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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/505,591	08/03/2010	7767657	064507-5014US01	5739

43850 7590 07/14/2010

MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

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 348 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):

Stephen J. Baker, Mountain View, CA;
Tsutomu Akama, Sunnyvale, CA;
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Virginia Sanders, San Francisco, CA;
Yong-Kang Zhang, San Jose, CA;
Kirk R. Maples, San Jose, CA;
Gregory T. Fieldson, Morgantown, WV;

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NOTICE OF ALLOWANCE AND FEE(S) DUE

43850 7590 08/07/2009

MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

EXAMINER	
SHIAO, REI TSANG	
ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 08/07/2009

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/505,591	08/16/2006	Stephen J. Baker	064507-5014US01	5739

TITLE OF INVENTION: BORON-CONTAINING SMALL MOLECULES

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	11/09/2009

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
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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)

43850 7590 08/07/2009

MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

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.
11/505,591	08/16/2006	Stephen J. Baker	064507-5014US01	5739

TITLE OF INVENTION: BORON-CONTAINING SMALL MOLECULES

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	11/09/2009

EXAMINER	ART UNIT	CLASS-SUBCLASS
SHIAO, REI TSANG	1626	514-064000

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.
11/505,591	08/16/2006	Stephen J. Baker	064507-5014US01	5739

43850 7590 08/07/2009

MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

EXAMINER	
SHIAO, REI TSANG	
ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 08/07/2009

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 179 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 179 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.

Notice of Allowability	Application No.	Applicant(s)	
	11/505,591	BAKER ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	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 *amendment filed on 7/28/2009*.

2. ☒ The allowed claim(s) is/are *121 and 193-215 , now are 1-24*.

3. ☐ 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.

4. ☐ 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.

5. ☐ 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).

6. ☐ 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 _____
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 _____.

/REI-TSANG SHIAO /
Primary Examiner, Art Unit 1626

DETAILED ACTION

1. This application claims benefit of the provisional application: 60/755,227 with a filing date 12/30/2005; and 60/746,361 with a filing date 05/03/2006.

2. Amendment of claim 195, cancellation of claims 1-120 and 122-192, addition of claim 215, and request for a corrected filing receipt in the amendment filed on July 28, 2009 is acknowledged. Claims 121 and 193-215 are pending in the application. No new matter is found. Since the newly added claim 215 is commensurate with the scope of the invention, claims 121 and 193-215 are prosecuted in the case.

Reasons for Allowance

3. The rejection of claim 195 under 35 U.S.C. 112, first paragraph has been overcome in the amendment filed on 7/28/2009.

4. Applicant's arguments regarding the rejection of claims 121 and 193-214 under 35 U.S.C. 103(a) over Austin et al. '188 in view of Austin et al. '024 filed on May 18, 2009 have been fully considered and they are persuasive. Since Austin et al. '188 does not disclose the instant pharmaceutical composition, therefore Austin et al. '188 is distinct from the instant invention. The rejection of claims 121 and 193-214 under 35 U.S.C. 103(a) over Austin et al. '188 in view of Austin et al. '024 has been withdrawn herein.

5. Claims 121 and 193-215 are neither anticipated nor rendered obvious over the art of record, and therefore are allowable. A suggestion for modification of above

reference to obtain the instant pharmaceutical compositions has not been found.

Claims 121 and 193-215 are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance".

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rei-tsang Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO /
Primary Examiner, Art Unit 1626

Julu 29, 2009

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/505,591	BAKER ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

SEARCHED			
Class	Subclass	Date	Examiner
514	64	7/29/2009	R.S.
558	288	7/29/2009	R.S.

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**64**	7/29/2009	**R.S.**
558	288	7/29/2009	R.S.

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
EAST class/subclass	7/29/2009	R.S.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	308	514/64	USPAT	OR	OFF	2009/07/29 10:26
L3	82	558/288	USPAT	OR	OFF	2009/07/29 10:26

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	82	558/288	USPAT; UPAD	OR	OFF	2009/07/29 10:26
L5	318	514/64	USPAT; UPAD	OR	OFF	2009/07/29 10:26

7/29/2009 10:27:40 AM

Issue Classification	Application/Control No. 11/505,591	Applicant(s)/Patent under Reexamination BAKER ET AL.
	Examiner REI-TSANG SHIAO	Art Unit 1626

ISSUE CLASSIFICATION

ORIGINAL		INTERNATIONAL CLASSIFICATION											
CLASS	SUBCLASS	CLAIMED							NON-CLAIMED				
514	64	A	61	K	31	/69							/
CROSS REFERENCES						/							/
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)												
558	288					/							/
						/							/
						/							/
						/							/
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(Assistant Examiner) (Date)	/Rei-tsang Shiao/ 7/29/09	Total Claims Allowed: 24	
(Legal Instruments Examiner) (Date)	(Primary Examiner) (Date)	O.G. Print Claim(s) 1	O.G. Print Fig. NONE

☐ 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
1	121												
2	193												
3	194												
4	195												
5	196												
6	197												
7	198												
8	199												
9	200												
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24	215												

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BIB DATA SHEET

CONFIRMATION NO. 5739

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/505,591	08/16/2006 RULE	514	1626	064507-5014US01

APPLICANTS

Stephen J. Baker, Mountain View, CA;
Tsutomu Akama, Sunnyvale, CA;
Michael Richard Kevin Alley, Santa Clara, CA;
Steven J. Benkovic, State College, PA;
Michael DiPierro, Wadsworth, IL;
Vincent S. Hernandez, Watsonville, CA;
Karin M. Hold, Belmont, CA;
Isaac Kennedy, Bolingbrook, IL;
Igor Likhotvorik, Naperville, IL;
Weimin Mao, Sunnyvale, CA;
Kirk R. Maples, San Jose, CA;
Jacob J. Plattner, Berkeley, CA;
Fernando Rock, Los Altos, CA;
Virginia Sanders, San Francisco, CA;
Aaron M. Stemphoski, Florence, SC;
George Petros Yiannikouros, Florence, SC;
Siead Zegar, Orland Park, IL;
Yong-Kang Zhang, San Jose, CA;
Huchen Zhou, Shanghai, CHINA;

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

This appln claims benefit of 60/755,227 12/30/2005
and claims benefit of 60/746,361 05/03/2006
and is a CIP of 11/357,687 02/16/2006 and claims benefit of 60/654,060 02/16/2005. R.S.

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

UNITED STATES OF AMERICA PCT/US06/05542 02/16/2006

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
10/03/2006

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /REI-TSANG SHIAO/ Examiner's Signature	☐ Met after Allowance R.S Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	63	~~192~~ 24	21

ADDRESS

MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105
UNITED STATES

TITLE

Boron-containing small molecules

		☐ All Fees

BIB (Rev. 05/07).

FILING FEE RECEIVED 7845	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

Amendments to the Specification:

Applicants respectfully request the first paragraph on page 1 of the application be replaced by the following paragraph which encompasses the information from the specification filed on August 16, 2006, with the two priority applications claimed in the accepted Petition of March 5, 2007.

> **[0001]** The present application is a continuation-in-part of U.S. Patent Application 11/357,687 filed February 16, 2006, which claims the benefit of U.S. Provisional Patent Application 60/654,060 filed February 16, 2005, which is incorporated by reference in its entirety for all purposes. The present application claims the benefit of U.S. Provisional Patent Application 60/755,227 filed December 30, 2005. The present application claims the benefit of U.S. Provisional Patent Application 60/746,361 filed May 3, 2006.

/Rei Tsang Shiao/ Entered 7/29/09

CERTIFICATE OF ELECTRONIC TRANSMISSION

I hereby certify that this correspondence, including listed enclosures is being electronically transmitted in Portable Document Form (PDF) through EFS-Web via Hyper Text Transfer Protocol to the United States Patent and Trademark Office's Patent Electronic Business Center on:

Dated: 5/18/09

Signed: Candida Rubalcaba-Rivera

Candida Rubalcaba-Rivera

Attorney Docket No.: 064507-5014-US01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5739
Stephen J. BAKER, *et al.*	Examiner: SHIAO, Rei Tsang
Application No.: 11/505,591	Art Unit: 1626
Filed: August 16, 2006	RESPONSE TO OFFICE ACTION
For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

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

Madam:

In response to the Office Action dated January 27, 2009, please enter the following amendments and remarks.

Amendments to the Claims are reflected in the listing of claims which begins on page **2** of this paper.

Remarks/Arguments begin on page **7** of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims:

1.-120. (Cancelled)

121. (Previously presented) A pharmaceutical formulation, comprising:

(a) 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a salt thereof; and

(b) a pharmaceutically acceptable excipient

wherein said pharmaceutical formulation is for topical administration to an animal suffering from an infection by a microorganism.

122. – 192. (Cancelled).

193. (Previously presented) The formulation of claim **121**, wherein said formulation is a member selected from a lacquer, lotion, cream, gel, ointment and spray.

194. (Previously presented) The formulation of claim **121**, wherein said formulation is a lacquer.

195. (Previously presented) The formulation of claim **121**, wherein said formulation further comprises one or more members selected from an emulsifier, emollient, antioxidant, perservative, chelating agent, neutralizing agent, viscosity increasing agent, nail penetration enhancer, anti-inflammatory agent, vitamin, anti-aging agent, sunscreen and acne-treating agent.

196. (Previously presented) The formulation of claim **121**, wherein said formulation comprises one or more members selected from ethanol and propylene glycol.

197. (Previously presented) The formulation of claim **121**, comprising: about propylene glycol:ethanol in a ratio of about 1:4, and about 1:10 wt/ volume of said 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

198. (Previously presented) The formulation of claim **121**, comprising: about 70% ethanol; about 20% poly(vinyl methyl ether-alt-maleic acid monobutyl ester) and about 10% of said 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

199. (Previously presented) The formulation of claim **121**, comprising: about 56% ethanol; about 14% water; about 15% poly(2-hydroxyethyl methacrylate); about 5% dibutyl sebacate and about 10% of said 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

200. (Previously presented) The formulation of claim **121**, comprising: about 55% ethanol; about 15% ethyl acetate; about 15% poly(vinyl acetate); about 5% dibutyl sebacate and about 10% 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

201. (Previously presented) The formulation of claim **121**, wherein said 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole is present in said formulation in a concentration from about 0.5% to about 15% w/v.

202. (Previously presented) The formulation of claim **121**, wherein said 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or salt thereof, is present in a form which is a member selected from a hydrate with water, a solvate with an alcohol, an adduct with an amino compound, and an adduct with an acid.

203. (Previously presented) The formulation of claim **121**, wherein said formulation is in a cosmetically effective amount.

204. (Previously presented) The formulation of claim **121**, wherein a site of said topical administration is skin or nail or hair or skin surrounding the nail or skin surrounding the hair.

205. (Previously presented) The formulation of claim **121**, wherein the microorganism is a fungus or a yeast.

206. (Previously presented) The formulation of claim **205**, wherein said fungus or yeast is a member selected from *Candida* species, *Trichophyton* species, *Microsporium* species, *Aspergillus* species, *Cryptococcus* species, *Blastomyces* species, *Cocciodiodes* species, *Histoplasma* species, *Paracoccidiodes* species, *Phycomycetes* species, *Malassezia* species, *Fusarium* species, *Epidermophyton* species, *Scytalidium* species, *Scopulariopsis* species, *Alternaria* species, *Penicillium* species, *Phialophora* species, *Rhizopus* species, *Scedosporium* species and *Zygomycetes* species.

207. (Previously presented) The formulation of claim **205**, wherein said fungus or yeast is a member selected from *Aspergilus fumigatus*, *Blastomyces dermatitidis, Candida albicans*, *Candida glabrata*, *Candida krusei*, *Cryptococcus neoformans*, *Candida parapsilosis*, *Candida tropicalis*, *Cocciodiodes immitis, Epidermophyton floccosum*, *Fusarium solani*, *Histoplasma capsulatum*, *Malassezia furfur*, *Malassezia pachydermatis*, *Malassezia sympodialis*, *Microsporum audouinii*, *Microsporum canis*, *Microsporum gypseum*, *Paracoccidiodes brasiliensis, Trichophyton mentagrophytes*, *Trichophyton rubrum* and *Trichophyton tonsurans.*

208. (Previously presented) The formulation of claim **205**, wherein said fungus or yeast is a member selected from *Trichophyton concentricum, Trichophyton violaceum, Trichophyton schoenleinii, Trichophyton verrucosum, Trichophyton soudanense, Microsporum gypseum, Microsporum equinum, Candida guilliermondii, Malassezia globosa, Malassezia obtuse, Malassezia restricta, Malassezia slooffiae* and *Aspergillus flavus.*

209. (Previously presented) The formulation of claim **205**, wherein said fungus or yeast is a dermatophyte.

210. (Previously presented) The formulation of claim **205**, wherein said fungus or yeast is a member selected from *Tinea unguium*, *Trichophyton rubrum* and *Trichophyton mentagrophytes.*

211. (Previously presented) The formulation of claim **121**, wherein the infection is a cutaneous infection.

212. (Previously presented) The formulation of claim **121**, wherein the infection is a member selected from an ungual, periungual and subungual infection.

213. (Previously presented) The formulation of claim **121**, wherein the infection is onychomycosis.

214. (Previously presented) The formulation of claim **121**, wherein the animal is a human.

REMARKS/ARGUMENTS

I. Status of the Claims

Claims 121 and 193-214 are pending.

II. Response to the Rejections

35 USC § 112, first paragraph

Claim 195 is rejected under 35 USC § 112, first paragraph, because the Examiner alleges that while the specification enables an anti-aging agent selected from niacinamide and an acne-treating agent selected from salicylic acid, the specification does not reasonably provide enablement for any anti-aging agent or acne-treating agent.

Applicants traverse. The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the application coupled with information known in the art without undue experimentation. See MPEP 2164.01 (citing *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)). In determining whether experimentation would be undue, the Examiner must consider a number of factors set forth by the Federal Circuit in *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988). Here, the Examiner has improperly analyzed a number of the *Wands* factors and thus has failed to establish a basis for concluding that the experimentation needed to make and use the invention is undue.

The state of the prior art

The Examiner on page 4 of the instant office action states that "the state of the prior art is Austin et al. US 5,880,188 ("Austin"), it discloses similar compositions or formulation, see column 28." Austin, however, states that "The present invention relates to the use of oxaboroles and salts thereof as **industrial** biocides..." Col. 1, lines 6-8. A previous citation in the literature (FR 7329370) "discloses that an oxaborole is . . . useful in inhibiting the growth of micro organisms in **aviation fuels**." Col. 1, lines 39-45. Austin suggests that the disclosed compounds "containing an oxaborole ring are particularly effective against . . . fungi, especially fungi which cause degradation of **plastics** materials." Col. 1, lines 46-50.

Austin contemplates using oxaboroles for "the protection of a medium susceptible to microbial attack." Col. 1, lines 54 & 55. Examples of a "medium" according to Austin include

"solvent-based paint", col. 5, line 8; "a plastics material", col. 5, line 11; "an aqueous medium" col. 5, line 15. Austin suggests use of oxaboroles in systems such as

> liquid, particularly aqueous, systems such as cooling water liquors, paper mill liquors, metal working fluids, geological drilling lubricants, polymer emulsions and especially surface coating compositions such as paints, varnishes and lacquers and more especially solid materials such as wood, plastics materials[,] leather[, and] plastics materials such as plasticised PVC and urethanes[.]

Col. 8, lines 1-10. Further, 5-fluoro substituted benzoxaboroles are taught to provide "particularly useful effects . . . in plastics materials and paint films." Col. 4, lines 50-54. Column 28 of Austin, to which the Examiner has pointed specifically, discloses compositions comprising an oxaborole and a carrier exemplified by a paint film, a plastics material, plasticized PVC or polyurethane and a stabilizer or plasticizer for a plastics material. Thus, in the state of art according to Austin, oxaboroles were recognized as useful in industry. In contrast, claim 195 is directed to a **pharmaceutical** formulation comprising in part a **pharmaceutically acceptable** excipient.

The amount of direction or guidance present

The Examiner on page 5 of the instant office action states that "the only direction or guidance present in the instant specification is that anti-aging agent selected from niacinamide and acne-treating agent is selected from salicylic acid, see page 168 of the specification." This characterization of the specification is incorrect. The specification, page 168, paragraph 406, states that "anti-aging agents include, but are not limited to, niacinamide, retinol and retinoid derivatives, AHA, Ascorbic acid, lipoic acid, coenzyme Q 10, beta hydroxy acids, salicylic acid, copper binding peptides, dimethylaminoethyl (DAEA), and the like." The specification, page 168, paragraph 408, states that "acne-treating agents include, but are not limited to, salicylic acid, benzoyl peroxide, coal tar, selenium sulfide, zinc oxide, pyrithione (zinc and/or sodium), tazarotene, calcipotriene, tretinoin, adapalene and the like." Thus, the specification provides at least 11 examples of anti-aging agents and at least 10 types of acne-treating agents. It is therefore inaccurate to assert that an anti-aging agent is exemplified by only niacinamide and an acne-treating agent is exemplified by only salicylic acid in the specification.

The presence or absence of working examples

The Examiner states that "there is no data present in the instant anti-aging agent and acne-treating agent, which is not limited." Applicants note, however, that "[w]hen considering the factors relating to a determination of non-enablement, if all the other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled." MPEP 2164.02. As discussed herein, claim 195 is fully enabled by the specification coupled with knowledge in the art, and the Examiner has not established a factual basis for concluding otherwise.

The breadth of the claims

The Examiner states that "the instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include any anti-aging agent and acne-treating agent, which are not limited." Applicants disagree. In paragraphs 404-409, the specification describes commercially available additional active agents that may find use in the claimed invention. Particularly, anti-aging agents and acne-treating agents are exemplified by no fewer than 10 different types of each of those agents. Thus, while the terms "anti-aging agent" and "acne-treating agent" are generic terms embracing a number of compounds, many examples of those compounds are provided in the specification. The disclosure fully supports the use of these terms in the claims.

Quantity or experimentation needed and the level of skill in the art

As stated by the Examiner, the level of skill in the chemical arts is high. In view of this finding, Applicants submit that the specification, coupled with the knowledge generally known in the art, is sufficient to enable practice of the full scope of the rejected claim. Claim 195 encompasses a pharmaceutical formulation comprising 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole ("C10") or a salt thereof, a pharmaceutically acceptable excipient and at least one of the members recited in the claim. Methods of making C10 are described in Examples 5-7, and characterization data are provided in paragraph 457. Figures 2-7 show the effectiveness of C10 in inhibiting the growth of numerous microorganisms. Numerous formulations of C10 are described in paragraphs 211-213 and 346-402 and exemplified in paragraph 514, 551 and 556. Other formulations may be made based on excipients, additives and methods known in the art. See, e.g., Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott, Williams &

Wilkins (2005), incorporated by reference in paragraph 72. Formulations comprising an additional active agent such as those listed in claim 195 can be made by one of skill in the art. Specific additional active agents such as anti-aging agents and acne-treating agents are known according to the teachings of the present specification. See paragraph 406 ("Anti-aging agents include, but are not limited to, niacinamide, retinol and retinoid derivatives, AHA, Ascorbic acid, lipoic acid, coenzyme Q 10, beta hydroxy acids, salicylic acid, copper binding peptides, dimethylaminoethyl (DAEA), and the like.") and paragraph 408 ("acne-treating agents include, but are not limited to, salicylic acid, benzoyl peroxide, coal tar, selenium sulfide, zinc oxide, pyrithione (zinc and/or sodium), tazarotene, calcipotriene, tretinoin, adapalene and the like.")). These and many other anti-aging and acne-treating agents, as well as methods of formulating them for pharmaceutical use, are well-known in the art. See, e.g, US Patent Application Publication Nos. 2006/0083777 ("Treatment of acne"); 2006/0008537 ("Method of treating acne"); 2004/0092482 ("Hydroxy acids based delivery systems for skin resurfacing and anti-aging compositions"); 2004/0067890 ("Ascorbic acid salts of organic bases with enhanced bioavailability for synergi[s]tic anti-aging and skin protective cosmetic compositions"); and 2004/0001897 ("Skin vitalizing composition for external use anti-aging preparation"). In view of the specification and the teachings of the art, claim 195, which recites a pharmaceutical formulation that may comprise at least one anti-aging agent and/or acne-treating agent, can be practiced without undue experimentation by one of ordinary skill in the art.

The Examiner has failed to establish a sufficient factual basis under the *Wands* factors to conclude that the claims are not enabled in view of the specification and the art. Withdrawal of the rejection is therefore respectfully requested.

35 USC § 103

Claims 121 and 193-214 are rejected under 35 USC § 103 as allegedly being unpatentable over Austin et al., US Patent No. 5,880,188 ("Austin I") in view of Austin et al., CAPLUS Document No. 124:234024 ("Austin II").

To establish a *prima facie* case of obviousness, the Examiner is required to perform a factual analysis according to the *Graham* factors and to provide some articulated reasoning with some rational underpinning to support the legal conclusion of obviousenss. See *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1734, 1741 (2007).

As discussed above, Austin I is directed to uses of oxaboroles in industrial settings, such as inhibiting bacterial or fungal growth in aviation fuels, plastics materials, cooling water liquors, paper mill liquors, metal working fluids, geological drilling lubricants, polymer emulsions, surface coating compositions such as paints, varnishes and lacquers, and solid materials such as wood, plastics materials, leather, and plastics materials such as plasticized PVC and urethanes.

Austin II discloses 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. However, Austin II also suggests that the oxaboroles disclosed therein are useful in industrial settings. See Austin II, page 1, second to the last line, which discloses "oxaboroles and salts and their use as biocides for plastics". Furthermore, Austin II is a chemical database record showing a number of patent applications that claim priority to PCT Application No. GB1995/01206 ("Austin PCT Application"), filed May 26, 1995. One such application is Austin I, which is the US national phase filing of the Austin PCT Application. Thus, in view of Austin I, Austin II does not appear to disclose any additional information relating to the use of oxaboroles outside of an industrial setting.

The Examiner states that "the motivation to make the claimed compounds derived from the known compounds/compositions would possess similar activity (i.e., fungicide or treating fungal infection) to that which is claimed in the reference." However, the fact that Austin I and Austin II disclose **industrial** uses of oxaboroles does not suggest to one of skill in the art to use the claimed benzoxaboroles in a **pharmaceutical** formulation. Applicants submit that one of skill in the art would not presumptively consider a compound to be suitable for administration to an animal, especially a human, merely because a compound has been shown to have antifungal effects in paint or aviation fuel. In fact, a reference ("Answers.com", attached as Exhibit A) cited by the Examiner against the parent of this case (Application No. 11/357,687) teaches away from presuming that any antifungal compound can be administered to an animal. For example, Answers.com, page 3, states that

> Most fungicides can cause acute toxicity, and some cause chronic toxicity as well. Hexachlorobenzene, now banned or severely restricted in most parts of the world, has been associated with human poisoning from contaminated seed grain and poisoning of infants from misuse in laundry solutions. Metam sodium and other thiocarbanates are skin irritants that can cause reactive airway disease at low doses and severe toxicity and even death at high doses. The ethylene bis dithiocarbamates (EBCDs) are suspected human carcinogens and are tightly regulated in the United States.

Answers.com, page 4 teaches that "some fungicides are dangerous to human health, such as vinclozolin, which has now been removed from use [citation to Hrelia et al., The genetic and non-genetic toxicity of the fungicide Vinclozolin. *Mutagenesis* 1996, 11: 445-453]." Certain fungicides, such as captafol, pentachlorophenol, pentachlorophenate sodium, fentin, cycloheximide, chlorobenzilate, and copper arsenate hydroxide, are banned in Thailand because of their adverse effects on humans. See http://thailand.ipm-info.org/pesticides/pesticides_banned.htm. Thus, the art teaches that compounds that are useful for killing or inhibiting fungi may also harm animals, and thus teaches away from assuming that any fungicide can be used in a pharmaceutical formulation as claimed. Austin I and II, cited by the Examiner, teaches the use of oxaboroles in treating plastics and materials and in other industrial settings, and there is no reason why, in view of Answers.com, one of skill in the art would extrapolate such use for treating animals given the potential harm that may occur.

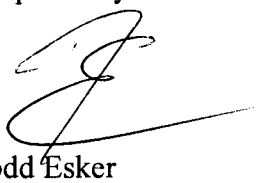
The Examiner has not provided any valid reasoning why one of skill in the art would find the claimed invention obvious in view of the cited references. Without this reasoning, the Examiner has not established a prima facie case of obviousness. Withdrawal of the rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1000.

Respectfully submitted,



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PTO/SB/22 (12-08)
Approved for use through 01/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2009** ***(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)***	Docket Number (Optional) 064507-5014-US01
Application Number 11/505,591	Filed 08/16/2006
For BORON-CONTAINING SMALL MOLECULES	
Art Unit 1626	Examiner SHIAO, Rei Tsang

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☑ One month (37 CFR 1.17(a)(1))	$130	$65	$ 130
☐ Two months (37 CFR 1.17(a)(2))	$490	$245	$
☐ Three months (37 CFR 1.17(a)(3))	$1110	$555	$
☐ Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐ Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

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

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-0310.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 46,690

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Signature	05/18/2009 Date
Todd Esker Typed or printed name	415-442-1000 Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☑ Total of 1 forms are submitted.

Electronic Patent Application Fee Transmittal

Application Number:	11505591
Filing Date:	16-Aug-2006
Title of Invention:	Boron-containing small molecules
First Named Inventor/Applicant Name:	Stephen J. Baker
Filer:	Jeffry S. Mann/Candida Rubalcaba-Rivera
Attorney Docket Number:	064507-5014US01

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:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	130	130

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

Electronic Acknowledgement Receipt

EFS ID:	5354556
Application Number:	11505591
International Application Number:	
Confirmation Number:	5739
Title of Invention:	Boron-containing small molecules
First Named Inventor/Applicant Name:	Stephen J. Baker
Customer Number:	43850
Filer:	Jeffry S. Mann/Candida Rubalcaba-Rivera
Filer Authorized By:	Jeffry S. Mann
Attorney Docket Number:	064507-5014US01
Receipt Date:	18-MAY-2009
Filing Date:	16-AUG-2006
Time Stamp:	17:32:42
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	3810
Deposit Account	500310
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		response5014us01.pdf	147107 bb01f9f0dab24fc7d2cb1b3cd38d71f5cbd2b6f1	yes	12

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	12

Warnings:					
Information:					
2	Extension of Time	eot5014us01.pdf	27102 71a0383c60c0e548cc28a0301119f5a007c5929c	no	1
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	30163 42ee4a658eade691c8331a74bc9ad1b2061ea0bf	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	204372		

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.

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
11/505,591	08/16/2006	

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 05/18/2009	(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))	* 23	Minus	** 197	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 1	Minus	***21	= 0	X $110 =	0	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	0	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	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:
/LAMONT MCLAUCHLIN/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/505,591	08/16/2006	Stephen J. Baker	064507-5014US01	5739

43850 7590 01/27/2009

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One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

EXAMINER	
SHIAO, REI TSANG	
ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
01/27/2009	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	11/505,591	BAKER ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *121 and 193-214* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121 and 193-214* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ 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:

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/7/07, 6/21/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application claims benefit of the provisional application: 60/755,227 with a filing date 12/30/2005; and 60/746,361 with a filing date 05/03/2006.

2. Amendment of claim 121, cancellation of claims 1-120 and 122-192, and addition of claims 193-214 in the amendment filed on December 03, 2008 is acknowledged. Claims 121 and 193-214 are pending in the application. No new matter is found. Since the newly added claims 193-214 are commensurate with the scope of the invention, claims 121 and 193-214 are prosecuted in the case.

Information Disclosure Statement

3. Applicant's Information Disclosure Statements, filed on May 07, 2007 and June 21, 2007 has been considered. Please refer to Applicant's copies of the 1449's submitted herein.

Responses to Election/Restriction

4. Applicant's election of Group XIII claims 121-136 (now are 121 and 193-214) in the reply filed on December 03, 2008 is acknowledged. Election of a species, i.e., 1, 3-dihydro-5-fluoro- 1-hydroxy-2, 1-benzoxaborole, is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 121 and 193-214 are pending in the application. The scope of the invention of the elected subject matter is as follows.

Claims 121 and 193-214 are drawn to a pharmaceutical formulation comprising a compound 1, 3-dihydro-5-fluoro- 1-hydroxy-2, 1-benzoxaborole or a salt thereof.

Claims 121 and 193-214 are prosecuted in the case.

The requirement is still deemed proper and therefore is made FINAL.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 195 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the instant anti-aging agent selected from niacinamide and acne-treating agent is selected from salicylic acid, does not reasonably provide enablement for instant anti-aging agent or acne-treating agent is not limited (i.e., no named compounds). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first

paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case:

The nature of the invention

The nature of the invention is a formulation, wherein the anti-aging agent or acne-treating agent is not limited (i.e., no named compounds), see claim 195.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is Austin et al. US 5,880,188, it discloses similar compositions or formulation, see column 28.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is that anti-aging agent selected from niacinamide and acne-treating agent is selected from salicylic acid, see page 168 of the specification. There is no data present in the instant anti-aging agent and acne-treating agent, which are not limited.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include any anti-aging agent and acne-treating agent, which are not limited.

The quantity or experimentation needed and the level of skill in the art

While the level of the skill in the chemical arts is high, it would require undue experimentation of one of ordinary skill in the art to resolve any anti-aging agent and acne-treating agent, which are not limited. There is no guidance or working examples present for constitutional any anti-aging agent and acne-treating agent, which are not limited. Incorporation of the limitation of the limitation of anti-aging agent and acne-treating agent (e.g., niacinamide or salicylic acid) into claim 195 would overcome this rejection.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

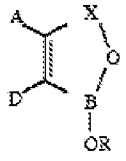
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 121 and 193-214 are rejected under 35 U.S.C. 103(a) as being unpatentable over Austin et al. US 5,880,188 in view of Austin et al. CAS:124:234024.

Applicants claim a pharmaceutical formulation (i.e., compositions) comprising (a)a compound 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole or a salt, and (b) a pharmaceutical acceptable excipient, see claim 121.

Determination of the scope and content of the prior art (MPEP §2141.01)

Austin et al. '188 discloses a composition (i.e., formulation) comprising a carrier and a fungicide oxaborate compound of formula (I), i.e., 

, wherein the variable A and D together form a 6-membered fused ring (i.e., benzene) which is substituted with a halogen (i.e., fluoro or bromo), the variable R represents hydrogen, the variable X represents –CR1R2 and R1 or R2 independently represents hydrogen, see lines 42-53 of column 28. The carrier may be a solid but is preferably a liquid-medium and the biocide composition is preferably a solution, suspension or emulsion of the oxaborole in a liquid medium, see lines 1-5 in column 5.

Austin et al. '124 disclose the instant compound 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole as fungicide, see RN: 174671-46-6.

Determination of the difference between the prior art and the claims (MPEP §2141.02)

The difference between instant claims and Austin et al. is that the Austin et al.

using 5- and 6-fluoro or bromo-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, while the instant claim is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

Austin et al. compositions inherently overlap with the instant invention.

Finding of prima facie obviousness-rational and motivation (MPEP §2142-2143)

One having ordinary skill in the art would find the claims 121 and 193-214 prima facie obvious because one would be motivated to employ the compositions of Austin et al. to obtain instant formulation comprising 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole and pharmaceutical acceptable excipient. Dependent claims 193-214 are also rejected along with claim 121 under 35 U.S.C. 103(a).

The motivation to make the claimed compounds derived from the known compounds/compositions would possess similar activity (i.e., fungicide or treating fungal infection) to that which is claimed in the reference.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rei-tsang Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO /

Rei-tsang Shiao, Ph.D.
Primary Examiner
Art Unit 1626

January 21, 2009

Notice of References Cited	Application/Control No. 11/505,591	Applicant(s)/Patent Under Reexamination BAKER ET AL.	
	Examiner REI-TSANG SHIAO	Art Unit 1626	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,880,188	03-1999	Austin et al.	524/109
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Austin et al., 1996, CAS:124:234024.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
11/505,591	BAKER ET AL.
Examiner	**Art Unit**
REI-TSANG SHIAO	1626

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date								
Final	Original	1/22/09								
	121	√								
	193	√								
	194	√								
	195	√								
	196	√								
	197	√								
	198	√								
	199	√								
	200	√								
	201	√								
	202	√								
	203	√								
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	205	√								
	206	√								
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	208	√								
	209	√								
	210	√								
	211	√								
	212	√								
	213	√								
	214	√								

Claim		Date								
Final	Original									

Claim		Date								
Final	Original									

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/505,591	BAKER ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

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

BIB DATA SHEET

CONFIRMATION NO. 5739

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/505,591	08/16/2006 RULE	514	1626	064507-5014US01

APPLICANTS

Stephen J. Baker, Mountain View, CA;
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Siead Zegar, Orland Park, IL;
Yong-Kang Zhang, San Jose, CA;
Huchen Zhou, Shanghai, CHINA;

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

This appln claims benefit of 60/755,227 12/30/2005
and claims benefit of 60/746,361 05/03/2006
and is a CIP of 11/357,687 02/16/2006

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

UNITED STATES OF AMERICA PCT/US06/05542 02/16/2006

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
10/03/2006

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /REI-TSANG SHIAO/ Examiner's Signature	☐ Met after Allowance R.S Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	63	192	21

ADDRESS

MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105
UNITED STATES

TITLE

Boron-containing small molecules

		☐ All Fees

BIB (Rev. 05/07).

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	141	(558/288).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2009/01/22 09:26
L5	547	(514/64).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2009/01/22 09:26

1/22/2009 9:27:02 AM
C:\Documents and Settings\rshiao\My Documents\EAST\\default.wsp

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/505,591
Filing Date	August 16, 2006
First Named Inventor	Baker, Stephen J.
Art Unit	1626
Examiner Name	~~Unassigned~~ Reitsang Shiao
Attorney Docket Number	64507-5014-US01

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

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]

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]
	AA	Sudaxshina Murdan, "Drug Delivery to the Nail Following Topical Application," *International Journal of Pharmaceutics*, 236:1-26 (2002)	
	AB	S. J. Baker, *et al.*, "Progress on New Therapeutics for Fungal Nail Infections," *Annual Reports in Medicinal Chemistry*," 40:323-335 (2005)	

Examiner Signature	/Rei Tsang Shiao/ (01/21/2009)	Date Considered	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /RS/

Substitute for form 1449B/PTO

Complete if Known

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	11/505,591
Filing Date	August 16, 2006
First Named Inventor	Baker, Stephen J.
Art Unit	1626
Examiner Name	~~Unassigned~~ Reitsang Shiao
Attorney Docket Number	64507-5014-US01

(use as many sheets as necessary)

Sheet 1 of 1

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

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]
	AA	WO	2005/013892	A3	02-17-2005	Anacor Pharmaceuticals, Inc.	Claims 1-39	

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]

Examiner Signature	/Rei Tsang Shiao/ (01/21/2009)	Date Considered	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /RS/

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/505,591	BAKER ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

SEARCHED			
Class	Subclass	Date	Examiner
558	288	1/22/2009	R.S.
514	64	1/22/2009	R.S.

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STN structure, inventor names	12/11/2008	R.S.
EAST class/subclass	1/22/2009	R.S.
PALM inventor names	1/22/2009	R.S.

PRO/SB/05 (04-05)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	64507-5014-US01
First Inventor	BAKER, Stephen J.
Title	BORON-CONTAINING SMALL MOLECULES
Express Mail Label No.	EV670586133US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450**

1. ☒ **Fee Transmittal Form** (e.g., PTO/SB/17) *(Submit an original and a duplicate for fee processing)*
2. ☒ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☒ **Specification** [Total Pages 316] Both the claims and abstract must start on a new page *(For information on the preferred arrangement, see MPEP 608.01(a))*
4. ☒ **Drawing(s)** *(35 U.S. 113)* [*Total Sheets* 63]
5. ☐ **Oath or Declaration** [*Total Sheets* _____]
   a. ☐ Newly executed (original or copy)
   b. ☐ A copy from a prior application (37 CFR 1.63(d) *(for continuation/divisional with Box 18 completed)*
      i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☒ **Application Data Sheet.** See 37 CFR 1.76
7. ☐ **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape Table on CD
8. ☐ **Nucleotide and/or Amino Acid Sequence Submission** *(if applicable, items a. – c. are required)*
   a. ☐ Computer Readable Form CRF)
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ **Assignment Papers** (cover sheet & document(s))
   Name of Assignee _____
10. ☐ **37 CFR 3.73(b) Statement** *(when there is an assignee)* ☐ **Power of Attorney**
11. ☐ **English Translation Document** *(if applicable)*
12. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
13. ☐ **Preliminary Amendment**
14. ☒ **Return Receipt Postcard** (MPEP 503) *(Should be specifically itemized)*
15. ☐ **Certified Copy of Priority Document(s)** *(if foreign priority is claimed)*
16. ☐ **Nonpublication Request** under 35 U.S.C. 122(b)(2)(B)(i) Applicant must attach form PTO/SB/35 or equivalent.
17. ☐ Other: _____

18. ☐ If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following their title, or in an Application Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☒ Continuation-in-part (CIP) of prior application No. .....

Prior application information: *Examiner* _____ *Art Unit:* _____

19. CORRESPONDENCE ADDRESS

☒ The address associated with Customer Number: 43850 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature		Date	August 16, 2006	
Name (Print/Type)	Todd Esker		Registration No. Attorney/Agent	46,690

PTO/SB/17 (12-04)
Approved for use through 07/31/2006. OMB 0651-0032
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

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☒ Applicant claims small entity status. See 37 CFR 1.27

Total Amount of Payment ($) 6,625

Complete if Known	
Application Number	Not Yet Assigned
Filing Date	August 15, 2006
First Named Investor	BAKER, Stephen J.
Examiner Name	Not Yet Assigned
Art Unit	Not Yet Assigned
Attorney Docket No.	64507-5014-US01

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number **50-0310** Deposit Account Name: **Morgan, Lewis & Bockius LLP**

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims		Fee ($)		Fee Paid ($)	Multiple Dependent Claims	
192	- 20 or HP =	172	x	25	=	4,300	Fee ($1)	Fee Paid ($1)

HP = highest number of total claims paid for, if greater than 20

Indep. Claims		Extra Claims		Fee ($)		Fee Paid ($)
20	- 3 or HP =	17	x	100	=	1,700

HP = highest number of total claims paid for, if greater than 3

3. APPLICATION SIZE FEE

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).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee($)		Fee Paid ($)
318	- 100 =	218	/ 50 =	5 (round up to a whole number)	x	125	=	625

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other: _____	

SUBMITTED BY

Signature		Registration No. 46,690 (Attorney/Agent)	Telephone
Name (Print/Type)	Todd Esker		Date August 16, 2006

This collection of information is required by 37 CFR 1.136. 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 30 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, 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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PATENT APPLICATION

BORON-CONTAINING SMALL MOLECULES

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AS FILED WITH THE USPTO ON AUGUST 16, 2006

BORON-CONTAINING SMALL MOLECULES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is continuation-in-part of U.S. Patent Application 11/357,687 filed February 16, 2006, which is related to U.S. Provisional Patent Application 60/654,060 filed February 16, 2005, which is incorporated by reference in its entirety for all purposes.

BACKGROUND FOR THE INVENTION

[0002] Infections of the nail and hoof, known as ungual and/or periungual infections, pose serious problems in dermatology. These ungual and/or periungual can be caused by sources such as fungi, viruses, yeast, bacteria and parasites. Onychomycosis is an example of these serious ungual and/or periungual infections and is caused by at least one fungus. Current treatment for ungual and/or periungual infections generally falls into three categories: systemic administration of medicine; surgical removal of all or part of the nail or hoof followed by topical treatment of the exposed tissue; or topical application of conventional creams, lotions, gels or solutions, frequently including the use of bandages to keep these dosage forms in place on the nail or hoof. All of these approaches have major drawbacks. The following discussion is particularly directed to drawbacks associated with current treatment of ungual and/or periungual antifungal infections.

[0003] Long term systemic (oral) administration of an antifungal agent for the treatment of onychomycosis is often required to produce a therapeutic effect in the nail bed. For example, oral treatment with the antifungal compound terbinafine typically requires administration of 200 to 400 mg/day for 12 weeks before any significant therapeutic benefit is realized. Such long term, high dose systemic therapy can have significant adverse effects. For example, terbinafine has been reported to have liver toxicity effects and reduces testosterone levels in blood due to adverse effects on the testes. Patient compliance is a problem with such long term therapies especially those which involve serious adverse effects. Moreover, this type of long term oral therapy is inconvenient in the treatment of a horse or other ruminants

afflicted with fungal infections of the hoof. Accordingly, the risks associated with parenteral treatments generate significant disincentive against their use and considerable patient non-compliance.

[0004] Surgical removal of all or part of the nail followed by topical treatment also has severe drawbacks. The pain and discomfort associated with the surgery and the undesirable cosmetic appearance of the nail or nail bed represent significant problems, particularly for patients more sensitive to physical appearance. Generally, this type of treatment is not realistic for ruminants such as horses.

[0005] Topical therapy has significant problems too. Topical dosage forms such as creams, lotions, gels etc., can not keep the drug in intimate contact with the infected area for therapeutically effective periods of time. Bandages have been used to hold drug reservoirs in place in an attempt to enhance absorption of the pharmaceutical agent. However the bandages are thick, awkward, troublesome and generally lead to poor patient compliance.

[0006] Hydrophilic and hydrophobic film forming topical antifungal solutions have also been developed. These dosage forms provide improved contact between the drug and the nail. Topical formulations for fungal infection treatment have largely tried to deliver the drug to the target site (an infected nail bed) by diffusion across or through the nail.

[0007] Nail is more like hair than stratum corneum with respect to chemical composition and permeability. Nitrogen is the major component of the nail attesting to the nail's proteinaceous nature. The total lipid content of mature nail is 0.1-1.0%, while the stratum corneum lipid is about 10% w/w. The nail is 100-200 times thicker than the stratum corneum and has a very high affinity and capacity for binding and retaining antifungal drugs. Consequently little if any drug penetrates through the nail to reach the target site. Because of these reasons topical therapy for fungal infections have generally been ineffective.

[0008] Compounds known as penetration or permeation enhancers are well known in the art to produce an increase in the permeability of skin or other body membranes to a pharmacologically active agent. The increased permeability allows an increase in the rate at which the drug permeates through the skin and enters the blood stream. Penetration enhancers have been successful in overcoming the

impermeability of pharmaceutical agents through the skin. However, the thin stratum corneum layer of the skin, which is about 10 to 15 cells thick and is formed naturally by cells migrating toward the skin surface from the basal layer, has been easier to penetrate than nails. Moreover, known penetration enhancers have not proven to be useful in facilitating drug migration through the nail tissue.

[0009] Antimicrobial compositions for controlling bacterial and fungal infections comprising a metal chelate of 8-hydroxyquinoline and an alkyl benzene sulfonic acid have been shown to be efficacious due to the increased ability of the oleophilic group to penetrate the lipoid layers of micro-cells. The compounds however, do not effectively increase the ability to carry the pharmaceutically active antifungal through the cornified layer or stratum corneum of the skin. U.S. Pat. No. 4,602,011, West et al., Jul. 22, 1986; U.S. Pat. No. 4,766,113, West et al., Aug. 23, 1988.

[0010] Therefore, there is a need in the art for compounds which can effectively penetrate the nail. There is also need in the art for compounds which can effectively treat ungual and/or periungual infections. These and other needs are addressed by the current invention.

[0011] Aminoacyl-tRNA synthetases (ARS) are a family of essential enzymes that attach amino acids to the 3' terminal adenosine end of tRNAs, the charged tRNAs are then used by the translation machinery to synthesis proteins from mRNA. Although there are few exceptions, for example in Gram-positive bacteria and archaea, most organisms have at least one ARS for each amino acid. In the case of eukaryotes, they have two ARS, one is localized to the cytoplasm while the other ARS is located in the organelle(s). The ARS catalyzes two reactions, as outlined below, the first reaction adenylates the amino acid with ATP followed by its transfer to the 2'- or 3'- hydroxyl of the terminal adenosine of tRNA.

$$\text{Amino acid (AA)} + \text{ATP} \rightarrow \text{AA-AMP} + \text{PPi};$$

$$\text{AA-AMP} + \text{tRNA} \rightarrow \text{tRNA-AA} + \text{AMP}$$

[0012] The family of 20 ARS fall into two distinct structural classes as determined by their crystal structure. Class I, which have a Rossman like fold, include the ARS for the following amino acids-arginine, cysteine, glutamate, glutamine, isolelucine, leucine, lysine (in archaea and some bacteria), valine, methionine, tryptophan and

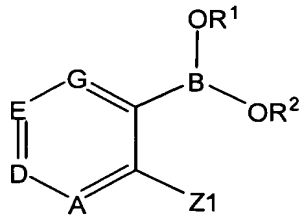
tyrosine. Class II ARS include the enzymes for the amino acids, alanine, asparagine, aspartate, glycine, histidine, lysine, phenylalanine, proline, serine and threonine. The ARS mediated reaction is the major checkpoint of specificity that ensures the correct amino acid is charged to its cognate tRNA. Since some amino acids only differ by a single methylene group, for example valine and isoleucine, it has been postulated that the specificity of the synthetic reaction alone can't explain the observed *in vivo* accuracy of tRNA charging. The synthetic active site should be able to exclude amino acids that are not close analogs of the cognate amino acid, but analogous amino acids pose a bigger problem. Therefore to increase specificity, proof-reading and editing must occur. So far nine ARS have been shown to have an editing mechanism that significantly reduces the frequency of mischarged tRNAs. The enzymes for the following amino acids have been shown to have editing activity-alanine, isoleucine, leucine, methionine, lysine, phenylalanine, proline, threonine and valine. These ARS can hydrolyse the incorrectly adenylated amino acid AA-AMP (pre-transfer editing) or the incorrectly charged tRNA (post-transfer editing). To date the isoleucyl, leucyl and valyl-tRNA synthetases have the best-characterized editing mechanisms; an additional structural domain called the connective polypeptide I (CP1) inserted in the synthetic domain has been shown to contain the editing active site. This is located more than 25Å away from the synthetic active site, which suggests that both the adenylated amino acid intermediate and amino acid tethered to the 3'end of the tRNA must be moved from the active site in the synthetic domain to the editing site for the reaction to be proof-read. It has been postulated that the 3'end of the charged tRNA is translocated in a similar manner to that of the proof-reading mechanism of DNA polymerases. Much less is known about the translocation of the adenylated amino acid. A similar CP1 domain is also present in the methionine and cysteine ARS enzymes, but it is much smaller than that found in the valine, isoleucine and leucine enzymes. Despite the absence of a direct homolog to the CP1-like domain in class II ARS, separate editing domains have been found in the enzymes for proline and threonine. Although editing is important to ensure the correct charging of tRNAs, it is not essential for viability and is not required for the synthesis of charged tRNAs. For example, in *Escherichia coli*, in which 10 amino acids in the editing domain of isoleucyl-tRNA synthetase were changed to alanine, the resulting mutant was still viable, although it did have many pleiotropic effects, including a noticeable cell growth defect.

[0013] In spite of significant homologies between human, bacterial and fungal ARS there are a number of compounds that have been developed as anti-infectives. The most notable example of an ARS inhibitor is the commercial antibiotic mupirocin (pseudomonic acid), which is sold under the label Bactroban. Mupirocin specifically inhibits bacterial isoleucyl-tRNA synthetases, while its activity against the human homolog is more than 1,000 times less active. Mupirocin binds specifically to the synthetic active site and mutants that are resistant to this drug have mutations in the synthetic domain of leucyl-tRNA synthetase. Likewise, reveromycin A inhibits the eukaryotic isoleucyl-tRNA synthetases: *Saccharomyces cerevisiae* resistance mutants have mutations in the synthetic domain. So far all attempts to develop better ARS inhibitors than mupirocin, an isoleucine-adenylate analogue, have relied on inhibiting the synthetic reactions.

[0014] Since it has been previously thought not to be essential for the synthesis of charged tRNAs, the editing domain of tRNA synthetases has not been thought a promising target for drug development. Data from mutational analysis of the ARS editing domains tend to suggest that inhibition of the editing mechanism leads only to an increase in mischarged tRNAs and does not lead to cell death. Compounds that are active against, and specific for, the editing domain of the tRNA synthetase would provide access to a new class of antimicrobial therapeutics to augment the arsenal of agents currently in use. Quite surprisingly, the present invention provides such compounds and methods of using these compounds.

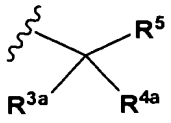
SUMMARY OF THE INVENTION

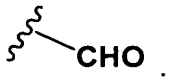
[0015] In one aspect, the invention provides a structure according to the following formula:



in which R^1 and R^2 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^1 and R^2, together with the atoms to which they are attached, can be optionally joined to form a 4- to 7-membered ring. Z1 is a member selected from



and


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R^{3a} and R^{4a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^5 is a member selected from halogen and OR^8. R^8 is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A is a member selected from CR^{9a} and N. D is a member selected from CR^{10a} and N. E is a member selected from CR^{11a} and N. G is a member selected from CR^{12a} and N. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R$*, $-S(O)_2NR$*R**, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. Each R* and R** are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{9a} and R^{10a}, along with the atoms to which they are attached, are optionally joined to form a ring. R^{10a} and R^{11a}, along with the atoms to which they are attached, are optionally joined to form a ring. R^{11a} and R^{12a}, along with the atoms to which they are attached, are optionally joined to form a ring. The combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] **FIG. 1** is a table of minimum inhibitory concentration (MIC) data of cyclic boronic esters against various fungi.

[0017] **FIG. 2A** displays minimum inhibitory concentration (MIC) for **C10**, ciclopirox, terbinafine, fluconazole and itraconazole (comparator drugs) against 19 test strains of fungi.

[0018] **FIG. 2B** displays minimum fungicidal concentration (MFC) for **C10**, ciclopirox, terbinafine and itraconazole (comparator drugs) against 2 test strains of fungi.

[0019] **FIG. 3** displays a comparison of Normalized **C10** and Ciclopirox Equivalent in Each Part of Nail Plate Samples after 14-day Treatment.

[0020] **FIG. 4** displays a comparison of **C10** and Ciclopirox Equivalent in Cotton Ball Supporting Bed Samples after 14-day Treatment.

[0021] **FIG. 5** displays the results of a placebo for **C10** (50:50 propylene glycol and ethyl acetate) applied per day over five days. Full carpet growth of the organism *T. rubrum* was observed.

[0022] **FIG. 6** displays the results of a 40 $\mu L/cm^2$ aliquot of **C10** 10% w/v solution applied per day over five days. Zones of inhibition (in the order of the cells shown in the figure) of 100%, 67%, 46%, 57%, 38% and 71% were observed for the growth of *T. rubrum*. Green arrow indicates the measurement of zone of inhibition.

[0023] **FIG. 7** displays the results of a 40 $\mu L/cm^2$ aliquot of **C10** 10% w/v solution applied per day over five days. Zones of inhibition (in the order of the cells shown in the figure) of 74%, 86%, 100%, 82%, 100% and 84% were observed for the growth of *T. rubrum*.

[0024] **FIG. 8** displays the results of a 40 $\mu L/cm^2$ aliquot of 8% ciclopirox in w/w commercial lacquer applied per day over five days. No zone of inhibition observed; full carpet growth of *T. rubrum*.

[0025] **FIG. 9** displays the results of a 40 $\mu L/cm^2$ aliquot of 5% amorolfine w/v in commercial lacquer applied per day over five days. No zone of inhibition observed; full carpet growth of *T. rubrum*.

[0026] **FIG. 10** Amino acid sequences for leucyl-tRNA synthetase editing domains and nucleotide sequences for tRNA-Leu and tRNA-Ile. (A) Amino acid sequences for leucyl-tRNA synthetase editing domain from S.cerivisiae in wild type

(SEQ ID NO:1) and over-expressing form (SEQ ID NO: 2); (B) Amino acid sequences for leucyl-tRNA synthetase editing domains from indicated species; (C) Genomic nucleotide sequence for tRNA-leu and tRNA-ile from S.cerivisiae; in one embodiment of the invention, an aminoacyl tRNA synthetase will bind to the transcribed and methylated products for which these sequences serve as a template; (D) tRNA-Leu nucleotide sequences from indicated species.

[0027] **FIG. 11** displays structures of cyclic boronic esters.

[0028] **FIG. 12** displays different structures for portions of the compounds of the invention.

[0029] **FIG. 13** Effect of ATP on binding of **C10** to cdc60. The binding assay was conducted with an initial **[C10]** concentration of approximately 72-79μM (pre-equilibrium).

[0030] **FIG. 14** Binding curve of cdc60 against concentration of free **[C10]**.

[0031] **FIG. 15** Data from PPi exchange reaction experiment to determine rate of editing in the presence and absence of **C10**.

[0032] **FIG. 16** Data from an aminoacylation experiment showing the effect of **C10** at different concentrations on the aminoacylation of $tRNA^{leu}$.

[0033] **FIG. 17** Results from post transfer editing assay conducted in *S. cerevisiae* at differing concentrations of **C10** across a range of time points.

[0034] **FIG. 18** displays the names of exemplary compounds of the invention.

[0035] **FIG. 19** displays exemplary compounds of the invention.

[0036] **FIG. 20** displays exemplary compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions and Abbreviations

[0037] The abbreviations used herein generally have their conventional meaning within the chemical and biological arts.

[0038] "Compound of the invention," as used herein refers to the compounds discussed herein, pharmaceutically acceptable salts and prodrugs of these compounds.

[0039] "Boron containing compounds", as used herein, refers to the compounds of the invention that contain boron as part of their chemical formula.

[0040] MIC, or minimum inhibitory concentration, is the point where the compound stops more than 50% of cell growth, preferably 60% of cell growth, preferably 70% of cell growth, preferably 80% of cell growth, preferably 90% of cell growth, relative to an untreated control.

[0041] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents, which would result from writing the structure from right to left, *e.g.*, $-CH_2O-$ is intended to also recite $-OCH_2-$.

[0042] The term "poly" as used herein means at least 2. For example, a polyvalent metal ion is a metal ion having a valency of at least 2.

[0043] "Moiety" refers to the radical of a molecule that is attached to another moiety.

[0044] The symbol ~~~, whether utilized as a bond or displayed perpendicular to a bond, indicates the point at which the displayed moiety is attached to the remainder of the molecule.

[0045] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C_1-C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below, such as

"heteroalkyl." Alkyl groups that are limited to hydrocarbon groups are termed "homoalkyl".

[0046] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified, but not limited, by –$CH_2CH_2CH_2CH_2$-, and further includes those groups described below as "heteroalkylene." Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0047] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[0048] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom. In an exemplary embodiment, the heteroatoms can be selected from the group consisting of B, O, N and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) B, O, N and S may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, -CH_2-CH_2-O-CH_3, -CH_2-CH_2-NH-CH_3, -CH_2-CH_2-N(CH_3)-CH_3, -CH_2-S-CH_2-CH_3, -CH_2-CH_2,-S(O)-CH_3, -CH_2-CH_2-S(O)$_2$-CH_3, -CH=CH-O-CH_3, -CH_2-CH=N-OCH_3, and –CH=CH-N(CH_3)-CH_3. Up to two heteroatoms may be consecutive, such as, for example, -CH_2-NH-OCH_3. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH_2-CH_2-S-CH_2-CH_2- and –CH_2-S-CH_2-CH_2-NH-CH_2-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.,* alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the

direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$.

[0049] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1 –(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 –piperazinyl, 2-piperazinyl, and the like.

[0050] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0051] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, substituent that can be a single ring or multiple rings (preferably from 1 to 3 rings), which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms. In an exemplary embodiment, the heteroatom is selected from B, N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, 6-quinolyl,

dioxaborolane, dioxaborinane and dioxaborepane. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0052] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[0053] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0054] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) are generically referred to as "alkyl group substituents," and they can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and –NO_2 in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R", R"' and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, *e.g.*, aryl substituted with 1-3 halogens, substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"' and R"" groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to

include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (*e.g.*, $-CF_3$ and $-CH_2CF_3$) and acyl (*e.g.*, $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0055] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are generically referred to as "aryl group substituents." The substituents are selected from, for example: halogen, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, $-OC(O)R'$, $-C(O)R'$, $-CO_2R'$, -CONR'R", $-OC(O)NR'R"$, $-NR"C(O)R'$, $-NR'-C(O)NR"R"'$, $-NR"C(O)_2R'$, $-NR-C(NR'R"R"')=NR""$, $-NR-C(NR'R")=NR'"$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -CN and $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R"' and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"' and R"" groups when more than one of these groups is present.

[0056] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-T-C(O)-(CRR')_q-U-$, wherein T and U are independently –NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, wherein A and B are independently –CRR'-, -O-, -NR-, -S-, -S(O)-, $-S(O)_2-$, $-S(O)_2NR'-$ or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X-(CR"R"')_d-$, where s and d are independently integers of from 0 to 3, and X is –O-, -NR'-, -S-, -S(O)-, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituents R, R', R" and R"' are preferably independently selected from hydrogen or substituted or unsubstituted (C_1-C_6)alkyl.

[0057] "Ring" as used herein, means a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. A ring includes fused ring moieties. The number of atoms in a ring is typically defined by the number of members in the ring. For example, a "5- to 7-membered ring" means there are 5 to 7 atoms in the encircling arrangement. The ring optionally included a heteroatom. Thus, the term "5- to 7-membered ring" includes, for example pyridinyl and piperidinyl. The term "ring" further includes a ring system comprising more than one "ring", wherein each "ring" is independently defined as above.

[0058] As used herein, the term "heteroatom" includes atoms other than carbon (C) and hydrogen (H). Examples include oxygen (O), nitrogen (N) sulfur (S), silicon (Si), germanium (Ge), aluminum (Al) and boron (B).

[0059] The symbol "R" is a general abbreviation that represents a substituent group that is selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted heterocycloalkyl groups.

[0060] The term "derived from" includes its plain language meaning and also refers to a molecule that is 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80%, 75%, 70%, 65%, or 60% homologous to a referenced molecule. The molecules referred to in this definition include chains of RNA or DNA, oligonucleotides, polypeptides, or proteins of any length and composition.

[0061] The term "immunological marker" includes oligonucleotides, proteins, antibodies, peptides, polypeptides, enzymes, or any other molecule able to induce an immune response in appropriate animals or cells or to bind with specific antibodies.

[0062] The term "noncognate" is meant to encompass both the singular and plural forms of the word, i.e. the phrase "noncognate amino acid" comprises one or more amino acids.

[0063] By "effective" amount of a drug, formulation, or permeant is meant a sufficient amount of a active agent to provide the desired local or systemic effect. A

"Topically effective," "Cosmetically effective," "pharmaceutically effective," or "therapeutically effective" amount refers to the amount of drug needed to effect the desired therapeutic result.

[0064] "Topically effective" refers to a material that, when applied to the skin, nail, hair, claw or hoof produces a desired pharmacological result either locally at the place of application or systemically as a result of transdermal passage of an active ingredient in the material.

[0065] "Cosmetically effective" refers to a material that, when applied to the skin, nail, hair, claw or hoof, produces a desired cosmetic result locally at the place of application of an active ingredient in the material.

[0066] The term "pharmaceutically acceptable salts" is meant to include salts of the compounds of the invention which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science 66: 1-19 (1977)). Certain specific compounds of the present invention

contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0067] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compounds in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0068] In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds or complexes described herein readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment.

[0069] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0070] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are encompassed within the scope of the present invention.

[0071] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0072] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" refers to any formulation or carrier medium that provides the

appropriate delivery of an effective amount of a active agent as defined herein, does not interfere with the effectiveness of the biological activity of the active agent, and that is sufficiently non-toxic to the host or patient. Representative carriers include water, oils, both vegetable and mineral, cream bases, lotion bases, ointment bases and the like. These bases include suspending agents, thickeners, penetration enhancers, and the like. Their formulation is well known to those in the art of cosmetics and topical pharmaceuticals. Additional information concerning carriers can be found in Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott, Williams & Wilkins (2005) which is incorporated herein by reference.

[0073] "Pharmaceutically acceptable topical carrier" and equivalent terms refer to pharmaceutically acceptable carriers, as described herein above, suitable for topical application. An inactive liquid or cream vehicle capable of suspending or dissolving the active agent(s), and having the properties of being nontoxic and non-inflammatory when applied to the skin, nail, hair, claw or hoof is an example of a pharmaceutically-acceptable topical carrier. This term is specifically intended to encompass carrier materials approved for use in topical cosmetics as well.

[0074] The term "pharmaceutically acceptable additive" refers to preservatives, antioxidants, fragrances, emulsifiers, dyes and excipients known or used in the field of drug formulation and that do not unduly interfere with the effectiveness of the biological activity of the active agent, and that is sufficiently non-toxic to the host or patient. Additives for topical formulations are well-known in the art, and may be added to the topical composition, as long as they are pharmaceutically acceptable and not deleterious to the epithelial cells or their function. Further, they should not cause deterioration in the stability of the composition. For example, inert fillers, anti-irritants, tackifiers, excipients, fragrances, opacifiers, antioxidants, gelling agents, stabilizers, surfactant, emollients, coloring agents, preservatives, buffering agents, other permeation enhancers, and other conventional components of topical or transdermal delivery formulations as are known in the art.

[0075] The terms "enhancement," "penetration enhancement" or "permeation enhancement" relate to an increase in the permeability of the skin, nail, hair, claw or hoof to a drug, so as to increase the rate at which the drug permeates through the skin, nail, hair, claw or hoof. The enhanced permeation effected through the use of such

enhancers can be observed, for example, by measuring the rate of diffusion of the drug through animal or human skin, nail, hair, claw or hoof using a diffusion cell apparatus. A diffusion cell is described by Merritt et al. Diffusion Apparatus for Skin Penetration, *J of Controlled Release*, 1 (1984) pp. 161-162. The term "permeation enhancer" or "penetration enhancer" intends an agent or a mixture of agents, which, alone or in combination, act to increase the permeability of the skin, nail, hair or hoof to a drug.

[0076] The term "excipients" is conventionally known to mean carriers, diluents and/or vehicles used in formulating drug compositions effective for the desired use.

[0077] The term "topical administration" refers to the application of a pharmaceutical agent to the external surface of the skin, nail, hair, claw or hoof, such that the agent crosses the external surface of the skin, nail, hair, claw or hoof and enters the underlying tissues. Topical administration includes application of the composition to intact skin, nail, hair, claw or hoof, or to an broken, raw or open wound of skin, nail, hair, claw or hoof. Topical administration of a pharmaceutical agent can result in a limited distribution of the agent to the skin and surrounding tissues or, when the agent is removed from the treatment area by the bloodstream, can result in systemic distribution of the agent.

[0078] The term "transdermal delivery" refers to the diffusion of an agent across the barrier of the skin, nail, hair, claw or hoof resulting from topical administration or other application of a composition. The stratum corneum acts as a barrier and few pharmaceutical agents are able to penetrate intact skin. In contrast, the epidermis and dermis are permeable to many solutes and absorption of drugs therefore occurs more readily through skin, nail, hair, claw or hoof that is abraded or otherwise stripped of the stratum corneum to expose the epidermis. Transdermal delivery includes injection or other delivery through any portion of the skin, nail, hair, claw or hoof or mucous membrane and absorption or permeation through the remaining portion. Absorption through intact skin, nail, hair, claw or hoof can be enhanced by placing the active agent in an appropriate pharmaceutically acceptable vehicle before application to the skin, nail, hair, claw or hoof. Passive topical administration may consist of applying the active agent directly to the treatment site in combination with emollients or penetration enhancers. As used herein, transdermal delivery is intended to include

delivery by permeation through or past the integument, i.e. skin, nail, hair, claw or hoof.

