joseph K. McKane
Attorney Docket Number	5006-004-CON

NON-PATENT LITERATURE DOCUMENTS

		FRIDMAN, R., et al., "Expression of human recombinant 72 kDa gelatinase and tissue inhibitor of metalloproteinase-2 (TIMP-2): characterization of complex and free enzyme", Biochemical Journal, 289(Pt 2), (January 15, 1993), 411-416	
		GREENWALD, R A., et al., "Thirty-six Years in the Clinic without an MMP Inhibitor: What Hath Collagenase Wrought?", Annals of the New York Academy of Sciences, 878, (June 1999), 412-419	
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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	13/047,605
				Filing Date	November 19, 2007
				First Named Inventor	Mijoon Lee
				Art Unit	1626
				Examiner Name	Joseph K. McKane
Sheet	5	of	5	Attorney Docket Number	5006-004-CON

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		NELSON, AMY R., et al., "Matrix Metalloproteinases: Biologic Activity and Clinical Implications", Journal of Clinical Oncology, 18(5), (March 1, 2000), 1135-1149	
		OLSON, MATTHEW W, "Characterization of the monomeric and dimeric forms of latent and active matrix metalloproteinase-9. Differential rates for activation by stromelysin 1", Journal of Biological Chemistry, 275(4), (January 28, 2000), 2661-2668	
		PYKE, C., et al., "Localization of messenger RNA for Mr 72,000 and 92,000 type IV collagenases in human skin cancers by in situ hybridization", Cancer Research, 52(5), (March 1, 1992), 1336-1341	
		SALO, TUULA, et al., "Purification and Characterization of a Murine Basement Membrane Collagen-degrading Enzyme Secreted by Metastatic Tumor Cells", Journal of Biological Chemistry, 258(5), (March 10, 1983), 3058-3063	
		SURYADEVARA, RADHIKA, et al., "Regulation fo Tissue Inhibitor of Metalloproteinase-1 by Astrocytes", GLIA 44, (2003), 47-56	
		TAMURA, Y., "Highly Selective and Orally Active Inhibitors of Type IV Collagenase (MMP-9 and MMP-2): N-Sulfonylamino Acid Derivatives", Journal of Medicinal Chemistry, 41(4), (February 12, 1998), 640-649	
		TOFT-HANSEN, HENRIK, et al., "Key Metalloproteinases Are Expressed by Specific Cell Types in Experimental Autoimmune Encephalomyelitis", The Journal of Immunology, (2004), 5209-5218	
		VERMAELEN, KARIM Y, et al., "Matrix Metalloproteinase-9-Mediated Dendritic Cell Recruitment into the Airways Is a Critical Step in a Mouse Model of Asthma", The Journal of Immunology, (2003), 1016-1022	
		WESTERMARCK, JUKKA, et al., "Regulation of Matrix Metalloproteinase Expression in Tumor Invasion", FASEB Journal, 13(8), (May 1999), 781-792	
		ZHANG, KUNYAN, et al., "HIV-induced metalloproteinase processing of the chemokine stromal cell derived factor-1 causes neurodegeneration", Nature Neuroscience Vol 6, No. 10, (21 September 2003), 1064-1071	
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Electronic Acknowledgement Receipt

EFS ID:	10533420
Application Number:	13047605
International Application Number:	
Confirmation Number:	7167
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Customer Number:	44163
Filer:	Michael Hans Haukaas/Angela Zwack
Filer Authorized By:	Michael Hans Haukaas
Attorney Docket Number:	5006-004-CON
Receipt Date:	15-JUL-2011
Filing Date:	14-MAR-2011
Time Stamp:	17:34:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		IDS.pdf	649516 cf93275c82a56192708e368515921837df8d d36d	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	1
	Information Disclosure Statement (IDS) Form (SB08)	2	5
Warnings:			
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	Total Files Size (in bytes):	649516	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Mijoon Lee et al.	Examiner:	Joseph K. McKane
Serial No.:	13/047,605	Art Unit:	1626
Filed:	March 14, 2011	Confirmation No.:	7167
Customer No.:	44163	Docket No.:	5006-004-CON
Title:	INHIBITORS OF MATRIX METALLOPROTEINASES		

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Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

In compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 et. seq., the referenced materials are brought to the attention of the Examiner for consideration in connection with the above-identified patent application. Applicants respectfully request that this Information Disclosure Statement be entered and the documents listed on the attached Form 1449 be considered by the Examiner and made of record. Pursuant to the provisions of MPEP 609, Applicants request that a copy of the 1449 forms, initialed as being considered by the Examiner, be returned to the Applicants with the next official communication.

Copies of foreign patent documents and non-patent literature cited in the attached 1449 forms were previously submitted in parent application number 11/914,933, now U.S. Patent No. 7,928,127, and are therefore not submitted herewith. If there are any questions the Examiner is invited to contact the undersigned.

No fees are believed to be necessary as this IDS is being filed before the mailing of a first action on the merits in accordance with 37 C.F.R. § 1.97(b)(3). If any fees are required the Commissioner is authorized to deduct the necessary fees from Deposit Account No. 50-3141 and is requested to notify us of the same.

Respectfully submitted,

Dated: July 15, 2011

By /Michael Haukaas/

Michael Haukaas, Reg. No. 57,111
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/047,605	03/14/2011	1614	597	5006-004-CON	1	1

CONFIRMATION NO. 7167

UPDATED FILING RECEIPT

44163
Clise, Billion & Cyr, P.A.
605 U.S. Highway 169
Suite 300
Plymouth, MN 55441

OC000000048068326

Date Mailed: 06/08/2011

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Mijoon Lee, Mishawaka, IN;
Masahiro Ikejiri, Osaka, JAPAN;
Mayland Chang, Granger, IN;
Rafael Fridman, West Bloomfield, MI;
Shahriar Mobashery, Granger, IN;

Assignment For Published Patent Application

NOTRE DAME UNIVERSITY, Notre Dame, IN
WAYNE STATE UNIVERSITY, Detroit, MI

Power of Attorney: The patent practitioners associated with Customer Number 21186

Domestic Priority data as claimed by applicant

This application is a CON of 11/914,933 07/31/2008 PAT 7,928,127
which is a 371 of PCT/US06/19656 05/19/2006 *
which claims benefit of 60/682,385 05/19/2005
and claims benefit of 60/743,467 03/13/2006
(*)Data provided by applicant is not consistent with PTO records.

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 03/23/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/047,605**

Projected Publication Date: 09/15/2011

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

INHIBITORS OF MATRIX METALLOPROTEINASES

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/047,605

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	82		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	110		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	1 minus 20 =	*	x 26 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 110 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			135			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	597		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re. Appln of:	Mijoon Lee et al.
Serial No.:	13/047,605
Filing Date:	March 14, 2011
Title:	Inhibitors of Matrix Metalloproteinases
Attorney Docket No.:	5006-004-CON

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Please enter the following amendments prior to calculating the filing fee and examining this application.

Amendments to the claims begin on page 2.

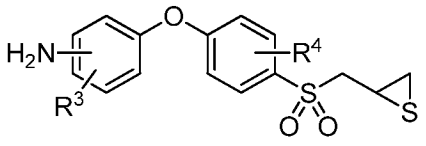
Remarks begin on page 5.

IN THE CLAIMS

Please amend the claims as follows:

1. (Cancelled)

2. (New) A compound of Formula (30):



(30)

wherein

R^3 and R^4 are each independently H, OH, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R^5)_2$, NR^5R^5, or $COOR^5$;

each R^5 is independently H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, $(C_6\text{-}C_{10})$aroyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_6)$alkyl, or a nitrogen protecting group;

any alkyl, amino, aryl, or heteroaryl is optionally substituted with 1 to about 5 $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, nitro, halo, amino, or hydroxy groups;

or a pharmaceutically acceptable salt thereof.

3. (New) The compound of claim 2 wherein R^3 is H.

4. (New) The compound of claim 2 wherein R^4 is H.

5. (New) The compound of claim 2 wherein both R^3 and R^4 are H.

6. (New) The compound of claim 2 wherein the position of the $-NH_2$ of Formula (30) is ortho or para to the oxygen linking the two aryl rings in Formula (30).

7. (New) The compound of claim 2 wherein the position of the $-NH_2$ of Formula (30) is ortho or meta to the oxygen linking the two aryl rings in Formula (30).

8. (New) The compound of claim 5 wherein the position of the $-NH_2$ of Formula (30) is ortho or para to the oxygen linking the two aryl rings in Formula (30).

9. (New) The compound of claim 5 wherein the position of the $-NH_2$ of Formula (30) is ortho or meta to the oxygen linking the two aryl rings in Formula (30).

10. (New) The compound of claim 2 wherein the compound is in the form of a pharmaceutically acceptable salt.

11. (New) The compound of claim 5 wherein the compound is in the form of a pharmaceutically acceptable salt.

12. (New) The pharmaceutically acceptable salt of claim 10 wherein the salt is derived from hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, acetic acid, propionic acid, succinic acid, glycolic acid, stearic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, pamoic acid, maleic acid, hydroxymaleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, sulfanilic acid, 2-acetoxybenzoic acid, fumaric acid, toluenesulfonic acid, methanesulfonic acid, ethane disulfonic acid, oxalic acid, or isethionic acid.

13. (New) A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or excipient.

14. (New) The composition of claim 13 wherein the compound is present at about 0.075% w/w to 20% w/w.

15. (New) The composition of claim 14 wherein the compound is present at about 0.2% w/w to 15% w/w.

16. (New) The composition of claim 13 wherein the composition is formulated for injection, oral administration, or topical administration.

17. (New) The composition of claim 16 wherein the composition is formulated for injection and the composition comprises a buffer.

18. (New) The composition of claim 16 wherein the composition is formulated for injection and the composition is an isotonic sterile injectable preparation.

19. (New) The composition of claim 16 wherein the composition is formulated for injection and the composition has a pH of about 7 to 10.

20. (New) The composition of claim 16 wherein the composition is formulated for oral administration and the composition is a tablet, troche, capsule, lozenge, emulsion, aqueous or oil suspension, dispersible powder or granule, syrup, or elixir.

21. (New) The composition of claim 16 wherein the composition is formulated for topical administration and composition is an ointment or cream.

REMARKS

This amendment is being filed prior to examination of this application. Claim 1 is cancelled and claims 2-21 are added. Accordingly, claims 2-21 are pending. Entry of the above amendment prior to calculating the filing fee is requested.

Support for claims 2-9 can be found at least at page 84, line 24 to page 88, line 6, and in particular, Scheme 10 at page 86 (compound 30). Support for claims 10-12 can be found at least at page 13, lines 1-14. Support for claim 13 can be found at least at page 39, lines 27-28. Support for claims 14-15 can be found at least at page 41, lines 12-15. Support for claim 16 can be found at least at page 39, lines 29-30; page 40, lines 25-26; page 41, lines 10-11; and page 44, lines 25-26. Support for claim 17 can be found at least at page 46, line 14. Support for claim 18 can be found at least at page 39, lines 29-31; at page 44, lines 25-26; and at page 45, line 2. Support for claim 19 can be found at least at page 40, lines 6-7. Support for claim 20 can be found at least at page 42, lines 24-25. Support for claim 21 can be found at least at page 41, line 11. Accordingly, no new matter has been added.

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to telephone Applicants' attorney at (763) 587-7082 to facilitate prosecution of this application.

It is believed that no fees are due in connection with the filing of this response. However, if any other fees are due, please apply them to Deposit Account No 50-3141 and reference attorney docket number 5006-004-CON.

Respectfully submitted,

Clise, Billion & Cyr, P.A.
Customer Number 44163
605 U.S. Highway 169 North, Suite 300
Plymouth, MN 55441
Telephone: (763) 587-7082

Date: June 8, 2011

By: / Michael Haukaas /

Michael H. Haukaas
Reg. No. 57,111

Electronic Acknowledgement Receipt

EFS ID:	10259685
Application Number:	13047605
International Application Number:	
Confirmation Number:	7167
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Customer Number:	44163
Filer:	Michael Hans Haukaas/Angela Zwack
Filer Authorized By:	Michael Hans Haukaas
Attorney Docket Number:	5006-004-CON
Receipt Date:	08-JUN-2011
Filing Date:	14-MAR-2011
Time Stamp:	14:46:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		5006-004-CONPreliminaryAmendment.pdf	520995 4f681d212cdfdf0ff1883d4bead6b7041368b4ff	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	5
Warnings:			
Information:			
	Total Files Size (in bytes):	520995	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/047,605	03/14/2011	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☒ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☒ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 06/08/2011

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 20	Minus	** 20	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	* 2	Minus	***3	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ROBERT SHERMAN/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re. Appln of:	Mijoon Lee et al.
Serial No.:	13/047,605
Filing Date:	March 14, 2011
Title:	INHIBITORS OF MATRIX METALLOPROTEINASES
Attorney Docket No.:	5006-004-CON

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

In response to the Notice to File Corrected Application Papers mailed March 28, 2011, submitted herewith are Replacement Drawing Sheets for FIGs. 3A and 4A-4E.

The application is now in proper order and in condition for examination. If any additional fee is required for entry of this paper, the Commissioner is authorized to charge our Deposit Account No. 50-3141 and is requested to notify us of the same.

Respectfully submitted,

Dated: May 31, 2011

By /Michael Haukaas/

Michael Haukaas, Reg. No. 57,111
Attorney for Applicants
Customer No. 44163
Clise, Billion & Cyr, P.A.
Telephone: (763) 587-7082

Electronic Acknowledgement Receipt

EFS ID:	10200545
Application Number:	13047605
International Application Number:	
Confirmation Number:	7167
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Customer Number:	44163
Filer:	Michael Hans Haukaas/Angela Zwack
Filer Authorized By:	Michael Hans Haukaas
Attorney Docket Number:	5006-004-CON
Receipt Date:	31-MAY-2011
Filing Date:	14-MAR-2011
Time Stamp:	18:34:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Drawings-only black and white line drawings	ReplacementDrawingSheets.pdf	418093 31fe285ff2ecc8b9217facdb1f2666a9e6b18e3d	no	6

Warnings:	
Information:	

2	Applicant Response to Pre-Exam Formalities Notice	ResponsetoNoticetoFileCorrectedAppPapers.pdf	508529 9ee11603317b452baef92053e66e17434ff3e441	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	926622

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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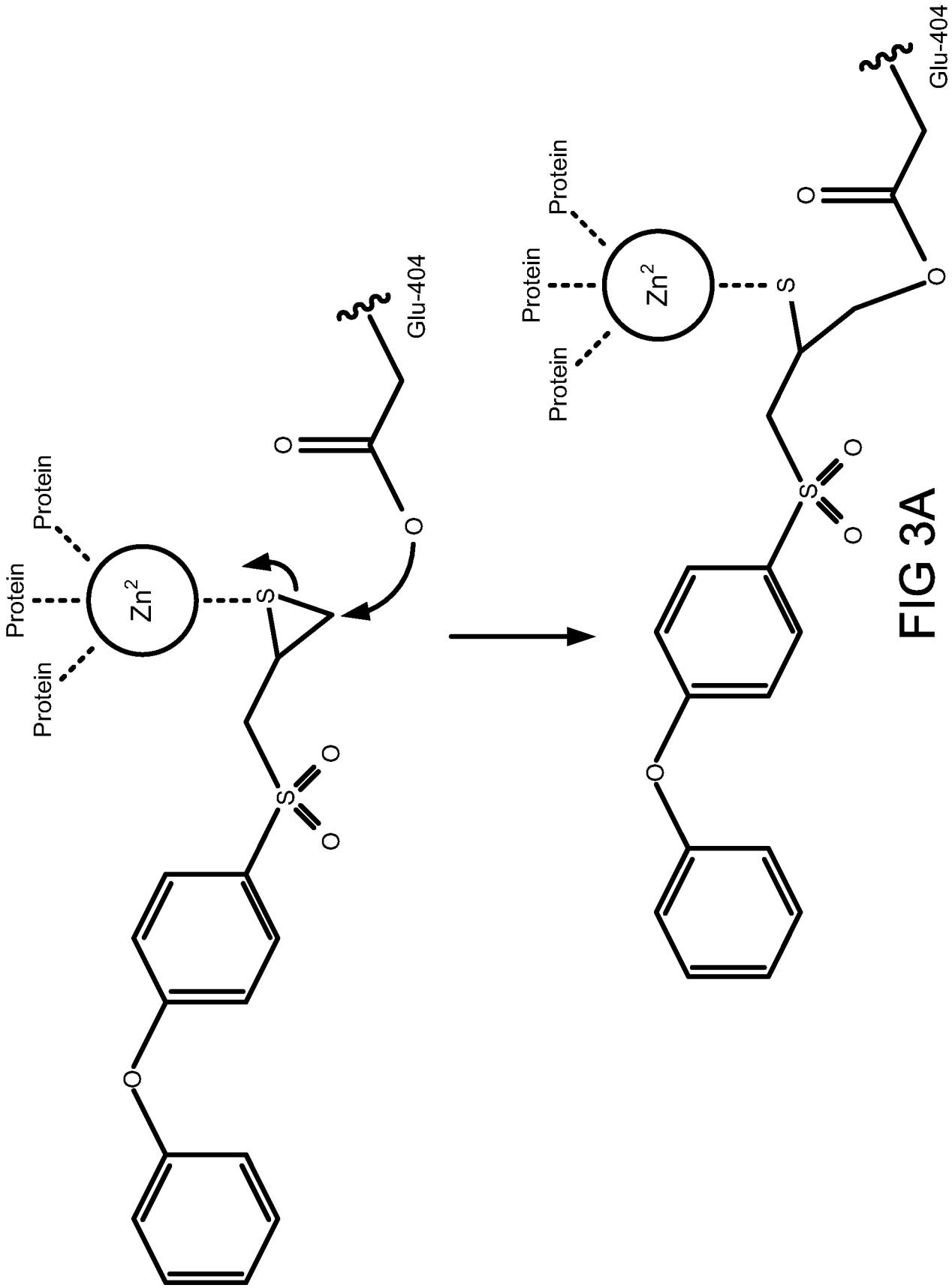
National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.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Protein
Zn2
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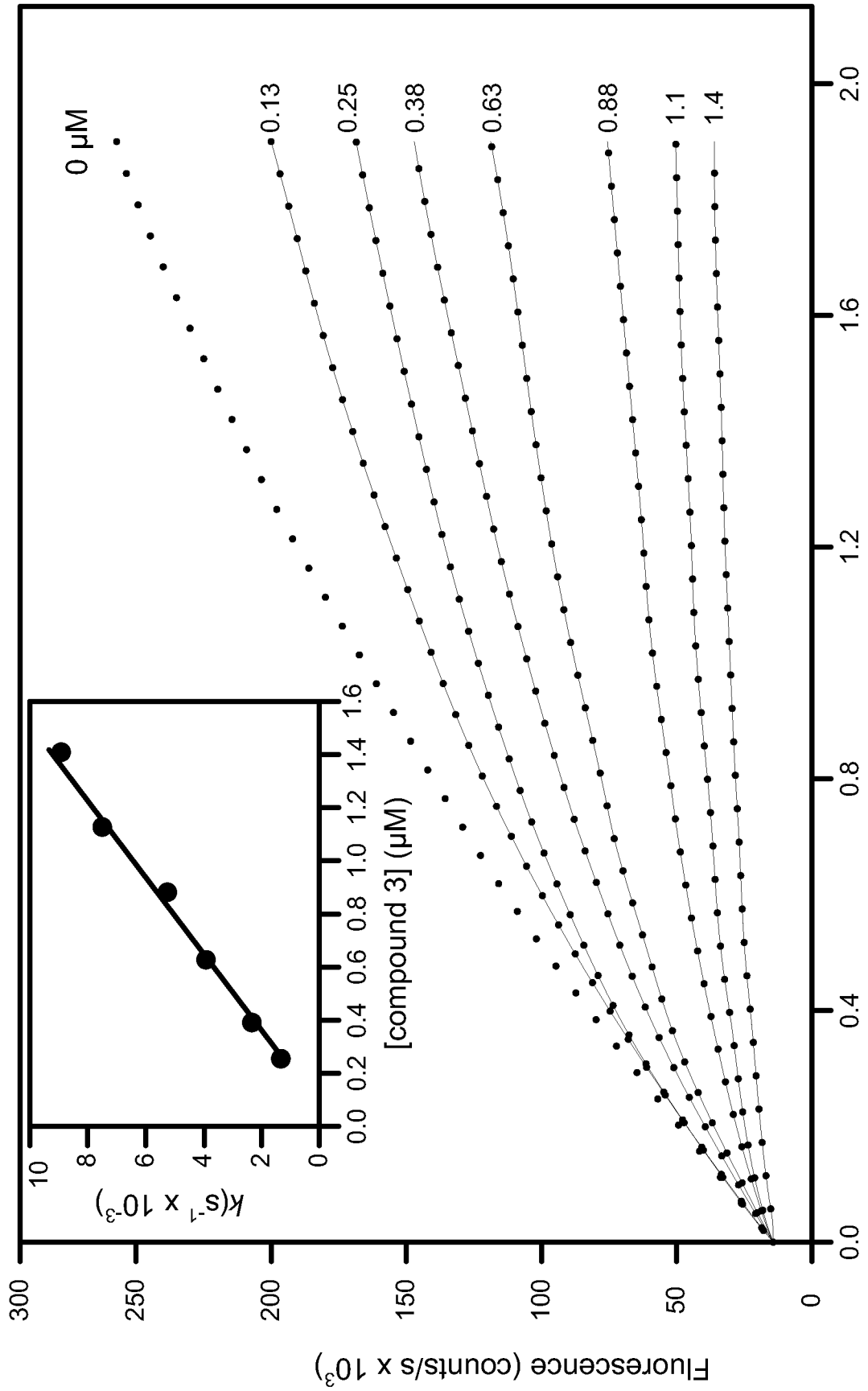
S
O
O
O
O
O
Glu-404
Glu-404

FIG 3A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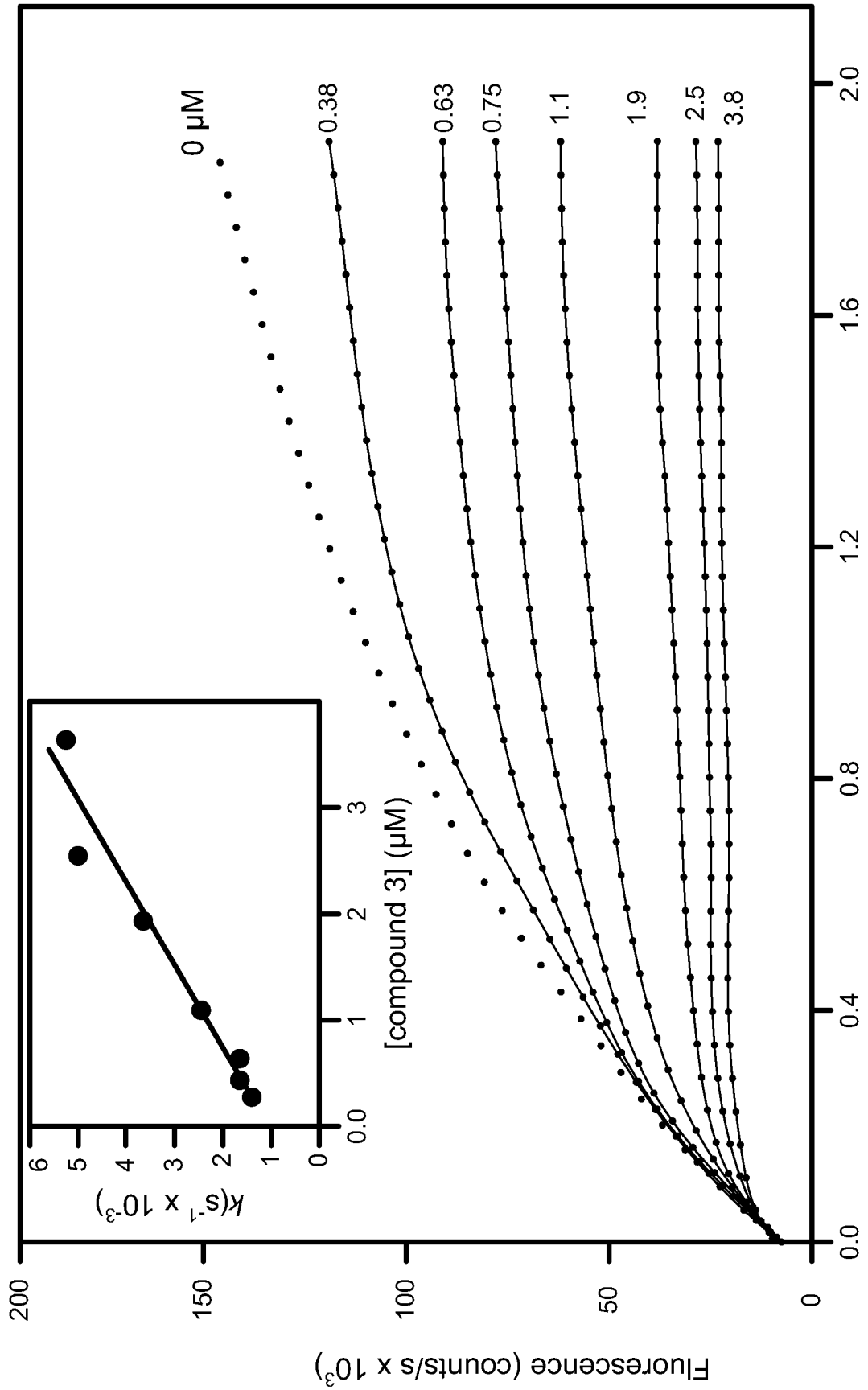
0
50
100
150
200
250
300
0.0
0.4
0.8
1.2
1.6
2.0
0 µM
0.13
0.25
0.38
0.63
0.88
1.1
1.4
k(s⁻¹ x 10⁻³)
0
2
4
6
8
10
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
[compound 3] (µM)

FIG 4A


Fluorescence (counts/s x 10³)
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100
150
200
0.0
0.4
0.8
1.2
1.6
2.0
0 µM
0.38
0.63
0.75
1.1
1.9
2.5
3.8
[compound 3] (µM)
0.0
1
2
3
k(s⁻¹ x 10⁻³)
0
1
2
3
4
5
6

FIG 4B

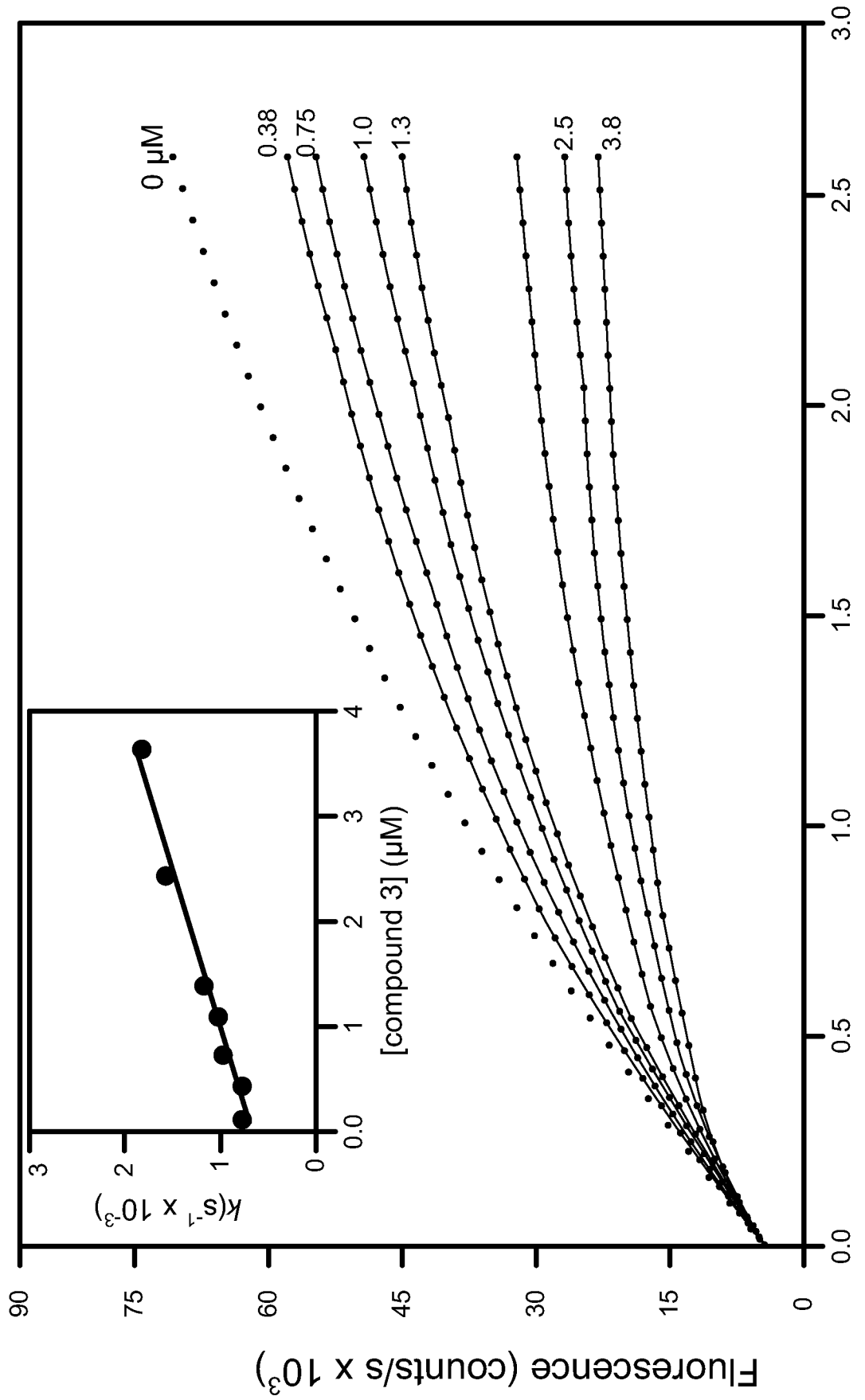
Fluorescence (counts/s x 10³)
0
15
30
45
60
75
90
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0 µM
0.38
0.75
1.0
1.3
2.5
3.8
k(s⁻¹ x 10⁻³)
0
1
2
3
0.0
1
2
3
4
[compound 3] (µM)

FIG 4C

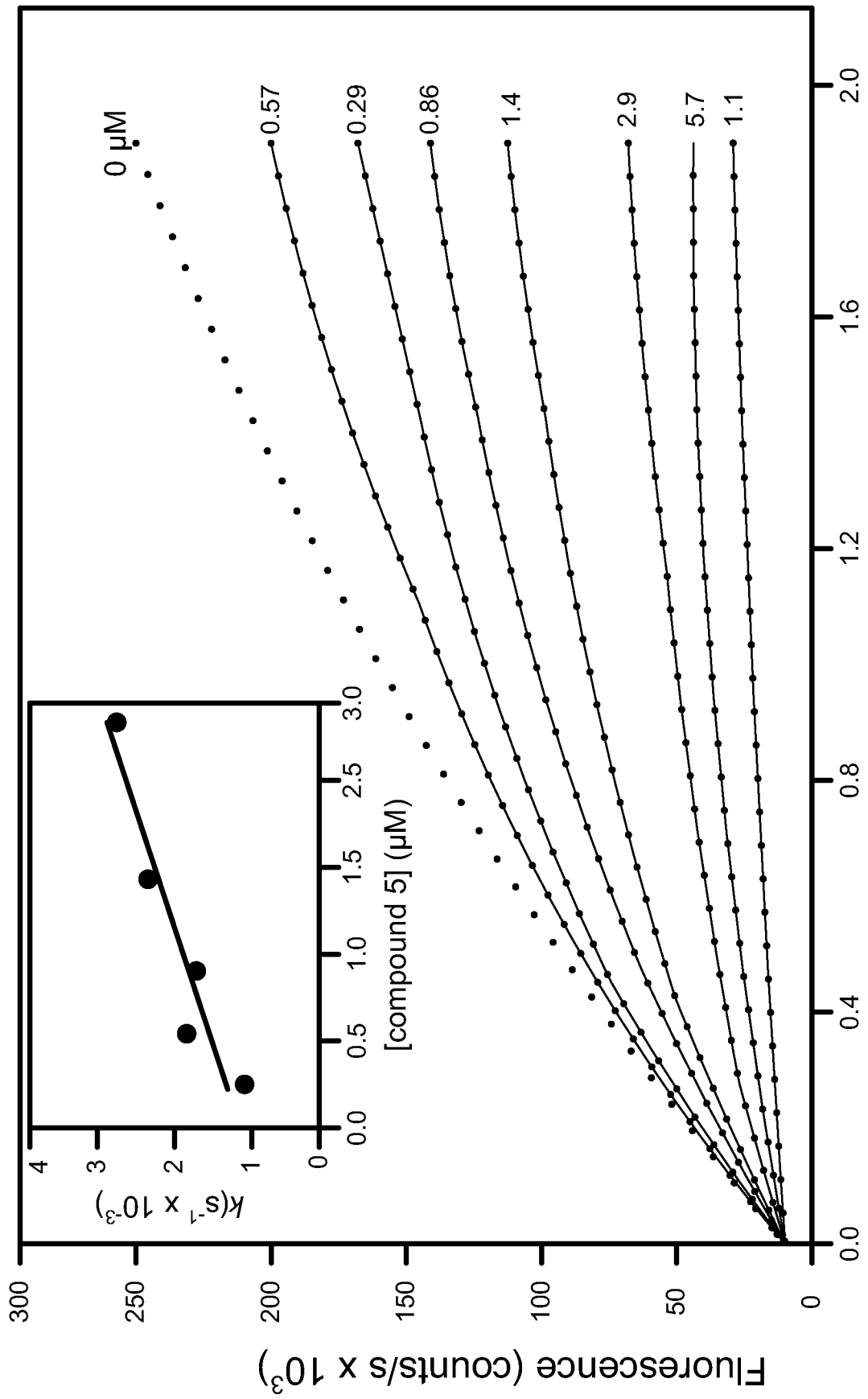
Fluorescence (counts/s x 10³)
0
50
100
150
200
250
300
0.0
0.4
0.8
1.2
1.6
2.0
0 µM
0.57
0.29
0.86
1.4
2.9
5.7
1.1
k(s⁻¹ x 10⁻³)
0
1
2
3
4
0.0
0.5
1.0
1.5
2.5
3.0
[compound 5] (µM)

FIG 4D

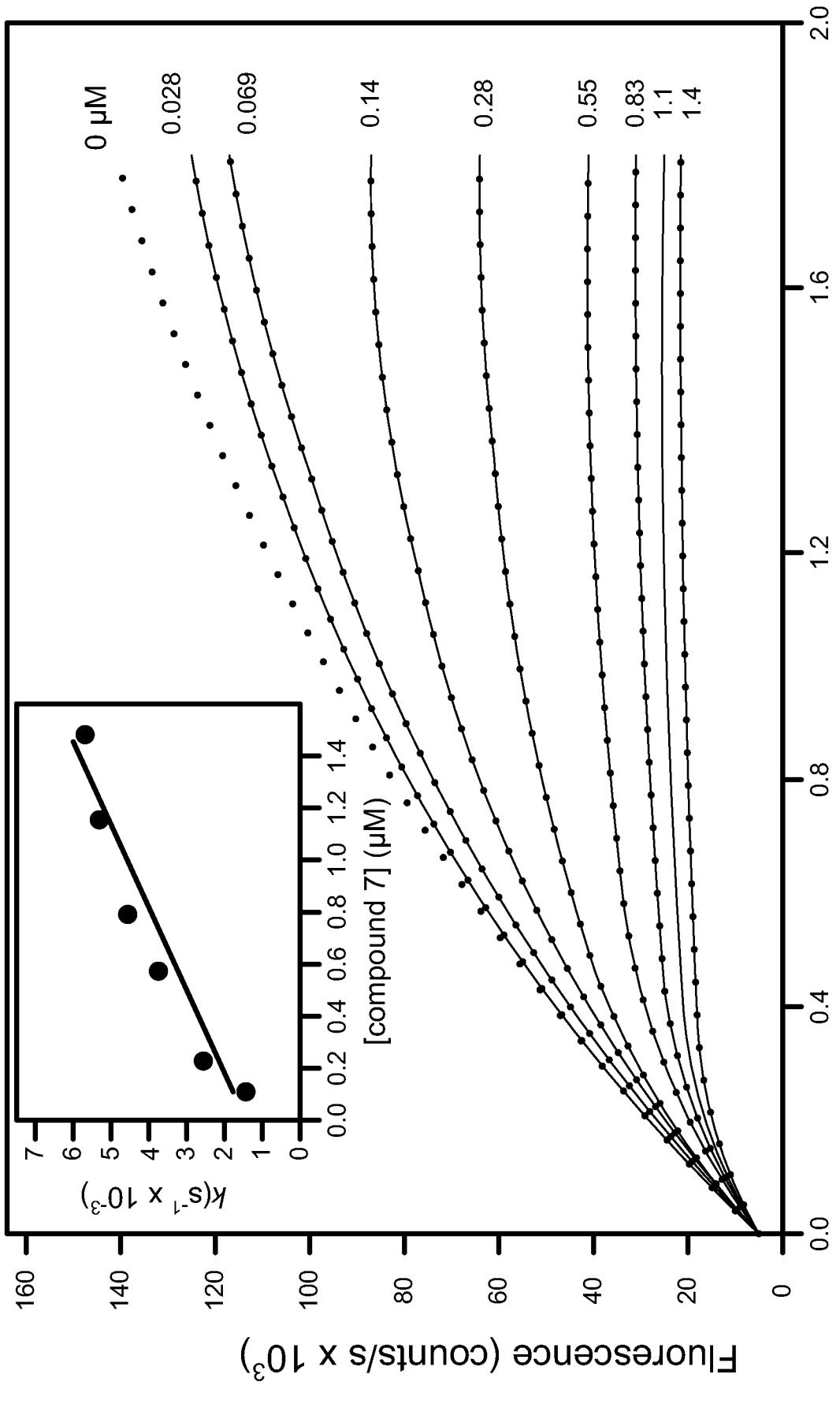
Fluorescence (counts/s x 10³)
0
20
40
60
80
100
120
140
160
0.0
0.4
0.8
1.2
1.6
2.0
0 µM
0.028
0.069
0.14
0.28
0.55
0.83
1.1
1.4
k(s⁻¹ x 10⁻³)
0
1
2
3
4
5
6
7
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
[compound 7] (µM)

FIG 4E

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/047,605

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	82		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	110		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	1 minus 20 =	*	x 26 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 110 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			135			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	597		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/047,605	03/14/2011	Mijoon Lee	5006-004-CON

CONFIRMATION NO. 7167

44163
Clise, Billion & Cyr, P.A.
605 U.S. Highway 169
Suite 300
Plymouth, MN 55441

FORMALITIES LETTER

OC000000046754027

Date Mailed: 03/28/2011

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - Numbers, letters, and reference characters on the drawings must measure at least 0.32 cm (1/8 inch) in height. See Figure(s) 3A, 4A-4E.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/fly/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/047,605	03/14/2011	1614	597	5006-004-CON	1	1

CONFIRMATION NO. 7167

44163
Clise, Billion & Cyr, P.A.
605 U.S. Highway 169
Suite 300
Plymouth, MN 55441

FILING RECEIPT

Date Mailed: 03/28/2011

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Mijoon Lee, Mishawaka, IN;
Masahiro Ikejiri, Osaka, JAPAN;
Mayland Chang, Granger, IN;
Rafael Fridman, West Bloomfield, MI;
Shahriar Mobashery, Granger, IN;

Assignment For Published Patent Application

NOTRE DAME UNIVERSITY, Notre Dame, IN
WAYNE STATE UNIVERSITY, Detroit, MI

Power of Attorney: The patent practitioners associated with Customer Number 21186

Domestic Priority data as claimed by applicant

This application is a CON of 11/914,933 07/31/2008
which is a 371 of PCT/US06/19656 05/19/2006 *
which claims benefit of 60/682,385 05/19/2005
and claims benefit of 60/743,467 03/13/2006
(*)Data provided by applicant is not consistent with PTO records.

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 03/23/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/047,605**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

INHIBITORS OF MATRIX METALLOPROTEINASES

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

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SCHWEGMAN ■ LUNDBERG ■ WOESSNER

United States Patent Application

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: **INHIBITORS OF MATRIX METALLOPROTEINASES**,

the specification of which was filed on November 19, 2007 as application serial no. 11/914,933.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability of this application in accordance with 37 C.F.R. § 1.56 (attached hereto). I also acknowledge my duty to disclose all information known to be material to patentability which became available between a filing date of a prior application and the national or PCT international filing date in the event this is a Continuation-In-Part application in accordance with 37 C.F.R. § 1.63(e).

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

No such claim for priority is being made at this time.

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Number	Filing Date
60743467	March 13, 2006

I hereby claim the benefit under 35 U.S.C. § 120 or 365(c) of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. § 1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Number	Filing Date	Status
PCTUS2006019656	May 19, 2006	Pending

I hereby appoint the attorneys associated with the customer number listed below to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

Customer Number: 21186

I hereby authorize them to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/organization/who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Schwegman, Lundberg & Woessner, P.A. to the contrary.

Please direct all correspondence in this case to **Schwegman, Lundberg & Woessner, P.A. at** the address indicated below:
Customer Number. 21186

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of joint inventor number 1 : **Mijoon Lee**
Citizenship: **Republic of Korea** Residence: **Seoul, Korea Republic of Korea**
Post Office Address: 537-19 Yeonhui-1-dong
Seodaemun-gu
Seoul, Korea
Republic of Korea

Signature: _____ Date: 06-26-08
Mijoon Lee

Full Name of joint inventor number 2 : **Masahiro Ikejiri**
Citizenship: **Japan** Residence: **Sanuki City, Kagawa Prefecture Japan**
Post Office Address: 4346-4-B104 Shido
Sanuki City, Kagawa Prefecture 769-2101
Japan

Signature: _____ Date: _____
Masahiro Ikejiri

Full Name of joint inventor number 3 : **Mayland Chang**
Citizenship: **United States of America** Residence: **Granger, IN**
Post Office Address: 14542 Heatherton Drive
Granger, IN 46530

Signature: _____ Date: 6/26/08
Mayland Chang

X Additional inventors are being named on separately numbered sheets, attached hereto.

Full Name of joint inventor number 4 : **Rafael Fridman**
Citizenship: **United States of America** Residence: **West Bloomfield, MI**
Post Office Address: 4926 Hardwoods Dr.
West Bloomfield, MI 48323

Signature: _____ Date: _____
Rafael Fridman

Full Name of joint inventor number 5 : **Shahriar Mobashery**
Citizenship: **United States of America** Residence: **Granger, IN**
Post Office Address: 14542 Heatherton Drive
Granger, IN 46530

Signature: _____ Date: 6/26/08
Shahriar Mobashery

§ 1.56 Duty to disclose information material to patentability.

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

(1) Each inventor named in the application:

(2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.

SCHWEGMAN ■ LUNDBERG ■ WOESSNER

United States Patent Application

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: **INHIBITORS OF MATRIX METALLOPROTEINASES**,

the specification of which is attached hereto.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability of this application in accordance with 37 C.F.R. § 1.56 (attached hereto). I also acknowledge my duty to disclose all information known to be material to patentability which became available between a filing date of a prior application and the national or PCT international filing date in the event this is a Continuation-In-Part application in accordance with 37 C.F.R. § 1.63(e).

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

No such claim for priority is being made at this time.

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Number	Filing Date
60/743,467	March 13, 2006

I hereby claim the benefit under 35 U.S.C. § 120 or 365(c) of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. § 1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Number	Filing Date	Status
PCT/US2006/019656	May 19, 2006	Published November 23, 2006, as WO 2006/125208

I hereby appoint the attorneys associated with the customer number listed below to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

Customer Number: 21186

I hereby authorize them to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/organization/who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Schwegman, Lundberg & Woessner, P.A. to the contrary.

Please direct all correspondence in this case to **Schwegman, Lundberg & Woessner, P.A.** at the address indicated below:
Customer Number. 21186

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of joint inventor number 1 : **Mijoon Lee**
Citizenship: **Republic of Korea** Residence: **Seoul, Korea Republic of Korea**
Post Office Address: 537-19 Yeonhui-1-dong
Seodaemun-gu
Seoul, Korea
Republic of Korea

Signature: _____ Date: _____
Mijoon Lee

Full Name of joint inventor number 2 : **Masahiro Ikejiri**
Citizenship: **Japan** Residence: **Osaka, Japan**
Post Office Address: 2-16-26-304 Shinke
Tondabayashi, Osaka 584-0085
Japan

Signature: Masahiro Ikejiri Date: July 14, 2008
Masahiro Ikejiri

Full Name of joint inventor number 3 : **Mayland Chang**
Citizenship: **United States of America** Residence: **Granger, IN**
Post Office Address: 14542 Heatherton Drive
Granger, IN 46530

Signature: _____ Date: _____
Mayland Chang

X Additional inventors are being named on separately numbered sheets, attached hereto.

Full Name of joint inventor number 4 : **Rafael Fridman**
Citizenship: **United States of America** Residence: **West Bloomfield, MI**
Post Office Address: 4926 Hardwoods Dr.
West Bloomfield, MI 48323

Signature: Fridman Date: 7/28/08
Rafael Fridman

Full Name of joint inventor number 5 : **Shahriar Mobashery**
Citizenship: **United States of America** Residence: **Granger, IN**
Post Office Address: 14542 Heatherton Drive
Granger, IN 46530

Signature: _____ Date: _____
Shahriar Mobashery

§ 1.56 Duty to disclose information material to patentability.

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

(1) Each inventor named in the application:

(2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.

INHIBITORS OF MATRIX METALLOPROTEINASES

RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 11/914,933, with a filing date of July 31, 2008, which is a U.S. National Stage Application under 35 U.S.C. 371 of International Application No. PCT/US2006/019656, filed May 19, 2006 and published in English as WO 06/125208 on November 23, 2006, which claims the benefit under 35 U.S.C. 119(e) of both U.S. Provisional Application No. 60/682,385, filed May 19, 2005, and U.S. Provisional Application No. 60/743,467, filed March 13, 2006, which applications and publication are incorporated herein by reference.

GOVERNMENT FUNDING

This invention was made with Government support under grant NCI-CA100475 awarded by the National Institutes of Health. The United States Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

Specific interactions of cells within the extracellular matrix are critical for the normal function of organisms. Alterations of the extracellular matrix are carried out by a family of zinc-dependent endopeptidases called matrix metalloproteinases (MMPs). The alterations are carried out in various cellular processes such as organ development, ovulation, fetus implantation in the uterus, embryogenesis, wound healing, and angiogenesis.

Twenty-six different MMPs are currently known. MMPs consist of five major groups of enzymes: gelatinases, collagenases, stromelysins, membrane-type MMPs, and matrilysins. The activities of MMPs in normal tissue functions are strictly regulated by a series of complicated zymogen activation processes and inhibition by protein tissue inhibitors for matrix metalloproteinases (TIMPs).

Excessive MMP activity, when the regulation process fails, has been implicated in cancer growth, tumor metastasis, angiogenesis in tumors, arthritis and connective tissue diseases, cardiovascular disease, inflammation, autoimmune diseases, respiratory diseases, and neurological disorders.

Increased levels of activity for the human gelatinases MMP-2 and MMP-9 have been implicated in several metabolic processes, for example, cancer, tumor metastasis, angiogenesis in tumors, arthritis and connective tissue diseases, cardiovascular disease, inflammation, autoimmune diseases, respiratory diseases, and neurological disorders. Gelatinases are also of particular importance for both female ovulation and implantation of zygotes in the womb (for example, see U.S. Patent No. 6.703,415). As a result, selective inhibitors of MMPs are highly sought.

Several competitive inhibitors of MMPs are currently known. These inhibitors of MMPs take advantage of chelation to the active site zinc for inhibition of activity. Because of this general property, these competitive inhibitors for MMPs are often toxic to the host, which has been a major impediment in their clinical use.

Accordingly, there is a current need for new inhibitors of MMPs. Such inhibitors would be useful to treat or prevent cancer, tumor metastasis, angiogenesis in tumors, contraception, arthritis and connective tissue diseases, cardiovascular disease, inflammation, autoimmune diseases, respiratory diseases, or neurological disorders. Also needed are inhibitors that exhibit selectivity for one or more specific MMPs. Such inhibitors will preferably not include negative long-term side-effects.

SUMMARY OF THE INVENTION

The present invention relates to compounds of formulas I-IX, compositions that include compounds of formulas I-IX, methods of their preparation, and methods of their use. The pharmaceutical composition can include other therapeutic agents that are compatible with the compound of the invention. The compounds can be used in medical therapy, for example to treat cancer, angiogenesis, cardiovascular disease, neurological disease, eye disease, inflammation, autoimmune disease, and

for regulating contraception, and other conditions that are affected by the regulation of MMPs.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the invention may be best understood by referring to the following detailed description and the accompanying drawings which illustrate certain embodiments.

FIG. 1 is a schematic illustration wherein a coordinated thiirane moiety is predisposed to nucleophilic attack by the active site glutamate (Glu-404 in MMP-2) in MMP enzymes, a process that leads to covalent modification of the enzyme and the attendant loss of activity.

FIG. 2 illustrates a stereoview of compound **1.3** bound to the active site of MMP-2. A Connolly solvent-accessible surface is constructed in the active site (shown in green), while the protein is rendered in purple. Compound **1.3**, along with the active site Glu-404 and the three histidines that are coordinated to the catalytic zinc are shown in capped-stick representation, colored according to atom types (yellow, red, blue, and white for S, O, N, and C, respectively). The zinc ion is shown as an orange sphere. The white arrow points to the S1' pocket. The side chain hydroxyl of Thr428 is expected to hydrogen bond (2.8 Å) to the ester carbonyl of compound **1.3**. The methyl group of compound **1.3** is located near Leu399, Leu420, and Phe431, resulting in favorable hydrophobic interactions that would likely contribute to the overall binding affinity.

FIG. 3 illustrates a schematic depiction of the mechanism of action of inhibitor **2.1**. (*A*) Coordination of the thiirane with the zinc ion is a prerequisite for the inhibition process. (*B*) Stereoview of the computational model for the non-covalent binding of inhibitor **2.1** in the active site of MMP-2. The active site of the enzyme is depicted as a Connolly surface in green. The active site zinc ion is depicted as an orange sphere, with the three coordinating histidine residues depicted in capped sticks. Inhibitor **2.1** (in capped sticks and colored according to atom types) is shown coordinated to the active site zinc ion via the thiirane sulfur. The loop that constitutes the S_1' subsite of the enzyme is drawn as a tube in purple, so the

terminal phenyl group of the inhibitor is visible. The site of structure elaboration in arriving at molecules **2.2-2.7** is indicated by the white arrow.

FIG. 4 illustrates slow-binding MMP inhibition by synthetic inhibitors of Example 2. Progress curves were obtained by monitoring the fluorescence of the synthetic substrate MOCAcPLGLA$_2$pr(Dnp)AR-NH$_2$ (7 μM) in solutions of buffer R containing 0.5-1 nM of MMP-2 (*A*), MMP-9 (*B*) and MMP-14$_{cat}$ (*C*) and inhibitor **2.3**, as described under the Experimental Procedures section of Example 2. Inhibition of MMP-2 (0.5-1 nM) activity by compounds **2.5** (*D*) and **2.7** (*E*), under the same conditions. The *lines* represent nonlinear least-squares fits of the data to Equation 1, using the program Scientist. *Insets*, nonlinear least squares fits of the apparent rate constant *k* variation with inhibitor concentration to Equation 2, describing a one-step association mechanism. In FIG. 4, compounds 3, 5, and 7 refer to compounds **2.3**, **2.5**, and **2.7** of Example 2, respectively.

FIG. 5 illustrates equilibrium dialysis of MMP:inhibitor complexes. MMP-2 (*A*), MMP-9 (*B*) and MMP-14 (*C*) (10 nM each) were incubated in the absence (■) and presence of either compound **2.3** (▨), **2.5** (▩) and **2.7** (▩) (1 mM each), in buffer R, for 3 hours, at room temperature. The remaining MMP activity was monitored with MOCAcPLGLA$_2$pr(Dnp)AR-NH$_2$ (0 hours). Part of the reaction mixtures was subjected to extensive dialysis *against* buffer R, containing no dimethyl sulfoxide, as described under "Experimental Procedures" of Example 2, and the remaining solution was placed on a rotator. After 48 hours, the enzymatic activity in both the non-dialyzed (48 hours w/o dialysis) and dialyzed (48 hours w/dialysis) solutions was measured with the aforementioned fluorogenic substrate.

FIG. 6 illustrates that GM6001 (hydroxamate inhibitor), but not inhibitor **2.3**, enhances MT1-MMP-dependent pro-MMP-2 activation by BS-C-1 cells. BS-C-1 cells, co-infected to express MT1-MMP, as described under the Experimental Procedures of Example 2, were incubated for 16 hours with serum-free DMEM medium containing the indicated inhibitor concentrations. After rinsing, the cells were incubated for 5 hours with serum-free DMEM supplemented with recombinant pro-MMP-2 (10 nM). (*A*) The media were collected and analyzed by gelatin zymography. L, I and A refer to the latent, intermediate and active forms of MMP-

2, respectively. (*B*) The cells were lysed and the lysates were subjected to immunoblot analysis using the anti-MT1-MMP polyclonal antibody 815. The 60- and 57-kDa forms represent pro- and active MT1-MMP, respectively.