[0079] The term "microbial infection" refers to any infection of a host tissue by an infectious agent including, but not limited to, viruses, bacteria, mycobacteria, fungus and parasites (see, *e.g.,* Harrison's Principles of Internal Medicine, pp. 93-98 (Wilson *et al.*, eds., 12th ed. 1991); Williams *et al., J. of Medicinal Chem.* **42**:1481-1485 (1999), herein each incorporated by reference in their entirety).

[0080] "Biological medium," as used herein refers to both *in vitro* and *in vivo* biological milieus. Exemplary *in vitro* "biological media" include, but are not limited to, cell culture, tissue culture, homogenates, plasma and blood. *In vivo* applications are generally performed in mammals, preferably humans.

[0081] "Inhibiting" and "blocking," are used interchangeably herein to refer to the partial or full blockade of an editing domain of a tRNA synthetase.

[0082] "Ventral/intermediate center" as used herein refers to powdered nail samples drilled from the center of the inner surface (facing the nail bed) approximately 0.3 - 0.5 mm in depth to the surface. The area is beneath the dosed site of the nail place but does not include dosed surface (dorsal nail surface).

[0083] "Ventral/intermediate center" as used herein refers to the immediate area of dosed site.

[0084] "Remainder nail" as used herein refers to the remaining part of the nail that has not been dosed.

[0085] "Supporting bed" as used herein refers to the cotton ball placed within the Teflon chamber of the diffusion cell to provide moisture to the nail plate and also to receive chemicals penetrating through the nail plate.

[0086] "Surfacing washing" as used herein refers to ethanol (or other organic solvents) and soap/water washing on the surface of the dosed site.

[0087] "Cell washing" as used herein, refers to ethanol (or other organic solvents) and soap / water wash of the inside of the diffusion cell.

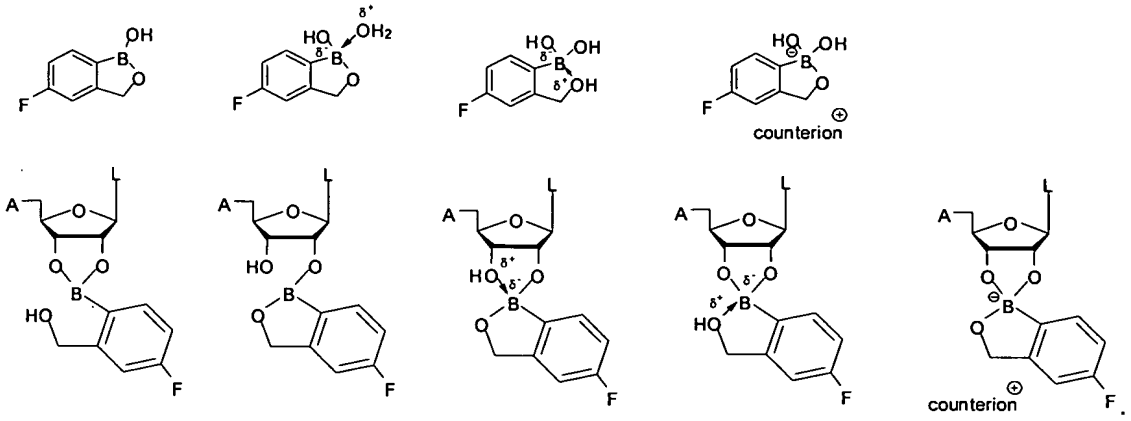
[0088] A "human nail unit", as defined herein, can be the nail plate, the nail bed, proximal nail fold, lateral nail fold and combinations thereof.

[0089] The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include triflate, chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

[0090] The term "amino-protecting group" means a protecting group suitable for preventing undesired reactions at an amino nitrogen. Representative amino-protecting groups include, but are not limited to, formyl; acyl groups, for example alkanoyl groups, such as acetyl, trichloroacetyl or trifluoroacetyl; alkoxycarbonyl groups, such as tert-butoxycarbonyl (Boc); arylmethoxycarbonyl groups, such as benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc); arylmethyl groups, such as benzyl (Bn), trityl (Tr), and 1,1-di-(4'-methoxyphenyl)methyl; silyl groups, such as trimethylsilyl (TMS) and tert-butyldimethylsilyl (TBS); and the like.

[0091] The term "hydroxy-protecting group" means a protecting group suitable for preventing undesired reactions at a hydroxy group. Representative hydroxy-protecting groups include, but are not limited to, alkyl groups, such as methyl, ethyl, and tert-butyl; acyl groups, for example alkanoyl groups, such as acetyl; arylmethyl groups, such as benzyl (Bn), p-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), and diphenylmethyl (benzhydryl, DPM); silyl groups, such as trimethylsilyl (TMS) and tert-butyldimethylsilyl (TBS); and the like.

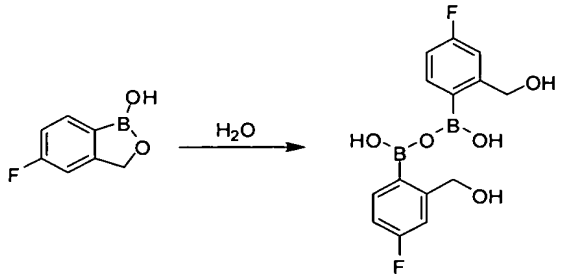
[0092] Boron is able to form dative bonds with oxygen, sulfur or nitrogen under some circumstances in this invention. Dative bonds are usually weaker than covalent bonds. In situations where a boron is covalently bonded to at least one oxygen, sulfur or nitrogen, and is at the same time datively bonded to an oxygen, sulfur or nitrogen, respectively, the dative bond and covalent bond between the boron and the two identical heteroatoms can interconvert or be in the form of a resonance hybrid. There is potential uncertainty surrounding the exact nature and extent of electron sharing in these situations. The structures supplied are not intended to include any and all possible bonding scenarios between boron and the atom to which it is bound. Non limiting examples of these bonds are as follows:



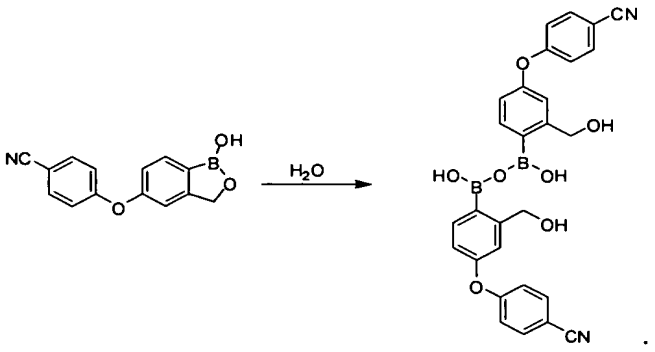
[0093] "Salt counterion", as used herein, refers to positively charged ions that associate with a compound of the invention when the boron is fully negatively or partially negatively charged. Examples of salt counterions include H^+, H_3O^+, ammonium, potassium, calcium, magnesium and sodium.

[0094] The compounds comprising a boron bonded to a carbon and three heteroatoms (such as three oxygens described in this section) can optionally contain a fully negatively charged boron or partially negatively charged boron, due to the nature of the dative bond between the boron and one of the oxygens. Due to the negative charge, a positively charged counterion may associate with this compound, thus forming a salt. Examples of positively charged counterions include H^+, H_3O^+, calcium, sodium, ammonium, potassium. The salts of these compounds are implicitly contained in descriptions of these compounds.

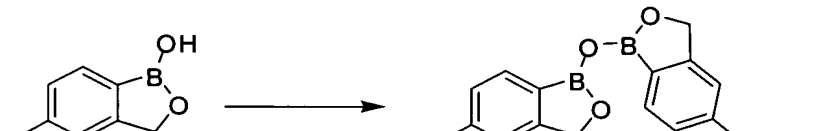
[0095] The present invention also encompasses compounds that are poly- or multi-valent species, including, for example, species such as dimers, trimers, tetramers and higher homologs of the compounds of use in the invention or reactive analogues thereof. For example, dimers of C10 can form under the following conditions:



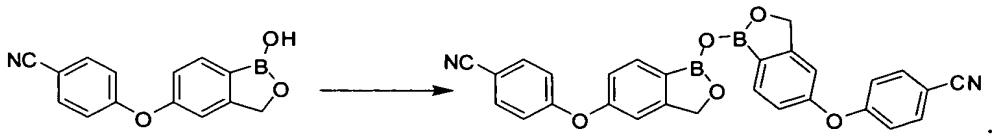
In another example, dimers of C17 can form under the following conditions:



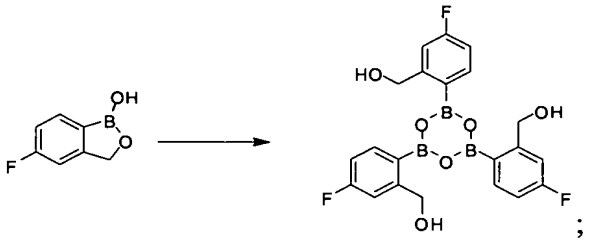
[0096] The present invention also encompasses compounds that are anhydrides of the cyclic boronic esters are synthesized by subjecting these compounds to dehydrating conditions. Examples of these anhydrides are provided below:



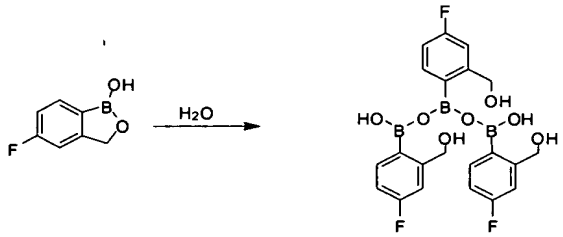
and

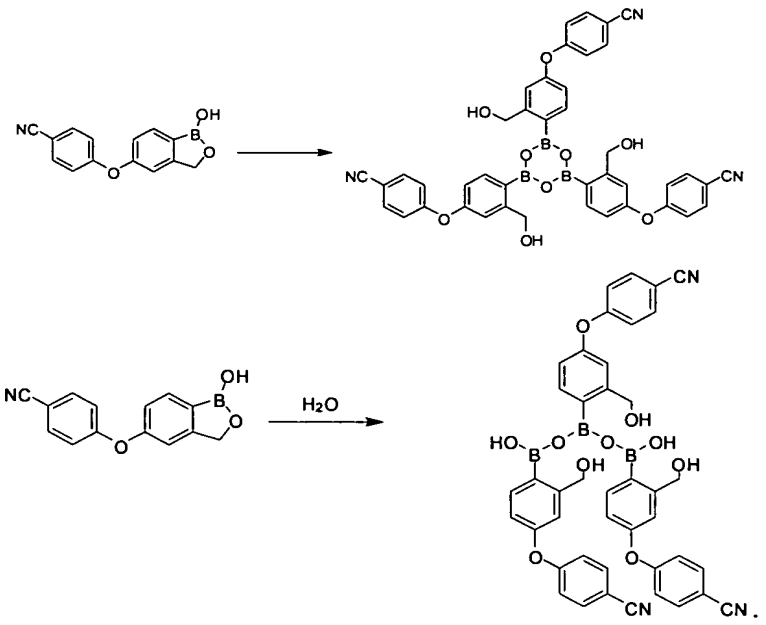


[0097] Trimers of the compounds of the invention are also produced. For example, trimers of acyclic boronic esters can be formed as follows:

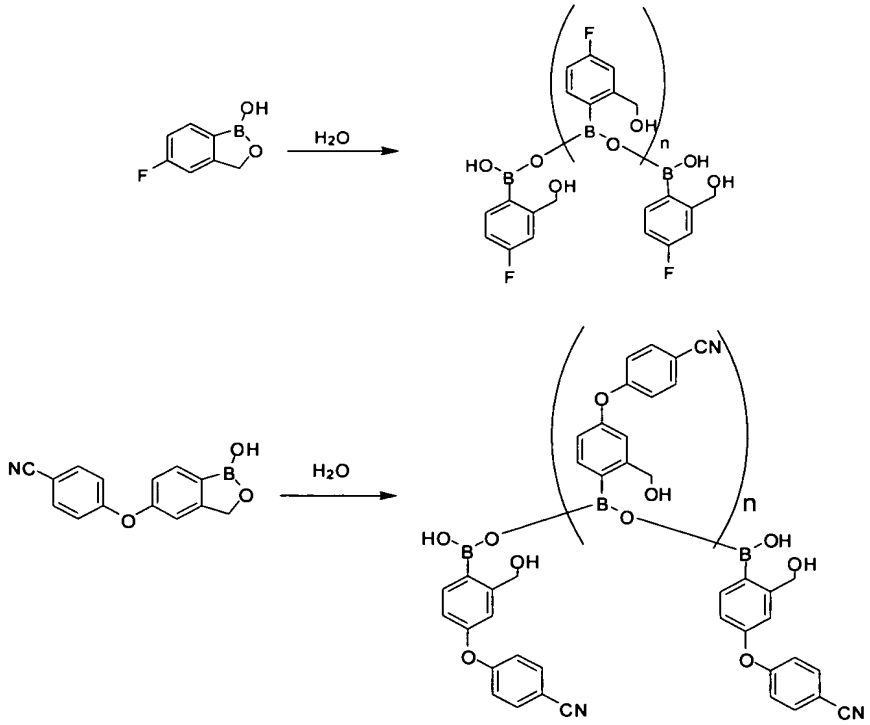


;





[0098] Polymers of the compounds of the invention are also produced through the removal of certain protecting groups in strong acid. For example, trimers of acyclic boronic esters can be formed as follows:



[0099] Also of use in the present invention are compounds that are poly- or multi-valent species, including, for example, species such as dimers, trimers, tetramers and higher homologs of the compounds of use in the invention or reactive analogues

thereof. The poly- and multi-valent species can be assembled from a single species or more than one species of the invention. For example, a dimeric construct can be "homo-dimeric" or "heterodimeric." Moreover, poly- and multi-valent constructs in which a compound of the invention or a reactive analogue thereof, is attached to an oligomeric or polymeric framework (e.g., polylysine, dextran, hydroxyethyl starch and the like) are within the scope of the present invention. The framework is preferably polyfunctional (i.e. having an array of reactive sites for attaching compounds of use in the invention). Moreover, the framework can be derivatized with a single species of the invention or more than one species of the invention.

[0100] Moreover, the present invention includes the use of compounds within the motif set forth in the formulae contained herein, which are functionalized to afford compounds having water-solubility that is enhanced relative to analogous compounds that are not similarly functionalized. Thus, any of the substituents set forth herein can be replaced with analogous radicals that have enhanced water solubility. For example, it is within the scope of the invention to replace a hydroxyl group with a diol, or an amine with a quaternary amine, hydroxy amine or similar more water-soluble moiety. In a preferred embodiment, additional water solubility is imparted by substitution at a site not essential for the activity towards the editing domain of the compounds set forth herein with a moiety that enhances the water solubility of the parent compounds. Methods of enhancing the water-solubility of organic compounds are known in the art. Such methods include, but are not limited to, functionalizing an organic nucleus with a permanently charged moiety, *e.g.*, quaternary ammonium, or a group that is charged at a physiologically relevant pH, *e.g.* carboxylic acid, amine. Other methods include, appending to the organic nucleus hydroxyl- or amine-containing groups, e.g. alcohols, polyols, polyethers, and the like. Representative examples include, but are not limited to, polylysine, polyethyleneimine, poly(ethyleneglycol) and poly(propyleneglycol). Suitable functionalization chemistries and strategies for these compounds are known in the art. See, for example, Dunn, R. L., et al., Eds. POLYMERIC DRUGS AND DRUG DELIVERY SYSTEMS, ACS Symposium Series Vol. 469, American Chemical Society, Washington, D.C. 1991.

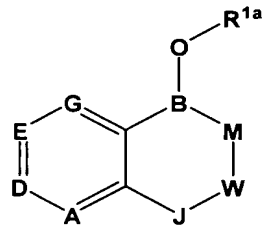
II. Introduction

[0101] The present invention provides novel boron compounds and methods for the preparation of these molecules. The invention further provides boron compounds as analogs comprising a functional moiety, such as a drug moiety and methods of use for said analogs.

III. The Compounds

III.a) Cyclic Boronic Esters

[0102] In a first aspect, the invention provides a compound having a structure according to Formula I:

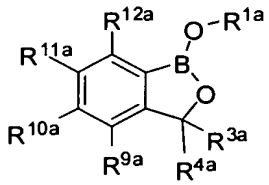


(I)

wherein B is boron. R^{1a} is a member selected from a negative charge, a salt counterion, H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. M is a member selected from oxygen, sulfur and NR^{2a}. R^{2a} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. J is a member selected from $(CR^{3a}R^{4a})_{n1}$ and CR^{5a}. R^{3a}, R^{4a}, and R^{5a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The index n1 is an integer selected from 0 to 2. W is a member selected from C=O (carbonyl), $(CR^{6a}R^{7a})_{m1}$ and CR^{8a}. R^{6a}, R^{7a}, and R^{8a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The index m1 is an integer selected from 0

and 1. A is a member selected from CR^{9a} and N. D is a member selected from CR^{10a} and N. E is a member selected from CR^{11a} and N. G is a member selected from CR^{12a} and N. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R^*$, $-S(O)_2NR^*R^{**}$, -C(O)R*, -C(O)OR*, -C(O)NR*R**, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. Each R* and R** are members independently selected from H, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3. A member selected from R^{3a}, R^{4a} and R^{5a} and a member selected from R^{6a}, R^{7a} and R^{8a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{3a} and R^{4a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{6a} and R^{7a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{9a} and R^{10a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{10a} and R^{11a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{11a} and R^{12a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

[0103] In an exemplary embodiment, the compound has a structure according to Formula (Ia):



(Ia).

[0104] In another exemplary embodiment, each R^{3a} and R^{4a} is a member independently selected from H, cyano, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted mercaptomethyl,

substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted indolyl and substituted or unsubstituted amido. In another exemplary embodiment, each R^{3a} and R^{4a} is a member independently selected from cyano, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted indolyl, substituted or unsubstituted amido.

[0105] In another exemplary embodiment, each R^{3a} and R^{4a} is a member selected from H, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted butyl, substituted or unsubstituted t-butyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl. In another exemplary embodiment, R^{3a} and R^{4a} is a member selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In another exemplary embodiment, R^{3a} is H and R^{4a} is a member selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In another exemplary embodiment, R^{3a} is H and R^{4a} H.

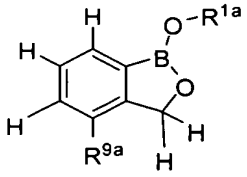
[0106] In another exemplary embodiment, each R^{9a}, R^{10a}, R^{11a} and R^{12a} is a member independently selected from H, OR*, NR*R**, SR*, -S(O)R*, -$S(O)_2$R*, -$S(O)_2$NR*R**, -C(O)R*, -C(O)OR*, -C(O)NR*R**, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or

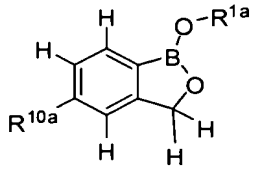
unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl. In an exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are selected from the previous list of substituents with the exception of -C(O)R*, -C(O)OR*, -C(O)NR*R**.

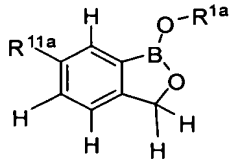
[0107] In another exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl,

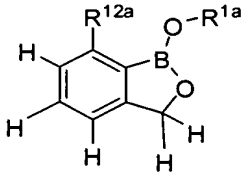
thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, 4-fluorobenzyloxy, unsubstituted phenyl, unsubstituted benzyl. In an exemplary embodiment, R^{9a} is H and R^{12a} is H.

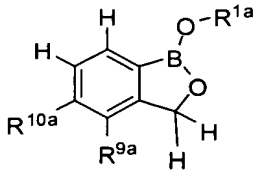
[0108] In an exemplary embodiment, the compound according to Formula (I) or Formula (Ia) is a member selected from:

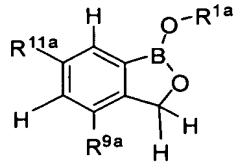

(Ib);

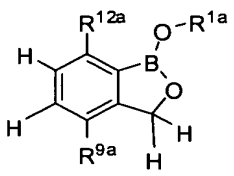
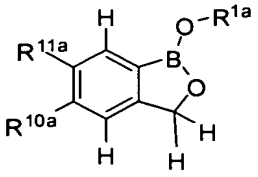
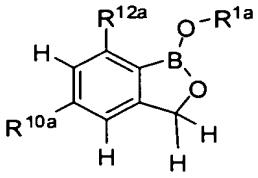
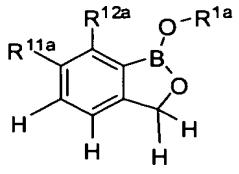
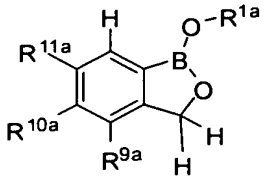
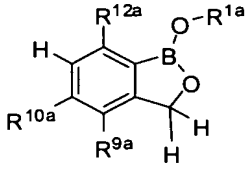
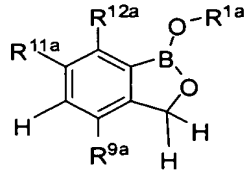
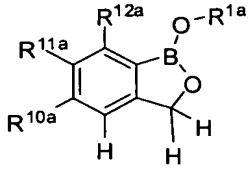

(Ic);


(Id);


(Ie);


(If);


(Ig);


(Ih);

(Ii);

(Ij);

(Ik);

(Il);

(Im);

(In);

(Io);

In an exemplary embodiment, the compound has a structure according to one of Formulae I-Io with substituent selections for R^{9a}, R^{10a}, R^{11a} and R^{12a} including all the possiblities contained in paragraph 106 except for H. In an exemplary embodiment, the compound has a structure according to one of Formulae Ib-Io with substituent selections for R^{9a}, R^{10a}, R^{11a} and R^{12a} including all the possiblities contained in paragraph 107 except for H.

[0109] In an exemplary embodiment, the compound has a formula according to Formulae (Ib)-(Ie) wherein R^{1a} is a member selected from H, a negative charge and a salt counterion and the remaining R group (R^{9a} in Ib, R^{10a} in Ic, R^{11a} in Id, and R^{12a} in Ie) is a member selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-

yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy and 4-fluorobenzyloxy.

[0110] In an exemplary embodiment, the compound has a formula according to Formulae (If)-(Ik) wherein R^{1a} is a member selected from H, a negative charge and a salt counterion and each of the remaining two R groups (R^{9a} and R^{10a} in If, R^{9a} and R^{11a} in Ig, R^{9a} and R^{12a} in Ih, R^{10a} and R^{11a} in Ii, R^{10a} and R^{12a} in Ij, R^{11a} and R^{12a} in Ik) is a member independently selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-

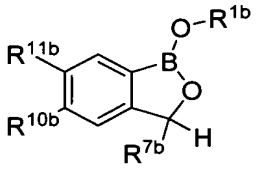
yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

[0111] In an exemplary embodiment, the compound has a formula according to Formulae (Il)-(Io) wherein R^{1a} is a member selected from H, a negative charge and a salt counterion and each of the remaining three R groups (R^{9a}, R^{10a}, R^{11a} in (Il), R^{9a}, R^{10a}, R^{12a} in (Im), R^{9a}, R^{11a}, R^{12a} in (In), R^{10a}, R^{11a}, R^{12a} in (Io)) is a member independently selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-

methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

[0112] In an exemplary embodiment, there is a proviso that the compound cannot be a member selected from Figure 11. In another exemplary embodiment, there is a proviso that the compound cannot be a member selected from C1-C40.

[0113] In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix):

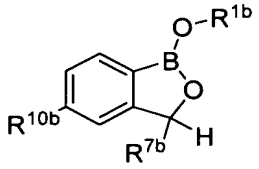


(Ix)

wherein R^{7b} is a member selected from H, methyl, ethyl and phenyl. R^{10b} is a member selected from H, OH, NH_2, SH, halogen, substituted or unsubstituted phenoxy, substituted or unsubstituted phenylalkyloxy, substituted or unsubstituted phenylthio and substituted or unsubstituted phenylalkylthio. R^{11b} is a member selected from H, OH, NH_2, SH, methyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenylalkyloxy, substituted or unsubstituted phenylthio and substituted or unsubstituted phenylalkylthio. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{1b} is a member selected from a negative charge, H and a salt counterion. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{10b} and R^{11b} are H. In another exemplary

embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein one member selected from R^{10b} and R^{11b} is H and the other member selected from R^{10b} and R^{11b} is a member selected from halo, methyl, cyano, methoxy, hydroxymethyl and p-cyanophenyloxy. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{10b} and R^{11b} are members independently selected from fluoro, chloro, methyl, cyano, methoxy, hydroxymethyl, and p-cyanophenyl. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{1b} is a member selected from a negative charge, H and a salt counterion; R^{7b} is H; R^{10b} is F and R^{11b} is H. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{11b} and R^{12b}, along with the atoms to which they are attached, are joined to form a phenyl group. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{1b} is a member selected from a negative charge, H and a salt counterion; R^{7b} is H; R^{10b} is 4-cyanophenoxy; and R^{11b} is H.

[0114] In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Iy)



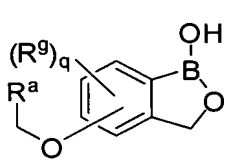
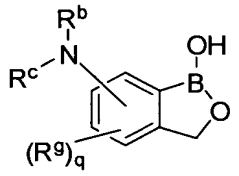
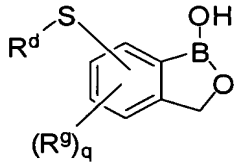
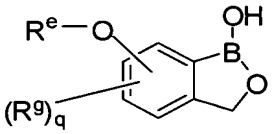
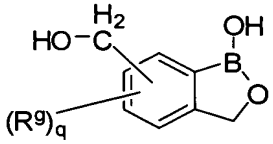
(Iy)

wherein R^{10b} is a member selected from H, halogen, CN and substituted or unsubstituted C_{1-4} alkyl.

[0115] In another exemplary embodiment, there is a proviso that a structure does not have the which is a member selected from Formulae (I) to (Io) at least one member selected from R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a} and R^{12a} is nitro, cyano or halogen. In another exemplary embodiment, there is a proviso that when M is oxygen, W is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A is CR^{9a}, D is CR^{10a}, E is CR^{11a}, G is CR^{12a}, the R^{9a} is not halogen, methyl, ethyl, or optionally joined with R^{10a} to form a phenyl ring; R^{10a} is not unsubstituted phenoxy, $C(CH_3)_3$, halogen, CF_3, methoxy, ethoxy, or optionally joined with R^{9a} to form a phenyl ring; R^{11a} is not halogen or

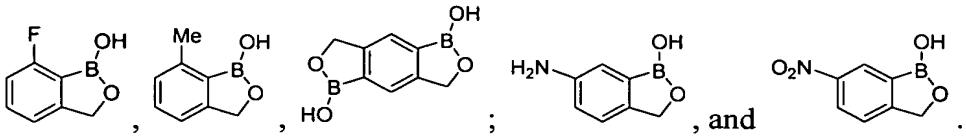
optionally joined with R^{10a} to form a phenyl ring; and R^{12a} is not halogen. In another exemplary embodiment, there is a proviso that when M is oxygen, W is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A is CR^{9a}, D is CR^{10a}, E is CR^{11a}, G1 is CR^{12a}, then neither R^{6a} nor R^{7a} are halophenyl. In another exemplary embodiment, there is a proviso that when M is oxygen, W is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A is CR^{9a}, D is CR^{10a}, E is CR^{11a}, G is CR^{12a}, and R^{9a}, R^{10a} and R^{11a} are H, then R^{6a}, R^{7a} and R^{12a} are not H. In another exemplary embodiment, there is a proviso that when M is oxygen wherein n1 is 1, J is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 0, A is CR^{9a}, D is CR^{10a}, E is CR^{11a}, G is CR^{12a}, R^{9a} is H, R^{10a} is H, R^{11a} is H, R^{6a} is H, R^{7a} is H, R^{12a} is H, then W is not C=O (carbonyl). In another exemplary embodiment, there is a proviso that when M is oxygen, W is CR^{5a}, J is CR^{8a}, A is CR^{9a}, D is CR^{10a}, E is CR^{11a}, G is CR^{12a}, R^{6a}, R^{7a}, R^{9a}, R^{10a}, R^{11a} and R^{12a} are H, then R^{5a} and R^{8a}, together with the atoms to which they are attached, do not form a phenyl ring.

[0116] In an exemplary embodiment, the compound of the invention has a structure which is a member selected from:

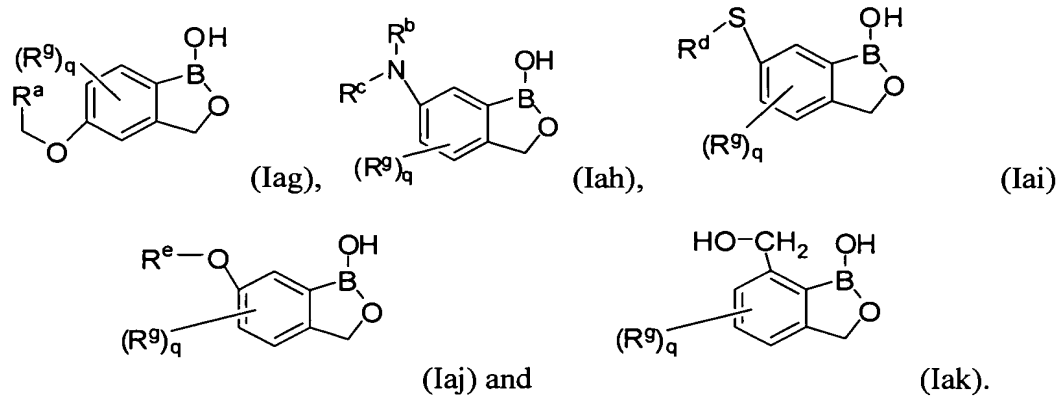

(Iab),

(Iac),

(Iad),

(Ia), and

(Iaf),

in which q is a number between 0 and 1. R^g is halogen. R^a, R^b, R^c, R^d and R^e are members independently selected from a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In an exemplary

embodiment, there is a proviso that the compound is not a member selected from

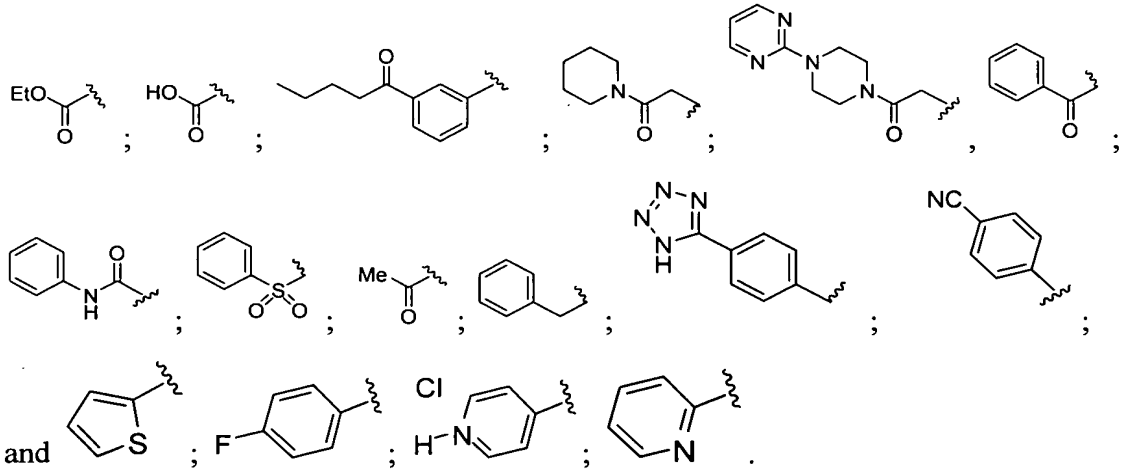


[0117] In an exemplary embodiment, the compound has a structure is a member selected from:

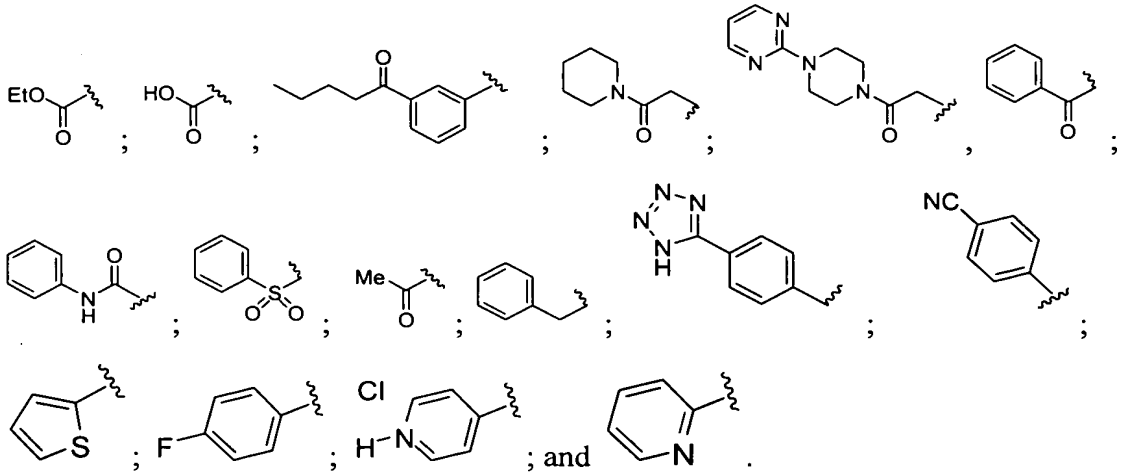


(Iag), (Iah), (Iai) (Iaj) and (Iak).

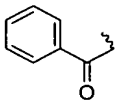
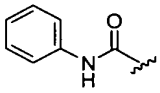
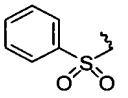
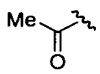
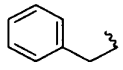
[0118] In an exemplary embodiment, R^a, R^d and R^e are each members indepenently selected from:

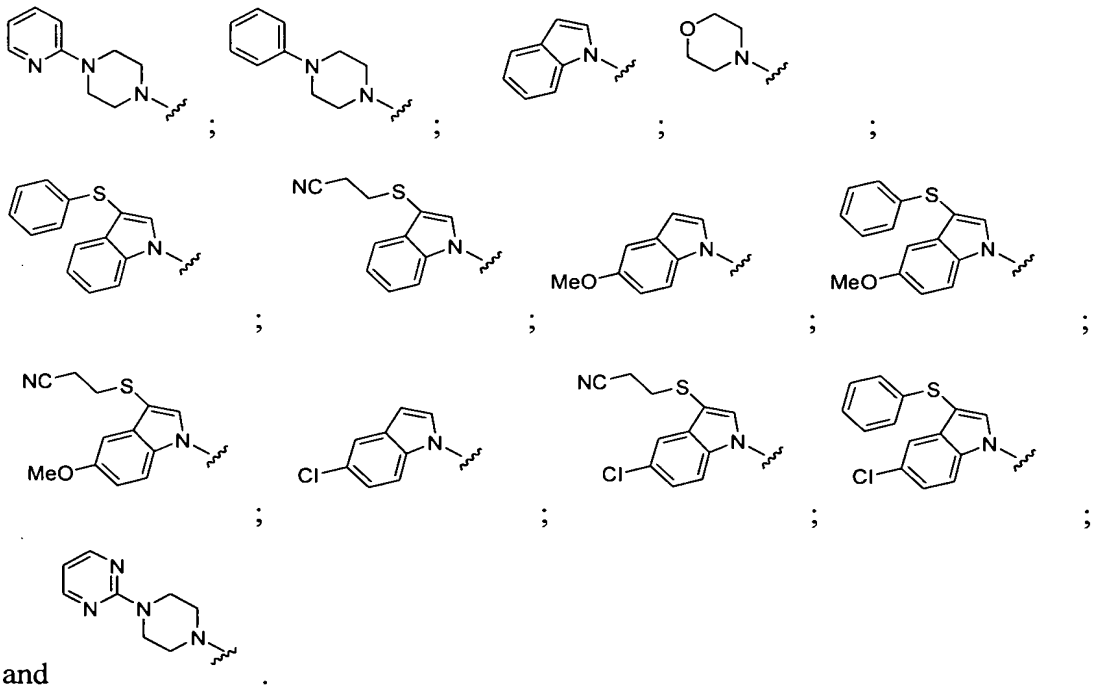


[0119] In an exemplary embodiment, R^b and R^c are members independently selected from H, methyl,



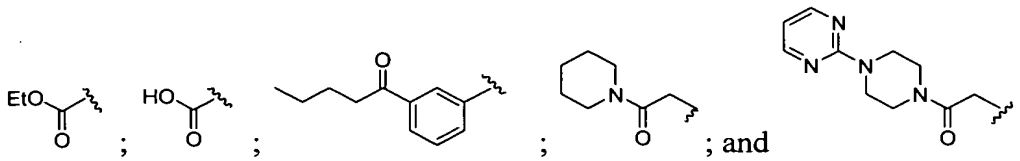
[0120] In another exemplary embodiment, R^b is H and R^c is a member selected from

H, methyl,  ;  ;  ;  ; and  . In another exemplary embodiment, R^b and R^c are, together with the nitrogen to which they are attached, optionally joined to form a member selected from

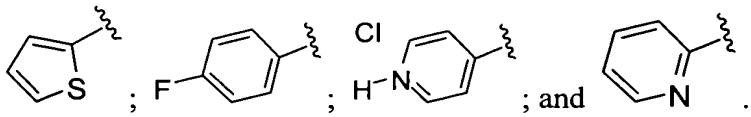


and .

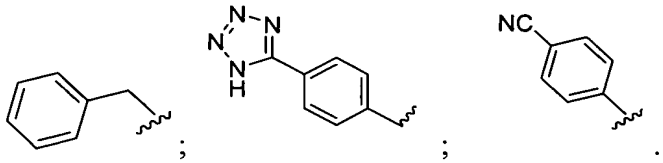
[0121] In an exemplary embodiment, R^a is a member selected from



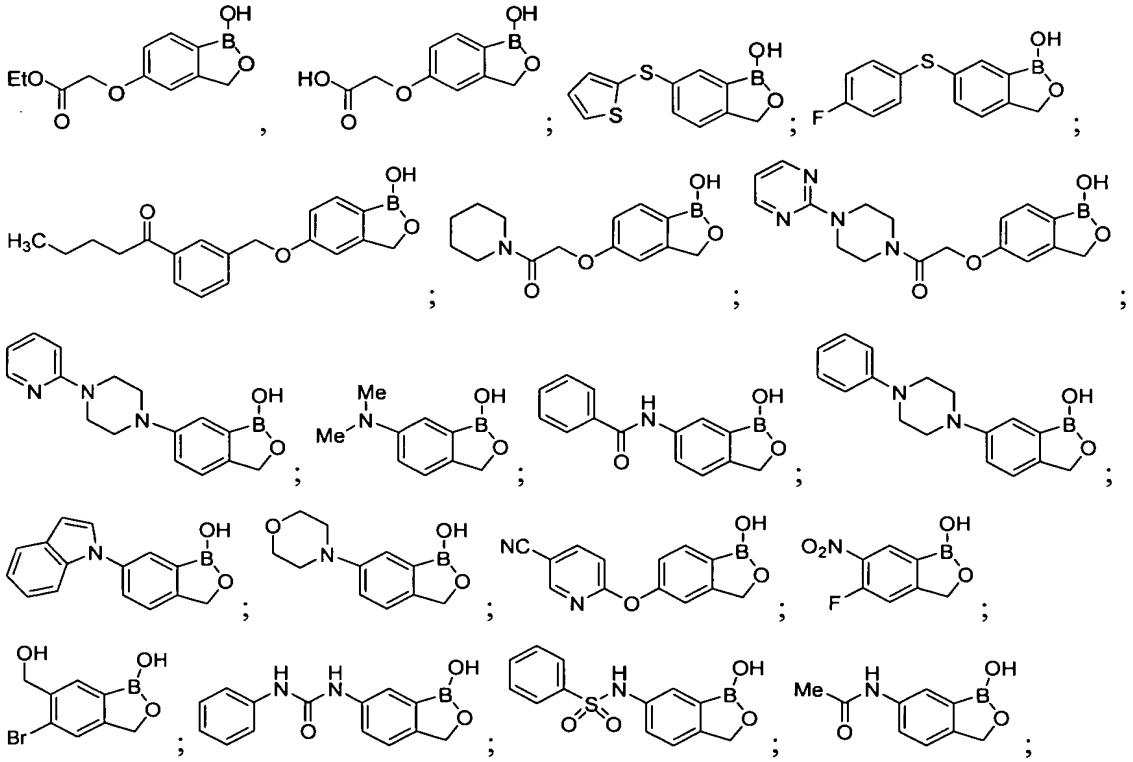
[0122] In an exemplary embodiment, R^d is a member selected from

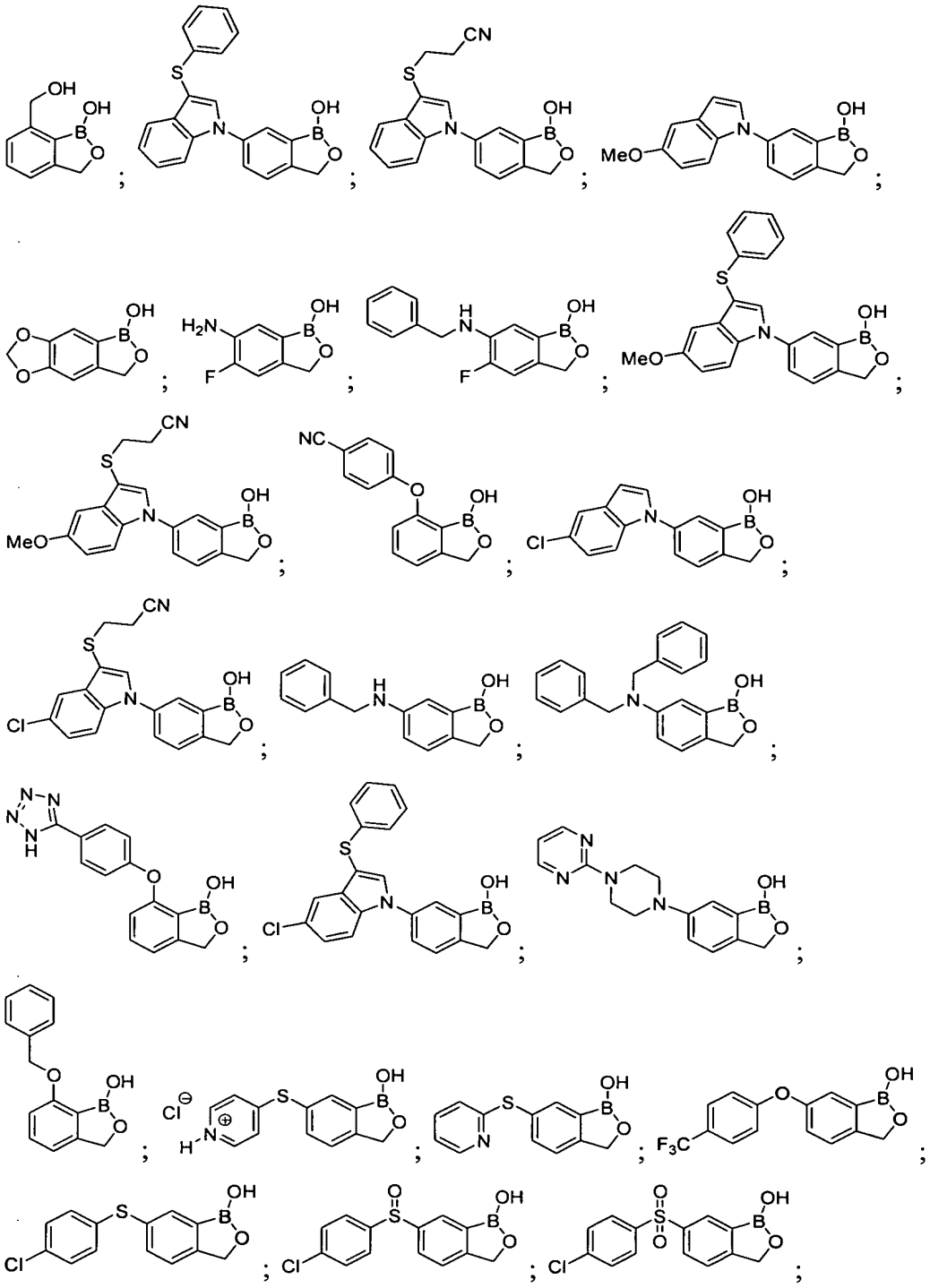


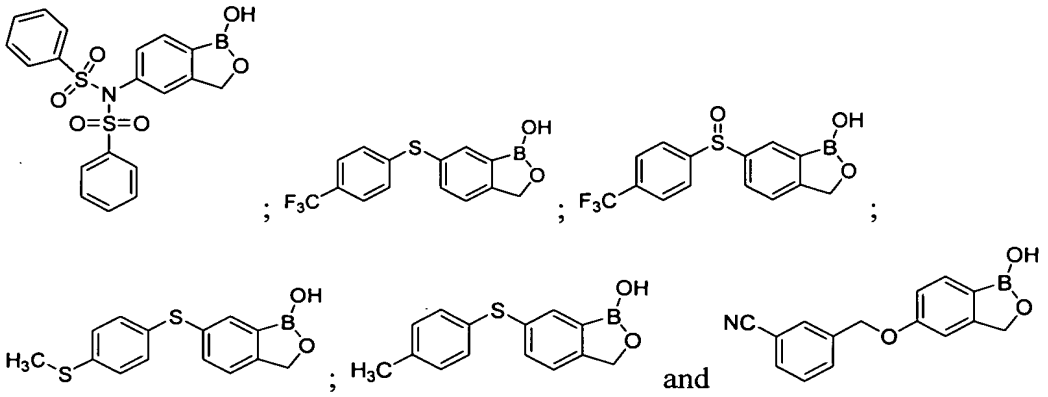
[0123] In an exemplary embodiment, R^e is a member selected from



[0124] In an exemplary embodiment, the compound is a member selected from





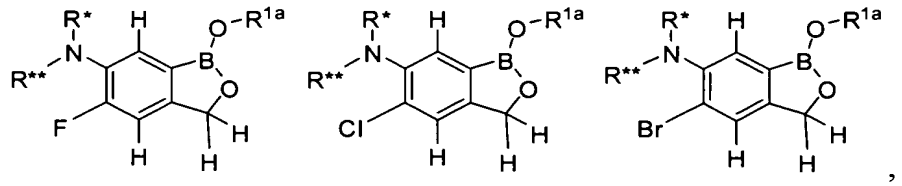


[0125] In an exemplary embodiment, the compound has a structure which is described in Figure 19. In an exemplary embodiment, the compound has a structure which is described in Figure 20.

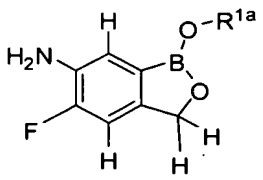
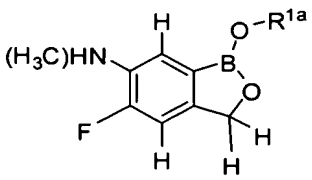
[0126] In an exemplary embodiment, the compound has a structure according to a member selected from Formulae I(b), I(c), I(d), and I(e) wherein said remaining R group (R^{9a} for I(b), R^{10a} for I(c), R^{11a} for I(d) and R^{12a} for I(e)) is carboxymethoxy.

[0127] In an exemplary embodiment, the compound has a structure which is a member selected from Formulae (If) – (Ik), wherein either R^{9a} or R^{10a} for Formula (If), either R^{9a} or R^{11a} for Formula (Ig), either R^{9a} or R^{12a} for Formula (Ih), either R^{10a} or R^{11a} for Formula (Ii), either R^{10a} or R^{12a} for Formula (Ij), either R^{11a} or R^{12a} for Formula (Ik) is halogen, and the other substituent in the pairing (ex. if R^{9a} is F in Formula (If), then R^{10a} is selected from the following substituent listing), is a member selected from NH_2, $N(CH_3)H$, and $N(CH_3)_2$.

[0128] In another exemplary embodiment, the compound has a structure which is a member selected from:



in which R* and R** are members selected from: H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In an exemplary embodiment, the compound is a member selected from


,

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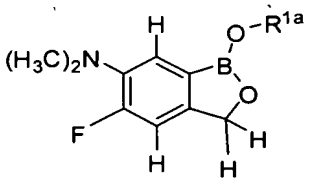
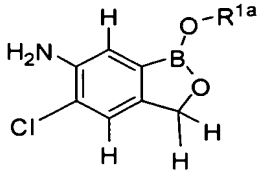
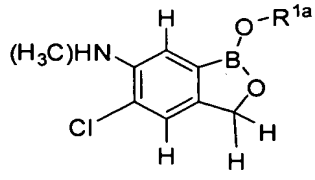

,

,

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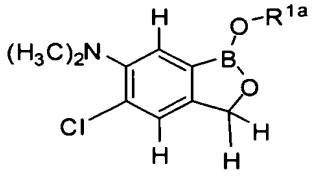
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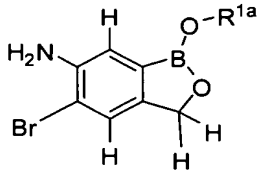
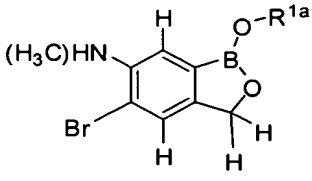
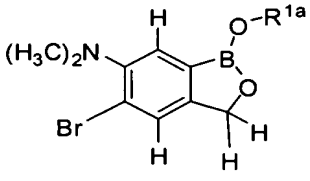
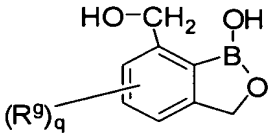

,

and

,

wherein R^{1a} is a member selected from a negative charge, H and a salt counterion.

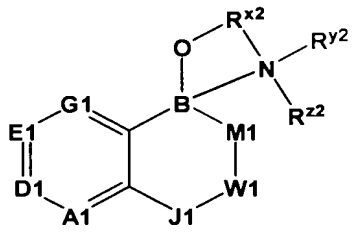
[0129] In another exemplary embodiment, the compound has a structure which is a member selected from:



(Iak), wherein q is 1 and R^g is a member selected from fluoro, chloro and bromo.

[0130] In another exemplary embodiment, the compounds and embodiments described above in Formulae (I)-(Io) can form a hydrate with water, a solvate with an alcohol (e.g. methanol, ethanol, propanol); an adduct with an amino compound (e.g. ammonia, methylamine, ethylamine); an adduct with an acid (e.g. formic acid, acetic acid); complexes with ethanolamine, quinoline, amino acids, and the like.

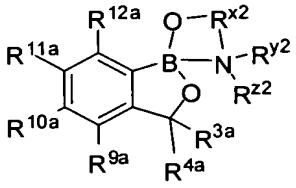
[0131] In another exemplary embodiment, the compound has a structure according to Formula (Ip):



(Ip)

in which R^{x2} is a member selected from substituted or unsubstituted C_1-C_5 alkyl and substituted or unsubstituted C_1-C_5 heteroalkyl. R^{y2} and R^{z2} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

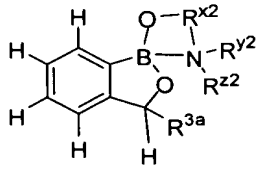
[0132] In another exemplary embodiment, the compound has a structure according to Formula (Iq):



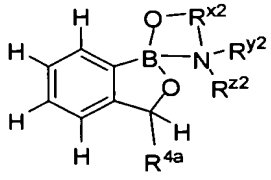
(Iq)

wherein B is boron. R^{x2} is a member selected from substituted or unsubstituted C_1-C_5 alkyl and substituted or unsubstituted C_1-C_5 heteroalkyl. R^{y2} and R^{z2} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In another exemplary embodiment, at least one member selected from R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a} and R^{12a} is a member selected from nitro, cyano and halogen.

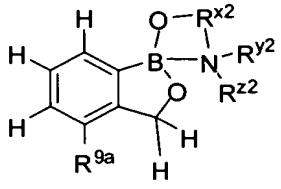
[0133] In another exemplary embodiment, the compound has a structure which is a member selected from the following Formulae:



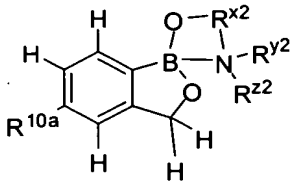
(Ir),



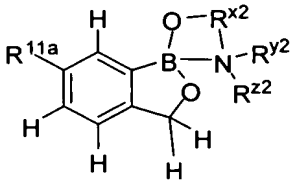
(Is),



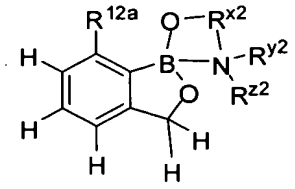
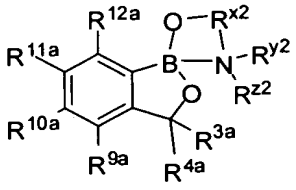
(It),



(Iu),

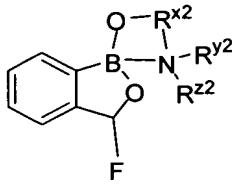
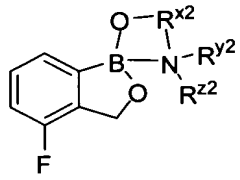
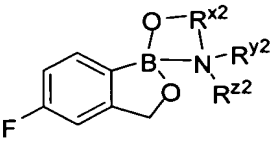
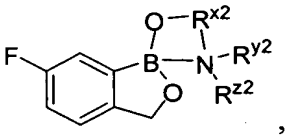
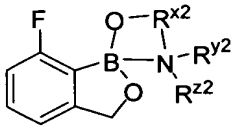
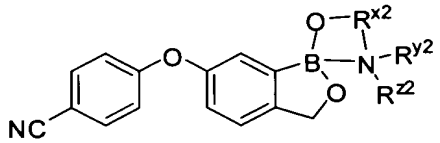
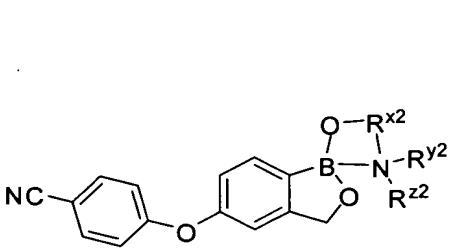
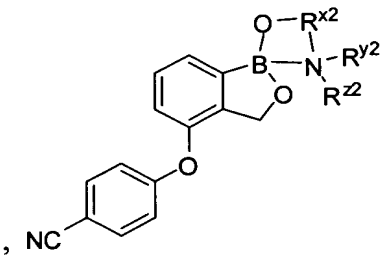


(Iv),

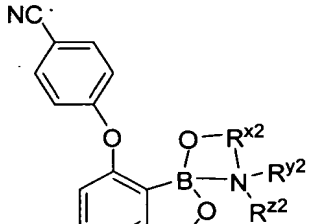



(Iw) and (Iz).

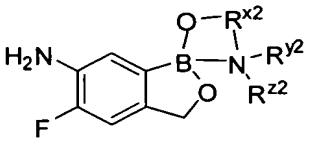
In another exemplary embodiment, the compound has a formula according to Formulae (Ib)-(Ie) wherein at least one member selected from R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a} and R^{12a} is a member selected from nitro, cyano, fluro, chloro, bromo and cyanophenoxy. In another exemplary embodiment, the compound is a member selected from

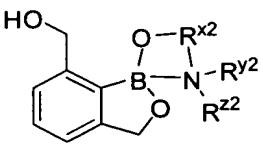
and



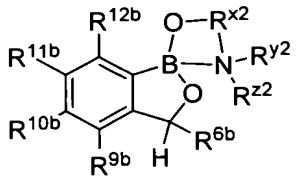
[0134] In another exemplary embodiment, the compound is a member selected from



and



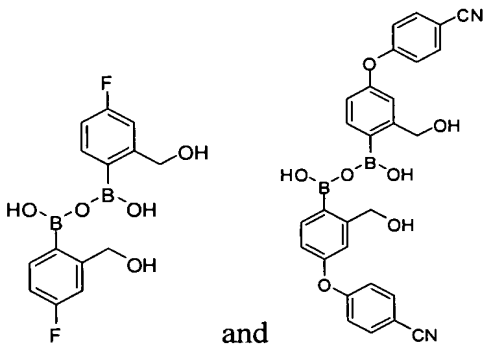
[0135] In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Iaa):



(Iaa)

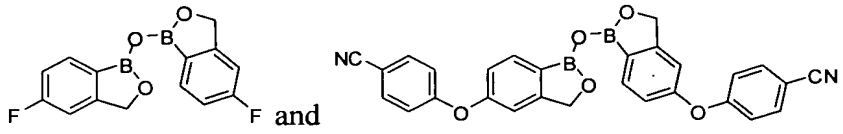
wherein R^{6b}, R^{9b}, R^{10b}, R^{11b} and R^{12b} have the same substituent listings as described for Formulae (Ix) and (Iy) above.

[0136] In another exemplary embodiment, the invention provides poly- or mutli-valent species of the compounds of the invention. In an exemplary embodiment, the invention provides a dimer of the compounds described herein. In an exemplary embodiment, the invention provides a dimer of the compounds described herein. In an exemplary embodiment, the invention provides a dimer of a compound which is a member selected from **C1-C96**. In an exemplary embodiment the dimer is a member selected from



and

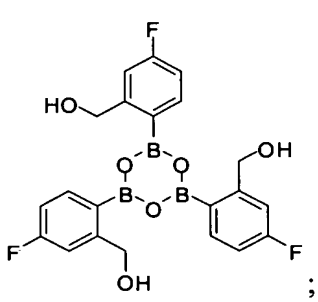
[0137] In an exemplary embodiment, the invention provides an anhydride of the compounds described herein. In an exemplary embodiment, the invention provides an anhydride of the compounds described herein. In an exemplary embodiment, the invention provides an anhydride of a compound which is a member selected from **C1-C96**. In an exemplary embodiment the anhydride is a member selected from



and

[0138] In an exemplary embodiment, the invention provides a trimer of the compounds described herein. In an exemplary embodiment, the invention provides a

trimer of the compounds described herein. In an exemplary embodiment, the invention provides a trimer of a compound which is a member selected from **C1-C96**. In an exemplary embodiment the trimer is a member selected from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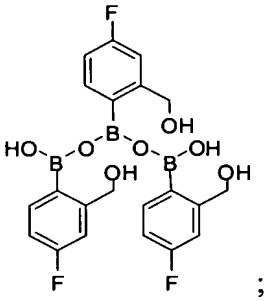
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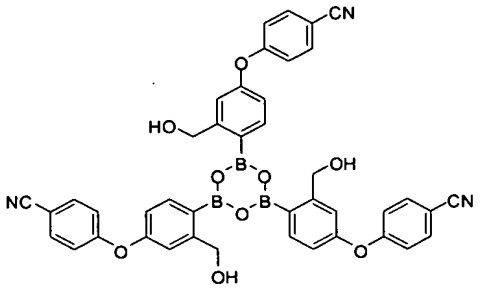
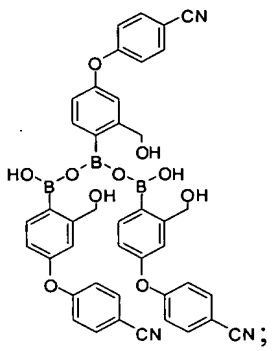
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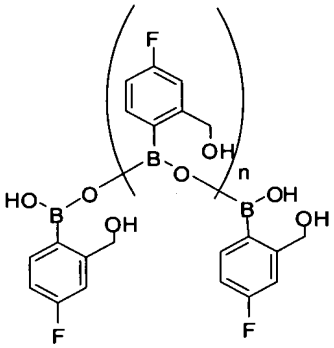
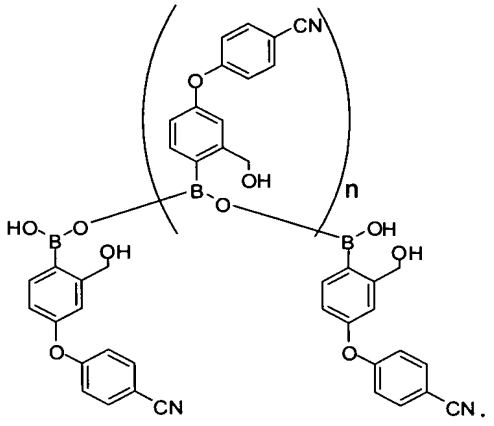
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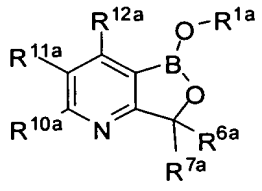
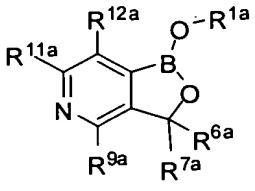
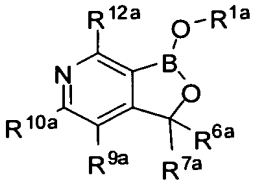
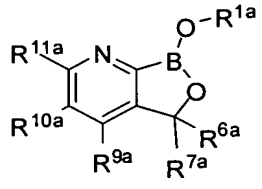
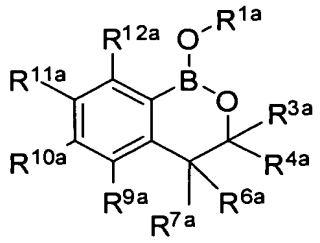
Pyridinyloxaboroles

[0139] In an exemplary embodiment, the compound has a structure which is a member selected from Formulae (IIa) (IIb) (IIc) and (IId).


(IIa);

(IIb);

(IIc);

(IId).

Oxaborines

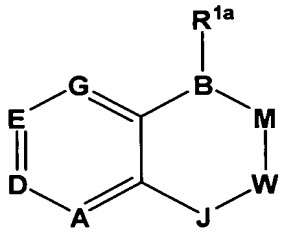
[0140] In an exemplary embodiment, the compound has a structure according to Formula (III):



(III).

I. b.) ***Cyclic Borinic Esters***

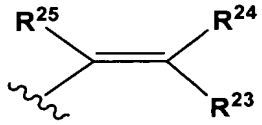
[0141] In one aspect, the invention provides compounds useful in the methods which have a structure according to Formula VII:



(VII)

wherein the variables R^{1a}, A, D, E, G, J, W and M are described elsewhere herein.

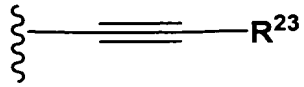
[0142] In an exemplary embodiment of Formula (VII), R^1 is substituted or unsubstituted alkyl (C_1 - C_4). In an exemplary embodiment of Formula (VII), R^1 is substituted or unsubstituted alkyloxy. In an exemplary embodiment of Formula (VII), R^1 is substituted or unsubstituted cycloalkyl (C_3 – C_7). In an exemplary embodiment of Formula (VII), R^1 is substituted or unsubstituted alkenyl. In a further exemplary embodiment thereof, the substituted alkenyl has the structure



(VIIa)

wherein R^{23}, R^{24}, and R^{25} are each members independently selected from H, haloalkyl, aralkyl, substituted aralkyl, $(CH_2)_rOH$ (where r = 1 to 3), $CH_2NR^{26}R^{27}$ (wherein R^{26} and R^{27} are independently selected from hydrogen and alkyl), CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

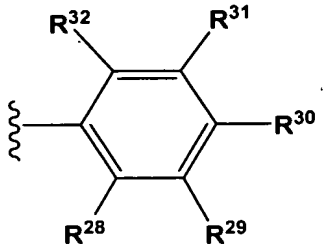
[0143] In another exemplary embodiment of Formula (VII), R^1 is a substituted or unsubstituted alkynyl. In a further exemplary embodiment thereof, the substituted alkynyl has the structure



(VIIb)

wherein R^{23} is defined as before.

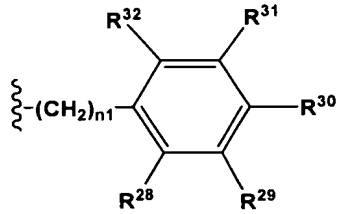
[0144] In an exemplary embodiment of Formula (VII), R^1 is substituted or unsubstituted aryl. In a further exemplary embodiment thereof the substituted aryl has the structure



(VIIc)

wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} are each members independently selected from H, aralkyl, substituted aralkyl, $(CH_2)_sOH$ (where s = 1 to 3), CO_2H, CO_2alkyl, $CONH_2$, CONHalkyl, $CON(alkyl)_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, $(CH_2)_tNR^{26}R^{27}$ (wherein R^{26} and R^{27} are independently selected from hydrogen, alkyl, and alkanoyl)(t = 0 to 2), SO_2NH_2, $OCH_2CH_2NH_2$, $OCH_2CH_2NHalkyl$, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, alkyl substituted oxazolidin-2-yl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

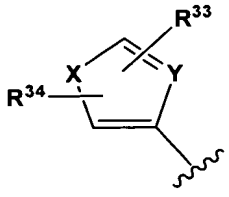
[0145] In an exemplary embodiment of Formula (VII), R^1 is a substituted or unsubstituted aralkyl. In a further exemplary embodiment thereof the substituted aralkyl has the structure

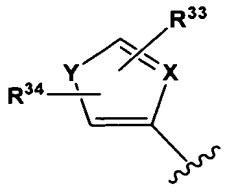


(VIId)

wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} are defined as before, and n1 is an integer selected from 1 to 15.

[0146] In an exemplary embodiment of Formula (VII), R^1 is a substituted or unsubstituted heteroaryl. In a further exemplary embodiment thereof, heteroaryl has the structure

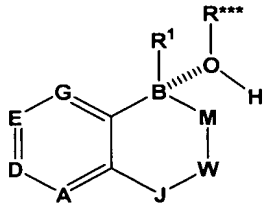


(VIIe) or


(VIIf)

wherein X is a member selected from CH=CH, N=CH, NR^{35} (wherein R^{35}= H, alkyl, aryl or benzyl), O, or S. Y = CH or N. R^{33} and R^{34} are each members independently selected from H, haloalkyl, aralkyl, substituted aralkyl, $(CH_2)_uOH$ (where u = 1, 2 or 3), $(CH_2)_vNR^{26}R^{27}$ (wherein R^{26} and R^{27} are independently selected from hydrogen, alkyl and alkanoyl)(v = 0 to 3), CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0147] The structures of the invention also permit solvent interactions that may afford structures (Formula VIIg) that include atoms derived from the solvent encountered by the compounds of the invention during synthetic manipulations and therapeutic uses. Structure VIIg arises from the formation of a dative bond between the solvent(s) with the Lewis acidic boron center. Thus, such solvent complexes could be stable entities with comparative bioactivities. Such structures are expressly contemplated by the present invention where R*** is H or alkyl.



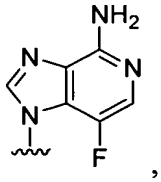
Formula (VIIg)

[0148] In an exemplary embodiment, the compound has a structure which is a member selected from 2-(3-Chlorophenyl)-[1,3,2]-dioxaborolane, (3-Chlorophenyl)(4'-fluoro-(2'-(methoxymethoxy)-methyl)-phenyl)-borinic acid, 1-(3-Chlorophenyl)-5-fluoro-1,3-dihydrobenzo[c][1,2]oxaborole, 1-(3-Chlorophenyl)-6-fluoro-1,3-dihydrobenzo[c][1,2]oxaborole, 1-(3-Chlorophenyl)-1,3-dihydrobenzo[c][1,2]oxaborole, 5-Chloro-1-(3-Fluorophenyl)-1,3-dihydrobenzo[c][1,2]oxaborole, 2-(3-fluorophenyl)-[1,3,2]-dioxaborolane, 3-(Benzo[c][1,2]oxaborol-1(3H)-yl)benzonitrile, 2-(3-cyanophenyl)-[1,3,2]-

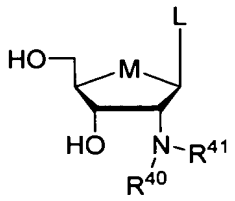
dioxaborolane, (3-Chlorophenyl)(5'-fluoro-(2'-(methoxymethoxy)methyl)-phenyl)-borinic acid, 1-(3-Chlorophenyl)-1,3-dihydro-3,3dimethylbenzo[c][1,2]oxaborole, (3-Chlorophenyl)(2-(2-(methoxymethoxy)propan-2yl)phenylborinic acid, 1-(3-Chlorophenyl)-1,3-dihydro-3,3-dimethylbenzo[c][1,2]oxaborole, 1-(4-Chlorophenyl)-1,3-dihydrobenzo[c][1,2]oxaborole, 2-(4-chlorophenyl)-[1,3,2]-dioxaborolane, 4-(Benzo[c][1,2]oxaborol-1(3H)-yl)benzonitrile, 2-(4-cyanophenyl)-[1,3,2]-dioxaborolane, 4-(5-Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)benzonitrile, 2-(4-cyanophenyl)-[1,3,2]-dioxaborolane, 3-(5-Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)benzonitrile, 2-(3-cyanophenyl)-[1,3,2]-dioxaborolane, 3-(6-Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)benzonitrile, 2-(3-cyanophenyl)-[1,3,2]-dioxaborolane, 1-(3-Cyanophenyl)-5,6-dimethoxy-1,3-dihydrobenzo[c][1,2]-oxaborole, 2-(3-chlorophenyl)-[1,3,2]-dioxaborolane, (4-(5-(Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)phenylmethanamine, 5-Fluoro-2-(methoxymethoxymethyl)phenyl]-[1,3,2]-dioxaborolane, 4-(5-(Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)phenylmethanamine, (3-(5-(Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)-phenylmethanamine, (4-(5-(Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)phenyl)methanol, (3-(5-(Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)phenyl)methanol, 3-(6-Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)phenol, 3-(5-Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)pyridine, (2-(Benzo[c][1,2]oxaborol-1(3H)-yl)phenyl)methanol, 2-[(Methoxymethoxy)methyl]phenyl boronic acid, 2-[(Methoxymethoxymethyl)pheny]-[1,3,2]-dioxaborolane, Bis [2-(methoxymethoxymethyl)phenyl]borinic acid, (2-(Benzo[c][1,2]oxaborol-1(3H)-yl)phenyl)methanol, (2-(Benzo[c][1,2]oxaborol-1(3H)-yl)phenyl)-N,N-dimethylmethanamine, (2-(Benzo[c][1,2]oxaborol-1(3H)-yl)-5-chlorophenyl)-N,N-dimethylmethanamine, (2-(Benzo[c][1,2]oxaborol-1(3H)-yl)-5-chlorophenyl)methanol, (2-(Benzo[c][1,2]oxaborol-1(3H)-yl)-5-chlorophenyl)methanol, (5-Chloro-2-(5-chlorobenzo[c][1,2]oxaborol-1(3H)-yl)phenyl)methanol, Bis[4-chloro-2-(methoxymethoxymethyl)phenyl]borinic acid, (5-Chloro-2-(5-chlorobenzo[c][1,2]oxaborol-1(3H)-yl)phenyl)methanol, (5-Chloro-2-(5-chlorobenzo[c][1,2]oxaborol-1(3H)-yl)phenyl-N,N-dimethylmethanamine, 1-(4-chloro-2-methoxyphenyl)-1,3-dihydrobenzo[c][1,2]benzoxaborole, 4-Chloro-2-methoxyphenylboronic acid ethylene glycol ester, 1-(4-chloro-2-methoxyphenyl)-1,3-dihydrobenzo[c][1,2]benzoxaborole, 2-(Benzo[c][1,2]oxaboral-1(3H)-yl)-5-chlorophenol, 2-(3-(Benzo[c][1.2]oxaborol-1(3H)-yl)phenoxy)-5-chlorophenol, 2-(3-

(Benzo[c][1,2]oxaborol-1(3H)-yl)Phenoxy)-5-chlorophenol 4-((3-(5-Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)phenyl)methyl)morpholine, 3-(5-Fluorobenzo[c][1,2]oxaborol-1(3H)-yl]phenyl)-methyl 8-hydroxy-quinoline-2-carboxylate, 1-(3-Chlorophenyl)-2,3-dihydro-2-(methoxymethy)-1H-benzo[c][1,2]azaborole, 3-Chlorophenyl 2-[N,N-bis(methoxymethyl)aminomethyl] phenylborinic acid, 1-(3-Chlorophenyl)-2,3-dihydro-2-(methoxymethy)-1H-benzo[c][1,2]azaborole, 1-(3-Chlorophenyl)-1,3,4,5-tetrahydrobenzo-[c][1,2]-oxaborepine, 1-(3-Chlorophenyl)-1,3,4,5-tetrahydrobenzo[c][1,2]oxaborepine, 1-(3-Chlorophenyl)-3,4-dihydro-1H-benzo[c][1,2]-oxaborinine, 2-(3-Chlorophenyl)-[1,3,2]dioxaborolane, (3-Chlorophenyl)(2'-(2-(methoxymethoxy)ethyl)phenyl)borinic acid, and 1-(3-Chlorophenyl)-3,4-dihydro-1H-benzo[c][1,2]oxaborinine.

I. c.) 2'-amino ribofuranoses

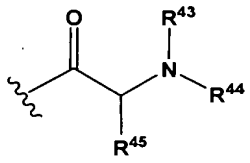
[0149] In another aspect, the invention provides compounds useful in the methods which is a 2'-amino ribofuranose. In an exemplary embodiment, the 1'-position of the ribofuranose is substituted with a member selected from substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. In another exemplary embodiment, the 1'-position of the ribofuranose is substituted with a member selected from substituted or unsubstituted purine, substituted or unsubstituted pyrimidine, substituted or unsubstituted pyridine and substituted or unsubstituted imidazole. In another exemplary embodiment, the 1'-position of the ribofuranose is substituted with a member selected from substituted or unsubstituted nicotinic acid, substituted or unsubstituted nicotinamide, substituted or unsubstituted nucleic acid base, substituted or unsubstituted adenine, 

, substituted or unsubstituted cytosine, substituted or unsubstituted guanine, substituted or unsubstituted thymine, substituted or unsubstituted uracil, substituted or unsubstituted N,N-dimethyl guanine, substituted or unsubstituted dihydrouracil, substituted or unsubstituted 4-thiouridine and substituted or unsubstituted inosine. In another exemplary embodiment, the compound has a structure according to Formula (VIII):

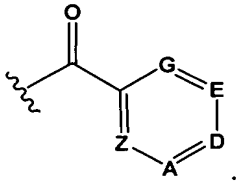


(VIII)

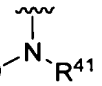
wherein L is a member selected from substituted or unsubstituted purine, substituted or unsubstituted pyrimidine, substituted or unsubstituted pyridine and substituted or unsubstituted imidazole. M, as defined herein earlier, is a member selected from O, S, and NR^2. R^{40} and R^{41} are each members independently selected from H, aralkyl, substituted aralkyl, $(CH_2)_sOH$ (where s = 1 to 3), CO_2H, CO_2alkyl, $C(O)NH_2$, C(O)NHalkyl, CON(alkyl)$_2$, $C(O)R^{23}$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, $(CH_2)_tNR^{26}R^{27}$ (wherein R^{26} and R^{27} are independently selected from hydrogen, alkyl, and alkanoyl)(t = 0 to 2), SO_2NH_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, OCH_2CH_2N(alkyl)$_2$, oxazolidin-2-yl, alkyl substituted oxazolidin-2-yl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

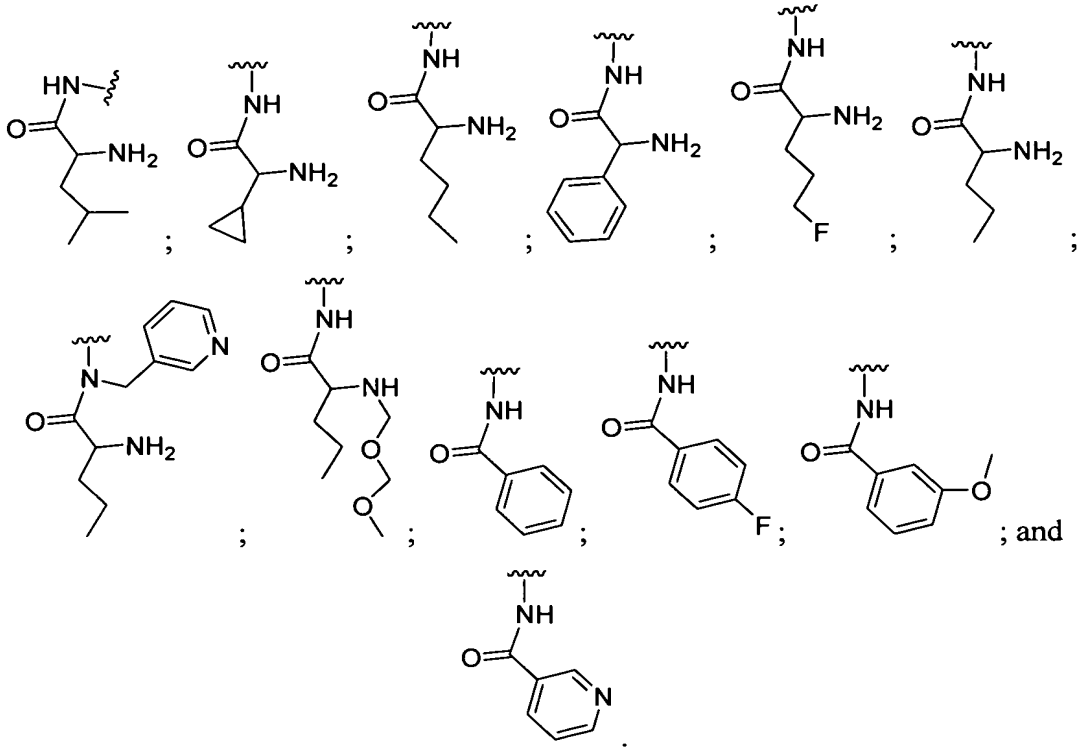


and

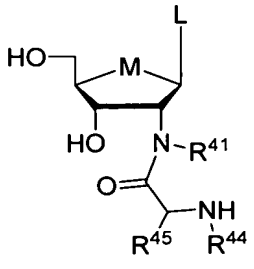
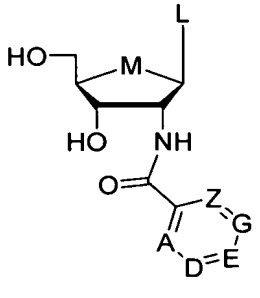


. R^{43}, R^{44}, and R^{45} are each members independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^{43} and R^{44}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{43} and R^{45}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{44} and R^{45}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. A, D, E and G are all defined elsewhere herein. Z is a member selected from CR^{46} and N. The combinations of nitrogens (A + D + E + G + Z) is an integer selected from 0 to 4. At least two members selected from R^9, R^{10}, R^{11}, R^{12} and R^{46}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

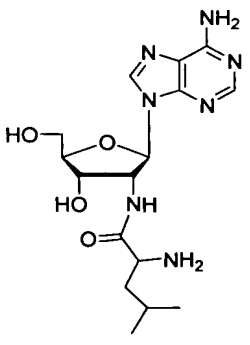
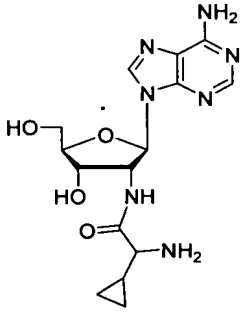
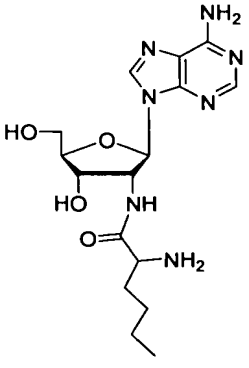
[0150] In an exemplary embodiment,  is a member selected from:

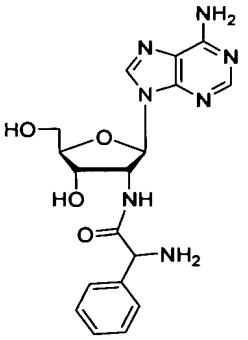


[0151] In another exemplary embodiment, the compound has a formula according to the following formulae:

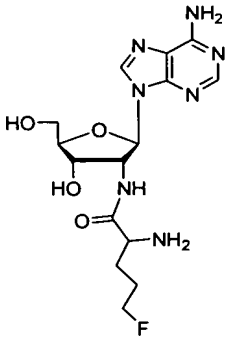
 (VIIIa) and  (VIIIb)

In an exemplary embodiment, the compound is a member selected from:

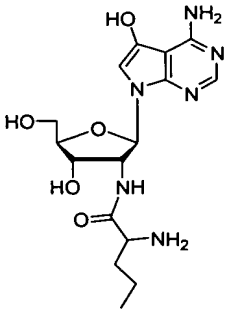
 **(D1);**  **(D2);**  **(D3);**



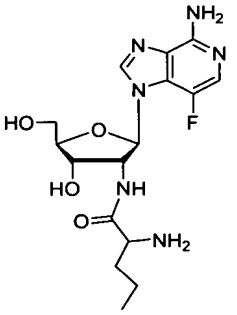
(D4);



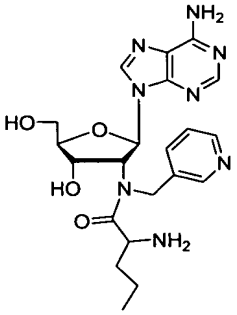
(D5);



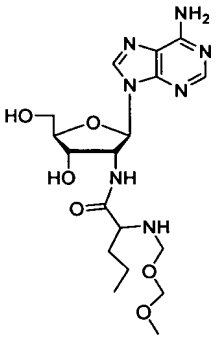
(D6);



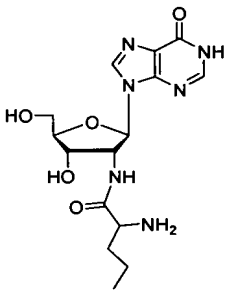
(D7);



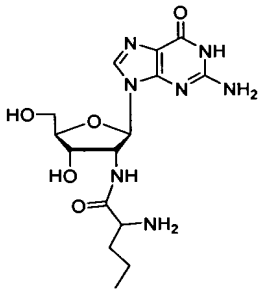
(D8);



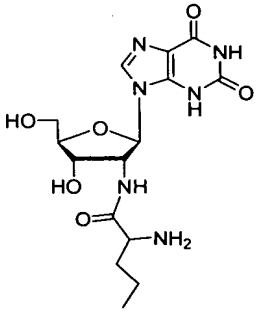
(D9);



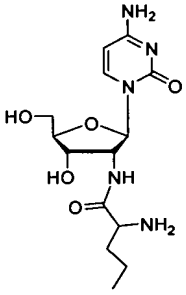
(D10);



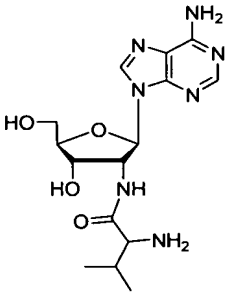
(D11);



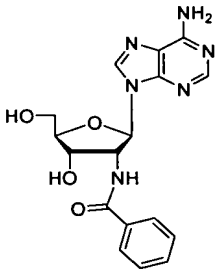
(D12);



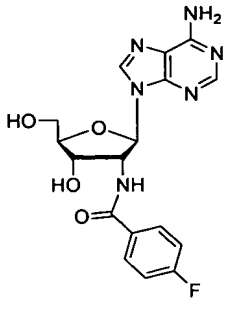
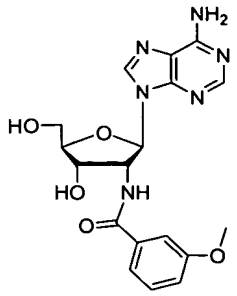
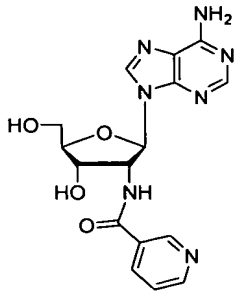
(D13);

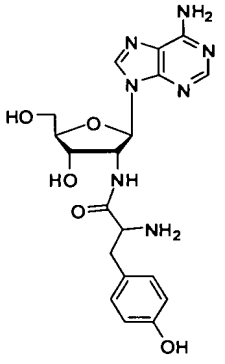


(D14);



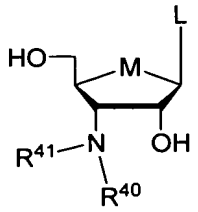
(D15);

 **(D16);**  **(D17);**  **(D18)** and

 **(D19)**

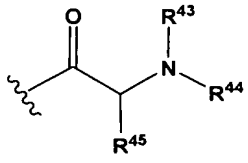
I. d.) <u>3'-amino ribofuranoses</u>

[0152] In another aspect, the invention provides compounds useful in the methods which is a 3'-amino ribofuranose. In an exemplary embodiment, the 1'-position of the ribofuranose is substituted with a member selected from substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. In another exemplary embodiment, the 1'-position of the ribofuranose is substituted with a member selected from substituted or unsubstituted purine, substituted or unsubstituted pyrimidine, substituted or unsubstituted pyridine, and substituted or unsubstituted imidazole. In another exemplary embodiment, the 1'-position of the ribofuranose is substituted with a member selected from substituted or unsubstituted nicotinic acid, substituted or unsubstituted nicotinamide, substituted or unsubstituted nucleic acid base, substituted or unsubstituted adenine,  , substituted or unsubstituted cytosine, substituted or unsubstituted guanine, substituted or unsubstituted thymine, substituted or unsubstituted uracil, substituted or unsubstituted N,N-dimethyl guanine, substituted or unsubstituted dihydrouracil, substituted or unsubstituted 4-thiouridine and substituted or unsubstituted inosine. In another exemplary embodiment, the compound has a structure according to Formula (VIIIc):

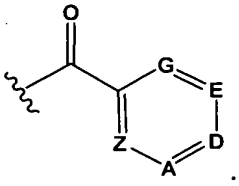


(VIIIc)

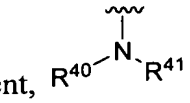
wherein L is a member selected from substituted or unsubstituted purine, substituted or unsubstituted pyrimidine, substituted or unsubstituted pyridine and substituted or unsubstituted imidazole. M, as defined herein earlier, is a member selected from O, S, and NR^2. R^{40} and R^{41} are each members independently selected from H, aralkyl, substituted aralkyl, $(CH_2)_sOH$ (where s = 1 to 3), CO_2H, CO_2alkyl, $C(O)NH_2$, C(O)NHalkyl, $CON(alkyl)_2$, $C(O)R^{23}$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, $(CH_2)_tNR^{26}R^{27}$ (wherein R^{26} and R^{27} are independently selected from hydrogen, alkyl, and alkanoyl)(t = 0 to 2), SO_2NH_2, $OCH_2CH_2NH_2$, $OCH_2CH_2NHalkyl$, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, alkyl substituted oxazolidin-2-yl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

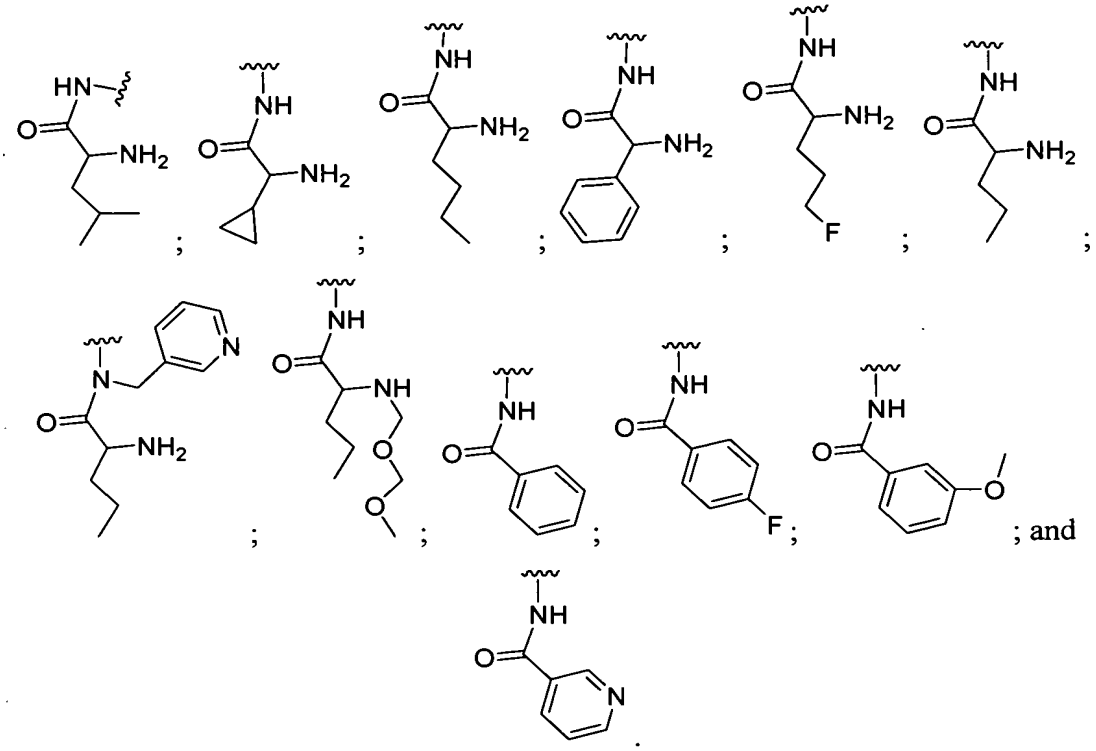


and

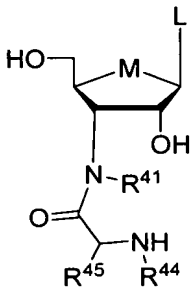


. R^{43}, R^{44}, and R^{45} are each members independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^{43} and R^{44}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{43} and R^{45}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{44} and R^{45}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. A, D, E and G are all defined elsewhere herein. Z is a member selected from CR^{46} and N. The combinations of nitrogens (A + D + E + G + Z) is an integer selected from 0 to 4. At least two members selected from R^9, R^{10}, R^{11}, R^{12} and R^{46}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

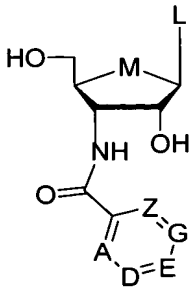
[0153] In an exemplary embodiment,  is a member selected from:



[0154] In another exemplary embodiment, the compound has a formula according to the following formulae:

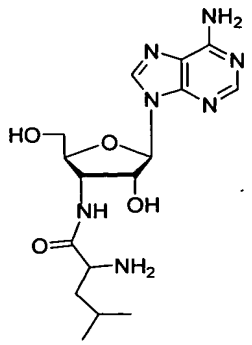


(VIIId) and

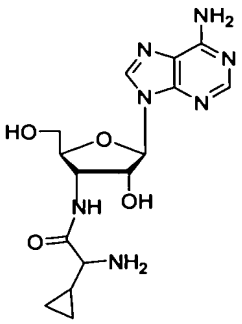


(VIIIe)

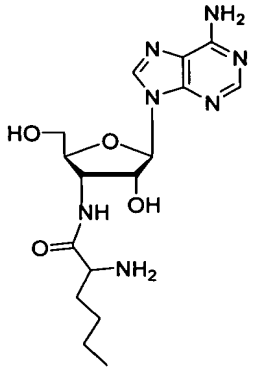
In an exemplary embodiment, the compound is a member selected from:



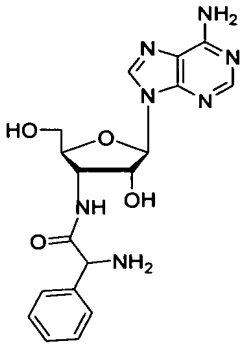
(E1);



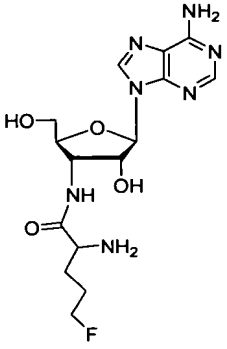
(E2);



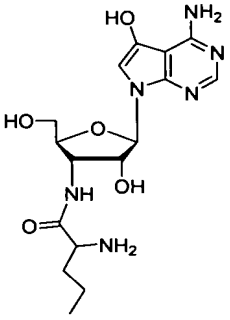
(E3);



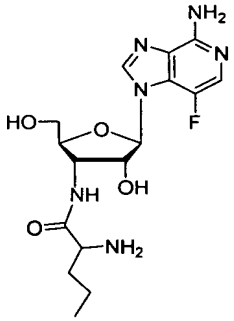
(E4);



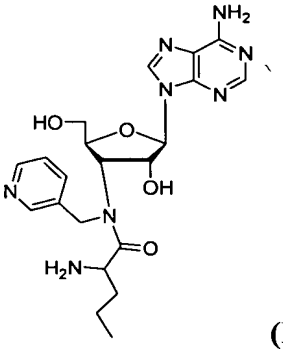
(E5);



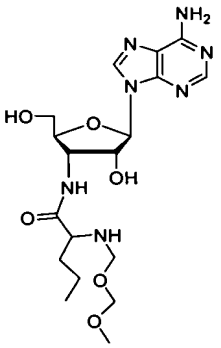
(E6);



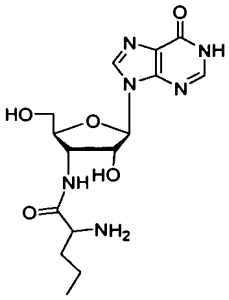
(E7);



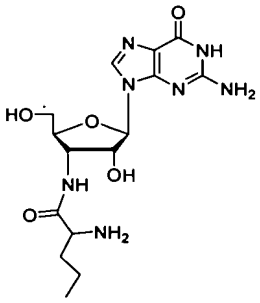
(E8);



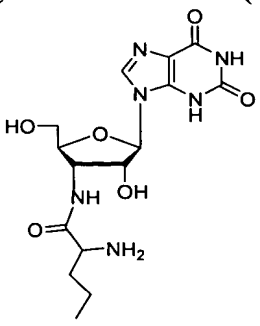
(E9);



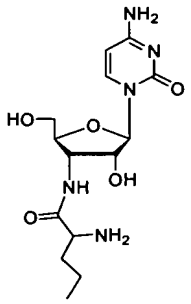
(E10);



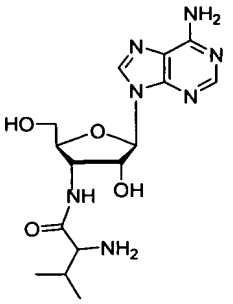
(E11);



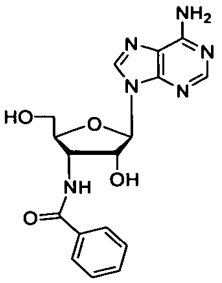
(E12);



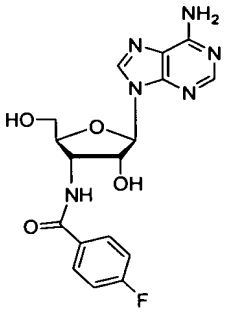
(E13);



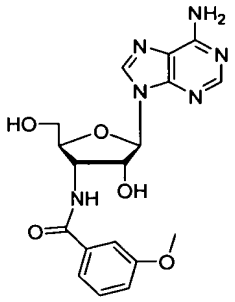
(E14);



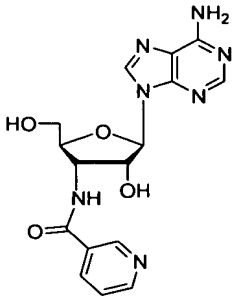
(E15);



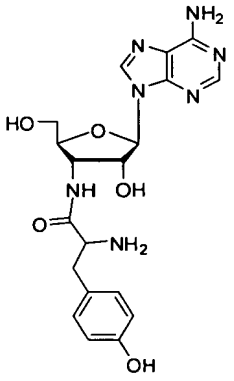
(E16);



(E17);



(E18) and

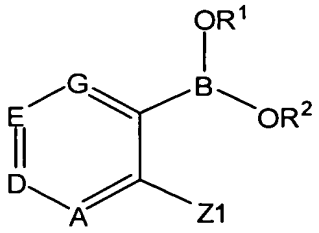


(E19).

I. e.) ***Acyclic Boronic Acids and Esters, part I***

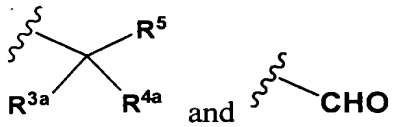
[0155] Acyclic boronic acids and esters such as those described in this section can also be utilized in the invention. These compounds can be used to kill or inhibit the growth of the microorganisms described herein, as well as treat the diseases described herein. In addition, these compounds can be used as synthetic intermediates in the generation of the compounds described herein.

[0156] In another aspect, the compound has a structure according to the following formula:



(IX)

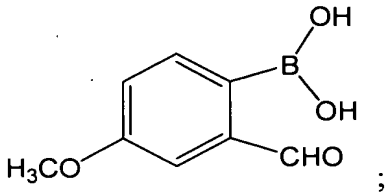
in which R^1 and R^2 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^1 and R^2, together with the atoms to which they are attached, can be optionally joined to form a 4- to 7-membered ring. Z1 is a member selected from



wherein each R^{3a} and R^{4a} is a member independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^5 is a member selected from halogen and OR^6. R^6 is a member selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A is a member selected from CR^{9a} and N. D is a member selected from CR^{10a} and N. E is a member selected from CR^{11a} and N. G is a member selected from CR^{12a} and N. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R$*, $-S(O)_2NR$*R**, -C(O)R*, -C(O)OR*, -C(O)NR*R**, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. Each R* and R** is a member independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and

substituted or unsubstituted heteroaryl. R^{9a} and R^{10a}, along with the atoms to which they are attached, are optionally joined to form a ring. R^{10a} and R^{11a}, along with the atoms to which they are attached, are optionally joined to form a ring. R^{11a} and R^{12a}, along with the atoms to which they are attached, are optionally joined to form a ring. The combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3.

[0157] In an exemplary embodiment, there is a proviso that the compound is not a member selected from:



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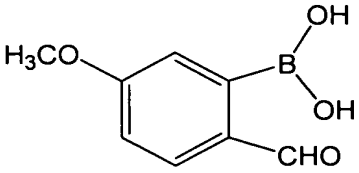
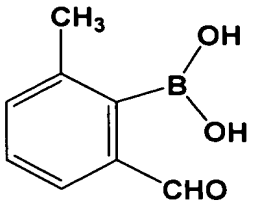
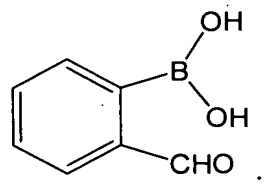
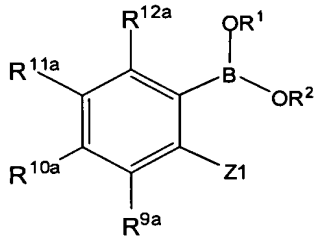






and .

[0158] In an exemplary embodiment, the compound has a structure according to Formula IXa



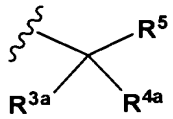
(IXa).

[0159] In another exemplary embodiment, each R^{3a} and R^{4a} is a member independently selected from H, cyano, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted indolyl and substituted or unsubstituted amido. In another exemplary embodiment, each R^{3a} and R^{4a} is a member independently selected from cyano,

substituted or unsubstituted methyl, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted indolyl, substituted or unsubstituted amido.

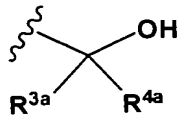
[0160] In another exemplary embodiment, each R^{3a} and R^{4a} is a member selected from H, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted butyl, substituted or unsubstituted t-butyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl. In another exemplary embodiment, R^{3a} and R^{4a} is a member selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In another exemplary embodiment, R^{3a} is H and R^{4a} is a member selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In another exemplary embodiment, R^{3a} is H and R^{4a} H.

[0161] In another exemplary embodiment, Z1 is CHO. In another exemplary embodiment, Z1 is



wherein R^5 is a member selected from OH, substituted or unsubstituted methoxy, substituted or unsubstituted ethoxy, substituted or unsubstituted methoxymethoxy, substituted or unsubstituted ethoxyethoxy, substituted or unsubstituted trialkylsialyl, and substituted or unsubstituted tetrahydro-2H-pyran-2yloxy. In another exemplary embodiment, R^5 is substituted or unsubstituted trialkylsialyl, wherein said trialkylsialyl is a member selected from substituted or unsubstituted trimethylsilyl, substituted or unsubstituted *tert*-butyldimethylsilyl, and substituted or unsubstituted tributylsilyl. In another exemplary embodiment, R^5 is substituted or unsubstituted methoxy, substituted or unsubstituted ethoxy, substituted or unsubstituted methoxymethoxy, substituted or unsubstituted ethoxyethoxy, and substituted or unsubstituted tetrahydro-2H-pyran-2yloxy. In another exemplary embodiment, R^5 is

a member selected from methoxy, ethoxy, methoxymethoxy, ethoxyethoxy and tetrahydro-2H-pyran-2yloxy. In another exemplary embodiment, Z1 is



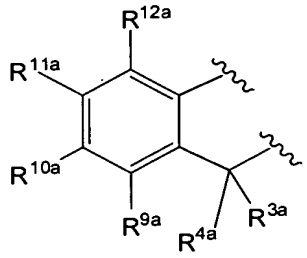
[0162] In an exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} is a member independently selected from H, OR*, NR*R**, SR*, -S(O)R*, -$S(O)_2$R*, -$S(O)_2$NR*R**, -C(O)R*, -C(O)OR*, -C(O)NR*R**, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino,

substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl. In an exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are selected from the previous list of substituents with the exception of -C(O)R*, -C(O)OR*, -C(O)NR*R**.

[0163] In another exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-

chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, 4-fluorobenzyloxy, unsubstituted phenyl, unsubstituted benzyl. In an exemplary embodiment, R^{9a} is H and R^{12a} is H. In an exemplary embodiment, the compound has a subsitutent combination for R^{9a}, R^{10a}, R^{11a}, and R^{12a} which is a member selected from those described in Formulae (I), (Ia) (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak), above, and/or the subsequent paragraphs describing Formulae (I), (Ia) (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak).

[0164] In an exemplary embodiment, the compound is an acyclic boronic acid or ester in which a portion of the acyclic boronic acid or ester as in Figure (IXb) below



(IXb)

is a member selected from a structure in **FIG. 12**. In another exemplary embodiment, the compound is a dimer, anhydride or trimer of an acyclic boronic acid or ester described herein. In another exemplary embodiment, the compound is a dimer, anhydride or trimer of an acyclic boronic acid or ester in which a portion of the acyclic boronic acid or ester as in Figure (IXb) is a member selected a structure in **FIG. 12**.

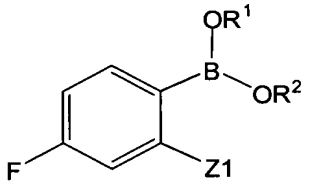
[0165] In an exemplary embodiment, R^1 and R^2 are each members independently selected from H, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted butyl, substituted or unsubstituted t-butyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl. R^1 and R^2, together with the atoms to which they are joined, can optionally form a member selected from substituted or unsubstituted dioxaborolane, substituted or unsubstituted

dioxaborinane, substituted or unsubstituted dioxaborepane.

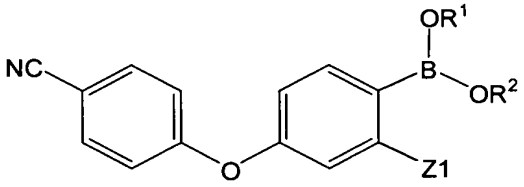
[0166] In an exemplary embodiment, R^1 and R^2 are each members independently selected from H, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In an exemplary embodiment, R^1 and R^2 are each members independently selected from H, methyl, isopropyl, and phenyl. In an exemplary embodiment, R^1 and R^2 are methyl. In an exemplary embodiment, R^1 and R^2 are isopropyl. In an exemplary embodiment, R^1 and R^2 are H.

[0167] In another exemplary embodiment, R^1 and R^2, together with the atoms to which they are joined, form a member selected from substituted or unsubstituted dioxaborolane, substituted or unsubstituted dioxaborinane, substituted or unsubstituted dioxaborepane. In another exemplary embodiment, R^1 and R^2, together with the atoms to which they are joined, form a member selected from dioxaborolane, substituted or unsubstituted tetramethyldioxaborolane, substituted or unsubstituted phenyldioxaborolane, dioxaborinane, dimethyldioxaborinane and dioxaborepane.

[0168] In an exemplary embodiment, the compound is a member selected from

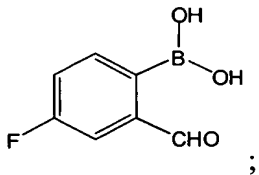


(IXc) and



(IXd).

[0169] In an exemplary embodiment, the compound is a member selected from:



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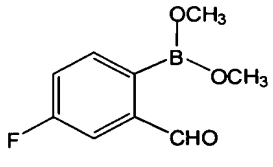

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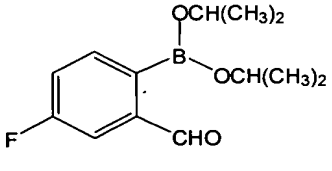

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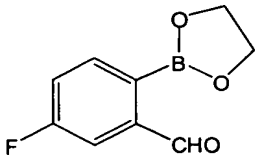

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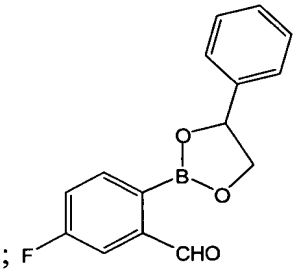

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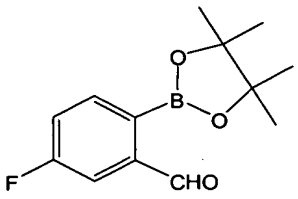

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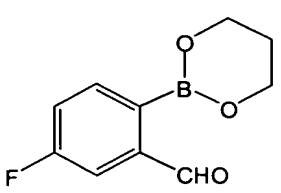
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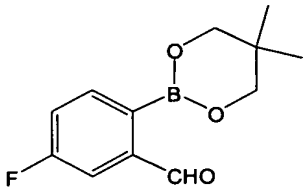
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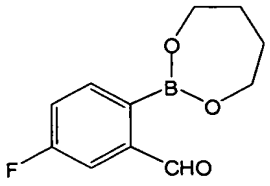
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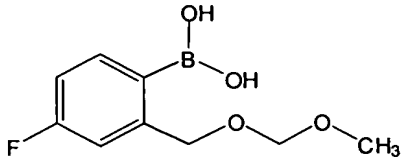
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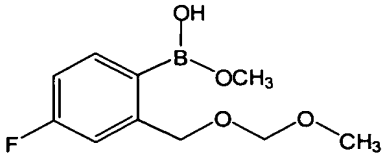
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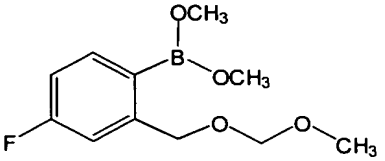
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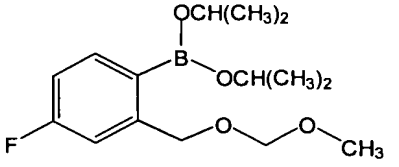
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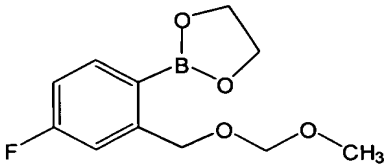
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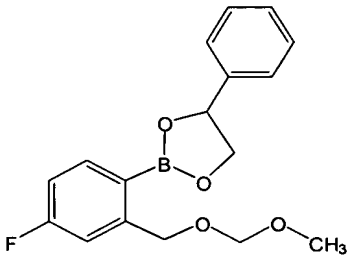
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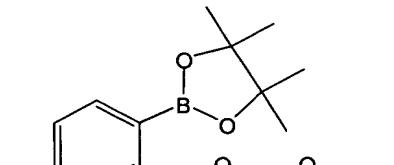
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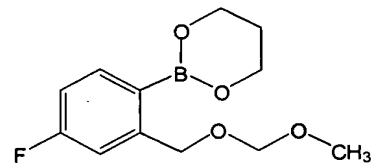
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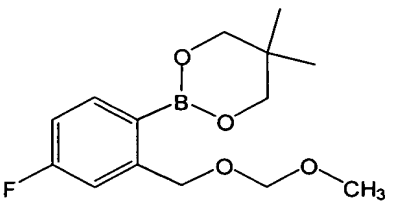
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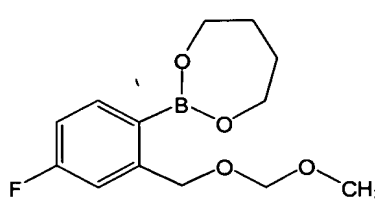
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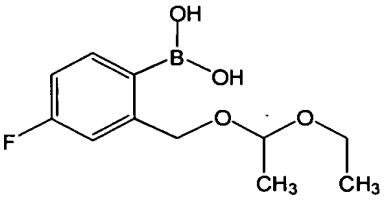
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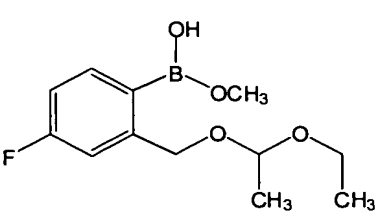
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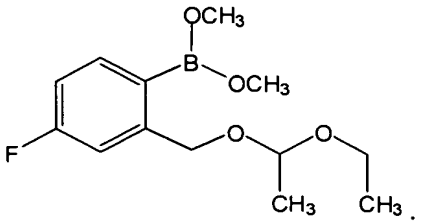
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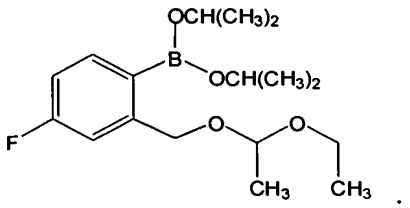
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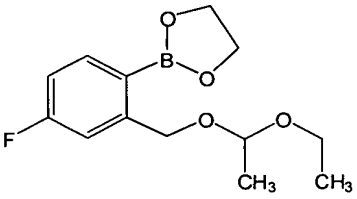
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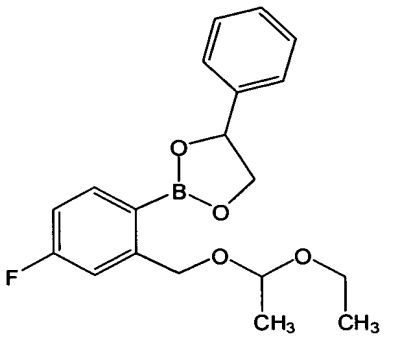
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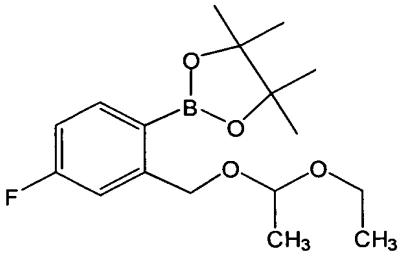
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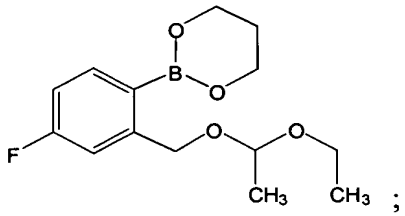
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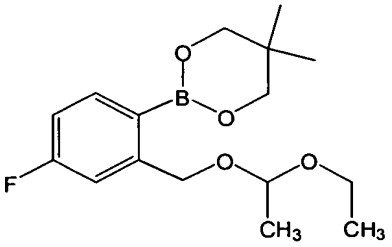
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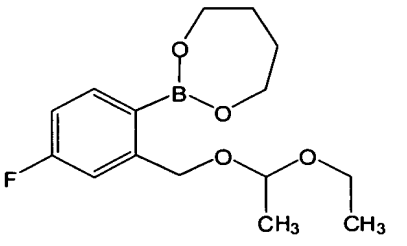
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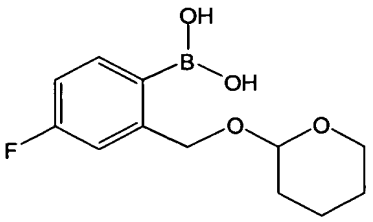
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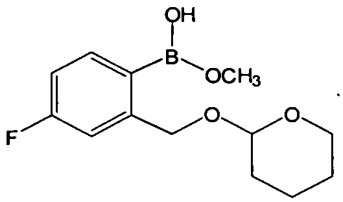
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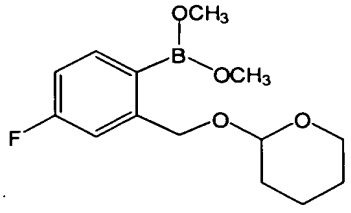
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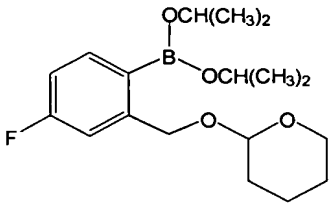
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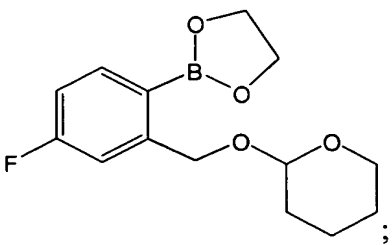
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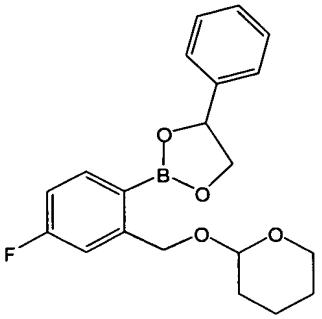
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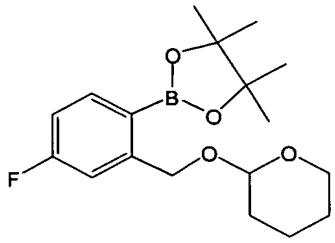
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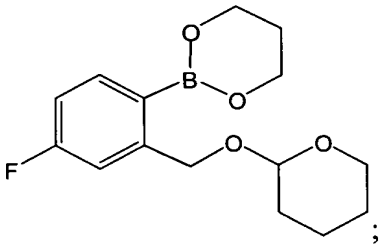
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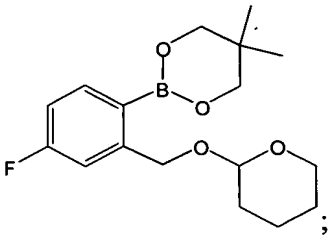
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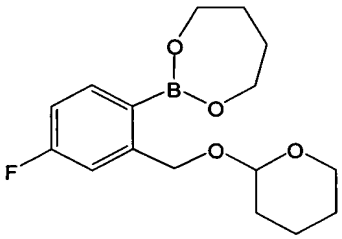
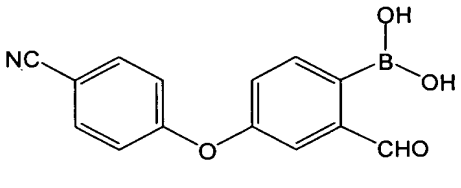


[0170] In an exemplary embodiment, the compound is a member selected from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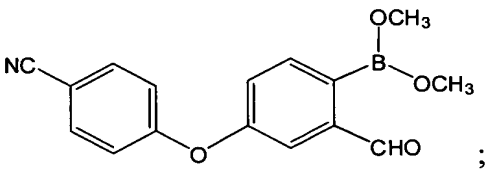
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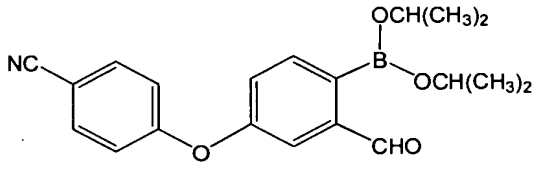
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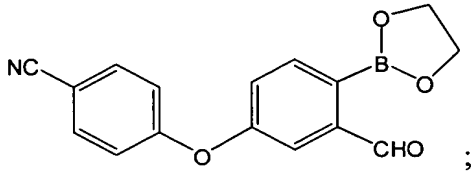
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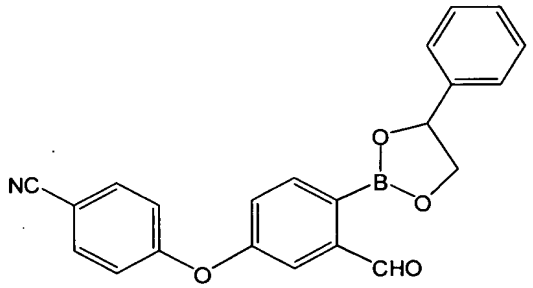
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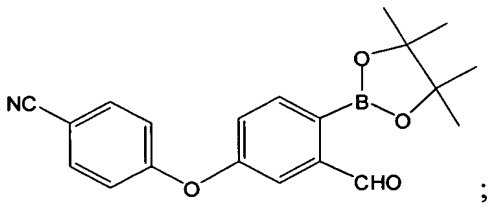
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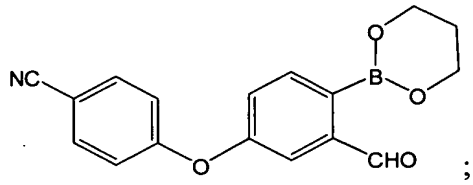
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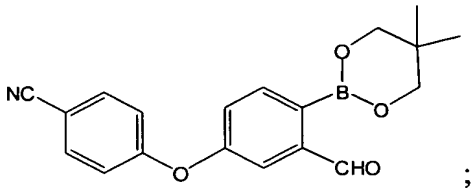
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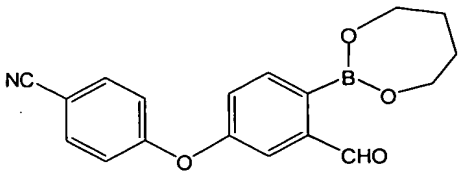
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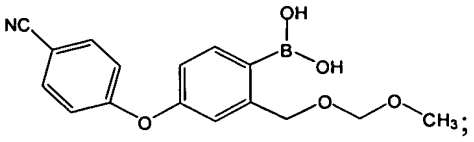
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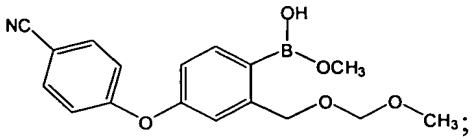
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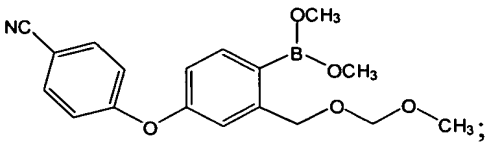
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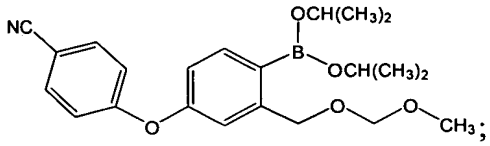
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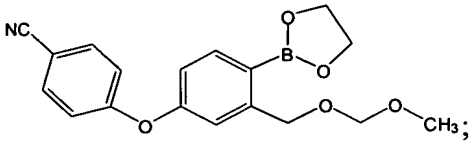
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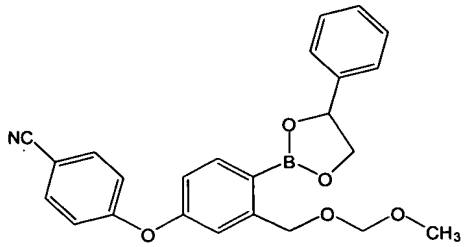
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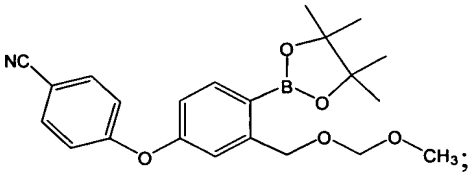
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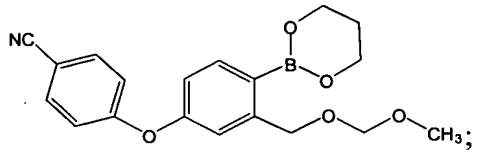
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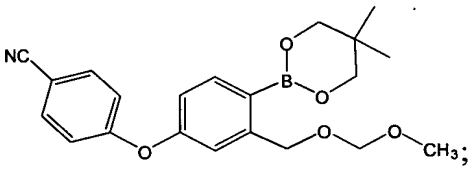
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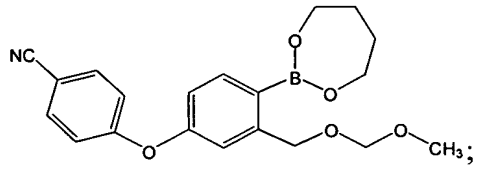
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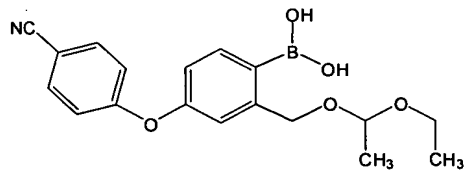
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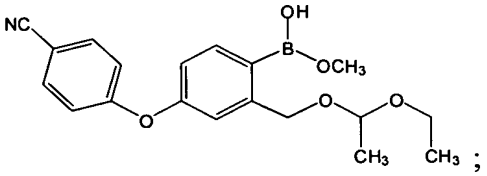
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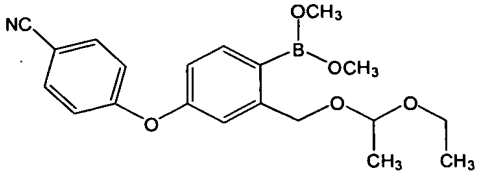
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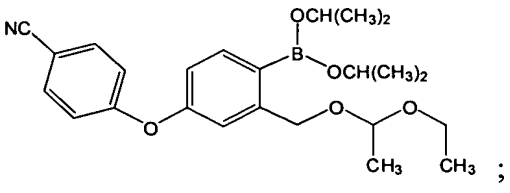
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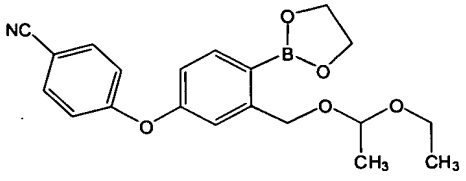
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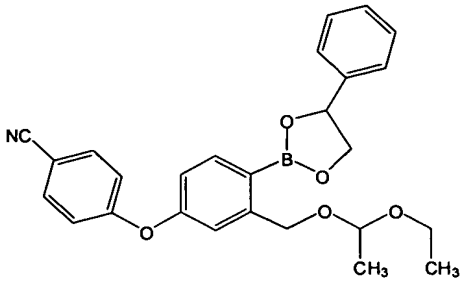
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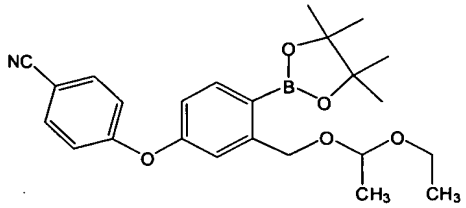
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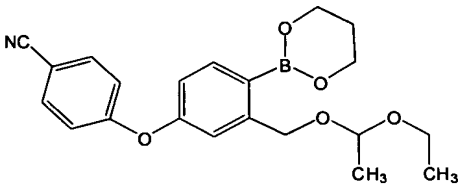
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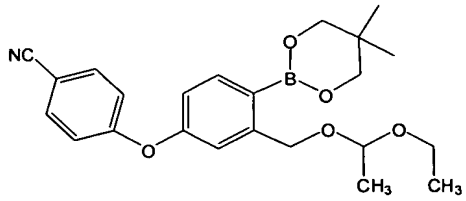
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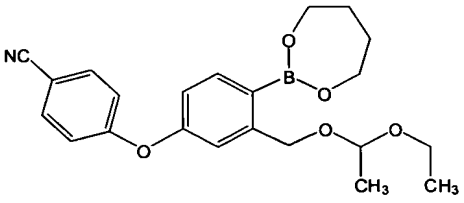
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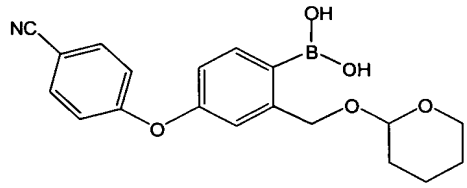
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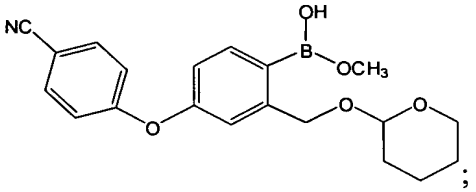
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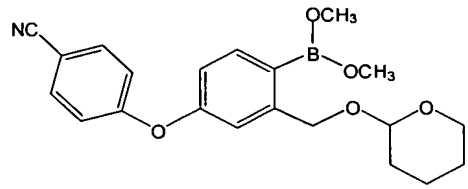
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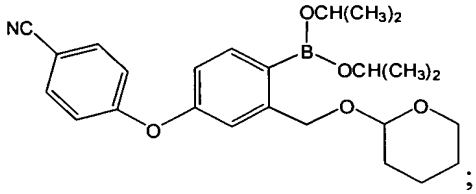
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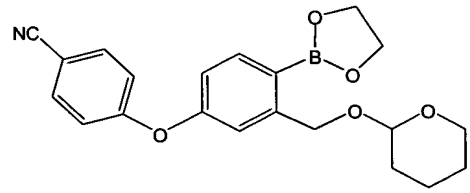
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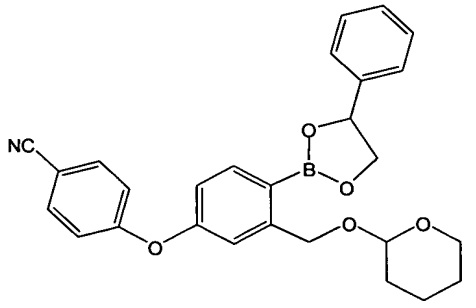
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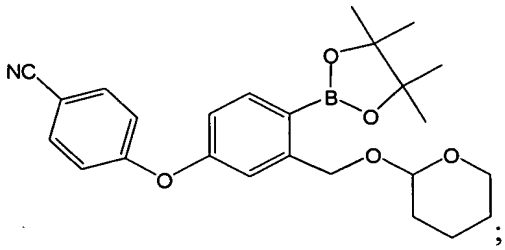
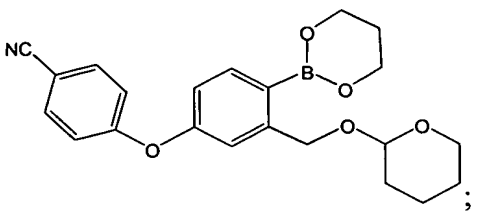
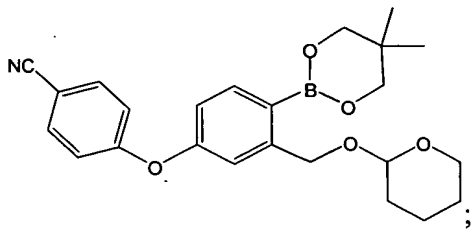
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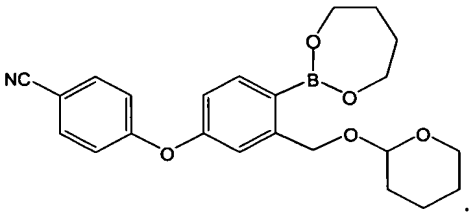


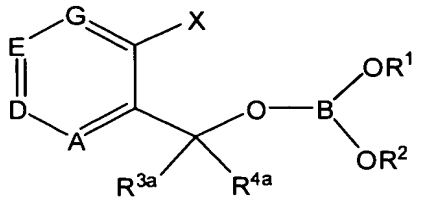
[0171] In another exemplary embodiment, the compounds and embodiments described herein can form a hydrate with water, a solvate with an alcohol (e.g. methanol, ethanol, propanol); an adduct with an amino compound (e.g. ammonia, methylamine, ethylamine); an adduct with an acid (e.g. formic acid, acetic acid); complexes with ethanolamine, quinoline, amino acids, and the like.