FIG. 7 illustrates inhibition of HT1080 cell motility and invasion by inhibitor **2.3**. *A-B*: Confluent cultures of HT1080 cells in 6-well plates were treated with mitomycin C (25 μg/ml) in serum-free DMEM media for 30 minutes. Scratch wounds were made on the monolayers and the wounded cultures were then incubated with serum-free DMEM supplemented without or with various amounts of inhibitor **2.3** (0-20 μM) for up to 20 hours. At each time period, the cultures were photographed (*A*) and the width of the scratch wound was measured as described under the Experimental Procedures section of Example 2. (*C*): HT1080 cells were seeded in 8-μm pore Transwell filters coated with Matrigel (50 μg/filter) in the presence or absence of inhibitor **2.3** (0.1-10 μM). The number of cells that invaded to the lower side of the filter was counted in three representative fields. Each value represents the mean ± SE of four independent determinations. $* P <$ 0.05, and $* P < 0.001$ when tested against the control using Tukey-Kramer Multiple Comparisons Test ($P = 0.004$ by ANOVA). In FIG. 7, inhibitor 3 refers to compound **2.3** of Example 2.

FIG. 8 illustrates specific compounds according to various embodiments of the invention. These compounds have been prepared according to the methods described herein.

FIG. 9 illustrates certain specific and general compounds of the invention, according to various embodiments.

DETAILED DESCRIPTION

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures, formulas, and Examples. While the invention will be described in conjunction with the enumerated claims, it will be understood that they are not intended to limit the invention to those claims. On the contrary, the invention is intended to cover all

alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

The present invention relates to compounds of formulas I-IX, compositions that include compounds of formulas I-IX, methods of their preparation, and methods of their use. When describing the compounds and methods, the following terms have the following meanings, unless otherwise indicated.

Definitions

References in the specification to "one embodiment", "an embodiment", "an example embodiment", etc., indicate that the embodiment described may include a particular feature, structure, or characteristic, but every embodiment may not necessarily include that particular feature, structure, or characteristic. Moreover, such phrases are not necessarily referring to the same embodiment. Further, when a particular feature, structure, or characteristic is described in connection with an embodiment, it is submitted that it is within the knowledge of one skilled in the art to affect such feature, structure, or characteristic in connection with other embodiments whether or not explicitly described.

"Substituted" is intended to indicate that one or more hydrogens on a group indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Suitable indicated groups include, e.g., alkyl, alkenyl, alkylidenyl, alkenylidenyl, alkoxy, aryloxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, aroyl, acyloxy, aroyloxy, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyanato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle,

cycloalkyl or hydroxy. As would be readily understood by one skilled in the art, when a substituent is keto (i.e., =O) or thioxo (i.e., =S), or the like, then two hydrogen atoms on the substituted atom are replaced.

As used herein, the terms "optional" or "optionally" mean that the subsequently described event or condition may but need not occur, and that the description includes instances where the event or condition occurs and instances in which it does not. For example, "optionally substituted" means that the named substituent may be present but need not be present, and the description includes situations where the named substituent is included and situations where the named substituent is not included.

Specific values described for radicals, substituents, and ranges, as well as specific embodiments of the invention described herein, are for illustration only; they do not exclude other defined values or other values within defined ranges, as would be recognized by one skilled in the art.

As used herein, the term "alkyl" refers to a branched, unbranched, or cyclic hydrocarbon having, for example, from 1 to 12 carbon atoms, and often 1 to 6 carbon atoms. Examples include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (*n*-Pr, *n*-propyl, $-CH_2CH_2CH_3$), 2-propyl (*i*-Pr, *i*-propyl, $-CH(CH_3)_2$), 1-butyl (*n*-Bu, *n*-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (*s*-Bu, *s*-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, $-C(CH_3)_3$), 1-pentyl (*n*-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), and 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, hexyl, octyl, decyl, or dodecyl. The alkyl can be unsubstituted or substituted. The alkyl can also be optionally partially or

fully unsaturated. As such, the recitation of an alkyl group includes both alkenyl and alkynyl groups. The alkyl can be a monovalent hydrocarbon radical, as described and exemplified above, or it can be a divalent hydrocarbon radical (i.e., alkylene).

The alkyl can optionally be substituted with one or more alkyl, alkenyl, alkylidenyl, alkenylidenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxy. The alkyl can optionally be interrupted with one or more non-peroxide oxy (-O-), thio (-S-), imino (-N(H)-), methylene dioxy ($-OCH_2O-$), carbonyl (-C(=O)-), carboxy (-C(=O)O-), carbonyldioxy (-OC(=O)O-), carboxylato (-OC(=O)-), imine (C=NH), sulfinyl (SO) or sulfonyl (SO_2) groups.

The term "alkenyl" refers to a C_2-C_{12} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp^2 double bond. Examples include, but are not limited to: ethylene or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2\ CH_2CH_2CH_2CH=CH_2$). The alkenyl can be a movalent hydrocarbon radical, as described and exemplified above, or it can be a divalent hydrocarbon radical (i.e., alkenylene). An alkenyl group can be substituted as described for alkyl groups above.

The term "alkynyl" refers to a monoradical branched or unbranched hydrocarbon chain, having a point of complete unsaturation (i.e. a carbon-carbon, *sp* triple bond). In one embodiment, the alkynyl group can have from 2 to 10 carbon atoms, or 2 to 6 carbon atoms. In another embodiment, the alkynyl group can have

from 2 to 4 carbon atoms. This term is exemplified by groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1-octynyl, and the like. The alkynyl can be unsubstituted or substituted, as described above for alkyl groups.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like. The cycloalkyl can optionally be partially unsaturated, thereby providing a cycloalkenyl. The cycloalkyl group can be monovalent or divalent, and can be optionally substituted as described above for alkyl groups.

The term "alkoxy" refers to the group alkyl-O-, where alkyl is as defined herein. Preferred alkoxy groups include, e.g., methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like. Alkoxy groups can optionally be substituted as described above for alkyl groups.

As used herein, "aryl" refers to an aromatic hydrocarbon group derived from the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. The radical can be at a saturated or unsaturated carbon atom of the parent ring system. The aryl group itself can have from 6 to 18 carbon atoms (excluding substituents). The aryl group can have a single ring (e.g., phenyl) or multiple condensed (fused) rings, wherein at least one ring is aromatic (e.g., naphthyl, dihydrophenanthrenyl, fluorenyl, or anthryl). Typical aryl groups include, but are not limited to, radicals derived from benzene, naphthalene, anthracene, biphenyl, and the like. The aryl can be unsubstituted or optionally substituted, as described above for alkyl groups.

The term "halo" refers to fluoro, chloro, bromo, and iodo. Similarly, the term "halogen" refers to fluorine, chlorine, bromine, and iodine.

The term "haloalkyl" refers to alkyl as defined herein substituted by 1 or more halo groups as defined herein, which may be the same or different. In one embodiment, the haloalkyl can be substituted with 1, 2, 3, 4, or 5 halo groups. In

another embodiment, the haloalkyl can by substituted with 1, 2, or 3 halo groups. The term haloalkyl also include perfluoro-alkyl groups. Representative haloalkyl groups include, by way of example, trifluoromethyl, 3-fluorododecyl, 12,12,12-trifluorododecyl, 2-bromooctyl, 3-bromo-6-chloroheptyl, 1H,1H-perfluorooctyl, and the like.

The term "heteroaryl" is defined herein as a monocyclic, bicyclic, or tricyclic ring system containing one, two, or three aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring, and which can be unsubstituted or substituted, for example, with one or more, and in particular one to three, substituents, as described above in the definition of "substituted". Examples of heteroaryl groups include, but are not limited to, 2H-pyrrolyl, 3H-indolyl, 4H-quinolizinyl, acridinyl, benzo[b]thienyl, benzothiazolyl, β-carbolinyl, carbazolyl, chromenyl, cinnolinyl, dibenzo[b,d]furanyl, furazanyl, furyl, imidazolyl, imidizolyl, indazolyl, indolisinyl, indolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, perimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thianthrenyl, thiazolyl, thienyl, triazolyl, tetrazolyl, and xanthenyl. In one embodiment the term "heteroaryl" denotes a monocyclic aromatic ring containing five or six ring atoms containing carbon and 1, 2, 3, or 4 heteroatoms independently selected from non-peroxide oxygen, sulfur, and N(Z) wherein Z is absent or is H, O, alkyl, aryl, or (C_1-C_6)alkylaryl. In another embodiment heteroaryl denotes an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

The term "heterocycle" refers to a saturated or partially unsaturated ring system, containing at least one heteroatom selected from the group oxygen, nitrogen, and sulfur, and optionally substituted with one or more groups as defined herein under the term "substituted". A heterocycle can be a monocyclic, bicyclic, or tricyclic group containing one or more heteroatoms. A heterocycle group also can

contain an oxo group (=O) attached to the ring. Non-limiting examples of heterocycle groups include 1,3-dihydrobenzofuran, 1,3-dioxolane, 1,4-dioxane, 1,4-dithiane, 2*H*-pyran, 2-pyrazoline, 4*H*-pyran, chromanyl, imidazolidinyl, imidazolinyl, indolinyl, isochromanyl, isoindolinyl, morpholine, piperazinyl, piperidine, piperidyl, pyrazolidine, pyrazolidinyl, pyrazolinyl, pyrrolidine, pyrroline, quinuclidine, and thiomorpholine. Other heterocycles include those described by Paquette in Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; and in The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* **1960**, *82*, 5566.

The term "alkanoyl" or "acyl" refers to –C(=O)R, wherein R is an alkyl group as previously defined.

The term "aroyl" refers to –C(=O)Ar, wherein Ar is an aryl group as previously defined.

The term "alkoxycarbonyl" refers to –C(=O)OR, wherein R is an alkyl group as previously defined.

The term "acyloxy" refers to –O-C(=O)R, wherein R is an alkyl group as previously defined. Examples of acyloxy groups include, but are not limited to, acetoxy, propanoyloxy, butanoyloxy, and pentanoyloxy. Any alkyl group as defined above can be used to form an acyloxy group.

The term "amino" refers to $-NH_2$. The amino group can be optionally substituted as defined herein for the term "substituted". The term "alkylamino" refers to $-NR_2$, wherein at least one R is alkyl and the second R is alkyl or hydrogen. The term "acylamino" refers to N(R)C(=O)R, wherein each R is independently hydrogen, alkyl, or aryl.

As to any of the above groups, which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

One diastereomer of a compound disclosed herein may display superior properties or activity compared with another. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as described by Thomas J. Tucker, et al., *J. Med. Chem.* **1994**, *37*, 2437-2444. A chiral compound may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., as described by Mark A. Huffman, et al., *J. Org. Chem.* **1995**, *60*, 1590-1594.

Selected substituents within the compounds described herein are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry and organic chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an claim of the invention, the total number will be determined as set forth above.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Only stable compounds are contemplated herein.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to compounds described herein, wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, and alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include conventional non-toxic salts or quaternary ammonium salts of the parent compound formed, for example, from inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the compounds described herein can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, (1985), 1418, the disclosure of which is incorporated herein by reference.

As used herein, "treating" or "treat" includes preventing a pathologic condition from occurring (e.g. prophylaxis); inhibiting the pathologic condition or arresting its development; relieving a subject of the pathologic condition; and/or diminishing symptoms associated with the pathologic condition. "Treat," "treating" or "treatment" includes treating, reversing, preventing, ameliorating, or inhibiting an injury or disease-related condition or a symptom of an injury or disease-related condition.

As used herein, "contacting" refers to the act of touching, making contact, or of bringing into immediate proximity.

The term "therapeutically effective amount" or "effective amount" is intended to include an amount of a compound described herein, or an amount of the combination of compounds described herein, e.g., to treat or prevent a disease or disorder, or to treat the symptoms of a disease or disorder, typically in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay (*Adv. Enzyme Regul.*, **1984**, *22*, 27), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased activity, or some other beneficial effect of the combination compared with the individual components.

As used herein, a "therapeutic agent" is a compound that has biological activity against any of tumor metastasis, angiogenesis in tumors, cancer, arthritis and connective tissue diseases, cardiovascular disease, inflammation, autoimmune diseases, respiratory diseases, or neurological disorders. The therapeutic agent can be administered to a patient with a compound of formulas I-IX without losing its therapeutic activity. Suitable therapeutic agents include, e.g., anti-inflammatory agents, antibiotics, anti-viral agents, anticoagulants, α-adrenergic agonists, β-adrenergic agonists, analgesics, antineoplasts, adjuncts, androgen inhibitors, antibiotic derivatives, antiestrogens, antimetabolites, cytotoxic agents, hormones, immunomodulators, nitrogen mustard derivatives and steroids. Other therapeutic agents that can be used in conjunction with the compounds of the invention are disclosed in the Physicians' Desk Reference, 59th Ed.; Thompson PDR: Montvale, NJ (2005).

A "subject" can be a vertebrate, preferably a mammal, more preferably a human. Mammals include, but are not limited to, humans, farm animals, sport animals, and companion animals.

The term "protecting group" refers to any group which, when bound to a hydroxyl, nitrogen, or other heteroatom prevents undesired reactions from occurring at this group and which can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl group. The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as, for example, allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidine, phenacyl, methyl methoxy, silyl ethers (e.g., trimethylsilyl (TMS), *t*-butyl-diphenylsilyl (TBDPS), or *t*-butyldimethylsilyl (TBS)) and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product.

A large number of protecting groups and corresponding chemical cleavage reactions are described in *Protective Groups in Organic Synthesis*, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene", which is incorporated herein by reference in its entirety). Included therein are nitrogen protecting groups, for example, amide-forming groups. In particular, see Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 4, Carboxyl Protecting Groups, pages 118-154, and Chapter 5, Carbonyl Protecting Groups, pages 155-184. See also Kocienski, Philip J.; *Protecting Groups* (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated herein by reference in its entirety. Some specific protecting groups that can be employed in conjunction with the methods of the invention are discussed below.

Typical nitrogen protecting groups described in Greene (pages 14-118) include benzyl ethers, silyl ethers, esters including sulfonic acid esters, carbonates, sulfates, and sulfonates. For example:

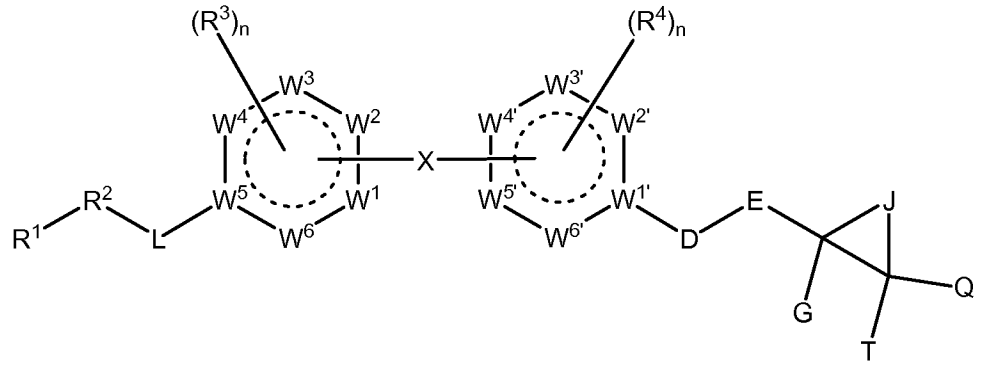
- substituted methyl ethers;
- substituted ethyl ethers;
- *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl;
- substituted benzyl ethers (*p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl,

p-phenylbenzyl, 2- and 4-picolyl, diphenylmethyl, 5-dibenzosuberyl, triphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 1,3-benzodithiolan-2-yl, benzisothiazolyl *S,S*-dioxido);

- silyl ethers (silyloxy groups) (trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, *t*-butylmethoxyphenylsilyl);
- esters (formate, benzoylformate, acetate, choroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate));
- carbonates (methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, 2-(triphenylphosphonio)ethyl, isobutyl, vinyl, allyl, *p*-nitrophenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *S*-benzyl thiocarbonate, 4-ethoxy-1-naphthyl, methyl dithiocarbonate);
- groups with assisted cleavage (2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl carbonate, 4-(methylthiomethoxy)butyrate,
- miscellaneous esters (2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3 tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinate, (*E*)-2-methyl-2-butenoate (tigloate), *o*-(methoxycarbonyl)benzoate, *p*-poly-benzoate, α-naphthoate, nitrate, alkyl *N,N,N′,N′*-tetramethyl-phosphorodiamidate, *n*-phenylcarbamate, borate, 2,4-dinitrophenylsulfenate); and
- sulfonates (sulfate, methanesulfonate (mesylate), benzylsulfonate, tosylate, triflate).

Compounds of the Invention

The present invention provides compounds of formulas I-IX, compositions that include such compounds, methods of their preparation, and methods of their use. Specifically, the invention provides a compound of formula I:



(I)

wherein

R^1 is $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkoxy, heteroaryl$(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, hydroxy, SR^5, NR^5R^5, or absent;

R^2 is CH_2, carbonyl, SO_2, or OH;

L is CH_2, NR^5, or O;

W^1-W^6 are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

$W^{1'}$-$W^{6'}$ are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

the dashed circles within the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$ denote optional double bonds of the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$;

R^3 and R^4 are each independently hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R_5)_2$, NR^5R^5, or $COOR^5$;

each n is independently 0 to 4;

each R^5 is independently H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, $(C_6\text{-}C_{10})$aroyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_6)$alkyl, or a nitrogen protecting group;

X is O, S, SO, SO_2, CH_2-O, CH_2-S, CH_2-NR^5, NR^5, carbonyl, or a direct bond;

D is S, SO, SO_2, P(O)OH, P(O)O(C_1-C_6)alkyl, P(O(C_1-C_6)alkyl)$_2$, C=N-OH, or carbonyl;

E is a direct bond, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, or (C_3-C_8)heterocycle;

J is S, O, or NR^5;

G, T, and Q are each independently H, (C_1-C_6)alkyl, or cyano;

any alkyl, amino, aryl, heteroaryl, or cycloalkyl is optionally substituted with 1 to about 5 (C_1-C_6)alkyl, (C_1-C_6)alkoxy, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, nitro, halo, amino, or hydroxy groups;

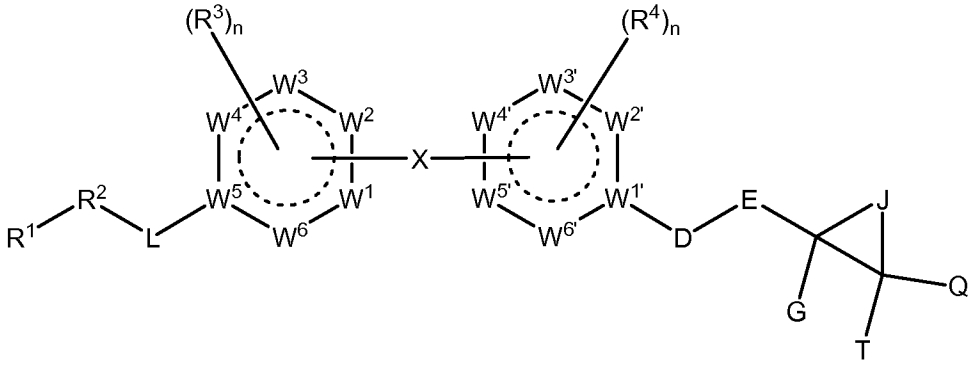
or a pharmaceutically acceptable salt thereof;

provided that when L is CH_2 or O, and R^2 is CH_2, R^1 is not (C_1-C_6)alkyl;

when L is O and R^2 is carbonyl, R^1 is not (C_1-C_6)alkyl; and

when L is NR^5, R^2 is CH_2.

The invention also provides a compound of formula II:



(II)

wherein

R^1 is H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy, heteroaryl(C_1-C_6)alkoxy, aryl, heteroaryl, hydroxy, nitro, cyano, halo, trifluoromethyl, trifluoromethoxy, SR^5, NR^5R^5, or CO_2R^5;

R^2 is CH_2, carbonyl, SO_2, or a direct bond;

L is CH_2, NR^5, O, S, SO, SO_2, or a direct bond;

W^1-W^6 are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

$W^{1'}$-$W^{6'}$ are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

the dashed circles within the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$ denote optional double bonds of the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$;

R^3 and R^4 are each independently hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkanoyl, $(C_1$-$C_6)$alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R_5)_2$, NR^5R^5, or $COOR^5$;

each n is independently 0 to 4;

each R^5 is independently H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, $(C_6$-$C_{10})$aroyl, aryl, aryl$(C_1$-$C_6)$alkyl, heteroaryl, heteroaryl$(C_1$-$C_6)$alkyl, or a nitrogen protecting group;

X is CH_2-O, CH_2-NR^5, CH_2-S, or carbonyl;

D is S, SO, SO_2, P(O)OH, P(O)O$(C_1$-$C_6)$alkyl, P(O$(C_1$-$C_6)$alkyl$)_2$, C=N-OH, or carbonyl;

E is a direct bond, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, or $(C_3$-$C_8)$heterocycle;

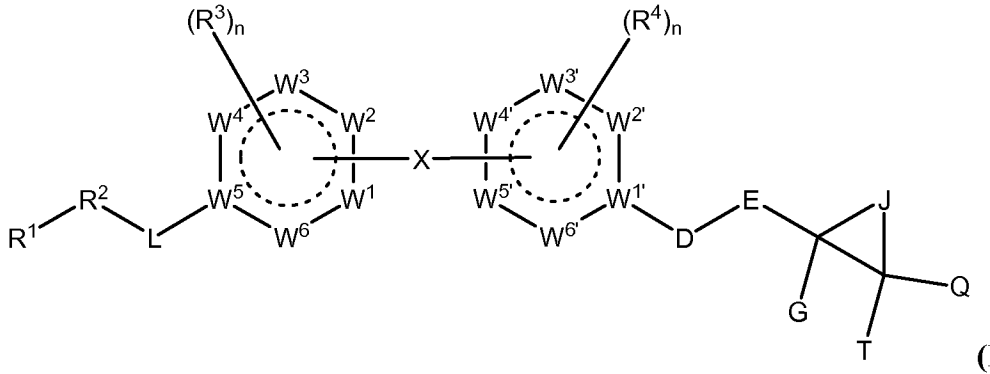
J is S, O, or NR^5;

G, T, and Q are each independently H, $(C_1$-$C_6)$alkyl, or cyano;

any alkyl, amino, aryl, heteroaryl, or cycloalkyl is optionally substituted with 1 to about 5 $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkenyl, $(C_1$-$C_6)$alkynyl, $(C_1$-$C_6)$alkoxy, aryl, heteroaryl, aryl$(C_1$-$C_6)$alkyl, heteroaryl$(C_1$-$C_6)$alkyl, nitro, halo, amino, or hydroxy groups;

or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula III:



(III)

wherein

R^1 is H, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkoxy, heteroaryl$(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, hydroxy, nitro, cyano, halo, trifluoromethyl, trifluoromethoxy, SR^5, NR^5R^5, or CO_2R^5;

R^2 is CH_2, carbonyl, SO_2, or a direct bond;

L is CH_2, NR^5, O, S, SO, SO_2, or a direct bond;

W^1-W^6 are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

$W^{1'}$-$W^{6'}$ are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

the dashed circles within the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$ denote optional double bonds of the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$;

R^3 and R^4 are each independently hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R_5)_2$, NR^5R^5, or $COOR^5$;

each n is independently 0 to 4;

each R^5 is independently H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, $(C_6\text{-}C_{10})$aroyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_6)$alkyl, or a nitrogen protecting group;

X is O, S, SO, SO_2, CH_2-O, CH_2-NR^5, CH_2-S, N(R^6), carbonyl, or a direct bond;

D is P(O)OH, P(O)O(C_1-C_6)alkyl, P(O(C_1-C_6)alkyl)$_2$, C=N-OH, or carbonyl;

E is a direct bond, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, or (C_3-C_8)heterocycle;

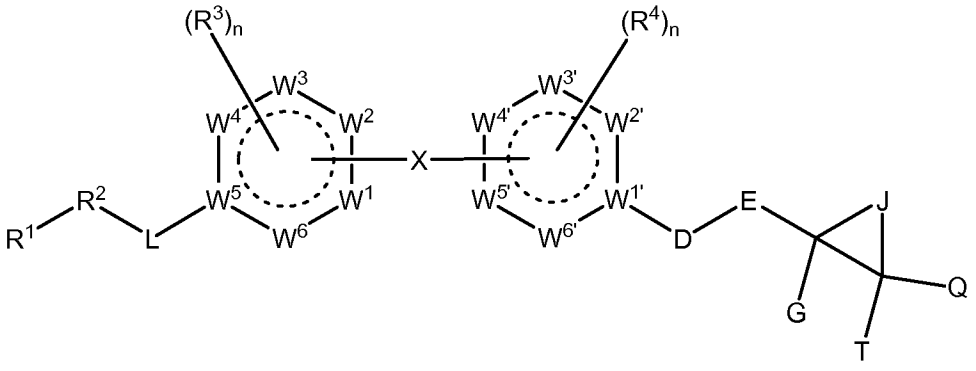
J is S, O, or NR^5;

G, T, and Q are each independently H, (C_1-C_6)alkyl, or cyano;

any alkyl, amino, aryl, heteroaryl, or cycloalkyl is optionally substituted with 1 to about 5 (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_1-C_6)alkoxy, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, nitro, halo, amino, or hydroxy groups;

or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula IV:



(IV)

wherein

R^1 is H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy, heteroaryl(C_1-C_6)alkoxy, aryl, heteroaryl, hydroxy, nitro, cyano, halo, trifluoromethyl, trifluoromethoxy, SR^5, NR^5R^5, or CO_2R^5;

R^2 is CH_2, carbonyl, SO_2, or a direct bond;

L is CH_2, NR^5, O, S, SO, SO_2, or a direct bond;

W^1-W^6 are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

$W^{1'}$-$W^{6'}$ are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

the dashed circles within the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$ denote optional double bonds of the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$;

R^3 and R^4 are each independently hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkanoyl, $(C_1$-$C_6)$alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R_5)_2$, NR^5R^5, or $COOR^5$;

each n is independently 0 to 4;

each R^5 is independently H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, $(C_6$-$C_{10})$aroyl, aryl, aryl$(C_1$-$C_6)$alkyl, heteroaryl, heteroaryl$(C_1$-$C_6)$alkyl, or a nitrogen protecting group;

X is NR^6;

R^6 is $(C_1$-$C_6)$alkanoyl, $(C_6$-$C_{10})$aroyl, aryl, aryl$(C_1$-$C_6)$alkyl, heteroaryl, heteroaryl$(C_1$-$C_6)$alkyl, or a nitrogen protecting group;

D is S, SO, SO_2, P(O)OH, P(O)O$(C_1$-$C_6)$alkyl, P(O$(C_1$-$C_6)$alkyl$)_2$, C=N-OH, or carbonyl;

E is a direct bond, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, or $(C_3$-$C_8)$heterocycle;

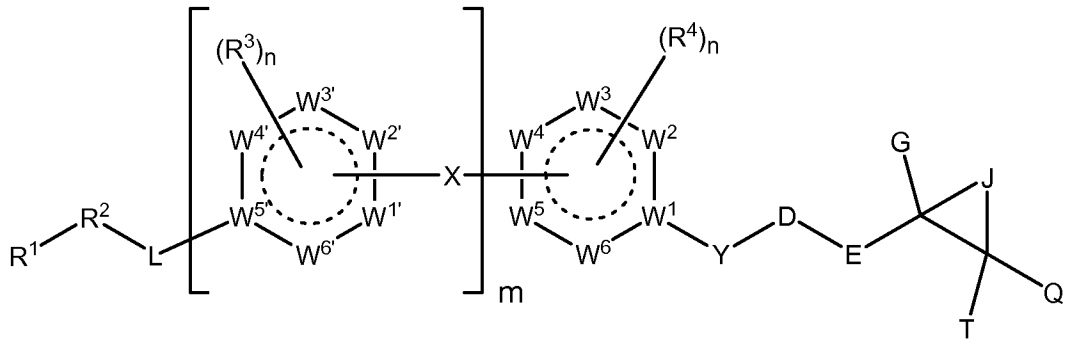
J is S, O, or NR^5;

G, T, and Q are each independently H, $(C_1$-$C_6)$alkyl, or cyano;

any alkyl, amino, aryl, heteroaryl, or cycloalkyl is optionally substituted with 1 to about 5 $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkenyl, $(C_1$-$C_6)$alkynyl, $(C_1$-$C_6)$alkoxy, aryl, heteroaryl, aryl$(C_1$-$C_6)$alkyl, heteroaryl$(C_1$-$C_6)$alkyl, nitro, halo, amino, or hydroxy groups;

or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula V:



(V)

wherein

R^1 is H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy, heteroaryl(C_1-C_6)alkoxy, aryl, heteroaryl, heterocycle, hydroxy, nitro, cyano, halo, trifluoromethyl, trifluoromethoxy, SR^5, NR^5R^5, or CO_2R^5;

R^2 is CH_2, carbonyl, SO_2, or a direct bond;

L is CH_2, NR^5, O, S, SO, SO_2, or a direct bond;

W^1-W^6 are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

$W^{1'}$-$W^{6'}$ are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

the dashed circles within the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$ denote optional double bonds of the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$;

R^3 and R^4 are each independently hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R_5)_2$, NR^5R^5, or $COOR^5$;

each n is independently 0 to 4;

m is 0 or 1;

each R^5 is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, (C_6-C_{10})aroyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl, heteroaryl(C_1-C_6)alkyl, or a nitrogen protecting group;

X is O, S, SO, SO_2, CH_2-O, NR^5, carbonyl, or a direct bond;

Y is O or NR^5;

D is S, SO, SO_2, P(O)OH, P(O)O(C_1-C_6)alkyl, P(O(C_1-C_6)alkyl)$_2$, C=N-OH, or carbonyl;

E is a direct bond, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, or (C_3-C_8)heterocycle;

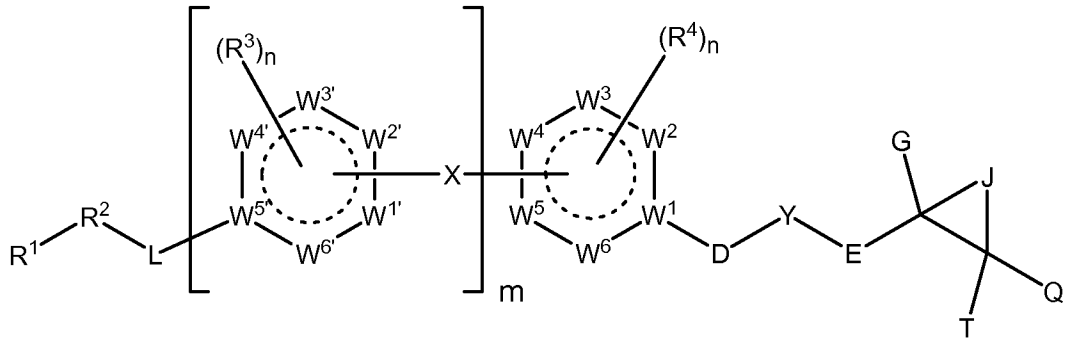
J is S, O, or NR^5;

G, T, and Q are each independently H, (C_1-C_6)alkyl, or cyano;

any alkyl, amino, aryl, heteroaryl, or cycloalkyl is optionally substituted with 1 to about 5 (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_1-C_6)alkoxy, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, nitro, halo, amino, or hydroxy groups;

or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula VI:



(VI)

wherein

R^1 is H, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, aryl(C_1-C_6)alkoxy, heteroaryl(C_1-C_6)alkoxy, aryl, heteroaryl, heterocycle, hydroxy, nitro, cyano, halo, trifluoromethyl, trifluoromethoxy, SR^5, NR^5R^5, or CO_2R^5;

R^2 is CH_2, carbonyl, SO_2, or a direct bond;

L is CH_2, NR^5, O, S, SO, SO_2, or a direct bond;

W^1-W^6 are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

$W^{1'}$-$W^{6'}$ are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

the dashed circles within the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$ denote optional double bonds of the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$;

R^3 and R^4 are each independently hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R_5)_2$, NR^5R^5, or $COOR^5$;

each n is independently 0 to 4;

m is 0 or 1;

each R^5 is independently H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, (C_6-C_{10})aroyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl, heteroaryl(C_1-C_6)alkyl, or a nitrogen protecting group;

X is O, S, SO, SO_2, CH_2-O, NR^5, carbonyl, or a direct bond;

Y is O or NR^5;

D is S, SO, SO_2, P(O)OH, P(O)O(C_1-C_6)alkyl, P(O(C_1-C_6)alkyl)$_2$, C=N-OH, or carbonyl;

E is a direct bond, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, or (C_3-C_8)heterocycle;

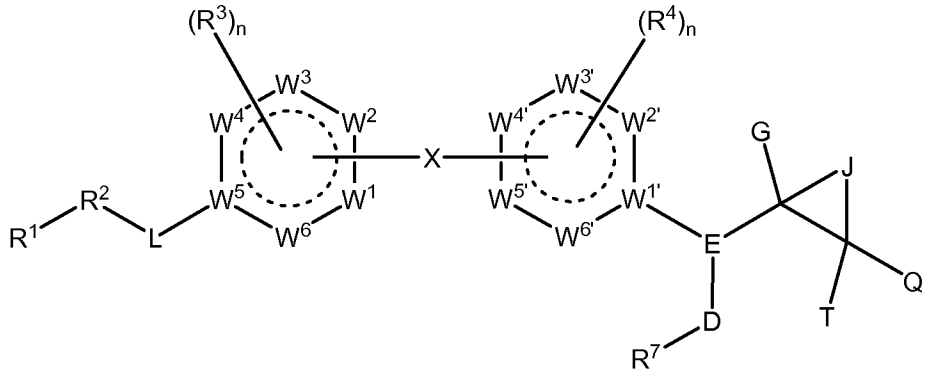
J is S, O, or NR^5;

G, T, and Q are each independently H, (C_1-C_6)alkyl, or cyano;

any alkyl, amino, aryl, heteroaryl, or cycloalkyl is optionally substituted with 1 to about 5 (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_1-C_6)alkoxy, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, nitro, halo, amino, or hydroxy groups;

or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula VII:



(VII)

wherein

R^1 is H, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkoxy, heteroaryl$(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, heterocycle, hydroxy, nitro, cyano, halo, trifluoromethyl, trifluoromethoxy, SR^5, NR^5R^5, or CO_2R^5;

R^2 is CH_2, carbonyl, SO_2, or a direct bond;

L is CH_2, NR^5, O, S, SO, SO_2, or a direct bond;

W^1-W^6 are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

$W^{1'}$-$W^{6'}$ are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

the dashed circles within the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$ denote optional double bonds of the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$;

R^3 and R^4 are each independently hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R_5)_2$, NR^5R^5, or $COOR^5$;

each n is independently 0 to 4;

m is 0 or 1;

each R^5 is independently H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, $(C_6\text{-}C_{10})$aroyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_6)$alkyl, or a nitrogen protecting group;

X is O, S, SO, SO_2, CH_2-O, NR^5, carbonyl, or a direct bond;

D is S, SO, SO_2, P(O)OH, P(O)O$(C_1\text{-}C_6)$alkyl, P(O$(C_1\text{-}C_6)$alkyl$)_2$, C=N-OH, or carbonyl;

R^7 is H, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkoxy, heteroaryl$(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, heterocycle, halo, trifluoromethyl, trifluoromethoxy, NR^5R^5, or CO_2R^5;

E is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, or $(C_3\text{-}C_8)$heterocycle;

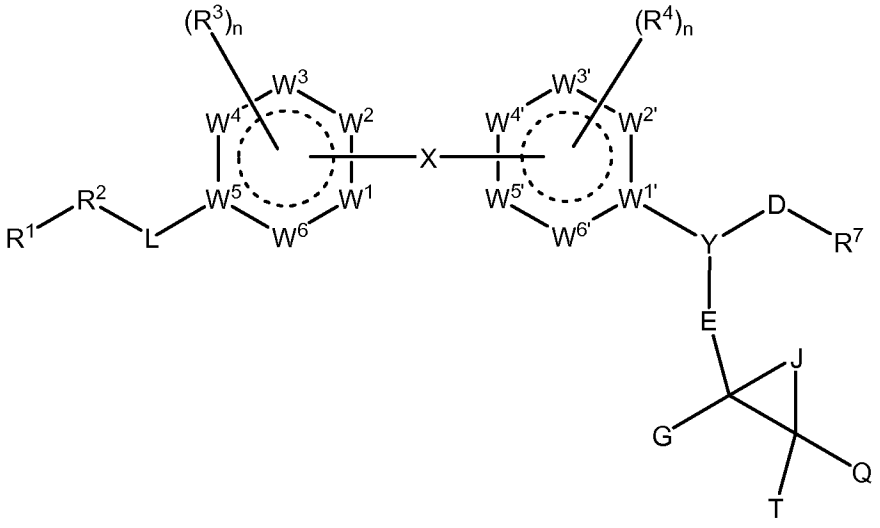
J is S, O, or NR^5;

G, T, and Q are each independently H, $(C_1\text{-}C_6)$alkyl, or cyano;

any alkyl, amino, aryl, heteroaryl, or cycloalkyl is optionally substituted with 1 to about 5 $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, nitro, halo, amino, or hydroxy groups;

or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula VIII:



(VIII)

wherein

R^1 is H, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkoxy, heteroaryl$(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, heterocycle, hydroxy, nitro, cyano, halo, trifluoromethyl, trifluoromethoxy, SR^5, NR^5R^5, or CO_2R^5;

R^2 is CH_2, carbonyl, SO_2, or a direct bond;

L is CH_2, NR^5, O, S, SO, SO_2, or a direct bond;

W^1-W^6 are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

$W^{1'}$-$W^{6'}$ are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

the dashed circles within the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$ denote optional double bonds of the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$;

R^3 and R^4 are each independently hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R_5)_2$, NR^5R^5, or $COOR^5$;

each n is independently 0 to 4;

m is 0 or 1;

each R^5 is independently H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, $(C_6\text{-}C_{10})$aroyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_6)$alkyl, or a nitrogen protecting group;

X is O, S, SO, SO_2, CH_2-O, NR^5, carbonyl, or a direct bond;

Y is $C(R^5)$ or N;

D is S, SO, SO_2, P(O)OH, P(O)O$(C_1\text{-}C_6)$alkyl, P(O$(C_1\text{-}C_6)$alkyl$)_2$, C=N-OH, or carbonyl;

R^7 is H, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkoxy, heteroaryl$(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, heterocycle, halo, trifluoromethyl, trifluoromethoxy, NR^5R^5, or CO_2R^5;

E is a direct bond, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, or $(C_3\text{-}C_8)$heterocycle;

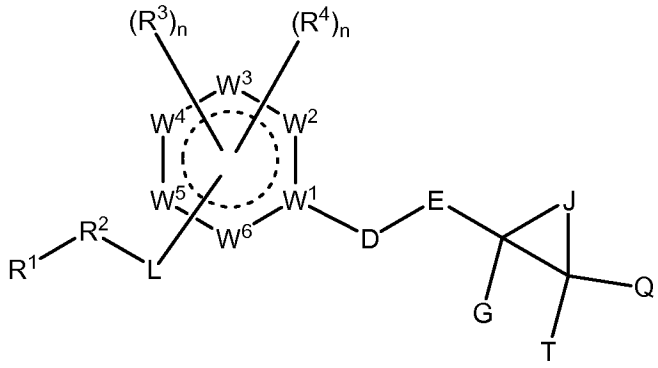
J is S, O, or NR^5;

G, T, and Q are each independently H, $(C_1\text{-}C_6)$alkyl, or cyano;

any alkyl, amino, aryl, heteroaryl, or cycloalkyl is optionally substituted with 1 to about 5 $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, nitro, halo, amino, or hydroxy groups;

or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula IX:



(IX)

wherein

R^1 is H, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkoxy, heteroaryl$(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, hydroxy, nitro, cyano, halo, trifluoromethyl, trifluoromethoxy, SR^5, NR^5R^5, or CO_2R^5;

R^2 is CH_2, carbonyl, SO_2, or a direct bond;

L is CH_2, NR^5, O, S, SO, SO_2, or a direct bond;

W^1-W^6 are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

the dashed circles within the rings formed by W^1-W^6 denote optional double bonds of the ring formed by W^1-W^6;

each n is independently 0 to 4 and the sum of n groups is not greater than 4;

each R^3 and R^4 are independently hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R_5)_2$, NR^5R^5, or $COOR^5$;

or each n is 1 and R^3 and R^4 together form an ortho-fused aryl, heteroaryl, carbocycle, or heterocycle attached to two of W^2-W^6;

each R^5 is independently H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, $(C_6\text{-}C_{10})$aroyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_6)$alkyl, or a nitrogen protecting group;

D is S, SO, SO_2, P(O)OH, P(O)O$(C_1\text{-}C_6)$alkyl, P(O$(C_1\text{-}C_6)$alkyl$)_2$, C=N-OH, carbonyl, or absent;

E is a direct bond, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, or $(C_3\text{-}C_8)$heterocycle;

J is S, O, or NR^5;

G, T, and Q are each independently H, $(C_1\text{-}C_6)$alkyl, or cyano;

any alkyl, amino, aryl, heteroaryl, heterocycle, carbocycle, or cycloalkyl is optionally substituted with 1 to about 5 $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, nitro, halo, amino, or hydroxy groups;

or a pharmaceutically acceptable salt thereof.

The following definitions apply to compounds of each of formulas I-IX, unless otherwise noted.

One value of R^1 is $(C_1\text{-}C_6)$alkyl. A specific value of R^1 is methyl. R^1 can also be ethyl, *n*-propyl, *iso*-propyl, or *sec*-butyl.

Another value for R^1 is $(C_1\text{-}C_6)$alkoxy. R^1 can also be methoxy or hydroxy.

Another value for R^1 is heteroaryl$(C_1\text{-}C_6)$alkoxy. Specific values of R^1 include pyridylmethyloxy, furanylmethyloxy, and thiophenylmethyloxy.

Another value for R^1 is halo$(C_1\text{-}C_6)$alkyl. A specific value of R^1 is bromopentyl.

Another value for R^1 is aryl$(C_1\text{-}C_6)$alkyl. A specific value of R^1 is benzyl.

Another value for R^1 is aryl. A specific value of R^1 is phenyl.

The group R^1 can be aryl substituted with 1 to about 5 $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, nitro, halo, amino, or hydroxy groups. Specifically, R^1 can be aryl substituted with methyl, methoxy, *iso*-propyl, nitro, halo, amino, or hydroxy.

Another value for R^1 is NR^5R^5. In one embodiment, each R^5 can independently be H or $(C_1\text{-}C_6)$alkyl. One specific value of R^1 is diethylamino.

In one embodiment, R^1 is absent and R^2 is OH.

For the compounds of any one of formulas II-IX, a specific value for R^1 is H. In formulas II-IX, R^2 and L can both be absent. In certain specific embodiments of formulas II-IX, R^1 is H and R^2 and L are both absent.

One value for R^2 is CH_2. Another value for R^2 is carbonyl. A further value for R^2 is SO_2.

One value for L is CH_2. Another value for L is NR^5. Specific values for L include NR^5 wherein R^5 is H, $(C_1\text{-}C_6)$alkyl, or a nitrogen protecting group. Another specific value for L is O.

The rings formed by $W^1\text{-}W^6$ can form a phenyl ring. The rings formed by $W^1\text{-}W^6$ can also form a 6-membered heteroaryl ring, such a pyridyl ring. The rings formed by $W^1\text{-}W^6$ can also form a 5-membered heteroaryl ring. Examples of such 5-membered heteroaryl rings include imidazole, thiazole, triazole, tetrazole, furan, and thiophene rings.

For the compounds of any of formulas I-VIII, the rings formed by $W^{1'}$-$W^{6'}$ can form a phenyl ring. The rings formed by $W^{1'}$-$W^{6'}$ can also form a 6-membered heteroaryl ring, such a pyridyl ring. The rings formed by $W^{1'}$-$W^{6'}$ can also form a 5-membered heteroaryl ring. Examples of such 5-membered heteroaryl rings include imidazole, thiazole, triazole, tetrazole, furan, and thiophene rings.

The dashed circles within the ring formed by W^1-W^6 can be two or three conjugated double bonds. For the compounds of any of formulas I-VIII, the dashed circles within the ring formed by $W^{1'}$-$W^{6'}$ can also be two or three conjugated double bonds.

The value R^3 can be absent (i.e., the value of n is 0). In certain embodiments, values for R^3 include hydroxy, halo, amino, or combinations thereof. R^3 can also be hydroxyphenyl or halophenyl. In yet another embodiment, R^3 can be $SO_2N(R_5)_2$. In one embodiment, each R^5 of R^3 is H.

The value R^4 can be absent (i.e., the value of n is 0). In certain embodiments, values for R^4 include hydroxy, halo, amino, or combinations thereof. R^4 can also be hydroxyphenyl or halophenyl. In yet another embodiment, R^4 can be $SO_2N(R_5)_2$. In one embodiment, each R^5 of R^4 is H.

For the compounds of any of formulas I, III, and V-IX, X can be O. Other specific values for X include S, SO, SO_2, CH_2-O, CH_2-S, NR^5, CH_2-NR^5, carbonyl, and a direct bond.

The attachment of the groups CH_2-O, CH_2-S, and CH_2-NR^5 is 'reversible', i.e., the methylene group can be attached to either ring of formulas I, III, and V-IX. For example, the methylene group can be attached to the ring formed by W^1-W^6 or the ring formed by $W^{1'}$-$W^{6'}$. Accordingly, the heteroatom of the recited group would then be attached to the other ring.

For the compounds of any of formulas I, III, and V-IX, when X is NR^5, R^5 can be H. In other embodiments, R^5 can be (C_1-C_6)alkyl, for example, methyl. In another embodiment, R^5 can be aryl, for example, phenyl. In yet another embodiment, R^5 can be aryl(C_1-C_6)alkyl, for example, benzyl. In another embodiment, R^5 can be a heteroaryl(C_1-C_6)alkyl, such as pyridylmethyl, imidazolylmethyl, thiazolylmethyl, triazolylmethyl, tetrazolylmethyl,

furanylmethyl, or thiophenylmethyl. In yet another embodiment, R^5 can be a nitrogen protecting group.

For the compounds of any of formulas I, III, and V-IX, when X is CH_2-NR^5, R^5 can be H. In other embodiments, R^5 can be $(C_1$-$C_6)$alkyl, for example, methyl. In another embodiment, R^5 can be aryl, for example, phenyl. In yet another embodiment, R^5 can be aryl$(C_1$-$C_6)$alkyl, for example, benzyl. In another embodiment, R^5 can be a heteroaryl$(C_1$-$C_6)$alkyl, such as pyridylmethyl, imidazolylmethyl, thiazolylmethyl, triazolylmethyl, tetrazolylmethyl, furanylmethyl, or thiophenylmethyl. In yet another embodiment, R^5 can be a nitrogen protecting group.

For the compounds of any of formulas I-II and IV-IX, one specific value of D is S. Another specific value of D is SO. Yet another specific value of D is SO_2.

For the compounds of any of formulas I-IX, D can be P(O)OH, P(O)O$(C_1$-$C_6)$alkyl, for example, $P(O)OCH_3$, or P(O$(C_1$-$C_6)$alkyl$)_2$, for example, $P(OCH_3)_2$. In another embodiment, D can be C=N-OH. In yet another embodiment, D can be carbonyl.

The variable E can be a direct bond. E can also be $(C_1$-$C_6)$alkyl, for example, CH_2. In another embodiment, E can be $(C_3$-$C_8)$cycloalkyl, such as cyclohexyl, or a geminally-substituted cyclohexyl. E can also be $(C_2$-$C_6)$alkenyl, for example, 2-butenyl. Another value for E is $(C_2$-$C_6)$alkynyl. In a specific embodiment, E can be 2-butynyl. In other embodiments, E can be $(C_3$-$C_8)$heterocycle, for example, piperidynyl. The piperidynyl can be an *N*-substituted piperidynyl linked to both its neighboring groups at the 4-position.

The variable J can be S, O, or NR^5. In one embodiment, J is NR^5 and R^5 is H. In another embodiment, J can be NR^5 and R^5 can be $(C_1$-$C_6)$alkyl, for example, methyl. In another embodiment, J can be NR^5 and R^5 can be $(C_1$-$C_6)$alkanoyl, such as acetyl (-C(=O)CH_3). In yet another embodiment, J can be NR^5 and R^5 can be $(C_6$-$C_{10})$aroyl, for example, benzoyl; aryl, for example, phenyl; aryl$(C_1$-$C_6)$alkyl, for example, benzyl; heteroaryl, for example, imidazolyl, thiazolyl, triazolyl, tetrazolyl, furanyl, thiophenyl, or pyridinyl; heteroaryl$(C_1$-$C_6)$alkyl, for example, imidazolylmethyl, thiazolylmethyl, triazolylmethyl, tetrazolylmethyl,

furanylmethyl, thiophenylmethyl, or pyridinylmethyl; or a nitrogen protecting group.

The variable G can be H. Another value for G is (C_1-C_6)alkyl, for example, methyl. Yet another value for G is cyano.

The variable T can be H. Another value for T is (C_1-C_6)alkyl, for example, methyl. Yet another value for T is cyano.

The variable Q can be H. Another value for Q is (C_1-C_6)alkyl, for example, methyl. Yet another value for Q is cyano.

In one embodiment, G, T, and Q are each H.

For the compounds of formulas IV, X can be NR^6, wherein R^6 is (C_1-C_6)alkanoyl. In a specific embodiment, R^6 is acetyl. R^6 can also be (C_6-C_{10})aroyl, for example, benzoyl; aryl, for example, phenyl; aryl(C_1-C_6)alkyl, for example, benzyl; heteroaryl, for example, pyridyl, imidazolyl, thiazolyl, triazolyl, tetrazolyl, furanyl, or thiophenyl; heteroaryl(C_1-C_6)alkyl, for example, pyridylmethyl, imidazolylmethyl, thiazolylmethyl, triazolylmethyl, tetrazolylmethyl, furanylmethyl, or thiophenylmethyl; or a nitrogen protecting group.

For the compounds of formulas V or VI, the value of m can be 0. In other embodiments, the value of m can be 1.

For the compounds of formulas V or VI, Y can be O. In other embodiments, Y can be NR^5. In one embodiment, Y is NR^5, and R^5 is H. In other embodiments, Y can be NR^5, and R^5 can be (C_1-C_6)alkyl, for example, methyl; (C_1-C_6) alkanoyl, for example, acetyl; (C_6-C_{10})aroyl, for example, benzoyl; aryl, for example, phenyl; aryl(C_1-C_6)alkyl, for example, benzyl; heteroaryl, for example, pyridyl, imidazolyl, thiazolyl, triazolyl, tetrazolyl, furanyl, or thiophenyl; heteroaryl(C_1-C_6)alkyl, for example, pyridylmethyl, imidazolylmethyl, thiazolylmethyl, triazolylmethyl, tetrazolylmethyl, furanylmethyl, or thiophenylmethyl; or a nitrogen protecting group.

For the compounds of formulas VII and VIII, R^7 can be H. R^7 can also be hydroxy. Another value for R^7 is (C_1-C_6)alkyl, for example, methyl. Another value for R^7 is (C_2-C_6)alkenyl, for example, propenyl. Another value for R^7 is (C_2-

C_6)alkynyl, for example, propynyl. Another value for R^7 is halo(C_1-C_6)alkyl, for example, bromopentyl. Another value for R^7 is (C_1-C_6)alkoxy, for example, methoxy. Another value for R^7 is aryl(C_1-C_6)alkyl, for example, benzyl. Another value for R^7 is heteroaryl(C_1-C_6)alkyl, for example, pyridylmethyl, imidazolylmethyl, thiazolylmethyl, triazolylmethyl, tetrazolylmethyl, furanylmethyl, or thiophenylmethyl. Another value for R^7 is aryl(C_1-C_6)alkoxy, for example, benzyloxy. Another value for R^7 is heteroaryl(C_1-C_6)alkoxy, pyridylmethyloxy. Another value for R^7 is aryl, for example, phenyl. Another value for R^7 is heteroaryl, for example, pyridyl, imidazolyl, thiazolyl, triazolyl, tetrazolyl, furanyl, or thiophenyl. Another value for R^7 is heterocycle, for example, piperidinyl.

For the compounds of formulas VII and VIII, R^7 can also be halo, for example, fluoro, chloro, bromo, or iodo. Yet another value for R^7 is trifluoromethyl. Another value for R^7 is trifluoromethoxy. Another value for R^7 is NR^5R^5, wherein each R^5 is H. Another value for R^7 is NR^5R^5, wherein each R^5 is (C_1-C_6)alkyl. Another value for R^7 is NR^5R^5, wherein each R^5 is methyl. Another value for R^7 is NR^5R^5, wherein one R^5 is H and the other R^5 of $R^7$is a nitrogen protecting group. Another value for R^7 is CO_2R^5. Another value for R^7 is CO_2R^5, wherein R^5 is H. Another value for R^7 is CO_2R^5, wherein R^5 is (C_1-C_6)alkyl. Another value for R^7 is CO_2R^5, wherein R^5 is methyl. Another value for R^7 is CO_2R^5, wherein R^5 is aryl. Yet another value for R^7 is CO_2R^5, wherein R^5 is phenyl.

For the compounds of formula VIII, Y can be N or C(R^5). In one embodiment, Y is N. In another embodiment, Y is C(R^5). In one specific embodiment, Y is C(R^5), wherein R^5 is H. In another embodiment, Y is C(R^5), wherein R^5 is (C_1-C_6)alkyl. In one specific embodiment, Y is C(R^5), wherein R^5 is methyl.

For the compounds of formula IX, each n can be 1 and R^3 and R^4 together can form an ortho-fused furanyl group. In another embodiment, each n is 1 and R^3 and R^4 together form an ortho-fused 1,2,3,4-tetrahydrobenzofuranyl group.

Methods of Use and Medical Indications

The invention also provides a pharmaceutical composition that includes a compound of any of formulas I-IX, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The pharmaceutical composition can also include other therapeutic agents that are compatible with the compound of the invention.

The invention also provides a compound of any of formulas I-IX, for use in medical therapy. The medical therapy can be for the treatment of cancer, angiogenesis, cardiovascular disease, neurological disease, inflammation, eye disease, autoimmune disease, for regulating contraception, or other conditions that are affected by the regulation of MMPs.

The cancer can be pancreatic cancer, gastric cancer, lung cancer, colorectal cancer, prostate cancer, renal cell cancer, basal cell cancer, breast cancer, bone cancer, brain cancer, lymphoma, leukemia, melanoma, myeloma and other hematological cancers, and the like. The cancer can be primary, metastatic, or both. The treatment of cancer using a compound of the invention can affect angiogenesis.

The cardiovascular disease can be stroke, aneurysm, ischemia or reperfusion injury.

The neurological disease can be one that arises from at least one of painful neuropathy, neuropathic pain, diabetic neuropathy, drug dependence, drug withdrawal, depression, anxiety, movement disorders, tardive dyskinesia, cerebral infections that disrupt the blood-brain barrier, meningitis, stroke, hypoglycemia, cardiac arrest, spinal cord trauma, head trauma, and perinatal hypoxia. The neurological disease can also be a neurodegenerative disorder. The neurological disease can be epilepsy, Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis, or amyotrophic lateral sclerosis, as well as Alexander disease, Alper's disease, Ataxia telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), Canavan disease, Cockayne syndrome, Corticobasal degeneration, Creutzfeldt-Jakob disease, Kennedy's disease, Krabbe disease, lewy body dementia, Machado-Joseph disease (Spinocerebellar ataxia type 3), Multiple System Atrophy, Pelizaeus-Merzbacher disease, Pick's disease, primary

lateral sclerosis, Refsum's disease, Sandhoff disease, Schilder's disease, spinocerebellar ataxia (multiple types with varying characteristics), spinal muscular atrophy, Steele-Richardson-Olszewski disease, or tabes dorsalis.

The compounds of the invention can be used to treat conditions of the eye, including corneal wounds, glaucoma, dry eye disease, and macula degeneration. The compounds can also be used to treat eye conditions that involve, are caused by, are effected by, or are exacerbated by MMP-9.

The compounds of the invention can be used to treat inflammation, wherein the inflammation involves connective tissue, airway tissue, or central nervous system tissue. The inflammation can be acute asthma, chronic asthma, allergic asthma, or chronic obstructive pulmonary disease. In one embodiment, the inflammation is arthritis.

The compounds of the invention can be used to effect contraception, wherein the contraception occurs by inhibition of implantation.

The compounds of the invention can be used in medical therapy, wherein the medical therapy is treatment of a skin disease.

The compounds of the invention can also be used in imaging, wherein the inhibitor can be modified to be detectable by imaging techniques; for pre- and post-operative treatments for removal of tumors; and in combination with any other chemotherapeutic modalities (biological and non-biological).

The invention also provides the use of a compound of any of formulas I-IX, to prepare a medicament for treatment of cancer, angiogenesis, cardiovascular disease, neurological disease, inflammation, autoimmune disease, or contraception. The medicaments can also be used to treat any of the diseases or conditions discussed above.

The invention further provides a method to treat a disease comprising contacting a cell with a compound of formulas I-IX, wherein the compound is effective to inhibit a matrix metalloproteinase. The invention also provides a method to treat a subject in need thereof, comprising administering to the subject an effective amount of a matrix metalloproteinase inhibitor of a compound of formulas I-IX. The matrix metalloproteinase can be a gelatinase, collagenase, stromelysin,

membrane-type MMP, or matrilysin. The matrix metalloproteinase can be, for example, MMP-2, MMP-9, or MMP-14. The matrix metalloproteinase can be a human matrix metalloproteinase.

The matrix metalloproteinase inhibitor can be administered to the subject in a pharmaceutically acceptable excipient. The subject can be an animal, for example, a mammal. The subject can be a human. The methods employing the compound of formulas I-IX can be used to treat any of the diseases or conditions discussed above.

A compound of formulas I-IX, or a pharmaceutically acceptable salt thereof, can be administered to a mammal (e.g., human) in conjunction with a chemotherapeutic agent, or a pharmaceutically acceptable salt thereof. Accordingly, a compound of formulas I-IX can be administered in conjunction with a chemotherapeutic agent to treat a disease, a tumor, or cancer.

According to one embodiment of the invention, the matrix metalloproteinase can be contacted with the compound, e.g., a compound of any one of formulas I-IX , *in vitro*. Alternatively, the matrix metalloproteinase can be contacted with the compound, e.g., a compound of any one of formulas I-IX, *in vivo*.

An important aspect of the invention is that a compound of formulas I-IX can be selective for a particular matrix metalloproteinase over other matrix metalloproteinases. This selectivity can provide a significant benefit to treating the diseases and conditions discussed above because of the reduced dosage required for a given treatment.

Methods of Making the Compounds of the Invention.

Processes for preparing compounds of formulas I-IX and processes for preparing intermediates useful for preparing compounds of formulas I-IX are provided as further embodiments of the invention. Intermediates useful for preparing compounds of formulas I-IX are also provided as further embodiments of the invention.

The compounds described herein can be prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic

Synthetic Methods (John Wiley & Sons, New York) Vol. 1, Ian T. Harrison and Shuyen Harrison (1971); Vol. 2, Ian T. Harrison and Shuyen Harrison (1974); Vol. 3, Louis S. Hegedus and Leroy Wade (1977); Vol. 4, Leroy G. Wade Jr., (1980); Vol. 5, Leroy G. Wade Jr. (1984); and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, 3rd Edition, John Wiley & Sons, New York (1985); Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry, In 9 Volumes, Barry M. Trost, Editor-in-Chief, Pergamon Press, New York (1993); Advanced Organic Chemistry, Part B: Reactions and Synthesis, 4th Ed.; Carey and Sundberg; Kluwer Academic/Plenum Publishers: New York (2001); Advanced Organic Chemistry, Reactions, Mechanisms , and Structure, 2nd Edition, March, McGraw Hill (1977); Protecting Groups in Organic Synthesis, 2nd Edition, Greene, T.W., and Wutz, P.G.M., John Wiley & Sons, New York (1991); and Comprehensive Organic Transformations, 2nd Edition, Larock, R.C., John Wiley & Sons, New York (1999).

As would be recognized by one skilled in the art, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

Specific ranges, values, and embodiments provided herein are for illustrative purposes only and do not otherwise limit the scope of the invention, as defined by the claims.

Pharmaceutical Formulations:

The compounds described herein can be administered as the parent compound, a pro-drug of the parent compound, or an active metabolite of the parent compound.

The compounds of this invention can be formulated with conventional carriers and excipients, which can be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally

contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients, 5th Ed.; Rowe, Sheskey, and Owen, Eds.; American Pharmacists Association; Pharmaceutical Press: Washington, DC, 2006. Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethyl-cellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, include at least one active ingredient, as described herein, together with one or more acceptable carriers therefor, and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, (1985). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For administration to the eye or other external tissues *e.g.*, mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulfoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as

a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation.

Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the

acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hour can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes

in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of a given condition.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provided compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient.

Mechanism of Action of Compounds of the Invention

A specific group of the compounds of the present invention, that can be activated by zinc for nucleophilic substitution and that can form a covalent bond

with a nucleophile of the matrix metalloproteinase, includes a thiirane ring. Another specific group of the compounds of the present invention, that can be activated by zinc for nucleophilic substitution and that can form a covalent bond with a nucleophile of the matrix metalloproteinase, includes an oxirane ring. In addition, a specific nucleophile of the matrix metalloproteinase which can form a covalent bond with the group of the compounds of the present invention (e.g., thiirane or oxirane) is located at the amino acid residue corresponding to residue 404 of the matrix metalloproteinase, wherein the numbering is based on the active site general base for gelatinase A, which is observed in other MMPs. More specifically, the nucleophile is a carboxy (i.e., COO^-) oxygen atom located at amino acid residue corresponding to residue 404 of the matrix metalloproteinase, wherein the numbering is based on the active site general base for gelatinase A, which is observed in other MMPs. See, FIG. 1.

Pharmaceutical Kits

Pharmaceutical kits useful in the present invention, which include a therapeutically effective amount of a pharmaceutical composition that includes a compound of component (a) and one or more compounds of component (b), in one or more sterile containers, are also within the ambit of the present invention. Sterilization of the container may be carried out using conventional sterilization methodology well known to those skilled in the art. Component (a) and component (b) may be in the same sterile container or in separate sterile containers. The sterile containers or materials may include separate containers, or one or more multi-part containers, as desired. Component (a) and component (b), may be separate, or physically combined into a single dosage form or unit as described above.

Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as for example, one or more pharmaceutically acceptable carriers, additional vials for mixing the components, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered,

guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

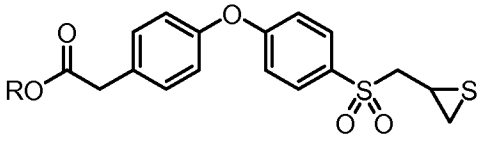
EXAMPLES

Several methods for the preparation of compounds of formulas I-IX are provided in the Examples hereinbelow. These methods are intended to illustrate the nature of such compounds and preparations and are not intended to limit the scope of the compounds and applicable synthetic methods of the invention.

Some abbreviations used herein include the following: Ac, acetyl; *m*CPBA, 3-chloroperoxybenzoic acid; DMF, *N,N*-dimethylformamide; Me, methyl; Ms, methanesulfonyl; THF, tetrahydrofuran; MMP, matrix metalloproteinase; DMEM, Dulbecco's modified Eagle's medium; DMSO, dimethyl sulfoxide (Me_2SO); PBS, phosphate buffer saline; FBS, fetal bovine serum.

EXAMPLE 1: Design, Synthesis, and Evaluation of a Mechanism-Based Inhibitor for Gelatinase A

The first mechanism-based inhibitor for MMPs have been previously described (*J. Am. Chem. Soc.* **2000**, *122*, 6799-6800), which in chemistry mediated by the active site zinc ion selectively and covalently inhibits MMP-2, MMP-3 and MMP-9. Computational analyses indicated that this selectivity in inhibition of MMPs could be improved by design of new variants of the inhibitor class. The syntheses of methyl 2-(4-{4-[(2-thiiranylpropyl) sulfonyl]phenoxy}phenyl)-acetate (**1.3**) and 2-(4-{4-[(2-thiiranylpropyl) sulfonyl]phenoxy} phenyl)acetic acid (**1.4**) are reported herein. The results of this Example show that compound **1.3** serves as a mechanism-based inhibitor exclusively for MMP-2. This molecule should prove useful in delineating the functions of MMP-2 in biological systems.



1.3 (R = Me)
1.4 (R = H)

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases with important pathological and physiological functions (Massova, I.; Kotra, L. P.; Fridman, R.; Mobashery, S. Matrix Metalloproteases: Structures, Evolution and Diversification, *FASEB J.* **1998**, *12*, 1075; see also *Can. J. Physiol. Pharmacol.* **1999**, *77*, 465-480; *J. Clin. Oncol.* **2000**, *18*, 1135-1149; *Cell* **2000**, *100,* 57-70; *Nature Rev.* **2002**, *2*, 563-572; *Nature Rev.* **2002**, *2*, 727-739; *Nature Rev.* **2002**, *3*, 1-6; *Nature Rev.* **2003**, *3*, 401-410; *Nature Med.* **2003**, *9*, 822-823; *Nature Med.* **2003**, *9*, 999-1000).

A total of 26 MMPs are known. Their unregulated and uncontrolled activities have been associated with a number of disease processes, including neurological disorders, arthritis, cardiovascular diseases and cancer, neurological disorders, and others. Inhibition of MMPs as a means to intervention of disease is highly sought (*Nature Rev.* **2002**, 1, 415-426; *Current Opinion Chem. Biol.* **1999**, *3*, 500-509; *Chem. Rev.* **1999**, *99*, 2735-2776; *Curr., Med. Chem.* **2001**, *8*, 425-474; and Lee, M.; Fridman, R.; Mobashery, S. *Chem. Soc. Rev.* **2004**, *33*, 401-409). With very few exceptions, the known inhibitors of MMPs are broad-spectrum molecules, designed to chelate the active-site zinc ions of these enzymes. This broad breadth of activity has been problematic in clinical trials of MMP inhibitors, as the molecules tend to show serious side effects (Egeblad and Werb, *Nature Rev. Cancer* **2002**, *2,* 161-174; Coussens et al. *Science* **2002**, *295,* 2387-2392).

This Example is an investigation into selective inhibition of gelatinases, MMP-2 and MMP-9 (also known as gelatinases A and B, respectively). The excessive and unregulated activities of these two enzymes have been indicated in a number of cancer metastases (*J. Surg. Res.* **2003**, *110*, 383-392; *Breast Cancer Res Treat* **2003**, *77*, 145-155; *Biochim. Biophys. Acta.* **2004**, *1705*, 69-89; *Gynecol. Oncol.* **2004**, *94*, 699-704; *Eur. J. Surg. Oncol.* **2004**, *30*, 560-4; and *Mod. Pathol.* **2004**, *17*, 496-502).

Mobashery and co-workers disclosed for the first time a novel strategy in mechanism-based inhibition of MMP by a thiirane-containing inhibitor, where the thiirane sulfur first coordinates with the active-site zinc ion (*J. Am. Chem. Soc.* **2000**, *122*, 6799-6800). The coordinated thiirane predisposes it to nucleophilic

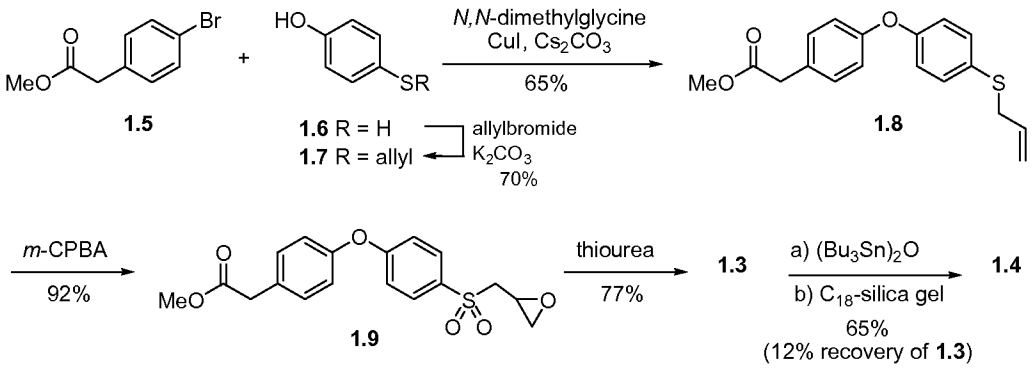
attack by the active site glutamate (Glu-404 in MMP-2) in these enzymes, a process that leads to covalent modification of the enzyme and the attendant loss of activity. This process is depicted in FIG. 1 for a known member (compound **1.1**) of this class of inhibitors (**1.1** → **1.2**).

Inhibitor **1.1** underwent the chemistry shown in FIG. 1 with three MMPs: MMP-2, MMP-3 and MMP-9. The goal of the experiments disclosed herein is to develop inhibitors of this class that show an even narrower spectrum of inhibition than that exhibited by compound **1.1**. Specific interactions at the bottom of the deep S1' pocket of MMP-2 and MMP-9 were identified that could be exploited with a structural variant of inhibitor **1.1** to enhance selectivity toward gelatinases (FIG. 2). Two such molecules, **1.3** and **1.4**, were designed by computational analyses. The syntheses of these molecules are reported herein. Furthermore, that compound **1.3** shows the pattern of slow-binding inhibition that leads to covalent chemistry only with MMP-2 is documented.

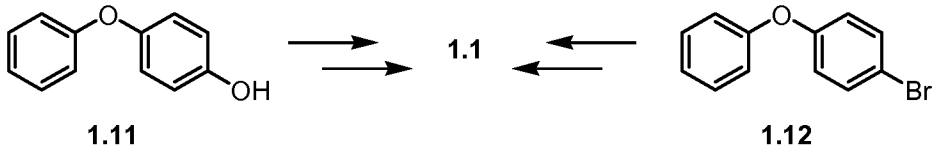
The syntheses of compounds **1.3** and **1.4** were accomplished according to Scheme 1 below. An *N*,*N*-dimethyl glycine-promoted Ullmann coupling reaction between the commercially available aryl bromide **1.5** and phenol **1.7**, which was in turn prepared from 4-hydroxythiophenol (**1.6**) by chemoselective allylation, proceeded smoothly to give **1.8** in 65% yield. Oxidation of the sulfur and olefin moieties in **1.8** was achieved by the use of an excess of *m*-CPBA (12 equiv.) to afford oxirane **1.9** in 92% yield, which was treated with thiourea to provide thiirane **1.3** in 77% yield.

Attempts at hydrolysis of the methyl ester of **1.3** to the corresponding carboxylic acid **1.4** under various basic conditions were unsuccessful, probably due to the deprotonation of the acidic α-position to the sulfonyl moiety, followed by β-elimination of the thiolate. The method of Mascaretti with the use of $(Bu_3Sn)_2O$ in toluene at 80 °C was found to be most effective for this conversion. Under these conditions, methyl ester **1.3** was converted to the corresponding tin ester, which was subsequently hydrolyzed on C_{18}-reverse phase silica gel to afford the desired carboxylic acid **1.4** in 65% yield (with an attendant 12% recovery of **1.3**).

Scheme 1



The synthetic route to compounds **1.3** and **1.4** is different than those reported for inhibitor **1.1**. (*J. Am. Chem. Soc.* **2000**, *122*, 6799-6800; *J. Org. Chem.* **2004**, *69*, 3572-3573.) Syntheses of **1.1** began from the commercially available diphenyl ethers **1.11** or **1.12** illustrated below. The synthetic route of Scheme 1 allows more flexibility in creating structural diversity in the two ring systems and should find more general applicability for entries into this molecular class of versatile enzyme inhibitors.



Compounds **1.3** and **1.4** were evaluated with a representative set of MMPs. As shown in Table 1, compound **1.4** inhibits MMP-2 with a K_i of 460 nM. Whereas compound **1.3** exhibits dissociation constants for MMP-2 and -9 in the low nanomolar levels, it behaves as a slow-binding inhibitor that leads to mechanism-based inhibition only with MMP-2. Therefore, compound **1.3** is a selective and potent mechanism-based inhibitor of MMP-2 (gelatinase A). Both compounds are merely poor competitive inhibitors (micromolar) of the other MMP that were tested. Hence, high selectivity in inhibition of MMP-2 has been achieved.

Table 1. Kinetic Parameters for Competitive Inhibition of MMPs by the Synthetic Inhibitors

	K_i (nM)	
	1.3	**1.4**
MMP-2	50 ± 14[a]	460 ± 30
MMP-9	40 ± 2	$(4.1 \pm 0.2) \times 10^3$
MMP-14_{cat}	590 ± 70	$(5.3 \pm 0.3) \times 10^4$
MMP-1	$(1.1 \pm 0.2) \times 10^4$	$(4.5 \pm 0.9) \times 10^3$
MMP-3	$(8.7 \pm 0.5) \times 10^3$	$(5.4 \pm 1.0) \times 10^5$
MMP-7	1.3×10^4	$(2.5 \pm 0.1) \times 10^5$

[a] Parameters for slow-binding component of inhibition: $k_{on} = (1.2 \pm 0.3)$ 10^4 $M^{-1}s^{-1}$, $k_{off} = (6.2 \pm 0.7) \times 10^{-4}$ s^{-1}.

Superimposition of the X-ray structures for MMP-2 and MMP-9 reveals some important differences (*J. Biol. Chem.* **2003**, *278*, 51646-51653). Midway through the S1' loop, an arginine residue is present in MMP-9, as opposed to a threonine in MMP-2. The pocket of MMP-9 appears to be more constricted than that of MMP-2, as the backbone of the S1' loop of MMP-9 is about 2-3 Å inward. This could potentially lead to unfavorable steric interaction for the methyl moiety of compound **1.3** in MMP-9.

Methods: Enzyme kinetics were performed as previously described (*J. Am. Chem. Soc.* **2000**, *122*, 6799-6800).

Experimental Procedures and Data for Compounds of Example 1

4-(Allylthio)phenol (1.7). To a stirred solution of 4-hydroxythiophenol (**1.6**) (4.30 g, 34.1 mmol) in DMF (25 mL) were added K_2CO_3 (4.71 g, 34.1 mmol) and allyl bromide (3.09 mL, 34.1 mmol) at ice-water temperature, and the mixture was stirred for 15 minutes, prior to stirring overnight at room temperature. After the

addition of 1 M aqueous HCl, the mixture was extracted with ether (3x). The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/10 to 1/6) to give **1.7** (5.74 g, 70%) as a white semi-solid. The ^1H and ^{13}C NMR spectra and mass spectrum were identical to the reported values (*Tetrahedron* **1994**, *50*, 10321-10330).

Methyl 2-{4-[4-(Allylthio)phenoxy]phenyl}acetate (1.8). A mixture of **1.5** (1.51 g, 6.59 mmol), **7** (1.64 g, 9.88 mmol), Cs_2CO_3 (4.30 g, 13.2 mmol), *N*, *N*-dimethylglycine hydrochloride salt (276 mg, 1.98 mmol), CuI (125 mg, 0.659 mmol), and degassed 1,4-dioxane (14 mL) was heated at 90 °C for 22 hours under a nitrogen atmosphere. After dilution with water, the mixture was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/12) to give **1.8** (1.35 g, 65%) as a pale yellow semi-solid. ^1H NMR (300 MHz, $CDCl_3$): δ 3.49 (d, 2H, J = 7.2 Hz), 3.61 (s, 2H), 3.71 (s, 3H), 5.03-5.10 (m, 2H), 5.86 (m, 1H), 6.91-6.97 (m, 4H), 7.23-7.26 (m, 2H), 7.32-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.5, 40.3, 52.1, 117.5, 119.0, 119.1, 129.0, 129.3, 130.6, 132.9, 133.7, 156.0, 156.3, 172.0; HRMS (FAB) calcd for $C_{18}H_{18}O_3S$ (M^+) 314.0977, found 314.0986.

Methyl 2-(4-{4-[(2-Oxiranylpropyl)sulfonyl]phenoxy}phenyl)-acetate (1.9). To a stirred solution of **1.8** (500 mg, 1.59 mmol) in CH_2Cl_2 (20 mL) was added *m*-CPBA (ca. 70%, 4.7 g, 19.1 mmol) at ice-water temperature, and the mixture was subsequently stirred at room temperature for eight days. With ice-cooling, the reaction was quenched with a saturated $Na_2S_2O_3$ solution, followed by saturated $NaHCO_3$ solution, and the mixture was extracted with ethyl acetate (3x). The combined organic layer was washed with saturated $Na_2S_2O_3$ solution, saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/2 to 2/3) to give **1.9** (528 mg, 92%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 2.47 (dd, 1H, J = 5.0, 2.0 Hz), 2.82

(m, 1H), 3.26-3.33 (m, 3H), 3.65 (s, 2H), 3.72 (s, 3H), 7.03-7.05 (m, 2H), 7.08-7.10 (m, 2H), 7.32-7.34 (m, 2H), 7.86-7.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.3, 45.8, 52.1, 59.6, 117.6, 120.6, 130.5, 130.9, 131.1, 132.4, 153.8, 162.8, 171.8; HRMS (FAB) calcd for $C_{18}H_{18}O_6S$ (M^+) 362.0824, found 362.0829.

Methyl 2-(4-{4-[(2-Thiiranylpropyl)sulfonyl]phenoxy}phenyl)-acetate (1.3). To a stirred solution of **1.9** (500 mg, 1.38 mmol) in MeOH-CH_2Cl_2 (10:1, 11 mL) was added thiourea (262 mg, 3.45 mmol) at room temperature, and the mixture was stirred overnight. After concentration under reduced pressure, the residue was dissolved in ethyl ether. The ethyl ether solution was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 2/5) to give **1.3** (400 mg, 77%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.15 (dd, 1H, J = 5.5, 2.0 Hz), 2.53 (dd, 1H, J = 6.5, 2.0 Hz), 3.05 (m, 1H), 3.17 (dd, 1H, J = 14.5, 7.0 Hz), 3.51 (dd, 1H, J = 14.5, 5.5 Hz), 3.65 (s, 2H), 3.72 (s, 3H), 7.03-7.05 (m, 2H), 7.08-7.10 (m, 2H), 7.33-7.34 (m, 2H), 7.85-7.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2, 26.0, 40.3, 52.1, 62.6, 117.7, 120.5, 130.7, 130.9, 131.1, 131.9, 153.8, 162.8, 171.8; HRMS (FAB) calcd for $C_{18}H_{19}O_5S_2$ ($M+H^+$) 379.0674, found 379.0645.

2-(4-{4-[(2-Thiiranylpropyl)sulfonyl]phenoxy}phenyl)acetic acid (1.4). To a stirred solution of **3** (312 mg, 0.83 mmol) in toluene (11 mL) was added bis(tributyltin)oxide (1.05 mL, 2.06 mmol) at room temperature, and the mixture was stirred at 80 °C for 12 hours. The solution was cooled to room temperature and was concentrated to dryness under reduced pressure. The residue was dissolved in acetonitrile, and the solution was washed with hexane (3x) and concentrated under reduced pressure to leave the crude tin ester **1.10** (532 mg) as a pale-yellow oil. Subsequently, **1.10** was passed through a C_{18}-reverse phase silica gel pad (ODS silica gel 20 g, washed with water, 1:2 water/acetonitrile and acetonitrile) to afford a mixture of **1.3** and **1.4**, which was purified by silica gel column chromatography (chloroform/methanol = 30/1 to 10/1) to give **1.4** (195 mg, 65%) as a white solid with the recovery of some of **1.3** (38 mg, 12%). Compound **1.10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 9H, J = 7.2 Hz), 1.23-1.38 (m, 12H), 1.54-1.64 (m, 6H),

2.16 (dd, 1H, J = 5.4, 1.8 Hz), 2.54 (dd, 1H, J = 6.0, 1.8 Hz), 3.07 (m, 1H), 3.15 (dd, 1H, J = 13.8, 7.8 Hz), 3.54 (dd, 1H, J = 13.8, 5.1 Hz), 3.64 (s, 2H), 7.03 (m, 2H), 7.08 (m, 2H), 7.35 (m, 2H), 7.86 (m, 2H); Mass (FAB): *m/z* 655 ($M+H^+$); Rf value = 0.3 (chloroform/methanol = 10/1). Compound **1.4**: mp 133-134 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.16 (d, 1H, J = 4.0 Hz), 2.54 (d, 1H, J = 5.5 Hz), 3.06 (m, 1H), 3.19 (dd, 1H, J = 14.0, 8.0 Hz), 3.52 (dd, 1H, J = 14.0, 6.0 Hz), 3.68 (s, 2H), 7.05 (br d, 2H, J = 8.5 Hz), 7.10 (br d, 2H, J = 8.5 Hz), 7.35 (br d, 2H, J = 8.5 Hz), 7.86 (br d, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2, 26.0, 40.2, 62.6, 117.8, 120.5, 130.2, 130.7, 131.3, 132.0, 154.1, 162.7, 177.1; HRMS (FAB) calcd for $C_{17}H_{17}O_5S_2$ ($M+H^+$) 365.0517, found 365.0495; Rf value = 0.2 (chloroform/methanol = 10/1).

Computational Procedures. The X-ray structure of MMP-2 provided the Cartesian coordinates for the molecular docking study (RCSB code 1QIB). The Sybyl program (Tripos Inc., St. Louis, MO) was used for the manipulation and visualization of all structures and for the protonation of the bound ligand. AM1-BCC charges were computed for the ligand using the antechamber module from the AMBER 7 suite of programs (Case et al., AMBER 7 ed.; University of California: San Francisco, 2002). The ligand was docked into the active site of MMP-2 using a Lamarckian genetic algorithm as implemented in the AutoDock 3.04 program (Morris et al. *J. Comp. Chem.* **1998**, *19*, 1639-1662). Parameters for the docking runs were similar to those used previously (Morris et al. *J. Comp. Chem.* **1998**, *19*, 1639-1662), except for the following differences: the quaternion step, the translation step, and the torsion step were set to 0.2, 5, and 5, respectively. The number of evaluations was increased to 2.5×10^7 from 250,000 and the ligand was fully flexible during the docking runs.

EXAMPLE 2. Potent Mechanism-Based Inhibitors For Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that play important roles in physiological and pathological conditions. Both gelatinases (MMP-2 and MMP-9) and membrane-type 1 MMP (MMP-14) are important targets for inhibition since their roles in various diseases, including cancer, have been well

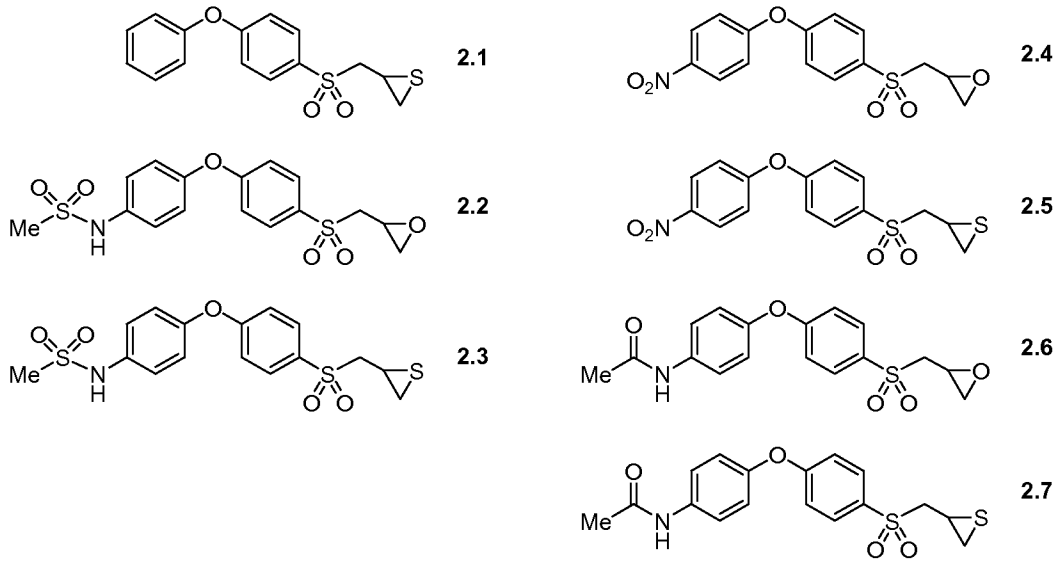
established. This Example describes a set of mechanism-based inhibitors that show high selectivity to gelatinases and MMP-14 (inhibitor **2.3**) and to only MMP-2 (inhibitors **2.5** and **2.7**). These molecules bind to the active sites of these enzymes, initiating a slow-binding profile for the onset of inhibition, which leads to covalent enzyme modification. The full kinetic analysis for the inhibitors is reported. These are nanomolar inhibitors (K_i) for the formation of the non-covalent enzyme-inhibitor complexes. The onset of slow-binding inhibition is rapid (k_{on} of 10^2 to 10^4 $M^{-1}s^{-1}$) and the reversal of the process is slow (k_{off} of 10^{-3} to 10^{-4} s^{-1}). However, with the onset of covalent chemistry with the best of these inhibitors (e.g., inhibitor **2.3**), very little recovery of activity (<10%) was seen over 48 hours of dialysis. We previously reported that broad-spectrum MMP inhibitors like GM6001 (hydroxamate inhibitor) enhance MT1-MMP-dependent activation of pro-MMP-2 in the presence of TIMP-2. Herein, we show that inhibitor **2.3**, in contrast to GM6001, had no effect on pro-MMP-2 activation by MT1-MMP. Furthermore, inhibitor **2.3** reduced tumor cell migration and invasion *in vitro*. These results show that these new inhibitors are promising candidates for selective inhibition of MMPs in animal models of relevant human diseases.

Extracellular proteolysis is an essential aspect of both physiological and pathological processes. Several enzyme families have been implicated in extracellular proteolysis, of which the matrix metalloproteinases (MMPs) constitute an important group. The MMPs are zinc-dependent endopeptidases that play key roles in embryonic development, neurological processes, wound healing, angiogenesis, arthritis, cardiovascular diseases and cancer, just to mention a few. In cancer, for instance, MMPs are implicated at all stages of tumor progression, including tumor growth, angiogenesis, and metastasis (Egeblad and Werb, (2002) *Nat Rev Cancer* **2**, 161-174). Two MMPs, gelatinases A and B (MMP-2 and MMP-9, respectively), are highly expressed in human cancer and a direct relationship between cancer progression and gelatinase expression and activity has been well established in many studies (McCawley and Matrisian, (2000) *Mol Med Today* **6**, 149-156). As tumors manifest high levels of gelatinase activity, inhibitors specific for the gelatinases are highly sought.

In the past eight years there have been numerous approaches aimed at targeting MMP activities in tumors and several clinical trials were carried out to test the efficacy of various inhibitors. Unfortunately, the results of these trials were disappointing due to the lack of an objective clinical response and undesired side effects. Many reasons have been postulated for these effects but at the core of the problem remains the issue of inhibitor selectivity (Pavlaki, M. and Zucker, S. (2003) *Cancer Metastasis Rev* **22**, 177-203; Coussens, L.M., Fingleton, B., and Matrisian, L.M. (2002) *Science* **295**, 2387-2392). Indeed, virtually all MMP inhibitors tested so far have been broad-spectrum inhibitors, designed around chelation of the active site zinc ion (Skiles et al. (2004) *Curr Med Chem* **11**, 2911-2977) and their spectrum of inhibition includes, in addition to MMPs, other metalloenzymes. Because targeting gelatinases remains to be of great promise in cancer therapy (Matrisian et al. (2003) *Cancer Res* **63**, 6105-6109), efforts aimed at developing better and selective gelatinase inhibitors continue.

A mere handful of selective inhibitors for MMPs have been reported in the literature (for a review see: Brown, S., Meroueh, S. O., Fridman, R., and Mobashery, S. (2004) *Curr Top Med Chem* **4**, 1227-1238). The design and properties of inhibitor **2.1** (Scheme 2) has been previously described. Inhibitor **2.1** is a selective mechanism-based inhibitor for gelatinases. This compound binds to the active sites of MMP-2 and MMP-9 with the thiirane moiety coordinating with the zinc ion. This coordination to the active site metal ion activates the thiirane ring for opening by the nucleophilic attack of the active site glutamate in these enzymes (FIG. 3a). A unique property of this inhibitor is that on binding to the active site zinc ion a pattern of slow-binding for inhibition sets in, leading to a rapid process for the on-set of inhibition with an attendant slow process for recovery from slow-binding at the non-covalent stage of inhibition. This non-covalent inhibited species leads to covalent inhibition by modification of the glutamate.

Scheme 2



The synthetic procedures for compounds **2.1**-**2.7** are given in the Experimental Procedures section below.

Inhibitor **2.1**, the prototype of this type of novel mechanism-based inhibitor for gelatinases, is showing promise in mouse models for diseases involving gelatinases (Gu, Z., Cui, J., Brown, S., Fridman, R., Mobashery, S., Strongin, A. Y., and Lipton, S. A. (2005) *J. Neurosci.* **25**, 6401-6408; Kruger, A., Arlt, M. J., Gerg, M., Kopitz, C., Bernardo, M. M., Chang, M., Mobashery, S., and Fridman, R. (2005) *Cancer Res.* **65**, 3523-3526). The poor solubility of this inhibitor in aqueous medium, however, is a limitation of the molecule. The compounds designed and described in this Example provide increased aqueous solubility over inhibitor **2.1**. Furthermore, the concept behind the inhibitor design in targeting other MMPs has been explored in this Example.

A computational model of the inhibitor bound in the active site of MMP-2 within the constraints of the data from X-ray absorption spectroscopy has been generated; see FIG. 2B; (Kleifeld, O., Kotra, L. P., Gervasi, D. C., Brown, S., Bernardo, M. M., Fridman, R., Mobashery, S., and Sagi, I. (2001) *J. Biol. Chem.* **276,** 17125-17131). This model for inhibition of inhibitor **2.1** led the way in exploration of the next generation of this type of MMP inhibitor. The possibility for specific electrostatic interactions near the terminal phenyl group in inhibitor **2.1**

bound to the active site of MMP-2 was anticipated for judiciously designed chemical functionalities into the molecular template of compound **2.1**.

Three new functional groups are introduced in MMP inhibitors in this Example, the methylsulfonamide (compounds **2.2** and **2.3**), the nitro (compounds **2.4** and **2.5**) and the acetamide (compounds **2.6** and **2.7**), at the terminal phenyl ring system to exploit these electrostatic interactions (Scheme 2). It was expected that these molecules would improve the solubility in aqueous solutions, while exhibiting high selectivity in inhibition toward gelatinases and the membrane-anchored MMP, MT1-MMP (MMP-14), which all share a deep S1' binding site. As will be described herein, these expectations have been borne out, making these inhibitors valuable tools in studies of the functions of MMPs in disease processes. Furthermore, oxirane variants of these molecules (compounds **2.2**, **2.4**, and **2.6**) have been prepared. The fact that the oxirane variants are either poor inhibitors or demonstrate no observable inhibitory properties toward MMPs underscore the importance of the thiirane group for this inhibitor class.

Experimental Procedures:

Synthesis — ^{1}H and ^{13}C NMR spectra were recorded on either a Varian UnityPlus 300 MHz or a Varian INOVA 500 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale. Mass spectra were recorded on a JEOL JMS-AX505HA and a Finnigan-MAT 8430 high-resolution magnetic sector mass spectrometers. For silica gel column chromatography, EMD Silica gel 60 was employed. Thin-layer chromatography was performed with Whatman 0.25 mm silica gel 60-F plates. All other reagents were purchased from Aldrich Chemical Company, Lancaster or Across Organics.

4-(Allylthio)phenol. To a stirred solution of 4-hydroxythiophenol (4.30 g, 34.1 mmol) in DMF (25 ml) were added K_2CO_3 (4.71 g, 34.1 mmol) and allyl bromide (3.09 ml, 34.1 mmol) at ice-water temperature, and the mixture was stirred for 15 minutes, prior to stirring overnight at room temperature. After the addition of 1 M aqueous HCl, the mixture was extracted with ether (3x). The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under

reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane, 1/10 to 1/6) to give **2.9** (5.74 g, 70%) as a white semi-solid. The ^{1}H and ^{13}C NMR spectra and mass spectrum were identical to the reported values (Goux, C., Lhoste, P., and Sinou, D. (1994) *Tetrahedron* **50**, 10321-10330).

1-Allylthio-4-(4-nitrophenoxy)benzene. To a stirred solution of **2.9** (3.46 g, 20.8 mmol) in DMF (100 ml) were added cesium carbonate (10.2 g, 31.2 mmol) and 1-fluoro-4-nitrobenzene (**2.10**) (2.94 g, 20.8 mmol) at room temperature, and the mixture was stirred at the same temperature for 2 days. After dilution with water, the mixture was extracted into hexane (3x). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give **2.11** (5.32 g, 89%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.55 (dt, 2H, J = 6.9, 1.2 Hz), 5.10 (dt, 1H, J = 10.2, 1.2 Hz), 5.13 (dt, 1H, J = 17.1, 1.2 Hz), 5.88 (ddt, 1H, J = 17.1, 10.2, 6.9 Hz), 6.98-7.04 (m, 4H), 7.38-7.43 (m, 2H), 8.18-8.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.8, 117.1, 117.9, 120.9, 126.0, 132.3, 132.5, 133.4, 142.7, 153.4, 163.1; HRMS (FAB) calcd for $C_{15}H_{13}NO_3S$ (M^+) 287.0616, found 287.0593.

1-Allylthio-4-[4-(methanesulfonamido)phenoxy]benzene. To a stirred solution of **2.11** (636 mg, 2.21 mmol) in THF (22 ml) were added acetic acid (2.54 ml, 44.2 mmol) and zinc powder (5.80 g, 88.4 mmol) at room temperature, and the suspension was stirred for 30 min (an exothermic reaction). After dilution with ethyl acetate, the mixture was filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude **2.12** (577 mg) as an orange oil, which was employed in the next reaction without purification.

To a stirred solution of **2.12** (577 mg) in CH_2Cl_2 (10 ml) were added pyridine (894 μL, 11.1 mmol) and methanesulfonyl chloride (205 μL, 2.65 mmol) at ice-water temperature. After 15 min, the mixture was warmed to room temperature and the stirring was continued for an additional 2 h. Subsequent to the addition of saturated $NaHCO_3$, the mixture was extracted with ethyl acetate (3x). The combined organic layer was washed with 1 M aqueous HCl, saturated $NaHCO_3$

solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (CH_2Cl_2) to give **2.13** (662 mg, 89% from **2.11**) as a pale red solid. Compound **2.12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.45 (br.d, 2H, J = 7.2 Hz), 3.59 (br.s, 2H), 5.01-5.06 (m, 2H), 5.84 (ddt, 1H, J = 17.1, 9.6, 6.9 Hz), 6.66-6.70 (m, 2H), 6.83-6.88 (m, 4H), 7.29-7.32 (m, 2H). Compound **2.13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.01 (s, 3H), 3.50 (dt, 2H, J = 7.2, 1.2 Hz), 5.04-5.11 (m, 2H), 5.86 (ddt, 1H, J = 16.8, 10.2, 6.9 Hz), 6.67 (br.s, 1H), 6.90-6.95 (m, 2H), 6.96-7.01 (m, 2H), 7.20-7.26 (m, 2H), 7.32-7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 38.4, 39.3, 117.5, 119.3, 119.9, 123.8, 130.2, 132.0, 132.9, 133.8, 155.2, 156.1; HRMS (FAB) calcd for $C_{16}H_{17}NO_3S_2$ (M^+) 335.0650, found 335.0639.

4-(4-Acetamidophenoxy)-1-allylthiobenzene. To a stirred solution of **2.12** (794 mg), which was prepared from **2.11** (830 mg, 2.89 mmol) in the same manner as described for compound **2.13**, in CH_2Cl_2 (15 ml) were added pyridine (500 μL, 6.18 mmol) and acetic anhydride (292 μL, 3.09 mmol) at ice-water temperature, and the mixture was stirred at the same temperature for 1h. Subsequent to the addition of saturated $NaHCO_3$, the mixture was extracted with ethyl acetate (3x). The combined organic layer was washed with 1 M aqueous HCl, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/CH_2Cl_2 = 1/8) to give **2.14** (782 mg, 99% from **2.11**) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.17 (s, 3H), 3.47 (d, 2H, J = 7.0 Hz), 5.04-5.07 (m, 2H), 5.85 (ddt, 1H, J = 17.0, 10.0, 7.0 Hz), 6.87-6.90 (m, 2H), 6.94-6.97 (m, 2H), 7.31-7.35 (m, 2H), 7.44-7.47 (m, 2H), 7.54 (br.s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 38.5, 117.5, 118.7, 119.6, 121.7, 129.0, 132.9, 133.6, 133.7, 153.1, 156.7, 168.4; HRMS (FAB) calcd for $C_{17}H_{17}NO_2S$ (M^+) 299.0980, found 299.0980.

{4-[4-(Methanesulfonamido)phenoxy]phenylsulfonyl}methyloxirane. To a stirred solution of **2.13** (544 mg, 1.62 mmol) in CH_2Cl_2 (20 ml) was added *m*CPBA (4.2 g, 17.05 mmol) at ice-water temperature, and the mixture was stirred at room temperature for 9 days. With ice-cooling, the reaction was quenched with saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ solutions, and the mixture was extracted with ethyl

acetate (3x). The combined organic layer was washed with saturated $Na_2S_2O_3$ solution, saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane = 3/2) to give **2.2** (386 mg, 62%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49 (dd, 1H, J = 5.1, 1.8 Hz), 2.83 (m, 1H), 3.06 (s, 3H), 3.27-3.36 (m, 3H), 6.77 (br.s, 1H), 7.08-7.11 (m, 4H), 7.28-7.33 (m, 2H), 7.88-7.93 (m, 2H); ^{13}C NMR (125 MHz, acetone-d_6): δ 39.4, 45.9, 46.6, 59.9, 118.3, 122.3, 123.6, 131.6, 134.6, 136.5, 152.7, 163.5; HRMS (FAB) calcd for $C_{16}H_{17}NO_6S_2$ (M^+) 383.0497, found 383.0496.

[4-(4-Nitrophenoxy)phenylsulfonyl]methyloxirane. This material was prepared in the same manner as described for **2.2**, with the exception that **2.11** was used in place of **2.13**. The crude material was purified by silica gel column chromatography (ethyl acetate/hexane, 2/3) to give **2.4** (56%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51 (dd, 1H, J = 4.5, 2.5 Hz), 2.83 (t, 1H, J = 4.5 Hz), 3.28 (dd, 1H, J = 14.0, 7.0 Hz), 3.35 (m, 1H), 3.41 (dd, 1H, J = 14.0, 4.0 Hz), 7.16-7.17 (m, 2H), 7.23-7.25 (m, 2H), 7.99-8.01 (m, 2H), 8.28-8.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 45.7, 45.8, 59.6, 119.1, 119.6, 126.2, 131.0, 134.9, 144.0, 160.2, 160.8; HRMS (FAB) calcd for $C_{15}H_{14}NO_6S$ ($M+H^+$) 336.0542, found 336.0545.

[4-(4-Acetamidophenoxy)phenylsulfonyl]methyloxirane. This material was prepared in the same manner as described for **2.2**, with the exception that **2.14** was used in place of **2.13**. The crude material was purified by silica gel column chromatography (ethyl acetate/hexane = 3/1) to give **2.6** (34%) as a white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.48 (dd, 1H, J = 4.5, 1.5 Hz), 2.82 (m, 1H), 3.26-3.34 (m, 3H), 7.03-7.08 (m, 4H), 7.41 (br.s, 1H), 7.55-7.58 (m, 2H), 7.85-7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 45.7, 45.8, 59.8, 117.6, 120.8, 122.0, 130.4, 133.0, 135.4, 151.1, 163.0, 168.5; HRMS (FAB) calcd for $C_{17}H_{18}NO_5S$ ($M+H^+$) 348.0906, found 348.0913.

{4-[4-(Methanesulfonamido)phenoxy]phenylsulfonyl}methylthiirane. To a stirred solution of **2.2** (82 mg, 0.21 mmol) in MeOH-THF (3:1, 2 ml) was added

thiourea (41 mg, 0.53 mmol) at room temperature, and the mixture was stirred overnight at the same temperature. After concentration under reduced pressure, the residue was dissolved into ethyl acetate. The ethyl acetate solution was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane, 1/1) to give **2.3** (67 mg, 77%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (dd, 1H, J = 5.1, 1.8 Hz), 2.55 (dd, 1H, J = 6.3, 1.2 Hz), 3.06 (s, 3H), 3.07 (m, 1H), 3.22 (dd, 1H, J = 14.1, 7.8 Hz), 3.50 (dd, 1H, J = 14.1, 5.7 Hz), 6.72 (br.s, 1H), 7.08-7.12 (m, 4H), 7.30-7.33 (m, 2H), 7.87-7.91 (m, 2H); ^{13}C NMR (125 MHz, acetone-d_6): δ 24.4, 27.2, 39.3, 62.6, 118.4, 122.3, 123.6, 131.9, 133.9, 136.4, 152.7, 163.6; HRMS (FAB) calcd for $C_{16}H_{17}NO_5S_3$ (M^+) 399.0269, found 399.0268.

[4-(4-Nitrophenoxy)phenylsulfonyl]methylthiirane. This material was prepared in the same manner as described for **2.3**, with the exception that **2.4** was used in place of **2.2**. The crude material was purified by silica gel column chromatography (ethyl acetate/hexane, 1/3) to give **5** (79%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.20 (dd, 1H, J = 5.5, 2.0 Hz), 2.58 (dd, 1H, J = 6.0, 2.0 Hz), 3.10 (m, 1H), 3.31 (dd, 1H, J = 14.0, 7.5 Hz), 3.52 (dd, 1H, J = 14.0, 6.5 Hz), 7.15-7.18 (m, 2H), 7.23-7.26 (m, 2H), 7.97-8.00 (m, 2H), 8.28-8.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 24.0, 26.0, 62.5, 119.1, 119.8, 126.2, 131.2, 134.4, 160.3, 160.8; ^{13}C NMR (125 MHz, acetone-d_6): δ 24.5, 27.2, 62.6, 120.2, 121.0, 127.1, 132.3, 136.2, 145.0, 161.1, 162.4; HRMS (FAB) calcd for $C_{15}H_{14}NO_5S_2$ ($M+H^+$) 352.0313, found 352.0297.

[4-(4-Acetamidophenoxy)phenylsulfonyl]methylthiirane. This material was prepared in the same manner as described for **2.3**, with the exception that **2.6** was used in place of **2.2**. The crude material was purified by silica gel column chromatography (ethyl acetate/hexane, 3/2 to 2/1) to give **7** (76%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (dd, 1H, J = 5.1, 1.8 Hz), 2.20 (s, 3H), 2.54 (dd, 1H, J = 6.3, 1.5 Hz), 3.06 (m, 1H), 3.19 (dd, 1H, J = 14.1, 7.8 Hz), 3.52 (dd, 1H, J = 14.1, 5.7 Hz), 7.03-7.08 (m, 4H), 7.52 (br.s, 1H), 7.56-7.59 (m, 2H), 7.84-

7.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.1, 24.4, 26.0, 62.6, 117.4, 121.0, 121.8, 130.7, 131.6, 135.2, 150.7, 163.1, 168.6; HRMS (FAB) calcd for $C_{17}H_{18}NO_4S_2$ ($M+H^+$) 364.0677, found 364.0651.

Assessment of Inhibitor Solubility — Aliquots (10 μL) of the solutions of the thiirane compounds **2.1**, **2.3**, **2.5**, and **2.7** in DMSO (e.g., 10 mM, 12 mM, 14 mM and higher concentrations) were added to 990 μL of buffer R [50 mM HEPES (pH 7.5), 0.15 M NaCl, 5 mM $CaCl_2$, 0.01% Brij-35, 1% DMSO] at 37 °C. Each mixture was inspected for clarity (or turbidity) to calculate the approximate upper limit of solubility.

Enzymatic Activity Assays — Enzymatic activity was monitored with synthetic peptide, fluorescence-quenched substrates from Peptides International, Inc. (Louisville, KY). The activities of MMP-2, MMP-9, MMP-7 and MMP-14 were monitored with MOCAcPLGLA$_2$pr(Dnp)AR-NH_2 at excitation and emission wavelengths of 328 and 393 nm, respectively, in buffer R MOCAcRPKPVE(Nva)WRK(Dnp)NH_2 was the fluorogenic substrate used to measure MMP-3 at 325 and 393 nm, in buffer R. MMP-1 was assayed with (Dnp)P(Cha)GC(Me)HAK(NMa)NH_2 at 340 and 440 nm, in a buffer consisting of 50 mM Tris (pH 7.6), 200 mM NaCl, 5 mM $CaCl_2$, 20 mM $ZnSO_4$, 0.05% Brij.35 . Less than 10% substrate hydrolysis was monitored (Knight, C. G. (1995) *Methods Enzymol* **248**, 18-34).

Fluorescence was measured using a Photon Technology International (PTI) spectrofluorometer, equipped with RadioMaster™ and FeliX™ hardware and software, respectively. The excitation and emission band passes were 1 and 3 nm, respectively. An integration time of 4 seconds was used for data acquisition. The assays were carried out at 25 °C and the cuvette holder was kept at the same temperature. Quartz or disposable acrylic micro or semi-micro cuvettes from Sarstedt (Newton, NC) and Perfector Scientific (Atascadero, CA), respectively, were used.