[0172] In an exemplary embodiment, acyclic boronic esters described herein can be used as intermediates in the synthesis of the compounds described herein. In another exemplary embodiment, the acyclic boronic esters described herein can be used as intermediates in the synthesis of a compound which is a member selected from Formulae (I), (Ia) (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak).

I. f.) Acyclic Boronic Acids and Esters, part II

[0173] Acyclic boronic acids and esters described herein can also be utilized in the invention. These compounds can be used to kill or inhibit the growth of the microorganisms described herein, as well as treat the diseases described herein. In addition, these compounds can be used as synthetic intermediates in the generation of other compounds described herein. In an exemplary embodiment, these other compounds are the cyclic boronic esters and cyclic borinic esters described herein.

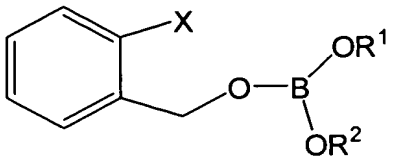
[0174] In another aspect, the compound has a structure according to the following formula:



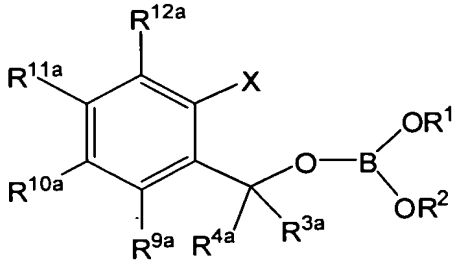
(X)

in which R^1 and R^2 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^1 and R^2, together with the atoms to which they are attached, can be optionally joined to form a 4- to 7-membered ring. X is a member selected from substituted or unsubstituted triflate, halogen, substituted or unsubstituted sulfonic esters and substituted or unsubstituted acyloxy groups, and substituted or unsubstituted diazo. R^{3a} and R^{4a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A is a member selected from CR^{9a} and N. D is a member selected from CR^{10a} and N. E is a member selected from CR^{11a} and N. G is a member selected from CR^{12a} and N. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R^*$, $-S(O)_2NR^*R^{**}$, -C(O)R*, -C(O)OR*, -C(O)NR*R**, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. Each R* and R** is a member independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{9a} and R^{10a}, along with the atoms to which they are attached, are optionally joined to form a ring. R^{10a} and R^{11a}, along with the atoms to which they are attached, are optionally joined to form a ring. R^{11a} and R^{12a}, along with the atoms to which they are attached, are optionally joined to form a ring. The combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3.

[0175] In an exemplary embodiment, this aspect has the proviso that the compound is not:



[0176] In an exemplary embodiment, the compound has a structure according to Formula (Xa)



(Xa)

[0177] In another exemplary embodiment, each R^{3a} and R^{4a} is a member independently selected from H, cyano, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted indolyl and substituted or unsubstituted amido. In another exemplary embodiment, each R^{3a} and R^{4a} is a member independently selected from cyano, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted indolyl, substituted or unsubstituted amido.

[0178] In another exemplary embodiment, each R^{3a} and R^{4a} is a member selected from H, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted

or unsubstituted butyl, substituted or unsubstituted t-butyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl. In another exemplary embodiment, R^{3a} and R^{4a} is a member selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In another exemplary embodiment, R^{3a} is H and R^{4a} is a member selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In another exemplary embodiment, R^{3a} is H and R^{4a} H.

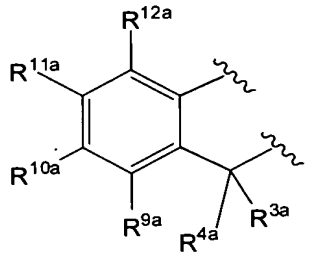
[0179] In another exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} is a member selected from H, OR*, NR*R**, SR*, -S(O)R*, -$S(O)_2$R*, -$S(O)_2$NR*R**, -C(O)R*, -C(O)OR*, -C(O)NR*R**, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted

benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl. In an exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are selected from the previous list of substituents with the exception of -C(O)R*, -C(O)OR*, -C(O)NR*R**.

[0180] In another exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-

chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, 4-fluorobenzyloxy, unsubstituted phenyl, unsubstituted benzyl. In an exemplary embodiment, R^{9a} is H and R^{12a} is H. In an exemplary embodiment, the compound has a subsitutent combination for R^{9a}, R^{10a}, R^{11a}, and R^{12a} which is a member selected from those described in Formulae (I), (Ia) (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak), above, and/or the subsequent paragraphs describing Formulae (I), (Ia) (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak).

[0181] In an exemplary embodiment, the compound is an acyclic boronic acid or ester in which a portion of the acyclic boronic acid or ester is as in Figure (IXb) below



(IXb)

is a member selected from a structure in **FIG. 12**. In another exemplary embodiment, the compound is a dimer, anhydride or trimer of an acyclic boronic acid or ester described herein. In another exemplary embodiment, the compound is a dimer, anhydride or trimer of an acyclic boronic acid or ester in which a portion of the acyclic boronic acid or ester as in Figure (IXb) is a member selected a structure in **FIG. 12**.

[0182] In an exemplary embodiment, R^1 and R^2 are each members independently selected from H, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted butyl, substituted or unsubstituted t-butyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl. R^1 and R^2, together with the atoms to which they are joined, can optionally form a member selected from substituted or unsubstituted dioxaborolane, substituted or unsubstituted

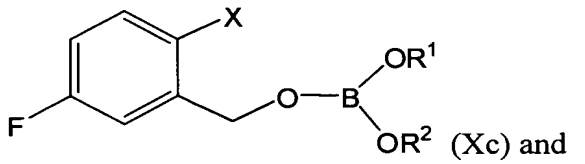
dioxaborinane, substituted or unsubstituted dioxaborepane.

[0183] In an exemplary embodiment, X is a member selected from triflate, chloro, bromo, iodo, substituted or unsubstituted sulfonic esters, substituted or unsubstituted acyloxy groups, and substituted or unsubstituted diazo. In an exemplary embodiment, X is a sulfonic ester group, which is a member selected from substituted or unsubstituted mesylate, substituted or unsubstituted tosylate, substituted or unsubstituted brosylate and substituted or unsubstituted nosylate. In an exemplary embodiment, X is an acyloxy group, which is a member selected from substituted or unsubstituted acetoxy and substituted or unsubstituted trifluoroacetoxy. In another exemplary embodiment, X is a member selected from bromo, iodo, mesylate and diazo. In another exemplary embodiment, X is a member selected from bromo and iodo.

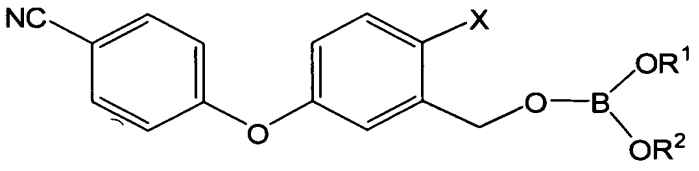
[0184] In another exemplary embodiment, R^1 and R^2, together with the atoms to which they are joined, form a member selected from dioxaborolane, substituted or unsubstituted tetramethyldioxaborolane, substituted or unsubstituted phenyldioxaborolane, dioxaborinane, dimethyldioxaborinane and dioxaborepane.

[0185] In another exemplary embodiment, R^{3a} and R^{4a} are each members independently selected from H, methyl, ethyl, propyl, butyl, phenyl, benzyl, cyano, halogen and nitro.

[0186] In an exemplary embodiment, the compound is a member selected from

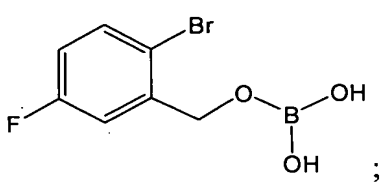
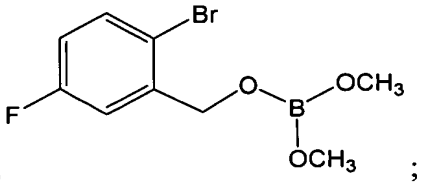
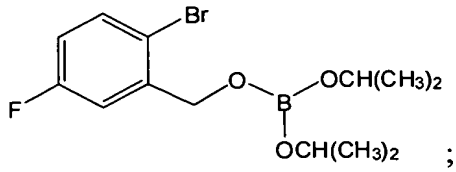
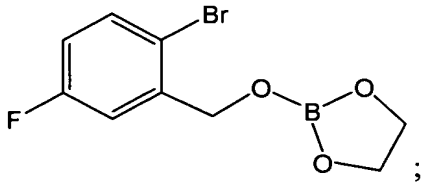
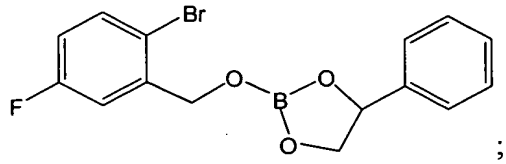
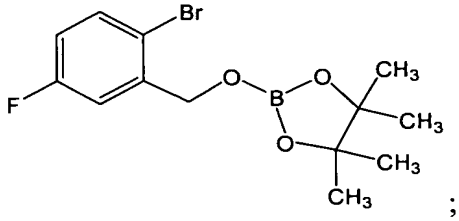
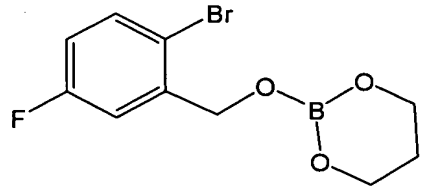
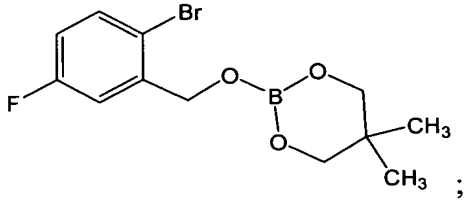
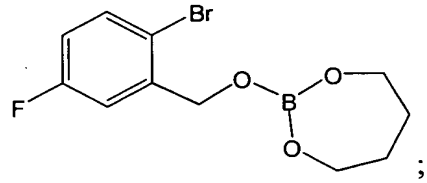
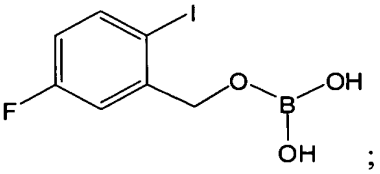
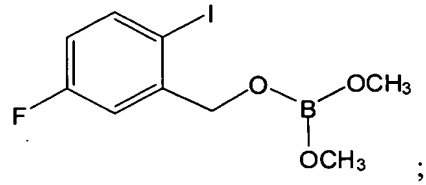
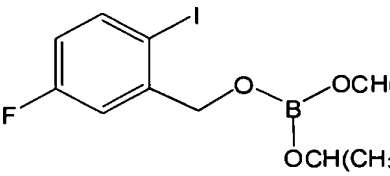
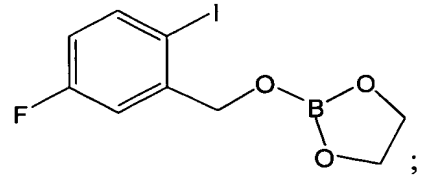
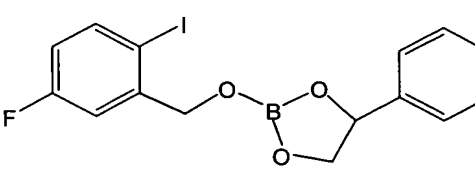
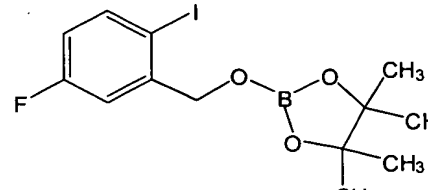
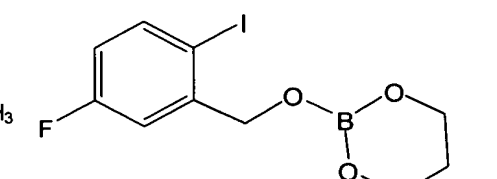


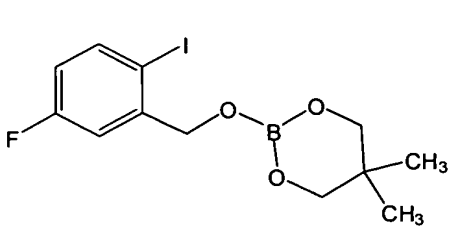
(Xc) and



(Xd)

[0187] In an exemplary embodiment, the compound is a member selected from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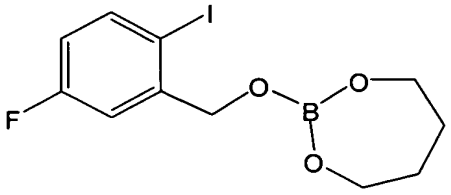
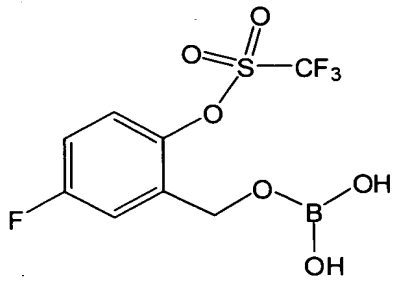
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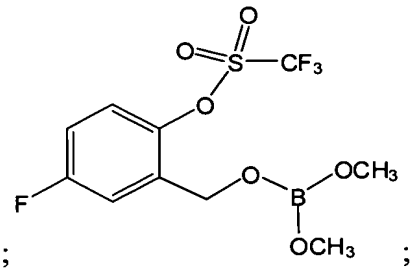
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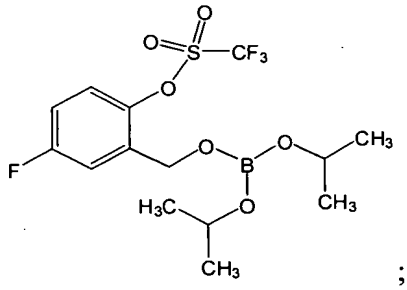
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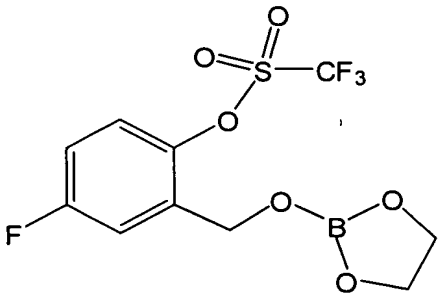
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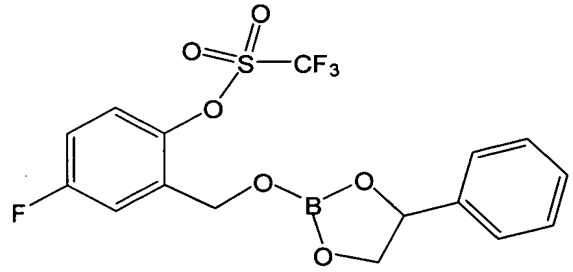
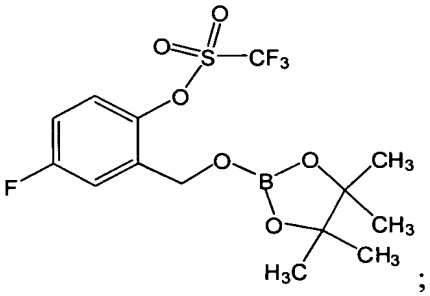
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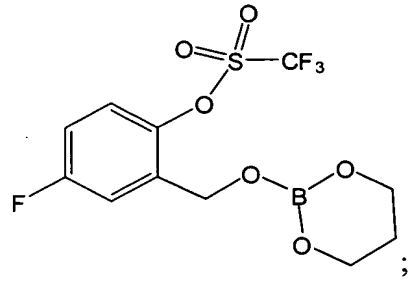
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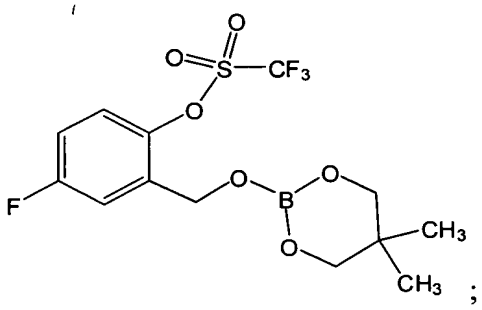
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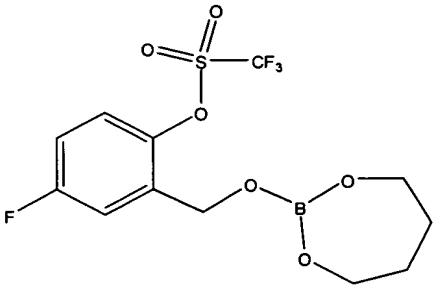
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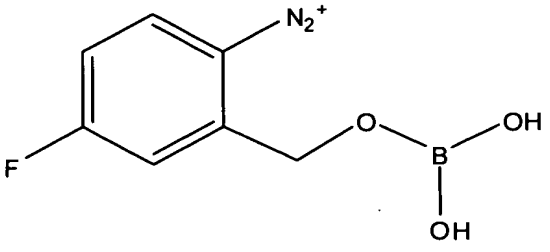
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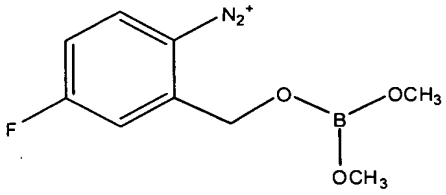
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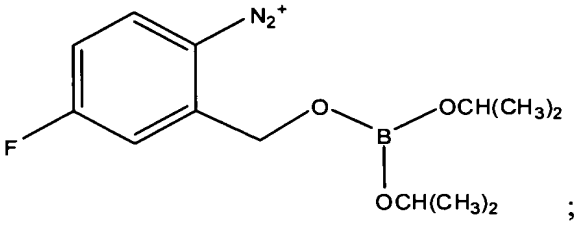
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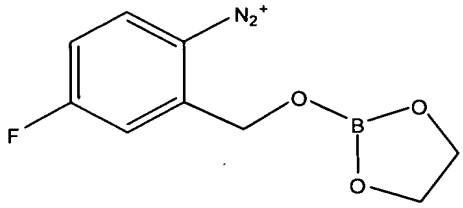
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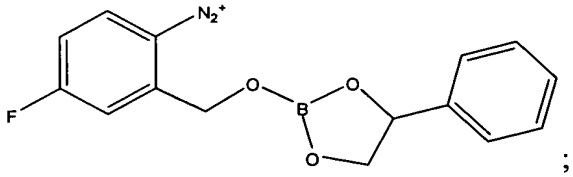
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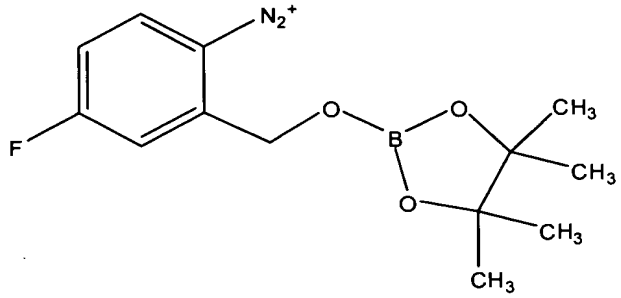
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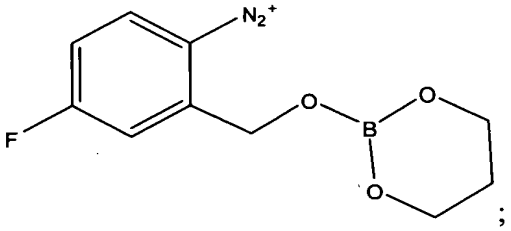
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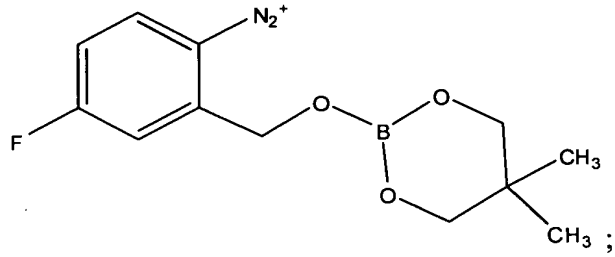
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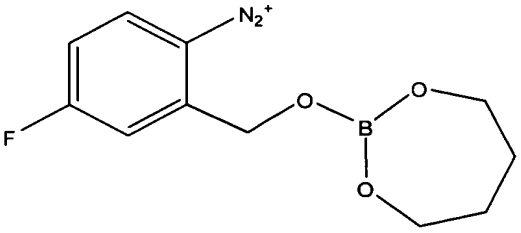
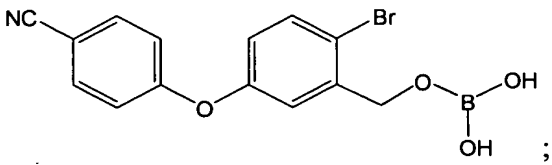
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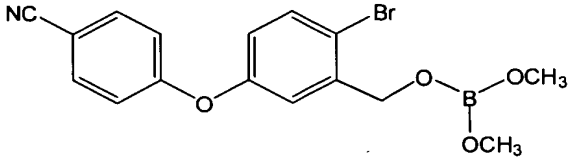

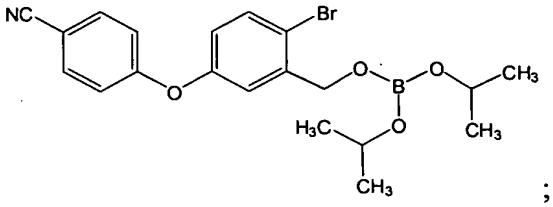
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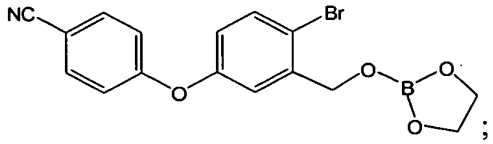
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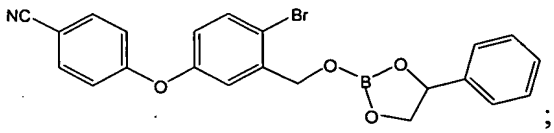
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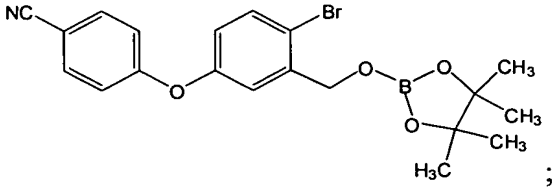
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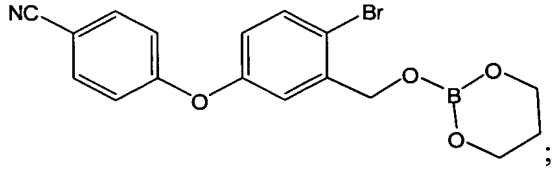
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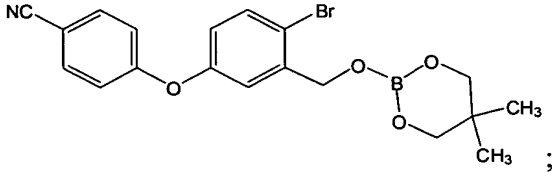
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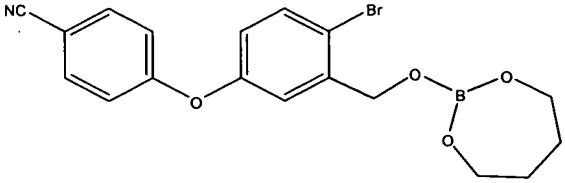
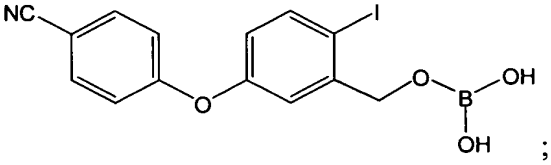
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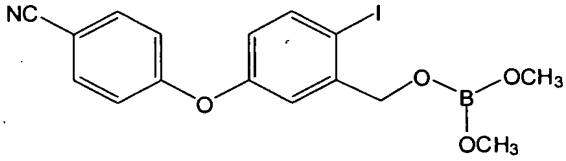
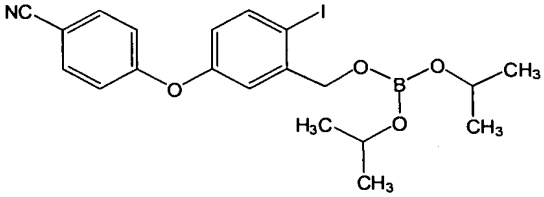
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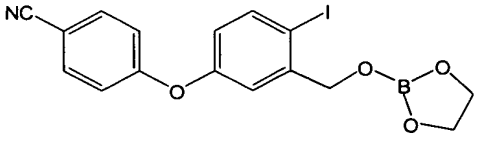
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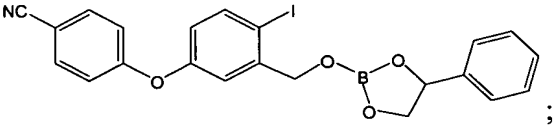
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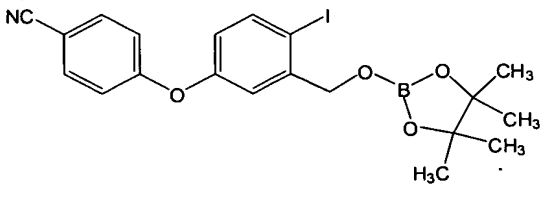
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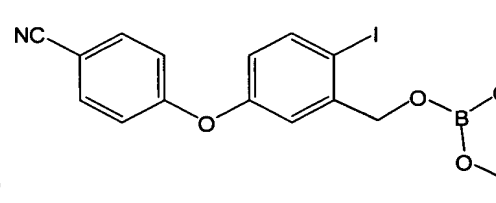
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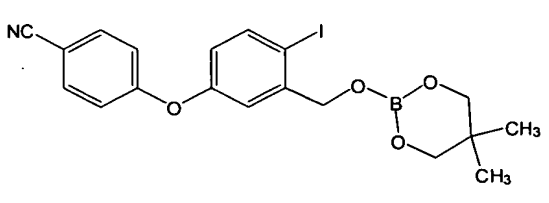
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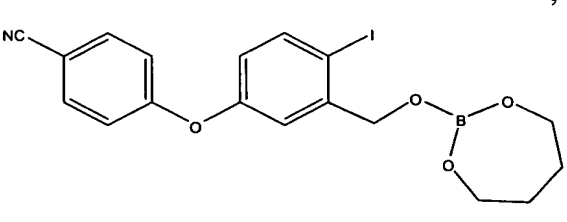
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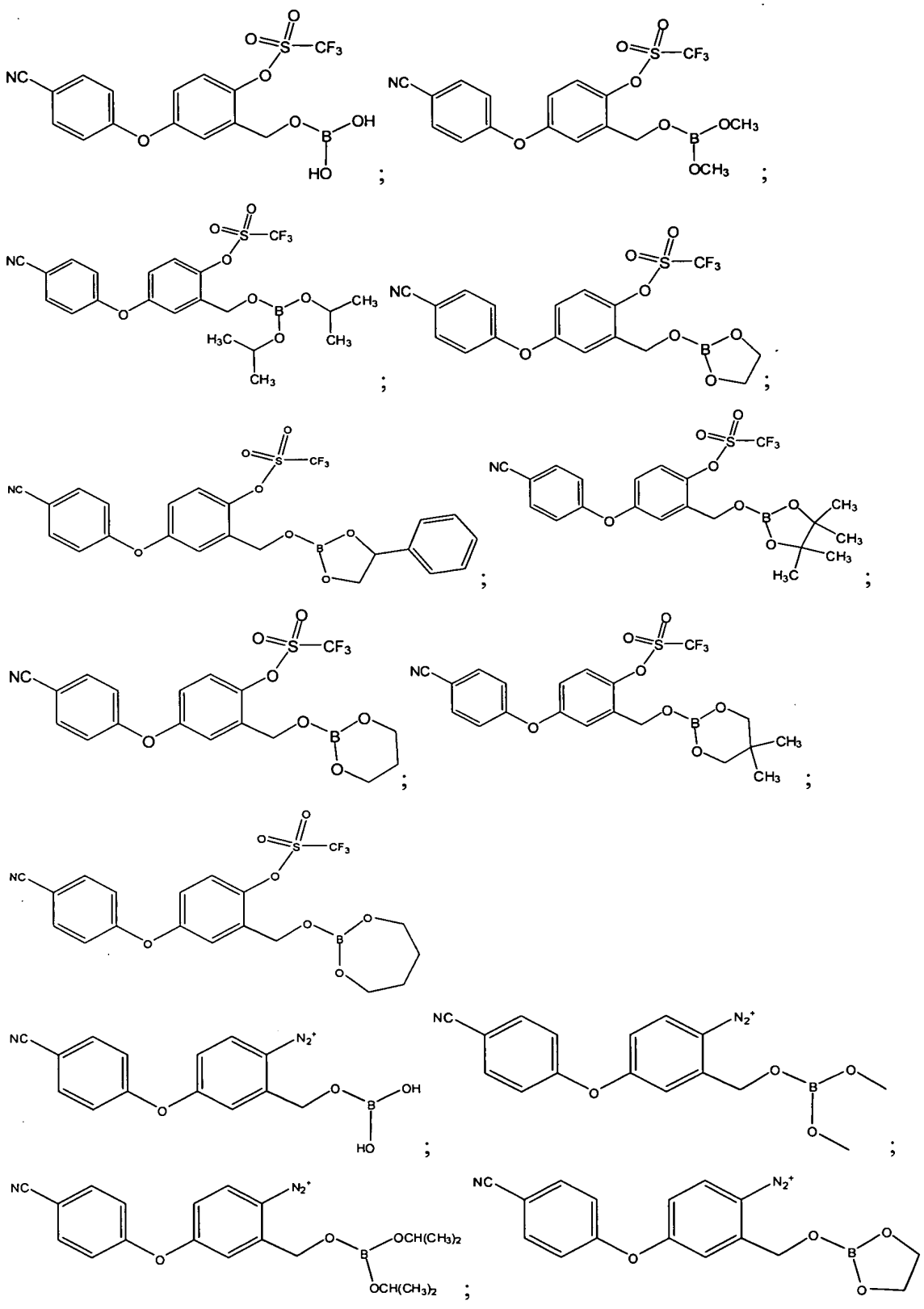
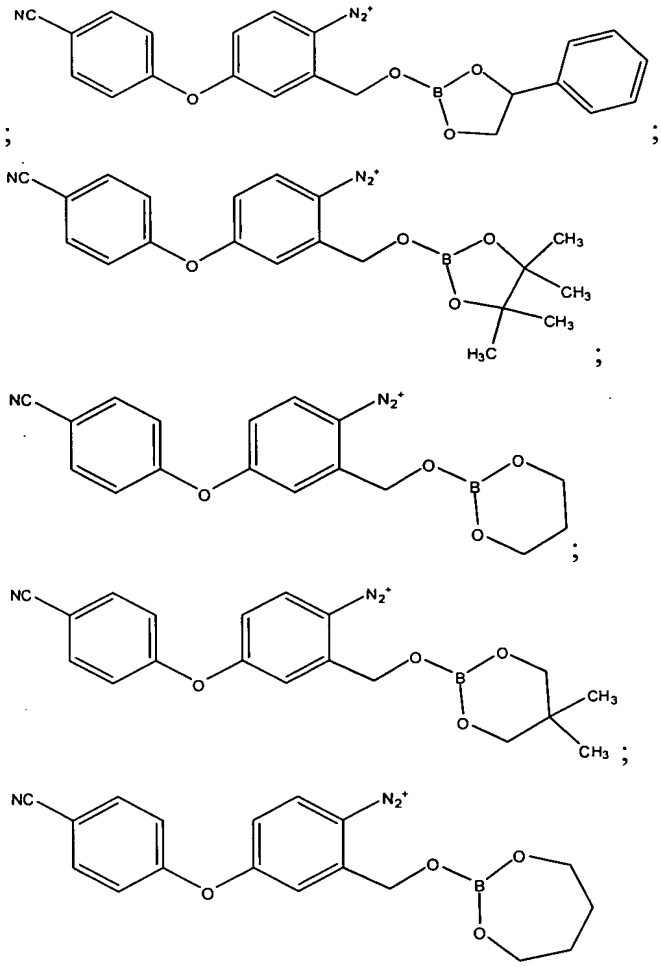




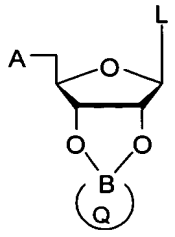
[0188] In an exemplary embodiment, acyclic boronic esters described herein can be used as intermediates in the synthesis of the compounds described herein. In another exemplary embodiment, the acyclic boronic esters described herein can be used as intermediates in the synthesis of a compound which is a member selected from Formulae (I), (Ia) (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak).

I. e.) Additional compounds

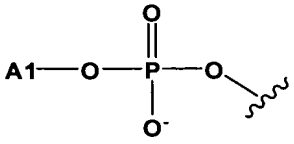
[0189] Compounds such as those described herein can also be utilized in the invention. The compounds of the invention can form between the 2',3' diol of the ribose ring of a nucleic acid, nucleoside or nucleotide, and a cyclic or acyclic boronic ester such as those described herein. These compounds can be used in a human or in an animal to kill or inhibit the growth of the microorganisms described herein, as well as to treat the diseases described herein. These compounds can be formed in vitro as

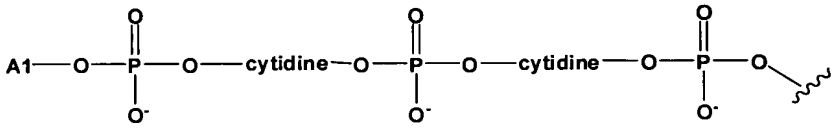
well as in vivo. Methods of making these compounds are provided in the Examples section.

[0190] In another aspect, the invention provides a compound having a structure according to the following formula:



(XII)

wherein B is boron. L is a member selected from OR^7, substituted or unsubstituted purine, substituted or unsubstituted pyrimidine, substituted or unsubstituted pyridine and substituted or unsubstituted imidazole. R^7 is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. A is a member selected from OH, substituted or unsubstituted monophosphate, substituted or unsubstituted diphosphate, substituted or unsubstituted triphosphate, 

; and 

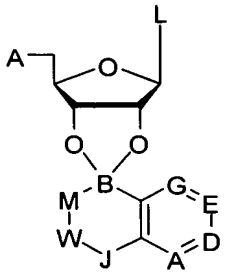
. A1 is a nucleic acid sequence which comprises between 1 and 100 nucleotides. Q is a member selected from substituted or unsubstituted heterocycloalkyl and substituted or unsubstituted heteroaryl. Q comprises said boron and at least one oxygen.

[0191] In an exemplary embodiment, the aspect has the proviso that the compound cannot comprise a member selected from C1-C40.

[0192] In an exemplary embodiment, the aspect has a proviso that the compound cannot comprise a member which is described in FIG. 11. In an exemplary embodiment, the aspect has a proviso that the compound cannot involve a compound which is described in expired U.S. Pat. No. 5,880,188.

[0193] In an exemplary embodiment, the compound has a structure according to

the following formula (XIIa):



(XIIa)

wherein M is a member selected from O and S. J is a member selected from $(CR^{3a}R^{4a})_{n1}$ and CR^{5a}. R^{3a}, R^{4a}, and R^{5a} are members independently selected from H, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. n1 is an integer selected from 0 to 2. W is a member selected from C=O (carbonyl), $(CR^{6a}R^{7a})_m$ and CR^{8a}. R^{6a}, R^{7a}, and R^{8a} are members independently selected from H, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The index m1 is an integer selected from 0 and 1. A is a member selected from CR^{9a} and N. D is a member selected from CR^{10a} and N. E is a member selected from CR^{11a} and N. G is a member selected from CR^{12a} and N. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R^*$, $-S(O)_2NR^*R^{**}$, -C(O)R*, -C(O)OR*, -C(O)NR*R**, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. Each R* and R** are members independently selected from H, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3. A member selected from R^{3a}, R^{4a} and R^{5a} and a member selected from R^{6a}, R^{7a} and R^{8a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{3a} and R^{4a}, together with the atoms to which they are

attached, are optionally joined to form a 4 to 7 membered ring. R^{6a} and R^{7a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{9a} and R^{10a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{10a} and R^{11a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{11a} and R^{12a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

[0194] In another exemplary embodiment, each R^{3a} and R^{4a} is a member independently selected from H, cyano, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted indolyl and substituted or unsubstituted amido. In another exemplary embodiment, each R^{3a} and R^{4a} is a member independently selected from cyano, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted indolyl, substituted or unsubstituted amido.

[0195] In another exemplary embodiment, each R^{3a} and R^{4a} is a member selected from H, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted butyl, substituted or unsubstituted t-butyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl. In another exemplary embodiment, R^{3a} and R^{4a} is a member selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In another exemplary embodiment, R^{3a} is H and R^{4a}

is a member selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In another exemplary embodiment, R^{3a} is H and R^{4a} H.

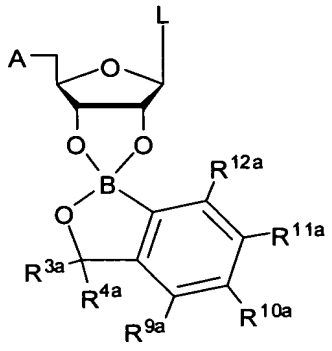
[0196] In another exemplary embodiment, each R^{9a}, R^{10a}, R^{11a} and R^{12a} is a member independently selected from H, OR*, NR*R**, SR*, -S(O)R*, -$S(O)_2$R*, -$S(O)_2$NR*R**, -C(O)R*, -C(O)OR*, -C(O)NR*R**, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or

unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl. In an exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are selected from the previous list of substituents with the exception of -C(O)R*, -C(O)OR*, -C(O)NR*R**.

[0197] In another exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-

fluorobenzyloxy, 3-fluorobenzyloxy, 4-fluorobenzyloxy, unsubstituted phenyl, unsubstituted benzyl.

[0198] In an exemplary embodiment, the compound has a structure according to the following formula:



(XIIb).

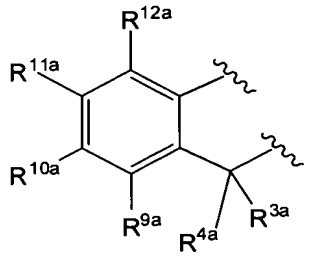
In another exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino,

substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl.

[0199] In another exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-

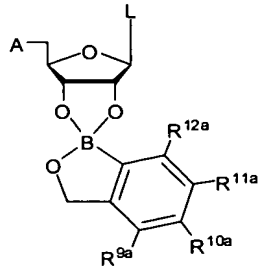
yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy. In an exemplary embodiment, R^{9a} is H and R^{12a} is H. In an exemplary embodiment, the compound has a subsitutent combination for R^{9a}, R^{10a}, R^{11a}, and R^{12a} which is a member selected from those described in Formulae (I), (Ia) (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak) above, and/or the subsequent paragraphs describing Formulae (I), (Ia) (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak).

[0200] In an exemplary embodiment, the portion of the cyclic boronic ester as in the figure below



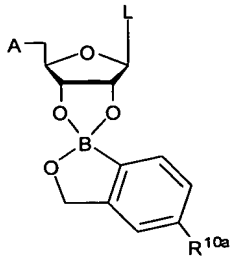
is a member selected from a structure in **FIG. 12**.

[0201] In an exemplary embodiment, the compound has a structure according to the following formula:



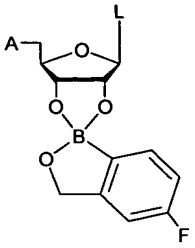
(XIIc)

[0202] In an exemplary embodiment, the compound has a structure according to the following formula:



(XIId)

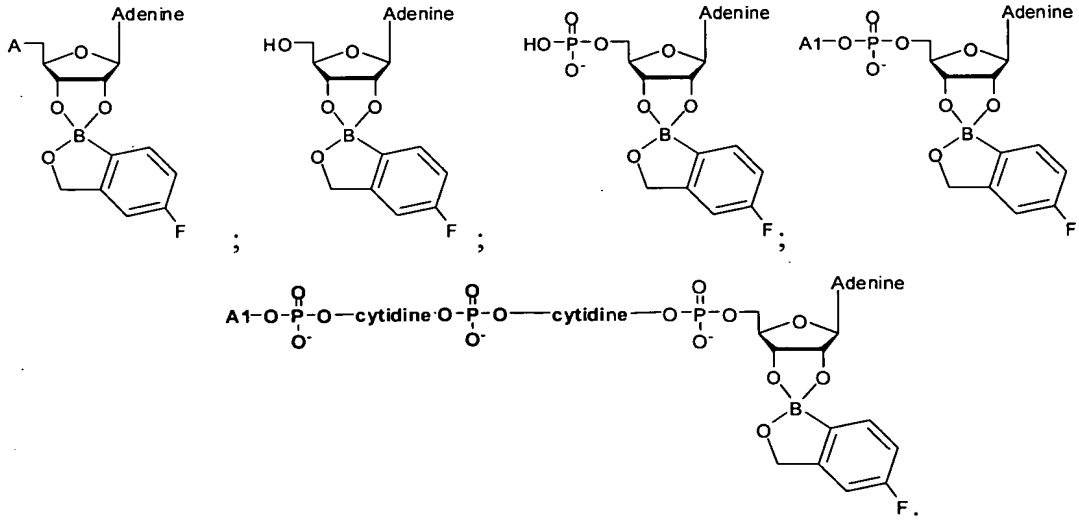
In an exemplary embodiment, the compound has a structure according to the following formula:



(XIIe)

[0203] In another exemplary embodiment, the compound has a structure which is a member selected from Formulae (XII), (XIIa), (XIIb), (XIIc), (XIId) and (XIIe) wherein L is a member selected from substituted or unsubstituted adenine, substituted or unsubstituted guanine, substituted or unsubstituted cytidine, substituted or unsubstituted uracil, and substituted or unsubstituted thymine. In another exemplary embodiment, L is OH. In another exemplary embodiment, L is adenine.

[0204] In another exemplary embodiment, the compound has a structure which is a member selected from



[0205] In another exemplary embodiment, A1 is a nucleic acid sequence between 72 and 90 nucleotides. In another exemplary embodiment, A1 is a nucleic acid sequence between 35 and 150 nucleotides. In another exemplary embodiment, A1 is a nucleic acid sequence between 50 and 100 nucleotides. In another exemplary embodiment, A1 is a nucleic acid sequence between 75 and 85 nucleotides. In another exemplary embodiment, A1 is a nucleic acid sequence which is a tRNA or a portion of a tRNA. In another exemplary embodiment, said tRNA or the portion of said tRNA is a member selected from alanyl tRNA, isoleucyl tRNA, leucyl tRNA, methionyl tRNA, lysyl tRNA, phenylalanyl tRNA, prolyl tRNA, threonyl tRNA and valyl tRNA. In another exemplary embodiment, said tRNA or the portion of said tRNA is leucyl tRNA. In another exemplary embodiment, said tRNA or the portion of said tRNA has a sequence which is a member selected from SEQ ID NOS: 18-62. In another exemplary embodiment, A1 is a nucleic acid sequence wherein two final nucleotides are each cytidine.

[0206] In another exemplary embodiment, the compound further comprises a tRNA synthetase or a portion of a tRNA synthetase which comprises the editing domain, wherein said compound is noncovalently attached to the editing domain of said tRNA synthetase. In another exemplary embodiment, the tRNA synthetase is a member selected from a mitochondrial tRNA synthetase and a cytoplasmic tRNA synthetase. In another exemplary embodiment, the tRNA synthetase is a member selected from alanyl tRNA synthetase, isoleucyl tRNA synthetase, leucyl tRNA synthetase, methionyl tRNA synthetase, lysyl tRNA synthetase, phenylalanyl tRNA synthetase, prolyl tRNA synthetase, threonyl tRNA synthetase and valyl tRNA synthetase.

[0207] In an exemplary embodiment, the compound described herein is present in a microorganism described in this application.

[0208] In another exemplary embodiment, there is a proviso that the compound is not present in a microorganism that is a member selected from *Saccharomyces cerevisiae*, *Aspergillus niger*, *Pseudomonas aeruginosa*, *Staphlococcus aureus*, *Aureobasidium pullulans*, *Fusarium solani*, *Penicillium pinophilum*, *Scopulariopsis brevicaulis*, *Streptoverticillium waksmanii*, *Alternaria alternata*, *Cladosporium herbarum*, *Phoma violacea*, *Stemphylium dentriticum*, *Candida albicans*, *Escherichia coli*, and *Glioclasium roseum*. In another exemplary embodiment, there is a proviso

that when the compound is present in a fungus, the fungus is not a member selected from *Saccharomyces cerevisiae, Aspergillus niger, Fusarium solani, Penicillium pinophilum, Scopulariopsis brevicaulis, Streptoverticillium waksmanii, Alternaria alternata, Cladosporium herbarum, Phoma violacea, Stemphylium dentriticum, Candida albicans,* and *Glioclasium roseum.*

[0209] In an exemplary embodiment, the compound is present in a microorganism which is a member selected from a dermatophyte, *Trichophyton, Microsporum, Epidermophyton* and yeast-like fungi. In an exemplary embodiment, there is a proviso that when the compound is present in a yeast-like fungus, that yeast-like fungus is not a member selected from *Aspergillus niger* and *Candida albicans.* In another exemplary embodiment, the microorganism is a member selected from a dermatophyte, *Trichophyton, Microsporum, Epidermophyton* and yeast-like fungi. In an exemplary embodiment, the microorganism is a dermatophyte. In another exemplary embodiment, the microorganism is a member selected from *Trichophyton* species. In an exemplary embodiment, the microorganism is a member selected from is a member selected from *T. rubrum* and *T. menagrophytes.* In an exemplary embodiment, the microorganism is a dermatophyte and said dermatophyte is a member selected from *T. rubrum* and *T. menagrophytes.*

[0210] In another exemplary embodiment, the compound is present in a human or an animal. In another exemplary embodiment, the compound is present in a microorganism which is in, or on the surface of, a human or an animal. In another exemplary embodiment, the compound is present in a microoganism which is present in a human nail unit of a human or a nail, hoof, or horn component of an animal. In another exemplary embodiment, the compound is present in a microoganism which is present in a member selected from a human nail plate, human nail bed, proximal nail fold, lateral nail fold and combinations thereof. In another exemplary embodiment, the compound is present in a microoganism which is present in a member selected from a human nail plate and a human nail bed. In another exemplary embodiment, the compound is present in a microoganism which is present in a member selected from a proximal nail fold and a lateral nail fold. In another exemplary embodiment, the microorganism is a member selected from dermatophyte, *Trichophyton, Microsporum, Epidermophyton* and yeast-like fungi. In another exemplary embodiment, wherein said compound is a dermatophyte. In another exemplary

embodiment, the dermatophyte is a member selected from *T. rubrum* and *T. menagrophytes*.

I. f.) ***Formulations with keratin***

[0211] When a compound of the invention described herein is applied to a nail component of a human, the compound absorbs or penetrates into the nail. The human nail is primarily composed of keratin (i.e. hair keratin or α-keratin) as well as trace amounts of lipid components. Therefore, in the process of treating a disease of the nail or killing or inhibiting the growth of a microorganism, a formulation comprising a human nail unit and a compound of the invention is formed.

[0212] In another aspect, the invention provides a formulation comprising: (a) a compound which is a member selected from a boron-containing compound, a 2'-amino ribofuranose-containing compound, a 3'-amino ribofuranose-containing compound, and combinations thereof; and (b) a keratin containing component which is a member selected from a human nail unit, skin and hair. In an exemplary embodiment, the compound of part (a) contacts the component of part (b). In an exemplary embodiment, the keratin containing component is a nail plate of the human nail unit. In an exemplary embodiment, the keratin containing component is a nail bed of the human nail unit. In an exemplary embodiment, the keratin containing component is a proximal nail fold of the human nail unit. In an exemplary embodiment, the keratin containing component is a lateral nail fold of the human nail unit. In another exemplary embodiment, the human nail unit comprises a member selected from keratin and lipid. In another exemplary embodiment, keratin is a member selected from skin keratin and nail/hair keratin. In another exemplary embodiment, lipid is a member selected from cholesterol sulfate, cerebroside, ceramide, free sterol, free fatty acids, triglycerides, sterol esters, wax esters, and squalene.

[0213] In an exemplary embodiment, the compound is present in the formulation at a concentration which is a member selected from about 0.001%, about 0.01%, about 0.05%, about 0.1%, about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%. In another exemplary embodiment, the keratin is present in said formulation at a concentration which is a member selected from about 99.99%, about 99.95%, about 99.90%, about 99.5%, about 99.0%, about 98.5%, about 98.0%, about 97.5% and

about 97%. In another exemplary embodiment, the compound is a compound described herein. In another exemplary embodiment, the compound is as described in Formulae (I), (Ia) (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), (Il), (Im), (In), (Io), (Ip), (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak), (II), (IIa), (IIb), (IIc), (IId), and (III). In another exemplary embodiment, the compound is an acyclic boronic ester as described herein. In another exemplary embodiment, the compound is a member selected from C1-C96 described herein. In another exemplary embodiment, the compound is a member selected from a compound appearing in Figure 19. In another exemplary embodiment, the compound is a member selected from a compound appearing in Figure 20. In another exemplary embodiment, the compound is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. In another exemplary embodiment, 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole is present is said formulation at a concentration which is a member selected from about 0.001%, about 0.01%, about 0.05%, about 0.1%, about 0.5%, about 1%, and about 1.5%.

[0214] In another aspect, the invention provides a method of forming this formulation, wherein said method comprises applying said compound to a formulation comprising keratin, thereby forming said formulation. In an exemplary embodiment, the formulation comprising keratin is a human nail unit. In an exemplary embodiment, the formulation comprising keratin is a member selected from a nail plate, nail bed, proximal nail fold, and lateral nail fold. Methods of making these formulations are described in the Examples section.

I. g.) Preparation of Boron-Containing Editing Domain Inhibitors

[0215] Compounds of use in the present invention can be prepared using commercially available starting materials, known intermediates, or by using the synthetic methods published in references described and incorporated by reference herein.

I. h.) Boronic Esters

[0216] The following exemplary schemes illustrate methods of preparing boron-containing molecules of the present invention. These methods are not limited to producing the compounds shown, but can be used to prepare a variety of molecules such as the compounds and complexes described herein. The compounds of the

present invention can also be synthesized by methods not explicitly illustrated in the schemes but are well within the skill of one in the art. The compounds can be prepared using readily available materials of known intermediates.

[0217] In the following schemes, the symbol X represents bromo or iodo. The symbol Y is selected from H, lower alkyl, and arylalkyl. The symbol Z is selected from H, alkyl, and aryl. The symbol PG represents protecting group. The symbols A, D, E, G, R^x, R^y, R^z, R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a}, and R^{12a} can be used to refer to the corresponding symbols in the compounds described herein.

Boronic Acid Preparation Strategy #1

[0218] In Scheme 1, Step 1 and 2, compounds 1 or 2 are converted into alcohol 3. In step 1, compound 1 is treated with a reducing agent in an appropriate solvent. Suitable reducing agents include borane complexes, such as borane-tetrahydrofuran, borane-dimethylsulfide, combinations thereof and the like. Lithium aluminum hydride, or sodium borohydride can also be used as reducing agents. The reducing agents can be used in quantities ranging from 0.5 to 5 equivalents, relative to compound 1 or 2. Suitable solvents include diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, combinations thereof and the like. Reaction temperatures range from 0°C to the boiling point of the solvent used; reaction completion times range from 1 to 24 h.

[0219] In Step 2, the carbonyl group of compound 2 is treated with a reducing agent in an appropriate solvent. Suitable reducing agents include borane complexes, such as borane-tetrahydrofuran, borane-dimethylsulfide, combinations thereof and the like. Lithium aluminum hydride, or sodium borohydride can also be used as reducing agents. The reducing agents can be used in quantities ranging from 0.5 to 5 equivalents, relative to compound 2. Suitable solvents include lower alcohol, such as methanol, ethanol, and propanol, diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane, combinations thereof and the like. Reaction temperatures range from 0°C to the boiling point of the solvent used; reaction completion times range from 1 to 24 h.

[0220] In Step 3, the hydroxyl group of compound 3 is protected with a protecting group which is stable under neutral or basic conditions. The protecting group is typically selected from methoxymethyl, ethoxyethyl, tetrahydropyran-2-yl,

trimethylsilyl, *tert*-butyldimethylsilyl, tributylsilyl, combinations thereof and the like. In the case of methoxymethyl, compound 3 is treated with 1 to 3 equivalents of chloromethyl methyl ether in the presence of a base. Suitable bases include sodium hydride, potassium *tert*-butoxide, tertiary amines, such as diisopropylethylamine, triethylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene, and inorganic bases, such as sodium hydroxide, sodium carbonate, potassium hydroxide, potassium carbonate, combinations thereof and the like. The bases can be used in quantities ranging from 1 to 3 equivalents, relative to compound 3. Reaction temperatures range from 0°C to the boiling point of the solvent used; preferably between 0 and 40 °C; reaction completion times range from 1 h to 5 days.

[0221] In the case of tetrahydropyran-2-yl, compound 3 is treated with 1 to 3 equivalents of 3,4-dihydro-2*H*-pyran in the presence of 1 to 10 mol% of acid catalyst. Suitable acid catalysts include pyridinium *p*-toluenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, methanesulfonic acid, hydrogen chloride, sulfuric acid, combinations thereof and the like. Suitable solvents include dichloromethane, chloroform, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, toluene, benzene, and acetonitrile combinations thereof and the like. Reaction temperatures range from 0°C to the boiling point of the solvent used; preferably between 0 and 60 °C, and is complete in 1h to 5 days.

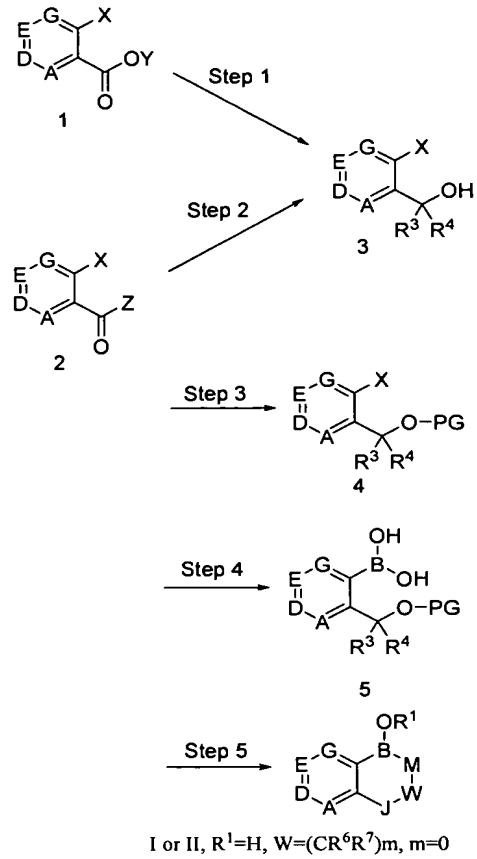
[0222] In the case of trialkylsilyl, compound 3 is treated with 1 to 3 equivalents of chlorotrialkylsilyane in the presence of 1 to 3 equivalents of base. Suitable bases include tertiary amines, such as imidazole, diisopropylethylamine, triethylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene, combinations thereof and the like. Reaction temperatures range from 0°C to the boiling point of the solvent used; preferably between 0 and 40 °C; reaction completion times range from 1 to 48 h.

[0223] In Step 4, compound 4 is converted into boronic acid (5) through halogen metal exchange reaction. Compound 4 is treated with 1 to 3 equivalents of alkylmetal reagent relative to compound 4, such as *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, isopropylmagnesium chloride or Mg turnings with or without an initiator such as diisobutylaluminum hydride (DiBAl), followed by the addition of 1 to 3 equivalents of trialkyl borate relative to compound 4, such as trimethyl borate, triisopropyl borate, or tributyl borate. Suitable solvents include tetrahydrofuran,

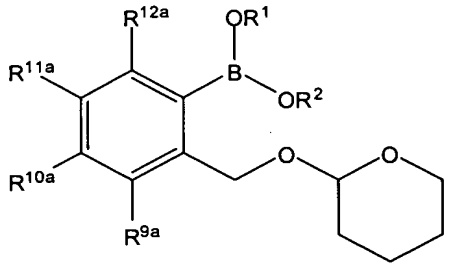
ether, 1,4-dioxane, 1,2-dimethoxyethane, toluene, hexanes, combinations thereof and the like. Alkylmetal reagent may also be added in the presence of trialkyl borate. The addition of butyllithium is carried out at between -100 and 0 °C, preferably at between -80 and -40 °C. The addition of isopropylmagnesium chloride is carried out at between -80 and 40 °C, preferably at between -20 and 30 °C. The addition of Mg turnings, with or without the addition of DiBAl, is carried out at between -80 and 40 °C, preferably at between -35 and 30 °C. The addition of the trialkyl borate is carried out at between -100 and 20 °C. After the addition of trialkyl borate, the reaction is allowed to warm to room temperature, which is typically between -30 and 30 °C. When alkylmetal reagent is added in the presence of trialkyl borate, the reaction mixture is allowed to warm to room temperature after the addition. Reaction completion times range from 1 to 12 h. Compound 5 may not be isolated and may be used for the next step without purification or in one pot.

[0224] In Step 5, the protecting group of compound 5 is removed under acidic conditions to give compound of the invention. Suitable acids include acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, *p*-toluenesulfonic acid and the like. The acids can be used in quantities ranging from 0.1 to 20 equivalents, relative to compound 5. When the protecting group is trialkylsilyl, basic reagents, such as tetrabutylammonium fluoride, can also be used. Suitable solvents include tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, methanol, ethanol, propanol, acetonitrile, acetone, combination thereof and the like. Reaction temperatures range from 0°C to the boiling point of the solvent used; preferably between 10 °C and reflux temperature of the solvent; reaction completion times range from 0.5 to 48 h. The product can be purified by methods known to those of skill in the art.

Scheme 1

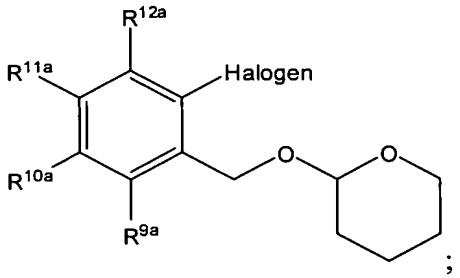


[0225] In another aspect, the invention provides a method of making a tetrahydropyran-containing boronic ester, said ester having a structure according to the following formula:



wherein R^1 and R_2 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^1 and R^2, together with the atoms to which they are attached, can be optionally joined to form a 4- to 7-membered ring. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R^*$, $-S(O)_2NR^*R^{**}$, nitro, halogen, cyano,

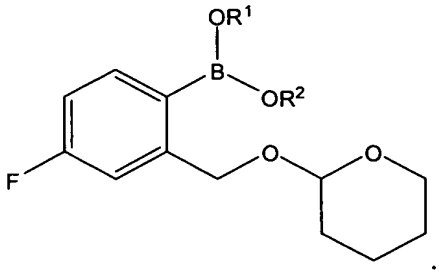
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R* and R** is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The method comprises: a) subjecting a first compound to Grignard or organolithium conditions, said first compound having a structure according to the following formula:



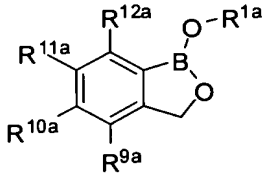
;

b) contacting the product of step a) with a borate ester, thereby forming said tetrahydropyran-containing boronic ester. In an exemplary embodiment, halogen is a member selected from iodo and bromo. In another exemplary embodiment, the borate ester is a member selected from $B(OR^1)_2(OR^2)$, wherein R^1 and R^2 are each members independently selected from H, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted butyl, substituted or unsubstituted t-butyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl. R^1 and R^2, together with the atoms to which they are joined, can optionally form a member selected from substituted or unsubstituted dioxaborolane, substituted or unsubstituted dioxaborinane and substituted or unsubstituted dioxaborepane. In another exemplary embodiment, the borate ester is a member selected from $B(OR^1)_2(OR^2)$, wherein R^1 and R^2, together with the atoms to which they are joined, form a member selected from dioxaborolane, substituted or unsubstituted tetramethyldioxaborolane, substituted or unsubstituted phenyldioxaborolane, dioxaborinane, dimethyldioxaborinane and dioxaborepane. In another exemplary embodiment, the Grignard or organolithium conditions further comprise diisobutyl aluminum hydride. In another exemplary embodiment, the

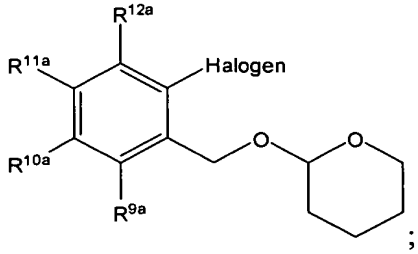
temperature of the Grignard reaction does not exceed about 35°C. In another exemplary embodiment, the temperature of the Grignard reaction does not exceed about 40°C. In another exemplary embodiment, the temperature of the Grignard reaction does not exceed about 45°C. In an exemplary embodiment, step (b) is performed at a temperature of from about -30°C to about -20°C. In another exemplary embodiment, step (b) is performed at a temperature of from about -35°C to about -25°C. In another exemplary embodiment, step (b) is performed at a temperature of from about -50°C to about -0°C. In another exemplary embodiment, step (b) is performed at a temperature of from about -40°C to about -20°C. In another exemplary embodiment, the tetrahydropyran-containing boronic ester is



[0226] In another aspect, the invention provides a method of making a compound having a structure according to the following formula



said method comprising: a) subjecting a first compound to Grignard or organolithium conditions, said first compound having a structure according to the following formula:



;

b) quenching said subjecting reaction with water and a organic acid, thereby forming said compound. In an exemplary embodiment, wherein said organic acid is a member selected from acetic acid. In another exemplary embodiment, the quenching step is

essentially not contacted with a strong acid. In another exemplary embodiment, the compound is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. In another exemplary embodiment, the compound is purified by recrystallization from a recrystallization solvent, wherein said recrystallization solvent essentially does not contain acetonitrile. In an exemplary embodiment, the recrystallization solvent contains less than 2% acetonitrile. In an exemplary embodiment, the recrystallization solvent contains less than 1% acetonitrile. In an exemplary embodiment, the recrystallization solvent contains less than 0.5% acetonitrile. In an exemplary embodiment, the recrystallization solvent contains less than 0.1% acetonitrile. In an exemplary embodiment, the recrystallization solvent contains toluene and a hydrocarbon solvent. In an exemplary embodiment, the recrystallization solvent contains about 1:1 toluene: hydrocarbon solvent. In an exemplary embodiment, the recrystallization solvent contains about 2:1 toluene: hydrocarbon solvent. In an exemplary embodiment, the recrystallization solvent contains about 3:1 toluene: hydrocarbon solvent. In an exemplary embodiment, the recrystallization solvent contains about 4:1 toluene: hydrocarbon solvent. In an exemplary embodiment, the hydrocarbon solvent is a member selected from heptane, octane, hexane, pentane and nonane. In an exemplary embodiment, the recrystallization solvent is 3:1 toluene: heptane.