Enzyme Inhibition Studies — Slow-binding enzyme inhibition was monitored continuously for 20-60 min, by adding the enzyme (0.5-1 nM) to a solution of buffer R containing the appropriate fluorogenic substrate and increasing

concentrations of the inhibitor (final volume 2 ml) in acrylic cuvettes with stirring. The progress curves were non-linear least squares fitted to Equation 1 (Muller-Steffner et al. (1992) *J Biol Chem* **267**, 9606-9611):

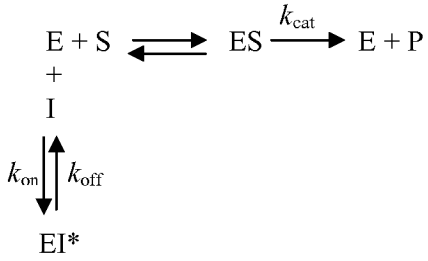
$$F = v_s t + (v_o - v_s)\,(1\text{-}\exp(\text{-}kt))/k + F_o \qquad \text{(Eq. 1)}$$

where v_o represents the initial rate, v_s the steady state rate, k the apparent first-order rate constant characterizing the formation of the steady-state enzyme-inhibitor complex, and F_o the initial fluorescence, using the program Scientist (MicroMath Scientific Software, Salt Lake City, UT). Association and dissociation rate constants (k_{on} and k_{off}, respectively) were obtained from the slope and intercept, respectively, of plots of the apparent first-order rate constant k *versus* the inhibitor concentration according to Equation 2:

$$k = k_{off} + k_{on}[I]/(1+[S]/K_m) \qquad \text{(Eq. 2)}$$

describing a one-step association mechanism (Scheme 3),

Scheme 3



where S is the fluorogenic peptide substrate used and the EI* is the product of slow-binding inhibition. The expression for k_{on} includes the requisite conformational change necessary for the formation of EI*. The K_m values used for the reaction of MMP-2, MMP-9 and MMP-14 with the fluorogenic substrate MOCAcPLGLA$_2$pr(Dnp)AR-NH$_2$ were 2.46 $\pm$ 0.34, 3.06 $\pm$ 0.74 (Olson, M. W., Gervasi, D. C., Mobashery, S., and Fridman, R. (1997) *J Biol Chem* **272**, 29975-29983) and 6.9 $\pm$ 0.6 μM (Toth, M., Bernardo, M. M., Gervasi, D. C., Soloway, P. D., Wang, Z., Bigg, H. F., Overall, C. M., DeClerck, Y. A., Tschesche, H., Cher, M.

L., Brown, S., Mobashery, S., and Fridman, R. (2000) *J Biol Chem* **275**, 41415-41423), respectively. The inhibition constant, K_i, was given by k_{off}/k_{on}. Alternatively, K_i values were obtained by plotting $(v_o-v_s)/v_s$ *versus* the inhibitor concentration, according to Equation 3:

$$(v_o - v_s)/v_s = [I]/(K_i(1+[S]/K_m)) \qquad \text{(Eq. 3)}.$$

For analysis of simple linear competitive inhibition, reaction mixtures containing the enzyme (~1 nM) and increasing concentrations of the inhibitor, in buffer R (final volume 1 mL), were incubated for ~ 16 hours, at 25 °C in semi-micro acrylic cuvettes. The remaining enzymatic activity was measured with the appropriate synthetic peptide fluorogenic substrate for 5-10 minutes. The initial velocities for the reaction of the enzyme with the substrate were determined by linear regression analysis of the fluorescence *versus* time traces using FeliX™. These initial rates were fitted to Equation 4 (Segel, I. H. *Enzyme Kinetics*, John Wiley & Sons, Inc.: New York (1975)):

$$v_i/v_o = (K_m + [S])/(K_m(1 + [I]/K_i) + [S])) \qquad \text{(Eq. 4)}$$

where v_i and v_o represent the initial velocity in the presence and absence of inhibitor, respectively, using the program Scientist.

Equilibrium Dialysis — Mixtures of enzyme (10 nM) in the presence and absence of inhibitor (1 mM) were incubated at room temperature for ~3 hours. The remaining enzyme activity was measured with the appropriate fluorogenic substrate, as described above. Part of the reaction mixture (~150 µL) was dialyzed in either dialysis tubing (Invitrogen) or in a 0.1-0.5 mL capacity Slide-A-Lyzer® dialysis cassette (Pierce), against buffer R (3 x 1 L) containing no DMSO, at room temperature, for >4 hour periods prior to change of buffer to allow for equilibration, over a 48 hour period. The remaining of the inhibition mixture was left on a rotator, at room temperature, over the same period of time. Both the dialyzed and non-dialyzed solutions were tested for MMP activity using the proper fluorogenic

substrate. Enzyme activity was expressed in percentage relative to that in the absence of inhibitor.

Cell Culture — Human HeLa S3 cells were obtained from the American Type Culture Collection (ATTC, Manassas, VA) (CCL-2.2) and grown in suspension in MEM Spinner (Quality Biologicals, Inc., Gaithersburg, MD) supplemented with 5% horse serum. Nonmalignant, monkey kidney epithelial cells, BS-C-1 (CCL-26), and human fibrosarcoma cells, HT1080 (CCL-2.2), were obtained from ATCC and cultured in Dulbecco's modified Eagle's medium (DMEM, Invitrogen, Carlsbad, CA), supplemented with 10% fetal bovine serum (FBS) and antibiotics.

Recombinant Vaccinia Viruses — Recombinant vaccinia viruses encoding for T7 RNA polymerase (vTF7-3) or pro-MMP-2 (vT7-72), pro-MMP-9 (vT7-92), MT1-MMP (vTF-MT1), TIMP-1 (vTF-TIMP-1) and TIMP-2 (vSC59-T2) were produced by homologous recombination as previously described (Fuerst, T. R., Earl, P. L., and Moss, B. (1987) *Mol Cell Biol* **7**, 2538-2544).

Recombinant Proteins, Enzymes and Inhibitors — Human recombinant pro-MMP-2 and pro-MMP-9, TIMP-1 and TIMP-2 were expressed in HeLa S3 cells infected with the corresponding recombinant vaccinia viruses and purified to homogeneity from the media as previously described (Olson, M. W., Gervasi, D. C., Mobashery, S., and Fridman, R. (1997) *J Biol Chem* **272**, 29975-29983). Pro-MMP-2 and pro-MMP-9 were activated by incubation with 1 mM *p*-aminophenylmercuric acetate (APMA) for ~2 hours at 37 °C as previously described (Olson, M. W., Gervasi, D. C., Mobashery, S., and Fridman, R. (1997) *J Biol Chem* **272**, 29975-29983). APMA was dialyzed out in collagenase buffer (50 mM Tris-HCl (pH 7.5) 5 mM $CaCl_2$, 150 mM NaCl and 0.02% Brij-35).

Human recombinant active MMP-1, and MMP-7 were from R&D Systems (Minneapolis, Minnesota) and Chemicon International (Temecula, CA), respectively, and the recombinant catalytic domains of human MMP-3 and MMP-14 were from CalBiochem (San Diego, CA). Active enzyme concentration was determined by active-site titration with solutions of either TIMP-1 or TIMP-2 with known concentration. The hydroxamate-based MMP inhibitor BB-94 was

synthesized in the Mobashery laboratory and GM6001 (hydroxamate inhibitor) was purchased from Chemicon. Stock solutions of BB-94, GM6001, and compounds **2.2-2.7** were prepared in DMSO in the mM concentration range.

Pro-MMP-2 Activation on Cells – Confluent BS-C-1 cells in 12-well plates, were co-infected with v-TF7-3 and vTF-MT1 viruses for 45 min, in infection medium (DMEM supplemented with 2.5% FBS and antibiotics), at 37 °C, as described by Hernandez-Barrantes et al. ((2000) *J Biol Chem* **275**, 12080-12089). The infection medium was removed and the cells were incubated overnight with serum-free DMEM supplemented with L-glutamine and antibiotics containing increasing concentrations (0-5 μM) of the synthetic MMP inhibitors (MMPIs). The cells were washed twice with phosphate buffer saline (PBS), and incubated for 6 hours with serum-free DMEM containing pro-MMP-2 (10 nM). The cells were rinsed twice with cold PBS and lysed with cold lysis buffer (25 mM Tris-HCl (pH 7.5), 1% IGEPAL CA-630, 100 mM NaCl) containing protease inhibitors (1 pellet of Complete Mini, EDTA-free protease inhibitor mixture from Roche Diagnostics/10 mL of buffer). The lysates were then subjected to gelatin zymography to monitor pro-MMP-2 activation and to immunoblot analysis to detect MT1-MMP expression and processing.

Gelatin Zymography and Immunoblot Analysis — Gelatin zymography was performed using 10% Tris-glycine SDS-polyacrylamide gels, containing 0.1% gelatin, as previously described (Toth, M., Gervasi, D. C., and Fridman, R. (1997) *Cancer Res.* **57**, 3159-3167). The samples for immunoblot analysis were subjected to reducing SDS-PAGE followed by transfer to nitrocellulose membranes. MT1-MMP was probed with rabbit polyclonal antibody 815 to MT1-MMP, from Chemicon.

Migration and Invasion Assays — For migration assays, HT1080 cells were cultured in 6-well plates in complete media until they reached confluence. Prior to the migration assay, the cells were treated with serum-free media containing mitomycin C (25 μg/mL), in the presence and absence of concanavalin A (ConA) (20 μg/mL, 30 minutes) to induce pro-MMP-2 activation (Gervasi, D. C., Raz, A., Dehem, M., Yang, M., Kurkinen, M., and Fridman, R. (1996) *Biochem Biophys Res*

Commun **228**, 530-538). Scratch wounds were then carefully made in the confluent monolayer using a disposable plastic pipette tip. After gentle rinsing twice with PBS to remove detached cells, serum-free media containing increasing concentrations of inhibitor **2.3** were added, and the cells were incubated at 37 °C for various times. Photographs were taken using an Olympus Model DF 12-2 camera connected to a Nikon TMS-F microscope at 10x magnification, at the indicated time points. The extent of wound closure in the presence or absence of inhibitor was quantified by measuring the width of the wound with a ruler using an amplified PowerPoint figure.

Tumor cell invasion was carried out in 8-μm pore Transwell inserts (Becton Dickinson, Boston, MA) coated with 50 μg Matrigel per filter. HT1080 cells suspended in serum-free DMEM containing 0.1 % bovine serum albumin (BSA) and various doses of inhibitor **2.3** (0.1–10 μM) or 1% DMSO (vehicle) were seeded ($2x10^5$ cells/insert) on the Matrigel-coated inserts. The lower compartment was filled with DMEM containing 5 % FBS. After an 18 h-incubation at 37 °C in a humidified atmosphere with 5% CO_2, the upper surface of the membrane in each insert was wiped off with a cotton swab to remove all of the non invading cells. The cells that migrated to the lower side of the Matrigel-coated filter were fixed and stained with Diff-Quik® (Dade Behring Inc., Newark, DE), and counted under a microscope in three different fields. Each treatment was assayed in quadruplicate.

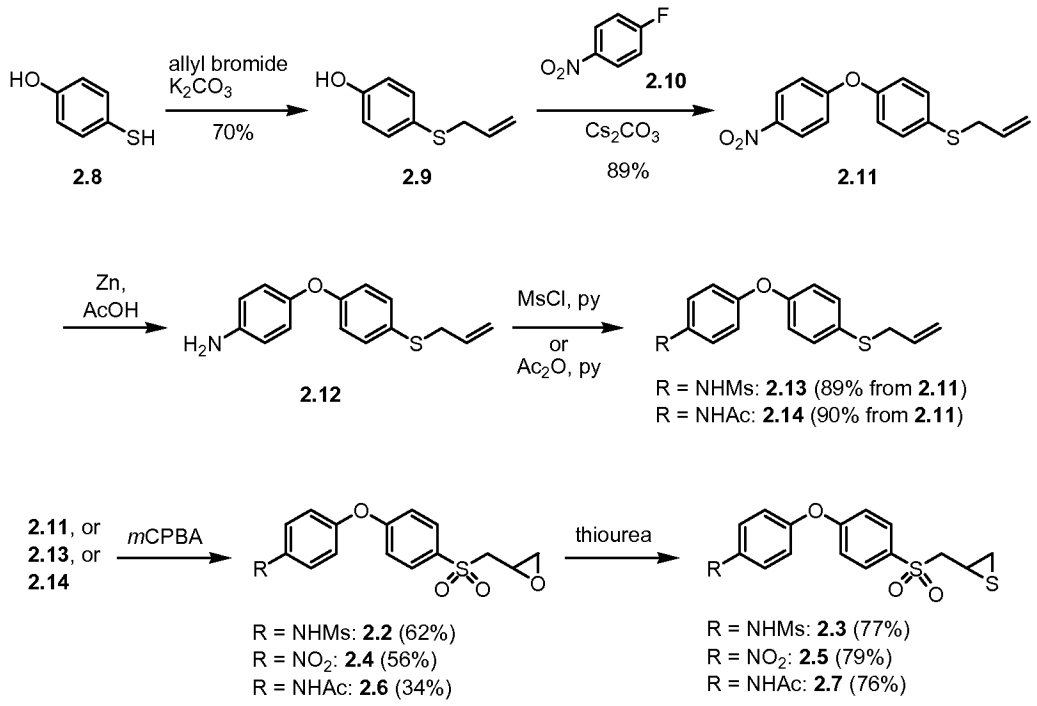
Chemosensitivity Assay – Cell viability after exposure of the cells to the inhibitors was assessed by 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium, monosodium salt (WST-1, Roche Diagnostics Gmbh, Mannheim, Germany) staining. Briefly, HT1080 cells ($2x10^4$ cells/well) were seeded in 96-well culture plates in complete medium. After overnight culture, the medium was replaced with serum and phenol-free media containing 0.1% BSA and supplemented with or without inhibitor **2.3** (0-10 μM final concentrations). Control medium was supplemented with 1% DMSO. After 18 hours incubation, WST-1 (10 µL/well) was added and the difference in absorbance at 450 and 655 (reference filter) nm was measured using a Bio-Rad Benchmark microplate reader. Data were collected using the Microplate Manager software. The absorbance of

blank wells containing control media but no cells (typically <5%) was subtracted. Each treatment was assayed in quadruplicate.

Results And Discussion:

Design and synthesis of MMP inhibitors — The computational model for binding of inhibitor **2.1** to the active site of MMP-2 is shown in FIG. 3B. The site for substitution at the *para* position of the terminal phenyl ring of the inhibitor is indicated by an arrow. Scheme 4 illustrates the synthetic route to oxiranes **2.2**, **2.4** and **2.6**, and thiiranes **2.3**, **2.5** and **2.7**.

Scheme 4



Chemoselective allylation of commercially available 4-hydroxythiophenol (**2.8**) provided phenol **2.9** (Goux et al. *Tetrahedron* **1994**, *50*, 10321-10330) in 70% yield, which was subsequently coupled with 1-fluoro-4-nitrobenzene (**2.10**) in the presence of cesium carbonate to afford the diphenyl ether **2.11** in 89% yield. The nitro group of **2.11** was reduced over elemental zinc and the resulting amine **2.12** was treated with methanesulfonyl chloride or acetic anhydride to give the

corresponding amides **2.13** and **2.14**, respectively, in high yields. Oxidation of **2.13**, **2.11** and **2.14** to their corresponding oxiranes **2.2**, **2.4** and **2.6** required excess of *m*CPBA (10-12 equiv.) and took long reaction time (9-10 days) due to the low reactivity of the olefin moieties; the isolated yields of the oxiranes were moderate (34-62%).

Finally, the conversion of compounds **2.2**, **2.4** and **2.6** to the corresponding thiiranes **2.3**, **2.5** and **2.7** was accomplished by the treatment with thiourea in good yields. Compounds **2.3** and **2.7** had improved solubility in aqueous solution compared to the prototypic inhibitor **2.1**. Solubility was investigated in 50 mM HEPES (pH 7.5), 0.15 M NaCl, 5 mM $CaCl_2$, 0.01% Brij-35, 1% DMSO, which was the buffer that we used for all the kinetic experiments (see below). The maximal solubility for the samples were **2.1**: 80 μM; **2.3**: 340 μM; **2.5**: 60 μM; **2.7**: 540 μM.

Enzyme inhibition kinetics — The mechanism of action of this class of MMP inhibitors stipulates that the thiirane sulfur would coordinate with the active-site zinc ion (FIG. 2). Consistent with this expectation, the three synthetic thiiranes of this study (compounds **2.3**, **2.5** and **2.7**) are excellent inhibitors of gelatinases (and of MT1-MMP in the case of inhibitor **2.3**) (Table 2), whereas the corresponding oxiranes (compounds **2.2**, **2.4** and **2.6**) are either poor inhibitors or not inhibitory at all toward all the tested MMPs (Table 3). For Table 2, the enzymes (0.5-1 nM) were added to a solution of the proper synthetic fluorogenic substrate and increasing concentrations of the inhibitor in buffer R. Substrate hydrolysis was monitored for up to 30 minutes. The kinetic parameters were evaluated as described above. For Table 2, the enzymes (0.5-1 nM) were incubated with increasing concentrations of inhibitor in buffer R. The remaining activity was measured with the appropriate synthetic fluorogenic substrate. The kinetic parameters for rapid, competitive inhibition were evaluated as described above.

TABLE 2

*Kinetic parameters for MMP inhibition by compounds **2.3**, **2.5**, and **2.7***

Enzyme	k_{on}	k_{off}	K_i
	$M^{-1}s^{-1}$	s^{-1}	μM
Compound **2.3**			
MMP-2	$(2.1 \pm 0.5) \times 10^4$	$(3.5 \pm 1.6) \times 10^{-4}$	0.016 ± 0.09
MMP-9	$(4.9 \pm 0.2) \times 10^3$	$(9.0 \pm 2.0) \times 10^{-4}$	0.18 ± 0.05
MMP-14	$(6.9 \pm 0.8) \times 10^2$	$(6.4 \pm 0.5) \times 10^{-4}$	0.9 ± 0.1
MMP-7			295 ± 10
MMP-3			3.6 ± 0.2
MMP-1			NI[a] up to 25 μM
Compound **2.5**			
MMP-2	$(1.9 \pm 0.6) \times 10^3$	$(1.3 \pm 0.2) \times 10^{-3}$	0.7 ± 0.2
MMP-9			1.0 ± 0.1
MMP-14			4.9 ± 0.3
MMP-7			153 ± 16
MMP-3			131 ± 9
MMP-1			67 ± 18
Compound **2.7**			
MMP-2	$(1.2 \pm 0.3) \times 10^4$	$(1.3 \pm 0.3) \times 10^{-3}$	0.11 ± 0.04
MMP-9			0.13 ± 0.01
MMP-14			0.68 ± 0.05
MMP-7			39 ± 3
MMP-3			12.2 ± 0.9
MMP-1			5.4 ± 0.4

[a]NI: not inhibiting

TABLE 3

Kinetic parameters for MMP inhibition by compounds ***2.2****,* ***2.4****, and* ***2.6***

Enzyme	K_i
	μM
Compound **2.2**	
MMP-2	2.4 ± 0.5
MMP-9	NI[a] up to 26 μM
MMP-14	NI up to 170 μM
MMP-7	379 ± 29
MMP-3	NI up to 170 μM
MMP-1	45 ± 9
Compound **2.4**	
MMP-2	13 ± 1
MMP-9	25 ± 5
MMP-14	76 ± 13
MMP-7	130 ± 15
MMP-3	NI up to 190 μM
MMP-1	NI up to 298 μM
Compound **2.6**	
MMP-2	0.84 ± 0.03
MMP-9	34 ± 3
MMP-14	NI up to 230 μM
MMP-7	NI up to 184 μM
MMP-3	NI up to 188 μM
MMP-1	NI up to 154 μM

[a]NI: not inhibiting

In slow-binding inhibition, on binding of the inhibitor to the enzyme, the complex undergoes a requisite conformational change that is not readily predisposed for the reversal of the inhibition (Duggleby et al. (1982) *Biochemistry* **21**, 3364-3370; Morrison et al. *Adv. Enzymol. Relat. Areas Mol. Biol.* **61**, 201-301; and Szedlacsek and Duggleby (1995) *Methods Enzymol.* **249**, 144-180). The slow-binding inhibitor shows a unique profile for the onset of inhibition that is discerned by non-linear progress curves. Slow-binding behavior was seen for inhibitor **2.3** (with MMP-2, MMP-9, and MMP-14), for inhibitor **2.5** (only with MMP-2), and for inhibitor **2.7** (only with MMP-2) (FIG. 4).

The second-order rate constants for the onset of slow-binding inhibition (k_{on}) are rapid (10^2 to 10^4 $M^{-1}s^{-1}$) and the first-order rate constants for the reversal of the process from the non-covalent enzyme-inhibitor complexes (k_{off}) are slow (10^{-4} to 10^{-3} s^{-1}; e.g., the $t_{1/2}$ for reversal for inhibitor **2.3** with MMP-2 and MMP-9 are 34 minutes and 13 minutes, respectively). The dissociation constants for the non-covalent complexes (K_i) that result from slow-binding inhibition are computed from the ratios of k_{off}/k_{on}. Compounds **2.3**, **2.5**, and **2.7** are clearly selective for gelatinases, with **2.3** showing the slow-binding behavior with MMP-14 as well. The K_i values of the slow-binding component for inhibition by **2.3** (16 ± 9 nM, 180 ± 50 nM, 0.9 ± 0.1 μM for MMP-2, MMP-9 and MMP-14, respectively), **2.5** (700 ± 200 nM for MMP-2), and **2.7** (110 ± 40 nM for MMP-2) are listed in Table 2.

It is noteworthy that the inhibition profiles for inhibitors **2.1**, **2.3**, **2.5**, and **2.7** as mechanism-based inhibitors are different from one another, despite the similar structural template for the class. Briefly, inhibitor **2.1** can inhibit both MMP-2 and MMP-9 (the gelatinases), inhibitor **2.3** inhibits the gelatinases plus MMP-14, and most interestingly, inhibitors **2.5** and **2.7** are mechanism-based inhibitors only for MMP-2. Furthermore, these are nanomolar inhibitors for their targeted enzymes and exhibit comparable values for the k_{on} and k_{off} parameters for the slow-binding components of their kinetics.

Covalent vs. non-covalent inhibition of MMPs — The thiirane class of MMP inhibitors was designed to be covalent enzyme inhibitors. On formation of the non-

covalent enzyme-inhibitor complex, the ubiquitous active site glutamates of MMPs (Glu^{404} for MMP-2, for example) were expected to be covalently modified by the inhibitor with the requisite thiirane ring opening (FIG. 2). The kinetics of inhibition indicate two components, a non-covalent stage (slow-binding) and a subsequent stage that may be attributed to the covalent modification of the active site glutamate, as will be outlined.

The covalent component of inhibition results in modification of the glutamate as an ester on its side chain carboxylate. The earlier X-ray absorption spectroscopy analysis with inhibitor **2.1** (Kleifeld et al. (2001) *J Biol Chem* **276**, 17125-17131) had provided evidence for the covalent bond formation, in that on the onset of inhibition the method revealed the formation of a thiolate from the thiirane of the inhibitor (ring opening), coordinated to the active site zinc ion.

Whereas a slow-binding step need not necessarily be a prerequisite for covalent chemistry, both the mechanism-based process leading to covalent enzyme modification and the slow-binding behavior produce time-dependence for the loss of activity seen with these inhibitors (FIG. 4). Our experience with inhibitor **2.1** had shown that slow-binding led to covalent chemistry, with a longevity for the final inhibited species substantially exceeding the duration that would have been anticipated from four times the $t_{1/2}$ for recovery of activity from the slow-binding component of inhibition (in other words, four half-lives leading to an anticipated 94% recovered of activity due to the non-covalent component). This is the case with inhibitors **2.3**, **2.5**, and **2.7** as well.

The slowest $t_{1/2}$ calculated for recovery of activity from the non-covalent slow-binding species for the best inhibition (compound **2.3** with MMP-2) is 34 minutes. Yet, a mere 1% of activity recovery was seen for MMP-2 inhibited by inhibitor **2.3** after 48 hours of dialysis. Four half-lives for recovery from inhibition (94% anticipated recovered activity) with this inhibitor and MMP-2 should be achieved in just under 2.5 hours (136 minutes), were it merely the slow-binding event that accounted for MMP-2 inhibition. This is clearly not the case and the inhibited enzyme is more stable than the k_{off} (from which $t_{1/2}$ is evaluated) indicates. The results of dialyses for inhibitors **2.3**, **2.5**, and **2.7** are given in FIG. 5.

Having documented above that mere slow-binding behavior cannot be responsible for the observed complete inhibition, an explanation was sought as to why any recovery of activity should be seen, if covalent chemistry is involved. The answer is that stability of covalent bonds is relative. Esters are among the least stable covalent bonds in aqueous solution (Westheimer, F. H. (1987) *Science* **235**, 1173-1178). This bond would undergo hydrolysis, resulting in recovery of activity. The process accelerates when there is a more significant exposure of the ester bond to water, conditions that can arise when the protein is denatured.

Matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF MS) analysis, performed on an Applied Biosystems Voyager-DE STR (Framingham, MA) at the Harvard Microchemistry and Proteomics Analysis Facility (Cambridge, MA), was attempted on samples containing MMP-2 (10 μM) in the presence and absence of inhibitor **2.3** to detect a shift in molecular mass consistent with a complex of active MMP-2 (~62 kDa) with the inhibitor. However, after several attempts with different conditions we failed to detect a 400 Da addition in molecular mass to the 62-kDa peak. The difficulty is that at this high end of mass detection the signals are broadened and the identification of the small incremental increase due to the mass of the inhibitor was not possible within the resolution of the instrument.

Effect of gelatinase inhibitors on pro-MMP-2 activation by MT1-MMP — MT1-MMP has been identified as the physiological activator of pro-MMP-2 (Strongin et al. (1993) *J Biol Chem* **268**, 14033-14039). This reaction is regulated at multiple levels and its rate is significantly enhanced by TIMP-2, which, by binding active MT1-MMP, acts as a "receptor" for pro-MMP-2 on the cell surface (Westheimer, F. H. (1987) *Science* **235**, 1173-1178). The binding of pro-MMP-2 to the MT1-MMP/TIMP-2 complex, facilitates the first pro-MMP-2 cleavage by a neighboring TIMP-2-free MT1-MMP molecule (Strongin et al. (1995) *J Biol Chem* **270**, 5331-5338). Pro-MMP-2 activation requires a second autolytic cleavage (Will et al. (1996) *J Biol Chem* **271**, 17119-17123), leading to full activation.

It has been shown previously that broad-spectrum synthetic MMP inhibitors, e.g. marimastat, enhance pro-MMP-2 activation by MT1-MMP in the presence of

TIMP-2 (Toth et al. (2000) *J Biol Chem* **275**, 41415-41423), a process that appears to involve stabilization of mature MT1-MMP at the cell surface by the MMP inhibitor. This enhancing effect on pro-MMP-2 activation was not observed when the cells were exposed to inhibitor **2.1**, which exhibits lower affinity towards MT1-MMP, a feature of its selectivity for inhibition of gelatinases.

Therefore, it was proposed that non-specific targeting of MT1-MMP by broad-spectrum MMP inhibitors might, under certain conditions, elicit a counterproductive effect by enhancing the activity of the MT1-MMP/gelatinase A axis (Bernardo, M. M., Brown, S., Li, Z. H., Fridman, R., and Mobashery, S. (2002) *J Biol Chem* **277**, 11201-11207). Because inhibitor **2.3** is also selective for the gelatinases, it was postulated that it might behave like inhibitor **2.1** in a cellular system of pro-MMP-2 activation by MT1-MMP in the presence of TIMP-2. To this end, BS-C-1 cells, which express low levels of endogenous TIMP-2, were infected to express MT1-MMP, and incubated with pro-MMP-2 in the presence of either GM6001, a broad-spectrum MMP inhibitor or inhibitor **2.3** , as described by Toth and co-workers ((2000) *J Biol Chem* **275**, 41415-41423). Pro-MMP-2 activation was followed by gelatin zymography. As shown in FIG. 6a, exposure of the MT1-MMP-expressing cells to as little as 40 nM GM6001, induced pro-MMP-2 activation, as determined by the appearance of the active form. Higher inhibitor concentrations further enhanced pro-MMP-2 activation, under these conditions.

Of note, this enhancing effect of broad-spectrum MMP inhibitors such as GM6001 requires the endogenous TIMP-2, as have shown previously shown by Toth and co-workers ((2000) *J Biol Chem* **275**, 41415-41423). Consistently, GM6001 caused a dose-dependent accumulation of active MT1-MMP (57 kDa) (FIG. 6B). In contrast, when the cells were incubated with inhibitor **2.3** (up to 4 μM), pro-MMP-2 activation was not observed. Also, the accumulation of active MT1-MMP was not observed with inhibitor **2.3**, consistent with its reduced affinity for this protease when compared to MMP-2 (Table 2).

Although inhibitor **2.3** is also a mechanism-based inhibitor for MT1-MMP, its lower affinity relative to MMP-2 is likely to preclude this inhibitor to influence pro-MMP-2 activation under these conditions. It is also possible that covalent

inhibition of MT1-MMP, as opposed to a reversible inhibition, alters the availability of the active site of MT1-MMP for TIMP-2 binding, a prerequisite for pro-MMP-2 activation ((2000) *J Biol Chem* **275**, 41415-41423). Although more studies are required, these results suggest that the concept behind inhibitor **2.3** is a promising framework from which to further develop more effective and selective MT1-MMP inhibitors, a key protease in tumor cell invasion. Nevertheless, these studies further demonstrate the selectivity of inhibitor **2.3** in a live cellular system and lend credit to the hypothesis that selectivity, rather than affinity, may be key to the successful therapeutic application of synthetic MMP inhibitors.

*Inhibitor **2.3** inhibits HT1080 cell migration and invasion* — It is well established that tumor cell migration and invasion depend on gelatinase activity. Therefore, we wished to evaluate the effect of inhibitor **2.3**, which is selective for the gelatinases, on the migration and invasion of HT1080 cells, as described above. Cell migration was monitored under conditions of pro-MMP-2 activation, which was achieved by ConA treatment, and inhibition of cell proliferation. As shown in FIGs. 7A and B, exposure of HT1080 cells to various doses (0-20 μM) of inhibitor **2.3** significantly inhibited (80% at 2 μM) their migration in a scratch wound assay when compared to untreated cells. Likewise, the ability of HT1080 cells to invade Matrigel-coated filters was significantly reduced by inhibitor **2.3** and as little as 100 nM of inhibitor caused >25% inhibition of HT1080 cell invasion (FIG. 7C).

These effects of inhibitor **2.3** could not be ascribed to cytotoxicity as no evidence of cell toxicity was detected when HT1080 cells were exposed to inhibitor **2.3** up to concentrations of 10 μM, as determined using the WST-1 chemosensitivity assay (data not shown). Given the high selectivity exhibited by this compound towards MMP-2 relative to other MMPs (Table 2), the slower migration in the presence of 200 nM of inhibitor **2.3**, a concentration too low to inhibit other MMPs including MT1-MMP, suggests that the observed effect was most likely due to MMP-2 inhibition. These results further demonstrate the ability of inhibitor **2.3** to act as a selective gelatinase inhibitor in cellular systems and to alter MMP-dependent processes. The new characteristics of inhibitor **2.3** and its high

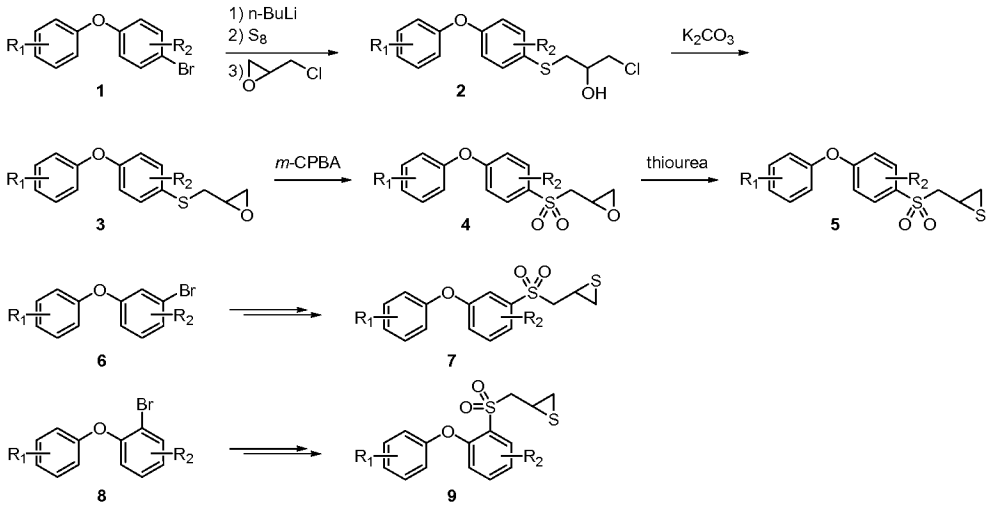
selectivity make this inhibitor an excellent candidate for future in vivo testing in relevant human disease models in mice.

The thiirane class of mechanism-based inhibitors was conceived, designed and prepared by us for the first time in our pursuit of selectivity in inhibition of MMPs of importance to several disease processes. We have revealed in the present report that inhibitor **2.3** targets MMP-2, -9, and -14, whereas inhibitors **2.5** and **2.7** are inhibitory only toward MMP-2. The activities for these new inhibitors provide a unique opportunity in investigations of the roles of these MMPs in various disease processes.

EXAMPLE 3. Synthetic Approach to Aromatic Sulfonylmethylthiiranes

A general strategy for the synthesis of aromatic sulfonylmethylthiiranes and their derivatives is described below (Scheme 5-9). The compounds explicitly depicted in the schemes of Example 3 have been synthesized and their compound data is provided in the Experimental Section following Scheme 29.

Scheme 5.

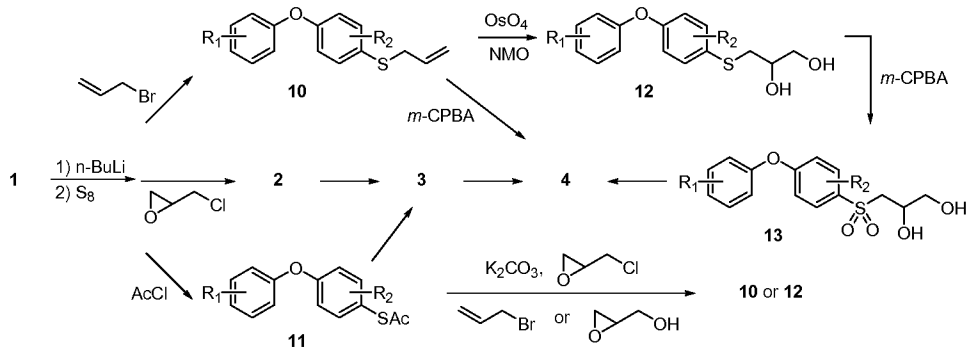


A suitable synthetic sequence to afford phenoxyphenylsulfonylmethyl-thiirane **5** is outlined in Scheme 5 (see Lee et al. *Org. Lett.* **2005**, *7*, 4463-4465; Lim, Brown, and Mobashery, *J. Org. Chem.* **2004**, *69*, 3572-3573). Synthesis commenced with a commercially available bromide, which was lithiated with n-BuLi, was then converted to the thiolate. The thiolate was alkylated with

epichlorohydrin to result in compound **2**. The hydrochloride moiety in compound **2** was transformed to an epoxide ring, followed by sulfide oxidation by use of *m*-CPBA. The resulting epoxide **4** was converted to thiirane **5** using thiourea. When *ortho*- or *meta*-bromide are used instead of para bromide **1**, corresponding sulfonylmethylthiiranes **7** or **9** can be obtained by the same sequence illustrated in Scheme 5.

The thiolate, which was generated by treatment of n-BuLi and sulfur, is a very useful intermediate because it can be reacted with other electrophiles, such as allylbromide and acetyl chloride, yielding compounds **10** and **11** (see Schemes 6 and 7), which can be ultimately converted to epoxide **4**, a precursor of thiirane **5** (Scheme 6). Allylthio-4-phenoxybenzene derivative **10** can be converted directly to sulfonylmethyloxirane **4** by *m*-CPBA. While this method cannot be applied in some cases, dihydroxylation (*J. Am. Chem. Soc.* **1997**, *119*, 311-325) serves as an alternative route to sulfonylmethyloxirane **4**. Diols **12** and **13** can be converted to the epoxide either via tosylation (*Heterocycles* **1990**, *31*, 1555-1562) or Mitsunobu reaction (*Synthesis* **1983**, 116-117). The sulfide can be oxidized to the sulfone before or after formation of the epoxide. The second alkylation product thioacetate **11** can directly give **3** by treatment with epichlorohydrin. When allyl bromide or glycidol are reacted with compound **11**, compounds **10** and **12** can be obtained.

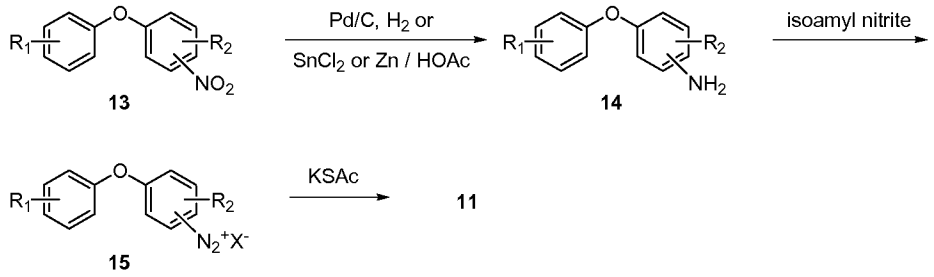
Scheme 6.



Aromatic amines or nitro compounds can be used to prepare compound **11** by the route in Scheme 7. Nitro compound **13** was reduced in the presence of Pd/C and H_2, or $SnCl_2$ or Zn in the presence of AcOH, to provide amine **14**. Aromatic amine **14**

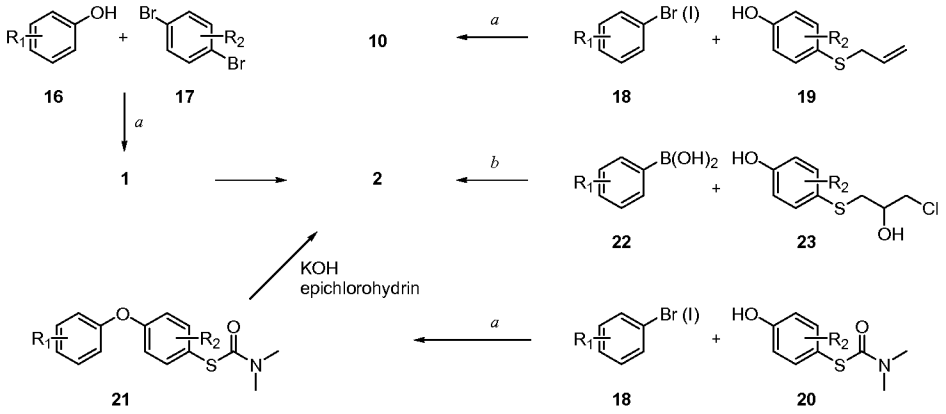
was then diazotized using isoamyl nitrite and reacted with potassium thioacetate to yield aromatic thioacetate **11** (*Synthesis* **2003**, 1225-1230). The resulting thioacetate **11** was then converted to compound **5**, by the route described in Scheme 6.

Scheme 7.



When aromatic bromide or amine are not commercially available, phenolic ethers can be prepares by several methods, as illustrated in Scheme 8.

Scheme 8.



a. CuI (I), N,N-dimethylglycine HCl salt, Cs_2CO_3; b. $Cu(OAc)_2$, Et_3N, 4 Å molecular seives

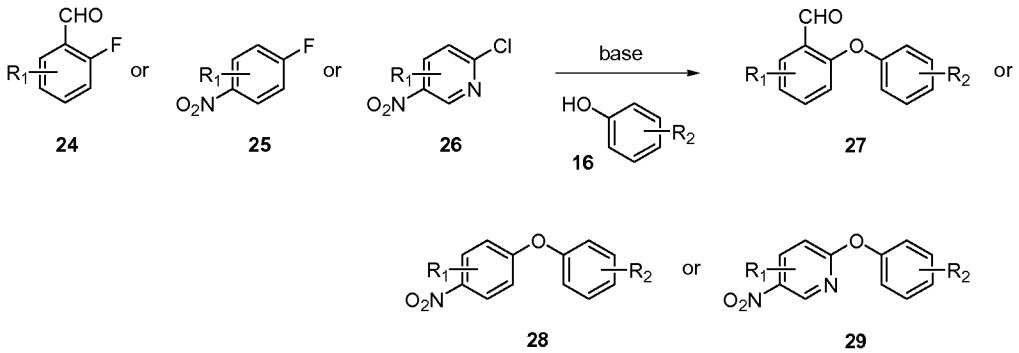
Phenolic ethers can be constructed by copper catalyzed reactions. One method is by Ullmann condensation between aromatic halides and phenol. Another method is by using aromatic boronic acid and phenol.

Phenoxyphenyl bromide was constructed by a *N*,*N*-dimethylglycine promoted Ullmann coupling reaction (*Org. Lett.* **2003**, *5*, 3799-3802) between phenol **16** and dibromobenzene **17** in the presence of copper (I) iodide. When substituted thiophenols are used, we can make thiol incorporated phenol ether, which obviates the step to introduce sulfur atom to the molecule. When allylthiophenol **19** is reacted with aromatic halide **18**, compound **10** can be made. When dimethyl-thiocarbamic acid S-(4-phenoxyphenyl) ester **20** is reacted with aromatic halide **18**, compound **21** can be formed, which was then hydrolyzed to give free thiol under basic condition and then alkylated with epichlorohydrin in the presence of potassium carbonate.

Phenoxyphenyl ring can be formed by the reaction of aromatic boronic acid **22**, which was reacted with phenol **23** in the presence of copper acetate. Copper-mediated arylation of phenol using boronic acid was previously reported by Chan and Evans (*Tetrahedron Lett.* **1998**, *39*, 2933-2936; and *Tetrahedron Lett.* **1998**, *39*, 2937-2940, respectively).

Some activated halides such as compounds **24-26** do not need copper catalyst. Compounds **24- 26** were smoothly transformed to phenol ether in the presence of base such as cesium carbonate, potassium carbonate or sodium hydroxide (Scheme 9).

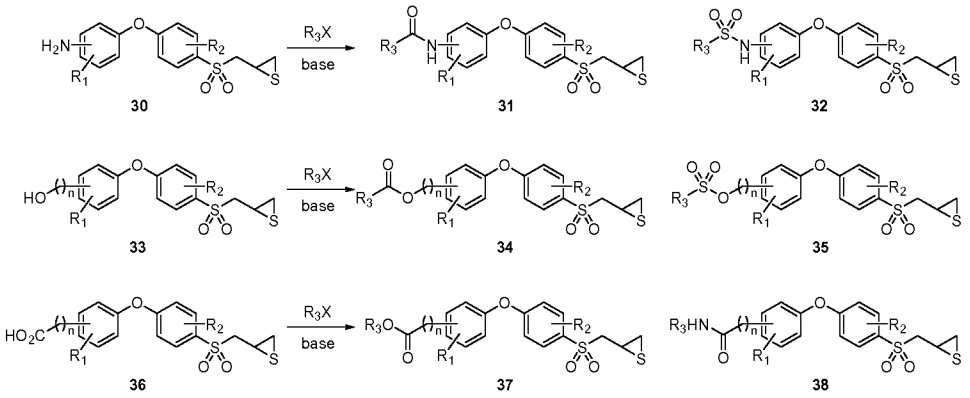
Scheme 9.



Compounds with functional groups such as amino (**30**) and hydroxyl (**33**) groups are useful because they can easily react with many different electrophiles, such as alkylbromides, acid chlorides, and sulfonyl chlorides (Scheme 10).

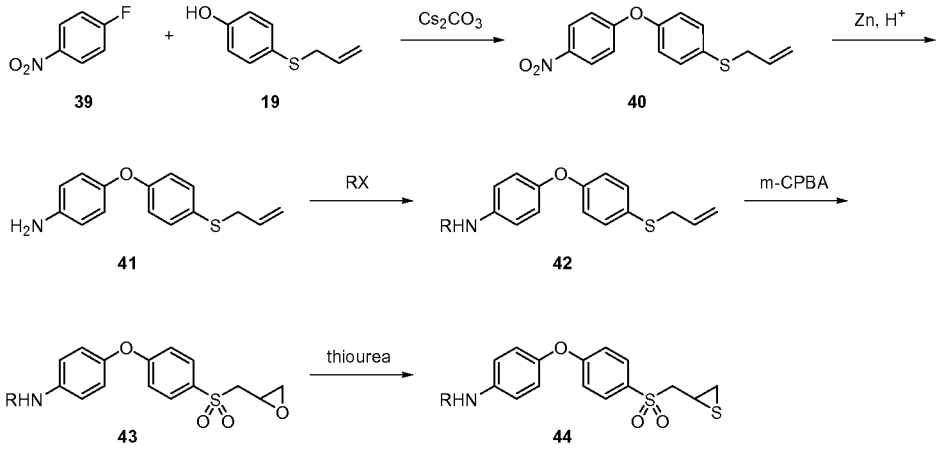
Carboxylic acid **36** is also useful in this sense for its reactivity with alcohols or amines to afford esters **37** or amide compounds **38**.

Scheme 10.



p-Aminophenylphenoxy derivatives were synthesized according to Scheme 11. 4-amino group was introduced by use of nitrobenzene fluoride **39**. This activated substrate was reacted with allylthiophenol **19** in the presence of cesium carbonate to yield 1-allylthio-4-(4-nitrophenyl)benzene **40**, which was then reduced to amine in the presence of zinc. Compound **42** was reacted with several electrophiles, followed by *m*-CPBA oxidation and thiirane formation reaction to afford compound **42**.

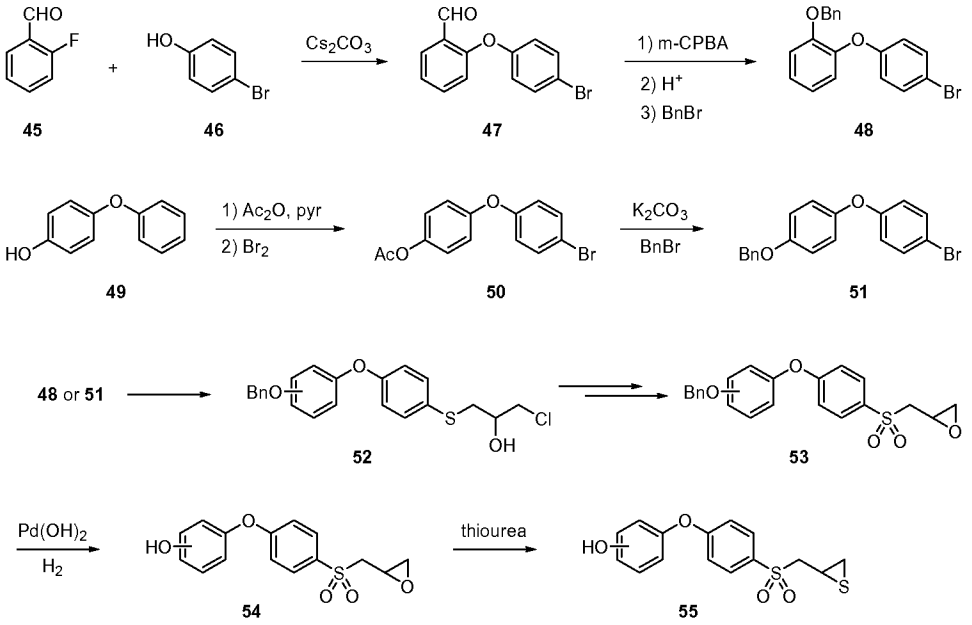
Scheme 11.



Schemes 12-14 cover the synthesis of *o*-, *m*-, *p*-hydroxy and *p*-hydroxymethyl substituted phenoxyphenyl thiirane derivatives (**55**, **61**, **33**). Different approaches were used to make *o*-, *m*-, and *p*-hydroxyl substituted compounds. The ortho derivative was constructed by the reaction of 2-fluorobenzaldehyde and 4-bromophenol to give compound **47**, then converted to **48**

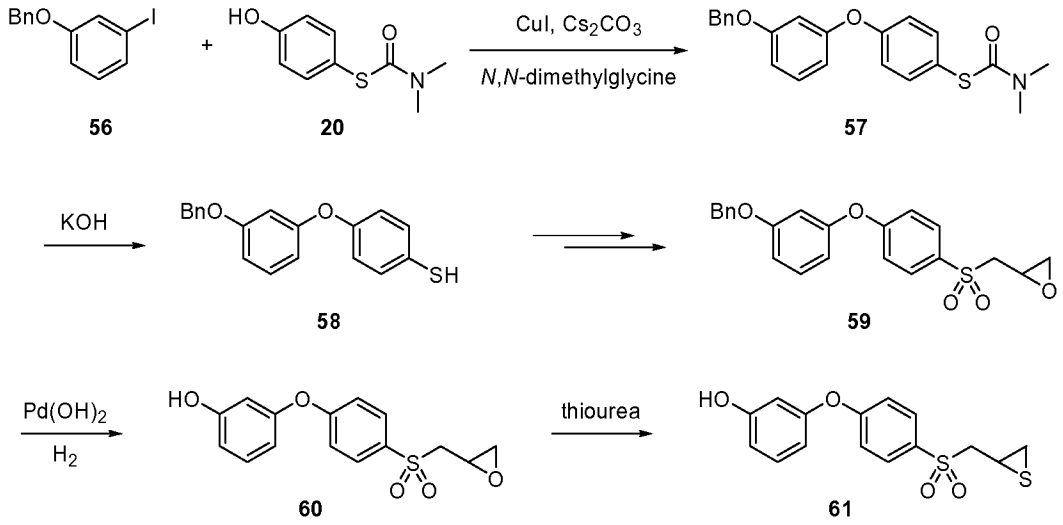
by three steps (Scheme 12) (*Synthesis* **1995**, 28-30). The *p*-hydroxy phenoxybenzene scaffold is incorporated by using 4-hydroxyphenoxy-phenybromide **49**, which was converted to compound **50** via acetylation and followed by selective bromination (*J. Med. Chem.* **1998**, *41*, 1540-1554). Compound **50** was then deacetylated and protected to give compound **51**. The rest of functional group transformations were followed as in Scheme 5, except for the selective deprotection of benzyl ether group of compound **53**. The benzyl ether was deprotected with $Pd(OH)_2$ in ethyl acetate and *i*-PrOH to give compound **54**.

Scheme 12.



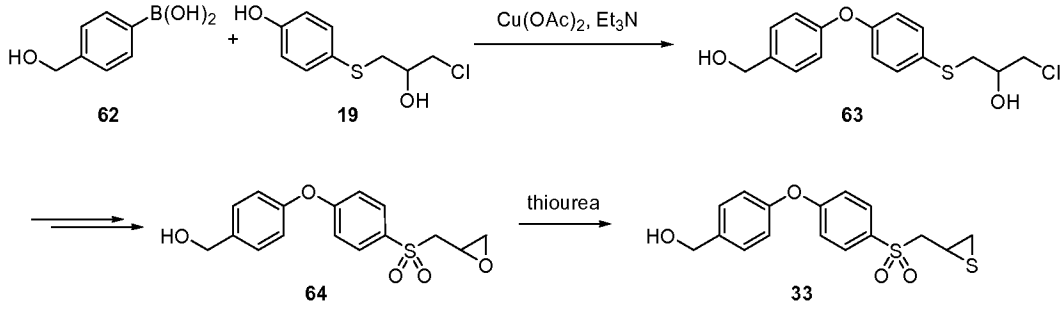
Meta Substituted scaffold was constructed by Ullmann condensation between 3-benzyloxyiodobenzene and compound **20** to afford compound **57** (Scheme 13) (see *Org. Lett.* **2003**, *5*, 3799-3802). Compound **57** was then hydrolyzed to give free thiol **58** and then alkylated with epichlorohydrin in the presence of potassium carbonate. Functional group transformation from compound **58** to compound **61** was followed in Scheme 6.

Scheme 13.



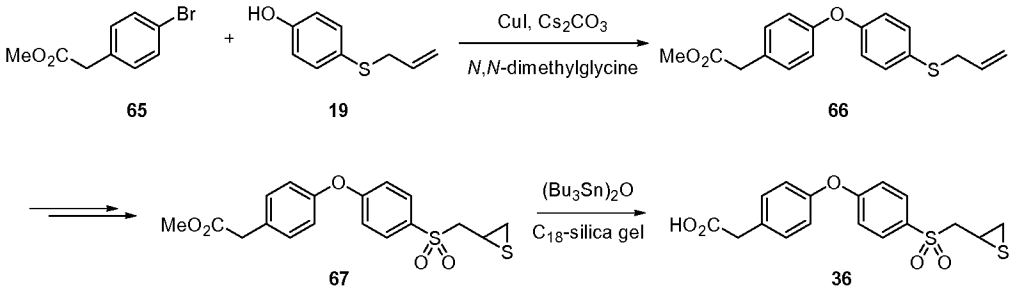
Hydroxymethyl group was introduced by Suzuki type reaction between hydroxyphenyl boronic acid **62** and compound **19** (Scheme 14) (*Tetrahedron Lett.* **1998**, *39*, 2933-2936; *Tetrahedron Lett.* **1998**, *39*, 2937-2940). The resulting compound **63** was converted to compound **33** by the same route in Scheme 5.