Boronic Acid Preparation Strategy #2

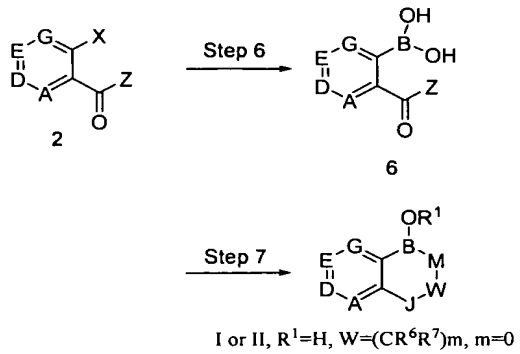
[0227] In Scheme 2, Step 6, compound 2 is converted into boronic acid (6) *via* a transition metal catalyzed cross-coupling reaction. Compound 2 is treated with 1 to 3 equivalents of bis(pinacolato)diboron or 4,4,5,5-tetramethyl-1,3,2-dioxaborolane in the presence of transition metal catalyst, with the use of appropriate ligand and base as necessary. Suitable transition metal catalysts include palladium(II) acetate, palladium(II) acetoacetonate, tetrakis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, [1,1'-bis(diphenylphosphino)ferrocen] dichloropalladium(II), combinations thereof and the like. The catalyst can be used in quantities ranging from 1 to 5 mol% relative to compound 2. Suitable ligands include triphenylphosphine, tri(*o*-tolyl)phosphine, tricyclohexylphosphine, combinations thereof and the like. The ligand can be used in quantities ranging from 1 to 5 equivalents relative to compound 2. Suitable bases include sodium carbonate, potassium carbonate, potassium phenoxide, triethylamine, combinations thereof and

the like. The base can be used in quantities ranging from 1 to 5 equivalents relative to compound 2. Suitable solvents include *N,N*-dimethylformamide, dimethylsufoxide, tetrahydrofuran, 1,4-dioxane, toluene, combinations thereof and the like. Reaction temperatures range from 20 °C to the boiling point of the solvent used; preferably between 50 and 150 °C; reaction completion times range from 1 to 72 h.

[0228] Pinacol ester is then oxidatively cleaved to give compound 6. Pinacol ester is treated with sodium periodate followed by acid. Sodium periodate can be used in quantities ranging from 2 to 5 equivalents relative to compound 6. Suitable solvents include tetrahydrofuran, 1,4-dioxane, acetonitrile, methanol, ethanol, combinations thereof and the like. Suitable acids include hydrochloric acid, hydrobromic acid, sulfuric acid combinations thereof and the like. Reaction temperatures range from 0 °C to the boiling point of the solvent used; preferably between 0 and 50 °C; reaction completion times range from 1 to 72 h.

[0229] In Step 7, the carbonyl group of compound 6 is treated with a reducing agent in an appropriate solvent to give a compound of the invention. Suitable reducing agents include borane complexes, such as borane-tetrahydrofuran, borane-dimethylsulfide, combinations thereof and the like. Lithium aluminum hydride, or sodium borohydride can also be used as reducing agents. The reducing agents can be used in quantities ranging from 0.5 to 5 equivalents, relative to compound 6. Suitable solvents include lower alcohol, such as methanol, ethanol, and propanol, diethyl ether, tetrahydrofuran, 1,4-dioxane and 1,2-dimethoxyethane, combinations thereof and the like. Reaction temperatures range from 0°C to the boiling point of the solvent used; reaction completion times range from 1 to 24 h.

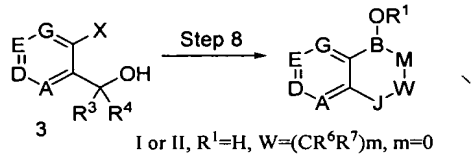
Scheme 2



Boronic Acid Preparation Strategy #3

[0230] In Scheme 3, Step 8, compounds of the invention can be prepared in one step from compound 3. Compound 3 is mixed with trialkyl borate then treated with alkylmetal reagent. Suitable alkylmetal reagents include *n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium combinations thereof and the like. Suitable trialkyl borates include trimethyl borate, triisopropyl borate, tributyl borate, combinations thereof and the like. The addition of butyllithium is carried out at between -100 and 0 °C, preferably at between -80 and -40 °C. The reaction mixture is allowed to warm to room temperature after the addition. Reaction completion times range from 1 to 12 h. The trialkyl borate can be used in quantities ranging from 1 to 5 equivalents relative to compound 3. The alkylmetal reagent can be used in quantities ranging from 1 to 2 equivalents relative to compound 3. Suitable solvents include tetrahydrofuran, ether, 1,4-dioxane, 1,2-dimethoxyethane, toluene, hexanes, combinations thereof and the like. Reaction completion times range from 1 to 12 h. Alternatively, a mixture of compound 3 and trialkyl borate can be refluxed for 1 to 3 h and the alcohol molecule formed upon the ester exchange can be distilled out before the addition of alkylmetal reagent.

Scheme 3



Boronic Acid Preparation Strategy #4

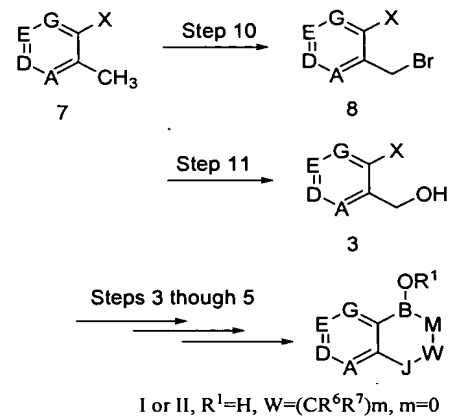
[0231] In Scheme 4, Step 10, the methyl group of compound 7 is brominated using *N*-bromosuccinimide. *N*-bromosuccinimide can be used in quantities ranging from 0.9 to 1.2 equivalents relative to compound 7. Suitable solvents include carbon tetrachloride, tetrahydrofuran, 1,4-dioxane, chlorobenzene, combinations thereof and the like. Reaction temperatures range from 20 °C to the boiling point of the solvent used; preferably between 50 and 150 °C; reaction completion times range from 1 to 12 h.

[0232] In Step 11, the bromomethylene group of compound 8 is converted to the benzyl alcohol 3. Compound 8 is treated with sodium acetate or potassium acetate. These acetates can be used in quantities ranging from 1 to 10 equivalents relative to

compound 8. Suitable solvents include tetrahydrofuran, 1,4-dioxane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, dimethylsulfoxide, combinations thereof and the like. Reaction temperatures range from 20 °C to the boiling point of the solvent used; preferably between 50 and 100 °C; reaction completion times range from 1 to 12 h. The resulting acetate is hydrolyzed to compound 3 under basic conditions. Suitable bases include sodium hydroxide, lithium hydroxide, potassium hydroxide, combinations thereof and the like. The base can be used in quantities ranging from 1 to 5 equivalents relative to compound 8. Suitable solvents include methanol, ethanol, tetrahydrofuran, water, combinations thereof and the like. Reaction temperatures range from 20 °C to the boiling point of the solvent used; preferably between 50 and 100 °C; reaction completion times range from 1 to 12 h. Alternatively, compound 8 can be directly converted into compound 3 under the similar condition above.

[0233] Steps 3 through 5 convert compound 3 into a compound of the invention.

Scheme 4



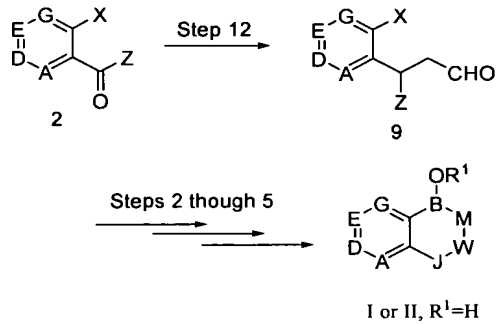
Boronic Acid Preparation Strategy #5

[0234] In Scheme 5, Step 12, compound 2 is treated with (methoxymethyl) triphenylphosphonium chloride or (methoxymethyl)triphenylphosphonium bromide in the presence of base followed by acid hydrolysis to give compound 9. Suitable bases include sodium hydride, potassium tert-butoxide, lithium diisopropylamide, butyllithium, lithium hexamethyldisilazane, combinations thereof and the like. The (methoxymethyl)triphenylphosphonium salt can be used in quantities ranging from 1 to 5 equivalents relative to compound 2. The base can be used in quantities ranging from 1 to 5 equivalents relative to compound 2. Suitable solvents include

tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, ether, toluene, hexane, *N,N*-dimethylformamide, combinations thereof and the like. Reaction temperatures range from 0 °C to the boiling point of the solvent used; preferably between 0 and 30 °C; reaction completion times range from 1 to 12 h. The enolether formed is hydrolyzed under acidic conditions. Suitable acids include hydrochloric acid, hydrobromic acid, sulfuric acid, and the like. Suitable solvents include tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, methanol, ethanol, combination thereof and the like. Reaction temperatures range from 20 °C to the boiling point of the solvent used; preferably between 50 and 100 °C; reaction completion times range from 1 to 12 h.

[0235] Steps 2 through 5 convert compound 9 into a compound of the invention.

Scheme 5

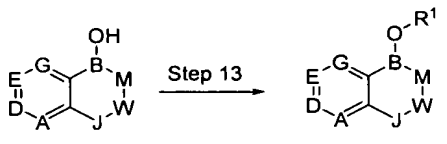


2 9

Boronic Acid Preparation Strategy #6

[0236] In Scheme 6, compound (I) wherein R^1 is H is converted into compound (I) wherein R^1 is alkyl by mixing with the corresponding alcohol, R^1OH. The suitable solvents include tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, toluene, combinations thereof and the like. The alcohol (R^1OH) can be used as the solvent as well. Reaction temperatures range from 20 °C to the boiling point of the solvent used; preferably between 50 and 100 °C; reaction completion times range from 1 to 12 h.

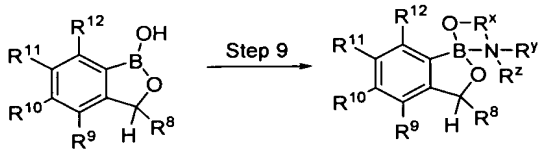
Scheme 6



Boronic Acid Preparation Strategy #7

[0237] In Scheme 7, compound (Ia) is converted into its aminoalcohol complex (Ib). Compound (Ia) is treated with $HOR^1NR^{1a}R^{1b}$. The aminoalcohol can be used in quantities ranging from 1 to 10 equivalents relative to compound (Ia). Suitable solvents include methanol, ethanol, propanol, tetrahydrofuran, acetone, acetonitrile, 1,2-dimethoxyethane, 1,4-dioxane, toluene, *N,N*-dimethylformamide, water, combination thereof and the like. Reaction temperatures range from 20 °C to the boiling point of the solvent used; preferably between 50 and 100 °C; reaction completion times range from 1 to 24 h.

Scheme 7



Ia or IIa Ib or IIb

[0238] The compounds of the invention can be converted into hydrates and solvates by methods similar to those described above.

I. h.) ***Borinic Esters***

[0239] Methods of making borinic esters are known in the art, and it is within the knowledge of one skilled in the art to use these methods in order to make the boronic esters described herein. Examples include U.S. Pat. No. 10/868,268 and U.S. Prov. Pat. No. _____ (Attorney Docket No. 64507-5021PR, filed May 2, 2006) which are herein incorporated by reference.

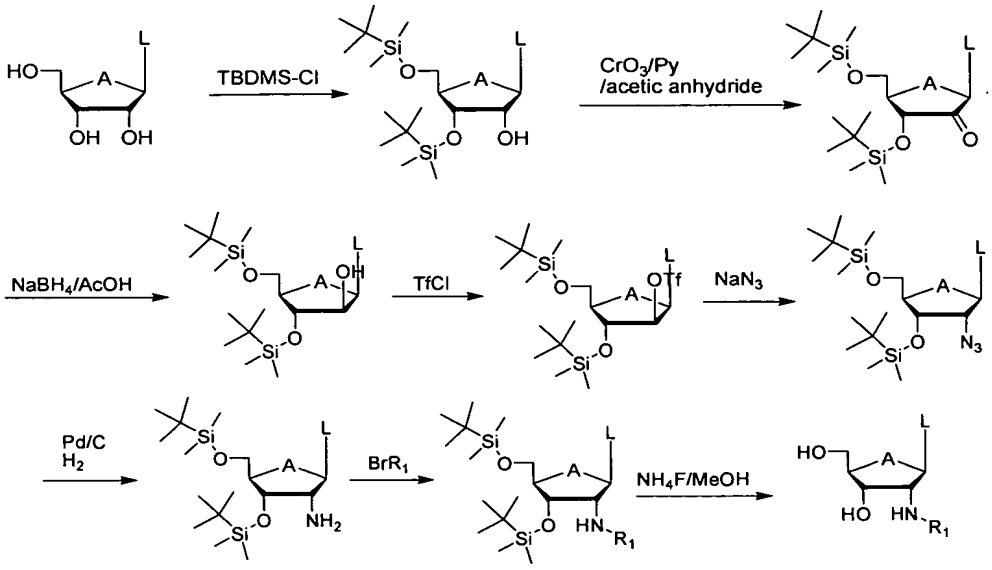
I. i.) ***2'-amino or 3'-amino ribofuranoses***

[0240] Methods of making 2'-amino ribofuranoses or 3'-amino ribofuranoses are known in the art, and it is within the knowledge of one skilled in the art to use these methods in order to make the 2'-amino ribofuranoses described herein.

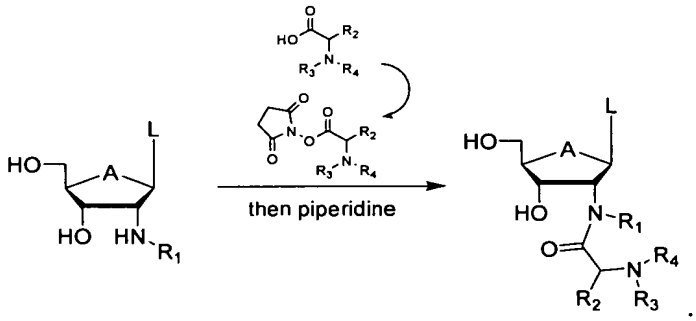
[0241] Ashton *et al.* (Can. Pat. App. 2,031,644 (1991)) and Durette, *et al.* (UK Pat. App. 2,207,678 (1989)) disclose the synthesis of the amino acid starting material for compound **D5**. Hardee, *et al.*, (PCT Int. App. WO2005020885 (2005)) discloses the synthesis of the nucleoside starting material for compound **D6**. Sakthivel, (Sakthivel, *et al.*, *Tet. Let.* 46(22): 3883-3887 (2005)) Sartorelli, *et al.*, (U.S. Pat. Appl. Pub.

2004116362); Roberts, *et al.*, (PCT Int. Appl. WO2003093290); Liu, *et al.*, *Nucleosides, Nucleotides & Nucleic Acids*, **20(12)**: 1975-2000 (2001); Minakawa, *et al., J. Org. Chem.*, **64(19)**: 7158-7172 (1999); Daelemans, *et al.*, *Molecular Pharmacology*, **52(6)**: 1157-1163 (1997) all disclose the synthesis of the nucleoside starting material for compound **D7**.

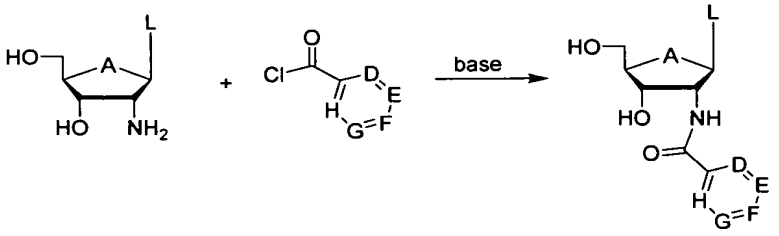
[0242] Examples of how to prepare these compounds is shown below:



[0243] Compounds 1-14 are produced by a final step (Lincecum, T. L. *et al.*, *S. Molecular Cell*, **11**: 951-963 (2003); Kim, B.-T. *et al.*, *J. Bull. Korean Chem. Soc.*, **25**: 243-248 (2004)):



[0244] Compounds 15-18 are produced by a final step (*See* Lincecum):



[0245] Methods for preparing dimers, trimers and higher homologs of small organic molecules, such as those of use in the present invention, as well as methods of functionalizing a polyfunctional framework molecule are well known to those of skill in the art. For example, an aromatic amine of the invention is converted to the corresponding isothiocyanate by the action of thiophosgene. The resulting isothiocyanate is coupled to an amine of the invention, thereby forming either a homo- or heterodimeric species. Alternatively, the isothiocyanate is coupled with an amine-containing backbone, such as polylysine, thereby forming a conjugate between a polyvalent framework and a compound of the invention. If it is desired to prepare a heterofunctionalized polyvalent species, the polylysine is underlabeled with the first isothiocyanate and subsequently labeled with one or more different isothiocyanates. Alternatively, a mixture of isothiocyanates is added to the backbone. Purification proceeds by, for example, size exclusion chromatography, dialysis, nanofiltration and the like.

II. Assays for Inhibitors of tRNA Synthetase Editing Domains

[0246] Art-recognized techniques of genetics and molecular biology are of use to identify compounds that bind to and/or inhibit the editing domain of a tRNA synthetase. Moreover, these techniques are of use to distinguish whether a compound binds to and/or inhibits the synthetic domain, the editing domain, or both the editing and synthetic domains.

[0247] In an exemplary assay, activity of a representative compound against the editing domain was confirmed. To identify the target of the novel boron-containing antifungal compound **C10**, mutants in *S. cerevisiae* showing resistance to compound **C10** were isolated. Characterization of 11 mutants showed that they have an 8-64 fold increase in resistance to **C10** over wildtype. The mutants were furthermore shown to be sensitive to various antifungal agents with known modes of action, suggesting that the cellular target of **C10** is distinct from the target of the other antifungal agents. Isolation of three different plasmids bearing CDC60 from plasmid libraries generated from three independently isolated mutants implicated CDC60, the gene for the cytoplasmic leucyl-tRNA synthetase in resistance against **C10**. Sequence analysis of CDC60 from the 11 mutants revealed that the mutations were all located in the editing domain of this enzyme. In a further series of experiments, additional copies of the CDC60 gene were introduced in *S. cerevisiae,* which gave rise to an

eight-fold increase in resistance to **C10**. These findings confirm a strong link between the editing activity of the enzyme and the inhibition of **C10**, which entails a novel mechanism of tRNA synthetase inhibition.

[0248] Assays to determine whether, and how effectively, a particular compound binds to and/or inhibits the editing domain of a selected tRNA synthetase are also set forth herein, and additional assays are readily available to those of skill in the art. Briefly, in an exemplary assay, an improperly charged tRNA and a tRNA synthetase that is capable of editing the improperly charged tRNA are combined. The resulting mixture is contacted with the putative inhibitor and the degree of editing inhibition is observed.

[0249] Another assay uses genetics to show that a drug works via the editing domain. In this assay, the compound is first tested against a strain of cells over-expressing copies of the tRNA synthetase gene. The compound's effect on the over-expressing strain is compared with a control strain to determine whether the compound is active against the synthetase. If the minimum inhibitory concentration (MIC) is 2-fold higher in the strain with extra copies of the synthetase gene than the MIC of the inhibitor against a wild type cell, a further genetic screen is conducted to determine whether the increased resistance is due to mutations in the editing domain. In this second screen, the control strain is challenged against a high concentration of the inhibitor. The colonies surviving the challenge are isolated and DNA from these cells is isolated. The editing domain is amplified using a proof-reading PCR enzyme and the appropriate primers. The PCR product can be purified using standard procedures. The sequence amplified mutant DNA is compared to wild-type. If the mutant DNA bears mutations in the editing domain, such results would suggest that the compound binds to the editing domain and affects the editing function of the molecule through this domain.

[0250] The assays set forth above are useful in essentially any microbial system, e.g., bacterial, fungal, parasitic, viral and the like.

[0251] Generally, the compounds to be tested are present in the assays in ranges from about 1 pM to about 100 mM, preferably from about 1 pM to about 1 μM. Other compounds range from about 1 nM to about 100 nM, preferably from about 1 nM to about 1 μM.

[0252] The effects of the test compounds upon the function of the enzymes can also be measured by any suitable physiological change. When the functional consequences are determined using intact cells or animals, one can also measure a variety of effects such as transmitter release, hormone release, transcriptional changes to both known and uncharacterized genetic markers, changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as Ca^{2+}, or cyclic nucleotides.

[0253] High throughput screening (HTS) is also of use in identifying promising candidates of the invention.

[0254] Utilizing the assays set forth herein and others readily available in the art, those of skill in the art will be able to readily and routinely determine other compounds and classes of compounds that operate to bind to and/or inhibit the editing domain of tRNA synthetases.

[0255] In another aspect, the invention provides a method for identifying a compound which binds to an editing domain of a tRNA synthetase comprising: a) contacting said editing domain with a test compound under conditions suitable for binding; and b) detecting binding of said test compound to said editing domain. In an exemplary embodiment, detecting binding of said compound comprises use of at least one detectable element, isotope, or chemical label attached to said compound. In an exemplary embodiment, the element, isotope or chemical label is detected by a fluorescent, luminescent, radioactive, or absorbance readout. In an exemplary embodiment, the contacting of said test compound with said editing domain also includes further contacting said test compound and said editing domain with a member selected from AMP and a molecule with a terminal adenosine. In an exemplary embodiment, said tRNA synthetase is derived from a member selected from alanyl tRNA synthetase, isoleucyl tRNA synthetase, leucyl tRNA synthetase, methionyl tRNA synthetase, lysyl tRNA synthetase, phenylalanyl tRNA synthetase, prolyl tRNA synthetase, threonyl tRNA synthetase and valyl tRNA synthetase. In an exemplary embodiment, the tRNA synthetase is derived from leucyl tRNA synthetase. In an exemplary embodiment, the tRNA synthetase is derived from a mutated tRNA synthetase, wherein said mutated tRNA synthetase comprises amino acid mutations in an editing domain. In another exemplary embodiment, the mutated tRNA synthetase

comprises amino acid mutations in the editing domain as listed in Table 4. In another exemplary embodiment, wherein said editing domain of a tRNA synthetase comprises the amino acid sequence of SEQ ID NOS: 1-15.

[0256] In another aspect, the invention provides a method for identifying a compound which binds to an editing domain of a tRNA synthetase, said assay comprising: a) contacting said editing domain of a tRNA synthetase with said compound under conditions suitable for binding of said compound with said editing domain of a tRNA synthetase; b) comparing a biological activity of said editing domain of a tRNA synthetase contacting said compound to said biological activity when not contacting said compound; and c) identifying said compound as binding to said editing domain of a tRNA synthetase if said biological activity of said editing domain of a tRNA synthetase is reduced when contacting said compound. In an exemplary embodiment, the biological activity is hydrolysis of noncognate amino acid. In another exemplary embodiment, the hydrolysis of said noncognate amino acid is detected through the use of one or more labels. In another exemplary embodiment, the labels include a radiolabel, a fluorescent marker, an antibody, or a combination thereof. In another exemplary embodiment, said labels can be detected using spectroscopy. In another exemplary embodiment, the editing domain of a tRNA synthetase is derived from a member selected from alanyl tRNA synthetase, isoleucyl tRNA synthetase, leucyl tRNA synthetase, methionyl tRNA synthetase, lysyl tRNA synthetase, phenylalanyl tRNA synthetase, prolyl tRNA synthetase, threonyl tRNA synthetase and valyl tRNA synthetase. In another exemplary embodiment, said editing domain of a tRNA synthetase is derived from leucyl tRNA synthetase.

[0257] In another aspect, the invention provides a method of generating tRNA molecules with noncognate amino acid comprising: a) creating or isolating a mutated tRNA synthetase with altered amino acid editing domains; and b) contacting a tRNA molecule with said mutated tRNA synthetase and a noncognate amino acid. In another exemplary embodiment, the mutated tRNA synthetase contains one or more amino acid mutations in an editing domain. In another exemplary embodiment, the mutated tRNA synthetase is unable to bind with 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. In another exemplary embodiment, the mutated tRNA synthetase is able to bind with 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

[0258] In another aspect, the invention provides a composition that comprises one or more tRNA molecules attached to noncognate amino acids, wherein said tRNA molecules are synthesized using one or more mutated tRNA synthetases isolated from a microorganism or a cell line derived from a microorganism. In an exemplary embodiment, the microorganism is a fungus or a yeast. In an exemplary embodiment, wherein said mutated tRNA synthetases contain amino acid mutations in their editing domains. In an exemplary embodiment, said mutated tRNA synthetases comprise point mutations in the editing domain as listed in Table 4.

III. Amino acid and nucleotide sequences used in assays

tRNA sequences that interact with the tRNA synthetase-**C10**-AMP complex

[0259] Transfer RNAs (tRNAs) translate mRNA into a protein on a ribosome. Each transfer RNA contains an anti-codon region that hybridizes with mRNA, and an amino acid which may be attached to the growing peptide. The structural gene of tRNA is about 72 to 90 nucleotides long and folds into a cloverleaf structure (Sharp S. J., Schaack J., Coolen L., Burke D. J. and Soll D., "Structure and transcription of eukaryotic tRNA genes", Crit. Rev. Biochem, 19:107 144 (1985); Geiduschek E. O., and Tocchini-Valentini, "Transcription by RNA polymerase III", Annu. Rev. Biochem. 57:873 914 (1988)).

[02610] In one embodiment, **C10** contacts AMP and a tRNA synthetase, and the tRNA synthetase in turn contacts a tRNA molecule. In another embodiment, **C10** contacts AMP from the tRNA molecules and a tRNA synthetase. The nucleotide sequence of the tRNA molecule can be determined by the identity of the tRNA synthetase involved. For example, for leucyl tRNA synthetase, the cognate tRNA molecule bound will be tRNA-leucine (SEQ ID NO: 3), but a noncognate tRNA, such as isoleucine, (SEQ ID NO: 4) may be bound under certain conditions. In this and other embodiments, the term "noncognate" is meant to encompass both the singular and plural forms of the word, i.e. the phrase "noncognate amino acid" comprises one or more amino acids.

[0261] **SEQ ID NO: 3** corresponds to the nucleotide sequence of the tRNA-Leu gene from *Saccharomyces cerevisiae*: gggagtttgg ccgagtggtt taaggcgtca gatttaggct ctgatatctt cggatgcaagggttcgaatc ccttagctct cacca

[0262] **SEQ ID NO: 4** corresponds to the nucleotide sequence of the tRNA-Ile gene from *Saccharomyces cerevisiae*: gaaactataa ttcaattggt tagaatagta ttttgataag gtacaaatat aggttcaatc cctgttagtt tcatcca

Polypeptides used in binding and inhibition assays

[0263] In some binding and inhibition assays, it is more effective to use a portion of a tRNA synthetase molecule rather than the whole protein itself. In such assays, polypeptides derived from tRNA synthetases are used in the experiment.

[0264] In one preferred embodiment, polypeptide fragments corresponding to the editing domain of a tRNA synthetase molecule are used in assay and binding experiments. Two such fragments are represented by SEQ ID NO:1 and SEQ ID NO:2.

[0265] **SEQ ID NO 1:**
TPQEYIGVKIEALEFADDAAKIIDSSSDLDKSKKFYFVAATLRPETMYGQTCCF
VSPTIEYGIFDAGDSYFITTERAFKNMSYQKLTPKRGFYKPIVTVPGKAFIGTKI
HAPQSVYPELRILPMETVIATKGTGVVTCVPSNSPDDYITTKDLLHKPEYYGIK
PEWIDHEIVPIMHTEKYGDLTAKAIVEEKKIQSPKDKNLLAEAKKIAYKEDYY
TGTMIYGPYKGEKVEQAKNKVKADMIAAGEAFVYNEPESQDP

[0266] **SEQ ID NO 2:**
MTPQEYIGVKIEALEFADDAAKIIDSSSDLDKSKKFYFVAATLRPETMYGQTC
CFVSPTIEYGIFDAGDSYFITTERAFKNMSYQKLTPKRGFYKPIVTVPGKAFIGT
KIHAPQSVYPELRILPMETVIATKGTGVVTCVPSNSPDDYITTKDLLHKPEYYG
IKPEWIDHEIVPIMHTEKYGDLTAKAIVEEKKIQSPKDKNLLAEAKKIAYKED
YYTGTMIYGPYKGEKVEQAKNKVKADMIAAGEAFVYNEPESQDPQDPNSSS
VDKLAAALEHHHHH

IV. *Methods for Inhibiting the Editing Domain of tRNA Synthetase*

[0267] According to another aspect of the invention, a method for binding to and/or inhibiting the editing domain of a tRNA synthetase is provided which comprises contacting a tRNA synthetase with a compound that inhibits the editing domain under the conditions in which the tRNA synthetase interacts with its substrate to form an aminoacyl adenylate intermediate and, preferably, to form a charged tRNA. Such conditions are known to those skilled in the art. In an exemplary embodiment, the compound is one described herein. The tRNA synthetase is contacted with an amount of inhibitor sufficient to result in a detectable amount of tRNA synthetase inhibition. This method can be performed on a tRNA synthetase that is contained within an organism or which is outside an organism. In an exemplary embodiment, the method is performed on a tRNA synthetase that is contained within a microorganism or a

microbial cell that is in, or on the surface of, a human or an animal. The method results in a decrease in the amount of charged tRNA produced by the tRNA synthetase that has an inhibited editing domain. In an exemplary embodiment, the inhibition takes place in a cell, such as a microbial cell. In another exemplary embodiment, the microbial cell is a bacteria, fungus, yeast or parasite. In another exemplary embodiment, the tRNA synthetase is a mitochondrial tRNA synthetase or a cytoplasmic tRNA synthetase.

[0268] In an exemplary embodiment, the invention provides a method of inhibiting conversion of a tRNA molecule into a charged tRNA molecule. The method involves contacting a tRNA synthetase with a compound effective to inhibit activity of an editing domain of said tRNA synthetase, under conditions sufficient to inhibit said activity, thereby inhibiting said conversion wherein the compound is a member selected from those compounds described herein. In an exemplary embodiment, the compound is a member selected from a cyclic boronic ester, cyclic borinic ester, 2'-amino ribofuranose moiety and a 3'-amino ribofuranose moiety. In an exemplary embodiment, the inhibition occurs within a cell, and the cell is a microbial cell. In another exemplary embodiment, the microbial cell is a member selected from a bacteria, fungus, yeast, and parasite. In an exemplary embodiment, the tRNA synthetase is a member selected from a mitochondrial tRNA synthetase and a cytoplasmic tRNA synthetase. In another exemplary embodiment, the tRNA synthetase is a member selected from alanyl tRNA synthetase, isoleucyl tRNA synthetase, leucyl tRNA synthetase, methionyl tRNA synthetase, lysyl tRNA synthetase, phenylalanyl tRNA synthetase, prolyl tRNA synthetase, threonyl tRNA synthetase and valyl tRNA synthetase. In another exemplary embodiment, the compound has a $K_{D,\ synthesis}$ of greater than 100 μM against a synthetic domain of said tRNA synthetase.

[0269] In certain embodiments, the mechanism of action of the compound is to inhibit the conversion of a tRNA molecule into a charged tRNA molecule by binding to and/or inhibiting at least the editing domain of the synthetase. The compounds of use in this method may also inhibit or otherwise interact with the synthetic domain (e.g., the active site of the synthetic domain). In a presently preferred embodiment, the editing domain is inhibited selectively in the presence of the synthetic domain. In a preferred embodiment, the synthetic domain is essentially uninhibited, while the

editing domain is inhibited at least 50%, preferably at least 60%, more preferably at least 70%, still more preferably, at least 80% and even still more preferably at least 90% of the activity of the tRNA synthetase. In another preferred embodiment, the synthetic domain is inhibited by at most 50%, preferably at most 30%, preferably at most 20%, 10%, preferably at most 8%, more preferably at most 5%, still more preferably, at most 3% and even still more preferably at most 1%. Inhibition of the editing domain produces a decrease in the amount of the properly charged tRNA which results in retardation or cessation of cell growth and division.

[0270] In another exemplary embodiment, the ratio of a minimum concentration of said compound inhibiting said editing domain to a minimum concentration of said compound inhibiting said synthetic domain of said tRNA synthetase, represented as $K_{D,\ edit}/K_{D,\ synthesis}$, is less than one. In another exemplary embodiment, the $K_{D,\ edit}/K_{D,\ synthesis}$ of the compound is a member selected from less than 0.5, less than 0.1 and less than 0.05.

V. Methods of Inhibiting Microorganism Growth or Killing Microorganisms

[0271] In a further aspect, the invention provides a method for inhibiting the growth, or killing, a microorganism, preferably a bacteria, fungus, virus, yeast or parasite, comprising contacting the microorganism with an inhibitor of a tRNA synthetase, e.g., a compound described by a formula listed herein, under conditions which permit entry of the compound into the organism. In a further aspect, the invention provides a method for inhibiting the growth, or killing, a microorganism, preferably a bacteria, fungus, virus, yeast or parasite, comprising contacting the microorganism with a compound which is a member selected from Formulae (I), (Ia), (Ib), (Ic), (Id) (Ie), (If), (Ig), (Ih) (Ii), (Ij), (Ik), (Il) (Im), (In), (Io), (Ip) (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Ix) (Iy), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak), (II), (IIa), (IIb), (IIc), (IId), (III), (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (VIIIe), (IX) e.g., a compound described by a formula listed herein, under conditions which permit entry of the compound into the organism. In a further aspect, the invention provides a method for inhibiting the growth, or killing, a microorganism, preferably a bacteria, fungus, virus, yeast or parasite, comprising contacting the microorganism with a compound which is described in either Figure 19 or Figure 20 e.g., a compound described by a formula listed herein, under conditions which permit entry of the compound into the organism. In an exemplary

embodiment, the compound inhibits the tRNA synthetase through the editing domain of the synthetase. Such conditions are known to one skilled in the art and specific conditions are set forth in the Examples appended hereto. This method involves contacting a microbial cell with a therapeutically-effective amount of an editing domain inhibitor to inhibit tRNA synthetase *in vivo* or *in vitro*.

[0272] In another aspect, the invention provides a method of inhibiting the growth of a microorganism, or killing a microorganism, or both, comprising contacting the microorganism with a compound described herein. Microorganisms are members selected from fungi, yeast, viruses, bacteria and parasites. In another exemplary embodiment, the microorganism is inside, or on the surface of an animal. In an exemplary embodiment, the animal is a member selected from human, cattle, deer, reindeer, goat, honey bee, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, camel, yak, elephant, ostrich, otter, chicken, duck, goose, guinea fowl, pigeon, swan, and turkey. In another exemplary embodiment, the animal is a human.

[0273] In an exemplary embodiment, the microorganism is a member selected from a fungus and a yeast. In another exemplary embodiment, the fungus or yeast is a member selected from *Candida* species, *Trichophyton* species, *Microsporium* species, *Aspergillus* species, *Cryptococcus* species, *Blastomyces* species, *Cocciodiodes* species, *Histoplasma* species, *Paracoccidiodes* species, *Phycomycetes* species, *Malassezia* species, *Fusarium* species, *Epidermophyton* species, *Scytalidium* species, *Scopulariopsis* species, *Alternaria* species, *Penicillium* species, *Phialophora* species, *Rhizopus* species, *Scedosporium* species and *Zygomycetes* class. In another exemplary embodiment, the fungus or yeast is a member selected from *Aspergilus fumigatus* (*A. fumigatus*), *Blastomyces dermatitidis, Candida Albicans* (*C. albicans*, both fluconazole sensitive and resistant strains), *Candida glabrata* (*C. glabrata*), *Candida krusei* (*C. krusei*), *Cryptococcus neoformans* (*C. neoformans*), *Candida parapsilosis* (*C. parapsilosis*), *Candida tropicalis* (*C. tropicalis*), *Cocciodiodes immitis, Epidermophyton floccosum* (*E. floccosum*), *Fusarium solani* (*F. solani*), *Histoplasma capsulatum*, *Malassezia furfur* (*M. furfur*), *Malassezia pachydermatis* (*M. pachydermatis*), *Malassezia sympodialis* (*M. sympodialis*), *Microsporum audouinii* (*M. audouinii*), *Microsporum canis* (*M. canis*), *Microsporum gypseum* (*M. gypseum*), *Paracoccidiodes brasiliensis* and *Phycomycetes* spp, *Trichophyton mentagrophytes* (*T. mentagrophytes*), *Trichophyton rubrum* (*T. rubrum*),

Trichophyton tonsurans (*T. tonsurans*). In another exemplary embodiment, the fungus or yeast is a member selected from *Trichophyton concentricum, T. violaceum, T. schoenleinii, T. verrucosum, T. soudanense, Microsporum gypseum, M. equinum, Candida guilliermondii, Malassezia globosa, M. obtuse, M. restricta, M. slooffiae*, and *Aspergillus flavus*. In another exemplary embodiment, the fungus or yeast is a member selected from dermatophytes, *Trichophyton*, *Microsporum*, *Epidermophyton* and yeast-like fungi.

[0274] In an exemplary embodiment, the microorganism is a bacteria. In an exemplary embodiment, the bacteria is a gram-positive bacteria. In another exemplary embodiment, the gram-positive bacteria is a member selected from *Staphylococcus* species, *Streptococcus* species, *Bacillus* species, *Mycobacterium* species, *Corynebacterium* species (*Propionibacterium* species), *Clostridium* species, *Actinomyces* species, *Enterococcus* species and *Streptomyces* species. In another exemplary embodiment, the bacteria is a gram-negative bacteria. In another exemplary embodiment, the gram-negative bacteria is a member selected from *Acinetobacter* species, *Neisseria* species, *Pseudomonas* species, *Brucella* species, *Agrobacterium* species, *Bordetella* species, *Escherichia* species, *Shigelia* species, *Yersinia* species, *Salmonella* species, *Klebsiella* species, *Enterobacter* species, *Haemophilus* species, *Pasteurella* species, *Streptobacillus* species, spirochetal species, *Campylobacter* species, *Vibrio* species and *Helicobacter* species. In another exemplary embodiment, the bacterium is a member selected from *Propionibacterium acnes*; *Staphylococcus aureus*; *Staphylococcus epidermidis, Staphylococcus saprophyticus*; *Streptococcus pyogenes*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*; *Enterococcus faecalis*; *Enterococcus faecium*; *Bacillus anthracis*; *Mycobacterium avium-intracellulare*; *Mycobacterium tuberculosis, Acinetobacter baumanii*; *Corynebacterium diphtheria*; *Clostridium perfringens*; *Clostridium botulinum*; *Clostridium tetani*; *Clostridium difficile; Neisseria gonorrhoeae*; *Neisseria meningitidis*; *Pseudomonas aeruginosa*; *Legionella pneumophila*; *Escherichia coli*; *Yersinia pestis*; *Haemophilus influenzae*; *Helicobacter pylori*; *Campylobacter fetus*; *Campylobacter jejuni*; *Vibrio cholerae*; *Vibrio parahemolyticus*; *Trepomena pallidum*; *Actinomyces israelii*; *Rickettsia prowazekii*; *Rickettsia rickettsii*; *Chlamydia trachomatis*; *Chlamydia psittaci*; *Brucella abortus*; *Agrobacterium tumefaciens*; and *Francisella tularensis*.

[0275] In an exemplary embodiment, the microorganism is a bacteria, which is a member selected from acid-fast bacterium, including *Mycobacterium* species; bacilli, including *Bacillus* species, *Corynebacterium* species (also Propionibacterium) and *Clostridium* species; filamentous bacteria, including *Actinomyces* species and *Streptomyces* species; bacilli, such as *Pseudomonas* species, *Brucella* species, *Agrobacterium* species, *Bordetella* species, *Escherichia* species, *Shigella* species, *Yersinia* species, *Salmonella* species, *Klebsiella* species, *Enterobacter* species, *Haemophilus* species, *Pasteurella* species, and *Streptobacillus* species; spirochetal species, *Campylobacter* species, *Vibrio* species; and intracellular bacteria including *Rickettsiae* species and *Chlamydia* species.

[0276] In an exemplary embodiment, the microorganism is a virus. In an exemplary embodiment, the virus is a member selected from hepatitis A-B, human rhinoviruses, Yellow fever virus, human respiratory coronaviruses, Severe acute respiratory syndrome (SARS), respiratory syncytial virus, influenza viruses, parainfluenza viruses 1-4, human immunodeficiency virus 1 (HIV-1), human immunodeficiency virus 2 (HIV-2), Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2), human cytomegalovirus (HCMV), Varicella zoster virus, Epstein-Barr (EBV), polioviruses, coxsackieviruses, echoviruses, rubella virus, neurodermatropic virus, variola virus, papoviruses, rabies virus, dengue virus, West Nile virus and SARS virus. In another exemplary embodiment, the virus is a member selected from *picornaviridae, flaviviridae, coronaviridae, paramyxoviridae, orthomyxoviridae, retroviridae, herpesviridae* and *hepadnaviridae*. In another exemplary embodiment, the virus is a member selected from a virus included in the following table:

Table A. Viruses

Virus Category	**Pertinent Human Infections**
	RNA Viruses
Picomaviridae	Polio Human hepatitis A Human rhinovirus
Togaviridae and Flaviviridae	*Rubella* – German measles

Virus Category	Pertinent Human Infections
	Yellow fever
Coronaviridae	Human respiratory coronavirus (HCV)
	Severe acute respiratory syndrome (SAR)
Rhabdoviridae	*Lyssavirus* – Rabies
	Paramyxovirus – Mumps
Paramyxoviridae	*Morbillvirus* – measles
	Pneumovirus – respiratory syncytial virus
Orthomyxoviridae	Influenza A-C
	Bunyavirus – Bunyamwera (BUN)
	Hantavirus – Hantaan (HTN)
Bunyaviridae	*Nairevirus* – Crimean-Congo hemorrhagic fever (CCHF)
	Phlebovirus – Sandfly fever (SFN)
	Uukuvirus – Uukuniemi (UUK)
	Rift Valley Fever (RVFN)
	Junin – Argentine hemorrhagic fever
Arenaviridae	*Machupo* – Bolivian hemorrhagic fever
	Lassa – Lassa fever
	LCM – aseptic lymphocyctic choriomeningitis
	Rotovirus
Reoviridae	*Reovirus*
	Orbivirus
	Human immunodeficiency virus 1 (HIV-1)
Retroviridae	Human immunodeficiency virus 2 (HIV-2)
	Simian immunodeficiency virus (SIV)
	DNA Viruses
Papovaviridae	Pediatric viruses that reside in kidney

Virus Category	Pertinent Human Infections
Adenoviridae	Human respiratory distress and some deep-seated eye infections
Parvoviridae	Human gastro-intestinal distress (Norwalk Virus)
Herpesviridae	Herpes simplex virus 1 (HSV-1)
	Herpes simplex virus 2 (HSV-2)
	Human cytomegalovirus (HCMV)
	Varicella zoster virus (VZV)
	Epstein-Barr virus (EBV)
	Human herpes virus 6 (HHV6)
Poxviridae	Orthopoxvirus is sub-genus for smallpox
Hepadnaviridae	Hepatitis B virus (HBV)
	Hepatitis C virus (HCV)

[0277] In another exemplary embodiment, the microorganism is a parasite. In an exemplary embodiment, the parasite is a member selected from *Plasmodium falciparum, P. vivax, P. ovale P. malariae, P. berghei, Leishmania donovani, L. infantum, L. chagasi, L. mexicana, L. amazonensis, L. venezuelensis, L. tropics, L. major, L. minor, L. aethiopica, L. Biana braziliensis, L. (V.) guyanensis, L. (V.) panamensis, L. (V.) peruviana, Trypanosoma brucei rhodesiense, T. brucei gambiense, T. cruzi, Giardia intestinalis, G. lambda, Toxoplasma gondii, Entamoeba histolytica, Trichomonas vaginalis, Pneumocystis carinii,* and *Cryptosporidium parvum.*

VI. Methods of Treating or Preventing Infections

[0278] In another aspect, the invention provides a method of treating or preventing an infection. The method includes administering to the animal a therapeutically effective amount of the compound of the invention, sufficient to treat or prevent said infection. In an exemplary embodiment, the compound is a compound described herein. In another exemplary embodiment, the compound has a structure according to Formulae (I) to (Iak) and (II) to (XI). In another exemplary embodiment,

the compound has a structure which is described in Figure 19. In another exemplary embodiment, the compound has a structure which is described in Figure 20. In another exemplary embodiment, the animal is a member selected from human, cattle, deer, reindeer, goat, honey bee, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, camel, yak, elephant, ostrich, otter, chicken, duck, goose, guinea fowl, pigeon, swan, and turkey. In another exemplary embodiment, the animal is a human. In another exemplary embodiment, the animal is a member selected from a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey. In another exemplary embodiment, the infection is a member selected from a systemic infection, a cutaneous infection, and an ungual, periungual or subungual infection.

[0279] In another exemplary embodiment, the treatment of a disorder or condition occurs through inhibition of an editing domain of an aminoacyl tRNA synthetase.

VI. a) ***Methods of Treating of Preventing Ungual and/or Periungual Infections***

[0280] In another aspect, the invention provides a method of treating or preventing an ungual and/or periungual infection. The method includes administering to the animal a therapeutically effective amount of a compound or pharmaceutical formulation of the invention, sufficient to treat or prevent said infection. In another exemplary embodiment, the method includes administering the compound or pharmaceutical formulation of the invention at a site which is a member selected from the skin, nail, hair, hoof, claw and the skin surrounding the nail, hair, hoof and claw.

VI. a) 1) ***Onychomycosis***

[0281] Onychomycosis is a disease of the nail caused by yeast, dermatophytes, or other molds, and represents approximately 50% of all nail disorders. Toenail infection accounts for approximately 80% of onychomycosis incidence, while fingernails are affected in about 20% of the cases. Dermatophytes are the most frequent cause of nail plate invasion, particularly in toenail onychomycosis. Onychomycosis caused by a dermatophyte is termed *Tinea unguium*. *Trichophyton rubrum* is by far the most frequently isolated dermatophyte, followed by T. mentagrophytes. Distal subungual onychomycosis is the most common presentation of tinea unguium, with the main site of entry through the hyponychium (the thickened

epidermis underneath the free distal end of a nail) progressing in time to involve the nail bed and the nail plate. Discoloration, onycholysis, and accumulation of subungual debris and nail plate dystrophy characterize the disease. The disease adversely affects the quality of life of its victims, with subject complaints ranging from unsightly nails and discomfort with footwear, to more serious complications including secondary bacterial infections.

[0282] Many methods are known for the treatment of fungal infections, including the oral and topical use of antibiotics (e.g., nystatin and amphotericin B), imidazole anti-fungal agents such as miconazole, clotrimazole, fluconazole, econazole and sulconazole, and non-imidazole fungal agents such as the allylamine derivatives terbinafine and naftifine, and the benzylamine butenafine.

[0283] However, onychomycosis has proven to be resistant to most treatments. Nail fungal infections reside in an area difficult to access by conventional topical treatment and anti-fungal drugs cannot readily penetrate the nail plate to reach the infection sites under the nail. Therefore, onychomycosis has traditionally been treated by oral administration of anti-fungal drugs; however, clearly this is undesirable due to the potential for side effects of such drugs, in particular those caused by the more potent anti-fungal drugs such as itraconazole and ketoconazole. An alternative method of treatment of onychomycosis is by removal of the nail before treating with a topically active anti-fungal agent; such a method of treatment is equally undesirable. Systemic antimycotic agents require prolonged use and have the potential for significant side effects. Topical agents have usually been of little benefit, primarily because of poor penetration of the anti-fungal agents into and through the nail mass.

[0284] In an exemplary embodiment, the invention provides a method of treating or preventing onychomycosis. The method includes administering to a human or an animal a therapeutically effective amount of a compound of the invention, or a pharmaceutical formulation of the invention, sufficient to treat or prevent onychomycosis. In another exemplary embodiment, the method includes administering the pharmaceutical formulation of the invention at a site which is a member selected from the skin, nail, hair, hoof, claw and the skin surrounding the nail, hair, hoof and claw. In another exemplary embodiment, the pharmaceutical formulation includes a compound described herein. The method includes

administering to a human or an animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, sufficient to treat or prevent onychomycosis.

VI. a) 2) ***Other Unugal and Periungual Infections***

[0285] In an exemplary embodiment, the invention provides a method of treating or preventing an ungual or periungual infection in a human or an animal. This method comprising administering to the human or the animal a therapeutically effective amount of a compound of the invention, thereby treating or preventing the ungual or periungual infection. In an exemplary embodiment, the ungual or periungual infection is onychomycosis. In an exemplary embodiment, the ungual or periungual infection is a member selected from: onychomycosis, chloronychia, paronychias, erysipeloid, onychorrhexis, gonorrhea, swimming-pool granuloma, larva migrans, leprosy, Orf nodule, milkers' nodules, herpetic whitlow, acute bacterial perionyxis, chronic perionyxis, sporotrichosis, syphilis, tuberculosis verrucosa cutis, tularemia, tungiasis, peri- and subungual warts, zona, nail dystrophy (trachyonychia), and dermatological diseases with an effect on the nails, such as psoriasis, pustular psoriasis, alopecia aerata, parakeratosis pustulosa, contact dermatosis, Reiter's syndrome, psoriasiform acral dermatitis, lichen planus, idiopathy atrophy in the nails, lichin nitidus, lichen striatus, inflammatory linear verrucous epidermal naevus (ILVEN), alopecia, pemphigus, bullous pemphigoid, acquired epidermolysis bullosa, Darier's disease, pityriasis rubra pilaris, palmoplantar keratoderma, contact eczema, polymorphic erythema, scabies, Bazex syndrome, systemic scleroderma, systemic lupus erythematosus, chronic lupus erythematosus, dermatomyositus.

[0286] The compounds and pharmaceutical formulations of the invention useful for ungual and periungual applications also find application in the cosmetics field, in particular for the treatment of irregularities of the nails, koilonychias, Beau's lines, longitudinal ridging, ingrown nails.

[0287] In an exemplary embodiment, the infection is of the skin, nail, hair, claw or hoof, hair, ear and eye and is a member selected from Sporotrichosis, Mycotic keratitis, Extension oculomycosis, Endogenous oculomycosis, Lobomycosis, Mycetoma, Piedra, Pityriasis versicolor, Tinea corporis, Tinea cruris, Tinea pedis, Tinea barbae, Tinea capitis, Tinea nigra, Otomycosis, Tinea favosa, Chromomycosis,

and Tinea Imbricata. In an exemplary embodiment, the compound useful for treating these infections is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

VI. b) ***Methods of Treating Systemic Diseases***

[0288] In another aspect, the invention provides a method of treating a systemic disease. The method involves contacting an animal with a compound of the invention. The method of delivery for treatment of systemic disesases can be oral, intravenous, transdermal, inhalation, intraperitoneal, and subcutaneous. In an exemplary embodiment, the compound administered is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

[0289] In an exemplary embodiment, the infection is systemic and is a member selected from candidiasis, aspergillosis, coccidioidomycosis, cryptococcosis, histoplasmosis, blastomycosis, paracoccidioidomycosis, zygomycosis, phaeohyphomycosis and rhinosporidiosis.

VI. c) ***Methods of Treating Diseases Involving Viruses***

[0290] The compounds of the invention are useful for the treatment of diseases of both animals and humans, involving viruses. In an exemplary embodiment, the disease is a member selected from hepatitis A – B – C, yellow fever, respiratory syncytial, influenza, AIDS, herpes simplex, chicken pox, varicella zoster, and Epstein-Barr disease.

VI. d) ***Methods of Treating Diseases Involving Parasites***

[0291] The compounds of the invention are useful for the treatment of diseases of both animals and humans, involving parasites. In an exemplary embodiment, the disease is a member selected from malaria, Chagas' disease, Leishmaniasis, African sleeping sickness (African human trypanosomiasis), giardiasis, toxoplasmosis, amebiasis and cryptosporidiosis.

[0292] In any of the methods according to the present invention set forth above, it is preferred that the aminoacyl tRNA synthetase is an aminoacyl tRNA synthetase comprising an editing domain. The editing domain is encoded by a portion of the aminoacyl tRNA synthetase involved in proofreading. The editing domain is preferably encoded by a DNA portion having at least conserved residues compared

after alignment with the editing site of the leucyl-tRNA synthetase, valyl-tRNA synthetase and isoleucyl-tRNA synthetase. More preferably the synthetase is selected from the group consisting of the valyl-tRNA synthetase, isoleucyl-tRNA synthetase, leucyl-tRNA synthetase, alanyl-tRNA synthetase, prolyl-tRNA synthetase, threonyl-tRNA synthetase, phenyl-tRNA synthetase and lysyl-tRNA synthetase which are known to have an editing site or domain (see for Ile RS Baldwin, A. N. and Berg, P. (1966) J. Biol. Chem. 241, 839-845 and Eldred, E. W. and Schimmel, P. R. (1972) J. Biol. Chem. 247, 2961-2964; for Val RS, Fersht, A. R. and Kaethner, M. M. (1976) Biochemistry. 15 (15), 3342-3346; for Leu RS, English, S. et al., (1986) Nucleic Acids Research. 14 (19), 7529-7539; for Ala RS, Tsui, W. C. and Fersht, A. R. (1981) Nucleic Acids Research. 9, 7529-7539; for Pro RS, Beuning, P. J. and Musier-Forsyth, K. (2000) PNAS. 97 (16), 8916-8920; for Thr RS, Sankaranarayanan, R. et al., (2000) Nat. Struct. Biol. 7, 461-465 and Musier-Foryth, K. and Beuning, P. J. (2000) Nat. Struct. Biol. 7, 435-436; for PheRS, Yarus, M. (1972) PNAS. 69, 1915-1919 and for LysRS, Jakubowski, H. (1997) Biochemistry. 36, 11077-11085.

VII. Methods of Nail Penetration

[0293] It is believed that poor penetration of the active agent through the hoof or nail plate and/or excessive binding to keratin, (the major protein in nails and hair) are the reasons for the poor efficacy of 8% ciclopirox w/w in commercial lacquer and other topical treatments that have failed in clinical trials. In mild cases of onychomycosis, the pathogenic fungi reside in the nail plate only. In moderate to severe cases the pathogenic fungi establish a presence in the nail plate and in the nail bed. If the infection is cleared from the nail plate but not from the nail bed, the fungal pathogen can re-infect the nail plate. Therefore, to effectively treat onychomycosis, the infection must be eliminated from the nail plate and the nail bed. To do this, the active agent must penetrate and disseminate substantially throughout the nail plate and nail bed.

[0294] It is believed that in order for an active agent to be effective once disseminated throughout the infected area, it must be bioavailable to the fungal pathogen and cannot be so tightly bound to keratin that the drug cannot inhibit growth or kill the infecting fungi.

[0295] An understanding of the morphology of the nail plate suggests certain physicochemical properties of an active agent that would facilitate penetration of the nail plate. The desired physicochemical properties are described throughout. The tested compounds of the present invention are able to penetrate the nail plate and were also active against *Trichophyton rubrum* and *mentagrophytes* and other species. In addition, the tested compounds are also active against *Trichophyton rubrum* in the presence of 5% keratin powder.

[0296] In an exemplary embodiment, the invention provides a method of killing or inhibiting growth of a microorganism present in a human nail unit, wherein said human nail unit comprises a nail plate.' The method comprising contacting a dorsal layer of the nail plate with a compound capable of penetrating the nail plate, traveling through the nail plate to a nail bed underlying said nail plate, and contacting said microorganism, under conditions sufficient for said compound to penetrate said nail plate. In this embodiment, the compound has a molecular weight of between about 100 Da and about 200 Da, a log P value of between about 1.0 and about 2.6, a water solubility greater than about 0.1 mg/mL octanol/saturated water, and an MIC of less than 16 μg/mL against said microorganism, thereby killing or inhibiting the growth of said microorganism.

[0297] In an exemplary embodiment, the compound has a structure according to Formula (I) described herein. In another exemplary embodiment, the compound has a structure according to Formula (Ia)-(Iaa) described herein. In another exemplary embodiment, the compound has a structure according to a member selected from Formula (I) – (Iaa), wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from members independently selected from H, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or

unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl. In another exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-

yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy. In another exemplary embodiment, wherein R^{9a} is H and R^{12a} is H. In another exemplary embodiment, the compound is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

[0298] In another exemplary embodiment, the invention provides a method of treating a disease caused by a microorganism present in a human nail unit, wherein said human nail unit comprises a nail plate, said method comprising: contacting a dorsal layer of the nail plate with a compound capable of penetrating the nail plate, traveling through the nail plate to a nail bed underlying said nail plate, and contacting said microorganism, under conditions sufficient for said compound to penetrate said nail plate and to treat said disease. In this embodiment, the compound has a molecular weight of between about 100 Da and about 200 Da; a log P value of between about 1.0 and about 2.6; a water solubility greater than about 0.1 mg/mL octanol/saturated water, and an MIC of less than 16 μg/mL against said microorganism, thereby treating said disease. In an exemplary embodiment, the compound has a structure according to Formula (I) described herein. In another exemplary embodiment, the compound has a structure which is a member selected from Formula (Ia)-(Iaa) described herein.

[0299] In another aspect, the invention provides a method of delivering a compound from the dorsal layer of the nail plate to the nail bed. This method comprises contacting the cell with a compound capable of penetrating the nail plate, under conditions sufficient to penetrate the nail. The compound has a molecular weight of between about 100 and about 200 Da. The compound also has a log P value of between about 1.0 and about 2.6. The compound additionally has a water solubility between about 0.1 mg/mL and 1 g/mL octanol/saturated water, thereby delivering said compound.

[0300] In a preferred embodiment, the physicochemical properties of the compound of the invention, described by quantities predictive for migration of the compound through the nail plate, including, but not limited to, molecular weight, log P and solubility in water, and the like, are effective to provide substantial penetration of the nail plate.

[0301] Compounds with a molecular weight of less than 200 Da penetrate the nail plate in a manner superior to the commercially available treatment for onychomycosis. In one embodiment of the present invention the compound has a molecular weight of between 130 and 200. In another embodiment of this invention, the compound has a molecular weight of from about 140 to about 200 Da. In another embodiment of this invention, the compound has a molecular weight of from about 170 to about 200 Da. In another embodiment of this invention, the compound has a molecular weight of from about 155 to about 190 Da. In another embodiment of this invention, the compound has a molecular weight of from about 165 to about 185 Da. In another embodiment of this invention, the compound has a molecular weight of from about 145 to about 170 Da. In yet another embodiment the molecular weight is either 151.93 or 168.39 Da.

[0302] In one embodiment of the present invention the compound has a log P value of between about -3.5 to about 2.5. In another exemplary embodiment, the compound has a log P value of from about -1.0 to about 2.5. In another exemplary embodiment, the compound has a log P value of from about -1.0 to about 2.0. In another exemplary embodiment, the compound has a log P value of from about -0.5 to about 2.5. In another exemplary embodiment, the compound has a log P value of from about -0.5 to about 1.5. In another exemplary embodiment, the compound has a

log P value of from about 0.5 to about 2.5. In another exemplary embodiment, the compound has a log P value of from about 1.0 to about 2.5. In yet another exemplary embodiment, the compound has a log P value of 1.9 or 2.3.

[0303] Also contemplated by the present invention is a compound with a log P value less then 2.5, with a molecular weight less than 200 Da, that are still able to penetrate the nail plate.

[0304] In one embodiment of the present invention the compound has a water solubility between about 0.1 mg/mL to 1 g/mL in octanol saturated water. In one embodiment of the present invention the compound has a water solubility of between 0.1 mg/mL and 100 mg/mL. In another embodiment of this invention, the compound has a water solubility of from about 0.1 mg/mL and 10 mg/mL. In another embodiment of this invention, the compound has a water solubility of from about 0.1 mg/mL and 1 mg/mL. In another embodiment of this invention, the compound has a water solubility of from about 5 mg/mL and 1 g/mL. In another embodiment of this invention, the compound has a water solubility of from about 10 mg/mL and 500 g/mL. In another embodiment of this invention, the compound has a water solubility of from about 80 mg/mL and 250 mg/mL.

[0305] In an exemplary embodiment, the present invention provides a compound with a log P value selected from a range above, with a molecular weight selected from a range above, that are still able to penetrate the nail plate.

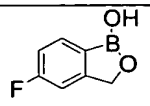
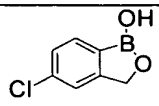
[0306] In an exemplary embodiment, the present invention provides compounds with a molecular weight selected from a range above, with a water solubility selected from a range above, that are still able to penetrate the nail plate.

[0307] In an exemplary embodiment, the present invention provides compounds with a log P selected from a range above, with a water solubility selected from a range above, that are still able to penetrate the nail plate.

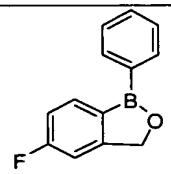
[0308] In an exemplary embodiment, the present invention provides compounds with a molecular weight selected from a range above, with a log P selected from a range above, and with a water solubility selected from a range above, that are still able to penetrate the nail plate.

[0309] Penetration of the nail by the active ingredient may be effected by the polarity of the formulation. However, the polarity of the formulation is not expected have as much influence on nail penetration as some of the other factors, such as the molecular weight or the log P of the active ingredient. The presence of penetration enhancing agents in the formulation is likely to increase penetration of the active agent when compared to similar formulations containing no penetration enhancing agent.

[0310] Some examples of molecules with optimal physicochemical properties are given in the table below.

Structure:	 (compound **1**)	 (compound **2**)
Formula:	$C_7H_6BFO_2$	$C_7H_6BClO_2$
Molecular weight (Da):	151.93	168.39
Plasma protein binding (%):	66	83
LogP:	1.9	2.3
Water solubility (μg/mL):	>100	>100

[0311] Compound 3 below is an example of a compound similar in molecular weight to ciclopirox, and like ciclopirox, penetrates the nail plate poorly.

Structure:	 (compound **3**)
Formula:	$C_{13}H_{10}BFO$
Molecular weight (Da):	212.03
Plasma protein binding (%):	100
cLogP:	3.55
Water solubility (μg/mL):	not determined

[0312] In a preferred embodiment the topical formulations including a compound described herein has a total molecular weight of less than 200 Da, has a Log P of less

than 2.5, and a minimum inhibitory concentration against *Trichophyton rubrum* that is substantially unchanged in the presence of 5% keratin.

[0313] The efficacy coefficient (defined as flux over MIC) of a compound also informs one of skill regarding whether the compound may be effective in killing a microorganism, inhibiting the growth of a microorganism, or treating a disease which is caused by a microorganism present in a human nail unit, wherein said human nail unit comprises a nail plate. The method comprises: contacting a dorsal layer of the nail plate with a compound capable of penetrating the nail plate, traveling through the nail plate to a nail bed underlying said nail plate, and contacting said microorganism, under conditions sufficient for said compound to penetrate said nail plate and to treat said disease, wherein the compound has an efficacy coefficient above 10.

[0314] In an exemplary embodiment, the compound has an efficacy coefficient between about 10 and about 1000. In an exemplary embodiment, the compound has an efficacy coefficient between about 30 and about 100. In an exemplary embodiment, the compound has an efficacy coefficient between about 100 and about 500. In an exemplary embodiment, the compound has an efficacy coefficient between about 25 and about 200.

[0315] This invention is still further directed to methods for treating a fungal infection mediated at least in part by dermatophytes, *Trichophyton*, *Microsporum* or *Epidermophyton* species, or a yeast-like fungi including *Candida* species, in a human or an animal, which methods comprise administering to a human or an animal, that has been diagnosed with said fungal infection or is at risk of developing said fungal infection, a pharmaceutical composition comprising a pharmaceutically acceptable diluent and a therapeutically effective amount of a compound described herein or mixtures of one or more of such compounds. In one embodiment the infection is onychomycosis.

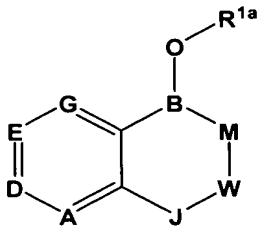
[0316] Compounds contemplated by the present invention may have broad spectrum antifungal activity and as such may be candidates for use against other cutaneous fungal infections.

[0317] The methods provided in this aspect of the invention are useful in the penetration of nails and hoofs, as well as the treatment of ungual and periungual conditions.

VIII. Pharmaceutical Formulations

[0318] In another aspect, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; and (b) a compound of the invention. In another aspect, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; and (b) a compound having a structure which is a member selected from Formulae (I), (Ia), (Ib), (Ic), (Id) (Ie), (If), (Ig), (Ih) (Ii), (Ij), (Ik), (Il) (Im), (In), (Io), (Ip) (Iq), (Ir), (Is), (It), (Iu), (Iv), (Iw), (Ix) (Iy), (Iz), (Iaa), (Iab), (Iac), (Iad), (Iae), (Iaf), (Iag), (Iah), (Iai), (Iaj), (Iak), (II), (IIa), (IIb), (IIc), (IId), (III). In another aspect, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; and (b) a compound which has a structure according to Formulae (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (VIIIe). In another aspect, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; and (b) a compound which has a structure which is a member selected from D1-D19, E1-E19, (VIII), (VIIIa), (VIIIb), (VIIIc), (VIIId), (VIIIe). In another aspect, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; and (b) a acyclic boronic ester of the invention. In an exemplary embodiment, the compound is described in Figure 19. In another exemplary embodiment, the compound is described in Figure 20. In another exemplary embodiment, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; and (b) a acyclic boronic ester of the invention.

[0319] In another aspect, the invention is a pharmaceutical formulation comprising: (a) a pharmaceutically acceptable excipient; and (b) a compound having a structure according to Formula I:



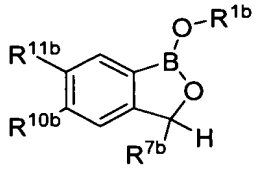
(I)

wherein B is boron. R^{1a} is a member selected from a negative charge, a salt counterion, H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted

heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. M is a member selected from oxygen, sulfur and NR^{2a}. R^{2a} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. J is a member selected from $(CR^{3a}R^{4a})_{n1}$ and CR^{5a}. R^{3a}, R^{4a}, and R^{5a} are members independently selected from H, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The index n1 is an integer selected from 0 to 2. W is a member selected from C=O (carbonyl), $(CR^{6a}R^{7a})_{m1}$ and CR^{8a}. R^{6a}, R^{7a}, and R^{8a} are members independently selected from H, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The index m1 is an integer selected from 0 and 1. A is a member selected from CR^{9a} and N. D is a member selected from CR^{10a} and N. E is a member selected from CR^{11a} and N. G is a member selected from CR^{12a} and N. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R^*$, $-S(O)_2NR^*R^{**}$, -C(O)R*, -C(O)OR*, -C(O)NR*R**, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. Each R* and R** are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3. A member selected from R^{3a}, R^{4a} and R^{5a} and a member selected from R^{6a}, R^{7a} and R^{8a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{3a} and R^{4a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{6a} and R^{7a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{9a} and R^{10a}, together with the

atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{10a} and R^{11a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{11a} and R^{12a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

[0320] In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix):

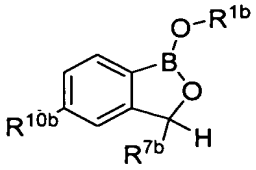


(Ix)

wherein R^{7b} is a member selected from H, methyl, ethyl and phenyl. R^{10b} is a member selected from H, OH, NH_2, SH, halogen, substituted or unsubstituted phenoxy, substituted or unsubstituted phenylalkyloxy, substituted or unsubstituted phenylthio and substituted or unsubstituted phenylalkylthio. R^{11b} is a member selected from H, OH, NH_2, SH, methyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenylalkyloxy, substituted or unsubstituted phenylthio and substituted or unsubstituted phenylalkylthio. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{1b} is a member selected from a negative charge, H and a salt counterion. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{10b} and R^{11b} are H. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein one member selected from R^{10b} and R^{11b} is H and the other member selected from R^{10b} and R^{11b} is a member selected from halo, methyl, cyano, methoxy, hydroxymethyl and p-cyanophenyloxy. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{10b} and R^{11b} are members independently selected from fluoro, chloro, methyl, cyano, methoxy, hydroxymethyl, and p-cyanophenyl. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{1b} is a member selected from a negative charge, H and a salt counterion; R^{7b} is H; R^{10b} is F and R^{11b} is H. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{11b} and R^{12b}, along with the atoms to which they are attached, are joined to

form a phenyl group. In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Ix) wherein R^{1b} is a member selected from a negative charge, H and a salt counterion; R^{7b} is H; R^{10b} is 4-cyanophenoxy; and R^{11b} is H.

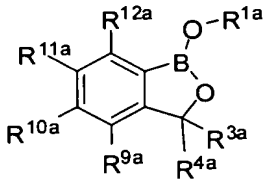
[0321] In another exemplary embodiment, there is a proviso that the compound cannot have a structure according to Formula (Iy)



(Iy)

wherein R^{10b} is a member selected from H, halogen, CN and substituted or unsubstituted C_{1-4} alkyl.

[0322] In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a structure according to Formula (Ia):



(Ia).

[0323] In another exemplary embodiment, each R^{3a} and R^{4a} is a member independently selected from H, cyano, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted indolyl and substituted or unsubstituted amido. In another exemplary embodiment, each R^{3a} and R^{4a} is a member independently selected from cyano, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted aminomethyl, substituted or

unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted indolyl, substituted or unsubstituted amido.

[0324] In another exemplary embodiment, each R^{3a} and R^{4a} is a member selected from H, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted butyl, substituted or unsubstituted t-butyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl. In another exemplary embodiment, R^{3a} and R^{4a} is a member selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In another exemplary embodiment, R^{3a} is H and R^{4a} is a member selected from methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl. In another exemplary embodiment, R^{3a} is H and R^{4a} H.

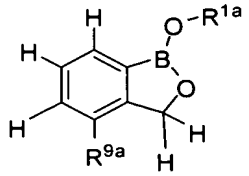
[0325] In another exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} is a member independently selected from H, OR*, NR*R**, SR*, -S(O)R*, -$S(O)_2$R*, -$S(O)_2$NR*R**, -C(O)R*, -C(O)OR*, -C(O)NR*R**, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or

unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl. In an exemplary embodiment, R^{9a}, R^{10a}, R^{11a} and R^{12a} are selected from the previous list of substituents with the exception of -C(O)R*, -C(O)OR*, -C(O)NR*R**.

[0326] In another exemplary embodiment, R^{6a}, R^{7a}, R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido,

phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, 4-fluorobenzyloxy, unsubstituted phenyl, unsubstituted benzyl.

[0327] In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a structure which is a member according the following formulas: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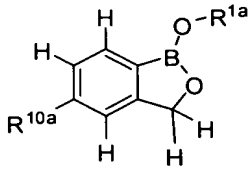
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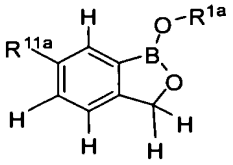
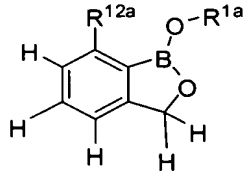

(Id);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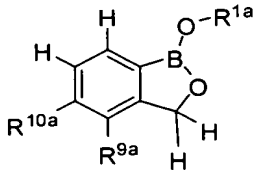
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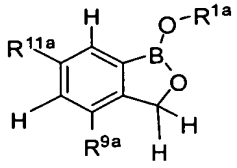
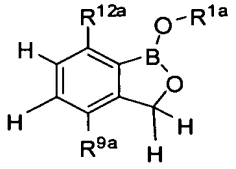

(Ig);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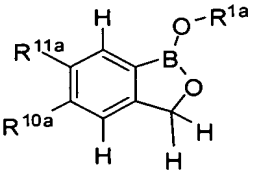
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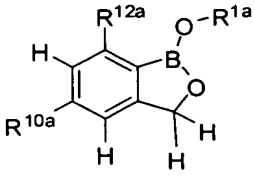
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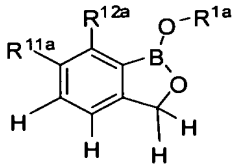
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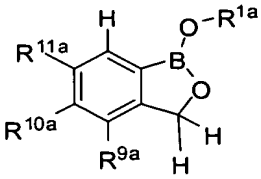
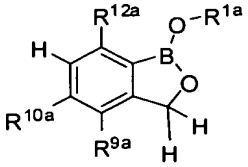
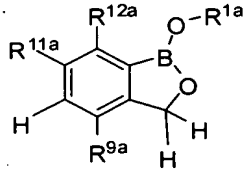
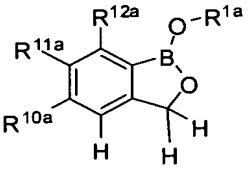

(Il);

(Im);


(In);

(Io);

In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a structure according to one of Formulae I-Io with substituent selections for R^{9a}, R^{10a}, R^{11a} and R^{12a} including all the possiblities contained in paragraph 106 except for H. In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a structure according to one of Formulae Ib-Io with substituent selections for R^{9a}, R^{10a}, R^{11a} and R^{12a} including all the possiblities contained in paragraph 107 except for H.

[0328] In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a formula according to Formulae (Ib)-(Ie) wherein R^{1a} is a member selected from H, a negative charge and a salt counterion and the remaining R group (R^{9a} in Ib, R^{10a} in Ic, R^{11a} in Id, and R^{12a} in Ie) is a member selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-

cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy and 4-fluorobenzyloxy.

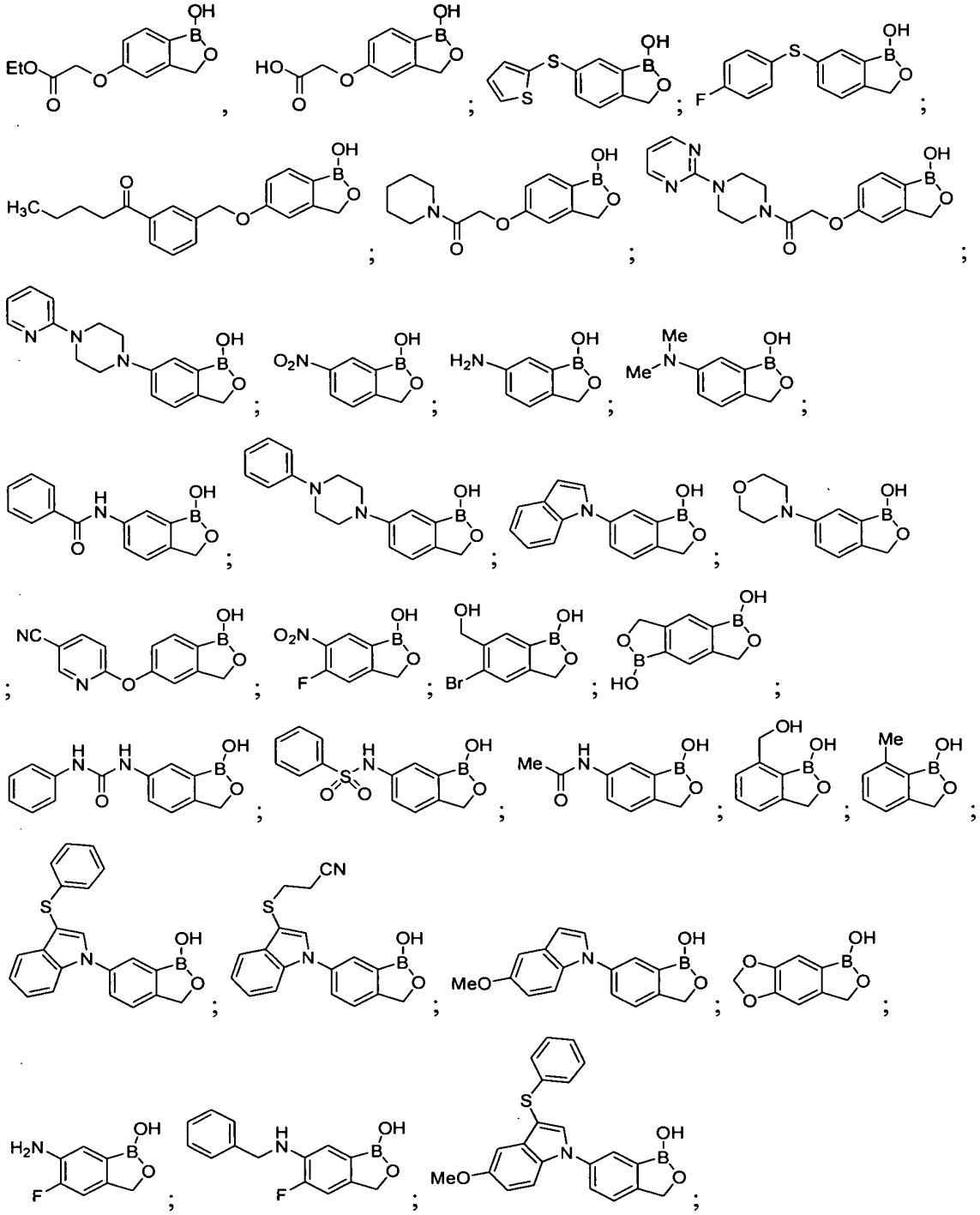
[0329] In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a formula according to Formulae (If)-(Ik) wherein R^{1a} is a member selected from H, a negative charge and a salt counterion and each of the remaining two R groups (R^{9a} and R^{10a} in If, R^{9a} and R^{11a} in Ig, R^{9a} and R^{12a} in Ih, R^{10a} and R^{11a} in Ii, R^{10a} and R^{12a} in Ij, R^{11a} and R^{12a} in Ik) is a member independently selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-

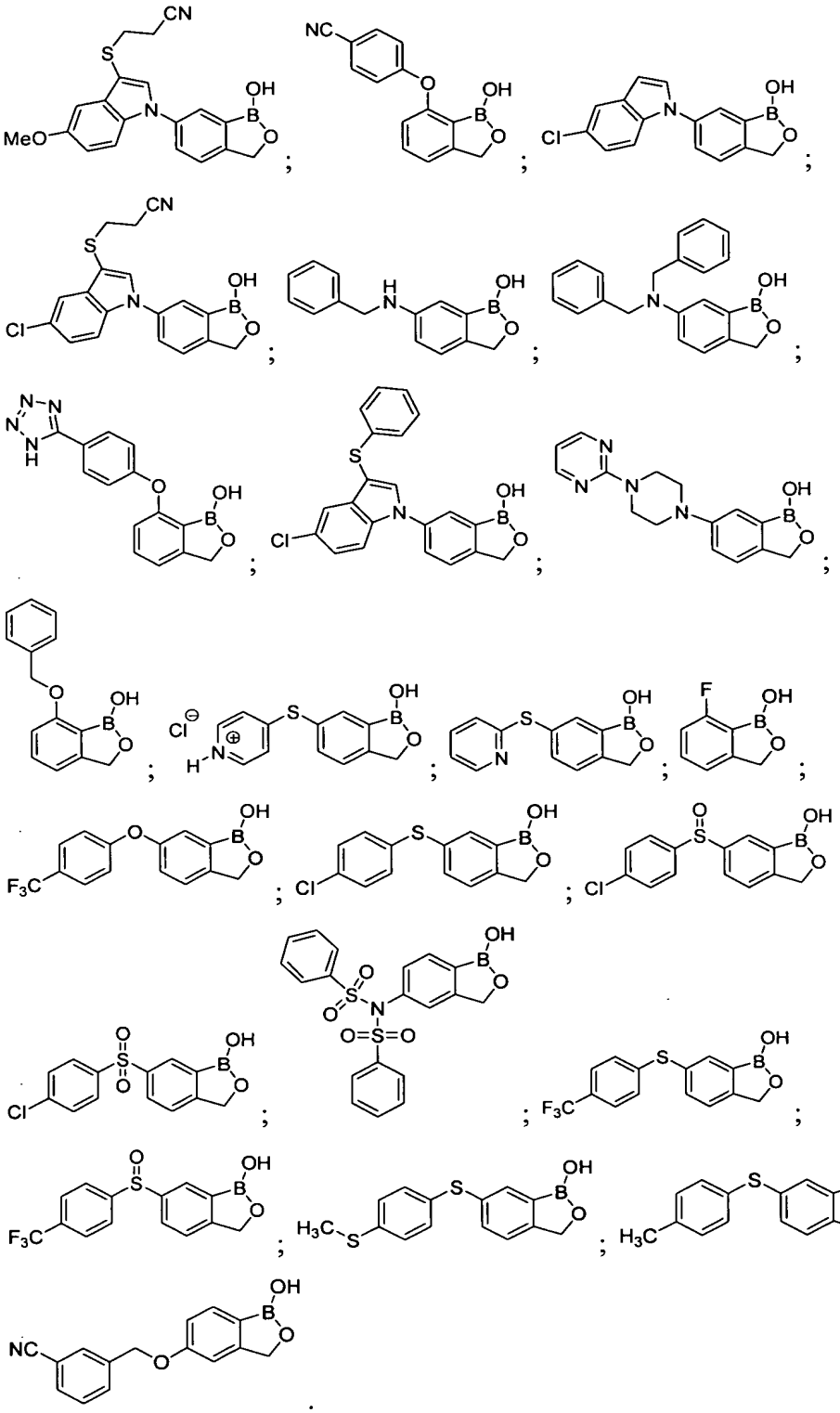
chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

[0330] In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a formula according to Formulae (Il)-(Io) wherein R^{1a} is a member selected from H, a negative charge and a salt counterion and each of the remaining three R groups (R^{9a}, R^{10a}, R^{11a} in (Il), R^{9a}, R^{10a}, R^{12a} in (Im), R^{9a}, R^{11a}, R^{12a} in (In), R^{10a}, R^{11a}, R^{12a} in (Io)) is a member independently selected from fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-

fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

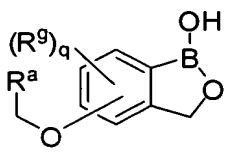
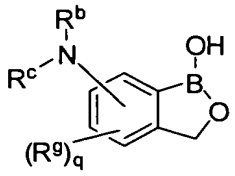
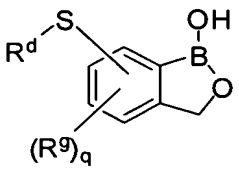
[0331] In an exemplary embodiment, the pharmaceutical formulation comprises a compound that is a member selected from:

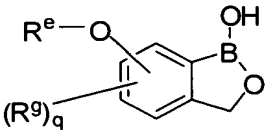
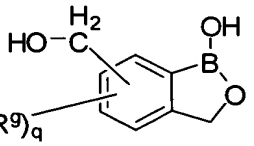


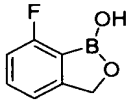
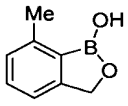
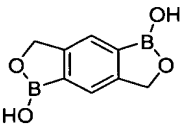
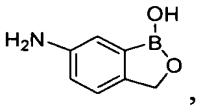
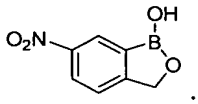


and

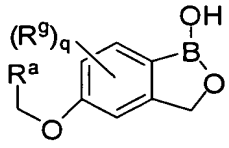
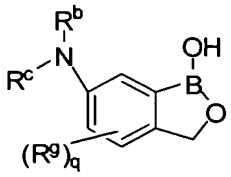
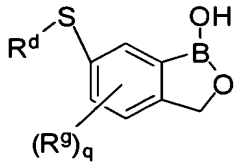
[0332] In an exemplary embodiment, the compound of the invention has a structure which is a member selected from:

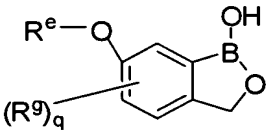
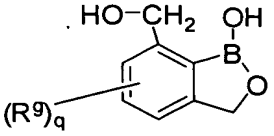

(Iab),

(Iac),

(Iad),


(Ia), and

(Iaf),

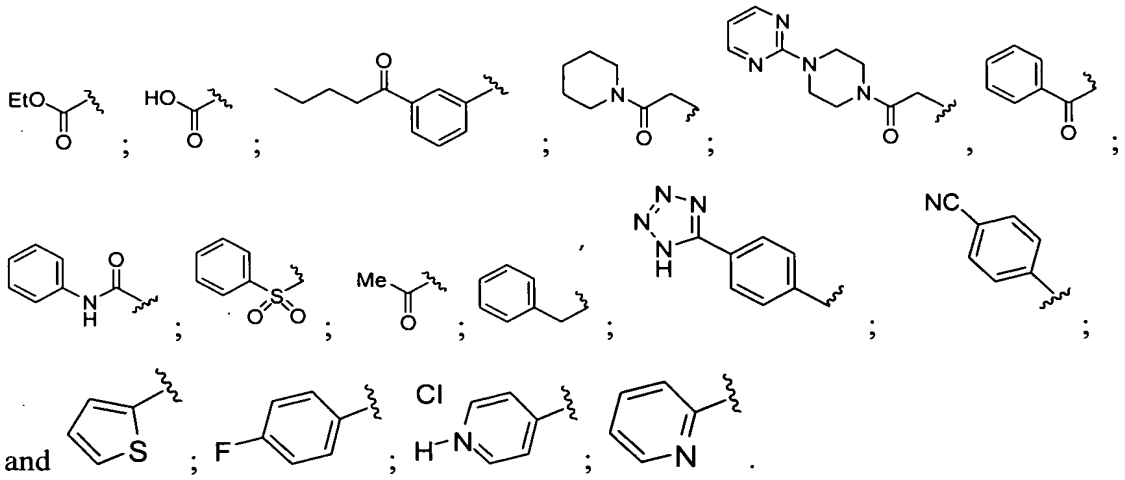
in which q is a number between 0 and 1. R^g is halogen. R^a, R^b, R^c, R^d and R^e are members independently selected from a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In an exemplary embodiment, the compound in the pharmaceutical formulation is a member selected from  ,  ,  ;  , and  .

[0333] In an exemplary embodiment, the compound has a structure is a member selected from:

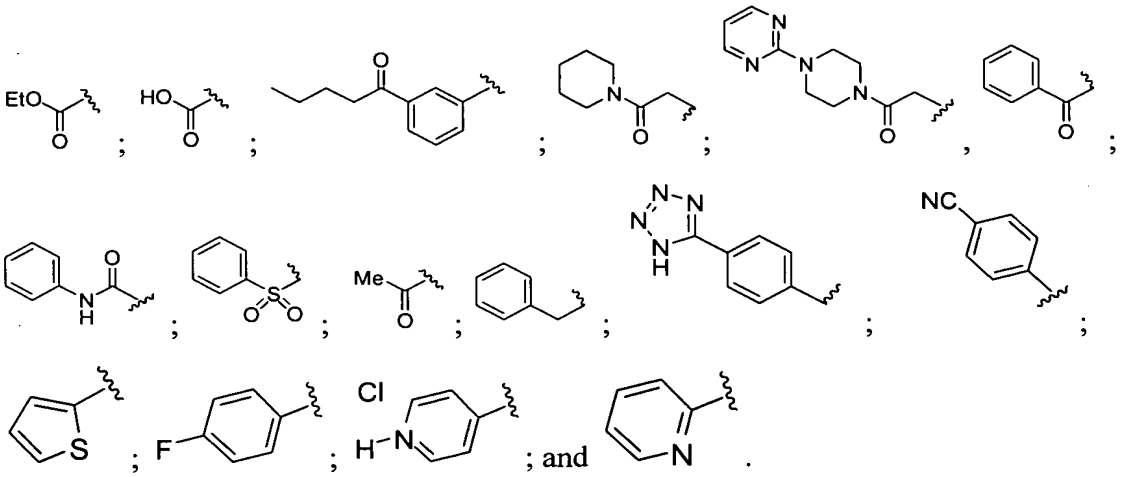

(Iag),

(Iah),

(Iai)


(Iaj) and

(Iak).

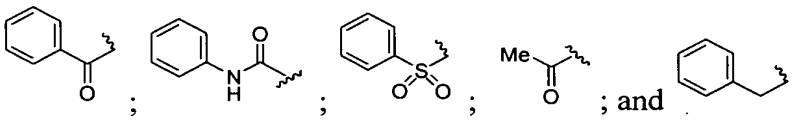
[0334] In an exemplary embodiment, R^a, R^d and R^e are each members indepenently selected from:

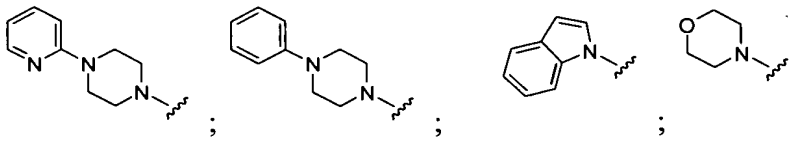


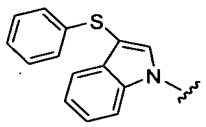
[0335] In an exemplary embodiment, R^b and R^c are members independently selected from H, methyl,



[0336] In another exemplary embodiment, R^b is H and R^c is a member selected from

H, methyl,  . In another exemplary embodiment, R^b and R^c are, together with the nitrogen to which they are attached, optionally joined to form a member selected from

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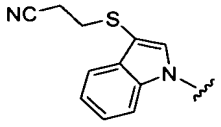
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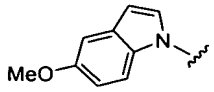
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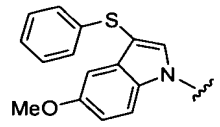
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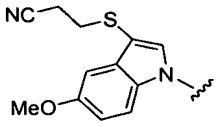
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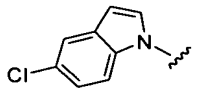
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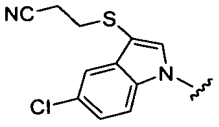
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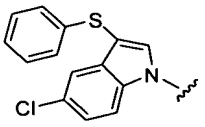
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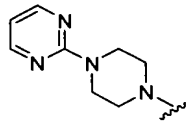
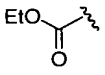

and .

[0337] In an exemplary embodiment, R^a is a member selected from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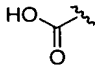
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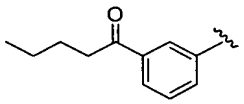
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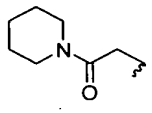
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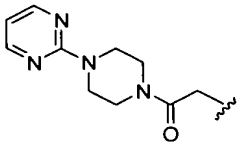
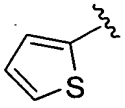

.

[0338] In an exemplary embodiment, R^d is a member selected from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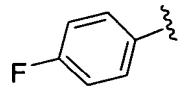
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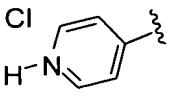
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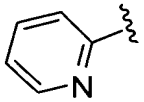
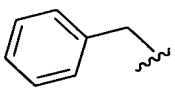

.

[0339] In an exemplary embodiment, R^e is a member selected from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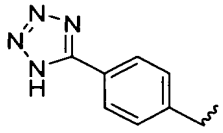
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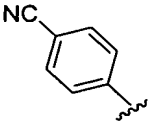
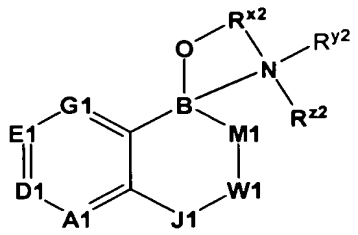

.

[0340] In another exemplary embodiment, the pharmaceutical formulations described herein can form a hydrate with water, a solvate with an alcohol (e.g. methanol, ethanol, propanol); an adduct with an amino compound (e.g. ammonia, methylamine, ethylamine); an adduct with an acid (e.g. formic acid, acetic acid); complexes with ethanolamine, quinoline, amino acids, and the like.

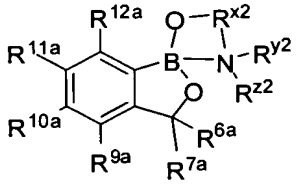
[0341] In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a structure according to Formula (Ip):



(Ip)

in which R^{x2} is a member selected from substituted or unsubstituted C_1-C_5 alkyl and substituted or unsubstituted C_1-C_5 heteroalkyl. R^{y2} and R^{z2} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

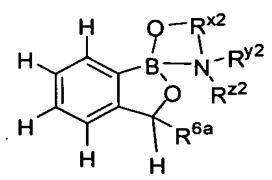
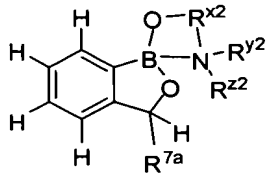
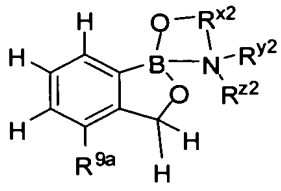
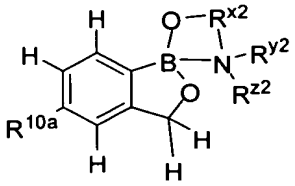
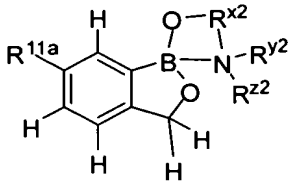
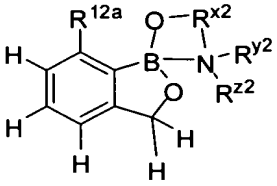
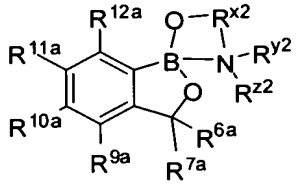
[0342] In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a structure according to Formula (Iq):



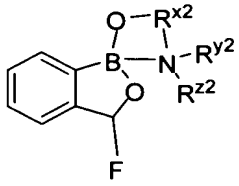
(Iq)

wherein B is boron. R^{x2} is a member selected from substituted or unsubstituted C_1-C_5 alkyl and substituted or unsubstituted C_1-C_5 heteroalkyl. R^{y2} and R^{z2} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In another exemplary embodiment, at least one member selected from R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a} and R^{12a} is a member selected from nitro, cyano and halogen.

[0343] In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a structure which is a member selected from the following Formulae:


(Ir),

(Is),

(It),

(Iu),

(Iv),

(Iw) and

(Iz).

In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a formula according to Formulae (Ib)-(Ie) wherein at least one member selected from R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a} and R^{12a} is a member selected from nitro, cyano, fluro, chloro, bromo and cyanophenoxy. In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a structure which is a member selected from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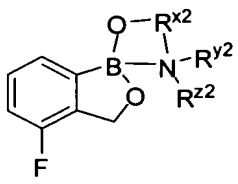
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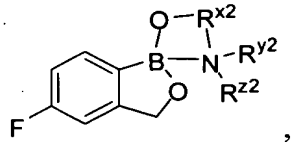
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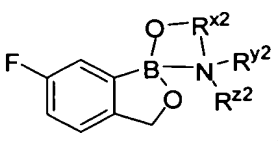
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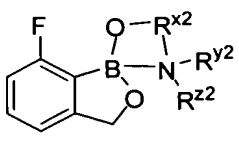
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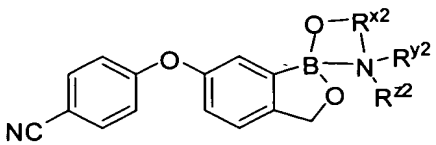
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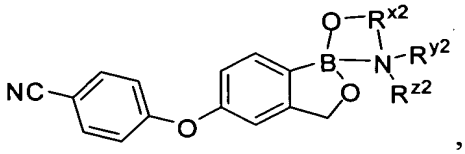
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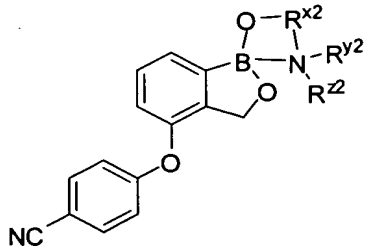
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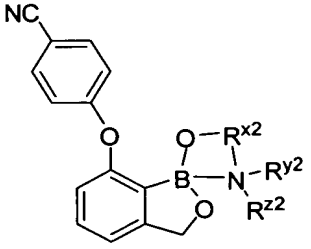
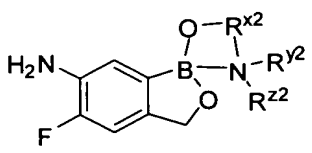
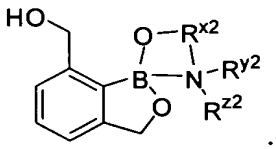

.

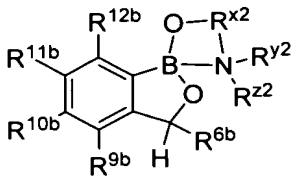
[0344] In an exemplary embodiment, the pharmaceutical formulation comprises a compound that has a structure that is a member selected from



and


.

[0345] In another exemplary embodiment, there is a proviso that the pharmaceutical formulation cannot comprise a structure according to Formula (Iaa):



(Iaa)

wherein R^{6b}, R^{9b}, R^{10b}, R^{11b} and R^{12b} have the same substituent listings as described for Formulae (Ix) and (Iy) above.

[0346] The pharmaceutical formulations of the invention can take a variety of forms adapted to the chosen route of administration. Those skilled in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutical formulations incorporating the compounds described herein. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water, ethanol, propylene glycol, mineral oil, vegetable oil and dimethylsulfoxide (DMSO).

[0347] The compositions of the invention may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It is further understood that the best method of administration may be a combination of methods. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques.

[0348] The pharmaceutical formulations containing compounds of the invention are preferably in a form suitable for oral use, for example, as tablets, troches,

lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0349] Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical formulations, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption 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 may be employed.

[0350] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0351] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; and dispersing or wetting agents, which may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene

sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0352] Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0353] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0354] Pharmaceutical formulations of the invention may also be in the form of oil-in-water emulsions and water-in-oil emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth; naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol; anhydrides, for example sorbitan monooleate; and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0355] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents. The pharmaceutical formulations may be in the form of 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, for example as a solution in 1,3-butanediol. 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 are conventionally 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 find use in the preparation of injectables.

[0356] The composition of the invention may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0357] Alternatively, the compositions can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[0358] For administration to non-human animals, the composition containing the therapeutic compound may be added to the animal's feed or drinking water. Also, it will be convenient to formulate animal feed and drinking water products so that the animal takes in an appropriate quantity of the compound in its diet. It will further be convenient to present the compound in a composition as a premix for addition to the feed or drinking water. The composition can also added as a food or drink supplement for humans.

[0359] Dosage levels of the order of from about 5 mg to about 250 mg per kilogram of body weight per day and more preferably from about 25 mg to about 150 mg per kilogram of body weight per day, are useful in the treatment of the above-indicated conditions. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the

condition being treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

[0360] Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[0361] Preferred compounds of the invention will have desirable pharmacological properties that include, but are not limited to, oral bioavailability, low toxicity, low serum protein binding and desirable in vitro and in vivo half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

[0362] Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocyctes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of laboratory animals that receive the compound intravenously.

[0363] Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcova, et al. (Journal of Chromatography B (1996) volume 677, pages 1-27).

[0364] Compound half-life is inversely proportional to the frequency of dosage of a compound. In vitro half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

[0365] The amount of the composition required for use in treatment will vary not only with the particular compound selected but also with the route of administration,

the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or clinician.

[0366] In an exemplary embodiment, the pharmaceutical formulation excipient comprises ethanol and the pharmaceutical formulation compound is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. In another exemplary embodiment, the pharmaceutical formulation excipient comprises propylene glycol and the pharmaceutical formulation compound is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. In an exemplary embodiment the pharmaceutical formulation comprises: about propylene glycol:ethanol 1:4, with 1:10 wt/ volume of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. In an exemplary embodiment the pharmaceutical formulation comprises: about 70% ethanol; about 20% poly(vinyl methyl ether-alt-maleic acid monobutyl ester); about 10% 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. In an exemplary embodiment the pharmaceutical formulation comprises: about 56% ethanol; about 14% water; about 15% poly(2-hydroxyethyl methacrylate); about 5% dibutyl sebacate; about 10% 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. In an exemplary embodiment the pharmaceutical formulation comprises: about 55% ethanol; about 15% ethyl acetate; about 15% poly(vinyl acetate); about 5% dibutyl sebacate; about 10% 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. In another exemplary embodiment, 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole is present in a pharmaceutical formulation in a concentration which is a member selected from 1%, 2.5%, 5%, 7.5%, 10% and 15% w/v. In another exemplary embodiment, the pharmaceutical formulation is a lacquer.

[0367] In an exemplary embodiment, the pharmaceutical formulation excipient comprises ethanol and the pharmaceutical formulation compound is 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. In another exemplary embodiment, the pharmaceutical formulation excipient comprises propylene glycol and the pharmaceutical formulation compound is 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. In an exemplary embodiment the pharmaceutical formulation comprises: about 20% propylene glycol; about 70% ethanol; about 10% 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. In an exemplary embodiment the pharmaceutical formulation comprises: about 70% ethanol; about 20% poly(vinyl methyl ether-alt-maleic acid monobutyl ester); about 10% 5-(4-

cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. In an exemplary embodiment the pharmaceutical formulation comprises: about 56% ethanol; about 14% water; about 15% poly(2-hydroxyethyl methacrylate); about 5% dibutyl sebacate; about 10% 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. In an exemplary embodiment the pharmaceutical formulation comprises: about 55% ethanol; about 15% ethyl acetate; about 15% poly(vinyl acetate); about 5% dibutyl sebacate; about 10% 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. In another exemplary embodiment, 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole is present in a pharmaceutical formulation in a concentration which is a member selected from 1%, 2.5%, 5%, 7.5%, 10% and 15% w/v. In another exemplary embodiment, the pharmaceutical formulation is a lacquer.

[0368] In an exemplary embodiment, the pharmaceutical formulation excipient comprises ethanol and the pharmaceutical formulation compound is a compound described herein. In another exemplary embodiment, the pharmaceutical formulation excipient comprises propylene glycol and the pharmaceutical formulation compound is a compound described herein. In an exemplary embodiment the pharmaceutical formulation comprises: about 20% propylene glycol; about 70% ethanol; about 10% of a compound described herein. In an exemplary embodiment the pharmaceutical formulation comprises: about 70% ethanol; about 20% poly(vinyl methyl ether-alt-maleic acid monobutyl ester); about 10% of a compound described herein. In an exemplary embodiment the pharmaceutical formulation comprises: about 56% ethanol; about 14% water; about 15% poly(2-hydroxyethyl methacrylate); about 5% dibutyl sebacate; about 10% of a compound described herein. In an exemplary embodiment the pharmaceutical formulation comprises: about 55% ethanol; about 15% ethyl acetate; about 15% poly(vinyl acetate); about 5% dibutyl sebacate; about 10% of a compound described herein. In another exemplary embodiment, a compound described herein is present in a pharmaceutical formulation in a concentration which is a member selected from 1%, 2.5%, 5%, 7.5%, 10% and 15% w/v. In another exemplary embodiment, the pharmaceutical formulation is a lacquer.

VII. a) <u>Topical formulations</u>

[0369] In a preferred embodiment, the methods of the invention can be used employed through the topical application of the compounds described herein.

[0370] The compositions of the present invention comprises fluid or semi-solid vehicles that may include but are not limited to polymers, thickeners, buffers, neutralizers, chelating agents, preservatives, surfactants or emulsifiers, antioxidants, waxes or oils, emollients, sunscreens, and a solvent or mixed solvent system. The solvent or mixed solvent system is important to the formation because it is primarily responsible for dissolving the drug. The best solvent or mixed solvent systems are also capable of maintaining clinically relevant levels of the drug in solution despite the addition of a poor solvent to the formulation. The topical compositions useful in the subject invention can be made into a wide variety of product types. These include, but are not limited to, lotions, creams, gels, sticks, sprays, ointments, pastes, foams, mousses, and cleansers. These product types can comprise several types of carrier systems including, but not limited to particles, nanoparticles, and liposomes. If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar or alginic acid or a salt thereof such as sodium alginate. Techniques for formulation and administration can be found in Remington: The Science and Practice of Pharmacy, supra. The formulation can be selected to maximize delivery to a desired target site in the body.

[0371] Lotions, which are preparations that are to be applied to the skin, nail, hair, claw or hoof surface without friction, are typically liquid or semi-liquid preparations in which finely divided solid, waxy, or liquid are dispersed. Lotions will typically contain suspending agents to produce better dispersions as well as compounds useful for localizing and holding the active agent in contact with the skin, nail, hair, claw or hoof, e.g., methylcellulose, sodium carboxymethyl-cellulose, or the like.

[0372] Creams containing the active agent for delivery according to the present invention are viscous liquid or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase is generally comprised of petrolatum or a fatty alcohol, such as cetyl- or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation, as explained in Remington: The Science and Practice of Pharmacy, supra, is generally a nonionic, anionic, cationic or amphoteric surfactant.

[0373] Gel formulations can also be used in connection with the present invention. As will be appreciated by those working in the field of topical drug formulation, gels are semisolid. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the carrier liquid, which is typically aqueous, but also may be a solvent or solvent blend.

[0374] Ointments, which are semisolid preparations, are typically based on petrolatum or other petroleum derivatives. As will be appreciated by the ordinarily skilled artisan, the specific ointment base to be used is one that provides for optimum delivery for the active agent chosen for a given formulation, and, preferably, provides for other desired characteristics as well, e.g., emolliency or the like. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing. As explained in Remington: The Science and Practice of Pharmacy, 19th Ed. (Easton, Pa.: Mack Publishing Co., 1995), at pages 1399-1404, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight; again, reference may be had to Remington: The Science and Practice of Pharmacy, supra, for further information.

[0375] Useful formulations of the invention also encompass sprays. Sprays generally provide the active agent in an aqueous and/or alcoholic solution which can be misted onto the skin, nail, hair, claw or hoof for delivery. Such sprays include those formulated to provide for concentration of the active agent solution at the site of administration following delivery, e.g., the spray solution can be primarily composed of alcohol or other like volatile liquid in which the drug or active agent can be dissolved. Upon delivery to the skin, nail, hair, claw or hoof, the carrier evaporates, leaving concentrated active agent at the site of administration.

[0376] The topical pharmaceutical compositions may also comprise suitable solid or gel phase carriers. Examples of such carriers include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0377] The topical pharmaceutical compositions may also comprise a suitable emulsifier which refers to an agent that enhances or facilitates mixing and suspending oil-in-water or water-in-oil. The emulsifying agent used herein may consist of a single emulsifying agent or may be a nonionic, anionic, cationic or amphoteric surfactant or blend of two or more such surfactants; preferred for use herein are nonionic or anionic emulsifiers. Such surface-active agents are described in "McCutcheon's Detergent and Emulsifiers," North American Edition, 1980 Annual published by the McCutcheon Division, MC Publishing Company, 175 Rock Road, Glen Rock, N.J. 07452, USA.

[0378] Preferred for use herein are high molecular weight alcohols such as cetearyl alcohol, cetyl alcohol, stearyl alcohol, emulsifying wax, glyceryl monostearate. Other examples are ethylene glycol distearate, sorbitan tristearate, propylene glycol monostearate, sorbitan monooleate, sorbitan monostearate (SPAN 60), diethylene glycol monolaurate, sorbitan monopalmitate, sucrose dioleate, sucrose stearate (CRODESTA F-160), polyoxyethylene lauryl ether (BRIJ 30), polyoxyethylene (2) stearyl ether (BRIJ 72), polyoxyethylene (21) stearyl ether (BRIJ 721), polyoxyethylene monostearate (Myrj 45), polyoxyethylene sorbitan monostearate (TWEEN 60), polyoxyethylene sorbitan monooleate (TWEEN 80), polyoxyethylene sorbitan monolaurate (TWEEN 20) and sodium oleate. Cholesterol and cholesterol derivatives may also be employed in externally used emulsions and promote w/o emulsions.

[0379] Especially suitable nonionic emulsifying agents are those with hydrophile-lipophile balances (HLB) of about 3 to 6 for w/o system and 8 to 18 for o/w system as determined by the method described by Paul L. Lindner in "Emulsions and Emulsion", edited by Kenneth Lissant, published by Dekker, New York, N.Y., 1974, pages 188-190. More preferred for use herein are one or more nonionic surfactants that produce a system having HLB of about 8 to about 18.

[0380] Examples of such nonionic emulsifiers include but are not limited to "BRIJ 72", the trade name for a polyoxyethylene (2) stearyl ether having an HLB of 4.9; "BRIJ 721 ", the trade name for a polyoxyethylene (21) stearyl ether having an HLB of 15.5, "Brij 30", the trade name for polyoxyethylene lauryl ether having an HLB of 9.7; "Polawax", the trade name for emulsifying wax having an HLB of 8.0; "Span 60", the trade name for sorbitan monostearate having an HLB of 4.7; "Crodesta F-160", the trade name for sucrose stearate" having an HLB of 14.5. All of these materials are available from Ruger Chemicals Inc.; Croda; ICI Americas, Inc.; Spectrum Chemicals; and BASF. When the topical formulations of the present invention contain at least one emulsifying agent, each emulsifying agent is present in amount from about 0.5 to about 2.5 wt%, preferably 0.5 to 2.0%, more preferably 1.0% or 1.8%. Preferably the emulsifying agent comprises a mixture of steareth 21 (at about 1.8 %) and steareth 2 (at about 1.0%).

[0381] The topical pharmaceutical compositions may also comprise suitable emollients. Emollients are materials used for the prevention or relief of dryness, as well as for the protection of the skin, nail, hair, claw or hoof. Useful emollients include, but are not limited to, cetyl alcohol, isopropyl myristate, stearyl alcohol, and the like. A wide variety of suitable emollients are known and can be used herein. See e.g., Sagarin, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 32-43 (1972), and U.S. Pat. No. 4,919,934, to Deckner et al., issued Apr. 24, 1990, both of which are incorporated herein by reference in their entirety. These materials are available from Ruger Chemical Co, (Irvington, NJ).

[0382] When the topical formulations of the present invention contain at least one emollient, each emollient is present in an amount from about 0.1 to 15%, preferably 0.1 to about 3.0, more preferably 0.5, 1.0, or 2.5 wt%. Preferably the emollient is a mixture of cetyl alcohol, isopropyl myristate and stearyl alcohol in a 1/5/2 ratio. The emollient may also be a mixture of cetyl alcohol and stearyl alcohol in a 1 /2 ratio.

[0383] The topical pharmaceutical compositions may also comprise suitable antioxidants, substances known to inhibit oxidation. Antioxidants suitable for use in accordance with the present invention include, but are not limited to, butylated hydroxytoluene, ascorbic acid, sodium ascorbate, calcium ascorbate, ascorbic palmitate, butylated hydroxyanisole, 2,4,5-trihydroxybutyrophenone, 4-

hydroxymethyl-2,6-di-*tert*-butylphenol, erythorbic acid, gum guaiac, propyl gallate, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone and tocopherols such as vitamin E, and the like, including pharmaceutically acceptable salts and esters of these compounds. Preferably, the antioxidant is butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, ascorbic acid, pharmaceutically acceptable salts or esters thereof, or mixtures thereof. Most preferably, the antioxidant is butylated hydroxytoluene. These materials are available from Ruger Chemical Co, (Irvington, NJ).

[0384] When the topical formulations of the present invention contain at least one antioxidant, the total amount of antioxidant present is from about 0.001 to 0.5 wt%, preferably 0.05 to about 0.5 wt%, more preferably 0.1%.

[0385] The topical pharmaceutical compositions may also comprise suitable preservatives. Preservatives are compounds added to a pharmaceutical formulation to act as an anti-microbial agent. Among preservatives known in the art as being effective and acceptable in parenteral formulations are benzalkonium chloride, benzethonium, chlorohexidine, phenol, m-cresol, benzyl alcohol, methylparaben, propylparaben, chlorobutanol, o-cresol, p-cresol, chlorocresol, phenylmercuric nitrate, thimerosal, benzoic acid, and various mixtures thereof. See, e.g., Wallhausser, K.-H., Develop. Biol. Standard, 24:9-28 (1974) (S. Krager, Basel). Preferably, the preservative is selected from methylparaben, propylparaben and mixtures thereof. These materials are available from Inolex Chemical Co (Philadelphia, PA) or Spectrum Chemicals.

[0386] When the topical formulations of the present invention contain at least one preservative, the total amount of preservative present is from about 0.01 to about 0.5 wt%, preferably from about 0.1 to 0.5%, more preferably from about 0.03 to about 0.15. Preferably the preservative is a mixture of methylparaben and proplybarben in a 5/1 ratio. When alcohol is used as a preservative, the amount is usually 15 to 20%.

[0387] The topical pharmaceutical compositions may also comprise suitable chelating agents to form complexes with metal cations that do not cross a lipid bilayer. Examples of suitable chelating agents include ethylene diamine tetraacetic acid (EDTA), ethylene glycol-bis(beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA) and 8-Amino-2-[(2-amino-5-methylphenoxy)methyl]-6-methoxyquinoline-

N,N,N',N'-tetraacetic acid, tetrapotassium salt (QUIN-2). Preferably the chelating agents are EDTA and citric acid. These materials are available from Spectrum Chemicals.

[0388] When the topical formulations of the present invention contain at least one chelating agent, the total amount of chelating agent present is from about 0.005% to 2.0% by weight, preferably from about 0.05% to about 0.5 wt%, more preferably about 0.1% by weight.

[0389] The topical pharmaceutical compositions may also comprise suitable neutralizing agents used to adjust the pH of the formulation to within a pharmaceutically acceptable range. Examples of neutralizing agents include but are not limited to trolamine, tromethamine, sodium hydroxide, hydrochloric acid, citric acid, and acetic acid. Such materials are available from are available from Spectrum Chemicals (Gardena, CA).

[0390] When the topical formulations of the present invention contain at least one neutralizing agent, the total amount of neutralizing agent present is from about 0.1 wt to about 10 wt %, preferably 0.1 wt % to about 5.0 wt%, and more preferably about 1.0 wt %. The neutralizing agent is generally added in whatever amount is required to bring the formulation to the desired pH.

[0391] The topical pharmaceutical compositions may also comprise suitable viscosity increasing agents. These components are diffusible compounds capable of increasing the viscosity of a polymer-containing solution through the interaction of the agent with the polymer. CARBOPOL ULTREZ 10 may be used as a viscosity-increasing agent. These materials are available from Noveon Chemicals, Cleveland, OH.

[0392] When the topical formulations of the present invention contain at least one viscosity increasing agent, the total amount of viscosity increasing agent present is from about 0.25% to about 5.0% by weight, preferably from about 0.25% to about 1.0 wt%, and more preferably from about 0.4% to about 0.6% by weight.

[0393] The topical pharmaceutical compositions may also comprise suitable nail penetration enhancers. Examples of nail penetration enhancers include mercaptan compounds, sulfites and bisulfites, keratolytic agents and surfactants. Nail

penetration enhancers suitable for use in the invention are described in greater detail in Malhotra *et al.*, *J. Pharm. Sci.*, **91**:2, 312-323 (2002), which is incorporated herein by reference in its entirety.

[0394] The topical pharmaceutical compositions may also comprise one or more suitable solvents. The ability of any solid substance (solute) to dissolve in any liquid substance (solvent) is dependent upon the physical properties of the solute and the solvent. When solutes and solvents have similar physical properties the solubility of the solute in the solvent will be the greatest. This gives rise to the traditional understanding that "like dissolves like." Solvents can be characterized in one extreme as non-polar, lipophilic oils, while in the other extreme as polar hydrophilic solvents. Oily solvents dissolve other non-polar substances by Van der Wals interactions while water and other hydrophilic solvents dissolve polar substances by ionic, dipole, or hydrogen bonding interactions. All solvents can be listed along a continuum from the least polar, i.e. hydrocarbons such as decane, to the most polar solvent being water. A solute will have its greatest solubility in solvents having equivalent polarity. Thus, for drugs having minimal solubility in water, less polar solvents will provide improved solubility with the solvent having polarity nearly equivalent to the solute providing maximum solubility. Most drugs have intermediate polarity, and thus experience maximum solubility in solvents such as propylene glycol or ethanol, which are significantly less polar than water. If the drug has greater solubility in propylene glycol (for example 8% (w/w)) than in water (for example 0.1 % (w/w)), then addition of water to propylene glycol should decrease the maximum amount of drug solubility for the solvent mixture compared with pure propylene glycol. Addition of a poor solvent to an excellent solvent will decrease the maximum solubility for the blend compared with the maximum solubility in the excellent solvent.

[0395] When compounds are incorporated into topical formulations the concentration of active ingredient in the formulation may be limited by the solubility of the active ingredient in the chosen solvent and/or carrier. Non-lipophilic drugs typically display very low solubility in pharmaceutically acceptable solvents and/or carriers. For example, the solubility of some compounds in the invention in water is less than 0.00025% wt/wt. The solubility of the same compounds in the invention can be less than about 2% wt/wt in either propylene glycol or isopropyl myristate. In one embodiment of the present invention, diethylene glycol monoethyl ether (DGME) is

the solvent used to dissolve the compounds of the invention. The compounds in the invention useful in the present formulation are believed to have a solubility of from about 10% wt/wt to about 25% wt/wt in DGME. In another embodiment a DGME water cosolvent system is used to dissolve the compounds of the invention. The solvent capacity of DGME drops when water is added; however, the DGME/water cosolvent system can be designed to maintain the desired concentration of from about 0.1 % to about 5% wt/wt active ingredient. Preferably the active ingredient is present from about 0.5 % to about 3% wt/wt, and more preferably at about 1% wt/wt, in the as-applied topical formulations. Because DGME is less volatile than water, as the topical formulation evaporates upon application, the active agent becomes more soluble in the cream formulation. This increased solubility reduces the likelihood of reduced bioavailability caused by the drug precipitating on the surface of the skin, nail, hair, claw or hoof.

[0396] Liquid forms, such as lotions suitable for topical administration or suitable for cosmetic application, may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, thickeners, penetration enhancers, and the like. Solid forms such as creams or pastes or the like may include, for example, any of the following ingredients, water, oil, alcohol or grease as a substrate with surfactant, polymers such as polyethylene glycol, thickeners, solids and the like. Liquid or solid formulations may include enhanced delivery technologies such as liposomes, microsomes, microsponges and the like.

[0397] Additionally, the compounds can be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art.

[0398] Topical treatment regimens according to the practice of this invention comprise applying the composition directly to the skin, nail, hair, claw or hoof at the application site, from one to several times daily.

[0399] Formulations of the present invention can be used to treat, ameliorate or prevent conditions or symptoms associated with bacterial infections, acne, inflammation and the like.

[0400] In an exemplary embodiment, the pharmaceutical formulation includes a simple solution. In an exemplary embodiment, the simple solution includes an alcohol. In an exemplary embodiment, the simple solution includes alcohol and water. In an exemplary embodiment, the alcohol is ethanol, ethylene glycol, propanol, polypropylene glycol, isopropanol or butanol. In another exemplary embodiment, the simple solution is a member selected from about 10% polypropylene glycol and about 90% ethanol; about 20% polypropylene glycol and about 80% ethanol; about 30% polypropylene glycol and about 70% ethanol; about 40% polypropylene glycol and about 60% ethanol; about 50% polypropylene glycol and about 50% ethanol; about 60% polypropylene glycol and about 40% ethanol; about 70% polypropylene glycol and about 30% ethanol; about 80% polypropylene glycol and about 20% ethanol; about 90% polypropylene glycol and about 10% ethanol.

[0401] In an exemplary embodiment, the pharmaceutical formulation is a lacquer. Please see Remington's, supra, for more information on the production of lacquers.

[0402] In an exemplary embodiment, the compound is present in said pharmaceutical formulation in a concentration of from about 0.5% to about 15%. In an exemplary embodiment, the compound is present in said pharmaceutical formulation in a concentration of from about 0.1% to about 12.5%. In an exemplary embodiment, the compound is present in said pharmaceutical formulation in a concentration of from about 1% to about 10%. In an exemplary embodiment, the compound is present in said pharmaceutical formulation in a concentration of from about 1% to about 5%. In an exemplary embodiment, the compound is present in said pharmaceutical formulation in a concentration of from about 0.5% to about 5%. In an exemplary embodiment, the compound is present in said pharmaceutical formulation in a concentration of from about 0.5% to about 7.5%. In an exemplary embodiment, the compound is present in said pharmaceutical formulation in a concentration of from about 5% to about 7.5%. In an exemplary embodiment, the compound is present in said pharmaceutical formulation in a concentration of from about 2% to about 8%. In an exemplary embodiment, the compound is present in said pharmaceutical formulation in a concentration of from about 4% to about 9%.

VII. b) ***Additional Active Agents***

[0403] The following are examples of the cosmetic and pharmaceutical agents that can be added to the topical pharmaceutical formulations of the present invention. The following agents are known compounds and are readily available commercially.

[0404] Anti-inflammatory agents include, but are not limited to, bisabolol, mentholatum, dapsone, aloe, hydrocortisone, and the like.

[0405] Vitamins include, but are not limited to, Vitamin B, Vitamin E, Vitamin A, Vitamin D, and the like and vitamin derivatives such as tazarotene, calcipotriene, tretinoin, adapalene and the like.

[0406] Anti-aging agents include, but are not limited to, niacinamide, retinol and retinoid derivatives, AHA, Ascorbic acid, lipoic acid, coenzyme Q 10, beta hydroxy acids, salicylic acid, copper binding peptides, dimethylaminoethyl (DAEA), and the like.

[0407] Sunscreens and or sunburn relief agents include, but are not limited to, PABA, jojoba, aloe, padimate-O, methoxycinnamates, proxamine HCl, lidocaine and the like. Sunless tanning agents include, but are not limited to, dihydroxyacetone (DHA).

[0408] Psoriasis-treating agents and/or acne-treating agents include, but are not limited to, salicylic acid, benzoyl peroxide, coal tar, selenium sulfide, zinc oxide, pyrithione (zinc and/or sodium), tazarotene, calcipotriene, tretinoin, adapalene and the like.

[0409] Agents that are effective to control or modify keratinization, including without limitation: tretinoin, tazarotene, and adapalene.

[0410] The compositions comprising an compound/active agent of the invention, and optionally at least one of these additional agents, are to be administered topically. In a primary application, this leads to the compounds of the invention and any other active agent working upon and treating the skin, nail, hair, claw or hoof. Alternatively, any one of the topically applied active agents may also be delivered systemically by transdermal routes.

[0411] In such compositions an additional cosmetically or pharmaceutically effective agent, such as an anti-inflammatory agent, vitamin, anti-aging agent, sunscreen, and/or acne-treating agent, for example, is usually a minor component (from about 0.001 % to about 20% by weight or preferably from about 0.01 % to about 10% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

VII. c) Testing

[0412] Preferred compounds for use in the present topical formulations will have certain pharmacological properties. Such properties include, but are not limited to, low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lives. Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcova et al. (1996, *J. Chromat.* B677: 1-27). Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gleschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

[0413] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Compounds that exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (*See*, e.g. Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1, p. 1).

VII. d) Administration

[0414] For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays, as disclosed herein. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the EC_{50} (effective dose for 50% increase) as determined in cell culture, *i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of bacterial cell growth. Such information can be used to more accurately determine useful doses in humans.

[0415] In general, the compounds prepared by the methods, and from the intermediates, described herein will be administered in a therapeutically or cosmetically effective amount by any of the accepted modes of administration for agents that serve similar utilities. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination, the severity of the particular disease undergoing therapy and the judgment of the prescribing physician. The drug can be administered from once or twice a day, or up to 3 or 4 times a day.

[0416] Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety that are sufficient to maintain bacterial cell growth inhibitory effects. Usual patient dosages for systemic administration range from 0.1 to 1000 mg/day, preferably, 1-500 mg/day, more preferably 10 - 200 mg/day, even more preferably 100 - 200 mg/day. Stated in terms of patient body surface areas, usual dosages range from 50-91 mg/m^2/day.

[0417] The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt%) basis, from about 0.01-10 wt% of the drug based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 0.1-3.0 wt%, more preferably, about 1.0 wt%.

[0418] The invention is further illustrated by the Examples that follow. The Examples are not intended to define or limit the scope of the invention.

EXAMPLES

[0419] Proton NMR are recorded on Varian AS 300 spectrometer and chemical shifts are reported as δ (ppm) down field from tetramethylsilane. Mass spectra are determined on Micromass Quattro II.

EXAMPLE 1

Preparation of 3 from 1

1.1 Reduction of Carboxylic Acid

[0420] To a solution of **1** (23.3 mmol) in anhydrous THF (70 mL) under nitrogen was added dropwise a BH_3 THF solution (1.0 M, 55 mL, 55 mmol) at 0°C and the reaction mixture was stirred overnight at room temperature. Then the mixture was cooled again with ice bath and MeOH (20 mL) was added dropwise to decompose excess BH_3. The resulting mixture was stirred until no bubble was released and then 10% NaOH (10 mL) was added. The mixture was concentrated and the residue was mixed with water (200 mL) and extracted with EtOAc. The residue from rotary evaporation was purified by flash column chromatography over silica gel to give 20.7 mmol of **3**.

1.2 Results

[0421] Exemplary compounds of structure **3** prepared by the method above are provided below.

1.2.a 2-Bromo-5-chlorobenzyl Alcohol

[0422] ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.57 (d, J = 8.7 Hz, 1H), 7.50-7.49 (m, 1H), 7.28-7.24 (m, 1H), 5.59 (t, J = 6.0 Hz, 1H) and 4.46 (d, J = 6.0 Hz, 2H) ppm.

1.2.b 2-Bromo-5-methoxybenzyl Alcohol

[0423] ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.42 (d, J = 8.7 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 6.77 (dd, J_1 = 3 Hz, J_2 = 3 Hz, 1H), 5.43 (t, J = 5.7 Hz, 1H), 4.44(d, J = 5.1 Hz, 2H), 3.76(s, 3H).

EXAMPLE 2

Preparation of 3 from 2

2.1. Reduction of Aldehyde

[0424] To a solution of **2** (Z = H, 10.7 mmol) in methanol (30 mL) was added sodium borohydride (5.40 mol), and the mixture was stirred at room temperature for 1 h. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford 9.9 mmol of **3**.

2.2 Results

[0425] Exemplary compounds of structure **3** prepared by the method above are provided below.