Scheme 14.



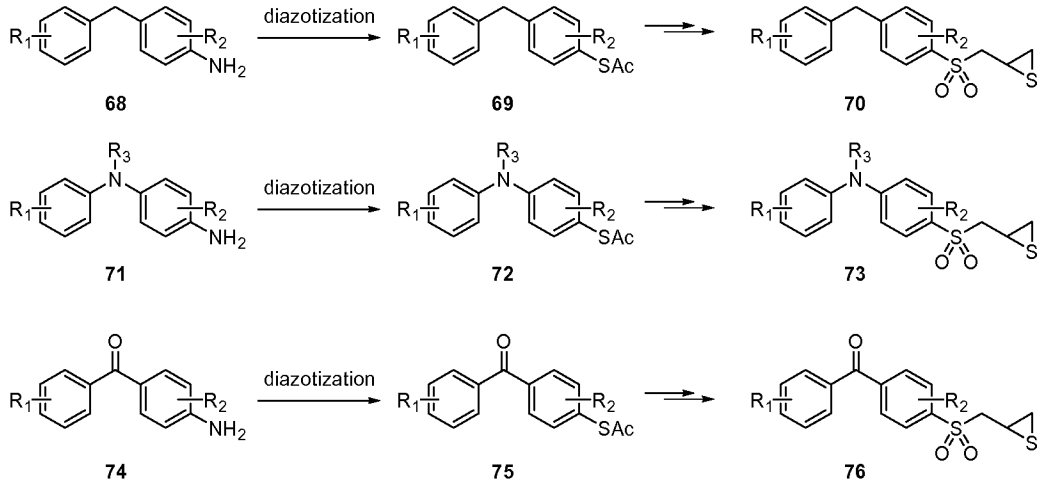
A carboxymethyl group was incorporated by Ullmann reaction to result in compound **66** (Scheme 15) (*Org. Lett.* **2003**, *5*, 3799-3802). The conversion of compound **66** to **67** was accomplished according to Scheme 6 which involves *m*-CPBA oxidation and thiirane formation using thiourea. Methyl ester in compound **67** was hydrolyzed to carboxylic acid **36** via formation of tributyltin ester intermediate by the treatment of di(tributyltin)oxide and C-18 silica gel.

Scheme 15.



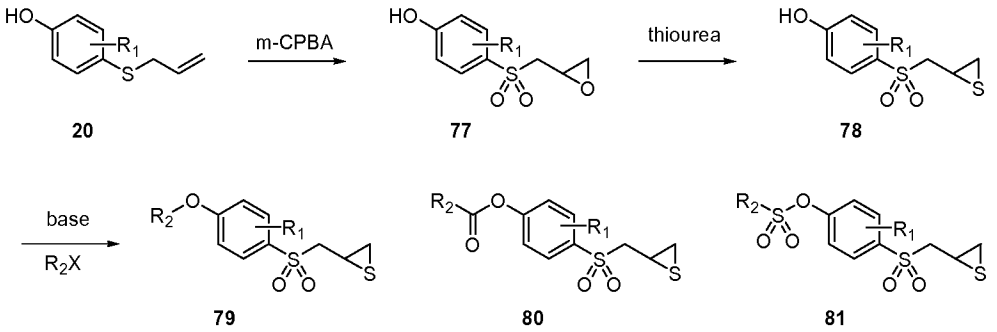
The possibility of introducing different bridges between two benzene rings instead of an oxygen bridge was investigated (Scheme 16). For these compounds, aromatic amines **68**, **71**, and **74** served as the initial starting materials, which were diazotized and then converted to the corresponding thioesters (**69**, **72**, **75**) (see *Synthesis* **1998**, 1171-1175 and *Synthesis* **2003**, 1225-1230). The remainder of the synthetic route from the thioacetate to sulfonylmethylthiirane was followed as in Scheme 6.

Scheme 16.



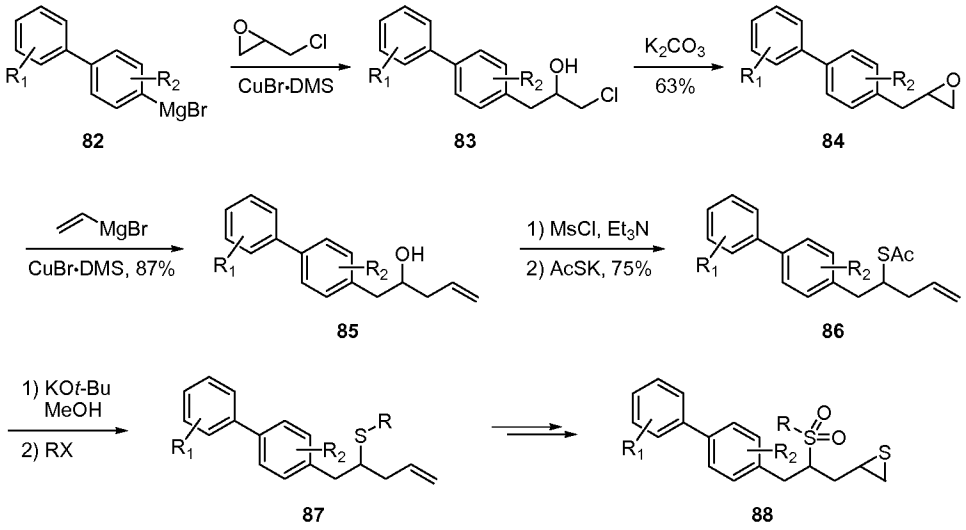
When 4-thiiranylmethanesulfonylphenol **78** was reacted with alkylhalides, acid chlorides, or sulfonyl chlorides, different bridged molecules such as compounds **79-81** were obtained (Scheme 17).

Scheme 17.



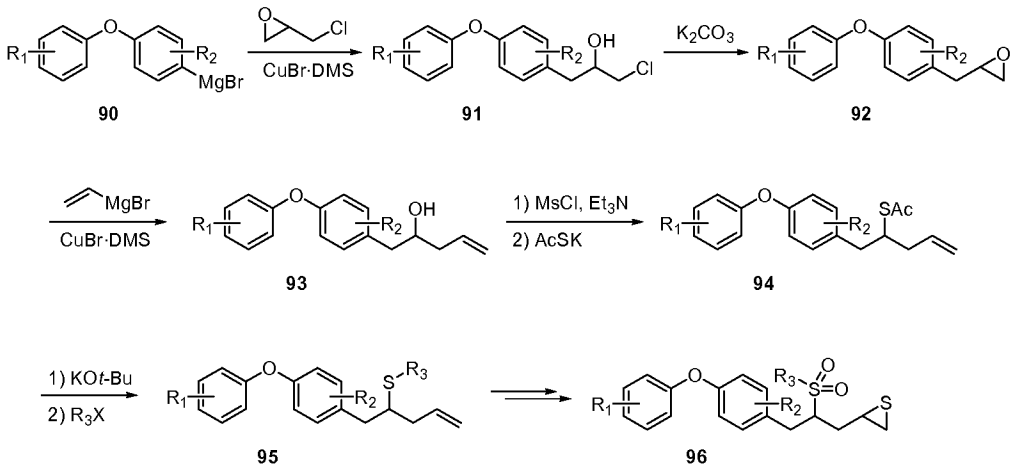
Aromatic sulfonyl thiirane other than phenoxyphenyl scaffolds were also prepared, as illustrated in Schemes 18-20. 4-Biphenylmagnesium bromide **82** was reacted with epichlorohydrin in the presence of CuBr·DMS to give compound **83** (Scheme 18). The resulting hydroxychloride **83** was converted to epoxide **84**, which was reacted with vinylmagnesium bromide. Secondary alcohol **85** was converted to a mesylate. The mesylate was then displaced placed by thioacetate, which was hydrolyzed and alkylated to afford thiol ether **87**. The conversion of the alkene moiety of **87** to thiirane **88** was same as outlined in Scheme 6, which involves oxidation and thiirane ring formation.

Scheme 18.



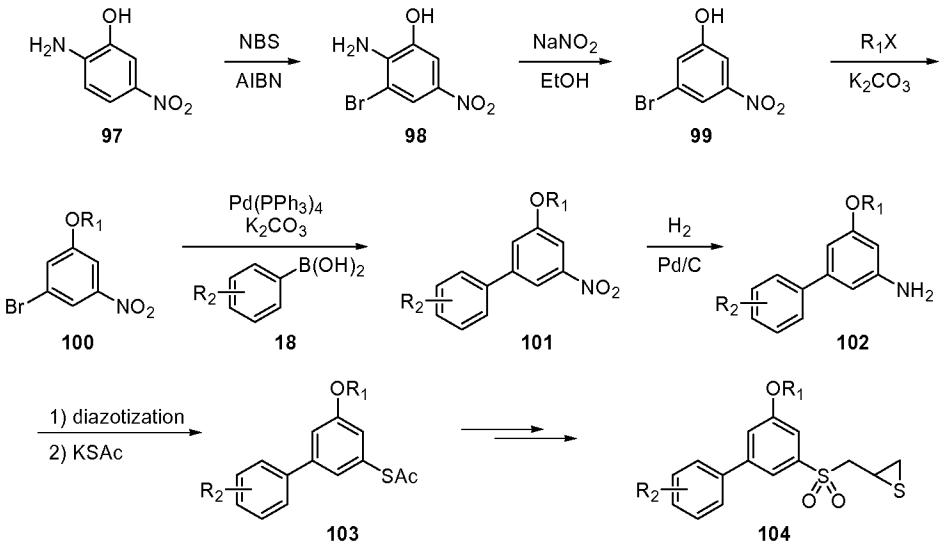
When phenoxyphenyl magnesiumbromide **90** is used instead of biphenylmagnesium bromide **82**, compound **96** can be obtained (Scheme 19). The remainder of synthetic route is similar to that of Scheme 14.

Scheme 19.



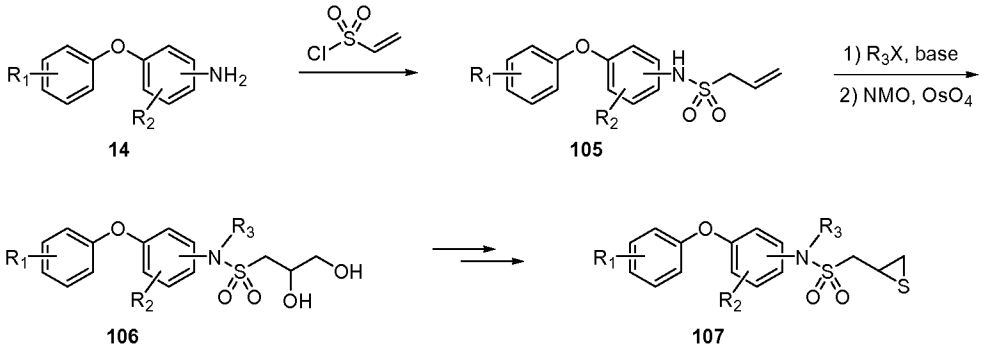
1,3,5-Substituted benzene was chosen since it contains three positions to be functionalized (Scheme 20). Synthesis commences from bromination of 2-amino-5-nitrophenol **97** using *N*-bromosuccinimide (*J. Am. Chem. Soc.* **1997**, *119*, 311-325). Deamination of compound **98** afforded construction of 1,3,5-substituted benzene scaffold. The resulting phenol **99** was alkylated with halides. Suzuki coupling of compound **100** with aromatic boronic acid **18** in the presence of tetrakis(triphenylphosphine)palladium catalyst resulted in biphenyl derivative **101** (*J. Med. Chem.* **1997**, *40*, 437-448). Nitro group in compound **101** was reduced to corresponding amine **102** by catalytic hydrogenation. Conversion of thioacetate **103** to **104** followed the method as described for Scheme 6.

Scheme 20.



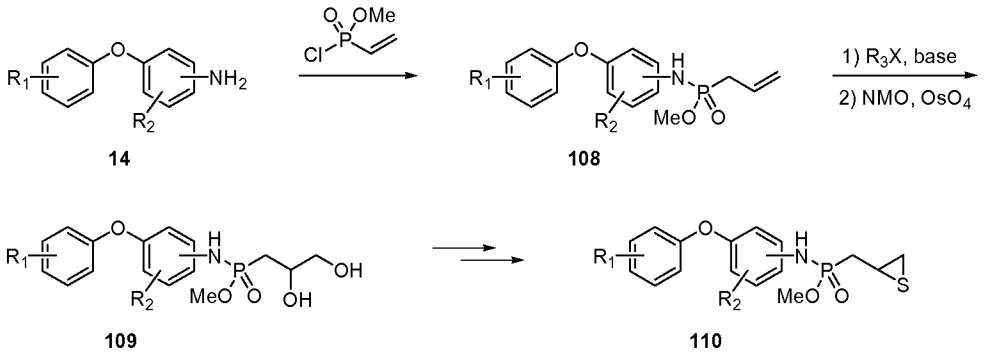
Sulfonamide and phosphoamide groups were introduced instead of sulfonyl group (Scheme 21-24). Sulfonamide was formed by the reaction of phenoxyaniline **14** and allylsulfonyl chloride to yield compound **105** (Scheme 21). After alkylation of amine in **105**, double bond was converted to diol **106**, which was converted to sulfonylmethylthiirane **107** by the similar method outlined in Scheme 6.

Scheme 21.



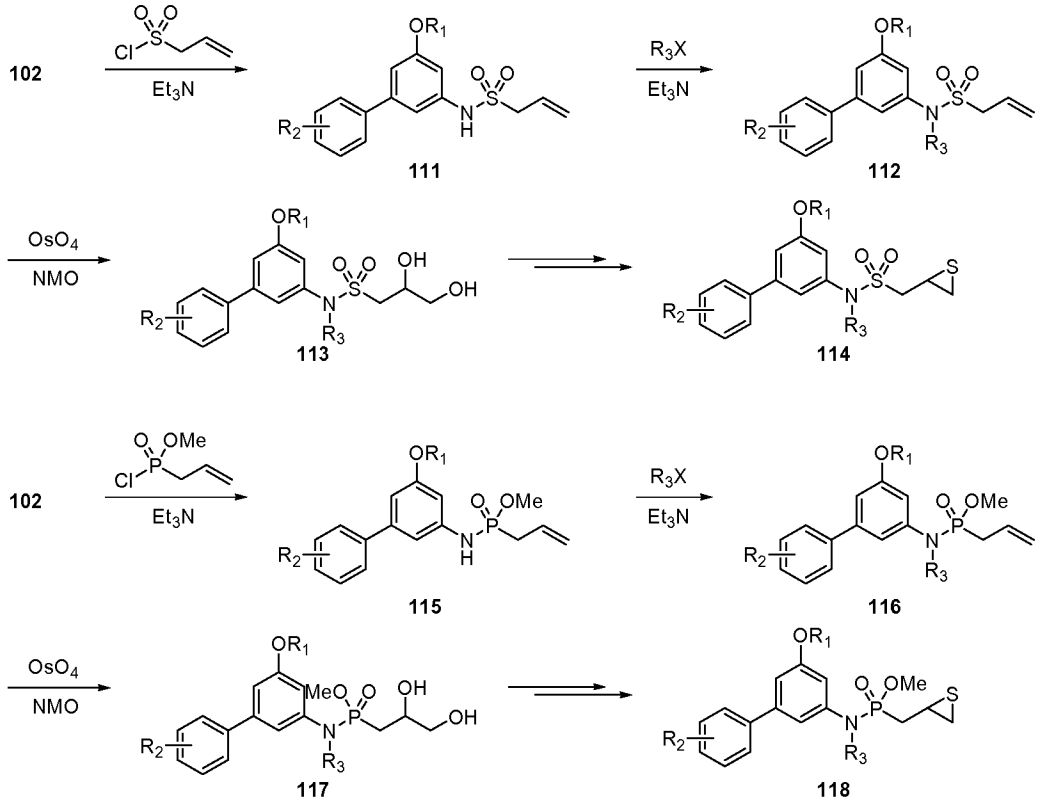
A phsphonamide can be a good surrogate of sulfonamide because they share the same tetrahedral geometry. Phosphonamide **110** was formed by using phenoxyphenylamine **14** and allylphosphonic acid chloride methyl ester instead of allylsulfonyl chloride to result in compound **108** (Scheme 22). The rest of synthetic conversion was followed by the same method outlined Scheme 21.

Scheme 22.



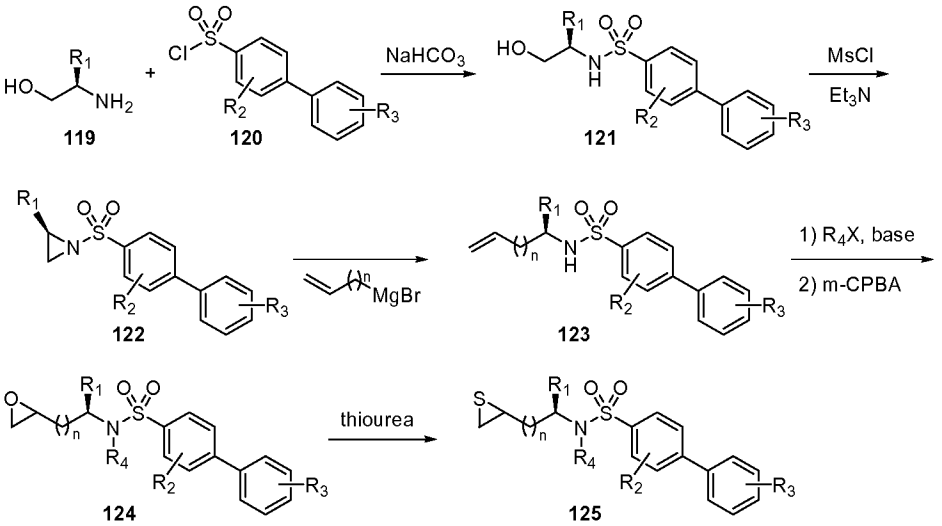
When biphenylamine **102** was reacted with allylsulfonyl chloride or allylphosphonic acid chloride methyl ester, compounds **111** and **115** were formed, respectively (Scheme 23). Those compounds were converted to corresponding sulfonamide thiirane **114** and phosphonamide thiirane **118** via corresponding diol intermediates **113** and **117**.

Scheme 23.



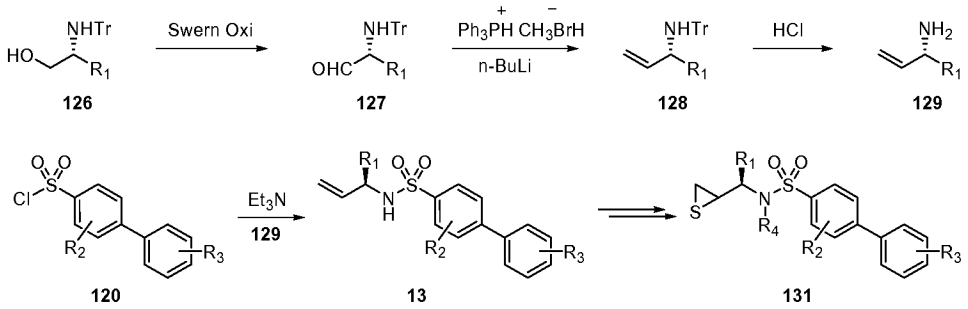
Biphenylsulfonamide (**125**, **131**) can be made by the reaction between aliphatic amines such as compounds **119** or **129** and biphenylsulfonylchloride (Scheme 24-25). D- or L-Phenylalaninol **119** was reacted with biphenylsulfonyl chloride **120** in the presence of sodium bicarbonate (Scheme 24). The resulting alcohol **121** was then mesylated and then converted to aziridine **122**. This aziridine intermediate **122** was reacted with alkene magnesium bromide to yield compound **123**, which was then converted to corresponding epoxide **124** and thiirane **125**.

Scheme 24.



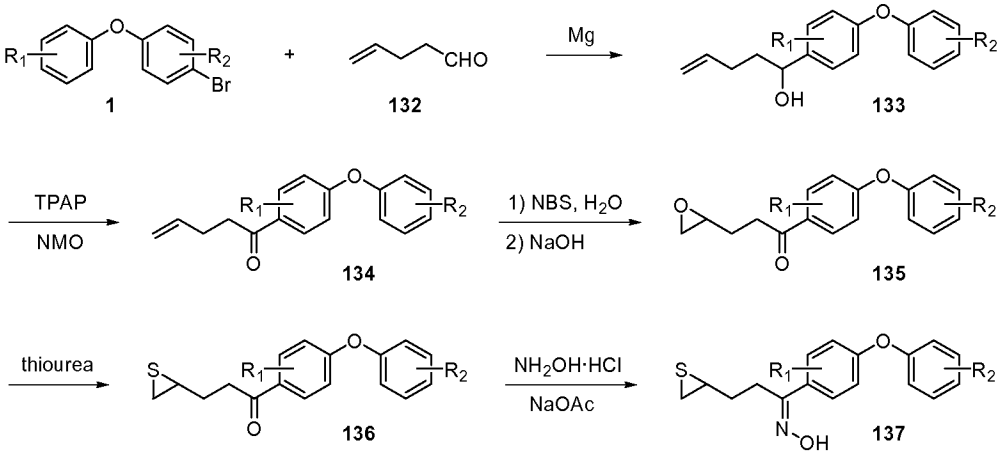
Trityl-protected D-or L-phenylalaninol **126** was oxidized under Swern oxidation condition (Scheme 25). The resulting aldehyde **127** was reacted with triphenylphosphonium methylbromide in the presence of n-BuLi. The trityl group in resultant Wittig product **128** was then removed in acidic condition to afford free amine **129**, which was then reacted with biphenylsulfonyl chloride **120**. Conversion of compound **130** to compound **131** was followed by the method illustrated in Scheme 24.

Scheme 25.



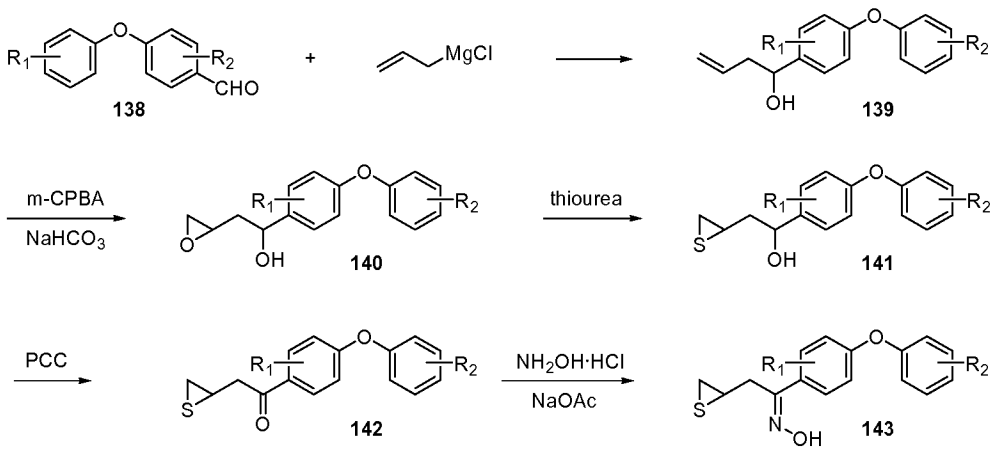
Ketones and oximes were considered to be surrogates of the sulfonyl group (Schemes 26-28). Phenoxyphenylmagnesium bromide was reacted with alkene aldehyde to result in secondary alcohol **133**, which was the oxidized to ketone **134** (Scheme 26). The double bond in compound **134** was converted to epoxide **135** via hydrobromination. Epoxide **135** then converted to thiirane using thiourea. Ketone **136** was transformed to oxime **137** in the presence of hydroxylamine hydrochloride and sodium acetate.

Scheme 26.



Phenoxybenzaldehyde **138** was reacted with allylmagnesium chloride to give compound **139** (Scheme 27). The rest of the functional group conversion to compound **143** is similar in Scheme 26, except oxidation to ketone was done after double bond oxidation and thiirane formation.

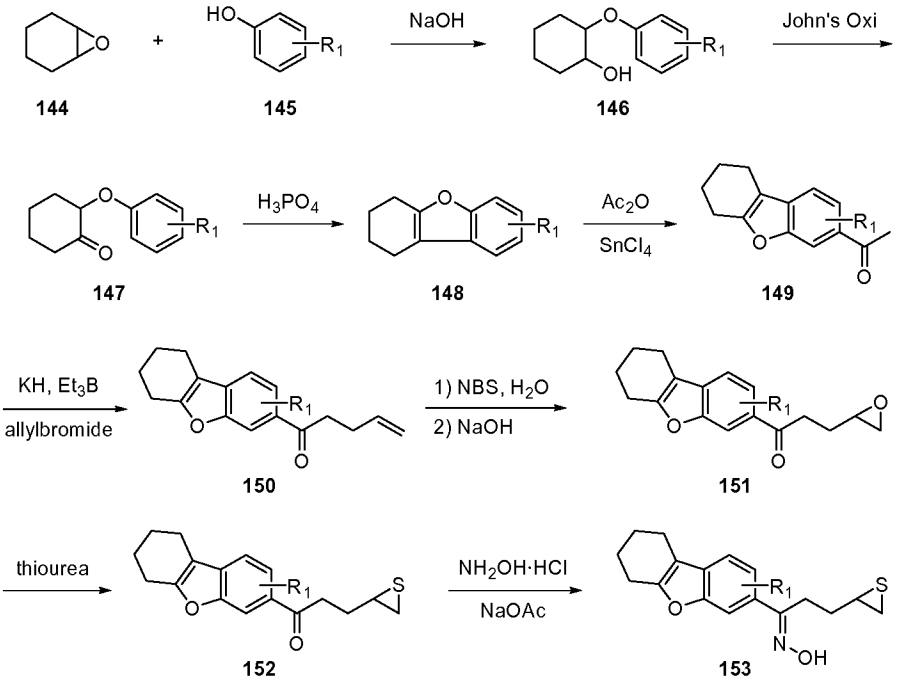
Scheme 27.



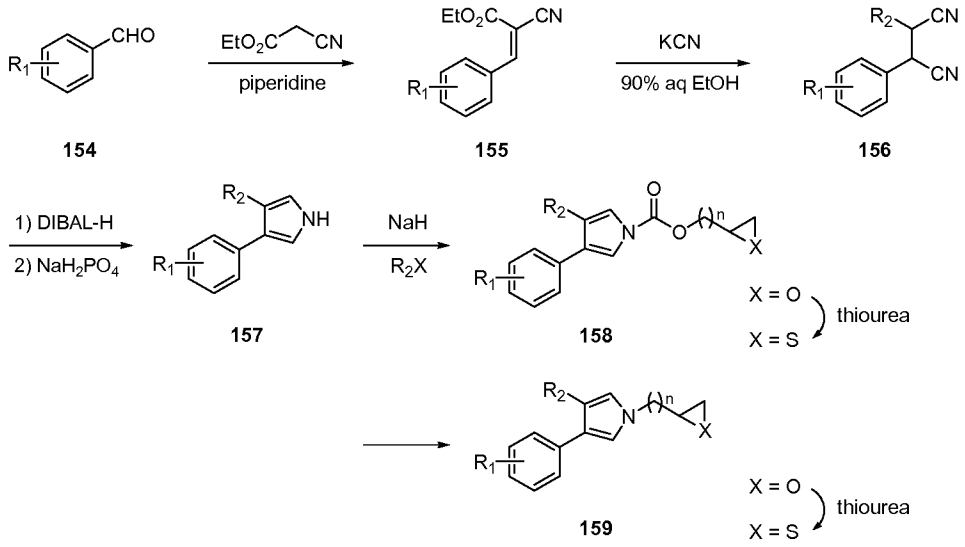
Tetrahydro-dibenzofurane moiety was investigated as a surrogate of phenoxyphenyl group. The synthesis of compound **153** is outlined in Scheme 28. Tetrahydrodibenzofuran derivative **149**, which was obtained from phenol and cyclohexene oxide according to literature procedures (*J. Am. Chem. Soc.* **1935**, *57*, 2095-2099; *Bull. Soc. Chim. Fr.* **1956**, 1817-1822), was converted **150** under Negishi's conditions (*Tetrahedron Lett.* **1979**, *20*, 845-848). Epoxidation of **150** was achieved via bromohydrin intermediates and the resulting oxirane **151** was treated with thiourea to give thiirane **152**. Finally, the conversion of **152** to oxime **153** was carried out by the $NH_2OH{\cdot}HCl$/AcONa (*Tetrahedron Lett.* **1989**, *30*, 3471-3472; *Chem. Pharm. Bull.* **2003**, *51*, 138-151; *Tetrahedron* **1968**, *24*, 3347-3360).

Aromatic pyrrol group was also designed as an aromatic scaffold (**158-159**). Substituted benzaldehyde **154** and ethyl cyanoacetate were subjected to Knoevenagel condensation in the presence of catalytic amount of piperidine to give α,β-unsaturated cyanoester **155**, followed by a tandem Michael addition-decarboxylation involving potassium cyanide. The resulting disuccinonitrile **156** was reduced to form pyrrole **157** using Dibal-H according to the method reported by Babler et al. (*Tetrahedron Lett.* **1984**, *25*, 1659-1660). Pyrrole **157** was deprotonated with sodium hydride and reacted with several electrophiles which containing oxirane (*Synlett* **1998**, 1411-1413; and Mueller, A. C., Shokal, E. C., (Shell Development Co.), US, 1957). Conversion of oxirane to thiirane was done under standard thiourea condition.

Scheme 28.



Scheme 29.



Example 3 Experimental Section:

Synthesis — ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Unity Plus 300 MHz or a Varian INOVA 500 MHz spectrometer. Chemical shifts are reported in from tetramethylsilane on the δ scale. Mass spectra were recorded

on a JEOL JMSAX505HA and a Finnigan-MAT 8430 high resolution magnetic sector mass spectrometers. For silica gel column chromatography, EMD Silica gel 60 was employed. Thin-layer chromatography was performed with Whatman 0.25 mm silica gel 60-F plates. All other reagents were purchased from Aldrich Chemical Company, Lancaster, or Across Organics.

Compounds of Scheme 5.

Compound 2a (R_1=R_2=H). *n*-BuLi (10.7 mL, 2.5 M in hexane) was added to a solution of 4-bromophenyl phenyl ether (4.7 mL, 26.8 mmol) in anhydrous THF (120 mL) with vigorous stirring at -78 °C. After stirring for 30 minutes, sulfur (0.86 g, 26.8 mmol) was added to the reaction mixture. The mixture was stirred for 0.5 hours, while temperature was raised to 0 °C. After cooled down to -78 °C, epichlorohydrin (2.2 mL, 28.1 mmol) was added dropwise to the reaction mixture. Stirring was continued for 1 hour, while temperature was raised to -20 °C. The reaction was quenched by the addition of a saturated solution of ammonium chloride. The mixture was extracted with EtOAc and the organic layer was washed with water, dried ($MgSO_4$), and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to afford the desired product (6.70 g, 85%). When allyl bromide or acetyl chloride were used instead of epichlorohydrin for this reaction, compound **10a** or **11a** were obtained; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4 (d, J = 8.4 Hz, 2H), 7.4 (dd, J = 8.4, 7.6 Hz, 2H), 7.1 (t, J = 7.4 Hz, 1H), 7.0 (d, J = 7.6 Hz, 2H), 7.0 (d, J = 8.6 Hz, 2H), 3.9 (m, 1H, C*H*OH), 3.7 (m, 2H, CH_2Cl), 3.1 (ddd, J = 42.5, 14.0 Hz, 5.6 Hz, 2H, SCH_2CH), 2.8 (brs, 1H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 156.7, 133.2, 130.0, 128.0, 123.9, 119.4, 119.3, 69.6, 48.1, 39.7; HRMS calcd for $C_{15}H_{15}ClO_2S$ (M^+) 294.0481, found 294.0465.

Compound 3a (R_1=R_2=H). Potassium carbonate (2.81 g, 20.4 mmol) was added to a solution of compound **2a** (3.00 g, 10.2 mmol) in a 1:2 mixture of methanol and acetonitrile (100 mL) in ice-water bath with vigorous stirring. After 10 minutes, ice-water bath was removed and stirring was continued for 1 hour at room temperature and was filtered through a small layer of silica gel. The filtrate

was concentrated under reduced pressure, and the residue was purified by column chromatography to afford the desired product (2.49 g, 95%) as an oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4 (d, J = 8.9 Hz, 2H), 7.4 (t, J = 8.0 Hz, 2H), 7.1 (t, J = 7.4 Hz, 1H), 7.0 (d, J = 8.6 Hz, 2H), 7.0 (d, J = 8.8 Hz, 2H), 3.2 (m, 1H), 3.1 (dd, J = 14.2, 5.2 Hz, 1H), 2.9 (dd, J = 14.0, 6.0 Hz, 1H), 2.8 (t, J = 4.8 Hz, 1H), 2.5 (dd, J = 5.0, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 156.7, 133.5, 129.9, 128.7, 123.8, 119.3, 119.2, 51.2, 47.4, 38.0; HRMS calcd for $C_{15}H_{14}O_2S$ (M^+) 258.0715, found 258.0729.

Compound 4a (R_1=R_2=H). To a solution of compound **3a** (2.00 g, 7.74 mmol) in dichloromethane (20 mL) was added a solution of *m*-chloroperoxybenzoic acid (3.47 g, 15.5 mmol, 77%) in ice-water bath. After 10 minutes, the suspension was filtered, and the filtrate was diluted with EtOAc and washed with 10% aqueous sodium thiosulfate, followed by saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate and was concentrated. The product was purified by silica gel chromatography to yield the title compound as an oil (1.96 g, 87%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (d, J = 8.8 Hz, 2H), 7.4 (dd, J = 8.4, 7.4 Hz, 2H), 7.2 (t, J = 6.9 Hz, 1H), 7.1 (d, J = 8.6 Hz, 4H), 3.3 (m, 3H), 2.8 (m, 1H), 2.5 (dd, J = 5.2, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 154.8, 132.5, 130.6, 130.4, 125.4, 120.6, 117.7, 59.7, 46.0, 46.0; HRMS calcd for $C_{15}H_{14}O_4S$ (M^+) 290.0613, found 290.0630.

Compound 5a (R_1=R_2=H). Thiourea (0.52 g, 6.89 mmol) was added to a solution of compound **4a** (1.00 g, 3.44 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was partitioned between ethyl ether and water, the organic layer was washed with water and brine, dried ($MgSO_4$), and the suspension was filtered. Evaporation of solvent gave the crude product, which was purified by column chromatography. The desired product was crystallized as white needles from 1-butanol (0.89 g, 84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 (d, J = 8.6 Hz, 2H), 7.5 (t, J = 7.8 Hz, 2H), 7.3 (t, J = 7.2 Hz, 1H), 7.1 (d, J = 8.6 Hz, 4H), 3.6 (dd, J = 14.2, 5.6 Hz, 1H), 3.2 (dd, J = 14.2, 7.8 Hz, 1H), 3.1 (m, 1H), 2.6 (dd, J = 6.0,

1.4 Hz, 1H), 2.2 (dd, J = 5.2, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 154.9, 132.0, 130.9, 125.5, 120.6, 117.9, 62.8, 26.3, 24.4; HRMS calcd for $C_{15}H_{14}O_3S_2$ (M^+) 306.0384, found 306.0396.

Compounds of Scheme 6.

Compound 4a (from compound **10a)**. Compound **10a** (2.40 g, 10.0 mmol) was dissolved in m-CPBA (11.5 g, 50.o mmol, 77% max) in ice-water bath and stirred for 7 days. The resulting suspension was filtered and filtrate was diluted with EtOAc and washed with 10% aqueous sodium thiosulfate, followed by saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate and was concentrated. The product was purified by silica gel chromatography to yield the title compound as an oil (2.50 g, 87%).

Compound 12a (R_1=R_2=H). A mixture of compound **10a** (0.27 g, 1.1 mmol) and *N*-methylmorpholine *N*-oxide (0.25 g, 2.1 mmol) in acetone-water (30 mL, 4:1) was treated with osmium tetraoxide (0.3 mL, 47 μmol, 4% aqueous solution) and the resultant solution was stirred at room temperature overnight under dark. Sodium sulfite (0.1 g) was added and the resulting mixture was stirred for an additional 1 hour. After filtration through a small layer of silica gel, the filtrate was evaporated and the residue was purified by column chromatography on silica gel to give the title compound (0.26 g, 85%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.4 (d, J = 8.4 Hz, 2H), 7.4 (dd, J = 8.4, 7.6 Hz, 2H), 7.1 (t, J = 7.4 Hz, 1H), 7.0 (d, J = 7.6 Hz, 2H), 7.0 (d, J = 8.6 Hz, 2H), 3.83 (brs, 1H), 3.51-3.68 (m, 2H), 3.15-3.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 156.7, 133.2, 130.0, 128.0, 123.9, 119.4, 119.3, 69.6, 48.1, 39.7.

Compound 13a (R_1=R_2=H). Compound **12a** was oxidized to compound **13a** by the same procedure for the preparation of compound **4a** from compound **3a**.

Compound 4a (from compound **13a)**. Conversion of diol to oxirane was done by two methods. The first method is using Mitsunobu condition. The second is via the formation of tosylated intermediate. A mixture of compound **13a** (163 mg, 530 μmol), triphenylphosphine (142 mg, 530 μmol), and diethylazodicarboxylate (90 μL, 530 μmol) was refluxed for 4 hours in anhydrous

benzene (10 mL) and the volatile was evaporated. The residue was purified by column chromatography on silica gel to afford the title compound (98.5 mg, 64%).

The second procedure involving formation of a tosylated intermediate: A mixture of compound **13a** (163 mg, 530 μmol) and tosyl chloride (111 mg, 583 μmol) in CH_2Cl_2 (2 mL) was treated with pyridine (138 μL, 1.75 mmol) and the resulting mixture was stirred overnight in ice-water bath. The reaction mixture was washed with water several times and volatile was concentrated. The crude product was used for the next step without further purification was dissolved in anhydrous THF (2 mL) and cooled down in ice-water bath. To this reaction mixture, NaH (35 mg, 875 μmol, 60% in oil) was added and the resulting mixture was stirred for 10 minutes and filtered through a small layer of silica gel and washed with THF. The combined filtrate was evaporated under reduced pressure and the resulting crude product was purified by column chromatography to afford the desired product as colorless oil (115 mg, 75%).

Compound 3a (from compound **11a**). Compound **11a** (0.61 g, 2.5 mmol) was stirred at room temperature for 0.5 hours in the presence of K_2CO_3 (1.38 g, 20 mmol) in 1:1 mixture of MeOH:acetonitrile (10 mL). Epibromohydrin (0.8 mL, 10.0 mmol) was added dropwise to the reaction mixture and the resulting solution was stirred at room temperature for additional 1 hour. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica gel to afford the desired product (0.56 g, 87%). When allyl bromide or glycidol were used for this reaction instead of epichlorohydrin, compound **10a** or **12a** were obtained in similar yield.

Compounds of Scheme 7.

Compound 11b (from compound 14a, R_1=R_2=H, 3-amino). A solution of *o*-benzenedisulfonimide (2.63 g, 12 mmol) in glacial acetic acid (40 mL) was slowly added, over a period of 10 minutes, to a solution of 3-phenoxyaniline (1.85 g, 10 mmol) in acetic acid (20 mL) in an ice bath. Isoamylnitrite (1.5 mL, 11 mmol) was added dropwise to the reaction mixture over 10 min and the resulting mixture was stirred for 0.5 hours at the same temperature. Addition of diethyl ether to the

reaction mixture resulted in diazonium salt as an orange powder, which was filtered and washed with cold diethyl ether. Potassium thioacetate (0.98 g, 10 mmol) in acetonitrile (10 mL) was added to the crude diazonium salt (2.0 g) in anhydrous acetonitrile (10 mL) and the resulting suspension was stirred at room temperature for 2 hours. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica gel to afford the desired product (0.97 g, 40%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.09-7.22 (m, 6H), 7.38-7.44 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.3, 119.4, 119.8, 123.9, 124.4, 129.1, 130.4, 156.7, 157.9; HRMS (FAB) calcd for $C_{14}H_{12}O_2S$ (M^+) 244.0558, found 244.0556.

Compound 3b (from compound 11b, R_1=R_2=H, 2-amino). Compound **11b** (0.61 g, 2.5 mmol) was stirred at room temperature for 0.5 hours in the presence of K_2CO_3 (1.38 g, 10 mmol) in 1:1 mixture of MeOH : acetonitrile (10 mL). Epibromohydrin (0.8 mL, 10.0 mmol) was added dropwise to the reaction mixture and the resulting solution was stirred at room temperature for additional 1 hour. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica gel to afford the desired product (0.56 g, 87%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.57 (dd, 1H, J = 2.2, 4.7 Hz), 2.81 (t, 1H, J = 4.2 Hz), 2.98 (q, 1H, J = 7.8 Hz), 3.16-3.20 (m, 2H), 6.88 (dd, 1H, J = 2.5, 7.9 Hz), 7.04-7.09 (m, 3H), 7.16 (t, 2H, J = 7.4 Hz), 7.28 (t, 1H, J = 7.8 Hz), 7.38 (t, 2H, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.3, 47.6, 51.0, 117.0, 119.3, 119.8, 123.8, 124.4, 130.0, 130.3, 137.4, 156.8, 157.9; HRMS (FAB) calcd for $C_{15}H_{14}O_2S$ (M^+) 258.0715, found 258.0713.

Conversion from compound **3b** to compounds **4b**, and **5b** was followed by the same method as described in Scheme 5.

Compound 4b (R_1=R_2=H, 2-amino). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.49 (dd, 1H, J = 1.0, 5.0 Hz), 2.84 (dd, 1H, J = 3.7, 4.7 Hz), 3.26-3.37 (m, 3H), 7.08 (dd, 1H, J = 1.2, 8.7 Hz), 7.22 (t, 1H, J = 7.4 Hz), 7.32 (m, 1H), 7.42 (dd, 2H, J = 7.4, 8.4 Hz), 7.56 (m, 2H), 7.68 (dt, 1H, J = 1.0, 8.4 Hz); ^{13}C NMR (125 MHz,

$CDCl_3$): δ 45.9, 46.1, 59.6, 117.7, 119.8, 122.5, 124.0, 124.9, 130.4, 131.0, 140.8, 155.9, 158.6; HRMS (FAB) calcd for $C_{15}H_{14}O_4S$ (M^+) 290.0613, found 290.0603.

Compound 5b (R_1=R_2=H, 2-amino). ^1H NMR (500 MHz, $CDCl_3$): δ 2.14 (dd, 1H, *J* = 1.7, 5.2 Hz), 2.51 (dd, 1H, *J* = 1.7, 6.2 Hz), 3.03 (m, 1H), 3.18 (dd, 1H, *J* = 7.7, 14.1 Hz), 3.51 (dd, 1H, *J* = 5.4, 14.3 Hz),7.05 (dd, 2H, *J* = 1.0, 8.9 Hz), 7.19 (t, 1H, *J* = 7.4 Hz), 7.29, 7.31 (2dd, 1H, *J* = 1.0, 2.5 Hz), 7.39 (dd, 2H, *J* = 7.4, 8.4 Hz), 7.52-7.55 (m, 2H), 7.64 (dt, 1H, *J* = 1.5, 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.3, 20.0, 62.4, 117.7, 119.8, 122.6, 123.9, 124.8, 130.3, 131.0, 140.2, 155.7, 158.6; HRMS (FAB) calcd for $C_{15}H_{15}O_3S_2$ (MH^+) 307.0463, found 307.0474.

Compounds of Scheme 8.

Compound 1b (R_1=H, R_2=d4, from compound **16a** and **17a**). The procedure was adapted from that reported by Ma et al. (*Org. Lett.* **2003**, *5*, 3799-3802). A mixture of 1,4-dibromobenzene-d4 (**17a**, 2.50 g, 10.4 mmol), phenol (**16a**, 1.47 g, 15.6 mmol), Cs_2CO_3 (6.80 g, 20.9 mmol), *N*,*N*-dimethylglycine hydrochloride salt (0.44 g, 3.15 mmol), CuI (0.20 mg, 1.05 mmol) in degassed 1,4-dioxane (20 mL) was heated at 90 °C for 22 hours under a nitrogen atmosphere. After dilution with water, the mixture was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resultant residue was purified by column chromatography to give the desired product as colorless oil (2.00 g, 76%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 115.5, 119.2, 120.2 (t, *J* = 25.5 Hz), 123.9, 130.1, 132.4 (t, *J* = 25.5 Hz), 156.7, 156.9; HRMS calcd for $C_{12}H_5D_4BrO$ (M^+) 252.0088, found 252.0072.

Conversion from compound **1b** to compounds **2c – 5c** was followed by the same method as described in Scheme 5.

Compound 2c (R_1=H, R_2=d4) ^1H NMR (500 MHz, $CDCl_3$) δ 3.03 (dd, *J* = 13.8, 7.2 Hz, 1H), 3.12 (dd, *J* = 14.1, 5.5 Hz, 1H), 3.64 - 3.74 (m, 2H), 3.88 - 3.94 (m, 1H), 7.03 (d, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 8.6, 7.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.8, 48.2, 69.6, 119.1 (t, *J* = 25.5 Hz), 119.4,

124.0, 127.7, 130.1, 132.9 (t, J = 25.5, 23.9 Hz), 156.7, 157.3; HRMS calcd for $C_{15}H_{11}D_4ClO_2S$ (M^+) 298.0732, found 298.0737.

Compound 3c (R_1=H, R_2=d4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (dd, J = 4.1, 1.4 Hz, 1H), 2.82 - 2.86 (m, 1H), 3.28 - 3.36 (m, 3H), 7.11 (dd, J = 8.6, 0.7 Hz, 2H), 7.27 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 8.3, 7.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 38.2, 47.6, 51.3, 119.0 (t, J = 25.7 Hz), 119.3, 123.9, 128.5, 130.0, 133.2 (t, J = 23.9 Hz), 156.8, 157.1 (m); HRMS calcd for $C_{15}H_{10}D_4O_2S$ (M^+) 262.0966, found 262.0949.

Compound 4c (R_1=H, R_2=d4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (dd, J = 4.1, 1.4 Hz, 1H), 2.84 (dd, J = 3.8, 2.4 Hz, 1H), 3.26 - 3.37 (m, 3H), 7.11 (d, J = 8.6 Hz, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 46.0, 46.1, 59.8, 117.4 (t, J = 25.5 Hz), 120.7, 125.4, 130.3 (t, J = 25.5 Hz), 130.4, 132.4, 154.9, 163.0; HRMS calcd for $C_{15}H_{10}D_4O_4S$ (M^+) 294.0864, found 294.0869.

Compound 5c (R_1=H, R_2=d4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (dd, J = 5.2, 1.7 Hz, 13H), 2.54 (dd, J = 6.2, 1.7 Hz, 1H), 3.04 - 3.10 (m, 1H), 3.18 (dd, J = 14.5, 7.9 Hz, 1H), 3.53 (dd, J = 14.1, 5.9 Hz, 1H), 7.10 (d, J = 7.6 Hz, 2H), 7.25 (t, J = 6.9 Hz, 1H), 7.44 (t, J = 7.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 26.3, 62.8, 117.5 (t, J = 24.7 Hz), 120.6, 125.4, 125.4, 130.5 (t, J = 25.5 Hz), 130.5, 131.9, 154.9, 163.0; HRMS calcd for $C_{15}H_{11}D_4O_3S_2$ ($M+H^+$) 311.0714, found 311.0700.

Compound 19a (R_2=H). To a stirred solution of 4-hydroxythiophenol (**6**) (4.30 g, 34.1 mmol) in DMF (25 mL) were added K_2CO_3 (4.71 g, 34.1 mmol) and allyl bromide (3.09 mL, 34.1 mmol) at ice-water temperature, and the mixture was stirred for 15 minutes, prior to stirring overnight at room temperature. After the addition of 1 M aqueous HCl, the mixture was extracted with ether (3x). The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/10 to 1/6) to give the product (5.74 g, 70%) as a white semi-solid.

Compound 10b (R_1=*p*-CH_2CO_2Et, R_2=H). A mixture of **18a** (1.51 g, 6.59 mmol), **19a** (1.64 g, 9.88 mmol), Cs_2CO_3 (4.30 g, 13.2 mmol), *N*,*N*-dimethylglycine hydrochloride salt (276 mg, 1.98 mmol), CuI (125 mg, 0.659 mmol), and degassed 1,4-dioxane (14 mL) was heated at 90 °C for 22 hours under a nitrogen atmosphere. After dilution with water, the mixture was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/12) to give the product (1.35 g, 65%) as a pale yellow semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.49 (d, 2H, *J* = 7.2 Hz), 3.61 (s, 2H), 3.71 (s, 3H), 5.03-5.10 (m, 2H), 5.86 (m, 1H), 6.91-6.97 (m, 4H), 7.23-7.26 (m, 2H), 7.32-7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.5, 40.3, 52.1, 117.5, 119.0, 119.1, 129.0, 129.3, 130.6, 132.9, 133.7, 156.0, 156.3, 172.0; HRMS (FAB) calcd for $C_{18}H_{18}O_3S$ (M^+) 314.0977, found 314.0986.

Compound 20a (R_2=H). Synthesis of compound **20a** was accomplished by the same method for the preparation of compound **19a** using dimethylcarbamoyl chloride instead of allyl bromide.

Compound 21a (R_1=3-benzyloxy, R_2=H). Synthesis of compound **21a** was accomplished by the same method for the preparation of compound **10b** using compound **20a** and 1-benzyloxy-3-iodobenzene (**18b**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.09 (d, *J* = 23.3 Hz, 6H), 5.06 - 5.08 (m, 2H), 6.70 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.75 (t, *J* = 2.2 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.34 - 7.51 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.9, 70.1, 106.4, 110.6, 111.9, 118.9, 127.6, 128.1, 128.6, 130.3, 136.7, 137.5, 157.5, 158.4, 160.1, 167.2.

Compound 3d (R_1=3-benzyloxy, R_2=H, from compound 21a). Compound **21a** (4.30 g, 11.3 mmol) was added to methanolic KOH (6.26 g, 88.2 mol) in MeOH (80 mL) and then refluxed for 3 hours. The solvent was removed under reduced pressure and the residue was diluted with methylene chloride / 2 N HCl. The aqueous layer was extracted with methylene chloride and the combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resultant residue was dissolved in

acetonitrile / MeOH (2:1, 60 mL) and K_2CO_3 (2.95 g, 21.4 mmol) was added. After 0.5 hours, epichlorohydrin (1.67 mL, 21.4 mmol) was added to the reaction mixture and was stirred at room temperature for 1 hour and was filtered through a layer of silica gel. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography to give compound **3d** as colorless oil (3.00 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.09 (d, *J* = 24.1 Hz, 6H), 5.04 - 5.08 (m, 2H), 6.69 (dd, *J* = 7.2, 3.1 Hz, 1H), 6.74 (t, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 7.28 (t, *J* = 8.3 Hz, 1H), 7.34 - 7.50 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 70.2, 106.4, 110.6, 112.0, 118.9, 122.4, 127.6, 128.1, 128.7, 130.4, 136.7, 137.5, 157.5, 158.4, 160.2, 167.2.

Compound 23a (R_2=H). Synthesis of compound **23a** was accomplished by the same method for the preparation of compound **19a** using epichlorohydrin instead of allyl bromide. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.95 (dd, *J* = 13.8, 7.2 Hz, 1H), 3.03 (dd, *J* = 13.8, 5.5 Hz, 1H), 3.25 (br.s., 1H), 3.66 (ddd, *J* = 21.4, 11.0, 4.1 Hz, 2H), 3.87 (m, 1H), 6.79 (d, *J* = 8.3 Hz, 2H), 7.22 (br.s., 1H), 7.31 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 40.3, 48.0, 69.6, 116.4, 124.0, 134.3, 156.4, 172.2; HRMS calcd for $C_9H_{11}ClO_2S$ (M^+) 218.0168, found 218.0172.