2.2.a 2-Bromo-5-(4-cyanophenoxy)benzyl Alcohol

[0426] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 2.00 (br s, 1H), 4.75 (s, 2H), 6.88 (dd, J = 8.5, 2.9 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 2.6 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.8 Hz, 2H).

2.2.b 2-Bromo-4-(4-cyanophenoxy)benzyl Alcohol

[0427] ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.83 (d, 2H), 7.58 (d, 1H), 7.39 (d, 1H), 7.18 (dd, 1H), 7.11 (d, 2H), 5.48 (t, 1H) and 4.50 (d, 2H) ppm.

2.2.c 5-(4-Cyanophenoxy)-1-Indanol

[0428] M.p.50-53°C. MS (ESI+): m/z = 252 (M+1). HPLC: 99.7% purity at 254 nm and 99.0% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.80 (d, 2H), 7.37 (d, 1H), 7.04 (d, 2H), 6.98-6.93 (m, 2H), 5.27 (d, 1H), 5.03 (q, 1H), 2.95-2.85 (m, 1H), 2.75-2.64 (m, 1H), 2.39-2.29 (m, 1H) and 1.85-1.74 (m, 1H) ppm.

2.2.d 2-Bromo-5-(tert-butyldimethylsiloxy)benzyl Alcohol

[0429] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 0.20 (s, 6H), 0.98 (s, 9H), 4.67 (br s,1H), 6.65 (dd, J = 8.2, 2.6 Hz, 1H), 6.98 (d, J = 2.9 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H).

[0430] Additional examples of compounds which can be produced by this method include 2-bromo-4-(3-cyanophenoxy)benzyl alcohol; 2-bromo-4-(4-chlorophenoxy)benzyl alcohol; 2-bromo-4-phenoxybenzyl alcohol; 2-bromo-5-(3,4-

dicyanophenoxy)benzyl alcohol; 2-(2-bromo-5-fluorophenyl)ethyl alcohol; 2-bromo-5-fluorobenzyl alcohol; and 1-bromo-2-naphthalenemethanol.

EXAMPLE 3

Preparation of 4 from 3

3.1 Protective Alkylation

[0431] Compound 3 (20.7 mmol) was dissolved in CH_2Cl_2 (150 mL) and cooled to 0°C with ice bath. To this solution under nitrogen were added in sequence N,N-di-isopropyl ethyl amine (5.4 mL, 31.02 mmol, 1.5 eq) and chloromethyl methyl ether (2 mL, 25.85 mmol, 1.25 eq). The reaction mixture was stirred overnight at room temperature and washed with $NaHCO_3$-saturated water and then NaCl-saturated water. The residue after rotary evaporation was purified by flash column chromatography over silica gel to give 17.6 mmol of 4.

3.2 Results

[0432] Exemplary compounds of structure **4** prepared by the method above are provided below.

3.2.a 2-Bromo-5-chloro-1-(methoxymethoxymethyl)benzene

[0433] ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.63 (d, J = 8.7 Hz, 1H), 7.50 (dd, J = 2.4 & 0.6 Hz, 1H), 7.32 (dd, J = 8.4 & 2.4 Hz, 1H), 4.71 (s, 2H), 4.53 (s, 2H) and 3.30 (s, 3H) ppm.

3.2.b 2-Bromo-5-fluoro-1-[1-(methoxymethoxy)ethyl]benzene

[0434] ^{1}H-NMR (300.058 MHz, $CDCl_3$) δ ppm 1.43 (d, J = 6.5 Hz, 3H), 3.38 (s, 3H), 4.55 (d, J = 6.5 Hz, 1H), 4.63 (d, J = 6.5 Hz, 1H), 5.07 (q, J = 6.5 Hz, 1H), 6.85 (m, 1H), 7.25 (dd, J = 9.7, 2.6 Hz, 1H), 7.46 (dd, J = 8.8, 5.3 Hz, 1H).

3.2.c 2-Bromo-5-fluoro-1-[2-(methoxymethoxy)ethyl]benzene

[0435] ^{1}H-NMR (300.058 MHz, $CDCl_3$) δ ppm 3.04 (t, J = 6.7 Hz, 2H), 3.31 (s, 3H), 3.77 (t, J = 6.7 Hz, 2H), 4.62 (s, 2H), 6.82 (td, J = 8.2, 3.2 Hz, 1H), 7.04 (dd, J = 9.4, 2.9 Hz, 1H), 7.48 (dd, J = 8.8, 5.3 Hz, 1H).

3.2.d 2-Bromo-4,5-difluoro-1-(methoxymethoxymethyl)benzene

[0436] ^{1}H-NMR (300.058 MHz, $CDCl_3$) δ ppm 3.42 (s, 3H), 4.57 (d, J = 1.2 Hz, 2H), 4.76 (s, 2H), 7.3-7.5 (m, 2H).

3.2.e *2-Bromo-5-cyano-1-(methoxymethoxymethyl)benzene*

[0437] ^{1}H-NMR (300.058 MHz, $CDCl_3$) δ ppm 3.43 (s, 3H), 4.65 (s, 2H), 4.80 (s, 2H), 7.43 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 4.1 Hz, 1H).

3.2.f *2-Bromo-5-methoxy-1-(methoxymethoxymethyl)benzene*

[0438] ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.48 (dd, J_1 = 1.2 Hz, J_2 = 1.2 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.83 (dd, J_1 = 3 Hz, J_2 = 3 Hz, 1H), 4.69 (d, J = 1.2 Hz, 2H), 4.5 (s, 2H), 3.74 (d, J = 1.5 Hz, 3H), 3.32 (d, J = 2.1 Hz, 3H) ppm.

3.2.g *1-Benzyl-1-(2-bromophenyl)-1-(methoxymethoxy)ethane*

[0439] ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.70-7.67 (m, 1H), 7.25-7.09 (m, 6H), 6.96-6.93 (m, 2H), 4.61 (d, 1H), 4.48 (d, 1H), 3.36-3.26 (m, 2H), 3.22 (s, 3H) and 1.63 (s, 3H) ppm.

3.2.h *2-Bromo-6-fluoro-1-(methoxymethoxymethyl)benzene*

[0440] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 3.43 (s, 3H), 4.74 (s, 2H), 4.76 (d, *J* = 2.1 Hz, 2H), 7.05 (t, *J* = 9.1 Hz, 1H), 7.18 (td, *J* = 8.2, 5.9 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H).

3.2.i *2-Bromo-4-(4-cyanophenoxy)-1-(methoxymethoxymethyl)benzene*

[0441] ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.84 (d, 2H), 7.56 (d, 1H), 7.44 (d, 1H), 7.19-7.12 (m, 3H), 4.69 (s, 2H), 4.56 (s, 2H) and 3.31 (s, 3H) ppm.

3.2.j *2-Bromo-5-(tert-butyldimethylsiloxy)-1-(methoxymethoxymethyl)benzene*

[0442] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 0.19 (s, 6H), 0.98 (s, 9H), 3.43 (s, 3H), 4.59 (s, 2H), 4.75 (s, 2H), 6.64 (dd, *J* = 8.5, 2.9 Hz, 1H), 6.98 (d, *J* = 2.9 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H).

3.2.k *2-Bromo-5-(2-cyanophenoxy)-1-(methoxymethoxymethyl)benzene*

[0443] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 3.41 (s, 3H), 4.64 (s, 2H), 4.76 (s, 2H), 6.8-6.9 (m, 2H), 7.16 (td, *J* = 7.6, 0.9 Hz, 1H), 7.28 (d, *J* = 2.9 Hz, 1H), 7.49 (ddd, *J* = 8.8, 7.6, 1.8 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.67 (dd, *J* = 7.9, 1.8 Hz, 1H).

3.2.1 *2-Bromo-5-phenoxy-1-(methoxymethoxymethyl)benzene*

[0444] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 3.40 (s, 3H), 4.62 (s, 2H), 4.74 (s, 2H), 6.80 (dd, J = 8.8, 2.9 hz, 1H), 7.01 (d, J = 8.5 Hz, 2H), 7.12 (t, J = 7.9 Hz, 1H), 7.19 (d, J = 2.9 hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 8.5 Hz, 1H).

[0445] Additional examples of compounds which can be produced by this method include 2-bromo-l-(methoxymethoxymethyl)benzene; 2-bromo-5-methyl-1-(methoxymethoxymethyl)benzene; 2-bromo-5-(methoxymethoxymethyl)-1-(methoxymethoxymethyl)benzene; 2-bromo-5-fluoro-1-(methoxymethoxymethyl)benzene; 1-bromo-2-(methoxymethoxymethyl)naphthalene; 2-bromo-4-fluoro-1-(methoxymethoxymethyl)benzene; 2-phenyl-1-(2-bromophenyl)-1-(methoxymethoxy)ethane; 2-bromo-5-(4-cyanophenoxy)-1-(methoxymethoxy methyl)benzene; 2-bromo-4-(3-cyanophenoxy)-1-(methoxymethoxymethyl)benzene; 2-bromo-4-(4-chlorophenoxy)-1-(methoxymethoxymethyl)benzene; 2-bromo-4-phenoxy-1-(methoxymethoxymethyl)benzene; 2-bromo-5-(3,4-dicyanophenoxy)-1-(methoxymethoxymethyl)benzene.

EXAMPLE 4

Preparation of I from 4 via 5

4.1 *Metallation and boronylation*

[0446] To a solution of **4** (17.3 mmol) in anhydrous THF (80 mL) at -78°C under nitrogen was added dropwise *tert*-BuLi or n-BuLi (11.7 mL) and the solution became brown colored. Then, $B(OMe)_3$ (1.93 mL, 17.3 mmol) was injected in one portion and the cooling bath was removed. The mixture was warmed gradually with stirring for 30 min and then stirred with a water bath for 2 h. After addition of 6N HCl (6 mL), the mixture was stirred overnight at room temperature and about 50% hydrolysis has happened as shown by TLC analysis. The solution was rotary evaporated and the residue was dissolved in MeOH (50 mL) and 6N HCl (4 mL). The solution was refluxed for 1 h and the hydrolysis was completed as indicated by TLC analysis. Rotary evaporation gave a residue which was dissolved in EtOAc, washed with water, dried and then evaporated. The crude product was purified by flash column chromatography over silica gel to provide a solid with 80% purity. The solid was further purified by washing with hexane to afford 7.2 mmol of **I**.

4.2 Results

[0447] Analytical data for exemplary compounds of structure **I** are provided below.

4.2.a 5-Chloro-1,3-dihydro-1 -hydroxy-2,1-benzoxaborole

5-chlorobenzo[c][1,2]oxaborol-1(3H)-ol **(C1)**

[0448] M.p. 142-150°C. MS (ESI): m/z = 169 (M+1, positive) and 167 (M-1, negative). HPLC (220 nm): 99% purity. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.30 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.49 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H) and 4.96 (s, 2H) ppm.

4.2.b 1,3-Dihydro-1-hydroxy-2,1-benzoxaborole

benzo[c][1,2]oxaborol-1(3H)-ol **(C2)**

[0449] M.p. 83-86°C. MS (ESI): m/z = 135 (M+1, positive) and 133 (M-1, negative). HPLC (220 nm): 95.4% purity. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.14 (s, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.32 (t, J = 7.1 Hz, 1H) and 4.97 (s, 2H) ppm.

4.2.c 5-chloro-3-methylbenzo[c][1,2]oxaborol-1(3H)-ol **(C3)**

[0450] ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm 1.37 (d, J = 6.4 Hz, 3H), 5.17 (q, J = 6.4 Hz, 1 H), 7.14 (m, 1H), 7.25 (dd, J = 9.7, 2.3 Hz, 1H), 7.70 (dd, J = 8.2, 5.9 Hz, 1H), 9.14 (s, 1H).

4.2.d 6-Fluoro-1-hydroxy-1,2,3,4-tetrahydro-2,1-benzoxaborine

6-fluoro-3,4-dihydrobenzo[c][1,2]oxaborinin-1-ol **(C4)**

[0451] ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm 2.86 (t, J = 5.9 Hz, 2H), 4.04 (t, J = 5.9 Hz, 2H), 7.0-7.1 (m, 2H), 7.69 (dd, J = 8.2, 7.2 Hz, 1H), 8.47 (s, 1H).

4.2.e 5,6-Difluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole

5,6-difluorobenzo[c][1,2]oxaborol-1(3H)-ol **(C5)**

[0452] ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm 4.94 (s, 2H), 7.50 (dd, J = 10.7, 6.8 Hz, 1H), 7.62 (dd, J = 9.7, 8.2 Hz, 1H), 9.34 (s, 1H).

4.2.f 5-Cyano-1,3-dihydro-1-hydroxy-2,1-benzoxaborole

1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-5-carbonitrile **(C6)**

[0453] ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm 5.03 (s, 2H), 7.76 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.90 (s, 1H), 9.53 (s, 1H).

4.2.g *1,3-Dihydro-1-hydroxy-5-methoxy-2,1-benzoxaborole*

5-methoxybenzo[c][1,2]oxaborol-1(3H)-ol **(C7)**

[0454] M.p. 102-104°C. MS ESI: m/z = 165.3 (M+1) and 162.9 (M-1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.95 (s, 1H), 7.60 (d, J = 8.1 Hz, 1H), 6.94 (s, 1H), 6.88 (d, J = 8.1 Hz, 1H), 4.91 (s, 2H), 3.77 (s,3 H) ppm.

4.2.h *1,3-Dihydro-1-hydroxy-5-methyl-2,1-benzoxaborole*

5-methylbenzo[c][1,2]oxaborol-1(3H)-ol **(C8)**

[0455] M.p. 124-128°C. MS ESI: m/z = 148.9 (M+1) and 146.9 (M-1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.05 (s, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.18 (s, 1H), 7.13 (d, J = 7.2 Hz, 2H), 4.91 (s, 2H), 2.33 (s, 3H) ppm.

4.2.i *1,3-Dihydro-1-hydroxy-5-hydroxymethyl-2,1-benzoxaborole*

5-(hydroxymethyl)benzo[c][1,2]oxaborol-1(3H)-ol **(C9)**

[0456] MS: m/z = 163 (M-1, ESI-). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.08 (s, 1H), 7.64 (d, 1H), 7.33 (s, 1H), 7.27 (d, 1H), 5.23 (t, 1H), 4.96 (s, 2H), 4.53 (d, 2H) ppm.

4.2.j *1,3-Dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole*

5-fluorobenzo[c][1,2]oxaborol-1(3H)-ol **(C10)**

[0457] M.p. 110-114°C. MS ESI: m/z = 150.9 (M-1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.20 (s, 1H), 7.73 (dd, J_1 = 6 Hz, J_2 = 6 Hz, 1H), 7.21 (m, 1H), 7.14 (m, 1H), 4.95 (s, 2H) ppm.

4.2.k *1,3-Dihydro-2-oxa-1-cyclopenta[á]naphthalene*

naphtho[1,2-c][1,2]oxaborol-1(3H)-ol **(C11)**

[0458] M.P. 139-143°C. MS ESI: m/z = 184.9 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.21 (s, 1H), 8.28 (dd, J_1 = 6.9 Hz, J_2 = 0.6 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 7.5 Hz, 1H), 7.59-7.47 (m, 3H), 5.09 (s, 2H) ppm.

4.2.m *1,3-Dihydro-6-fluoro-1-hydroxy-2,1-benzoxaborole*

6-fluorobenzo[c][1,2]oxaborol-1(3H)-ol **(C13)**

[0459] M.p.110-117.5°C. MS (ESI): m/z = 151 (M-1, negative). HPLC (220 nm): 100% purity. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.29 (s, 1H), 7.46-7.41 (m, 2H), 7.29 (td, 1H) and 4.95 (s, 2H) ppm.

4.2.n *3-Benzyl-1,3-dihydro-1-hydroxy-3-methyl-2,1-benzoxaborole*

3-benzyl-3-methylbenzo[c][1,2]oxaborol-1(3H)-ol **(C14)**

[0460] MS (ESI): m/z = 239 (M+1, positive). HPLC: 99.5% purity at 220 nm and 95.9% at 254 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.89 (s, 1H), 7.49-7.40 (m, 3H), 7.25-7.19 (m, 1H), 7.09-7.05 (m, 3H), 6.96-6.94 (m, 2H), 3.10 (d, 1H), 3.00 (d, 1H) and 1.44 (s, 3H) ppm.

4.2.o *3-Benzyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

3-benzylbenzo[c][1,2]oxaborol-1(3H)-ol **(C15)**

[0461] MS (ESI+): m/z = 225 (M+1). HPLC: 93.4% purity at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.08 (s, 1H), 7.63 (dd, 1H), 7.43 (t, 1H), 7.35-7.14 (m, 7H), 5.38 (dd, 1H), 3.21 (dd, 1H) and 2.77 (dd, 1H) ppm.

4.2.p *1,3-Dihydro-4-fluoro-1-hydroxy-2,1-benzoxaborole*

4-fluorobenzo[c][1,2]oxaborol-1(3H)-ol **(C16)**

[0462] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 5.06 (s, 2H), 7.26 (ddd, J = 9.7, 7.9, 0.6 Hz, 1H), 7.40 (td, J = 8.2, 4.7 Hz, 1H), 7.55 (d, J = 7.0 Hz, 1H), 9.41 (s, 1H).

4.2.q *5-(4-Cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)benzonitrile **(C17)**

[0463] ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm 4.95 (s, 2H), 7.08 (dd, J = 7.9, 2.1 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 2.1 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 9.1 Hz, 2H), 9.22 (s, 1H).

4.2.r *6-(4-Cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yloxy)benzonitrile **(C18)**

[0464] M.p.148-151°C. MS: m/z = 252 (M+1) (ESI+) and m/z = 250 (M-1) (ESI-). HPLC: 100% purity at 254 nm and 98.7% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.26 (s, 1H), 7.82 (d, 2H), 7.50 (d, 1H), 7.39 (d, 1H), 7.26 (dd, 1H), 7.08 (d, 2H) and 4.99 (s, 2H) ppm

4.2.s *6-(3-Cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yloxy)benzonitrile **(C19)**

[0465] M.p.146-149°C. MS: m/z = 252 (M+1) (ESI+) and m/z = 250 (M-1) (ESI-). HPLC: 100% purity at 254 nm and 97.9% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6):

δ 9.21 (s, 1H), 7.60-7.54 (m, 2H), 7.50-7.45 (m, 2H), 7.34-7.30 (m, 2H), 7.23 (dd, 1H) and 4.98 (s, 2H) ppm.

4.2.t *6-(4-Chlorophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

6-(4-chlorophenoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**C20**)

[0466] M.p.119-130°C. MS: m/z = 261 (M+1) (ESI+) and m/z = 259 (M-1) (ESI-). HPLC: 100% purity at 254 nm and 98.9% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.18 (s, 1H), 7.45-7.41 (m, 3H), 7.29 (d, 1H), 7.19 (dd, 1H), 7.01 (d, 2H) and 4.96 (s, 2H) ppm.

4.2.u *6-Phenoxy-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

6-phenoxybenzo[c][1,2]oxaborol-1(3H)-ol **(C21)**

[0467] M.p.95-99°C. MS: m/z = 227 (M+1) (ESI+) and m/z = 225 (M-1) (ESI-). HPLC: 100% purity at 254 nm and 98.4% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.17 (s, 1H), 7.43-7.35 (m, 3H), 7.28 (s, 1H), 7.19-7.09 (m, 2H), 6.99 (d, 2H) and 4.96 (s, 2H) ppm.

4.2.v *5-(4-Cyanobenzyloxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

4-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)methyl)benzonitrile **(C22)**

[0468] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 4.90 (s, 2H), 5.25 (s, 2H), 6.98 (dd, J = 7.9, 2.1 Hz, 1H), 7.03 (d, J = 1.8 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 1H), 9.01 (s, 1H).

4.2.w *5-(2-Cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)benzonitrile **(C23)**

[0469] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 4.95 (s, 2H), 7.0-7.2 (m, 3H), 7.32 (td, J = 7.6, 1.2 Hz, 1H), 7.68 (ddd, J = 9.1, 7.6, 1.8 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.91 (dd, J = 7.9, 1.8 Hz, 1H).

4.2.x *5-Phenoxy-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

5-phenoxybenzo[c][1,2]oxaborol-1(3H)-ol **(C24)**

[0470] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 4.91 (s, 2H), 6.94 (s, 1H), 6.96 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 7.6 Hz, 2H), 7.17 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.3 Hz, 2H), 7.70 (d, J = 8.5 Hz, 1H), 9.11 (s, 1H).

4.2.y *5-[4-(N,N-Diethylcarbamoyl)phenoxy]-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

N,N-diethyl-4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)benzamide **(C25)**

[0471] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 1.08 (br s, 6H), 3.1-3.5 (m, 4H), 4.93 (s, 2H), 7.0-7.1 (m, 4H), 7.37 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 7.9 Hz, 1H), 9.15 (s, 1H).

4.2.z *1,3-Dihydro-1-hydroxy-5-[4-(morpholinocarbonyl)phenoxy]-2,1-benzoxaborole*

(4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)phenyl)(morpholino)methanone **(C26)**

[0472] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 3.3-3.7 (m, 8H), 4.93 (s, 2H), 7.0-7.1 (m, 4H), 7.44 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 7.9 Hz, 1H), 9.16 (s, 1H).

4.2.aa *5-(3,4-Dicyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)phthalonitrile **(C27)**

[0473] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 4.97 (s, 2H), 7.13 (dd, J = 7.9, 2.1 Hz, 1H), 7.21 (d, J = 1.5 Hz, 1H), 7.43 (dd, J = 8.8, 2.6 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 2.6 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 9.26 (s, 1H).

4.2.ab *6-Phenylthio-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

6-(phenylthio)benzo[c][1,2]oxaborol-1(3H)-ol **(C28)**

[0474] M.p.121-124°C. MS: m/z = 243 (M+1) (ESI+) and m/z = 241 (M-1) (ESI-). HPLC: 99.6% purity at 254 nm and 99.6% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.25 (s, 1H), 7.72 (dd, 1H), 7.48 (dd, 1H), 7.43 (dd, 1H), 7.37-7.31 (m, 2H), 7.29-7.23 (m, 3H), and 4.98 (s, 2H) ppm.

4.2.ac *6-(4-trifluoromethoxyphenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

6-(4-(trifluoromethoxy)phenoxy)benzo[c][1,2]oxaborol-1(3H)-ol **(C29)**

[0475] M.p.97-101°C. MS: m/z = 311 (M+1) (ESI+) and m/z = 309 (M-1) (ESI-). HPLC: 100% purity at 254 nm and 100% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.20 (s, 1H), 7.45 (d, 1H), 7.37 (d, 2H), 7.33 (d, 1H), 7.21 (dd, 1H), 7.08 (d, 2H), and 4.97 (s, 2H) ppm.

4.2.ad *5-(N-Methyl-N-phenylsulfonylamino)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)-N-methylbenzenesulfonamide (**C30**)

[0476] M.p.85-95°C. MS: m/z = 304 (M+1) (ESI+) and m/z = 302 (M-1) (ESI-). HPLC: 96.6% purity at 254 nm and 89.8% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.23 (s, 1H), 7.72-7.63 (m, 2H), 7.56 (t, 2H), 7.50 (d, 2H), 7.16 (s, 1H), 7.03 (d, 1H), 4.91 (s, 2H) and 3.14 (s, 3H) ppm.

4.2.ae *6-(4-Methoxyphenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

6-(4-methoxyphenoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**C31**)

[0477] M.p.126-129°C. MS: m/z = 257 (M+1) (ESI+) and m/z = 255 (M-1) (ESI-). HPLC: 98.4% purity at 254 nm and 98.4% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.14 (s, 1H), 7.36 (d, 1H), 7.19 (s, 1H), 7.12 (d, 1H), 6.98 (d, 2H), 6.95 (d, 2H), 4.93 (s, 2H) and 3.73 (s, 3H) ppm.

4.2.af *6-(4-Methoxyphenylthio)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

6-(4-methoxyphenylthio)benzo[c][1,2]oxaborol-1(3H)-ol **(C32)**

[0478] M.p.95-100°C. MS: m/z = 272 (M+), 273 (M+1) (ESI+) and m/z = 271 (M-1) (ESI-). HPLC: 100% purity at 254 nm and 99.2% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.20 (s, 1H), 7.51 (d, 1H), 7.39-7.28 (m, 4H), 6.98 (d, 2H), 4.93 (s, 2H) and 3.76 (s, 3H) ppm.

4.2.ag *6-(4-Methoxyphenylsulfonyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

6-(4-methoxyphenylsulfonyl)benzo[c][1,2]oxaborol-1(3H)-ol **(C33)**

[0479] M.p.180-192°C. MS: m/z = 305 (M+1) (ESI+) and m/z = 303 (M-1) (ESI-). HPLC: 96.8% purity at 254 nm and 95.5% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.46 (s, 1H), 8.28 (s, 1H), 7.99 (d, 1H), 7.85 (d, 2H), 7.61 (d, 1H), 7.11 (d, 2H), 5.02 (s, 2H) and 3.80 (s, 3H) ppm.

4.2.ah *6-(4-Methoxyphenylsulfinyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

6-(4-methoxyphenylsulfinyl)benzo[c][1,2]oxaborol-1(3H)-ol (**C34**)

[0480] ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.37 (s, 1H), 8.02 (d, 1H), 7.71 (dd, 1H), 7.59 (d, 2H), 7.53 (d, 1H), 7.07 (d, 2H), 5.00 (s, 2H) and 3.76 (s, 3H) ppm.

4.2.ai *5-Trifluoromethyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

5-(trifluoromethyl)benzo[c][1,2]oxaborol-1(3H)-ol **(C35)**

[0481] M.p.113-118°C. MS: m/z = 203 (M+1) (ESI+) and m/z = 201 (M-1) (ESI-). HPLC: 100% purity at 254 nm and 100% at 220 nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.48 (s, 1H), 7.92 (d, 1H), 7.78 (s, 1H), 7.67 (d, 1H) and 5.06 (s, 2H) ppm.

4.2.aj *4-(4-Cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-4-yloxy)benzonitrile **(C36)**

[0482] For coupling reaction between 4-fluorobenzonitrile and substituted phenol to give starting material 2, see Igarashi, S.; *et al. Chemical & Pharmaceutical Bulletin* (2000), 48(11), 1689-1697.

[0483] ^{1}H-NMR (300 MHz, DMSO-d_6) (ppm) 4.84 (s, 2H), 7.08 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 7.9 Hz, 1H), 7.45 (t, J = 7.3 Hz, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.82 (d, J = 8.5 Hz, 2H).

4.2.ak *5-(3-Cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole*

3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)benzonitrile **(C37)**

[0484] For coupling between 3-fluorobenzonitrile and substituted phenol to give starting material **2**: Li, F. *et al.*, *Organic Letters* (2003), 5(12), 2169-2171.

[0485] ^{1}H-NMR (300 MHz, DMSO-d_6) (ppm) 4.93 (s, 2H), 7.0-7.1 (m, 2H), 7.3-7.4 (m, 1H), 7.5-7.7 (m, 3H), 7.75 (d, J = 8.2 Hz, 1H).

4.2.al *5-(4-Carboxyphenoxy)-1,3 dihydro-1-hydroxy-2,1-benzoxaborole*

4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)benzoic acid **(C38)**

[0486] To a solution of 5-(4-cyanophenoxy)-1-hydroxy-2,1-benzoxaborole obtained in **C17** (430 mg, 1.71 mmol) in ethanol (10 mL) was added 6 mol/L sodium hydroxide (2 mL), and the mixture was refluxed for 3 hours. Hydrochloric acid (6 mol/L, 3 mL) was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate) followed by trituration with diisopropyl ether to give the target compound (37 mg, 8%).

[0487] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 4.94 (s, 2H), 7.0-7.1 (m, 4H), 7.76 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 8.8 Hz, 2H), 9.19 (s, 1H), 12.8 (br s, 1H).

4.2.am *1-Hydroxy-1,3 dihydro-5-[4-(tetrazole-1-yl)phenoxy]-2,1-benzoxaborole*

5-(4-(1H-tetrazol-5-yl)phenoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**C39**)

[0488] A mixture of 5-(4-cyanophenoxy)-1-hydroxy-2,1-benzoxaborole (200 mg, 0.797 mmol), sodium azide (103 mg, 1.59 mmol), and ammonium chloride (85 mg, 1.6 mmol) in *N,N*-dimethylformamide (5 mL) was stirred at 80 °C for two days. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate) followed by trituration with ethyl acetate to give the target compound (55 mg, 23%).

[0489] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 4.95 (s, 2H), 7.0-7.1 (m, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 7.9 Hz, 1H), 8.05 (d, J = 8.5 Hz, 2H), 9.18 (br s, 1H).

EXAMPLE 5

Preparation of I from 2 via 6

5.1 *Catalytic Boronylation, Reduction and Cyclization*

[0490] A mixture of **2** (10.0 mmol), bis(pinacolato)diboron (2.79 g, 11.0 mmol), $PdCl_2$(dppf) (250 mg, 3 mol%), and potassium acetate (2.94 g, 30.0 mmol) in 1,4-dioxane (40 mL) was stirred at 80 °C for overnight. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure. The crude product was dissolved in tetrahydrofuran (80 mL), then sodium periodate (5.56 g, 26.0 mmol) was added. After stirring at room temperature for 30 min, 2N HCl (10 mL) was added, and the mixture was stirred at room temperature for overnight. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was treated with ether to afford 6.3 mmol of the corresponding boronic acid. To the solution of the obtained boronic acid (0.595 mmol) in methanol (5 mL) was added sodium borohydride (11

mg, 0.30 mmol), and the mixture was stirred at room temperature for 1 h. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give 0.217 mmol of **I**.

5.2 Results

[0491] Analytical data for exemplary compounds of structure **I** are provided below.

5.2.a 1,3-Dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole **(C10)**

[0492] Analytical data for this compound is listed in 4.2.j.

EXAMPLE 6

Preparation of I from 3

6.1 One-pot Boronylation and Cyclization

[0493] To a solution of **3** (4.88 mmol) and triisopropyl borate (1.35 mL, 5.86 mmol) in tetrahydrofuran (10 mL) was added *n*-butyllithium (1.6 mol/L in hexanes; 6.7 mL, 10.7 mmol) dropwise over 15 min at – 78 °C under nitrogen atmosphere, and the mixture was stirred for 2 h while allowing to warm to room temperature. The reaction was quenched with 2N HCl, and extracted with ethyl acetate. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography and treated with pentane to give 0.41 mmol of **I**.

6.2 Results

[0494] Analytical data for exemplary compounds of structure **I** are provided below.

6.2.a 1,3-Dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole **(C10)**

[0495] Analytical data for this compound is listed in 4.2.j.

EXAMPLE 7

Preparation of I from 3

7.1 One-pot Boronylation and Cyclization with Distillation

[0496] To a solution of **3** (4.88 mmol) in toluene (20 mL) was added triisopropyl borate (2.2 mL, 9.8 mmol), and the mixture was heated at reflux for 1 h. The solvent, the generated isopropyl alcohol and excess triisopropyl borate were removed under reduced pressure. The residue was dissolved in tetrahydrofuran (10 mL) and cooled to – 78 °C. *n*-Butyllithium (3.2 mL, 5.1 mmol) was added dropwise over 10 min, and the mixture was stirred for 1 h while allowing to warm to room temperature. The reaction was quenched with 2N HCl, and extracted with ethyl acetate. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give 1.54 mmol of **I**.

7.2 Results

[0497] Analytical data for exemplary compounds of structure **I** are provided below.

7.2.a 1,3-Dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole **(C10)**

[0498] Analytical data for this compound is listed in 4.2.j.

EXAMPLE 8

Preparation of 8 from 7

8.1 Bromination

[0499] To a solution of **7** (49.5 mmol) in carbon tetrachloride (200 mL) were added N-bromosuccinimide (8.81 g, 49.5 mmol) and *N,N*-azoisobutylonitrile (414 mg, 5 mol%), and the mixture was heated at reflux for 3 h. Water was added, and the mixture was extracted with chloroform. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the crude methyl-brominated intermediate **8**.

EXAMPLE 9

Preparation of 3 from 8

9.1 Hydroxylation

[0500] To crude **8** (49.5 mmol) were added dimethylformamide (150 mL) and sodium acetate (20.5 g, 250 mmol), and the mixture was stirred at 80°C for overnight. Water was added, and the mixture was extracted with ether. The organic layer was washed with water and brine, and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure. To the residue was added methanol (150 mL) and 1N sodium hydroxide (50 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated to about a third of volume under reduced pressure. Water and hydrochloric acid were added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography followed by trituration with dichloromethane to give 21.8 mmol of **3**.

9.2 Results

[0501] Exemplary compounds of structure **3** prepared by the method above are provided below.

9.2.a 2-Bromo-5-cyanobenzyl Alcohol

[0502] ^{1}H-NMR (300 MHz, DMSO-d_6) δ ppm 4.51 (d, J = 5.9 Hz, 2H), 5.67 (t, J = 5.6 Hz, 1H), 7.67 (dd, J = 8.2, 2.0 Hz, 1H), 7.80 (s, J = 8.2 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H).

[0503] Additional examples of compounds which can be produced by this method include 2-bromo-5-(4-cyanophenoxy)benzyl alcohol.

EXAMPLE 10

Preparation of 9 from 2

10.1 Reaction

[0504] A mixture of **2** (20.0 mmol), (methoxymethyl)triphenylphosphonium chloride (8.49 g, 24.0 mmol), and potassium *tert*-butoxide (2.83 g, 24.0 mol) in *N,N*-dimethylformamide (50 mL) was stirred at room temperature for overnight. The reaction was quenched with 6 N HCl, and the mixture was extracted with ethyl acetate. The organic layer was washed with water (x 2) and brine, and dried on anhydrous sodium sulfate. The solvent was removed under reduced. To the residue were added tetrahydrofuran (60 mL) and 6 N HCl, and the mixture was heated at reflux for 8 h. Water was added, and the mixture was extracted with ether. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford 16.6 mmol of **9**.

EXAMPLE 11

Preparation Method of Step 13

11.1 Reaction

[0505] A solution of **I** in an appropriate alcohol solvent (R^1-OH) was refluxed under nitrogen atmosphere and then distilled to remove the alcohol to give the corresponding ester.

EXAMPLE 12

Preparation of Ib from Ia

12.1 Reaction

[0506] To a solution of **Ia** in toluene was added amino alcohol and the participated solid was collected to give **Ib**.

12.2 Results

[0507] (500 mg, 3.3 mmol) was dissolved in toluene (37 mL) at 80°C and ethanolamine (0.20 mL, 3.3 mmol) was added. The mixture was cooled to room temperature, then ice bath, and filtered to give **C40** as a white powder (600.5 mg, 94%).

12.2a *Ethanolamine adduct of 1,3-Dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole* **(C40)**

[0508] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 2.88 (t, *J*=6.2 Hz, 2H), 3.75 (t, *J*=6.3 Hz, 2H), 4.66 (s, 2H), 5.77 (br, 2H), 6.85-6.91 (m, 2H), 7.31 (td, *J*=7.2, 1.2 Hz, 1H).

EXAMPLE 13

Formulations

[0509] Compounds of the present invention can be administered to a patient using a therapeutically effective amount of a compound described herein in any one of the following three lacquer formulations and one solvent formulation. The lacquer formulation provides good durability while the solvent formulation provides good ease of use. These compounds can also be applied using a spray formulation, paint-on lacquer, drops, or other.

1. 1:4 propylene glycol:ethanol; 1:10 wt/vol compound of invention;
2. 1:4 poly(vinyl methyl ether-alt-maleic acid monobutyl ester: ethanol; 1:10 wt/vol compound of the invention;
3. 56% ethanol; 14% water; 15% poly(2-hydroxyethyl methacrylate); 5% dibutyl sebacate; 10% compound of the invention;
4. 55% ethanol; 15% ethyl acetate; 15% poly(vinyl acetate); 5% dibutyl sebacate; 10% compound of the invention.

[0510] The preparation of these formulations is well known in the art and is found in references such as Remington: The Science and Practice of Pharmacy, supra.

EXAMPLE 14

Antifungal MIC Testing

[0511] All MIC testing followed the National Committee for Clinical Laboratory Standards (NCCLS) guidelines for antimicrobial testing of yeasts (M27-A2 NCCLS) and filamentous fungi (Pfaller *et al.*, NCCLS publication M38-A – Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi; Approved Standard. Wayne, PA: NCCLS; 2002 (Vol. 22, No. 16) except the *Malassezia* species which was incubated in a urea broth (Nakamura *et al.*, *Antimicrobial Agents And Chemotherapy*, **2000**, 44(8) p. 2185–2186). Results of the MIC testing is provided in **FIG.1**.

EXAMPLE 15

Keratin Assay

[0512] Many antifungal agents strongly bind to keratin which not only reduces their antifungal potency but also may restrict their penetration into the nail. The affinities of the compounds for keratin powder was determined by a method described in Tatsumi, *Antimicrobial Agents and Chemotherapy*, **46**(12):3797-3801 (2002).

[0513] A comparison of MIC data for several compounds of the invention against *T. rubrum*, with and without the presence of 5% keratin, is provided in **FIG. 1**.

EXAMPLE 16

(C10) Antifungal Spectrum of Activity

[0514] **(C10)** is a novel compound in development for use as a topical antifungal treatment. The purpose of this study was to determine the minimum inhibitory concentration (MIC) for **(C10)** against 19 test strains of fungi including: *Aspergilus fumigatus* (*A. fumigatus*), *Candida Albicans* (*C. albicans*, both fluconazole sensitive and resistant strains), *Candida glabrata* (*C. glabrata*), *Candida krusei* (*C. krusei*), *Cryptococcus neoformans* (*C. neoformans*), *Candida parapsilosis* (*C. parapsilosis*), *Candida tropicalis* (*C. tropicalis*), *Epidermophyton floccosum* (*E. floccosum*), *Fusarium solani* (*F. solani*), *Malassezia furfur* (*M. furfur*), *Malassezia pachydermatis* (*M. pachydermatis*), *Malassezia sympodialis* (*M. sympodialis*), *Microsporum audouinii* (*M. audouinii*), *Microsporum canis* (*M. canis*), *Microsporum gypseum* (*M. gypseum*), *Trichophyton mentagrophytes* (*T. mentagrophytes*), *Trichophyton rubrum* (*T. rubrum*), *Trichophyton tonsurans* (*T. tonsurans*). Fungal growth was evaluated after exposure to different concentrations of **(C10)**. In addition, the MIC for **(C10)** against *T. rubrum* in the presence of 5% keratin powder and the minimum fungicidal concentration (MFC) for **(C10)** against *T. rubrum* and *T. mentagrophytes* were also determined. Ciclopirox and/or terbinafine and/or fluconazole and/or itraconazole were used as comparators and tested in a similar manner. These studies were conducted at NAEJA Pharmaceutical, Inc.

Materials and Methods

[0515] **(C10)** was obtained from Anacor Pharmaceuticals, Inc. (Palo Alto, CA, USA). ATCC strains were obtained from ATCC (Manassas, VA, USA). Ciclopirox-olamine was obtained from Sigma-Aldrich Co. (St. Louis, MO, USA). Terbinafine,

fluconazole and itraconazole were synthesized at NAEJA Pharmaceutical Inc. (Edmonton, AB, Canada), experimental procedures and analytical data for these standards are stored in NAEJA archives.

[0516] All MIC testing followed the National Committee for Clinical Laboratory Standards (NCCLS) guidelines for antimicrobial testing of yeasts and filamentous fungi (Pfaller *et al.*, 2002) except the *Malassezia* species which were incubated in a urea broth (Nakamura *et al.*, 2000). The microbroth dilution method was used to test the *in vitro* activity of **(C10)** against 19 test strains of fungi. Briefly, compounds were dissolved in DMSO and diluted in sterile water to give a working stock. Two-fold serial dilutions of the working stock were prepared in 96-well plates and media was added. Media was RPMI, RPMI + MOPS, modified RPMI, or modified Urea broth. The plates were inoculated with the fungal suspensions to give a final inoculum size of 0.5-2.5 x 10^3 cells/mL for yeasts or 0.4-5 x 10^4 CFU/mL for filamentous fungi and then incubated for 24-168 h at 35 °C. The final concentration of DMSO did not exceed 5%. The MIC was defined as the lowest concentration that resulted in over 90% reduction of growth, as compared to a drug-free control. The MFC was defined as the lowest concentration that killed over 90% of the fungi, as compared to a drug-free control.

Results and Conclusions

[0517] The results for the MIC of **(C10)** and reference compounds against 19 strains of fungi are shown in FIG. 2. The results for the MFC of **C10** against 2 strains of fungi are shown in Table 2. **(C10)** had MIC values ranging from 0.25 – 2 μg/mL against all fungi tested. Addition of 5% keratin powder to the media did not effect the MIC against *T. rubrum*. **(C10)** had fungicidal activity against *T. rubrum* and *T. mentagrophytes* with MFC values of 8 and 16 μg/mL, respectively. Reference compounds had MIC values in the range defined by NCCLS.

EXAMPLE 17

The Solubility, Stability and Log P Determination of compounds of the present invention by LC/MS/MS

[0518] The solubility, room temperature stability and Log P of **C10** was determined by the following methodology.

Reagents and Standards:

[0519] Ethanol: 200 proof ACS Grade (EM Science, Gibbstown, NJ, USA); Octanol: Octyl alcohol (EM Science, Gibbstown, NJ, USA); Acetonitrile: HPLC Grade (Burdick & Jackson, Muskegon, MI, USA); Ammonium Acetate: lot 3272X49621 (Mallinckrodt, Phillipsburg, NJ, USA); **C10**: lot A032-103 (Anacor Pharmaceuticals, Palo Alto, CA, USA); p-Nitrophenol (PNP): lot OGNO1 (TCI America, Portland, OR, USA); Water: Deionized water (from Millipore systems, Billerica, MA, USA)

Solubility

[0520] N-Octanol and water were mutually pre-saturated by vigorously stirring a mixture of both solvents for up to 12 h and the mixture was allowed to separate. Solubility in each solvent was determined by adding 10 μL of 20, 40, 200, 1000 and 5000 μg/mL of **C10** in DMSO to the pre-saturated n-octanol or water. After the sample was vortexed for 10 sec, the sample was centrifuged for 10 min at ca. 3000 rpm. A visual inspection was made to determine if the sample was clear or if a pellet had formed on the bottom of the tube.

Log P

[0521] **C10** (10 μL of 5000 μ/mL) at 2X the final concentration was added to 0.5 mL pre-saturated n-octanol and mixed. An equal volume (0.5 mL) of pre-saturated water was added, vortex mixed and then mixed on a rotating shaker for one hour and 24 h in triplicate at ca. 25 °C. The organic and aqueous layers were separated by centrifugation for 5 min at ca. 2000 rpm. Twenty five μL of the octanol (top) layer were removed and placed in a pre-labeled tube. Twenty five μL of the aqueous layer (bottom) were removed, taking care to avoid octanol contamination, and placed in a pro-labeled tube.

Stability at Room Temperature

[0522] **C10** (10 μL of 5000 μg/mL) was added both to 0.5 mL n-octanol and 0.5 mL water in triplicate. Samples were mixed. At 0 h and 24 h samples were stored at *ca.* -20 °C. Twenty five μL of sample was used for analysis.

Extraction Procedure C10

[0523] For the octanol sample, 25 μL of ethanol, 25 μL of water and 300 μL of acetonitrile containing the internal standard was added. For the water sample, 25 μL

of ethanol, 25 µL of octanol and 300 µL of acetonitrile containing the internal standard [60 mL of acetonitrile add 6 µL of PNP (1000 µg/mL)] was added. For the calibrators 25 µL of octanol, 25 µL of water and 300 pL of acetonitrile containing the internal standard was added. The sample was vortexed for 10 seconds. Two hundred µL of the organic layer were transferred into a clean deactivated autosampler vial.

Calculations

[0524] A 1/concentration weighted linear regression was used for the quantitation of **C10**. All integration were performed with peak areas using Analyst version 1.3, Applied Biosystems. For **C10**, peak area ratios analyte to internal standard PNP were used for all quantitation.

[0525] The partition coefficient (P) was calculated according to the equation detailed below:

$$P = [\text{Sample concentration}]_{\text{octanol}} / [\text{Sample concentration}]_{\text{water}}$$

$$\text{Log } P = \log_{10}(\text{partition coefficient})$$

Results:

[0526] As shown in Table 17A the solubility of **C10** in both octanol and water is very good over the concentration range tested.

Table 17A. Solubility of **C10** in water and octanol

Targeted Conc (µg/mL)	**Water Visual**	**Octanol Visual**
0.800	Clear	Clear
4.00	Clear	Clear
20.0	Clear	Clear
100	Clear	Clear

[0527] Table 17B shows the results of the log P determination after 1 h and 24 h for **C10**. The mean log P after 1 h was 1.97 (n=3). After 24 h the concentrations in both the octanol and water layer remained the same. The mean log P after 24 h was 1.93 (n=3).

Table 17B. Log P of **C10**

Sample	Conc. in Water (μg/mL)	Conc. in Octanol (μg/mL)	Log P
1h-1	1.26	108	1.93
1h-2	1.21	103	1.93
1h-3	1.05	115	2.04
24h-1	1.27	104	1.91
24h-2	1.17	109	1.97
24h-3	1.28	99.0	1.89

[0528] A stability study for **C10** was initiated at room temperature over 24 h without continuous mixing. Table 17C shows that **C10** in pure water and octanol is stable over 24 h.

Table 17C. Water and Octanol stability for **C10** at room temperature after 24 h.

Sample	Mean (μg/mL)	SD	Percent Remaining 24 h versus 0 g
Water-0h	82.5	3.72	115
Water-24h	95.0	21.4	
Octanol-0h	115	3.06	93
Octanol-24h	107	6.11	

EXAMPLE 18

Determination of Penetration of C10 into the Human Nail

[0529] Two nail penetration studies were performed based on the protocol in Hui *et al.*, *Journal of Pharmaceutical Sciences*, **91(1)**: 189-195 (2002) ("Hui protocol"). The purpose of this study was to determine and compare the penetration and distribution of **C10** in vehicle into the human nail plate *in vitro* relative to 8% ciclopirox w/w in commercial lacquer (Penlac®).

MATERIALS AND METHODS

Test Article and Dosage Formulation

[0530] 8% ciclopirox w/w in commercial lacquer was manufactured by Dermick (Berwyn, PA). The radiochemical purity and specific activity of the chemical was determined as >95% and 12.5 mCi/mmol, respectively.

[0531] The study was composed of two groups. The compositions (weight %) of the dosage formulations are as follows:

Active radiolabeled compound in four groups.

Groups*	Dosing (x 14 days)	Test Chemical (%)	Radioactivity (per 10 μL)
A (**C10**)	qd	10	0.19 μCi
C (Ciclopirox)	qd	8	0.22 μCi

* A = **C10** group, C = Ciclopiriox group

Human Nails

[0532] Healthy human finger nail plates were collected from adult human cadavers and stored in a closed container at 0 - 4^{0}C. Before the experiment, the nail plates were gently washed with normal saline to remove any contamination, then re-hydrated by placing them for three hours on a cloth wetted with normal saline. The nail samples were randomly selected into four groups.

Dosing and Surface Washing Procedures

Dose preparation:

[0533] Radioactivity of each group is approximately 0.19 ± 0.01 and 0.22 ± 0.03 μCi/10 μL solutions respectively, for ^{14}C-**C10** (group A), and ^{14}C-ciclopirox (group C).

Experiment Procedure:

Study Day	Group A			Group C		
	wash	dose	sample	wash	dose	sample
1		D			D	
2	W	D		W	D	
3	W	D	C	W	D	C
4	W	D		W	D	
5	W	D		W	D	
6	W	D	C	W	D	C

7	W	D		W	D	
8	W	D		W	D	
9	W	D	C	W	D	C
10	W	D		W	D	
11	W	D		W	D	
12	W	D	C	W	D	C
13	W	D		W	D	
14	W	D		W	D	
15	W		C, N	W		C, N

W = once per day before dosing (9 ~ 10 AM).
D = once per day (9 ~ 10 AM).
C = changing/sampling cotton ball after surface washing before topical dosing.
N = Nail sampling.

Washing procedure

[0534] Surface washing was started in morning 10 min prior to next dosing, the surface of the nail was washed with cotton tips in a cycle, as follows:

a tip wetted with absolute ethanol, then
a tip wetted with absolute ethanol, then
a tip wetted with 50% IVORY liquid soap, then
a tip wetted with distilled water, then
a final tip wetted with distilled water.

[0535] The washing samples from each cycle of each nail were pooled and collected by breaking off the cotton tip into scintillation glass vials. Aliquots of 3.0 mL methanol were added into each vial to extract test material. The radioactivity of each sample was measured in a liquid scintillation counter.

Incubation System

[0536] A Teflon one-chamber diffusion cell (PermeGear, Inc., Hellertown, PA) was used to hold each nail. To approximate physiological conditions, a small cotton ball wetted with 0.1 mL normal saline was placed in the chamber to serve as a nail bed and provide moisture for the nail plate. Every 3 days, 0.1 mL normal saline was injected through the inlet into the chamber to keep the cotton ball wet. The nail plate was placed on a ledge inside the receptor (1.0 cm in diameter and 0.5 cm high). The ventral (inner) surface of the nail was placed face down and rested on the wet cotton ball. The cells were placed on a platform in a large glass holding tank filled with saturated sodium phosphate solution to keep the cells at a constant humidity of 40%.

Sampling Instrument

[0537] The nail sampling instrument had two parts, a nail sample stage and a drill. The nail sampling stage consists of a copper nail holder, three adjustments, and a nail powder capture. Three adjustments allow movement in vertical direction. The first coarse adjustment (on the top) was for changing the copper cell and taking powder samples from the capture. The other two adjustments (lower) were for sampling process. The second coarse adjustment allowed movement of 25 mm and the fine adjustment provides movement of 0.20 mm. The nail powder capture was located between the copper cell and the cutter. The inner shape of the capture was inverted funnel and the end of funnel connects to a vacuum. By placing a circle filter paper inside of the funnel, the nail powder samples were captured on the filter paper during the sampling process.

Sampling Procedure

[0538] After completion of the incubation phase, the nail plate was transferred from the diffusion cell to a clean copper nail holder for sampling process. The nail plate was inverted so that the ventral (nail bed) surface now faced up and the dorsal (outer) dosed surfaced faced down. The copper nail holder has an opening as it sits on top of the stage. When the sampling process initiated, the coarse adjustment was adjusted to move the position of the stage until the nail plate was just touching the tip of the cutter. Then the drill was turned on and the fine adjustment was turned to push the stage closer to the drill, removing a nail core sample. After the above process, approximate 0.40 - 0.50 mm in depth and 7.9 mm in diameter nail pulverized samples were harvested from the center of the ventral (nail bed) surface of the nail.

[0539] The powdered nail samples were collected into a glass scintillation vial and weighted. Aliquots of 5.0 mL Packard soluene-350 (Packard Instrument Company, Meriden, CT) was added to the scintillation vial to dissolve the powder. The upper part, the intermediate and dorsal layers of the center of the nail, including the area of application of the dose was cut in the same diameter as the sampled area and was then placed into a glass scintillation vial with 5.0 mL packard soluene-350. The rest of the nail was also placed in a glass scintillation vial with 5.0 mL packard soluene-350.

[0540] The amount of nail sample removed was measured by the difference in weight of the nail plate before and after drilling, and collecting the core of powder.

Radioactivity Measurement

[0541] All radioactivity measurements were conducted with a Model 1500 Liquid Scintillation Counter (Packard Instrument Company, Downer Grove, IL). The counter was audited for accuracy using sealed samples of quenched and unquenched standards as detailed by the instrument manual. The ^{14}C counting efficiency is equal to or greater than 95%. All nail samples pre-treated with packard soluene-350 were incubated at 40 °C for 48 hours followed by the addition of 10 mL scintillation cocktail (HIONIC-FLUOR, Packard Instrument Company, Meriden, CT). Other samples (standard dose, surface washing, and bedding material) were mixed directly with Universal ES scintillation cocktail (ICN Biomedicals, Costa Mesa, CA). Background control and test samples were counted for 3 minutes each for radioactivity.

Data Analysis

[0542] All sample counts (expressed as dpm) were transcribed by hand to a computerized spreadsheet (Microsoft Excel). The individual and mean (± S.D.) amount of test chemical equivalent in nail, bedding material, and wash samples are presented as dpm, μCi, percent administered dose, and mg equivalent at each time point. The concentration of ^{14}C-labeled test chemicals were calculated from the value based on the specific activity of each [^{14}C]-test chemical. The information of concentration of non-labeled test chemical in the topical formulation was obtained from the manufactures. Total concentration of test chemical equivalent is the sum of the concentration of ^{14}C-labeled test chemical and the concentration of non-labeled test chemical. The value of total amount of test chemical equivalent in each nail sample was calculated from those values based on radioactivity of the sample and the ratio of total mg test chemical equivalent and radioactivity of the test chemical. The data was further normalized by dividing with the weight of the sample. Statistical significant of nail samples from every two groups was analyzed by student t-test.

RESULTS

Characteristics of Nail Samples

[0543] For both groups (Group A group and Group C) the thickness of whole nail plate, the depth of the ventral surface core sample removed by cutter, the percentage

of the whole nail thickness, and the actual weight of powdered nail sample were collected. No statistical difference is found between two groups ($P > 0.05$).

Weight Normalized **C10** and Ciclopirox Equivalent in Nail

[0544] **FIG. 3** shows summarized normalized drug equivalents in each part (layer) of nail samples. After weight normalization, the concentration of **C10** equivalent in dorsal/intermediate center, ventral/intermediate center, and remainder nail samples was significantly higher than that of ciclopirox equivalent ($p \leq 0.002$).

C10 and Ciclopirox Equivalent in Cotton Ball Nail Supporting Bed

[0545] **FIG. 4** shows summarized **C10** and ciclopirox equivalent in supporting bed cotton ball samples. Similar to weight normalized **C10** equivalent in the nail plate samples, absolute amount of **C10** equivalent per cotton ball sample in group A (after 14 day dosing) was significantly higher than that of ciclopirox in group C ($p \leq 0.004$). The difference of these two test chemicals was 250 times.

Mass Balance of Radioactivity of [^{14}C]- **C10** and [^{14}C]-Ciclopirox after 14-day Treatment

[0546] Table 5 shows summarized radioactive recovery from washing, nail samples, and supporting bed cotton ball samples. Cumulative radioactivity recoveries of carbon-14 were 88 ± 9.21, and 89 ± 1.56 percent of applied dose in group A, and group C, respectively. 88% of the radiolabeled material was accounted for.

CONCLUSION

[0547] In this study, penetration rate of [^{14}C]-**C10** in Anacor topical formulation and [^{14}C]-ciclopirox (8% w/w in commercial lacquer) into human nail with four different dosing and washing methods was studied.

[0548] Results show that much more amount of [^{14}C]-**C10** penetrating into the deeper parts of the nail when compared with [^{14}C]-ciclopirox. Tables 3 and 4 show that the amount of [^{14}C]-**C10** equivalent in ventral/intermediate center of the nail layer and cotton ball supporting bed in the group A was statistically higher ($p \leq 0.002$) than group C after a 14-day dosing period.

EXAMPLE 19

Determination of Penetration of C10 into the Human Nail

[0549] The aim of the current study was to assess and compare the perungual absorption of **C10** in a simple vehicle using MedPharm's TurChub® model (see **http://www.medpharm.co.uk; specifically http://www.medpharm.co.uk/downloads/Skin%20and%20nail%20dec%202003.pdf; viewed February 14, 2006).** in a full scale experiment. Six replicates involving **C10** were conducted and Formulations Y (8% ciclopirox w/w in commercial lacquer) and Z (Loceryl, 5% amorolfine w/v in commercial lacquer) were used as the reference formulations.

[0550] The following materials were used in these experiments. These materials were used without any modifications.

[0551] A dose of 40 $\mu L/cm^2$ of the test compound **C10** in 50:50 propylene glycol:ethyl acetate was applied to a full thickness nail sample each day over a total duration of five days. Both the reference formulations were also applied at the same dose.

TurChub® Zone of Inhibition Experiment

[0552] Placebo, test item **C10** in vehicle and the reference formulations Y and Z were tested for their inhibition of *Trichophyton rubrum* (*T. rubrum*) growth after penetration through a full thickness human nail using a zone of inhibition measurement.

Formulation efficacy testing

[0553] **FIGs. 5-9** show the results obtained from the TurChub zone of inhibition assays. It can be observed that **C10** is a potent antifungal agent, which can penetrate through a full thickness nail to elicit its effect against the target organism *T. rubrum*. No zones of inhibition were observed with reference formulations Y and Z or with the placebo for **C10**. The experiment using **C10** was repeated for a second time to confirm the result and it can be observed from **FIGs. 6** and **7** that **C10** shows zones of inhibition of 100%, 67%, 46%, 57%, 38% and 71% in the first experiment and 74%, 86%, 100%, 82%, 100% and 84% in the second experiment. The measurement was taken from the nail to the first point of growth observed.

[0554] From the results obtained using MedPharm's TurChub zone of inhibition

assay as a test system, the test item **C10** was found to be a powerful antifungal agent and demonstrated superior results vs. the commercial reference formulations Y and Z. From these experiments it appears that the compound is permeating through a full thickness nail barrier to exhibit the antifungal activity.

EXAMPLE 20

Determination of Penetration of* C10 *into the Human Nail: Dose Response

[0555] The optimal dose-response range for penetration into the human nail was determined to be between 1% and 15%. The experiments to determine the optimal dose-response was conducted as follows.

[0556] Tests at different test compound concentrations were conducted on nails derived from the same cadaver. Cadaver nails were hydrated overnight, cut into 4 equally sized squares and placed onto individual poloxomer supports. Test articles were formulated in a lacquer at 1%, 2.5%, 5%, 7.5%, 10% and 15% w/v. A 40 $\mu L/cm^2$ dose is applied to the center of the nail piece and the nails are left for 24 hrs. Nails are removed from the poloxomer support. Poloxomer support is analyzed for quantity of compound using LC/MS/MS.

EXAMPLE 21

Preparation of pyridinyloxaboroles

21a. Metallation and boronylation

[0557] To a solution of 3-bromo-4-hydroxymethylpyridine (10.7 mmol) and $B(OMe)_3$ (2.73 mL, 11.9 mmol) in anhydrous THF (20 mL) at -78°C under nitrogen was added dropwise n-BuLi (13.6 mL, 21.8 mmol). The cooling bath was then removed. The mixture was warmed gradually with stirring for 30 min and then stirred with a water bath for 2 h. Brine was then added and the pH adjusted to 7 using 6N HCl. The mixture was washed with THF (x2) and the aqueous layer (containing product) was evaporated to dryness. The residue was washed with THF and the product was extracted into ethanol (x2). Ethanol was removed *in vacuo*, water was added to the residue and removed *in vacuo*. Toluene was added and removed *in vacuo*. The resulting residue was triturated with diethyl ether and the product was collected by filtration to afford **C12**.

21b. *7-Hydroxy-2,1-oxaborolano[5,4-c]pyridine [[1,2]oxaborolo[3,4-c]pyridin-1(3H)-ol]* **(C12)**

[0558] ^{1}H-NMR (300 MHz, DMSO-d_6): δ ppm 5.00 (s, 2H), 7.45 (d, J = 5.0 Hz, 1H), 8.57 (d, J = 5.3 Hz, 1H), 8.91 (s, 1H), 9.57 (s, 1H). ESI-MS *m/z* 134 $(M-H)^-$, $C_6H_6BNO_2$ = 135.

EXAMPLE 22

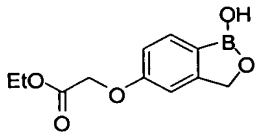
Cyclic Borinic Esters

[0559] Additional compounds can be produced by the methods described herein. By choosing the appropriate starting material such as **1** or **3**, Examples 1-7 can be used to formulate the following compounds. Where available, melting point characterization is provided for these compounds.

22. *Results*

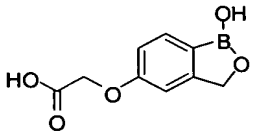
[0560] Analytical data for exemplary compounds of structure **I** are provided below.

22a *Ethyl 2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)acetate* **(C41)**



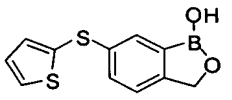
[0561] M.P. 134-137 °C. Exemplary starting material: ethyl 2-(4-bromo-3-(hydroxymethyl)phenoxy)acetate.

22b *2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)acetic acid* **(C42)**



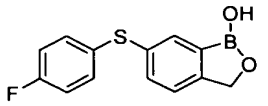
[0562] M.P. 163-166 °C. Exemplary starting material: ethyl 2-(4-bromo-3-(hydroxymethyl)phenoxy)acetate. The title compound is obtained after saponification of the corresponding ester.

22c *6-(thiophen-2-ylthio)benzo[c][1,2]oxaborol-1(3H)-ol* **(C43)**



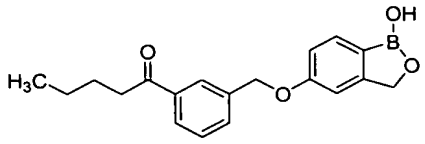
[0563] M.P. 99-104 °C. Exemplary starting material: (2-bromo-4-(thiophen-2-ylthio)phenyl)methanol.

22d *6-(4-fluorophenylthio)benzo[c][1,2]oxaborol-1(3H)-ol* **(C44)**



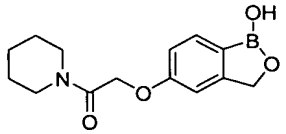
[0564] M.P. 135-138 °C. Exemplary starting material: (2-bromo-4-(4-fluorophenylthio)phenyl)methanol.

22e *1-(3-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)methyl)phenyl)pentan-1-one* **(C45)**



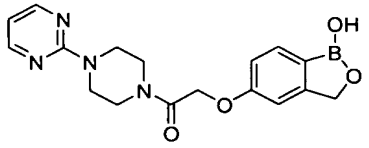
[0565] M.P. 96-98 °C. Exemplary starting material: 1-(3-((4-bromo-3-(hydroxymethyl)phenoxy)methyl)phenyl)pentan-1-one.

22f *2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)-1-(piperidin-1-yl)ethanone* **(C46)**



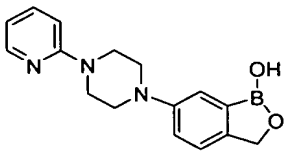
[0566] M.P. 158-163 °C. Exemplary starting material: 2-(4-bromo-3-(hydroxymethyl)phenoxy)-1-(piperidin-1-yl)ethanone.

22g *2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethanone* **(C47)**



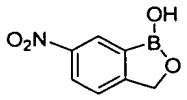
[0567] M.P. 190-195 °C. Exemplary starting material: 2-(4-bromo-3-(hydroxymethyl)phenoxy)-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethanone.

22h *6-(4-(pyridin-2-yl)piperazin-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C48)**



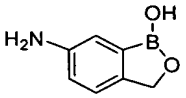
[0568] M.P. 135-138 °C. Exemplary starting material: (2-bromo-4-(4-(pyridin-2-yl)piperazin-1-yl)phenyl)methanol.

22i *6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol* **(C49)**



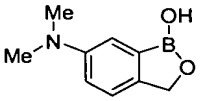
[0569] M.P. 163-171 °C. Exemplary starting material: benzo[c][1,2]oxaborol-1(3H)-ol. See JACS 82, 2172, 1960 for preparation.

22j *6-aminobenzo[c][1,2]oxaborol-1(3H)-ol* **(C50)**



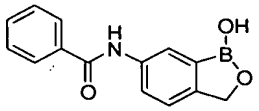
[0570] M.P. 145-148 °C. Exemplary starting material: 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol.