Compound 2e (R_2=d5, R_2=H, from compound **22a** and compound **23a**). The procedure was adapted from that reported by Evan et al. (*Tetrahedron Lett.* **1998**, *39*, 2937-2940). A mixture of compound **23a** (0.86 g, 3.93 mmol), $Cu(OAc)_2$ (0.72 g, 3.96 mmol), phenyl-d5 boronic acid (**22a**, 1.00 g, 7.87 mmol), and powdered 4 Å molecular sieves was stirred in CH_2Cl_2 and triethylamine (1.10 mL, 7.89 mmol) was added. After stirring for 18 hours at room temperature, the resulting slurry was filtered through a layer of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to give the desired product (0.85 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.95 (br.s., 1H), 3.09 (ddd, *J* = 42.0, 14.1, 5.5 Hz, 2H), 3.71 (ddd, *J* = 17.2, 11.0, 4.5 Hz, 2H), 3.94 (m, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.43 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.6, 48.1, 69.6, 118.9 (t, *J* = 24.7 Hz), 119.4,

123.4 (t, J = 24.7 Hz), 128.0, 129.5 (t, J = 23.9 Hz), 133.2, 156.6, 157.2; HRMS calcd for $C_{15}H_{10}D_5ClO_2S$ (M^+) 299.0795, found 299.0988.

Conversion from compound **2e** to compounds **3e** – **5e** was followed by the same method as described in Scheme 5.

Compound 3e (R_2=d5, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (dd, J = 4.8, 2.8 Hz, 1H), 2.79 (td, J = 8.6, 0.7 Hz, 1H), 2.89 (dd, J = 13.8, 5.9 Hz, 1H), 3.12 (dd, J = 13.8, 5.2 Hz, 1H), 3.16 - 3.21 (m, 1H), 6.96 (d, J = 9.0 Hz, 22H), 7.45 (d, J = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 38.1, 47.6, 51.3, 118.9 (t, J = 25.5 Hz), 119.3, 123.3 (t, J = 23.9 Hz), 128.7, 129.5 (t, J = 24.0 Hz), 133.6, 156.7, 157.2; HRMS calcd for $C_{15}H_9D_5O_2S$ (M^+) 263.1028, found 263.1035.

Compound 4e (R_2=d5, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (dd, J = 4.8, 2.1 Hz, 1H), 2.81 - 2.84 (m, 1H), 3.24 - 3.36 (m, 3H), 7.09 (d, J = 9.0 Hz, 2H), 7.89 (d, J = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 45.7, 45.8, 59.5, 117.6, 120.0 (t, J = 24.7 Hz), 124.7 (t, J = 23.9 Hz), 129.7 (t, J = 24.7 Hz), 130.5, 132.4, 154.6, 162.7; HRMS calcd for $C_{15}H_9D_5O_4S$ (M^+) 295.0926, found 295.0929.

Compound 5e (R_2=d5, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (dd, J = 5.2, 1.7 Hz, 1H), 2.54 (dd, J = 6.2, 1.4 Hz, 1H), 3.03 - 3.10 (m, 1H), 3.18 (dd, J = 14.1, 7.9 Hz, 1H), 3.53 (dd, J = 14.1, 5.5 Hz, 1H), 7.10 (d, J = 9.0 Hz, 2H), 7.87 (d, J = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 26.3, 62.8, 117.9, 120.2 (t, J = 23.9 Hz), 124.9 (t, J = 25.0 Hz), 129.9 (t, J = 24.7 Hz), 130.9, 132.0, 154.8, 163.1; HRMS calcd for $C_{15}H_{10}D_5O_3S_2$ ($M+H^+$) 312.0773, found 312.0796.

Compounds of Scheme 9.

Compound 28a (R_2=*p*-NO_2, R_2=allylthio). To a stirred solution of **19a** (3.46 g, 20.8 mmol) in DMF (100 ml) were added cesium carbonate (10.2 g, 31.2 mmol) and 1-fluoro-4-nitrobenzene (**25a**) (2.94 g, 20.8 mmol) at room temperature, and the mixture was stirred at the same temperature for 2 days. After dilution with water, the mixture was extracted into hexane (3x). The combined organic layer was washed with water and brine, dried over Na2SO4, and concentrated under reduced pressure to give **28a** (5.32 g, 89%) as a pale yellow oil. 1H NMR (300 MHz,

$CDCl_3$): δ 3.55 (dt, 2H, *J* = 6.9, 1.2 Hz), 5.10 (dt, 1H, *J* = 10.2, 1.2 Hz), 5.13 (dt, 1H, *J* = 17.1, 1.2 Hz), 5.88 (ddt, 1H, *J* = 17.1, 10.2, 6.9 Hz), 6.98-7.04 (m, 4H), 7.38-7.43 (m, 2H), 8.18-8.22 (m, 2H); ^{13}C NMR (125 MHz, CDCl3): δ 37.8, 117.1, 117.9, 120.9, 126.0, 132.3, 132.5, 133.4, 142.7, 153.4, 163.1; HRMS (FAB) calcd for $C_{16}H_{17}NO_3S_2$ (M^+) 287.0616, found 287.0593.

Compound 29a (R_2=*p*-NO_2, R_2=dimethylthiocarbamyl). Preparation of compound **29** was accomplished by the method for the synthesis of compound **28a** using 2-chloro-5-nitropyridine (**26a**) and compound **20a**. 1H NMR (500 MHz, $CDCl_3$) δ 3.12 (d, *J* = 33.3 Hz, 6H), 7.06 (d, *J* = 9.0 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 8.49 (m, 1H), 9.04 (d, *J* = 1.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.2, 111.7, 122.2, 125.7, 126.4, 135.2, 137.5, 145.1, 153.7, 166.7 (s); HRMS calcd for $C_{25}H_{30}N_5O_6S$ ($M+H^+$) 528.1917, found 528.1920.

Compounds of Scheme 10.

Compound 34a (R_1=R_2=H, R_3=Me, n=1, 4-carbonyloxy). A mixture of compound **33a** (100 mg, 310 μmol) and pyridine (50 μL, 620 μmol) in CH_2Cl_2 (1 mL) in ice-water bath was added acetic anhydride (32 μL, 340 μmol) and the resulting solution was stirred for 1 hour. The reaction mixture washed with water and the volatile was concentrated and the crude product was purified by column chromatography. 1H NMR (500 MHz, $CDCl_3$) δ 2.15 (dd, *J* = 4.8, 1.4 Hz, 1H), 2.31 (s, 3H), 2.52 (d, *J* = 6.2 Hz, 1H), 3.05 (m, 1H), 3.18 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.51 (dd, *J* = 14.3, 5.7 Hz, 1H), 7.07 - 7.16 (m, 6H), 7.86 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.2, 24.3, 26.2, 62.7, 117.8, 121.4, 123.5, 130.9, 132.2, 147.7, 152.3, 162.8, 169.5.

Compounds **34b-34h** were prepared in the same manner as described for **34a**, with the exception corresponding acid chlorides or anhydrides was used in place of acetic anhydride.

Compound 34b (R_1=R_2=H, R_3=t-Bu, n=1, 4-carbonyloxy). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.17 (dd, *J* = 5.2, 1.7 Hz, 1H), 2.55 (dd, *J* = 6.2, 1.7 Hz, 1H), 3.08 (m, 1H), 3.19 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.53 (dd, *J* = 14.1, 5.5 Hz,

1H), 7.09 - 7.14 (m, 6H), 7.87 (d, J = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 26.3, 27.3, 39.3, 62.8, 117.8, 121.5, 123.5, 130.9, 132.2, 148.2, 152.1, 163.1, 177.3.

Compound 34c (R_1=R_2=H, R_3=Ph, n=1, 4-carbonyloxy). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (dd, J = 5.2, 1.7 Hz, 1H), 2.54 (dd, J = 4.5, 1.7 Hz, 1H), 3.04 - 3.09 (m, 1H), 3.20 (dd, J = 14.3, 7.8 Hz, 1H), 3.53 (dd, J = 14.3, 5.7 Hz, 1H), 7.15 (t, J = 8.6 Hz, 4H), 7.29 (d, J = 9.0 Hz, 2H), 7.53 (t, J = 7.8 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 8.22 (d, J = 7.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 26.2, 62.7, 117.8, 121.5, 123.7, 128.8, 129.3, 130.3, 130.9, 132.3, 134.0, 148.0, 152.4, 162.9, 165.3.

Compound 34d (R_1=R_2=H, R_3=CH_2Ph, n=1, 4-carbonyloxy). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (m, 1H), 2.48 (s, 2H), 2.55 (t, J = 6.0 Hz, 1H), 3.08 (m, 1H), 3.19 (m, 1H), 3.52 (m, 1H), 3.89 (s, 1H), 7.09 (t, J = 8.6 Hz, 2H), 7.12 - 7.17 (m, 3H), 7.26 - 7.35 (m, 3H), 7.37 - 7.42 (m, 2H), 7.88 (ddd, J = 11.8, 8.9, 2.8 Hz, 2H), 8.11 (d, J = 7.9 Hz, 1H).

Compound 34e (R_1=R_2=H, R_3=$CH_2(CH_2)_9$Br, n=1, 4-carbonyloxy). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (m, 2H), 1.78 (m, 2H), 1.92 (m, 2H), 2.14 (dd, J = 5.2, 1.7 Hz, 1H), 2.52 (d, J = 6.2 Hz, 1H), 2.59 (t, J = 7.4 Hz, 3H), 3.04 (m, 1H), 3.18 (dd, J = 14.1, 7.9 Hz, 1H), 3.43 (t, J = 6.5 Hz, 3H), 3.50 (dd, J = 14.3, 5.7 Hz, 1H), 7.07 - 7.11 (m, 4H), 7.12 - 7.15 (m, 2H), 7.86 (d, J = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.1, 24.3, 26.2, 27.6, 32.4, 33.6, 34.1, 62.7, 117.8, 121.4, 123.4, 130.9, 132.2, 147.7, 152.2, 162.9, 172.0.

Compound 34f (R_1=R_2=H, R_3=4-methylphenyl, n=1, 4-carbonyloxy). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (d, J = 4.1 Hz, 1H), 2.47 (s, 3H), 2.56 (d, J = 5.9 Hz, 1H), 3.08 (m, 1H), 3.19 (dd, J = 14.1, 7.6 Hz, 1H), 3.54 (dd, J = 14.1, 5.5 Hz, 1H), 7.15 (dd, J = 8.8, 5.0 Hz, 4H), 7.30 (dd, J = 23.1, 7.9 Hz, 4H), 7.89 (d, J = 9.0 Hz, 2H), 8.11 (d, J = 8.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.0, 24.4, 26.3, 62.8, 117.9, 121.6, 123.8, 126.6, 129.6, 130.4, 131.0, 132.3, 144.9, 148.1, 152.3, 163.1, 165.4.

Compound 34g (R_1=R_2=H, R_3=4-nitrophenyl, n=1, 4-carbonyloxy). ^{1}H NMR (500 MHz, $CDCl_3$) δ2.18 (dd, *J* = 5.0, 1.9 Hz, 1H), 2.56 (d, *J* = 6.2 Hz, 1H), 3.08 (m, 1H), 3.22 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.53 (dd, *J* = 14.5, 5.9 Hz, 1H), 7.17 (dd, *J* = 14.8, 9.0 Hz, 4H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 2H), 8.34 - 8.43 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ24.4, 26.3, 62.8, 118.1, 121.7, 123.5, 124.0, 124.4, 131.1, 131.5, 131.9, 132.6, 134.8, 147.5, 151.2, 152.9, 162.8, 163.5.

Compound 34h (R_1=R_2=H, R_3=4-methoxyphenyl, n=1, 4-carbonyloxy). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (dd, *J* = 5.2, 1.7 Hz, 1H), 2.56 (dd, *J* = 6.2, 1.0 Hz, 1H), 3.08 (m, 1H), 3.19 (dd, *J* = 14.3, 7.8 Hz, 1H), 3.54 (dd, *J* = 14.3, 5.7 Hz, 1H), 3.92 (s, 3H), 7.01 (d, *J* = 9.0 Hz, 2H), 7.15 (dd, *J* = 9.0, 3.8 Hz, 4H), 7.28 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H), 8.17 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 26.3, 55.8, 62.8, 114.1, 117.9, 121.6, 121.6, 123.8, 131.0, 132.3, 132.5, 148.2, 152.3, 163.1, 164.3, 165.1.

Compound 35a (R_1=R_2=H, R_3=Me, n=1, 4-sulfonyloxy). A mixture of compound **33a** (100 mg, 310 μmol) and Et_3N (86 μL, 620 μmol) in CH_2Cl_2 (1 mL) in ice-water bath was added acetic anhydride (26 μL, 340 μmol) and the resulting solution was stirred for 1 hour. The reaction mixture washed with water and the volatile was concentrated and the crude product was purified by column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (dd, *J* = 5.2, 1.7 Hz, 1H), 2.51 (d, *J* = 6.2 Hz, 1H), 3.03 (m, 1H), 3.18 (s, 3H), 3.22 (dd, *J* = 14.1, 7.6 Hz, 1H), 3.47 (dd, *J* = 14.3, 6.0 Hz, 1H), 7.10 (dd, *J* = 9.0, 2.8 Hz, 4H), 7.32 (d, *J* = 9.3 Hz, 2H), 7.87 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.2, 26.1, 37.5, 62.5, 118.2, 121.6, 124.0, 130.9, 132.6, 145.6, 153.8, 162.1.

Compounds **35b-35g** were prepared in the same manner as described for **35a**, with the exception corresponding sulfonyl chlorides was used in place of mesylchloride.

Compound 35b (R_1=R_2=H, R_3=n-Pr, n=1, 4- sulfonyloxy). 1H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.5 Hz, 3H), 2.03 (m, 2H), 2.16 (dd, *J* = 5.0, 1.7 Hz, 1H), 2.53 (dd, *J* = 6.1, 1.7 Hz, 1H), 3.06 (m, 1H), 3.25 (m, 3H), 3.50 (dd, *J* = 14.4, 5.8 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 4H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.6 Hz,

2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 17.4, 24.2, 26.2, 52.2, 62.5, 118.1, 121.6, 124.1, 130.9, 132.6, 145.6, 153.6, 162.3.

Compound 35c (R_1=R_2=H, R_3=i-Pr, n=1, 4- sulfonyloxy). 1H NMR (300 MHz, $CDCl_3$) δ 1.56 (d, *J* = 6.6 Hz, 6H), 2.14 (dd, *J* = 5.2, 1.7 Hz, 1H), 2.52 (d, *J* = 6.1 Hz, 1H), 3.06 (m, 1H), 3.22 (dd, *J* = 14.1, 7.5 Hz, 1H), 3.50 (m, 2H), 7.10 (d, *J* = 8.6 Hz, 4H), 7.31 (d, *J* = 9.1 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 24.2, 26.1, 52.7, 62.5, 118.0, 121.5, 124.0, 130.9, 132.5, 145.5, 153.4, 162.3.

Compound 35d (R_1=R_2=H, R_3=Ph, n=1, 4- sulfonyloxy).

39phenylsulfonyl

1H NMR (500 MHz, $CDCl_3$) δ 2.16 (dd, *J* = 5.0, 1.6 Hz, 1H), 2.53 (dd, *J* = 6.2, 1.4 Hz, 1H), 3.05 (m, 1H), 3.22 (dd, *J* = 14.1, 7.6 Hz, 1H), 3.49 (dd, *J* = 14.5, 5.9 Hz, 1H), 6.98 - 7.05 (m, 4H), 7.07 (d, *J* = 9.0 Hz, 2H), 7.56 (t, *J* = 7.9 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.87 (dd, *J* = 8.6, 6.5 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.3, 26.2, 62.7, 118.2, 121.3, 124.4, 128.6, 129.4, 131.0, 132.8, 134.6, 135.2, 146.2, 153.7, 162.3.

Compound 35e (R_1=R_2=H, R_3=4-methylphenyl, n=1, 4- sulfonyloxy). 1H NMR (500 MHz, $CDCl_3$) δ 2.15 (dd, *J* = 5.2, 1.7 Hz, 1H), 2.46 (s, 3H), 2.53 (d, *J* = 6.2 Hz, 1H), 3.06 (m, 1H), 3.22 (dd, *J* = 14.5, 7.6 Hz, 1H), 3.48 (m, 1H), 7.01 (d, *J* = 12.1 Hz, 4H), 7.07 (d, *J* = 9.0 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.8, 24.3, 26.2, 62.7, 118.2, 121.3, 124.4, 128.7, 130.0, 131.0, 132.3, 132.8, 145.8, 146.4, 153.6, 162.4.

Compound 35f (R_1=R_2=H, R_3=4-methoxyphenyl, n=1, 4- sulfonyloxy).

1H NMR (500 MHz, $CDCl_3$) δ 2.14 (d, *J* = 5.2 Hz, 1H), 2.52 (d, *J* = 6.2 Hz, 1H), 3.04 (m, 1H), 3.21 (dd, *J* = 14.5, 7.6 Hz, 1H), 3.48 (dd, *J* = 14.1, 5.9 Hz, 1H), 3.88 (s, 3H), 7.00 (dd, *J* = 11.4, 9.6 Hz, 6H), 7.06 (d, *J* = 8.6 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.3, 26.2, 55.9, 62.6, 114.5, 118.1, 121.3, 124.4, 124.4, 126.3, 130.9, 131.0, 132.7, 146.3, 153.5, 162.3, 164.4.

Compound 35g (R_1=R_2=H, R_3=2,4,6-trimethylphenyl, n=1, 4-sulfonyloxy). 1H NMR (500 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.9 Hz, 12H), 1.27 (d, *J* = 7.2 Hz, 6H), 2.15 (dd, *J* = 5.2, 1.4 Hz, 1H), 2.53 (m, 1H), 2.94 (m, 1H), 3.05 (m, 1H), 3.21 (dd, *J* = 14.1, 7.6 Hz, 1H), 3.49 (dd, *J* = 14.5, 5.9 Hz, 1H), 4.08 (m, 1H), 7.01 - 7.06 (m, 6H), 7.21 - 7.23 (m, 2H), 7.86 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.7, 24.3, 24.7, 26.2, 29.9, 34.4, 62.7, 117.9, 121.5, 124.1, 124.6, 129.4, 130.9, 132.6, 146.3, 151.4, 153.5, 154.7, 162.5.

Compound 37b (R_1=R_2=H, R_3=i-Bu, n=1, 4-carboxymethyl). To s stirred solution of **36a** (50 mg, 0.14 mmol), EDC (53 mg, 0.28 mmol), DMAP (1.3 mg, 0.01 mmol) in CH_2Cl_2 (5 ml) was added iso-butanol (0.013 mml, 10.43 mg, 0.14 mmol) and the mixture was stirred at room temperature for 2 hours. The solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with 10% citric acid solution, saturated $NaHCO_3$-solution, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to give **37b** as a colorless oil (35 mg, 0.08 mmol, 60%). ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 0.92 (d, 6H, J = 6.7 Hz), 1.94 (sep, 1H, J = 6.7 Hz), 2.17 (dd, 1H, J = 5.1, 1.8 Hz), 2.55 (dd, 1H, J = 6.3, 1.7 Hz), 3.07 (m, 1H), 3.18 (dd, 1H, J = 14.0, 7.8 Hz), 3.53 (dd, 1H, J = 13.9, 5.4 Hz), 3.66 (s, 2H), 3.91 (d, 2H, J = 6.6 Hz), 7.07 (m, 4H), 7.35 (m,2H), 7.87 (m, 2H). ^{13}C-NMR (500 MHz, $CDCl_3$, TMS): δ 19.0, 24.3, 26.1, 27.7, 40.7, 62.7, 71.1, 117.4, 120.6, 130.7 (d), 131.2 (d), 131.3, 131.9, 153.7, 162.9, 171.4 MS (FAB) m/z 420.1046 (calcd for $C_{21}H_{24}O_5S_2$ $[M]^+$ 420.1065)

TLC R_f= 0.54 (1:1 hexanes/EtOAc)

Compounds **37c-37g** were prepared in the same manner as described for compound **37b** with the exception of corresponding alcohol was used instead of isobutanol.

Compound 37c (R_1=R_2=H, R_3=4-chlorobenzyl, n=1, 4-carboxymethyl). ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 2.16 (dd, 1H, 5.1, 1.7 Hz), 2.54 (dd, 1H, 6, 1.4 Hz), 3.06 (m, 1H), 3.18 (dd, 1H, 14.1, 7.8 Hz), 3.52 (dd, 1H, 13.8, 5.4 Hz), 3.69 (s, 2H), 5.12 (s, 2H), 7.06 (m, 4H), 7.29 (m, 6H), 7.86 (m, 2H) ^{13}C-NMR (500 MHz, $CDCl_3$, TMS): δ 24.3, 26.1, 40.5, 62.7, 66.0, 117.4, 117.8, 120.6, 128.8, 129.6,

130.7, 130.8, 131.2 (d), 132.0, 134.2, 153.9, 162.8, 171.1 MS (FAB) m/z 489.0576 (calcd for $C_{24}H_{22}ClO_5$ $[M+H]^+$ 489.0597) TLC R_f = 0.53 (1:1 hexanes/EtOAc)

Compound 37d (R_1=R_2=H, R_3=thiophen-2-yl, n=1, 4-carboxymethyl). ^{1}H-NMR (500 MHz, acetone, TMS): δ 2.18 (dd, 1H, J = 5.0, 1.4 Hz), 2.55 (dd, H, 6.0, 1.3 Hz), 3.06 (m, 1H), 3.40 (dd, 1H, 14.5, 7.3 Hz), 3.59 (dd, 1H, 14.5, 6.1 Hz), 3.74 (s, 2H), 5,33 (s, 2H), 7.01 (m, 1H), 7.14 (m, 5H), 7.41 (m, 2H), 7.48 (m, 1H), 7.94 (m, 2H) ^{13}C-NMR (500 MHz, $CDCl_3$, TMS): δ 24.3, 26.1, 40.4, 61.1, 62.7, 117.4, 117.7, 120.6, 126.9, 127.0, 128.3, 130.7, 130.8 (d), 131.2 (d), 131.9, 137.6, 153.9, 162.9, 171.1 MS (FAB) – (measurement was not possible) TLC R_f = 0.53 (1:1 hexanes/EtOAc)

Compound 37e (R_1=R_2=H, R_3= pyridin-2-yl)methyl, n=1, 4-carboxymethyl). ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 2.17 (dd, 1H, J = 5.1, 1.7 Hz), 2.54 (dd, 1H, J = 6.0, 1.4 Hz), 3.07 (m, 1H), 3.19 (dd, 1H, J = 13.8, 7.8 Hz), 3.53 (dd, 1H, J = 14.1, 5.4 Hz), 3.78 (s, 1H), 5.30 (s, 1H), 7.08 (m, 4H), 7.32 (m, 4H), 7.72 (d of t, 1H, J = 7.8, 1.5 Hz), 7.87 (m, 2H), 8.62 (d, 1H, J = 4.9 Hz), ^{13}C-NMR (500 MHz, $CDCl_3$, TMS): δ 24.3, 26.1, 40.4, 62.6, 67.3, 117.4, 117.8, 120.6, 121.9, 123.1, 130.8 (t), 131.3 (d), 132.0, 136.9, 149.5, 153.9, 155.4, 162.9, 171.1 MS (FAB) m/z 456.0943 (calcd for $C_{23}H_{22}O_5NS_2$ $[M+H]^+$ 456.0939) TLC R_f = 0.19 (1:1 hexanes/EtOAc)

Compound 37f (R_1=R_2=H, R_3= pyridin-3-yl)methyl, n=1, 4-carboxymethyl). ^{1}H-NMR (500 MHz, acetone, TMS): δ 2.18 (dd, 1H, J = 5.0, 1.4 Hz), 2.55 (dd, 1H, J = 6.5, 1.2 Hz), 3.06 (quinett t,t, 1H, J = 6.2, 1.1 Hz), 3.41 (dd, 1H, J = 14.5, 7.3 Hz), 3.59 (dd, 1H, J = 14.5, 6.1 Hz), 3.79 (s, 2H), 5.21 (s, 2H), 7.15 (m, 4H), 7.37 (ddd, 1H, J = 5.0, 8.0, 0.8 Hz), 7.43 (m, 2H), 7.77 (m, 1H), 7.95 (m, 2H), 8.54 (dd, 1H, J = 4.5, 1.6 Hz), 8.59 (d, 1H, J = 1.8 Hz) ^{13}C-NMR (500 MHz, $CDCl_3$, TMS): δ 24.3, 26.1, 40.4, 62.6, 64.2, 117.5, 117.8, 120.6, 123.6, 130.5, 130.8 (d), 131.2 (d), 132.0, 136.2, 149.4, 149.5, 154.0, 162.8, 171.1 MS (FAB) m/z 456.0961 (calcd for $C_{23}H_{22}O_5NS_2$ $[M+H]^+$ 456.0939) TLC R_f = 0.14 (1:1 hexanes/EtOAc)

Compound 37g (R_1=R_2=H, R_3= benzyl, n=1, 4-carboxymethyl). ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 2.17 (dd, 1H, J = 5.1, 1.7 Hz), 2.55 (dd, 1H, J = 6.0,

1.1 Hz), 3.07 (m, 1H), 3.19 (dd, 1H, J = 14.1, 7.9 Hz), 3.53 (dd, 1H, J = 14.1, 5.4 Hz), 3.71 (s, 1H), 5.17 (s, 1H), 7.08 (m, 4H), 7.35 (m, 6H), 7.87 (m, 2H) ^{13}C-NMR (500 MHz, $CDCl_3$, TMS): δ 24.2, 26.1, 40.6, 62.7, 66.8, 117.7, 120.6, 128.2, 128.4, 128.6, 130.7, 130.8, 130.9, 131.2, 132.0, 135.7, 153.9, 162.9, 171.2 MS (FAB) m/z 455.0989 (calcd for $C_{24}H_{23}O_5S_2$ $[M+H]^+$ 455.0987) TLC R_f = 0.53 (1:1 hexanes/EtOAc)

Compound 37h (R_1=R_2=H, R_3=perfluorophenyl, n=1, 4-carboxymethyl). To a stirred solution of **36a** (521 mg, 1.43 mmol), EDC (548 mg, 2.86 mmol), DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (30 ml) was added pentafluorophenol (PfP) (263 mg, 1.43 mmol) and the mixture was stirred overnight at room temperature. The solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with 10% citric acid solution, saturated $NaHCO_3$-solution, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude PfP-ester (636 mg). The crude material was used for the next step.

Compound 38a (R_1=R_2=H, R_3=diethyl, n=1, 4-acetamide). To a stirred solution of **37h** (54 mg, 0.10 mmol) in CH_2Cl_2 (5 ml) is added diethylamine (14.6 mg, 0.10 mmol) and the mixture is stirred overnight at room temperature. The solution was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with 10% citric acid solution, saturated $NaHCO_3$ solution, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/2) to give **38a** (23 mg, 0.055 mmol, 55%) as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$, TMS): δ 1.14 (t, 3H, J = 7.1 Hz), 1.16 (t, 3H, J = 7.1 Hz) 2.16 (dd, 1H, J = 5.0, 1.8 Hz), 2.54 (dd, 1H, J = 6.0, 1.1 Hz), 3.06 (m, 1H), 3.17 (dd, 1H, 14.0, 7.9 Hz), 3.36 (q, 2H, J = 7.1 Hz), 3.41 (q, 2H, J = 7.1 Hz), 3.52 (dd, 1H, J = 14.0, 5.5 Hz), 3.71 (s, 2H), 7.06 (m, 4H), 7.31 (m, 2H), 7.85 (m, 2H) ^{13}C-NMR (500 MHz, $CDCl_3$, TMS): δ 13.0, 14.4, 24.3, 26.1, 39.8, 40.4, 42.4, 62.6, 117.3, 117.6, 120.6, 130.7 (d), 130.8 (d), 131.8, 132.7, 153.4, 163.0, 169.8 MS (FAB) m/z 420.1306 (calcd for $C_{21}H_{26}O_4NS_2$ $[M+H]^+$420.1303) TLC R_f = 0.30 (1:2 hexanes/EtOAc)

Compounds **38b-38e** were prepared in the same manner as described for compound **38a** with the exception of corresponding amine was used instead of diethylamine.

Compound 38b (R_1=R_2=H, R_3=benzyl, n=1, 4-acetamide). ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ 2.17 (dd, 1H, J = 5.1, 1.8 Hz), 2.55 (dd, 1H, J = 6.0, 1.7 Hz), 3.07 (m, 1H), 3.19 (dd, 1H, J = 14.0, 7.8 Hz), 3.52 (dd, 1H, J = 14.1, 5.7 Hz), 3,63 (s, 2H), 4.46 (d, 2H, J = 5.7 Hz), 5.80 (m, 1H), 7.08 (m, 4H), 7.29 (m, 7H), 7.87 (m, 2H) ^{13}C-NMR (500 MHz, $CDCl_3$, TMS): δ 24.2, 26.1, 43.0, 43.8, 62.6, 117.5, 117.8, 117.9, 120.8, 127.7, 128.8, 130.8 (d), 131.2 (d), 131.8, 132.1, 138.0, 154.1, 162.7, 170.4 MS (FAB) m/z 454.1162 (calcd for $C_{24}H_{24}O_4NS_2$ $[M+2H]^+$ 454.1147) TLC R_f = 0.30 (1:1 hexanes/EtOAc)

Compound 38c (R_1=R_2=H, R_3=(furan-2-yl)methyl, n=1, 4-acetamide). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.17 (dd, 1H, J = 4.8, 1.8 Hz), 2.55 (dd, 1H, J = 6.0, 1.7 Hz), 3.07 (m, 1H), 3.20 (dd, 1H, J = 13.8, 7.7 Hz), 3.52 (dd, 1H, J = 14.1, 5.6 Hz), 3.61 (s, 2H), 4.45 (d, 2H, J = 5.6 Hz), 5.80 (m, 1H), 6.20 (d, 1H, J = 3.3 Hz), 6.32 (m, 1H), 7.09 (m, 4H), 7.33 (m, 3H), 7.87 (m, 2H) ^{13}C-NMR (500 MHz, $CDCl_3$, TMS): δ 24.2, 26.1, 36.7, 42.8, 62.7, 107.5, 110.4, 117.5, 117.8, 120.8, 130.8 (d), 131.2 (d), 131.6, 132.1, 142.3, 150.9, 154.1, 162.7, 170.3 MS (FAB) m/z 444.0920 (calcd for $C_{22}H_{22}O_5NS_2$ $[M+2H]^+$ 444.0939) TLC R_f = 0.32 (1:1 hexanes/EtOAc)

Compound 38d (R_1=R_2=H, R_3=(pyridin-2-yl)methyl, n=1, 4-acetamide). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.16 (dd 1H, J = 5.0, 1.8 Hz), 2.54 (dd 1H, J = 6.0, 1.5 Hz), 3.06 (m, 1H), 3.18 (dd, 1H, J = 14.5, 7.8 Hz), 3.52 (dd, 1H, J = 14.5, 5.6 Hz), 3.66 (s, 2H), 4.59 (d, 2H, J = 5.0 Hz), 7.07 (m, 4H), 7.32 (m, 4H), 7.80 (m, 3H), 8.51 (d, 1H, J = 5.0 Hz) ^{13}C-NMR (500 MHz, $CDCl_3$): δ 24.2, 26.1, 42.8, 44.1, 62.7, 117.4, 117.8 (d), 120.8, 122.8, 122.9, 130.8, 131.3 (d), 131.9 (d), 137.9, 148.0, 153.9, 155.7, 162.9, 170.8 MS (FAB) m/z 455.1100 (calcd for $C_{23}H_{23}O_4N_2S_2$ $[M+2H]^+$) TLC R_f = 0.42 (30:1 CH_2Cl_2/MeOH).

Compound 38e (R_1=R_2=H, R_3=(pyridin-3-yl)methyl, n=1, 4-acetamide). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.16 (dd, 1H, J = 5.0, 1.7 Hz), 2.54 (dd, 1H, J = 6.0, 1.8 Hz), 3.06 (m, 1H), 3.19 (dd, 1H, J = 14.5, 7.7 Hz), 3.50 (dd, 1H, J = 14.0,

5.7 Hz), 3.63 (s, 2H), 4.46 (d, 2H, J = 6.06 Hz), 5.98 (m, 1H), 7.07 (m, 4H), 7.30 (m, 3H), 7.60 (m, 1H), 7.83 (m, 2H), 8.47 (d, 1H, J = 2.1 Hz), 8.51 (dd, 1H, J = 5.0, 1.5 Hz) ^{13}C-NMR (500 MHz, $CDCl_3$): δ 24.2, 26.1, 41.2, 42.8, 62.6, 117.6, 117.9 (d), 120.8, 123.7, 130.8 (d), 131.2 (d), 131.5, 132.2, 133.9, 135.7, 148.8, 154.2, 162.6, 170.7 MS (FAB) m/z 455.1101 (calcd for $C_{23}H_{23}O_4N_2S_2$ $[M+2H]^+$ 455.1099) TLC R_f = 0.40 (30:1 CH_2Cl_2/MeOH).

Compounds of Scheme 11.

Compound 40 = compound 28a (R_2=*p*-NO_2, R_2=allylthio).

Compound 42a (R = SO_2CH_3). To a stirred solution of **40** (636 mg, 2.21 mmol) in THF (22 mL) were added acetic acid (2.54 mL, 44.2 mmol) and zinc powder (5.80 g, 88.4 mmol) at room temperature, and the suspension was stirred for 30 minutes (an exothermic reaction). After dilution with ethyl acetate, the mixture was filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a crude **41** (577 mg) as an orange oil, which was employed in the next reaction without purification. To a stirred solution of **41** (577 mg) in CH_2Cl_2 (10 ml) were added pyridine (894 μL, 11.1 mmol) and methanesulfonyl chloride (205 μL, 2.65 mmol) at ice-water temperature. After 15 minutes, the mixture was warmed to room temperature and the stirring was continued for an additional 2 hours. Subsequent to the addition of saturated $NaHCO_3$, the mixture was extracted with ethyl acetate (3x). The combined organic layer was washed with 1 M aqueous HCl, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure.

The resultant residue was purified by silica gel column chromatography (CH2Cl2) to give **42a** (662 mg, 89% from **40**) as a pale red solid. Compound **41**: 1H NMR (300 MHz, CDCl3): δ 3.45 (br.d, 2H, *J* = 7.2 Hz), 3.59 (br.s, 2H), 5.01-5.06 (m, 2H), 5.84 (ddt, 1H, *J* = 17.1, 9.6, 6.9 Hz), 6.66-6.70 (m, 2H), 6.83-6.88 (m, 4H), 7.29-7.32 (m, 2H). Compound **42**: 1H MR (300 MHz, CDCl3): δ 3.01 (s, 3H), 3.50 (dt, 2H, *J* = 7.2, 1.2 Hz), 5.04-5.11 (m, 2H), 5.86 (ddt, 1H, *J* = 16.8, 10.2, 6.9

Hz), 6.67 (br.s, 1H), 6.90- 6.95 (m, 2H), 6.96-7.01 (m, 2H), 7.20-7.26 (m, 2H), 7.32-7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.4, 39.3, 117.5, 119.3, 119.9, 123.8, 130.2, 132.0, 132.9, 133.8, 155.2, 156.1; HRMS (FAB) calcd for $C_{16}H_{17}NO_3S_2$ (M^+) 335.0650, found 335.0639.

Compound 42b (R = $COCH_3$). To a stirred solution of **41** (794 mg), which was prepared from **40** (830 mg, 2.89 mmol) in the same manner as described for compound **42**, in CH_2Cl_2 (15 ml) were added pyridine (500 μL, 6.18 mmol) and acetic anhydride (292 μL, 3.09 mmol) at ice-water temperature, and the mixture was stirred at the same temperature for 1 hour. Subsequent to the addition of saturated $NaHCO_3$, the mixture was extracted with ethyl acetate (3x). The combined organic layer was washed with 1 M aqueous HCl, saturated NaHCO3 solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure.

The resultant residue was purified by silica gel column chromatography (ethyl acetate/CH_2Cl_2 = 1/8) to give **42b** (782 mg, 99% from **40**) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.17 (s, 3H), 3.47 (d, 2H, *J* = 7.0 Hz), 5.04-5.07 (m, 2H), 5.85 (ddt, 1H, *J* = 17.0, 10.0, 7.0 Hz), 6.87-6.90 (m, 2H), 6.94-6.97 (m, 2H), 7.31- 7.35 (m, 2H), 7.44-7.47 (m, 2H), 7.54 (br.s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 38.5, 117.5, 118.7, 119.6, 121.7, 129.0, 132.9, 133.6, 133.7, 153.1, 156.7, 168.4; HRMS (FAB) calcd for C17H17NO2S (M+) 299.0980, found 299.0980.

Conversion from compounds **40**, **42a,** and **42b** to compounds **4f, 43-44** respectively was followed by the same method as described in Scheme 6.

Compound 4f (R_1=4-NO_2, R_2 =H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51 (dd, 1H, *J* = 4.5, 2.5 Hz), 2.83 (t, 1H, *J* = 4.5 Hz), 3.28 (dd, 1H, *J* = 14.0, 7.0 Hz), 3.35 (m, 1H), 3.41 (dd, 1H, *J* = 14.0, 4.0 Hz), 7.16-7.17 (m, 2H), 7.23-7.25 (m, 2H), 7.99-8.01 (m, 2H), 8.28-8.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 45.7, 45.8, 59.6, 119.1, 119.6, 126.2, 131.0, 134.9, 144.0, 160.2, 160.8; HRMS (FAB) calcd for C15H14NO6S (M+H+) 336.0542, found 336.0545.

Compound 5f (R_1=4-NO_2, R_2 =H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.58 (dd, 1H, *J* = 6.0, 2.0 Hz), 3.10 (m, 1H), 3.31 (dd, 1H, *J* = 14.0, 7.5 Hz), 3.52 (dd, 1H, *J* = 14.0, 6.5 Hz), 7.15-7.18 (m, 2H), 7.23-7.26 (m, 2H), 7.97-8.00 (m, 2H), 8.28-8.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.0, 26.0, 62.5, 119.1, 119.8, 126.2, 131.2, 134.4, 160.3, 160.8; ^{13}C NMR (125 MHz, acetone-*d*6): δ 24.5, 27.2, 62.6, 120.2, 121.0, 127.1, 132.3, 136.2, 145.0, 161.1, 162.4; HRMS (FAB) calcd for $C_{15}H_{14}NO_5S_2$ (M^+H^+) 352.0313, found 352.0297.

Compound 4g =compound 43a (R_1=4-CH_3SO_2NH, R_2 =H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49 (dd, 1H, *J* = 5.1, 1.8 Hz), 2.83 (m, 1H), 3.06 (s, 3H), 3.27-3.36 (m, 3H), 6.77 (br.s, 1H), 7.08-7.11 (m, 4H), 7.28-7.33 (m, 2H), 7.88-7.93 (m, 2H); ^{13}C NMR (125 MHz, acetone-*d*6): δ 39.4, 45.9, 46.6, 59.9, 118.3, 122.3, 123.6, 131.6, 134.6, 136.5, 152.7, 163.5; HRMS (FAB) calcd for $C_{16}H_{17}NO_6S_2$ (M^+) 383.0497, found 383.0496.

Compound 5g =compound 44a (R_1=4-CH_3SO_2NH, R_2 =H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (dd, 1H, *J* = 5.1, 1.8 Hz), 2.55 (dd, 1H, *J* = 6.3, 1.2 Hz), 3.06 (s, 3H), 3.07 (m, 1H), 3.22 (dd, 1H, *J* = 14.1, 7.8 Hz), 3.50 (dd, 1H, *J* = 14.1, 5.7 Hz), 6.72 (br.s, 1H), 7.08-7.12 (m, 4H), 7.30-7.33 (m, 2H), 7.87-7.91 (m,H); ^{13}C NMR (125 MHz, acetone-*d*6): δ 24.4, 27.2, 39.3, 62.6, 118.4, 122.3, 123.6, 131.9, 133.9, 136.4, 152.7, 163.6; HRMS (FAB) calcd for $C_{16}H_{17}NO_5S_3$ (M^+) 399.0269, found 399.0268.

Compound 4h =compound 43b (R_1=4-CH_3CONH, R_2 =H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.48 (dd, 1H, *J* = 4.5, 1.5 Hz), 2.82 (m, 1H), 3.26- 3.34 (m, 3H), 7.03-7.08 (m, 4H), 7.41 (br.s, 1H), 7.55-7.58 (m, 2H), 7.85-7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 45.7, 45.8, 59.8, 117.6, 120.8, 122.0, 130.4, 133.0, 135.4, 151.1, 163.0, 168.5; HRMS (FAB) calcd for $C_{17}H_{18}NO_5S$ (M^+H^+) 348.0906, found 348.0913.

Compound 5h =compound 44b (R_1=4-CH_3CONH, R_2 =H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (dd, 1H, *J* = 5.1, 1.8 Hz), 2.20 (s, 3H), 2.54 (dd, 1H, *J* = 6.3, 1.5 Hz), 3.06 (m, 1H), 3.19 (dd, 1H, *J* = 14.1, 7.8 Hz), 3.52 (dd, 1H, *J* = 14.1, 5.7 Hz), 7.03-7.08 (m, 4H), 7.52 (br.s, 1H), 7.56-7.59 (m, 2H), 7.84-7.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.1, 24.4, 26.0, 62.6, 117.4, 121.0, 121.8, 130.7, 131.6, 135.2, 150.7, 163.1, 168.6; HRMS (FAB) calcd for $C_{17}H_{18}NO_4S_2$ (M^+H^+) 364.0677, found 364.0651

Conversion from compound **29a** to compounds **3i** – **5i** was followed by the same method as described in Schemes 8 and 11.

Compound 21b (R_1=4-CH_3SO_2NH, 2-pyridyl, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (s, 3H), 3.03 (br.s., 3H), 3.10 (br.s., 3H), 6.96 (d, *J* = 9.0 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.77 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.99 (d, *J* = 2.8 Hz, 1H); HRMS calcd for $C_{25}H_{30}N_5O_6S$ ($M+H^+$) 528.1917, found 528.1920.

Compound 4i (R_1=4-CH_3SO_2NH, 2-pyridyl, R_2 =H). ^{1}H NMR (500 MHz, 5% CD_3OD in CD_2Cl_2) δ 2.46 (dd, *J* = 4.6, 2.0 Hz, 1H), 2.79 (t, *J* = 4.4 Hz, 1H), 2.96 (s, 3H), 3.24 - 3.40 (m, 3H), 7.03 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.79 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 2H), 8.05 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (126 MHz, 5% CD_3OD in CD_2Cl_2) δ 39.7, 46.2, 46.3, 60.1, 113.9, 121.3, 130.8, 132.0, 134.7, 134.9, 141.1, 159.9, 160.0 (s); HRMS calcd for $C_{15}H_{17}N_2O_6S_2$ ($M+H^+$) 385.0528, found 385.0531.

Compound 5i (R_1=4-CH_3SO_2NH, 2-pyridyl, R_2 =H). ^{1}H NMR (500 MHz, 5% CD_3OD in CD_2Cl_2) δ 2.16 (dd, *J* = 5.2, 1.8 Hz, 1H), 2.53 (dd, *J* = 6.6, 1.8 Hz, 1H), 2.97 (s, 3H), 3.06 (m, 1H), 3.25 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.52 (dd, *J* = 14.4, 6.0 Hz, 1H), 7.04 (dd, *J* = 8.8, 0.4 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.79 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (126 MHz, 5% CD_3OD in CD_2Cl_2) δ 24.5, 26.5, 39.8, 63.0, 113.8, 121.4, 131.0, 131.9, 134.4, 134.7, 141.1, 159.9, 160.1 (s); HRMS calcd for $C_{15}H_{17}N_2O_5S_3$ ($M+H^+$) 401.0300, found 401.0290.

Compound 48. 2-(4-Bromophenoxy)-phenol was prepared by reported method. A mixture of phenol (2.65 g, 10.0 mmol) and K_2CO_3 (1.45 g, 10.5 mmol) in DMF (20 mL) was stirred for 0.5 hours, and then benzylbromide (1.56 mL, m13.0 mmol) was added. The reaction mixture was stirred at room temperature for 3 hours, then was diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, 2 N HCl, sat'd $NaHCO_3$, and brine, dried under anhydrous $MgSO_4$, filtered, and dried under reduced pressure. The residue was purified by column chromatography to give the desired product as a white solid (3.00 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 - 5.13 (m, 2H), 6.85 (d, J = 9.0 Hz, 2H), 7.00 (t, J = 9.0 Hz, 1H), 7.05 - 7.23 (m, 5H), 7.26 - 7.37 (m, 3H), 7.42 (d, J = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 70.6, 114.6, 115.3, 118.6, 121.9, 122.4, 125.7, 127.2, 128.0, 128.6, 132.5, 136.8, 144.9, 150.7, 157.9;

Conversion from compound **48** to compounds **52a-55a** was followed by the same method as described in Scheme 5.

Compound 2j =compound 52a (R_1=2-benzyloxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.07 (ddd, J = 44.7, 13.8, 5.4 Hz, 2H), 3.68 (ddd, J = 19.9, 11.2, 4.4 Hz, 1H), 3.83 - 3.95 (m, 1H), 5.10 (s, 2H), 6.93 (d, J = 8.6 Hz, 2H), 7.02 (t, J = 7.6 Hz, 1H), 7.05 - 7.25 (m, 5H), 7.27 - 7.36 (m, 3H), 7.41 (d, J = 8.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 40.1, 48.1, 69.5, 70.8, 115.3, 117.5, 121.9, 122.4, 125.7, 126.6, 127.1, 127.9, 128.5, 132.1, 133.4, 136.8, 144.7, 150.7, 158.5.

Compound 3j (R_1=2-benzyloxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (dd, J = 4.8, 2.4 Hz, 1H), 2.78 (t, J = 4.4 Hz, 1H), 3.22 (dd, J = 14.0, 5.2 Hz, 1H), 3.26 - 3.30 (m, 1H), 5.04 - 5.08 (m, 2H), 7.03 - 7.08 (m, 3H), 7.09 - 7.21 (m, 4H), 7.22 - 7.33 (m, 4H), 7.87 (d, J = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 46.0, 46.1, 59.8, 70.7, 115.1, 116.5, 122.0, 123.1, 126.8, 127.1, 128.1, 128.6, 130.4, 131.9, 136.4, 143.2, 150.7, 163.4;

Compound 4j =compound 53a (R_1=2-benzyloxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (dd, J = 5.0, 2.6 Hz, 1H), 2.76 (t, J = 3.8 Hz, 1H), 2.88 (dd, J = 14.0, 6.2 Hz, 1H), 3.12 (dd, J = 13.6, 5.6 Hz, 1H), 3.16 - 3.20 (m, 1H), 5.09 -

5.12 (m, 2H), 6.95 (d, J = 9.0 Hz, 2H), 7.03 (td, J = 7.6, 1.6 Hz, 6H), 7.08 - 7.25 (m, 5H), 7.47 (d, J = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 38.2, 47.4, 51.1, 70.6, 115.1, 117.2, 121.7, 122.3, 125.5, 127.0, 127.2, 127.8, 128.4, 133.7, 136.7, 144.6, 150.6, 158.2;

Compound 4jj =compound 54a (R_1=2-hydroxy, R_2=H). Compound **4j** (0.50 g, 1.3 mmol) was stirred in the presence of $Pd(OH)_2$ (0.15 g) in ethylacetate / i-PrOH (20 mL) for 0.5 h in the atmosphere of H_2. The reaction mixture was filtered through a layer of celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to give the desired product (0.28 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (dd, J = 3.4, 1.8 Hz, 1H), 2.77 - 2.83 (m, 1H), 3.24 - 3.30 (m, 3H), 6.89 - 6.95 (m, 1H), 6.97 - 7.02 (m, 1H), 7.04 - 7.10 (m, 3H), 7.11 - 7.18 (m, 1H), 7.82 (d, J = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 46.0, 59.7, 117.2, 117.5, 121.3, 126.9, 130.7, 132.7, 141.4, 148.2, 162.5;

Compound 5j (R_1=2-benzyloxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (dd, J = 5.0, 1.6 Hz, 1H), 2.49 (d, J = 6.2 Hz, 1H), 3.04 (m, 1H), 3.13 (dd, J = 14.1, 8.1 Hz, 1H), 3.55 (dd, J = 14.2, 5.2 Hz, 1H), 5.07 (s, 2H), 7.04 - 7.09 (m, 3H), 7.11 - 7.17 (m, 3H), 7.23 - 7.31 (m, 5H), 7.85 (d, J = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.5, 26.3, 62.8, 70.7, 115.1, 116.6, 122.1, 123.0, 126.9, 127.1, 128.2, 128.6, 130.6, 131.4, 136.4, 143.2, 150.7, 163.5.

Compound 5jj =compound 55a (R_1=2-hydroxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (dd, J = 5.0, 1.6 Hz, 1H), 2.53 (dd, J = 6.0, 1.4 Hz, 8H), 3.01 - 3.08 (m, 1H), 3.18 (dd, J = 14.2, 7.8 Hz, 1H), 3.50 (dd, J = 14.4, 5.8 Hz, 1H), 5.78 - 5.85 (m, 1H), 6.94 (td, J = 8.0, 1.6 Hz, 1H), 7.00 (dd, J = 8.0, 1.2 Hz, 1H), 7.06 - 7.20 (m, 4H), 7.83 (d, J = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 26.2, 62.8, 117.5, 117.5, 121.1, 121.4, 126.9, 130.9, 132.4, 141.5, 148.1, 162.4.

Compounds of Scheme 12.

Compound 51. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 - 5.08 (m, 2H), 6.85 (d, J = 9.0 Hz, 2H), 6.97 - 7.00 (m, 4H), 7.34 - 7.50 (m, 7H); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 70.7, 115.0, 116.2, 119.5, 121.0, 127.7, 128.2, 128.8, 132.7, 137.1, 150.0, 155.5, 157.9.

Conversion from compound **51** to compounds **52b** – **55b** was followed by the same method as described in Scheme 5.

Compound 2k =compound 52b (R_1=4-benzyloxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.05 (ddd, *J* = 44.5, 13.8, 5.5 Hz, 2H), 3.67 (ddd, *J* = 17.6, 11.0, 4.5 Hz, 2H), 5.06 (s, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.98 (s, 4H), 7.34 - 7.47 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.9, 48.1, 69.6, 70.7, 116.2, 118.4, 121.2, 127.2, 127.6, 128.2, 128.8, 133.4, 137.1, 149.9, 155.5, 158.5.

Compound 3k (R_1=4-benzyloxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.79 (t, *J* = 4.5 Hz, 1H), 2.88 (dd, *J* = 13.8, 5.9 Hz, 1H), 3.10 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.15 - 3.21 (m, 1H), 5.08 (s, 2H), 6.92 (d, *J* = 8.6 Hz, 4H), 7.00 (s, 2H), 7.34 - 7.49 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 38.2, 47.5, 51.2, 70.6, 116.1, 118.2, 121.1, 127.6, 127.7, 128.1, 128.7, 133.8, 137.0, 149.9, 158.3.

Compound 4k =compound 53b (R_1=4-benzyloxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (dd, *J* = 5.0, 1.9 Hz, 1H), 2.82 (dd, *J* = 6.2, 2.8 Hz, 1H), 3.22 - 3.37 (m, 3H), 5.09 (s, 2H), 7.02 - 7.09 (m, 4H), 7.33 - 7.38 (m, 1H), 7.40 - 7.43 (m, 9H), 7.45 - 7.47 (m, 9H), 7.87 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 46.0, 59.8, 70.6, 116.4, 117.1, 122.0, 127.6, 128.3, 128.8, 130.6, 132.1, 136.8, 148.2, 156.4, 163.8.

Compound 4kk =compound 54b (R_1=4-hydroxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (dd, *J* = 5.5, 1.4 Hz, 1H), 2.81 (dd, *J* = 4.5, 2.4 Hz, 1H), 3.23 - 3.35 (m, 3H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 46.0, 59.8, 116.8, 117.0, 122.1, 130.6, 131.6, 147.3, 154.2, 163.6.

Compound 5k (R_1=4-benzyloxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (dd, *J* = 5.2, 1.7 Hz, 1H), 2.56 (dd, *J* = 6.2, 1.4 Hz, 1H), 3.08 (m, 1H), 3.19 (dd, *J* = 14.1, 7.9 Hz, 1H), 3.54 (dd, *J* = 14.1, 5.5 Hz, 1H), 5.11 (s, 2H), 7.06 (s, 5H), 7.08 (d, *J* = 9.0 Hz, 2H), 7.35 - 7.51 (m, 4H), 7.87 (d, *J* = 9.0 Hz, 2H); ^{13}C

NMR (126 MHz, $CDCl_3$) δ 24.4, 26.3, 62.8, 70.7, 116.4, 117.2, 121.9, 127.6, 128.2, 128.8, 130.8, 131.6, 136.8, 148.2, 156.4, 163.8.

Compound 5kk =compound 55b (R_1=4-hydroxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (dd, *J* = 5.2, 1.7 Hz, 1H), 2.55 (dd, *J* = 6.2, 1.7 Hz, 1H), 3.02 - 3.11 (m, 1H), 3.20 (dd, *J* = 14.5, 7.9 Hz, 1H), 3.54 (dd, *J* = 14.5, 5.9 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.06 (d, *J* = 9.0 Hz, 2H), 7.88 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 26.2, 62.8, 117.0, 117.2, 122.2, 130.8, 131.2, 147.9, 153.5, 164.0.

Compounds of Scheme 13.

Synthesis of compounds **57** (= compound **21a**), **58** (= compound **3d**) is described in Scheme 8. Conversion from compound **58** to compounds **59** – **61** was followed by the same method as described in Schemes 5 and 12.

Compound 4d = compound 59. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (dd, *J* = 5.4, 2.0 Hz, 1H), 2.81 (t, *J* = 4.4 Hz, 1H), 3.29 - 3.34 (m, 3H), 5.05 - 5.08 (m, 2H), 6.70 (dd, *J* = 10.2, 2.2 Hz, 1H), 6.73 (t, *J* = 2.2 Hz, 1H), 6.88 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.29 - 7.46 (m, 6H), 7.89 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 45.9, 45.9, 59.6, 70.2, 107.4, 111.8, 112.7, 117.8, 127.5, 128.2, 128.7, 130.5, 130.8, 132.6, 136.4, 155.8, 160.3, 162.6.

Compound 4dd =compound 60 (R_1=3-hydroxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (dd, *J* = 4.5, 1.7 Hz, 1H), 2.82 (m, 1H), 3.31 (m, 3H), 6.48 (br.s., 1H), 6.57 (t, *J* = 2.4 Hz, 1H), 6.60 (ddd, *J* = 8.3, 2.1, 0.7 Hz, 1H), 6.71 (ddd, *J* = 8.3, 2.4, 1.0 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 7.23 (t, *J* = 7.9 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 46.1, 59.8, 108.0, 112.4, 112.6, 118.0, 130.6, 131.0, 132.2, 155.9, 157.8, 162.9.

Compound 5d (R_1=3-benzyloxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (dd, *J* = 5.0, 1.4 Hz, 1H), 2.56 (d, *J* = 5.2 Hz, 1H), 3.09 (m, 1H), 3.21 (dd, *J* = 14.3, 7.9 Hz, 1H), 3.55 (dd, *J* = 14.2, 5.6 Hz, 1H), 5.09 (s, 2H), 6.69 - 6.76 (m, 2H), 6.90 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.33 - 7.38 (m, 2H), 7.40 - 7.46 (m, 4H), 7.89 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 26.2,

62.7, 70.3, 107.4, 111.9, 112.8, 118.0, 127.6, 128.3, 128.8, 130.8, 130.9, 132.1, 136.5, 156.0, 160.4, 162.7.

Compound 5dd =compound 61 (R_1=3-hydroxy, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (m, 1H), 2.50 (m, 1H), 3.02 (m, 1H), 3.21 (dd, *J* = 14.1, 7.6 Hz, 1H), 3.50 (dd, *J* = 14.1, 5.9 Hz, 1H), 6.60 (m, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.86 (br.s., 1H), 7.08 (d, *J* = 9.0 Hz, 2H), 7.22 (t, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.3, 26.1, 62.6, 107.9, 112.2, 112.6, 118.0, 130.7, 131.0, 131.4, 155.8, 157.8, 162.9.

Compounds of Scheme 14.

Compound 63. Synthesis of compound **63** was done by the similar method for the preparation of compound **2e** using 4-hydroxymethylphenyl-boronic acid (**62**) and compound **19**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.89 (br.s., 1H), 2.94 - 3.03 (m, 1H), 3.08 (dd, *J* = 13.8, 5.9 Hz, 1H), 3.58 - 3.66 (m, 2H), 3.85 - 3.91 (m, 1H), 4.54 (d, *J* = 17.6 Hz, 1H), 4.61 (s, 1H), 6.78 (t, *J* = 8.6 Hz, 1H), 6.91 (t, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 10.0, 8.3 Hz, 1H), 7.31 (t, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.8, 48.1, 65.1, 69.6, 116.7, 119.5, 119.5, 125.5, 128.4, 128.7, 129.0, 129.2, 133.3, 135.7, 157.3 (s).

Conversion from compound **63** to compounds **64** – **33** was followed by the same method as described in Scheme 5.

Compound 3l. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.74 (t, *J* = 4.3 Hz, 1H), 2.80 (br s, 1H), 2.86 (dd, *J* = 13.8, 5.9 Hz, 2H), 3.06 (dd, *J* = 13.8, 5.2 Hz, 1H), 3.13 (m, 1H), 4.61 (s, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.9, 47.4, 51.2, 64.5, 119.1, 119.2, 128.7, 133.4, 136.6, 156.0, 157.0.

Compound 4l = compound 64. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (dd, *J* = 5.0, 2.2 Hz, 1H), 2.76 (dd, *J* = 4.8, 3.8 Hz, 1H), 3.25 (m, 3H), 4.64 (s, 2H), 7.02 (dd, *J* = 8.6, 7.9 Hz, 4H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.82 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 45.9, 45.9, 59.5, 64.3, 117.6, 120.5, 128.9, 130.5, 132.3, 138.1, 153.9, 162.9.

Compound 5l=compound 33. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.14 (dd, J = 5.2, 1.7 Hz, 1H), 2.41 (br.s., 1H), 2.52 (d, J = 5.2 Hz, 1H), 3.03 (m, 1H), 3.18 (dd, J = 14.1, 7.6 Hz, 1H), 3.49 (dd, J = 14.3, 5.7 Hz, 2H), 4.69 (s, 2H), 7.07 (dd, J = 8.6, 6.9 Hz, 4H), 7.41 (d, J = 8.6 Hz, 2H), 7.84 (d, J = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.3, 26.2, 62.7, 64.5, 117.8, 120.6, 129.1, 130.8, 131.9, 138.2, 154.1, 163.0.

Compounds of Scheme 15.

Compound 66 = compound **10b**. The synthesis of compound **10b** was described previously. Conversion from compound **10b** to compounds **4m** – **5m** was followed by the same method as described in Scheme 6.

Compound 4m. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.47 (dd, 1H, J = 5.0, 2.0 Hz), 2.82 (m, 1H), 3.26-3.33 (m, 3H), 3.65 (s, 2H), 3.72 (s, 3H), 7.03-7.05 (m, 2H), 7.08-7.10 (m, 2H), 7.32-7.34 (m, 2H), 7.86-7.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.3, 45.8, 52.1, 59.6, 117.6, 120.6, 130.5, 130.9, 131.1, 132.4, 153.8, 162.8, 171.8; HRMS (FAB) calcd for $C_{18}H_{18}O_6S$ (M^+) 362.0824, found 362.0829.

Compound 5m=compound 67. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.15 (dd, 1H, J = 5.5, 2.0 Hz), 2.53 (dd, 1H, J = 6.5, 2.0 Hz), 3.05 (m, 1H), 3.17 (dd, 1H, J = 14.5, 7.0 Hz), 3.51 (dd, 1H, J = 14.5, 5.5 Hz), 3.65 (s, 2H), 3.72 (s, 3H), 7.03-7.05 (m, 2H), 7.08-7.10 (m, 2H), 7.33-7.34 (m, 2H), 7.85-7.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2, 26.0, 40.3, 52.1, 62.6, 117.7, 120.5, 130.7, 130.9, 131.1, 131.9, 153.8, 162.8, 171.8; HRMS (FAB) calcd for $C_{18}H_{19}O_5S_2$ ($M+H^+$) 379.0674, found 379.0645.

Compound 36a (R_1=R_2=H, n=1). To a stirred solution of **5m** (312 mg, 0.83 mmol) in toluene (11 mL) was added bis(tributyltin)oxide (1.05 mL, 2.06 mmol) at room temperature, and the mixture was stirred at 80 °C for 12 h. The solution was cooled to room temperature and was concentrated to dryness under reduced pressure. The residue was dissolved in acetonitrile, and the solution was washed with hexane (3x) and concentrated under reduced pressure to leave the crude tin ester (532 mg) as a pale-yellow oil. Subsequently, tin ester was passed through a C_{18}-reverse phase silica gel pad (ODS silica gel 20 g, washed with water,

1:2 water/acetonitrile and acetonitrile) to afford a mixture of **5m** and **36a**, which was purified by silica gel column chromatography (chloroform/methanol = 30/1 to 10/1) to give **36a** (195 mg, 65%) as a white solid with the recovery of some of **5m** (38 mg, 12%). mp 133-134 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.16 (d, 1H, J = 4.0 Hz), 2.54 (d, 1H, J = 5.5 Hz), 3.06 (m, 1H), 3.19 (dd, 1H, J = 14.0, 8.0 Hz), 3.52 (dd, 1H, J = 14.0, 6.0 Hz), 3.68 (s, 2H), 7.05 (br d, 2H, J = 8.5 Hz), 7.10 (br d, 2H, J = 8.5 Hz), 7.35 (br d, 2H, J = 8.5 Hz), 7.86 (br d, 2H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2, 26.0, 40.2, 62.6, 117.8, 120.5, 130.2, 130.7, 131.3, 132.0, 154.1, 162.7, 177.1; HRMS (FAB) calcd for $C_{17}H_{17}O_5S_2$ ($M+H^+$) 365.0517, found 365.0495; Rf value = 0.2 (chloroform/methanol = 10/1).

Compounds of Scheme 16.

Compound 69a (R_1=R_2=H). This material was prepared in the same manner as described for **11b** in Scheme 7, starting from **68a**. 1H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 4.08 (s, 2H), 7.27 - 7.33 (m, 5H), 7.38 (d, J = 7.0 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H).

Conversion from compound **69a** to compound **70a** was followed by the same method as described in Scheme 6.

Compound 70a (R_1=R_2=H). 1H NMR (500 MHz, $CDCl_3$) δ 2.16 (dd, J = 5.2, 1.8 Hz, 1H), 2.54 (dd, J = 6.2, 1.6 Hz, 1H), 3.06 (m, 1H), 3.17 (dd, J = 14.3, 8.1 Hz, 1H), 3.56 (dd, J = 14.2, 5.4 Hz, 1H), 4.11 (s, 2H), 7.20 (d, J = 7.0 Hz, 2H), 7.28 (d, J = 7.2 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H);^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 26.2, 41.9, 62.6, 126.8, 128.7, 128.9, 129.1, 130.0, 136.4, 139.4, 148.4 (s).

Compound 75a (R_1=R_2=H). This material was prepared in the same manner as described for **11b** in Scheme 7, starting from **74a**. 1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.39 - 7.60 (m, 5H), 7.68 - 7.81 (m, 4H).

Conversion from compound **75a** to compound **76a** was followed by the same method as described in Scheme 6.

Compound 76a (R_1=R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (dd, J = 5.1, 1.7 Hz, 1H), 2.57 (dd, J = 6.2, 1.8 Hz, 1H), 3.11 (m, 1H), 3.31 (dd, J = 14.4,

7.6 Hz, 1H), 3.57 (dd, J = 14.4, 6.0 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.81 (d, J = 7.4 Hz, 2H), 7.98 (d, J = 8.2 Hz, 2H), 8.08 (d, J = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.3, 26.0, 62.6, 128.7, 128.9, 130.3, 130.7, 133.7, 136.5, 141.8, 142.9, 195.3.

Compounds of Scheme 17.

Compound 77a (R_1=H). Compound **20a** (2.00 g, 12.0 mmol) was dissolved in CH_2Cl_2 (10 mL) in ice-water bath. *m*-CPBA (13.0 g, 58.0 mmol, 77%) was added to the reaction mixture and was stirred at room temperature for 3 days. *m*-Chlorobenzoic acid was filtered and washed with 10% sodium thiosulfate , and brine. The organic layer was dried under anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography to give the desired product as a white solid (1.80 g, 70%).

Compound 78a (R_1=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (dd, J = 5.2, 2.1 Hz, 1H), 2.45 (dd, J = 6.2, 2.1 Hz, 1H), 2.94 - 3.01 (m, 1H), 3.11 (dd, J = 14.1, 7.9 Hz, 1H), 3.47 (dd, J = 14.1, 5.5 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.2, 26.2, 62.7, 116.3, 128.2, 130.7, 162.6.

Compound 79a (R_1=H, R_2=benzyl). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (dd, J = 5.2, 1.6 Hz, 1H), 2.50 (dd, J = 6.2, 1.6 Hz, 1H), 3.01 - 3.08 (m, 1H), 3.15 (dd, J = 14.2, 8.0 Hz, 1H), 3.51 (dd, J = 14.2, 5.4 Hz, 1H), 5.16 (s, 2H), 7.11 (d, J = 8.8 Hz, 2H), 7.36 - 7.45 (m, 5H), 7.85 (d, J = 8.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.4, 26.3, 62.7, 70.5, 115.6, 127.6, 128.6, 128.9, 130.3, 130.7, 135.7, 163.3.

Compounds of Scheme 18.

Compound 84a (R_1=R_2=H). To a solution of Mg (0.33 g, 13.6 mmol) in anhydrous THF (4 mL), biphenylbromide (3.25 g, 12.8 mmol) in THF (6 mL) was added and the resulting solution was refluxed for 0.5 hours. Then the reaction mixture was diluted with THF (10 mL) and cooled down to -78 °C. CuBr·DMS (0.26 g, 1.29 mmol) was added and stirred for 20 minutes, followed by the addition

of epichlorohydrin (1.6 mL, 19.2 mmol). The reaction mixture was stirred for 1 hour while the reaction temperature was slowly increased to room temperature. The reaction was quenched by addition of sat'd NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with H_2O, 5% HCl, and brine. After removal of solvent, the residue was used for the next reaction without further purification. A suspension of crude **83a** (3.55 g, 14.4 mmol) and K_2CO_3 (5.98 g, 43.3 mmol) in 1:1 solution of MeOH : THF (60mL) was stirred for 1 hour and then was diluted with diethylether. The suspension was filtered and the filtrate was concentrated and the residue was purified by column chromatography to afford pure **84a** (2.37 g, 88%).

Compound 85a (R_1=R_2=H). Vinylmagnesium bromide (19.0 mL, 1.0 M in THF) in THF (5 mL) was added CuBr·DMS (0.11 g, 0.55 mmol) at -78 °C. After 20 minutes, compound **84a** (1.15 g, 5.48 mmol) was added to the reaction mixture and stirred for additional 1 hour at -78 °C. Stirring was continued for 3 hours, while the reaction was warmed to 0 °C. After quenching the reaction with addition of sat'd NH_4Cl at 0 °C and the solution was stirred for 0.5 hours and extracted with EtOAc. After washing with water and brine, organic layer was concentrated and purified by column chromatography (1.06 g, 82%).

Compound 86a (R_1=R_2=H). A solution of compound **85a** (1.00 g, 4.20 mmol) and Et_3N (0.73 mL, 5.27 mmol) was added methanesulfonyl chloride (0.39 mL, 5.04 mmol) and was stirred for 1 hour. Water was added to the reaction mixture, which was subsequently extracted with EtOAc. The organic layer was washed with sat'd $NaHCO_3$, 1 M $KHSO_4$, water and brine and evaporated to dryness. The crude material was used for the next reaction without further purification. A solution of crude material and potassium thioacetate (2.49 g, 21.8 mmol) in DMF (40 mL) was stirred at 50 °C for 17 hours. The reaction mixture was then diluted with ether/water and layers were separated. Combined organic layers were washed with $NaHCO_3$, H_2O and brine and dried. The residue was purified by column chromatography to give the desired product (0.79 g, 64%) as a semi solid

Compound 87a (R_1=R_2=H, R=Bn). *t*-BuOK (0.79 g, 7.04 mmol) was added to a solution of compound **86a** (0.52 g, 1.76 mmol) in 1:2 solution of MeOH :

THF (10 mL) and the resulting suspension was stirred for 15 minutes, followed by addition of benzyl chloride (1.62 mL, 14.1 mmol). After 3 hours, the reaction was quenched with ammonium hydroxide and was extracted with diethyl ether. The organic layer was washed with water, 5% HCl, and brine. The crude product was purified by column chromatography to give the desired product (0.55 g, 91%) as a colorless oil.

Compound 88a (R_1=R_2=H, R=Bn). This compound was prepared in the same manner as described in Scheme 5.

Compounds of Scheme 19.

Conversion from compound **90a** to compound **96a** was followed by the same method as described in Scheme 14.

Compound 91a (R_1=R_2=H).

Compound 92a (R_1=R_2=H).

Compound 93a (R_1=R_2=H).

Compound 94a (R_1=R_2=H).

Compound 95a (R_1=R_2=H, R_3=Bn).

Compound 96a (R_1=R_2=H, R_3=Bn).

Compounds of Scheme 20.

2-Amino-3-bromo-5-nitrophenol (98). A solution of 2-amino-5-nitrophenol (**97**, 24 g, 156 mmol) in CH_3CN (1 L) was treated with NBS (28.8 g, 160.8 mmol) at room temperature. After stirring for 1 hour, the solvent was removed to afford brown precipitate, which was taken up with ethyl acetate:hexane (1:1). The precipitate was filtered and was used for the next step without further purification (33 g, 91%). A small amount of sample was purified by column chromatography on silica gel for analysis; ^{1}H NMR (500 MHz, CD_3OD): δ 4.93 (brs, 3H), 7.50 (d, 1H, J = 2.4 Hz), 7.89 (d, 1H, J = 2.4 Hz); ^{13}C NMR (125 MHz, CD_3OD): δ 105.5, 108.7, 121.8, 138.5, 143.7, 144.8; HRMS (FAB) calcd for $C_6H_5BrN_2O_3$ (M^+) 231.9484, found 231.9479.

3-Bromo-5-nitrophenol (99). Compound **98** (33.0 g, 0.14 mol) was treated with sulfuric acid (13.7 mL) and was refluxed in EtOH (550 mL) for 0.5 hours, followed by addition of $NaNO_2$ (23.8 g, 0.35 mol). The resulting mixture was refluxed for additional 1 hour and the volatile was evaporated. The residue was taken up with ethyl acetate and water. The layers were separated and the organic layer was washed with water, saturated sodium bicarbonate, and brine. After removal of solvent, the residue was purified by column chromatography on silica gel to afford the title compound (26 g, 85%); ^{1}H NMR (500 MHz, CD_3OD): δ 5.00 (brs, 1H), 7.58 (dd, 1H, J = 1.7, 2.3 Hz), 7.47 (t, 1H, J = 2.1 Hz), 7.69 (t, 1H, J = 1.9 Hz); ^{13}C NMR (125 MHz, CD_3OD): δ 110.5, 118.1, 123.7, 125.6, 151.0, 160.5; HRMS (FAB) calcd for $C_6H_4BrNO_3$ (M^+) 216.9375, found 216.9374.

Compound 100a (R_1=iPr). A mixture of compound **99** (4.36 g, 20.0 mmol), K_2CO_3 (5.5 g, 40.0 mmol), and 2-iodopropane (4.0 mL, 40.0 mmol) in DMF (20 mL) was stirred at room temperature overnight. The solution was diluted with ethyl acetate and washed with water and brine, dried over $MgSO_4$, and the volatile was removed under reduced pressure. The residue was purified by column chromatography to yield the desired product (4.7 g, 90%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (d, 6H, J = 6.0 Hz), 4.62 (septet, 1H, J = 6.0 Hz), 7.33 (t, 1H, J = 2.0 Hz), 7.64 (t, 1H, J = 2.1 Hz), 7.91 (t, 1H, J = 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.9, 71.7, 109.3, 118.7, 123.1, 125.4, 149.7, 159.2; HRMS (FAB) calcd for $C_9H_{10}BrNO_3$ (M^+) 258.9844, found 258.9829.

Compound 101a (R_1=iPr, R_2=4-Cl). Compound **100a** (4.7 g, 18.1 mmol) dissolved in toluene (45 mL) was treated with sodium carbonate (18 mL, 2 M solution) and ethanol (12 mL). 4-Chlorophenylboronic acid (3.06 g, 20.1 mmol) was then added to the mixture followed by tetrakis(triphenylphosphine)palladium(0) (0.6 g, 0.54 mmol). The resulting mixture was refluxed for 3 hours. Brine was added (60 mL) and the mixture was extracted with CH_2Cl_2. The volatile was evaporated under reduced pressure and the residue was purified by column chromatography to afford the title compound (4.1 g, 77%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (d, 6H, J = 6.0 Hz), 4.70 (septet, 1H, J = 6.0 Hz), 7.37 (dd, 1H, J =

1.6, 2.4 Hz), 7.47 (d, 2H, J = 8.8 Hz), 7.53 (d, 2H, J = 8.8 Hz), 7.69 (t, 1H, J = 2.1 Hz), 7.97 (t, 1H, J = 1.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0, 71.2, 108.5, 114.1, 121.3, 128.5, 129.4, 134.9, 137.3, 142.4, 149.8, 159.0; HRMS (FAB) calcd for $C_{15}H_{14}ClNO_3$ (M^+) 291.0662, found 291.0688.

Compound 102a (R_1=iPr, R_2=H). Compound **101a** (4.0 g, 13.7 mmol) dissolved in ethyl acetate:ethanol (1:1, mL) was stirred for 4 hours in the presence of Pd/C under hydrogen atmosphere. The reaction mixture was filtered through a small layer of Celite and washed with THF and ethanol. The combined filtrate was concentrated under reduced pressure and the residue was used for the next reaction without further purification (3.1 g, quantitative); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (d, 6H, J = 6.0 Hz), 4.62 (septet, 1H, J = 6.0 Hz), 7.10 (dt, 2H, J = 1.9, 10.9 Hz), 7.32 (t, 1H, J = 1.5 Hz), 7.35-7.43 (m, 4H), 7.55 (dd, 2H, J = 1.5, 8.4 Hz), 10.64 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.1, 70.8, 109.3, 114.0, 115.7, 127.4, 128.4, 129.1, 131.2, 139.6, 144.7, 159.5; HRMS (FAB) calcd for $C_{15}H_{17}NO$ (MH^+) 228.1388, found 228.1372.

Compound 103a (R_1=iPr, R_2=4-Cl). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, J = 5.9 Hz, 6H), 2.45 (s, 3H), 4.61 (m, 1H), 6.96 (s, 1H), 7.11 (s, 1H), 7.17 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.2, 30.4, 70.5, 116.4, 120.1, 125.1, 128.6, 129.1, 129.5, 134.0, 138.7, 142.3, 158.7, 194.0.

Compound 104a (R_1=iPr, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (d, J = 5.9 Hz, 6H), 2.17 (dd, J = 4.9, 1.5 Hz, 1H), 2.53 (d, J = 5.9 Hz, 1H), 3.06 (m, 1H), 3.23 (dd, J = 14.3, 7.4 Hz, 1H), 3.55 (dd, J = 14.3, 5.9 Hz, 1H), 4.67 (m, 1H), 7.32 (s, 1H), 7.36 (s, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.63 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.0, 24.3, 26.1, 62.5, 71.1, 113.3, 118.8, 120.8, 128.5, 129.3, 134.8, 137.5, 140.4, 143.0, 159.0.

Compounds of Scheme 21.

Compound 105a (R_1=R_2=H). Compound **14a** (2.45 g, 13.2 mmol) was dissolved in THF (10 mL) and treated with triethylamine (2.2 mL, 15.8 mmol). Allylsulfonyl chloride (2.2 g, 15.8 mmol) in THF (5 mL) was slowly added

dropwise to the above solution at ice-water temperature over 0.5 hours. The resulting mixture was stirred for 1 hour, while the temperature was gradually warmed to room temperature. Additional triethylamine (2.2 mL, 15.8 mmol) was added to the reaction mixture and the resultant solution was stirred for 0.5 h. The reaction mixture was filtered through a small layer of silica gel and the volatile was evaporated. The residue was taken up in ethyl acetate and washed with water, 5% $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel to afford the desired product (2.73 g, 75%); 1H NMR (500 MHz, $CDCl_3$) δ 3.87 (d, J = 7.4 Hz, 2H), 5.32 (d, J = 17.3 Hz, 1H), 5.43 (d, J = 10.4 Hz, 1H), 5.88 (m, 1H), 6.78 (dd, J = 8.4, 2.0 Hz, 1H), 6.97 (s, 1H), 6.99 - 7.07 (m, 2H), 7.16 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 8.2 Hz, 1H), 7.37 (t, J = 7.9 Hz, 2H), 7.48 (br.s., 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.7, 110.8, 114.8, 114.9, 119.3, 123.9, 125.0, 130.0, 130.7, 138.5, 156.5, 158.5.

Conversion from compound **105a** to compounds **106a** – **107a** was followed by the same method as described in Scheme 6.

Compound 106a (R_1=R_2= R_3=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.24 (dd, J = 14.8, 3.0 Hz, 1H), 3.33 (dd, J = 14.8, 8.9 Hz, 1H), 3.52 (dd, J = 11.9, 6.4 Hz, 1H), 3.63 (dd, J = 12.4, 4.0 Hz, 1H), 4.32 (m, 1H), 6.71 (m, 1H), 6.98 - 7.01 (m, 4H), 7.11 (t, J = 7.4 Hz, 1H), 7.20 (dd, J = 8.4 Hz, 1H), 7.32 (t, J = 8.4, 7.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.4, 53.4, 65.3, 67.7, 111.5, 114.9, 115.6, 119.3, 123.9, 129.9, 130.7, 138.3, 156.4, 158.3.

Compound 106b (R_1=R_2=H, R_3=Me). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.4 (s, 3H), 3.1 - 3.3 (m, 2H), 3.9 (d, J = 4.0 Hz, 1H), 4.0 (d, J = 4.9 Hz, 2H), 4.5 (br.s., 1H), 6.8 (d, J = 8.9 Hz, 1H), 6.9 - 7.0 (m, 1H), 7.0 (d, J = 7.9 Hz, 1H), 7.1 (t, J = 7.4 Hz, 1H), 7.2 (t, J = 8.4 Hz, 1H), 7.5 (s, 1H), 7.8 (d, J = 8.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 52.7, 65.4, 71.8, 111.9, 115.3, 115.9, 119.4, 123.9, 128.1, 130.0, 130.2, 130.7, 131.9, 138.0, 145.6, 156.5, 158.4.

Compound 107a (R_1=R_2= R_3=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (d, J = 5.4 Hz, 1H), 2.64 (d, J = 5.9 Hz, 1H), 3.19 (m, 1H), 3.26 (dd, J = 14.3, 7.4 Hz,

1H), 3.57 (dd, J = 14.1, 5.7 Hz, 1H), 6.77 - 6.83 (m, 2H), 6.91 (s, 1H), 6.97 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 7.28 - 7.32 (m, 1H), 7.39 (t, J = 7.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.8, 26.7, 57.9, 110.5, 114.6, 115.1, 119.6, 124.2, 130.1, 131.0, 137.9, 156.4, 158.9.

Compounds of Scheme 23.

Synthesis of compounds **111a** – **118a** was followed by the same method as described in Schemes 21 and 22.

Compound 111a (R_1=iPr, R_2=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (d, J = 5.9 Hz, 6H), 3.92 (d, J = 7.9 Hz, 2H), 4.65 (m, 1H), 5.37 (d, J = 17.3 Hz, 1H), 5.48 (d, J = 10.4 Hz, 1H), 5.95 (m, 1H), 6.88 (m, 1H), 6.97 (s, 1H), 7.04 (m, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.59 (d, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 55.6, 70.4, 106.8, 111.5, 111.7, 125.1, 125.2, 127.3, 128.0, 129.0, 138.4, 140.4, 143.9, 159.3; HRMS (FAB) calcd for $C_{18}H_{21}NO_3S$ (MH^+) 332.1320, found 332.1313.

Compound 112a (R_1=iPr, R_2=H, R_3=Me). Compound **111a** (3.0 g, 9.1 mmol) was treated with sodium hydride (0.54 g, 13.6 mmol, 60%) in DMF (20 mL) in ice-water bath. The resulting suspension was stirred for 1 h while the temperature was gradually warmed to room temperature. Iodomethane (1.7 mL, 27.2 mmol) was added to above mixture and the resultant solution was stirred at room temperature overnight. After dilution with ethyl acetate, the organics was washed with water, 1 N HCl, and brine and was dried over $MgSO_4$. After removal of solvent, the residue was purified by short-path column chromatography on silica gel to yield the desired compound (2.9 g, 91%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (d, 6H, J = 6.0 Hz), 3.20 (s, 3H), 3.80 (d, 2H, J = 7.9 Hz), 4.61 (septet, 1H, J = 5.9 Hz), 5.41 (m, 2H), 5.95 (m, 1H), 6.92 (s, 1H), 7.00 (m, 1H), 7.18 (m, 1H), 7.40-7.60 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.1, 39.2, 54.8, 70.6, 106.8, 113.1, 113.6, 117.1, 117.2, 123.7, 127.2, 127.9, 128.5, 128.9, 129.1, 139.0, 140.6, 142.2, 159.0; HRMS (FAB) calcd for $C_{19}H_{24}NO_3S$ (MH^+) 346.1477, found 346.1480.

Compound 113a (R_1=iPr, R_2=H, R_3=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (d, J = 5.9 Hz, 6H), 3.20 (dd, J = 14.3, 2.5 Hz, 1H), 3.33 (dd, J = 14.6, 9.2 Hz,

1H), 3.50 (dd, J = 11.6, 6.2 Hz, 1H), 3.62 (dd, J = 11.6, 3.2 Hz, 1H), 4.34 (m, J = 3.0 Hz, 1H), 4.57 (m, 1H), 6.85 (m, 1H), 6.91 (m, 1H), 7.04 (m, 1H), 7.30 (t, J = 8.4, 7.4 Hz, 1H), 7.37 (t, J = 7.4 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.1, 53.4, 58.6, 65.5, 67.9, 70.5, 107.9, 112.0, 112.4, 127.3, 128.0, 129.0, 138.3, 140.4, 143.9, 159.2.

Compound 113b (R_1=iPr, R_2=H, R_3=Me). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (d, 6H, J = 6.0 Hz), 3.15-3.25 (m, 2H), 3.31, 3.34 (2s, 3H), 3.51-3.68 (m, 2H), 3.83 (brs, 1H), 4.61 (septet, 1H, J = 6.0 Hz), 6.92 (m, 1H), 7.01 (dt, 1H, J = 1.8, 15.6), 7.14 (dt, 1H, J = 1.6, 9.8), 7.35-7.56 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 22.2, 38.7, 52.8, 65.5, 67.5, 70.7, 113.5, 113.6, 114.1, 114.2, 117.4, 117.5, 127.3, 128.0, 128.6, 129.0, 129.1, 138.9, 140.4, 142.4, 159.1; HRMS (FAB) calcd for $C_{19}H_{25}NO_5S$ (M^+) 379.1453, found 379.1462.

Compound 114a (R_1=iPr, R_2=H, R_3=H). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, J = 5.9 Hz, 6H), 2.32 (dd, J = 3.5, 1.5 Hz, 1H), 2.63 (dd, J = 4.9, 1.0 Hz, 1H), 3.21 (m, 1H), 3.28 (dd, J = 14.3, 7.4 Hz, 1H), 3.61 (dd, J = 14.1, 5.7 Hz, 1H), 4.62 (m, 1H), 6.84 (s, 1H), 6.94 (s, 1H), 7.01 (s, 1H), 7.08 (s, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.56 (d, J = 7.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.2, 24.8, 26.7, 57.7, 70.5, 106.8, 111.4, 111.9, 127.3, 128.1, 129.0, 138.0, 140.4, 144.2, 159.4.

Compound 114b (R_1=iPr, R_2=H, R_3=Me). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (dd, J = 5.9, 1.5 Hz, 6H), 2.40 (m, 1H), 2.67 (d, J = 5.9 Hz, 1H), 3.05 (dt, J = 13.9, 8.4 Hz, 1H), 3.19 (m, 1H), 3.41 (d, J = 2.5 Hz, 3H), 3.57 (td, J = 13.1, 5.4 Hz, 1H), 6.94 (t, J = 2.5 Hz, 1H), 6.99 (t, J = 2.0 Hz, 1H), 7.04 (t, J = 2.0 Hz, 1H), 7.13 (t, J = 2.0 Hz, 1H), 7.16 (t, J = 1.5 Hz, 1H), 7.40 - 7.49 (m, 4H), 7.56 (d, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 25.3, 26.7, 38.9, 56.1, 70.5,113.0, 113.7, 113.9, 117.0, 117.1, 127.4, 128.1, 128.6, 129.1, 129.2, 142.5, 142.7, 143.7, 159.0; HRMS (FAB) calcd for $C_{19}H_{24}NO_3S_2$ (MH^+) 378.1198, found 378.1200.

Compound 116a (R_1=iPr, R_2=4-Cl, R_3=Me). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (d, J = 5.9 Hz, 6H), 2.67 (dd, J = 20.8, 7.4 Hz, 2H), 3.17 (t, J = 7.2 Hz, 3H), 3.68 (d, J = 10.9 Hz, 3H), 4.51 - 4.58 (m, 1H), 5.03 - 5.13 (m, 2H), 5.67 - 5.78 (m,

1H), 6.75 (s, 1H), 6.77 (s, 1H), 6.95 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.9, 30.9, 31.9, 36.3 (d, *J* = 3.6 Hz), 50.6 (d, *J* = 7.1 Hz), 69.9, 108.9 (d, *J* = 3.6 Hz), 109.6, 112.9 (d, *J* = 3.6 Hz), 120.1, 120.3, 127.0, 127.1, 128.3, 128.7, 129.6, 131.9, 133.4, 139.4, 141.7, 145.8 (d, *J* = 5.3 Hz), 158.7.

Compound 117a (R_1=iPr, R_2=4-Cl, R_3=Me). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, *J* = 5.9 Hz, 6H), 3.18 (dd, *J* = 17.3, 7.9 Hz, 3H), 3.44 (dd, *J* = 11.4, 5.9 Hz, 1H), 3.53 - 3.63 (m, 1H), 3.70 (d, *J* = 11.4 Hz, 3H), 4.01 (s, 1H), 4.08 - 4.15 (m, 1H), 4.54 - 4.62 (m, 1H), 6.76 - 6.81 (m, 2H), 6.96 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.1, 30.1, 36.2 (d, *J* = 3.6 Hz), 53.6, 66.8 (d, *J* = 16.0 Hz), 67.0 (d, *J* = 16.0 Hz), 67.2 (d, *J* = 3.6 Hz), 70.2 (d, *J* = 1.8 Hz), 109.3 (d, *J* = 3.6 Hz), 109.7 (d, *J* = 3.6 Hz), 110.0, 110.1, 110.8, 113.1 (d, *J* = 3.6 Hz), 113.7 (d, *J* = 2.7 Hz), 128.5, 129.0 (d, *J* = 1.8 Hz), 129.9, 133.8 (d, *J* = 5.3 Hz), 139.4 (d, *J* = 3.6 Hz), 142.1 (d, *J* = 14.3 Hz), 145.6 (t, *J* = 4.9 Hz), 159.0 (d, *J* = 8.0 Hz).

Compound 118a (R_1=iPr, R_2=4-Cl, R_3=Me). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (d, *J* = 5.9 Hz, 6H), 1.94 (m, 0.5H), 2.24 (td, *J* = 15.7, 6.2 Hz, 0.25H), 2.37 (td, *J* = 15.3, 5.4 Hz, 0.25H), 2.46 (m, 0.5H), 2.52 (m, 0.5H), 2.78 (m, 1H), 3.18 (m, 1H), 3.23 (d, *J* = 7.9 Hz, 3H), 3.77 (dd, *J* = 11.4, 7.9 Hz, 3H), 4.59 (m, 1H), 6.78 - 6.86 (m, 1H), 6.95 - 7.03 (m, 1H), 7.34 - 7.41 (m, *J* = 8.4 Hz, 1H), 7.42 - 7.48 (m, *J* = 7.7, 7.7 Hz, 3H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.66 (dd, *J* = 11.9, 6.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.1, 29.5 (d, *J* = 4.5 Hz), 30.5 (d, *J* = 4.5 Hz), 36.1 (d, *J* = 4.5 Hz), 36.4 (d, *J* = 4.5 Hz), 46.8, 47.3 (d, *J* = 6.2 Hz), 47.5 (d, *J* = 8.0 Hz), 50.7 (d, *J* = 7.1 Hz), 50.8 (d, *J* = 6.2 Hz), 70.2 (d, *J* = 1.8 Hz), 109.2 (d, *J* = 3.6 Hz), 109.9 (d, *J* = 3.6 Hz), 110.0, 110.4, 113.2 (d, *J* = 3.6 Hz), 113.9 (d, *J* = 3.6 Hz), 127.3, 128.5, 128.6, 128.7, 129.0 (d, *J* = 2.7 Hz), 132.1 (t, *J* = 2.7 Hz), 132.1, 132.2, 133.8 (d, *J* = 6.2 Hz), 139.5 (d, *J* = 2.7 Hz), 142.1, 142.2, 145.6 (dd, *J* = 8.0, 4.5 Hz), 159.0 (d, *J* = 6.2 Hz).

Compounds of Scheme 24.

Compound 121a (R_1=Bn, R_2=R_3=H). Biphenylsulfonyl chloride (1.59 g, 6.30 mmol) was added to a solution of compound **119a** (1.00 g, 6.61 mmol) in 3:1 mixture of THF : water in ice-water bath. The resulting mixture was stirred at room temperature overnight. Sodium bicarbonate (0.56 g, 6.94 mmol) was added and the resulting solution was stirred for 3 h and solvent was concentrated. The resultant was diluted with EtOAc and water and then layers were separated. The organic layer was washed with 5% HCl and water and was concentrated to dryness. The crude product was purified by column chromatography to give the desired product (1.97 g, 81%).

Compound 122a (R_1=Bn, R_2=R_3=H). Methanesulfonyl chloride (0.58 mL, 7.42 mmol) was added to a solution of compound **121a** (1.82 g, 4.95 mmol) and Et_3N (1.72 mL, 12.4 mmol) in acetonitrile (30 mL) in ice-water bath and stirred for 10 min. After stirring at room temperature for additional 10 min, the reaction mixture was diluted with 200 mL of MeOH and cooled down to ice-water bath. Potassium carbonate (1.37 g / 10 mL water) was added to the reaction mixture and stirred for 3 h at room temperature. Organic solvents were removed and then diluted with EtOAc and water. The layers were separated and the organic layer was washed with water and brine and concentrated. The crude product was purified by column chromatography to give the desired product (1.27 g, 73%).

Compound 123a (R_1=Bn, R_2=R_3=H, n=1). Vinyl magnesium bromide (4.5 mL, 1.0 M in THF) was added to a solution of CuI (85 mg, 0.45 mmol) in THF (3 mL) at -78 °C. After 20 minutes, compound **122a** (313 mg, 0.90 mmol) was added to the reaction mixture. The reaction mixture was slowly warmed to room temperature over 1.5 hours. After quenching with 5% HCl, the reaction mixture was extracted with EtOAc and organic layer was washed with 5% HCl and brine and volume was reduced. The crude product was purified by column chromatography to give the desired product (237 mg, 70%) as a yellow oil.

Compound 123b (R_1=Bn, R_2=R_3=H, n=2). This material was prepared in the same manner as described for **123a**, with the exception that allylmagnesium bromide was used in place of vinylmagnesium bromide.

Conversion from compound **123** to compound **124, 125** was followed by the same method as described in Scheme 5.

Compound 124a (R_1=Bn, R_2=R_3=H, n=1).

Compound 124b (R_1=Bn, R_2=R_3=H, n=2).

Compound 125a (R_1=Bn, R_2=R_3=H, n=1).

Compound 125b (R_1=Bn, R_2=R_3=H, n=2).

Compounds of Scheme 25.

Compound 130a (R_1=Bn, R_2=R_3=H). A solution of compound **129a** (183 mg, 1.25 mmol), **107a** (330 mg, 1.31 mmol), and Et_3N (0.21 mL, 1.50 mmol) in CH_2Cl_2 (6 mL) was stirred for 1 h at room temperature. The reaction mixture was washed with water and organic solvent was concentrated. The crude product was purified by column chromatography to give the desired product (389 mg, 86%) as a white solid.

Conversion from compound **130a** to compound **131a** was followed by the same method as described in Scheme 5.

Compound 131a (R_1=Bn, R_2=R_3=H).

Compounds of Scheme 26.

Compound 133a (R_1=Bn, R_2=R_3=H). Compound **132** (1.17 mL, 11.9 mmol) was added to a solution of phenoxyphenylmagnesium bromide (3.30 g, 12.0 mmol) in anhydrous THF (20 mL) in ice-water bath. After 15 minutes, stirring was continued at room temperature for 1 h and reaction was quenched with sat'd NH_4Cl solution. After extraction with EtOAc, the organic layer was washed with water and brine. The crude product was purified by column chromatography to give the desired product (2.39 g, 79%) as a white solid.

Compound 134a (R_1=Bn, R_2=R_3=H). A mixture of compound **133a** (100 mg, 0.39 mmol), TPAP (14 mg, 0.039 mmol), and NMO (138 mg, 1.30 mmol) in CH_2Cl_2 (mL) was stirred for 5 minutes and concentrated to dryness. The crude product was purified by column chromatography to give the desired product (88 mg, 89%) as a white solid.

Compound 135a (R_1=Bn, R_2=R_3=H). A mixture of compound **134a** (88 mg, 0.35 mmol) and NBS (68 mg, 0.39mmol) in 3:1 solution of THF:water was stirred at room temperature for 1 hour. 2.5 N NaOH (280 μL) was added to the reaction mixture and stirred for 3 h. The reaction mixture was diluted with diethyl ether and washed with brine. The crude product was purified by column chromatography to give the desired product (75 mg, 81%) as a colorless oil.

Conversion from compound **135a** to compound **136a** was followed by the same method as described in Scheme 5.

Compound 136a (R_1=Bn, R_2=R_3=H).

Compound 137a (R_1=Bn, R_2=R_3=H). A mixture of compound **136a** (66mg, 0.23 mmol), $NH_2OH{\cdot}HCl$ (24.2 mg, 0.38 mmol), and NaOAc (28.6 mg, 0.38 mmol) in 2:1 solution of EtOH:water was stirred at room temperature for 2 h. Additional batch of $NH_2OH{\cdot}HCl$ and NaOAc was to the reaction mixture and stirring was continued for 4 h. The resulting solution was diluted with EtOAc and water and layers were separated. Organic layer was washed with sat'd $NaHCO_3$, water and brine. The crude product was purified by column chromatography to give the desired product (53 mg, 76%) as a colorless oil.

Compounds of Scheme 27.

Preparation of compounds **139a-143a** was followed by the same method as described in Scheme 22.

Compound 139a (R_1=R_2=H).

Compound 140a (R_1=R_2=H).

Compound 141a (R_1=R_2=H).

Compound 142a (R_1=R_2=H).

Compound 143a (R_1=R_2=H).

Compounds of Scheme 28.

Compound 150a (R^1=H). A solution of compound **149a** (1.10 g, 5.12 mmol) in THF (5 mL) was added dropwise to a stirred suspension of KH (230 mg, 5.63 mmol) in THF (10 mL) at room temperature, and the whole was stirred at the

same temperature for 5 minutes. A hexane solution of triethylborane (1.0 M, 6.4 mL, 6.4 mmol) was added to the reaction mixture at room temperature, and the whole was stirred at the same temperature for 5 minutes. After addition of allylbromide (1.43 mL, 15.4 mmol) at room temperature, the reaction mixture was stirred at the same temperature for 36 hours. After addition of water, the solvent was removed under reduced pressure, and the resultant residue was partitioned with CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with water and brine, and then dried over Na_2SO_4.

After concentration under reduced pressure, the resultant residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:30) to give the desired product (837 mg, 64%) as a pale yellow solid with recovery of compound **149a** (254 mg, 23%); Compound **150a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.83-1.88 (m, 2H), 1.93-1.97 (m, 2H), 2.50-2.55 (m, 2H), 2.62-2.65 (m, 2H), 2.75-2.78 (m, 2H), 3.12 (t, 2H, J = 7.5 Hz), 5.02 (dq, 1H, J = 10.5, 1.0 Hz), 5.10 (dq, 1H, J = 17.0, 2.0 Hz), 5.93 (ddt, 1H, J = 17.0, 10.5, 6.5 Hz), 7.43 (d, 1H, J = 8.0 Hz), 7.85 (dd, 1H, J = 8.0, 1.5 Hz), 8.01 (d, 1H, J = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.5, 37.8, 110.7, 113.3, 115.2, 118.0, 122.5, 132.2, 133.3, 137.5, 154.0, 158.1, 199.0; HRMS (FAB) calcd for $C_{17}H_{19}O_2$ ($M+H^+$) 255.1385, found 255.1402.

Compound **149a**: m.p. 66-67 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82-1.90 (m, 2H), 1.92-2.00 (m, 2H), 2.61-2.67 (m, 2H), 2.65 (s, 3H), 2.75-2.80 (m, 2H), 7.43 (d, 1H, J = 8.4 Hz), 7.84 (dd, 1H, J = 1.2, 8.4 Hz), 8.00 (d, 1H, J = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 22.4, 22.6, 23.5, 26.6, 110.9, 113.3, 117.8, 122.8, 132.4, 133.2, 153.9, 158.1, 197.6; HRMS (FAB) calcd for $C_{14}H_{15}O_2$ ($M+H^+$) 215.1072, found 215.1056.

Compound 151a (R_1=H). NBS (650 mg, 3.66 mmol) was added to a stirred solution of compound **150a** (780 mg, 3.05 mmol) in THF-water (3:1, 15 mL) at room temperature, and the whole was stirred at the same temperature for 1 hour in the dark. Aqueous 2.5 M NaOH (3.7 mL, 9.25 mmol) was added at room temperature, and the whole was stirred at the same temperature for 30 minutes. After addition of a few drops of allyl alcohol, the mixture was stirred for 10 minutes. After dilution with ether and brine, the aqueous layer was extracted with

ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure.

The resultant residue was purified by silica gel column chromatography (1% triethylamine in ethyl acetate:hexane = 1:8) to give the title compound (540 mg, 65%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.83-1.90 (m, 3H), 1.93-1.98 (m, 2H), 2.19 (m, 1H), 2.56 (dd, 1H, *J* = 2.5, 5.0 Hz), 2.62-2.65 (m, 2H), 2.76-2.81 (m, 3H), 3.08 (m, 1H), 3.20 (t, 2H, *J* = 7.5 Hz), 7.44 (d, 1H, *J* = 8.0 Hz), 7.86 (dd, 1H, *J* = 1.0, 8.0 Hz), 8.02 (d, 1H, *J* = 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 4.6, 47.4, 51.7, 110.7, 113.4, 118.0, 122.5, 132.0, 133.4, 154.0, 158.3, 198.5; HRMS (FAB) calcd for $C_{17}H_{19}O_3$ ($M+H^+$) 271.1334, found 271.1343.

Compound 152a (R_1=H). Thiourea (349 mg, 4.60 mmol) was added to a stirred solution of compound **151a** (500 mg, 1.84 mmol) in MeOH (11 mL) at room temperature, and the whole was stirred at the same temperature overnight. After concentration under reduced pressure, the resultant was dissolved in ethyl acetate. The ethyl acetate solution was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:20) to give the desired product (410 mg, 78%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.72 (m, 1H), 1.84-1.88 (m, 2H), 1.93-1.98 (m, 2H), 2.25 (dd, 1H, *J* = 1.0, 5.5 Hz), 2.52 (m, 1H), 2.56 (dd, 1H, *J* = 1.0, 6.5 Hz), 2.62-2.65 (m, 2H), 2.76-2.79 (m, 2H), 3.07 (m, 1H), 3.19-3.29 (m, 2H), 7.43 (d, 1H, *J* = 8.5 Hz), 7.86 (dd, 1H, *J* = 1.5, 8.5 Hz), 8.02 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9, 22.4, 22.6, 23.6, 26.3, 31.0, 35.7, 38.0, 110.7, 113.4, 118.0, 122.5, 132.0, 133.4, 154.0, 158.3, 198.6; HRMS (FAB) calcd for $C_{17}H_{19}O_2S$ ($M+H^+$) 287.1106, found 287.1104.

Compound 153a (R^1=H). A solution of hydroxylamine hydrochloride (266 mg, 3.82 mmol) and sodium acetate (314 mg, 3.82 mmol) in water (1 mL) was added dropwise to a stirred solution of compound **152a** (365 mg, 1.27 mmol) in EtOH-CH_2Cl_2 (3:1, 12 mL) at room temperature, and the whole was stirred at the same temperature for 6 h. After dilution with water, the mixture was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue

was purified by silica gel column chromatography (ethyl acetate:hexane = 1:10) to give the desired product (320 mg, 83%) as a white solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.76 (m, 1H), 1.83-1.87 (m, 2H), 1.92-1.97 (m, 2H), 2.14-2.21 (m, 2H), 2.48 (d, 1H, *J* = 6.5 Hz), 2.62 (t, 2H, *J* = 6.0 Hz), 2.75 (t, 2H, *J* = 6.0 Hz), 2.96 (qn, 1H, *J* = 6.5 Hz), 3.02 (m, 1H), 3.14 (m, 1H), 7.40 (d, 1H, *J* = 7.5 Hz), 7.50 (d, 1H, *J* = 7.5 Hz), 7.67 (s, 1H), 9.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4, 22.5, 22.8, 23.5, 25.9, 26.0, 33.3, 35.5, 108.8, 113.0, 118.3, 120.5, 130.0, 130.4, 154.4, 155.7, 158.9; HRMS (FAB) calcd for $C_{17}H_{20}O_2NS$ ($M+H^+$) 302.1215, found 302.1212.

Compounds of Scheme 29.

Compound 155a (R_1=3-benzyloxy). A mixture of 3-benzyloxybenzaldehyde (9.5 g, 44.7 mmol) and ethyl cyanoacetate (5.2 mL, 48.9 mmol) in benzene (50 mL) was refluxed in the presence of catalytic amount of piperidine (0.5 mL) for 4 h. Evaporation of solvent under reduced pressure resulted in precipitate which was purified by recrystallization from ethanol (11.0 g, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, 3H, *J* = 7.20 Hz), 4.40 (q, 1H, *J* = 7.0 Hz), 5.14 (s, 2H), 7.19 (dd, 1H, *J* = 2.4, 8.0 Hz), 7.35-7.67 (m, 9H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 63.0, 70.3, 103.3, 115.7, 121.0, 124.6, 127.8, 128.4, 128.8, 130.5, 132.8, 136.4, 155.2, 159.2, 162.6; HRMS (ESI) calcd for $C_{19}H_{17}NNaO_3$ ($M+Na^+$) 330.1106, found 330.1112.

Compound 156a (R_1=3-benzyloxy, R_2=H). Potassium cyanide (2.85 g, 43.8 mmol) dissolved in water (5 mL) was added to a solution of compound **155a** (7.5 g, 24.4 mmol) in EtOH (40 mL). After reflux for 4 h, the reaction mixture was cooled down and was diluted with 1 N NaOH (25 mL) and 15% NaCl (400 mL), followed by extraction with CH_2Cl_2. The volatile was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to afford the desired product (5.8 g, 91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.96 (d, 2H, *J* = 6.8 Hz), 4.13 (t, 1H, *J* = 6.8 Hz), 5.10 (s, 2H), 7.00-7.04 (m, 3H), 7.36-7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 34.2, 70.4, 114.2, 115.4, 115.9, 117.9,

119.8, 127.8, 128.4, 128.9, 131.1, 133.8, 136.4, 159.7; HRMS (ESI) calcd for $C_{17}H_{14}N_2NaO$ ($M+Na^+$) 285.1004, found 285.1010.

Compound 157a (R_1=3-benzyloxy, R_2=H). Dibal-H (52.5 mL, 52.5 mmol, 1.0 N solution in toluene) was added dropwise to a solution of compound **156a** (5.3 g, 20.2 mmol) in benzene (140 mL) at ice-water temperature. The resulting mixture was stirred for 2 h, while the temperature was gradually warmed to room temperature over 2 h. Sodium dihydrogen phosphate (350 mL, 1.5 N aqueous solution) was added dropwise to the above solution and the resulting solution was refluxed for 1 hour. The reaction mixture was filtered through a layer of Celite and washed with ethyl acetate. The layers of the combined filtrate were separated and the organic layer was washed with water, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the desired product (2.0 g, 40%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15 (s, 2H), 7.00-7.04 (m, 3H), 7.36-7.46 (m, 5H), 8.27 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.1, 106.7, 111.8, 112.2, 115.0, 118.3, 119.1, 124.8, 127.8, 128.1, 128.8, 129.8, 137.3, 137.5, 159.3; HRMS (ESI) calcd for $C_{17}H_{15}NNaO$ ($M+Na^+$) 272.1051, found 272.1056.

Compound 158a (R_1=3-benzyloxy, R_2=H, n=1, X=O). Glycidol (2.6 mL, 40.0 mmol) dissolved in ethyl acetate (200 mL) was treated with triethylamine (5.6 mL, 40.2 mmol). Diphosgene (4.6 mL, 38.4 mmol) was slowly added to the above solution at –20 °C, and the reaction mixture was stirred at room temperature for 2 h. The precipitate was filtered off and the filtrate was evaporated. The residue was purified by short-path column chromatography on silica gel yielding 2,3-epoxypropyl chloroformate. Pyrrole **144a** (2.0 g, 8.0 mmol) in anhydrous acetonitrile (30 mL) was treated with NaH (0.64 g, 16.0 mmol, 60%) at ice-water temperature. The resulting mixture was stirred while temperature was gradually warmed to room temperature over 1 hour. After cooling in ice-bath, 2,3-epoxypropyl chloroformate (2.2 g, 16.4 mmol) in acetonitrile (5 mL) was added to the reaction mixture and was stirred while the temperature was gradually warmed to room temperature over 2 h. After stirring at 50 °C for additional 1 hour, the resulting mixture was filtered through a small layer of silica gel and the filtrate was

evaporated. The residue was taken up in ethyl acetate and was washed with water, brine, and dried over $MgSO_4$.

After removal of solvent, the residue was purified by column chromatography on silica gel to afford the desired product (1.5 g, 55%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.73 (dd, 1H, *J* = 2.4, 4.9 Hz), 2.92 (dd, 1H, *J* = 4.0, 4.9 Hz), 3.35 (sextet**, 1H, *J* = 3.2 Hz), 4.19 (dd, 1H, *J* = 6.5, 12.2 Hz), 4.71 (dd, 1H, *J* = 3.2, 12.2 Hz), 5.11 (s, 2H), 6.59 (dd, 1H, *J* = 1.6, 3.2 Hz), 6.89 (dd, 1H, *J* = 2.8, 8.4 Hz), 7.16-7.49 (m, 9H), 7.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.8, 49.3, 68.1, 70.3, 111.7, 112.6, 113.3, 116.3, 118.7, 121.3, 127.8, 128.2, 128.9, 130.1, 135.6, 137.2, 150.3, 159.4; HRMS (ESI) calcd for $C_{21}H_{19}NNaO_4$ ($M+Na^+$) 372.1212, found 372.1215.

Compound 158b (R_1=3-hydroxy, R_2=H, n=1, X=O). Compound **158a** (0.7 g, 2.0 mmol) was stirred for 2 hours in the presence of $Pd(OH)_2$ (0.2 g) in ethyl acetate:THF (1:1, 15 mL) under hydrogen atmosphere. The reaction mixture was filtered through a layer of celite and washed with methanol. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to afford the desired product (0.35 g, 67%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (dd, 1H, *J* = 2.8, 4.5 Hz), 2.93 (dd, 1H, *J* = 4.1, 4.8 Hz), 3.36 (m, 1H), 4.20 (dd, 1H, *J* = 6.5, 12.2 Hz), 4.72 (dd, 1H, *J* = 2.4, 12.2 Hz), 6.56 (dd, 1H, *J* = 1.6, 4.0 Hz), 6.73 (dd, 1H, *J* = 2.4, 8.0 Hz), 7.00-7.26 (m, 4H), 7.33 (m, 1H), 7.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.0, 49.5, 68.1, 111.8, 112.7, 114.2, 118.1, 121.3, 130.2, 135.6, 150.3, 156.5; HRMS (ESI) calcd for $C_{14}H_{13}NNaO_4$ ($M+Na^+$) 282.0742, found 282.0752.

Compound 158c (R_1=3-hydroxy, R_2=H, n=1, X=S). A mixture of compound **158b** (300 mg, 1.2 mmol) and thiourea (120 mg, 1.6 mmol) in anhydrous methanol (10 mL) was stirred at room temperature overnight. The volatile was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to afford the desired product (200 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (dd, 1H, *J* = 1.6, 5.7 Hz), 2.61 (d, 1H, *J* = 5.7 Hz), 3.26 (quintet, 1H, *J* = 5.7 Hz), 4.40 (dd, 1H, *J* = 7.3, 11.4 Hz), 4.48 (dd, 1H, *J* = 6.5, 11.3

Hz), 6.56 (dd, 1H, J = 1.6, 3.2 Hz), 6.74 (dd, 1H, J = 2.4, 8.1 Hz), 7.02 (dd, 1H, J = 1.6, 2.4 Hz), 7.12 (d, 1H, J = 8.1 Hz), 7.22-7.26 (m, 2H), 7.36-7.46 (m, 5H), 7.33 (dd, 1H, J = 1.6, 3.3 Hz), 7.55 (m, 1H), 8.27 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 30.5, 71.3, 111.7, 112.7, 116.2, 118.4, 121.3, 128.5, 130.2, 135.7, 150.2, 156.2; HRMS (ESI) calcd for $C_{14}H_{13}NNaO_3S$ ($M+Na^+$) 298.0514, found 298.0522.

Compounds **159a-f** were prepared in the same manner as described for **158**, with the exception that were used epichlorohydrin and 3,4-epoxybutylchloride in place of 2,3-epoxypropylchloroformate.

Compound 159a (R_1=3-benzyloxy, R_2=H, n=1, X=O).

Compound 159b (R_1=3-hydroxy, R_2=H, n=1, X=O).

Compound 159c (R_1=3-hydroxy, R_2=H, n=1, X=S).

Compound 159d (R_1=3-benzyloxy, R_2=H, n=2, X=O).

Compound 159e (R_1=3-hydroxy, R_2=H, n=2, X=O).

Compound 159f (R_1=3-hydroxy, R_2=H, n=2, X=S).

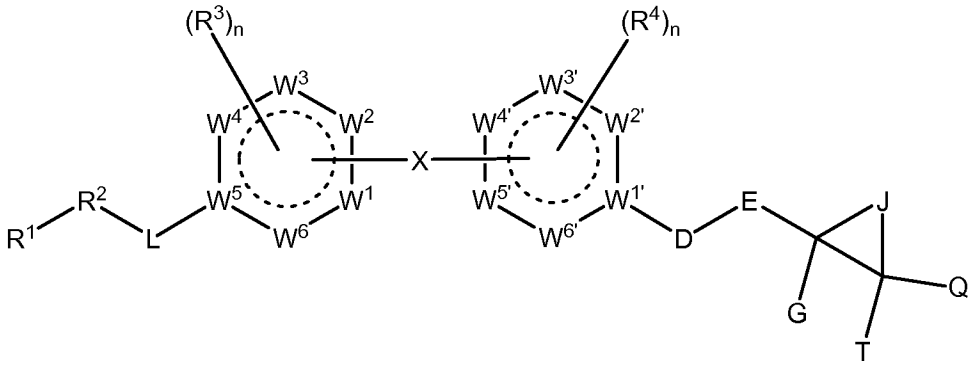
EXAMPLE 4. Other Compounds of the Invention

FIG. 9 illustrates several other species and classes of compounds of the invention. These compounds can be prepared according to the methods described in Example 3, by using appropriate starting materials, and by using other techniques well know to those of skill in the art.

All publications, patents, and patent documents referred to herein are incorporated by reference, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it will be apparent to those skilled in the art that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A compound of formula I:



(I)

wherein

R^1 is $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl$(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkoxy, heteroaryl$(C_1\text{-}C_6)$alkoxy, aryl, heteroaryl, hydroxy, SR^5, NR^5R^5, or absent;

R^2 is CH_2, carbonyl, SO_2, or OH;

L is CH_2, NR^5, or O;

W^1-W^6 are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

$W^{1'}$-$W^{6'}$ are each independently C, N, O, S, or absent, and form a 5 or 6 membered aryl, heterocycle, or heteroaryl ring;

the dashed circles within the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$ denote optional double bonds of the rings formed by W^1-W^6 and $W^{1'}$-$W^{6'}$;

R^3 and R^4 are each independently hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, aryl, heteroaryl, carboxy, cyano, nitro, halo, trifluoromethyl, trifluoromethoxy, SR^5, $SO_2N(R_5)_2$, NR^5R^5, or $COOR^5$;

each n is independently 0 to 4;

each R^5 is independently H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, $(C_6\text{-}C_{10})$aroyl, aryl, aryl$(C_1\text{-}C_6)$alkyl, heteroaryl, heteroaryl$(C_1\text{-}C_6)$alkyl, or a nitrogen protecting group;

X is O, S, SO, SO_2, CH_2-O, CH_2-S, CH_2-NR^5, NR^5, carbonyl, or a direct bond;

D is S, SO, SO_2, P(O)OH, P(O)O(C_1-C_6)alkyl, P(O(C_1-C_6)alkyl)$_2$, C=N-OH, or carbonyl;

E is a direct bond, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, or (C_3-C_8)heterocycle;

J is S, O, or NR^5;

G, T, and Q are each independently H, (C_1-C_6)alkyl, or cyano;

any alkyl, amino, aryl, heteroaryl, or cycloalkyl is optionally substituted with 1 to about 5 (C_1-C_6)alkyl, (C_1-C_6)alkoxy, aryl, heteroaryl, aryl(C_1-C_6)alkyl, heteroaryl(C_1-C_6)alkyl, nitro, halo, amino, or hydroxy groups;

or a pharmaceutically acceptable salt thereof;

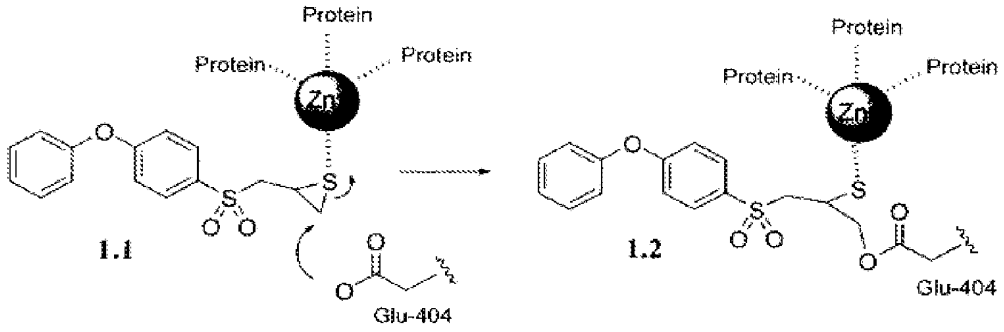
provided that when L is CH_2 or O, and R^2 is CH_2, R^1 is not (C_1-C_6)alkyl;

when L is O and R^2 is carbonyl, R^1 is not (C_1-C_6)alkyl; and

when L is NR^5, R^2 is CH_2.

ABSTRACT

The present invention provides novel compounds of formulas I-IX, as described herein. Also provided are compositions of compounds of formulas I-IX, methods of making compounds of formulas I-IX, and methods of using compounds of formulas I-IX. The compounds of the invention can be used to inhibit matrix metalloproteinases, and are useful to treat conditions and diseases associated therewith.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Protein
Protein
Zn
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O
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Protein
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O
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1.2
Glu-404

FIG. 1

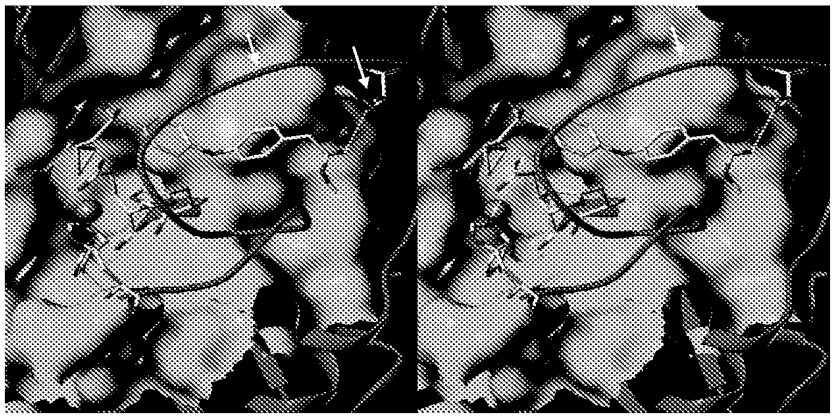
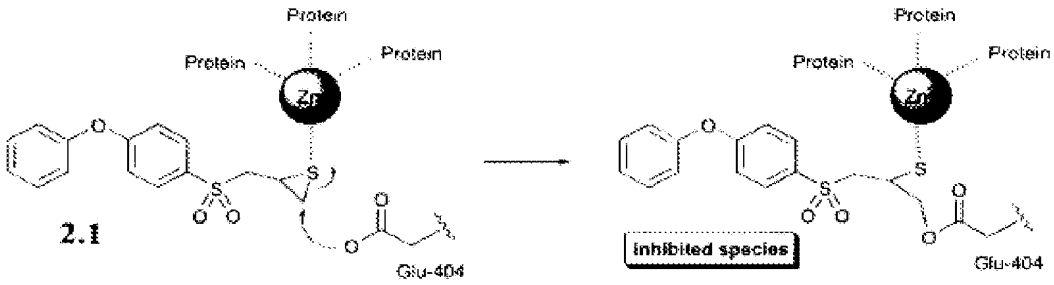


FIG. 2

A


Protein
Protein
Protein
Zn
2.1
Glu-404
Protein
Protein
Protein
Zn
inhibited species
Glu-404

B

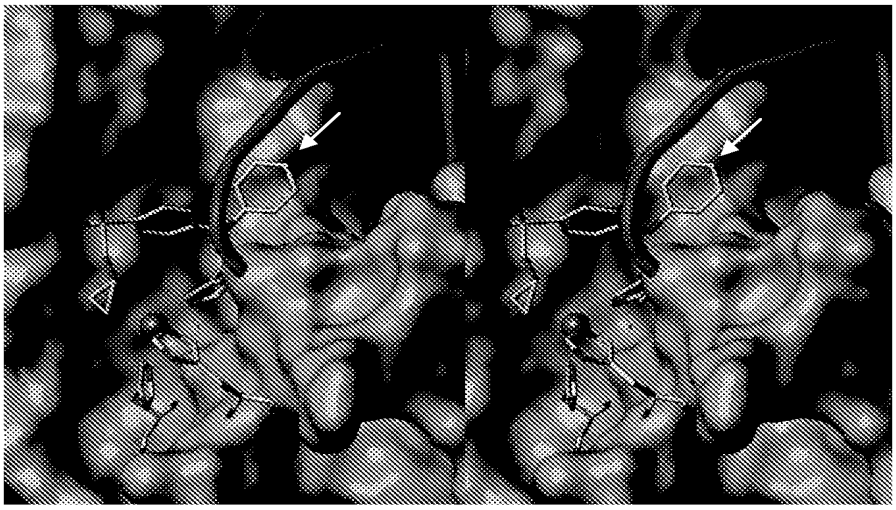


FIG. 3

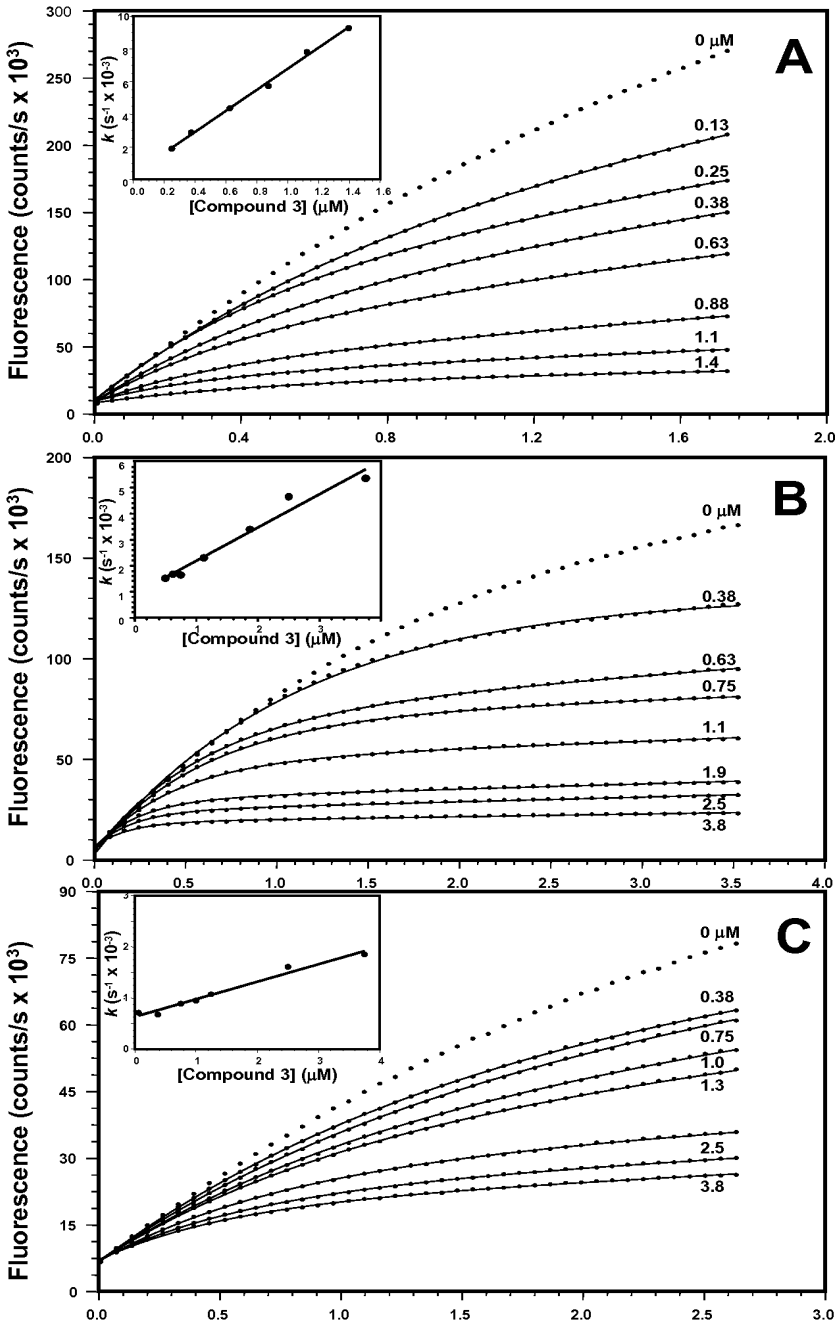

A
Fluorescence (counts/s x 10^3)
0 µM
0.13
0.25
0.38
0.63
0.88
1.1
1.4
k (s^-1 x 10^-3)
[Compound 3] (µM)
B
Fluorescence (counts/s x 10^3)
0 µM
0.38
0.63
0.75
1.1
1.9
2.5
3.8
k (s^-1 x 10^-3)
[Compound 3] (µM)
C
Fluorescence (counts/s x 10^3)
0 µM
0.38
0.75
1.0
1.3
2.5
3.8
k (s^-1 x 10^-3)
[Compound 3] (µM)

FIG. 4

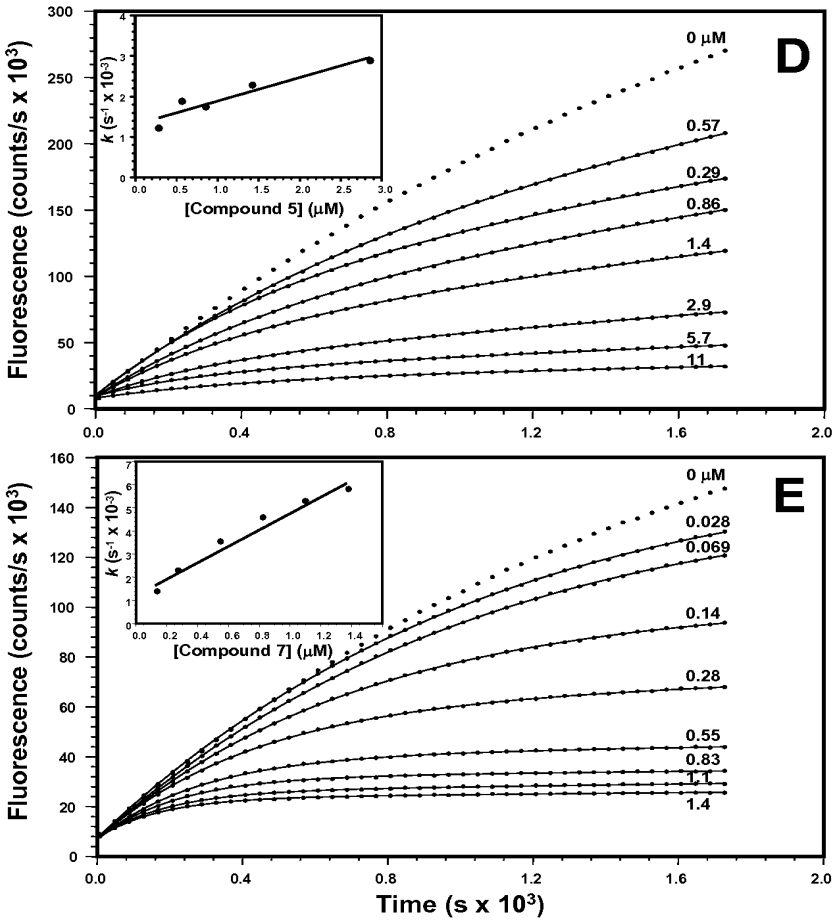

D
Fluorescence (counts/s x 10^3)
0 μM
0.57
0.29
0.86
1.4
2.9
5.7
11
k (s^-1 x 10^-3)
[Compound 5] (μM)
E
Fluorescence (counts/s x 10^3)
0 μM
0.028
0.069
0.14
0.28
0.55
0.83
1.1
1.4
k (s^-1 x 10^-3)
[Compound 7] (μM)
Time (s x 10^3)

***FIG. 4*, cont'd**

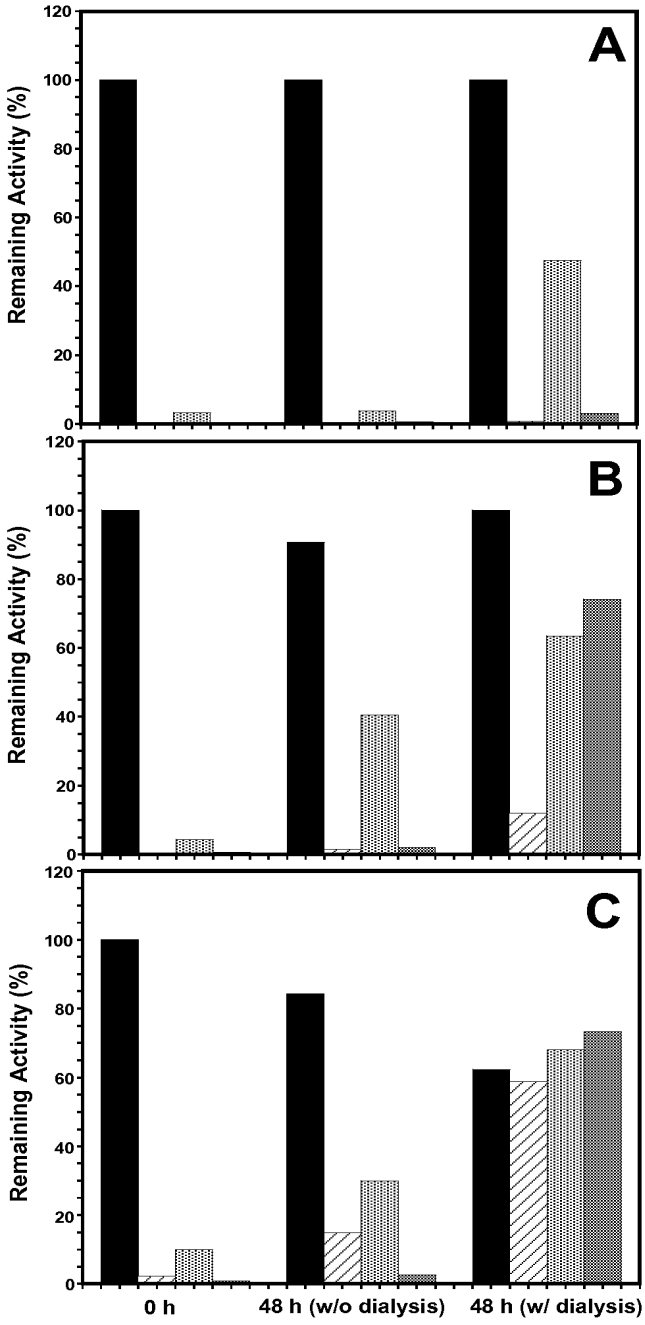

A
B
C
Remaining Activity (%)
120
100
80
60
40
20
0
0 h
48 h (w/o dialysis)
48 h (w/ dialysis)

FIG. 5

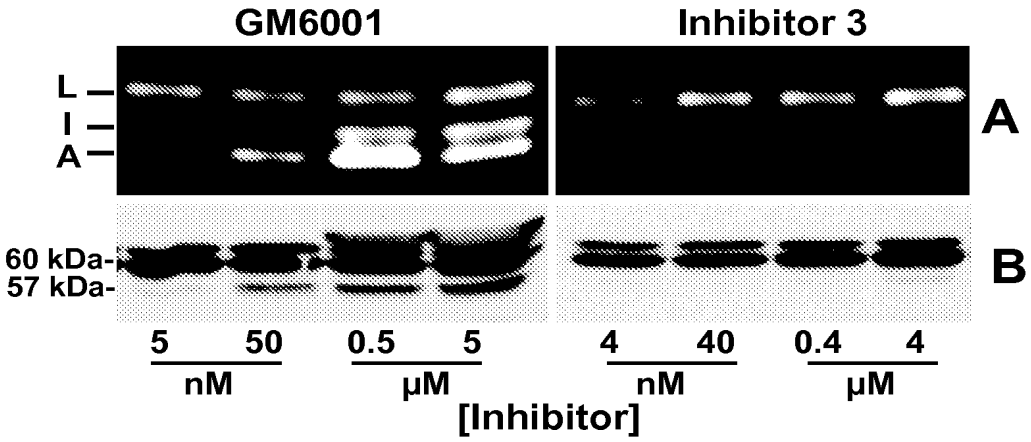

GM6001
Inhibitor 3
L
I
A
A
60 kDa-
57 kDa-
B
5
50
0.5
5
4
40
0.4
4
nM
µM
nM
µM
[Inhibitor]

FIG. 6

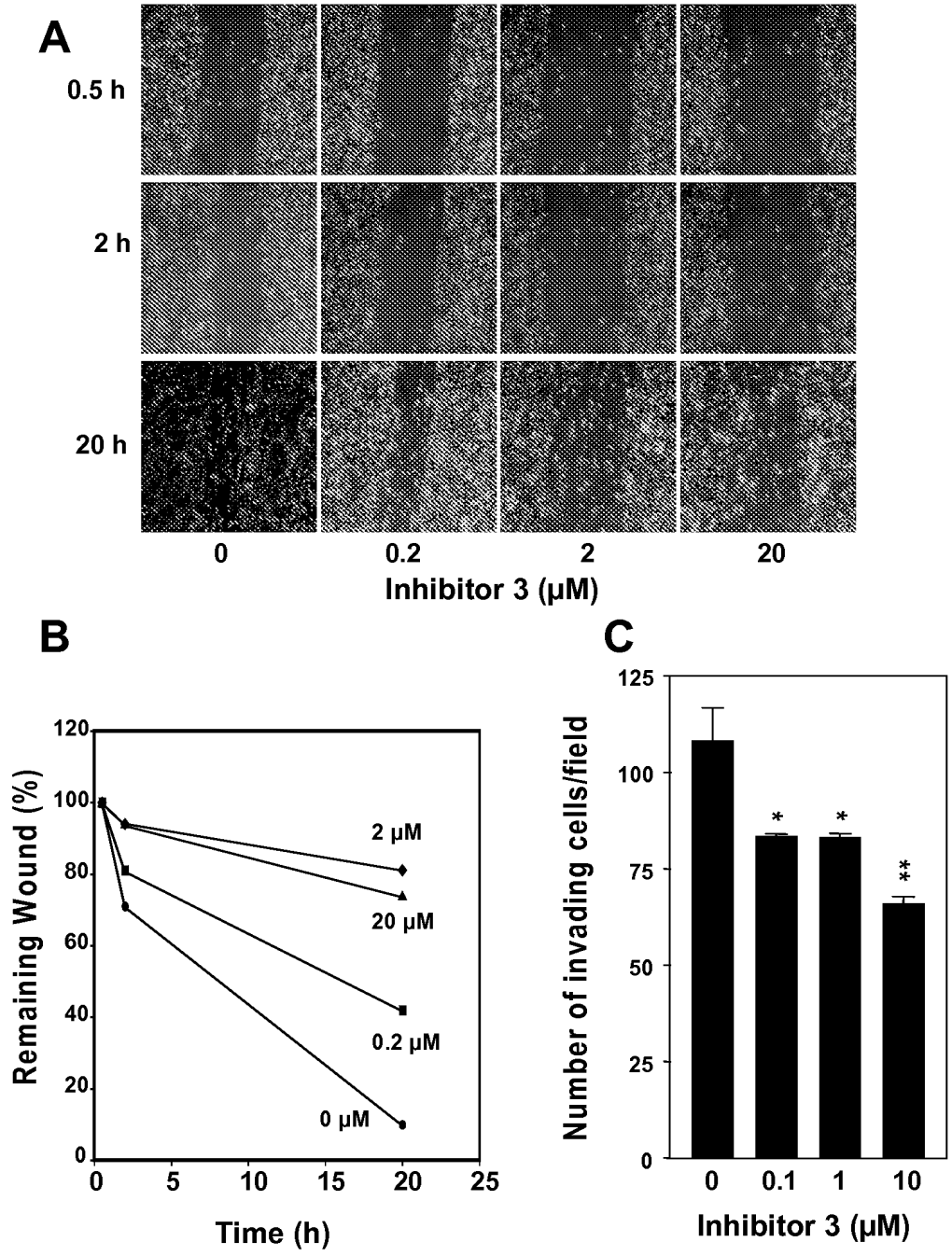

A
0.5 h
2 h
20 h
0
0.2
2
20
Inhibitor 3 (μM)
B
Remaining Wound (%)
120
100
80
60
40
20
0
2 μM
20 μM
0.2 μM
0 μM
0
5
10
15
20
25
Time (h)
C
Number of invading cells/field
125
100
75
50
25
0
*
*
**
0
0.1
1
10
Inhibitor 3 (μM)

FIG. 7

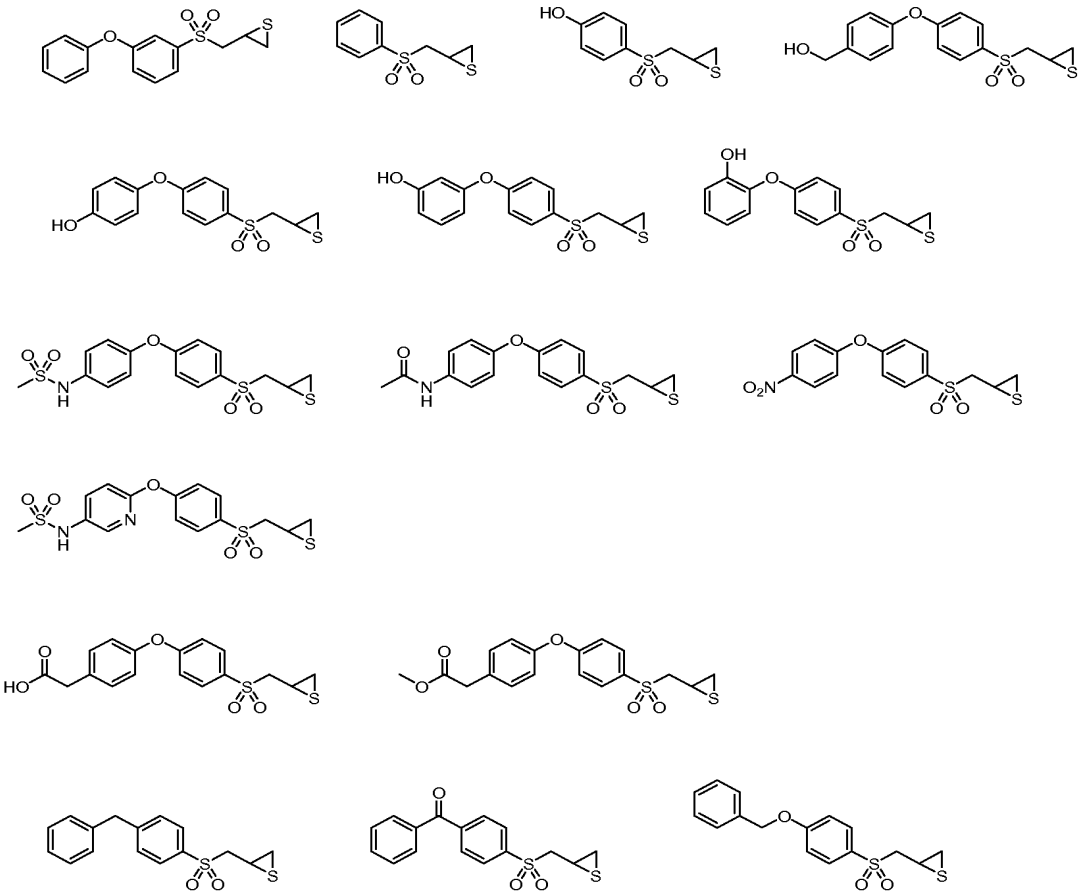


FIG. 8

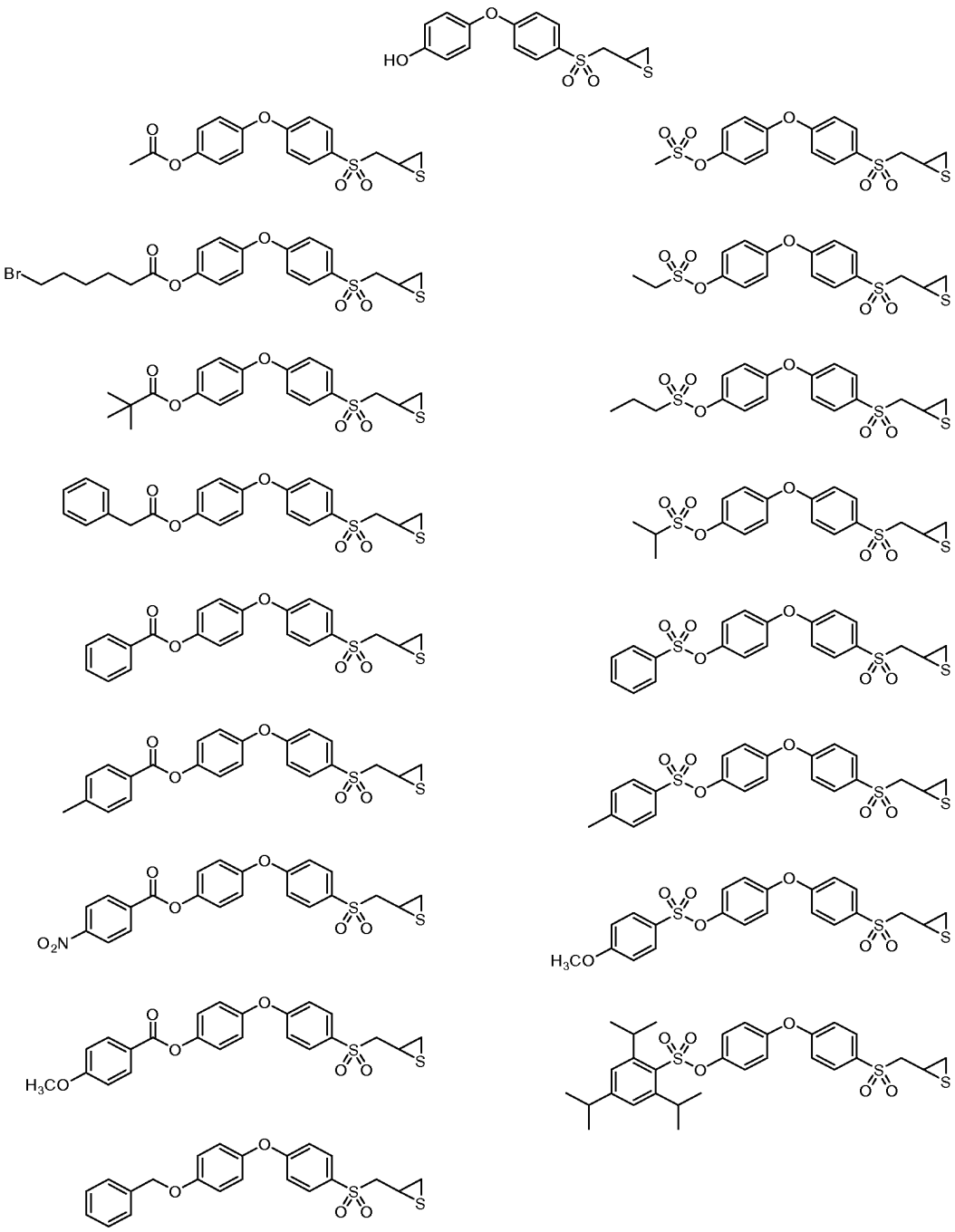


***FIG. 8,* cont'd**

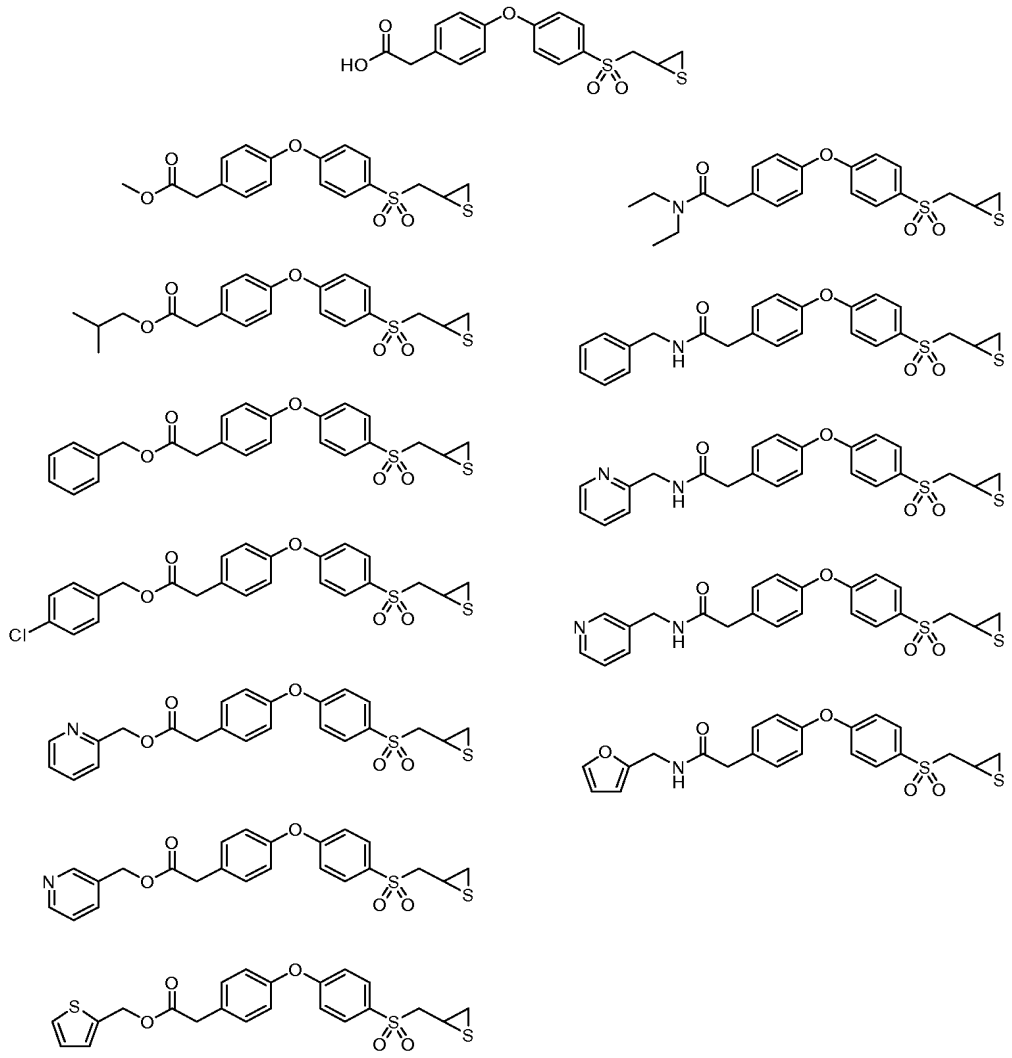


***FIG. 8,* cont'd**

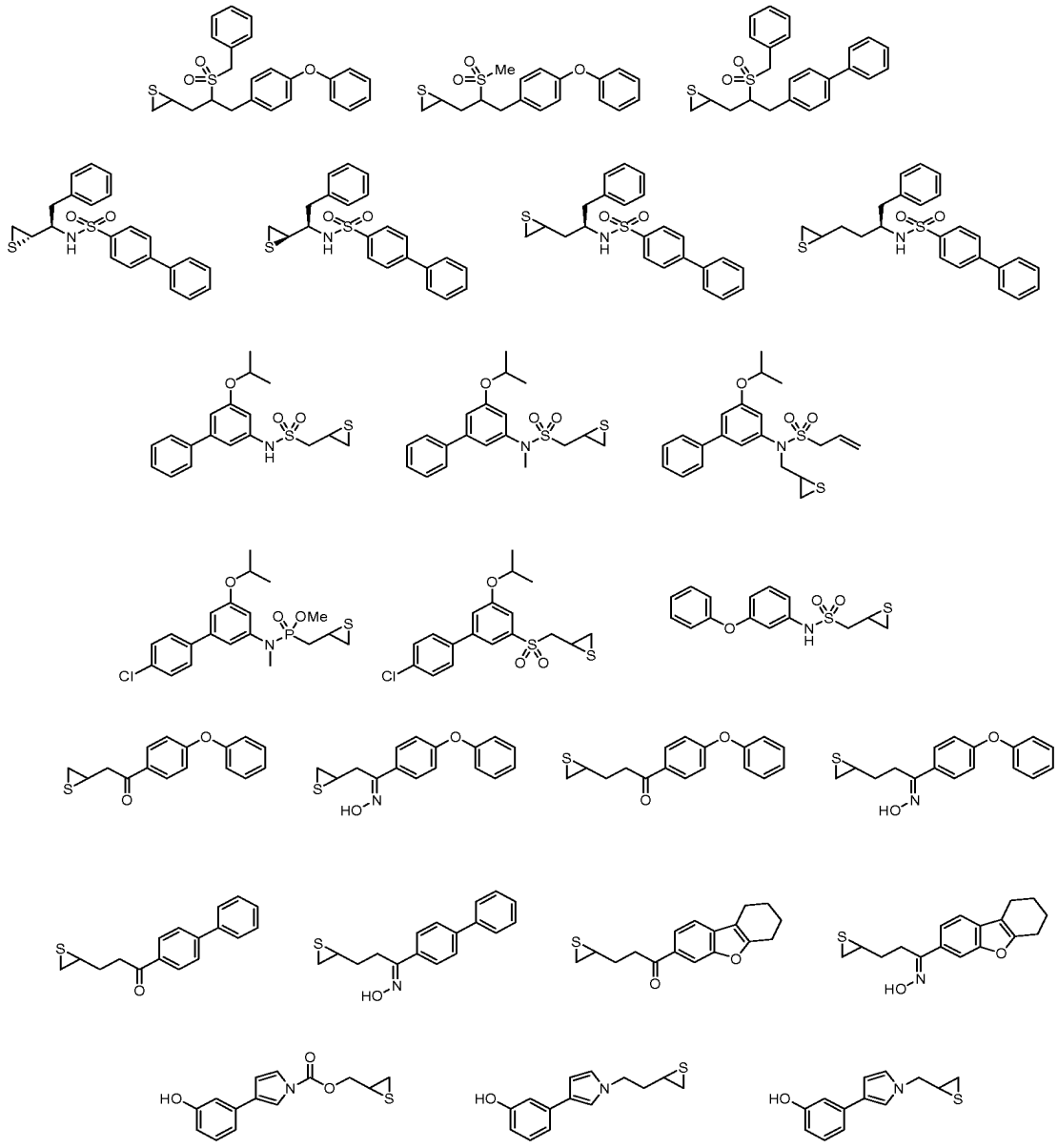
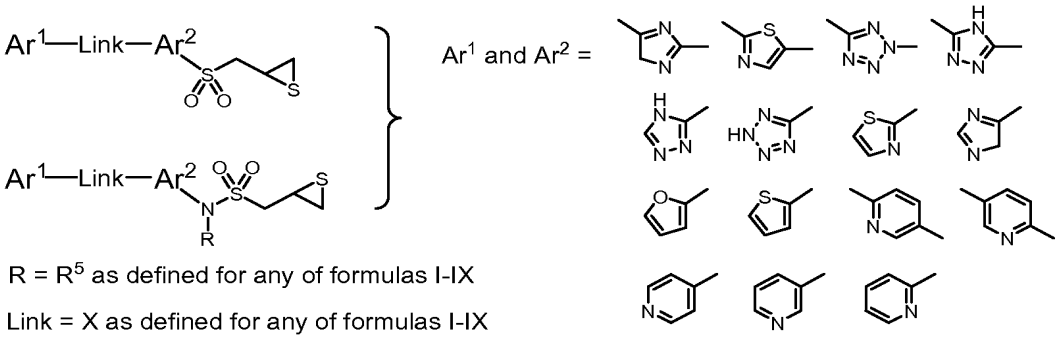
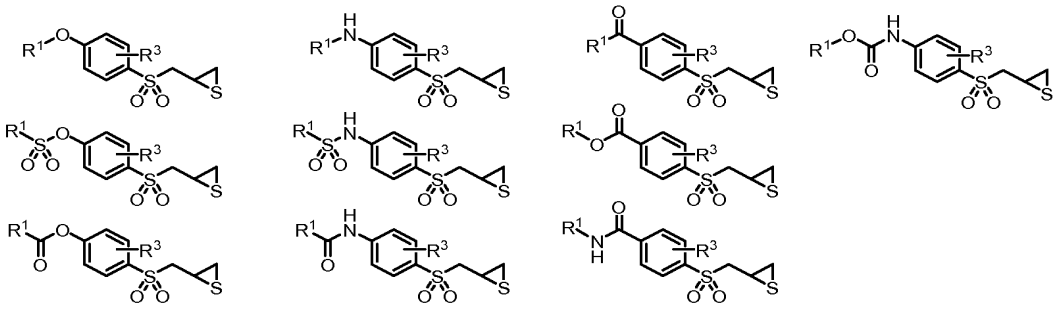


FIG. 8, **cont'd**

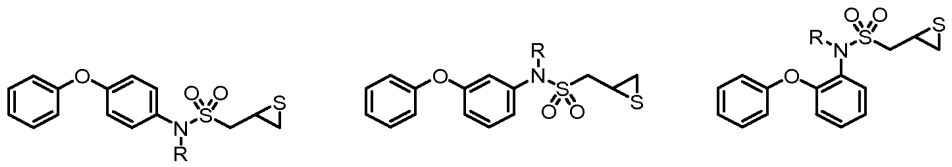


R = R^5 as defined for any of formulas I-IX

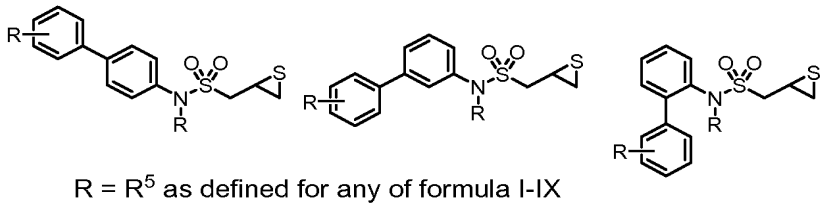
Link = X as defined for any of formulas I-IX



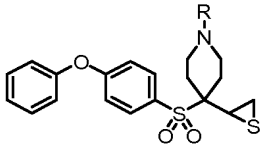
R^1 = R^1 as defined for any of formulas I-IX; R^3 = R^3 as defined for any of formulas I-IX



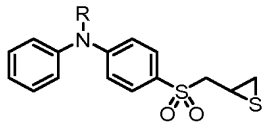
R = R^5 as defined for any of formulas I-IX



R = R^5 as defined for any of formula I-IX



R= H, benzyl, propargyl



R = CH_2Ph, Ph, CH_2-Pyridyl, etc.

FIG. 9

PTO/SB/14 (11-08)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	5006-004-CON
	Application Number	
Title of Invention	INHIBITORS OF MATRIX METALLOPROTEINASES	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mijoon		Lee	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Mishawaka	State/Province	IN	Country of Residence[i]	US

Citizenship under 37 CFR 1.41(b)[i] KR

Mailing Address of Applicant:

Address 1	551 University Park Court		
Address 2			
City	Mishawaka	State/Province	IN
Postal Code	46545	Country[i]	US

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Masahiro		Ikejiri	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Osaka	Country Of Residence[i]	JP

Citizenship under 37 CFR 1.41(b)[i] JP

Mailing Address of Applicant:

Address 1	2-16-26-304 Shinke		
Address 2	Tondabayashi		
City	Osaka	State/Province	
Postal Code	584-0085	Country[i]	JP

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mayland		Chang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Granger	State/Province	IN	Country of Residence[i]	US

PTO/SB/14 (11-08)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	5006-004-CON
	Application Number	
Title of Invention	INHIBITORS OF MATRIX METALLOPROTEINASES	

Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	14542 Heatherton Drive				
Address 2					
City	Granger	**State/Province**	IN		
Postal Code	46530	**Country**i	US		

Applicant 4 Remove

Applicant Authority (•) Inventor	( ) Legal Representative under 35 U.S.C. 117	( ) Party of Interest under 35 U.S.C. 118	
Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Rafael		Fridman	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City		**State/Province**	MI	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	4926 Hardwoods Drive				
Address 2					
City	West Bloomfield	**State/Province**	MI		
Postal Code	48323	**Country**i	US		

Applicant 5 Remove

Applicant Authority (•) Inventor	( ) Legal Representative under 35 U.S.C. 117	( ) Party of Interest under 35 U.S.C. 118	
Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Shahriar		Mobashery	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Granger	**State/Province**	IN	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	14542 Heatherton Drive				
Address 2					
City	Granger	**State/Province**	IN		
Postal Code	46530	**Country**i	US		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

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For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	44163

PTO/SB/14 (11-08)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	5006-004-CON
	Application Number	
Title of Invention	INHIBITORS OF MATRIX METALLOPROTEINASES	

Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	INHIBITORS OF MATRIX METALLOPROTEINASES		
Attorney Docket Number	5006-004-CON	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	12	**Suggested Figure for Publication (if any)**	1

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	44163		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	11914933	2008-07-31
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
11914933	a 371 of international	PCT/US06/19656	2006-05-19
Prior Application Status	Expired		Remove

PTO/SB/14 (11-08)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	5006-004-CON
	Application Number	
Title of Invention	INHIBITORS OF MATRIX METALLOPROTEINASES	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US06/19656	non provisional of	60682385	2005-05-19
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US06/19656	non provisional of	60743467	2006-03-13

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			○ Yes ◉ No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

If the Assignee is an Organization check here. ☒			
Organization Name	Notre Dame University		
Mailing Address Information:			
Address 1	203 Main Building		
Address 2			
City	Notre Dame	**State/Province**	IN
Country [i] US		Postal Code	46556
Phone Number		Fax Number	
Email Address			

Assignee 2 Remove

If the Assignee is an Organization check here. ☒	
Organization Name	Wayne State University

PTO/SB/14 (11-08)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	5006-004-CON
	Application Number	
Title of Invention	INHIBITORS OF MATRIX METALLOPROTEINASES	

Mailing Address Information:			
Address 1	656 West Kirby		
Address 2	4249 Faculty Administration Bldg.		
City	Detroit	**State/Province**	MI
Country [i]	US	Postal Code	48202
Phone Number		Fax Number	
Email Address			
Additional Assignee Data may be generated within this form by selecting the **Add** button.		Add	

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.					
Signature	/ Michael Haukaas /			Date (YYYY-MM-DD)	2011-03-14
First Name	Michael	Last Name	Haukaas	Registration Number	57111

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Filer:	Michael Hans Haukaas/Angela Zwack
Attorney Docket Number:	5006-004-CON

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	82	82
Utility Search Fee	2111	1	270	270
Utility Examination Fee	2311	1	110	110
Pages:				
Utility Appl Size fee per 50 sheets >100	2081	1	135	135
Claims:				
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**597**

Electronic Acknowledgement Receipt

EFS ID:	9656238
Application Number:	13047605
International Application Number:	
Confirmation Number:	7167
Title of Invention:	INHIBITORS OF MATRIX METALLOPROTEINASES
First Named Inventor/Applicant Name:	Mijoon Lee
Customer Number:	44163
Filer:	Michael Hans Haukaas/Angela Zwack
Filer Authorized By:	Michael Hans Haukaas
Attorney Docket Number:	5006-004-CON
Receipt Date:	14-MAR-2011
Filing Date:	
Time Stamp:	18:46:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$597
RAM confirmation Number	6031
Deposit Account	503141
Authorized User	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	Declaration-fromparent.pdf	371660 693f97521b10506290d9dedcc98feb21469043c9	no	8
Warnings:					
Information:					
2		ApplicationandDrawings.pdf	3157395 e4cd77c2d339ae67d8a91978af7a25ceec26500e	yes	159

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	144
Claims	145	146
Abstract	147	147
Drawings-only black and white line drawings	148	159

Warnings:					
Information:					
3	Application Data Sheet	ADS.pdf	1032515 6bedaf94930797c55a776f76d79ca758b9943a3d	no	6
Warnings:					
Information:					
4	Fee Worksheet (PTO-875)	fee-info.pdf	36838 a2f9c49106732f1e9028a16cf46a4215644bd8c4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4598408		

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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Application Number: 13047605 Document Date: 3/14/2011

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