22k *6-(dimethylamino)benzo[c][1,2]oxaborol-1(3H)-ol* **(C51)**



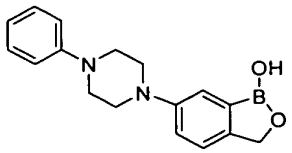
[0571] M.P. 120-123 °C. Exemplary starting material: 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol.

22l *N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)benzamide* **(C52)**



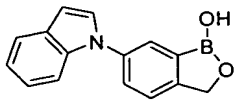
[0572] M.P. 186-193 °C. Exemplary starting material: 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol.

22m *6-(4-phenylpiperazin-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C53)**



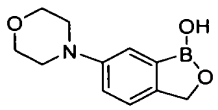
[0573] M.P. 159-161 °C. Exemplary starting material: (2-bromo-4-(4-phenylpiperazin-1-yl)phenyl)methanol.

22o *6-(1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C55)**



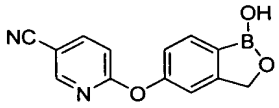
[0574] M.P. 135-140 °C. Exemplary starting material: (2-bromo-4-(1H-indol-1-yl)phenyl)methanol.

22p *6-morpholinobenzo[c][1,2]oxaborol-1(3H)-ol* **(C56)**



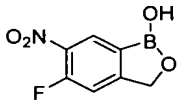
[0575] M.P. 128-132 °C. Exemplary starting material: (2-bromo-4-morpholinophenyl)methanol.

22q *6-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)nicotinonitrile* **(C57)**



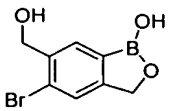
[0576] M.P. 193-198 °C. Exemplary starting material: 6-(4-bromo-3-(hydroxymethyl)phenoxy)nicotinonitrile.

22r *5-fluoro-6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol* **(C58)**



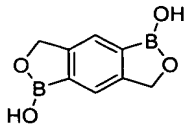
[0577] M.P. 162-167 °C. Exemplary starting material: 5-fluorobenzo[c][1,2]oxaborol-1(3H)-ol.

22s *5-bromo-6-(hydroxymethyl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C59)**



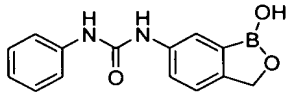
[0578] M.P. >257 °C. Exemplary starting material: (2,5-dibromo-4-(methoxymethyl)phenyl)methanol.

22t *3,7-dihydro-1,5-dihydroxy-1H,3H-Benzo[1,2-c:4,5-c']bis[1,2]oxaborole* **(C60)**



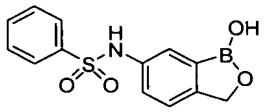
[0579] M.P. >250 °C. Exemplary starting material: (2,5-dibromo-1,4-phenylene)dimethanol.

22u *1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-3-phenylurea* **(C61)**



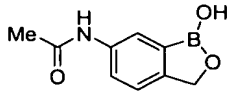
[0580] M.P. 213-215 °C. Exemplary starting material: 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol.

22v *N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)benzenesulfonamide* **(C62)**



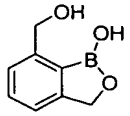
[0581] M.P. 175-184 °C. Exemplary starting material: 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol.

22w *N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)acetamide* **(C63)**



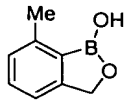
[0582] M.P. 176-185 °C. Exemplary starting material: 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol.

22x *7-(hydroxymethyl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C64)**



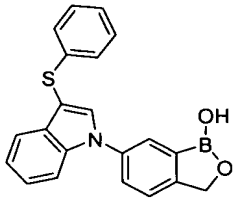
[0583] M.P. 241-250 °C. Exemplary starting material: (2-bromo-1,3-phenylene)dimethanol.

22y *7-methylbenzo[c][1,2]oxaborol-1(3H)-ol* **(C65)**



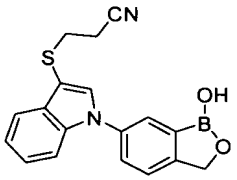
[0584] M.P. 107-111 °C. Exemplary starting material: (2-bromo-3-methylphenyl)methanol.

22z *6-(3-(phenylthio)-1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C66)**



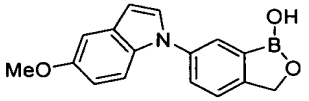
[0585] M.P. 159-163 °C. Exemplary starting material: (2-bromo-4-(3-(phenylthio)-1H-indol-1-yl)phenyl)methanol.

22aa *3-(1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-3-ylthio)propanenitrile* **(C67)**



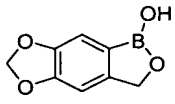
[0586] M.P. 135-141 °C. Exemplary starting material: 3-(1-(3-bromo-4-(hydroxymethyl)phenyl)-1H-indol-3-ylthio)propanenitrile.

22bb *6-(5-methoxy-1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C68)**



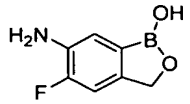
[0587] M.P. 120-124 °C. Exemplary starting material: (2-bromo-4-(5-methoxy-1H-indol-1-yl)phenyl)methanol.

22cc *5,6-methylenedioxybenzo[c][1,2]oxaborol-1(3H)-ol.* **(C69)**



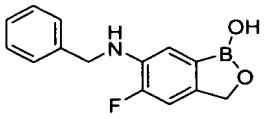
[0588] M.P. 185-189 °C. Exemplary starting material: (6-bromobenzo[d][1,3]dioxol-5-yl)methanol.

22dd *6-amino-5-fluorobenzo[c][1,2]oxaborol-1(3H)-ol* **(C70)**



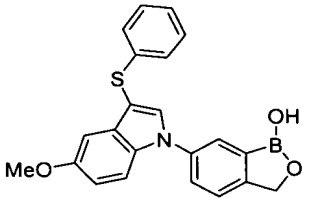
[0589] M.P. 142-145 °C. Exemplary starting material: 6-nitro-5-fluorobenzo[c][1,2]oxaborol-1(3H)-ol.

22ee *6-(benzylamino)-5-fluorobenzo[c][1,2]oxaborol-1(3H)-ol* **(C71)**



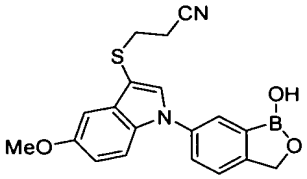
[0590] M.P. 159-164 °C. Exemplary starting material: 6-amino-5-fluorobenzo[c][1,2]oxaborol-1(3H)-ol.

22ff *6-(5-methoxy-3-(phenylthio)-1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C72)**



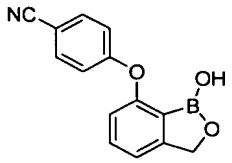
[0591] M.P. 135-141 °C. Exemplary starting material: (2-bromo-4-(5-methoxy-3-(phenylthio)-1H-indol-1-yl)phenyl)methanol.

22gg *3-(1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-5-methoxy-1H-indol-3-ylthio)propanenitrile* **(C73)**



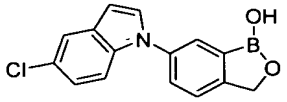
[0592] M.P. 149-154 °C. Exemplary starting material: 3-(1-(3-bromo-4-(hydroxymethyl)phenyl)-5-methoxy-1H-indol-3-ylthio)propanenitrile.

22hh *4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yloxy)benzonitrile* **(C74)**



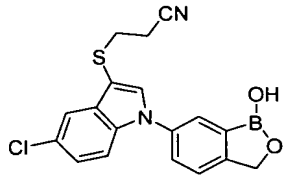
[0593] M.P. 148-153 °C. Exemplary starting material: 4-(2-bromo-3-(hydroxymethyl)phenoxy)benzonitrile.

22ii *6-(5-chloro-1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C75)**



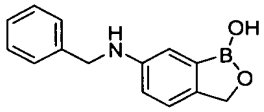
[0594] M.P. 149-154 °C. Exemplary starting material: (2-bromo-4-(5-chloro-1H-indol-1-yl)phenyl)methanol.

22jj *3-(5-chloro-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-3-ylthio)propanenitrile* **(C76)**



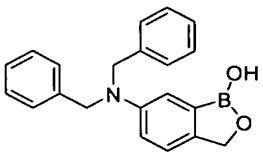
[0595] M.P. > 225 °C. Exemplary starting material: 3-(1-(3-bromo-4-(hydroxymethyl)phenyl)-5-chloro-1H-indol-3-ylthio)propanenitrile.

22kk *6-(benzylamino)benzo[c][1,2]oxaborol-1(3H)-ol* **(C77)**



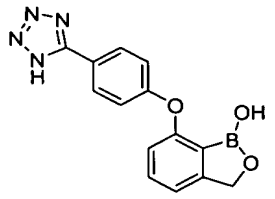
[0596] M.P. 126-133 °C. Exemplary starting material: 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol.

22ll *6-(dibenzylamino)benzo[c][1,2]oxaborol-1(3H)-ol* **(C78)**



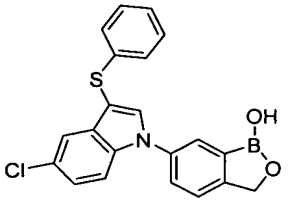
[0597] M.P. 115-123 °C. Exemplary starting material: 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol.

22mm *7-(4-(1H-tetrazol-5-yl)phenoxy)benzo[c][1,2]oxaborol-1(3H)-ol* **(C79)**



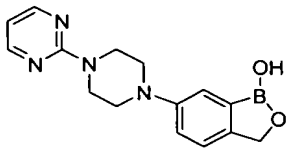
[0598] M.P. decomposition at 215 °C. Exemplary starting material: 4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yloxy)benzonitrile.

22nn *6-(5-chloro-3-(phenylthio)-1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C80)**



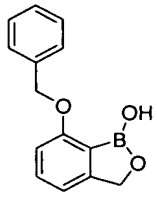
[0599] M.P. 145-151 °C. Exemplary starting material: (2-bromo-4-(5-chloro-3-(phenylthio)-1H-indol-1-yl)phenyl)methanol.

22pp *6-(4-(pyrimidin-2-yl)piperazin-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C82)**



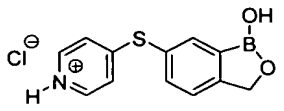
[0600] M.P. NA °C. Exemplary starting material: (2-bromo-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)methanol.

22qq *7-(benzyloxy)benzo[c][1,2]oxaborol-1(3H)-ol* **(C83)**



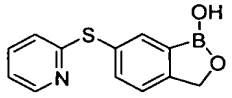
[0601] M.P. NA °C. Exemplary starting material: (3-(benzyloxy)-2-bromophenyl)methanol.

22rr *4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-ylthio)pyridinium chloride* **(C84)**



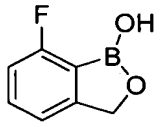
[0602] M.P. NA °C. Exemplary starting material: (2-bromo-4-(pyridin-4-ylthio)phenyl)methanol.

22ss *6-(pyridin-2-ylthio)benzo[c][1,2]oxaborol-1(3H)-ol* **(C85)**



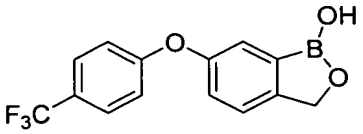
[0603] M.P. NA °C. Exemplary starting material: (2-bromo-4-(pyridin-2-ylthio)phenyl)methanol.

22tt *7-fluorobenzo[c][1,2]oxaborol-1(3H)-ol* **(C86)**



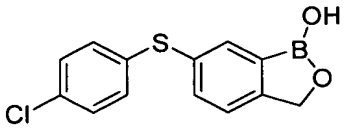
[0604] M.P. 120-124 °C. Exemplary starting material: (2-bromo-3-fluorophenyl)methanol.

22uu *6-(4-(trifluoromethyl)phenoxy)benzo[c][1,2]oxaborol-1(3H)-ol* **(C87)**



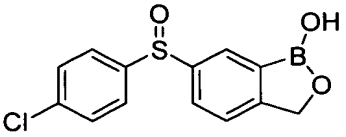
[0605] M.P. 98-105 °C. Exemplary starting material: (2-bromo-4-(4-(trifluoromethyl)phenoxy)phenyl)methanol.

22vv *6-(4-chlorophenylthio)benzo[c][1,2]oxaborol-1(3H)-ol* **(C88)**



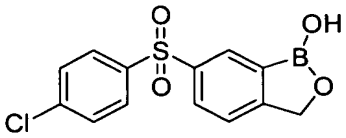
[0606] M.P. 157-161 °C. Exemplary starting material: (2-bromo-4-(4-chlorophenylthio)phenyl)methanol.

22ww *6-(4-chlorophenylsulfinyl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C89)**



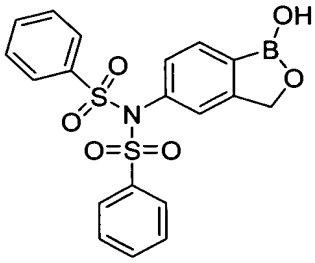
[0607] M.P. 154-161 °C. Exemplary starting material: 6-(4-chlorophenylthio)benzo[c][1,2]oxaborol-1(3H)-ol.

22xx *6-(4-chlorophenylsulfonyl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C90)**



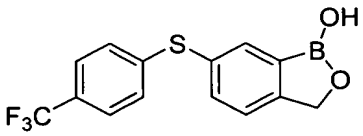
[0608] M.P. 157-163 °C. Exemplary starting material: 6-(4-chlorophenylthio)benzo[c][1,2]oxaborol-1(3H)-ol.

22yy *N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)-N-(phenylsulfonyl)benzenesulfonamide* **(C91)**



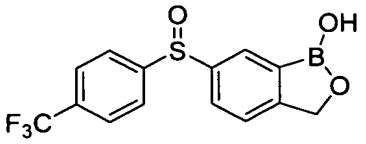
[0609] M.P. 142-152 °C. Exemplary starting material: N-(4-bromo-3-(hydroxymethyl)phenyl)-N-(phenylsulfonyl)benzenesulfonamide.

22zz *6-(4-(trifluoromethyl)phenylthio)benzo[c][1,2]oxaborol-1(3H)-ol* **(C92)**



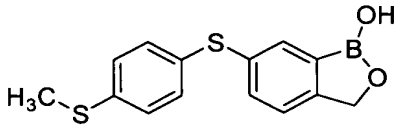
[0610] M.P. 111-113 °C. Exemplary starting material: (2-bromo-4-(4-(trifluoromethyl)phenylthio)phenyl)methanol.

22aaa *6-(4-(trifluoromethyl)phenylsulfinyl)benzo[c][1,2]oxaborol-1(3H)-ol* **(C93)**



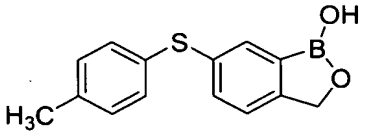
[0611] M.P. 79-88 °C. Exemplary starting material: 6-(4-(trifluoromethyl)phenylthio)benzo[c][1,2]oxaborol-1(3H)-ol.

22bbb *6-(4-(methylthio)phenylthio)benzo[c][1,2]oxaborol-1(3H)-ol* **(C94)**



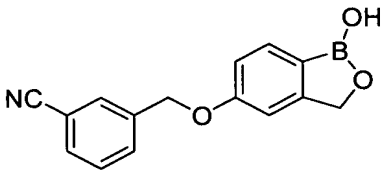
[0612] M.P. 117-120 °C. Exemplary starting material: (2-bromo-4-(4-(methylthio)phenylthio)phenyl)methanol.

22ccc *6-(p-tolylthio)benzo[c][1,2]oxaborol-1(3H)-ol* **(C95)**



[0613] M.P. 139-144 °C. Exemplary starting material: (2-bromo-4-(p-tolylthio)phenyl)methanol.

22ddd *3-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)methyl)benzonitrile* **(C96)**



[0614] M.P. 147-150 °C. Exemplary starting material: 3-((4-bromo-3-(hydroxymethyl)phenoxy)methyl)benzonitrile.

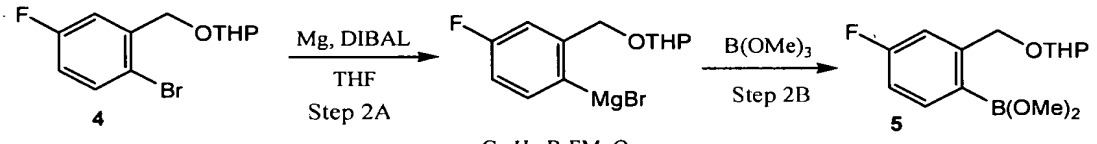
EXAMPLE 23

Alternative Preparation of 4 from 3

[0615] A 22.0 L 3-neck flask was equipped with a stir motor, N_2 inlet, addition funnel, heating mantle, and condenser. The flask was charged with 3500 g (17.1 mol) of 2-bromo-5-fluorobenzyl alcohol followed by the addition of 3556 g of tetrahydrofuran and 16.4 g (0.17 mol) of methanesulfonic acid. Next, 400 g (4.7 mol)

of 3,4-dihydro-2H-pyran was added at 10°C. This step is exothermic so no additional charges should be made until exotherm subsides. The temperature was increased to 27°C, stirred for 15 min and then charged with 400 g (4.7 mol) of 3,4-dihydro-2H-pyran at 24°C. Again the temperature increased (24°C to 38°C). The mixture was stirred for 15 min. Once the exotherm subsided, the flask was again charged with 400g (4.7 mol) of 3,4-dihydro-2H-pyran at 35°C. The temperature again increased to 47°C over a 20 min period. Once the exotherm subsided, the mixture was stirred for 15 min. Finally the remaining 400 g (4.7 mol) of 3,4-dihydro-2H-pyran was added at 44°C. The temperature increased to 51°C. After stirring for one hour, a sample was removed to check for removal of starting material. Upon reaction completion, contents were cooled to 20 ± 5 °C.

EXAMPLE 24



$C_{12}H_{14}BrFO_2$
Mol. Wt.: 289.14

$C_{12}H_{14}BrFMgO_2$
Mol. Wt.: 313.45

$C_{14}H_{20}BFO_4$
Mol. Wt.: 282.12

Alternative Preparation of 5 from 4

[0616] To a 22.0 L 3-neck flask equipped with a stir motor, N_2 inlet, addition funnel, cooling bath, and condenser was charged 436 g (17.96 mol) of magnesium turnings. 5334 g of tetrahydrofuran was then added followed by 291 g (0.51 mol) of diisobutylaluminum hydride (DIBAL) (25%wt) in toluene. The mixture was stirred for 60 min at 20 ± 5 °C. Some gas evolution was seen. Next, 260-430 g ~3-5% (by weight if solution of 4 was dropped to drums) of **4** in THF was added. The mixture was stirred for 15-30 min at which time a slight exotherm should be seen (ΔT = 10-15°C). Once the exotherm was observed, the reaction mixture was cooled to 5 ± 5 °C. To this mixture, the remaining 8.22-8.39 kg of **4** in THF was added at a rate such that the temperature was kept below 30°C (t = 3h). The reaction was stirred at 20-25 °C for 30 min, at which time an aliquot was removed, quench with 3 N HCl (10 mL), and analyzed.

[0617] Upon completion, the contents were cooled to -25 ± 5°C. A solution of trimethylborate in THF was prepared by mixing 2665 g (25.7 mol) of trimethyl borate and 6666 g of tetrahydrofuran. This solution can be prepared in a drum with stirring.

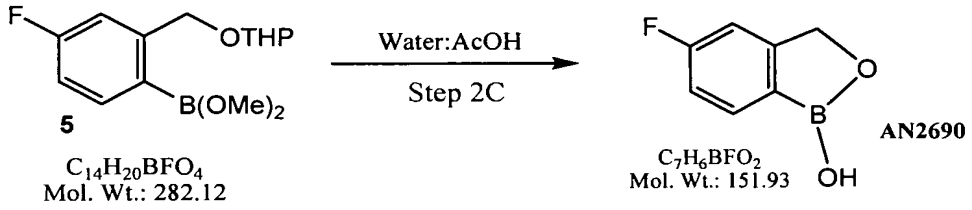
[0618] Next, the 9331 g of trimethyl borate in THF was added at a rate such that the temperature was kept between -35 and -20 °C (t = 2.5h). The mixture became very thick so THF was added. After stirring at -25 ± 5°C for 10 min, 50 mL aliquot was removed, quenched with 25 mL of 3N HCl, and submitted for CoR. Stirring continued at -25 ± 5°C for 1h, and then the mixture was allowed to warm to ambient temperature, where it was stirred for at least 12h. Pull two samples (one at 6h and the other at 12h).

Results:

[0619] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 1.45-1.75 (m, 6H), 3.53 (s, 6H), 3.45 (m, 1H), 3.75 (m, 1H), 4.69 (t, *J*=3 Hz, 1H), 4.97 (d, *J*=14.1 Hz, 1H), 5.14 (d, *J*=14.1 Hz, 1H), 7.03 ((td, *J*=8.4, 2.7 Hz, 1H), 7.24 (dd, *J*=10.8, 2.1 Hz, 1H), 7.89 (t, *J*=7.8 Hz, 1H), 8.76 (s, 1H).

EXAMPLE 25

Alternative Preparation of I from 5



5

$C_{14}H_{20}BFO_4$
Mol. Wt.: 282.12

$C_7H_6BFO_2$
Mol. Wt.: 151.93

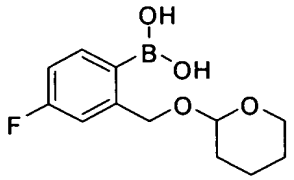
[0620] To the reaction mixture above was added 5.3 kg of USP water. After stirring for 30 min, the mixture was charged 5.3 kg of acetic acid. Gas evolution was seen. After stirring for 30 min, an aliquot was removed for analysis. Mixture was then heated to reflux for 36-48 hours. During the reflux period, 12-13 L of THF were removed.

[0621] When the reaction was complete, the contents were cooled by the reactor to ≤40°C by setting jacket and by charging 10.5 kg of USP water. THF was removed until distillate did not remain. Contents of the reactor were transferred to Rosenmund filter dryer and allowed to cool to 20 ± 5°C. Reactor was rinsed with water, filtered, and then washed again with 10.5 kg of USP water. The flask was charged with 10.5 kg of 10% ACN in water (v/v) and agitated for 1h. After filtering, the cake was washed with 10.5 kg of 10% ACN in water (v/v), and then charged with 10.5 kg 10% ACN in water (v/v). The contents were agitated for 1h. The contents were

subsequently washed with 10.5 kg of USP water, charged with 7.0 L of 5% Methyl t-Butyl Ether (MTBE)/Heptane (v/v), agitated for 1h, filtered, charged with 7.0 L of 5% MTBE/Heptanes (v/v) and again agitated for 1h. After filtering, the contents were charged again with 7.0 L of heptane and filtered. Solids were dried at ≤45°C to constant weight. Solids were recrystallized from toluene:heptane 75:25.

EXAMPLE 26

Alternative Preparation of C10-Intermediate



[[4-Fluoro-2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid

[0622] 2-Bromo-5-fluorobenzyl alcohol (5g, 24.4mmol) was dissolved in dichloromethane (100mL). To this solution was added 3,4-dihydro-2H-pyran (3.2mL, 36.6mmol) and (1S)-(+)-10-camphorsulfonic acid (117mg, 0.5mmol) and stirred at RT under nitrogen for 4h. Saturated sodium bicarbonate was added to quench the reaction. It was extracted using dichloromethane and the organic layer was washed with brine and dried over sodium sulfate, then concentrated *in vacuo* to give [1-bromo-4-fluoro-6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]benzene as a colorless oil (7g, 100%).

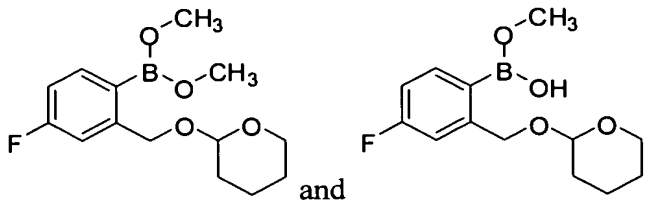
[0623] [1-Bromo-4-fluoro-6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]benzene (1.8g, 6.2mmol) was dissolved in THF and cooled to -78°C under nitrogen. To this solution was added n-butyllithium (1.6M in hexane)(6.2mL, 9.3mmol) dropwise, then added triisopropyl borate (2.2mL, 9.3mmol). The mixture was slowly warmed to RT and stirred for 3h. Water was added to quench the reaction. It was then extracted using ethyl acetate, washed with brine, dried over sodium sulfate and concentrated *in vacuo*. After column chromatography (silica gel; hexane:ethyl acetate=4:1 to 2:1) purification, [[4-Fluoro-2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid was obtained as a white solid (1.1g, 70%).

Results:

[0624] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 1.45-1.74 (m, 6H), 3.44 (m, 1H), 3.75 (m, 1H), 4.58(d, *J*=13.2 Hz, 1H), 4.64 (t, *J*=3 Hz, 1H), 4.79(d, *J*=13.2 Hz, 1H), 7.03 (td, *J*=8.4, 2.7 Hz, 1H), 7.13 (dd, *J*=10.8, 2.7 Hz, 1H), 7.50 (t, *J*=6.9 Hz, 1H).

EXAMPLE 27

Alternative Preparation of C10-Intermediate



[[4-Fluoro-2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid dimethyl ester

[0625] [[4-Fluoro-6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid (100 mg) was dissolved in dry methanol, the solution was distilled repeatedly to remove water. The resulting residue was immediately characterized by NMR and was found to be a mixture containing dimethyl ester and monomethyl ester.

[[4-Fluoro-2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid dimethyl ester.

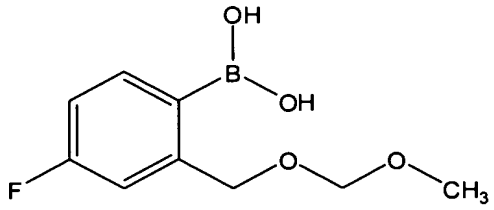
[0626] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 1.45-1.75 (m, 6H), 3.43 (s, 6H), 3.45 (m, 1H), 3.75 (m, 1H), 4.69 (t, *J*=3 Hz, 1H), 4.97 (d, *J*=14.1 Hz, 1H), 5.14 (d, *J*=14.1 Hz, 1H), 7.03 ((td, *J*=8.4, 2.7 Hz, 1H), 7.24 (dd, *J*=10.8, 2.1 Hz, 1H), 7.89 (t, *J*=7.8 Hz, 1H).

[[4-Fluoro-6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid monomethyl ester

[0627] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 1.45-1.75 (m, 6H), 3.53 (s, 6H), 3.45 (m, 1H), 3.75 (m, 1H), 4.69 (t, *J*=3 Hz, 1H), 4.97 (d, *J*=14.1 Hz, 1H), 5.14 (d, *J*=14.1 Hz, 1H), 7.03 ((td, *J*=8.4, 2.7 Hz, 1H), 7.24 (dd, *J*=10.8, 2.1 Hz, 1H), 7.89 (t, *J*=7.8 Hz, 1H), 8.76 (s, 1H).

EXAMPLE 28

Alternative Preparation of C10-Intermediate



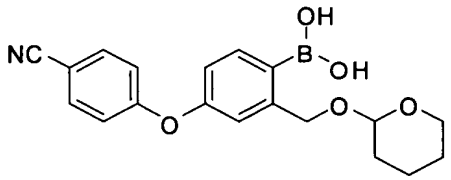
[(4-Fluoro-2-methoxymethoxymethyl)phenyl]boronic acid

[0628] [1-Bromo-4-fluoro-6-methoxymethoxymethyl]benzene (525mg, 2mmol) was dissolved in THF and cooled to -78°C under nitrogen. To this solution was added n-butyllithium (1.6M in hexane)(1.5mL, 2.4mmol) dropwise, then added triisopropyl borate (0.7mL, 2.4mmol). The mixture was slowly warmed to RT and stirred for 3h. Water was added to quench the reaction. It was then extracted using ethyl acetate, washed with brine, dried over sodium sulfate and concentrated *in vacuo*. After recrystallization from hexane:ethyl acetate=4:1 [(4-Fluoro-2-methoxymethoxymethyl)phenyl]boronic acid was obtained as a white solid (340 mg, 75%).

[0629] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 3.28 (s, 3H), 4.70 (s, 2H), 5.02(s, 2H), 7.04 (td, *J*=9.0, 3.0 Hz, 1H), 7.23 (dd, *J*=11.1, 2.4 Hz, 1H), 7.90 (t, *J*=7.8 Hz, 1H).

EXAMPLE 29

Alternative Preparation of C17-Intermediate



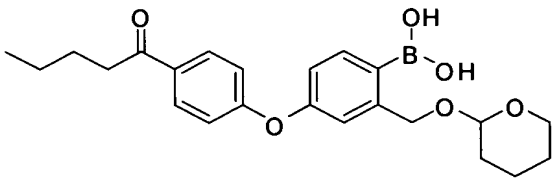
[[4-[4-cyanophenoxy]-2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid

[0630] 2-Bromo-5-(4-cyanophenoxy)benzyl alcohol (10.4g, 34.2 mmol) was dissolved in dichloromethane (110mL). To this solution was added 3,4-dihydro-2H-pyran (9.2mL, 101mmol) and (1S)-(+)-10-camphorsulfonic acid (156mg, 0.67mmol) and stirred at RT under nitrogen for 3h. Methanesulfonic acid (50 μL, 0.77 mmol) was then added and reaction was stirred overnight. Saturated sodium bicarbonate was

added to quench the reaction. It was extracted using ethyl acetate and the organic layer was washed with brine and dried over sodium sulfate, then concentrated *in vacuo* to give [1-bromo-4-(4-cyanophenoxy)-6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]benzene as a colorless oil (13.3g quant.).

[0631] [1-Bromo-4-(4-cyanophenoxy)-6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]benzene (13.3 g, 34.2mmol) was dissolved in THF (100mL), triisopropyl borate (8.5 mL, 37mmol) was added and the reaction was cooled to -78°C under nitrogen. To this solution was added n-butyllithium (1.6M in hexane)(22mL, 35.2mmol) dropwise. The mixture was slowly warmed to RT and stirred overnight. THF was removed *in vacuo* and the residue was dissolved in ethyl acetate. It was then washed with water, brine, dried over sodium sulfate and concentrated *in vacuo*. After column chromatography (silica gel; hexane:ethyl acetate 2:1) purification of a portion of crude , [[4-(4-cyanophenoxy)-6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid was obtained as a clear oil (500mg, 4%).

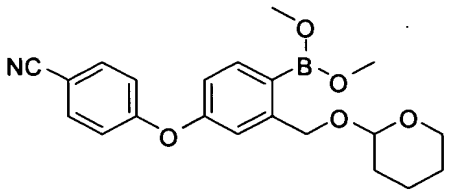
[0632] ^{1}H-NMR (300 MHz, DMSO-d_6 + D_2O) δ (ppm) 1.35-1.75 (m, 6H), 3.40 (m, 1H), 3.73 (m, 1H), 4.58 (d, *J*=13.2 Hz, 1H), 4.59 (s, 1H), 4.77 (d, *J*=12.7 Hz, 1H), 6.99 (dd, *J*=8.1, 2.2 Hz, 1H), 7.05 (m, 3H), 7.54 (d, *J*=7. 9 Hz, 1H), 7.81 (d, *J*=8.8 Hz, 2H).



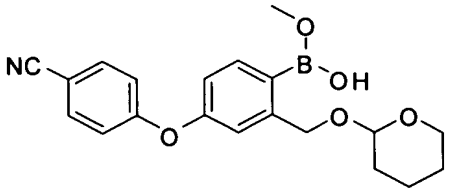
[0633] Also isolated was [[4-(4-pentanoylphenoxy)-6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid as a clear oil (500mg, 4%). ^{1}H-NMR (300 MHz, DMSO-d_6 + D_2O) δ (ppm)), 0.85 (t, *J*=7.5 Hz, 3H), 1.20-1.75 (m, 10H), 2.93 (t, *J*=7.0 Hz, 2H), 3.42 (m, 1H), 3.70 (m, 1H), 4.58 (d, *J*=12.8 Hz, 1H), 4.60 (s, 1H), 4.78 (d, *J*=13.2 Hz, 1H), 6.94 (d, *J*=8.4 Hz, 1H), 7.03 (d, *J*=8.4 Hz, 2H), 7.04 (s, 1H), 7.54 (d, *J*=8.4 Hz, 1H), 7.96 (d, *J*=8.4 Hz, 2H).

EXAMPLE 30

Alternative Preparation of C17-Intermediate



and



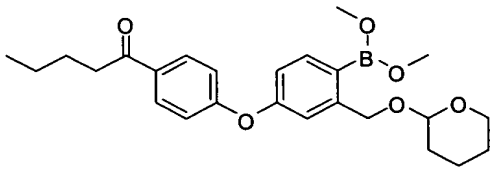
[[4-[4-cyanophenoxy]-2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid dimethyl ester

[0634] Using the same method as in C10 Example IIE, a mixture of mono- and dimethyl esters of [[4-(4-cyanophenoxy)-2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid were synthesized.

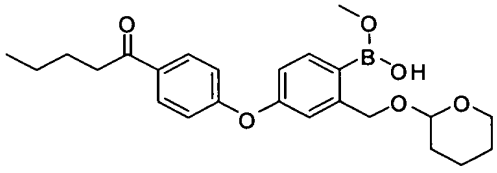
[0635] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 1.35-1.80 (m, 6H), 3.40-3.50 (m, 7H), 3.60-3.70 (m, 1H), 4.43 (d, *J*=12.7 Hz, 1H), 4.60-4.80 (m, 2H), 6.95-7.15 (m, 4H), 7.38 (d, *J*=8.4 Hz, 1H), 7.80-7.90 (m, 2H).

[[4-[4-cyanophenoxy]-6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid monomethyl ester

[0636] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 1.35-1.80 (m, 6H), 3.40-3.50 (m, 1H), 3.55 (s, 3H), 3.60-3.70 (m, 1H), 4.55 (d, *J*=12.8 Hz, 1H), 4.60-4.80 (m, 2H), 6.95-7.15 (m, 4H), 7.53(d, *J*=7.9 Hz, 1H), 7.80-7.90 (m, 2H), 8.77 (s, 1H).



and



[0637] Using the same method as above, a mixture of mono- and dimethyl esters of [[4-(4-pentanoylphenoxy)-2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid were synthesized.

[[4-(4-pentanoylphenoxy)-2-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid dimethyl ester

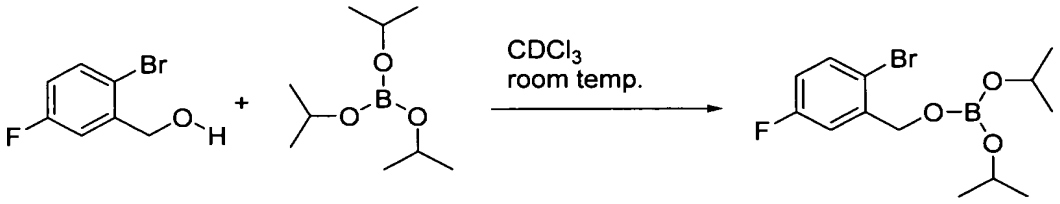
[0638] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 0.87 (t, *J*=7.3 Hz, 3H), 1.25-1.80 (m, 10H), 2.94 (t, *J*=7.3 Hz, 2H), 3.40-3.50 (m, 7H), 3.60-3.70 (m, 1H), 4.43 (d, *J*=12.8 Hz, 1H), 4.60-4.80 (m, 2H), 6.90-7.10 (m, 4H), 7.36 (d, *J*=7.9 Hz, 1H), 7.95-8.05 (m, 2H).

[[4-(4-pentanoylphenoxy)-6-[(tetrahydro-2H-pyran-2-yl)oxy]methyl]phenyl]boronic acid monomethyl ester

[0639] ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm) 0.87 (t, J=7.3 Hz, 3H), 1.25-1.80 (m, 10H), 2.94 (t, J=7.3 Hz, 2H), 3.40-3.50 (m, 1H), 3.55 (s, 3H), 3.60-3.70 (m, 1H), 4.55 (d, J=12.8 Hz, 1H), 4.60-4.80 (m, 2H), 6.95-7.15 (m, 4H), 7.52(d, J=7.9 Hz, 1H), 7.95-8.05 (m, 2H), 8.75 (s, 1H).

EXAMPLE 31

Alternative Preparation of C10-Intermediate



Alcohol Borate Alcohol-Borate Intermediate

[0640] To a pre-recorded NMR tube containing a solution of 2-bromo-5-fluorobenzyl alcohol (16 mg, 0.078 mmol) in $CDCl_3$ (0.75 mL) was injected triisopropyl borate (0.036 mL, 2 eq, 0.156 mmol) and the solution was sonicated briefly for 30 second at room temperature. ^{1}H NMR determination indicated there were 74.3 mol% of the desired alcohol-borate intermediate, 19.3 mol% of an unknown intermediate and 6.3 mol% of unreacted alcohol.

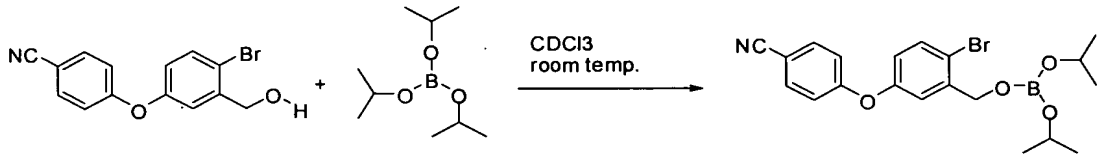
Results:

[0641] ^{1}H NMR ($CDCl_3$, 300 MHz) of (2-bromo-5-fluorobenzyl) diisopropyl borate: δ = 7.45 (dd, J = 8.7 Hz, J = 5.1 Hz, 1H), 7.20 (dd, J = 9.6 Hz, J = 2.7 Hz, 1H), 6.84 (td, J_t = 8.1 Hz, J_d = 3.3 Hz, 1H), 4.84 (s, 2H), 4.44 (septet, J = 6.0 Hz, 2H), 1.18 (d, J = 6.0 Hz, 12H) ppm. ^{1}H NMR ($CDCl_3$, 300 MHz) of an unknown intermediate: δ = 7.47-7.42 (1H overlap with product peaks), 7.16 (dd, 1H, partially overlap with product peak), 6.91-6.81 (1H, overlap with product peak), 4.94 (s, 2H), and other unknown peaks due to overlapping. ^{1}H NMR ($CDCl_3$, 300 MHz) of 2-bromo-5-fluorobenzyl alcohol pre-recorded before mixing: δ = 7.48 (dd, J = 9.0 Hz, J = 5.4 Hz, 1H, overlap with product peaks after mixing with triisopropyl borate), 7.26 (dd, J = 9.3 Hz, J = 3.3 Hz, 1H, intensity decreased but resolved after mixing), 6.88 (td, J_t = 8.3 Hz, J_d = 3.0 Hz, 1H, overlap with product peaks after mixing), 4.71 (s,

2H, CH_2 intensity decreased but resolved after mixing), 2.04 (s, 1H, OH disappeared after mixing with triisopropyl borate) ppm.

EXAMPLE 32

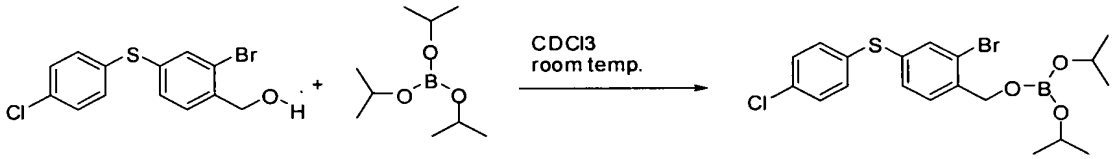
Alternative Preparation of C17-Intermediate



[0642] The procedure described in Example II I was followed for ^{1}H NMR characterization of the current alcohol-borate intermediate. ^{1}H NMR determination indicated there were 72.7 mol% of the desired alcohol-borate intermediate [2-bromo-5-(4-cyanophenoxy)benzyl] diisopropyl borate, 20.7 mol% of an unknown intermediate and 6.5 mol% of unreacted alcohol. ^{1}H NMR ($CDCl_3$, 300 MHz) of [2-bromo-5-(4-cyanophenoxy)benzyl] diisopropyl borate: δ = 7.61 (d, J = 9.0 Hz, 2H), 7.52 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 3.0 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 6.84 (dd, J = 8.7 Hz, J = 3.0 Hz, 1H), 4.85 (s, 2H), 4.35 (septet, J = 6.1 Hz, 2H), 1.11 (d, J = 6.1 Hz, 12H) ppm.

EXAMPLE 33

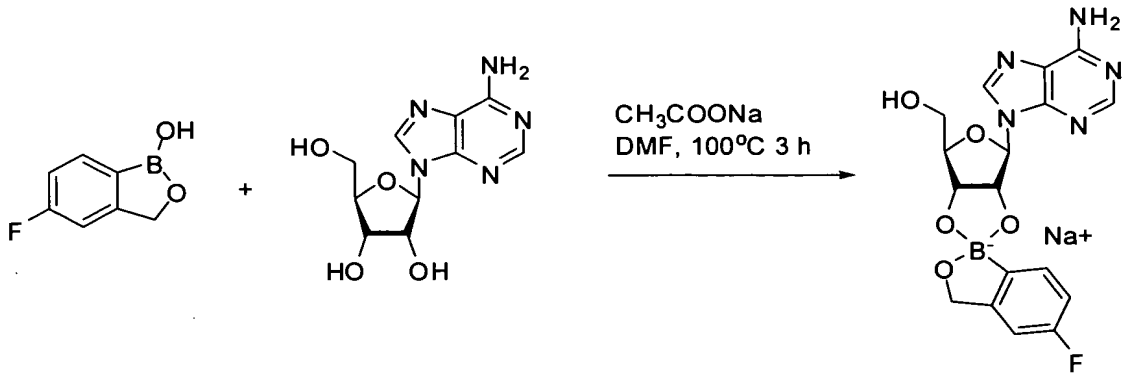
Alternative Preparation



[0643] The procedure described in Example II I was followed for ^{1}H NMR characterization of the current alcohol-borate intermediate. ^{1}H NMR determination indicated there were 73.5 mol% of the desired alcohol-borate intermediate [2-bromo-4-(4-chlorophenylthio)benzyl] diisopropyl borate, 20.2 mol% of an unknown intermediate and 6.2 mol% of unreacted alcohol. ^{1}H NMR ($CDCl_3$, 300 MHz) of [2-bromo-4-(4-chlorophenylthio)benzyl] diisopropyl borate: δ = 7.48 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.27 (s, 4H), 7.25 (dd, J = 8.3 Hz, J = 1.8 Hz, 1H), 4.86 (s, 2H), 4.42 (septet, J = 6.3 Hz, 2H), 1.16 (d, J = 6.3 Hz, 12H) ppm.

EXAMPLE 34

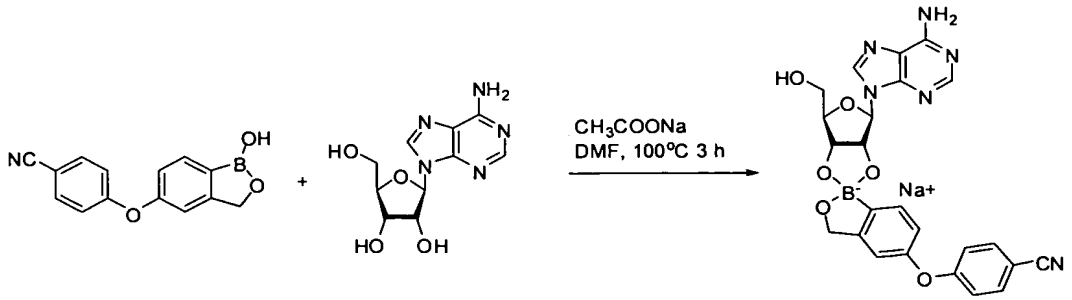
C10-Adenosine Complex



[0644] A mixture of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole (**C10**, 0.76 g, 5 mmol), adenosine (1.34 g, 5 mmol) and sodium acetate (0.41 g, 5 mmol) in dry DMF (100 mL) was stirred at 100°C for 3 h under nitrogen atmosphere. The homogeneous solution was rotary evaporated at 50°C under high vacuum. The residue was mixed with methylene chloride, sonicated and filtered under nitrogen atmosphere to give the desired complex as white solid that was pumped overnight (2.2 g, yield 100%). ^{1}H NMR indicated there were 5.7 mol% of unreacted adenosine, 5.5 mol% of unreacted **C10**, and the reaction conversion was more than 94%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.33 (s, 1H), 8.12 (s, 1H), 7.35-7.14 (broad m, 1H), 7.29 (s, 2H), 6.80 (broad m, 1H), 6.73 (d, J = 9.9 Hz, 1H), 5.99 (broad d, J = 2.1 Hz, 1H), 5.10 (very broad s, 1H), 4.71 (dd, J = 5.7 Hz, J = 3.9 Hz, 1H), 4.51 (s, 2H), 4.42 (dd, J = 6.3 Hz, J = 3.9 Hz, 1H), 4.07 (broad s, 1H), 3.64 (dd, J = 12 Hz, J = 3.6 Hz, 1H) and 3.52 (dd, J = 12 Hz, J = 5.1 Hz, 1H) ppm; M.p: started soften at 115°C due to residue solvents, remained as soften solid and started decomposing at 230°C; HPLC: 91.8% at 220 nm (adenosine was 5.3%); MS: m/z = 423 (M-, ESI-), 392 (M - CH_2OH, ESI+).

EXAMPLE 35

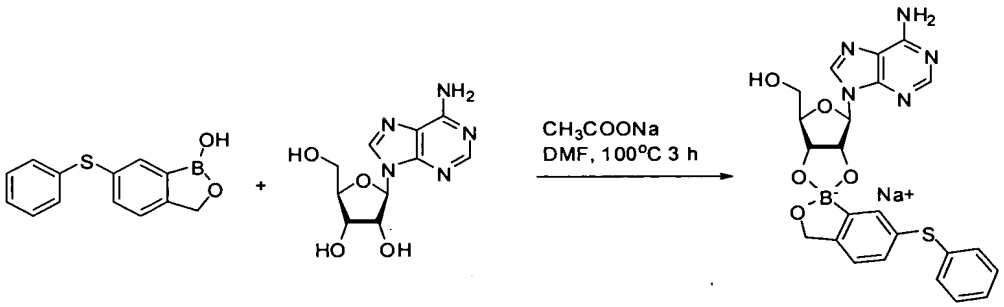
C17-Adenosine Complex



[0645] The procedure described above was adapted for the preparation of the title complex by replacing (**C10**) with 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**C17**, 1.25 g, 5 mmol). White solid product (2.7 g, yield 100%) was obtained after pumping overnight. ^{1}H NMR indicated there were 3.5 mol% of unreacted adenosine, 3.5 mol% of unreacted **C17**, and the reaction conversion was more than 96%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.35 (s, 1H), 8.13 (s, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.45-7.36 (broad m, 1H), 7.29 (s, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.81 (broad m, 1H), 6.73 (s, 1H), 6.01 (broad s, 1H), 5.10 (very broad s, 1H), 4.73 (dd, J = 6.0 Hz, J = 3.9 Hz, 1H), 4.54 (s, 2H), 4.45 (dd, J = 6.0 Hz, J = 3.9 Hz, 1H), 4.09 (broad s, 1H), 3.65 (dd, J = 12 Hz, J = 3.3 Hz, 1H) and 3.54 (dd, J = 12 Hz, J = 4.8 Hz, 1H) ppm; M.p: started soften at 120°C due to residue solvents, remained as soften solid and started decomposing at 230°C; HPLC: 92.1% at 220 nm (adenosine was 3.8%).

EXAMPLE 36

C28-Adenosine Complex

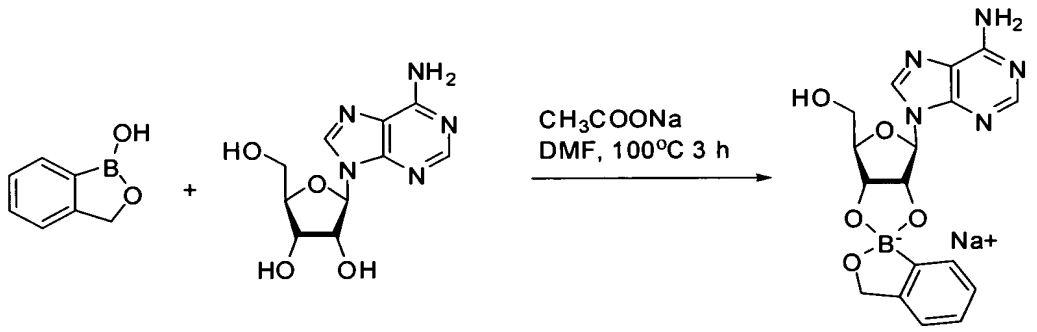


[0646] The procedure for the synthesis of **C10**-adenosine complex was adapted for the preparation of the title complex by replacing (**C10**) with 6-phenylthio-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**C28**, 1.21 g, 5 mmol). White solid product

(2.8 g, yield 100%) was obtained after pumping overnight. ^{1}H NMR indicated there was 5 mol% of unreacted **C28**, and the reaction conversion was 95%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.29 (s, 1H), 8.13 (s, 1H), 7.53 (broad s, 1H), 7.29 (s, 2H); 7.32-7.04 (m, 7H), 6.05-5.96 (broad m, 1H), 5.15 (very broad s, 1H), 4.73-4.70 (m, 1H), 4.58 (s, 2H), 4.46 (broad s, 1H), 4.12-4.03 (broad m, 1H), 3.63 (dd, J = 11.7 Hz, J = 3.3 Hz, 1H) and 3.52 (dd, J = 11.7 Hz, J = 4.8 Hz, 1H) ppm; M.p: started soften at 110°C due to residue solvents, remained as soften solid and started decomposing at 238°C. HPLC: 91.3% at 220 nm (adenosine was 3.8%).

EXAMPLE 37

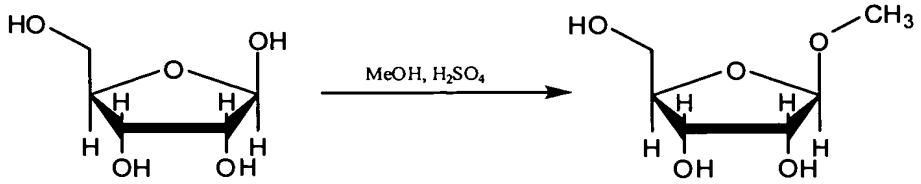
C2-Adenosine Complex



[0647] The procedure for the synthesis of **C10**-adenosine complex was adapted for the preparation of the title complex by replacing (**C10**) with 1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**C2**, 0.67 g, 5 mmol). Cream solid product (2.18 g, yield 100%) was obtained after pumping overnight. ^{1}H NMR indicated there was 4.5 mol% of unreacted **C2**, and the reaction conversion was more than 94%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.33 (s, 1H), 8.13 (s, 1H), 7.42-7.20 (broad m, 1H), 7.30 (s, 2H), 7.03-6.94 (m, 3H), 6.02 (d, J = 3.6 Hz, 1H), 5.25 (very broad s, 1H), 4.73 (dd, J = 5.7 Hz, J = 4.2 Hz, 1H), 4.56 (s, 2H), 4.46 (dd, J = 6.0 Hz, J = 3.9 Hz, 1H), 4.10 (broad q, J = 3.3 Hz, 1H), 3.66 (dd, J = 12 Hz, J = 2.7 Hz, 1H) and 3.52 (dd, J = 11.7 Hz, J = 4.8 Hz, 1H) ppm; M.p: started soften at 115°C due to residue solvents, remained as soften solid and started decomposing at 233°C. HPLC: 91.6% at 220 nm (adenosine was 5.9%).

EXAMPLE 38

Synthesis of Methyl β-D-ribofuranoside

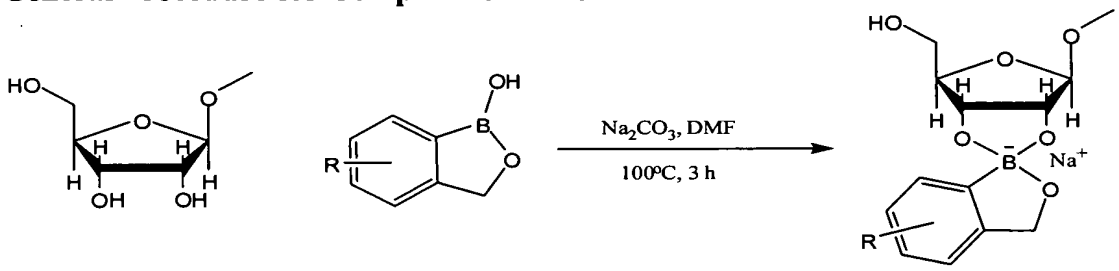


[0648] 5g of D-Ribose was dissolved in 100mL of methanol and cooled to 0°C. 0.5mL of concentrated sulfuric acid was added and the solution was stored at -20°C for 48hrs. Solution was neutralized by passage through a bed of sodium carbonate and evaporated under vacuum to a viscous oil. Crude material was purified on a silica column eluting with 10% methanol in ethyl acetate to yield 2.1 grams of methyl β-D-ribofuranoside.

[0649] ^{1}H NMR 300 MHz (DMSO-d_6) δ 4.97-4.99 (d, J=4.8 Hz, 1H), 4.76-4.79 (d, J=6.6 Hz, 1H), 4.57-4.62 (m, 2H), 3.76-3.80 (m, 1H), 3.72-3.74 (m, 1H), 3.66-3.71 (m, 1H), 3.44-3.50 (m, 1H), 3.26-3.34 (m, 1H), 3.19 (s, 3H)

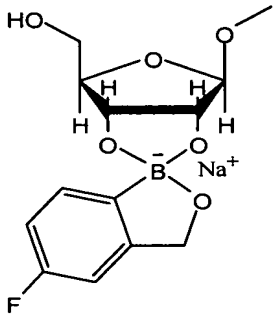
EXAMPLE 39

General Procedure for Complex Formation:



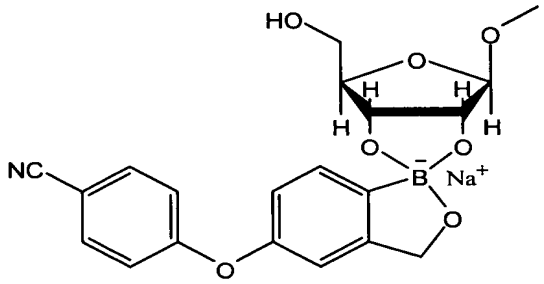
[0650] 300mg of methyl β-D-ribofuranoside was dissolved in 20ml of dimethylformamide. To this solution was added 1eq of boronic ester and 0.5eq of finely powdered sodium carbonate. Reaction mixture was heated to 100°C and stirred for 3 hours then stripped of solvent under vacuum. Residue was co-evaporated 2 times with ethyl acetate then sonicated in dichloromethane and filtered to yield an off-white solid.

C10-Methylribose Complex



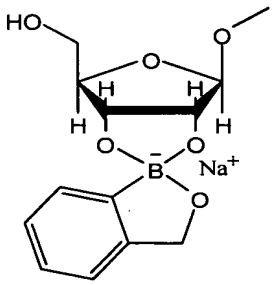
[0651] ^{1}H NMR 300 MHz (DMSO-d_6) δ 7.28 (bs, 1H), 6.68-6.77 (m, 2H), 4.71 (s, 1H), 4.52-4.55 (m, 3H), 4.26-4.28 (d, J=5.1 Hz, 1H), 4.17-4.19 (d, J=5.7 Hz, 1H), 3.95-4.00 (t, J=6.8 Hz, 1H), 3.31-3.36 (m, 2H), 3.19 (s, 3H).

C17-Methylribose Complex



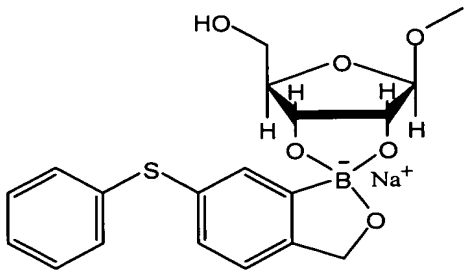
[0652] ^{1}H NMR 300 MHz (DMSO-d_6) δ 7.73-7.76 (d, J=6.9 Hz, 2H), 7.38-7.41 (d, J=7.8 Hz, 1H), 6.96-6.99 (d, J=6.9 Hz, 2H), 6.72-6.75 (d, J=7.5 Hz, 1H), 6.68 (s, 1H), 4.70 (s, 1H), 4.49-4.51 (m, 3H), 4.23-4.25 (d, J=5.4 Hz, 1H), 4.14-4.16 (d, J=5.4 Hz, 1H), 3.95-3.98 (m, 1H), 3.22-3.26 (t, J=6.0, 1H), 3.19 (s, 3H), 3.13-3.14 (d, J=2.1, 1H).

C2-Methylribose Complex



[0653] ^{1}H NMR 300 MHz (DMSO-d_6) δ 7.31 (bs, 1H), 6.87-6.95 (m, 3H), 4.70 (s, 1H), 4.46-4.50 (m, 3H), 4.20-4.22 (d, J=5.7, 1H), 4.12-4.14 (d, J=6.0 Hz, 1H), 3.94-3.99 (t, J=7.8 Hz, 1H), 3.30-3.34 (m, 2H), 3.19 (s, 3H)

C28-Methylribose Complex



[0654] ^{1}H NMR 300 MHz (DMSO-d_6) δ 7.48 (bs, 1H), 7.21-7.26 (m, 2H), 7.05-7.12 (m, 4H), 6.98-7.01 (d, J=7.8 Hz, 1H), 4.65 (s, 1H), 4.47-4.58 (m, 3H), 4.22-4.24 (d, J=5.7 Hz, 1H), 4.13-4.15 (d, J=6.0 Hz, 1H), 3.89-3.93 (t, J=6.6 Hz, 1H), 3.28-3.32 (t, J=6.5, 1H), 3.13-3.16 (m, 4H).

EXAMPLE 40

Mechanism of Action

[0655] The purpose of this study is to determine the mechanism of action (MOA) of **C10** in the model fungi *Saccharomyces cerevisiae*.

40.1 Methods

[0656] The haploid *Saccharomyces cerevisiae* strain ATCC 201388 was used in the selection of **C10** resistant mutants. Spontaneous and EMS-induced resistant mutants were isolated from YPD agar plates containing 4x, 8x, 16x MIC of **C10**. All minimal inhibitory concentrations (MIC) were determined using NCCLS protocol M27 with the exception of using YPD or synthetic defined media. All yeast and molecular genetic manipulations were essentially performed as described by Guthrie C., et al., *Methods in Enzymology*, **350**: Part B, (2002).

40.2 Results and Conclusions

[0657] A total of 11 **C10** resistant mutants were isolated from *S. cerevisiae*, all mutants were dominant and showed an 8 to 64-fold increase in the MIC to **C10**. Further characterization of these mutants showed that they were not resistant to several known antifungals including amphotericin B, cerulenin, itraconazole, aculeacin A, terbinafine, tunicamycin, ciclopirox, cyclohexamide and nikkomycin Z. All 11 mutations in the **C10** resistant mutants were mapped to 9 amino acid residues in the editing domain of CDC60, the essential cytoplasmic leucyl-tRNA synthetase, one of 40 aminoacyl-tRNA synthetases in *S. cerevisiae*. Furthermore, *S. cerevisiae*

strains bearing multiple copies of CDC60 on a 2 μM plasmid were eight times more resistant to **C10**. The combination of mutant and over-expression data predicts that CDC60 is the target for **C10**. The fact that all mutations were present in the editing domain of CDC60 indicates that **C10** inhibits CDC60 via a novel mechanism.

[0658] The lack of a genomic sequence or any genetic tools for *Trichophyton* spp. makes it difficult to study the mechanism of action of **C10** in either *Trichophyton* species, therefore, the model fungi *Saccharomyces cerevisiae* was used.

40.3 Materials and Methods

40.3a Chemicals, strains and plasmids

[0659] **C10** (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, was obtained from Anacor Pharmaceuticals, Inc. (Palo Alto, CA, USA). All *S. cerevisiae* strains and plasmids were obtained from ATCC (Manassas, VA, USA). The haploid *Saccharomyces cerevisiae* strain ATCC201388 (MATa *his3Δ1 leu2Δ0 met5Δ0 ura3Δ0*) was used for generating mutants, while ATCC 200901 (MATα *leu2Δ0 lys2Δ0 ura3Δ0*) was used to mate with **C10** resistant mutants to determine genetic dominance of the mutation. The yeast-*E.coli* shuttle plasmid pRS315 (Sikorski RS *et al.*, *Genetics* **122**: 19-27, (1989)), which has CEN6, leu2, ampR genes, and is a low copy plasmid in yeast was used in the construction of the genomic library. In the over-expression experiment, the shuttle vector pRS425 (Christianson TW *et al.*, *Gene* **110(1)**:119-22 (1992)), which has the leu2 and ampR genes, and is a high copy plasmid in yeast, was used.

40.3b Isolation of spontaneous resistant mutants

[0660] The haploid *S. cerevisiae* strain ATCC201388 was grown overnight in YPD broth (BD, NJ USA) at 30°C and 1 mL of cells was plated out onto YPD agar plates (YPD broth+1.5% Bacto-agar, BD, NJ USA) containing either 1.6, 3.2 or 6.4 μg/mL **C10** (equivalent to 4x, 8x,16x MIC of **C10**). Resistant mutants appeared after 2 d incubation at 30°C. Frequency of resistance was determined by dividing the number of resistant mutants by the total number of cells plated as determined by plating dilutions of the overnight culture on YPD plates.

40.3c EMS (ethylmethane sulfonate) mutagenesis

[0661] A 2.5mL of the overnight culture, which was grown in YPD media, was

centrifuged at 700 X *g* for 5 minutes. The cell pellet was resuspended in 10 mL 50mM potassium phosphate buffer, pH 7.0. The cell suspension was centrifuged again and the cell pellet was resuspended in phosphate buffer to obtain a cell density of 5 x 10^7 cells/mL as determined by counting the cells using a Petroff Hausser Counting Chamber (Horsham, PA USA). The cell suspension was shaken with 300 µL of EMS (Alfa Aesar, Ward Hill, MA, USA) for 30 min. at 30°C. The mutagenesis was stopped by adding 10% (w/v) sodium thiosulfate (Sigma-Aldrich, St. Louis, MO, USA), and the cells were pelleted by centrifugation at 700 X *g* for 5 min. and resuspended in 1 mL sterile H_2O. This was repeated once more before the cells were plated on YPD agar plates containing 1.6 µg/mL of **C10**.

40.3d *Determination of MICs*

[0662] The minimal inhibitory concentration (MIC) was essentially performed following the NCCLS guidelines outlined in the M27 protocol with the exception of using YPD or synthetic defined media (SDM).

40.3e *Yeast mating experiment*

[0663] The haploid mutants derived from *S. cerevisiae* ATCC201388 were mixed with *S. cerevisiae* ATCC 200901, and were incubated on YPD agar plates at 30°C for 4 h. The cell mixture was streaked out on synthetic defined media agar (BD, NJ USA) without the amino acids lysine and methionine, which are selective for diploids.

40.3f *Construction of plasmid genomic DNA library*

[0664] Genomic DNA from mutant strains was isolated using the DNeasy tissue kit from Qiagen (Valencia, CA, USA). Genomic DNA fragments of 4-10kb were generated by partial digestion with *Mbo* I from Fermantas (Hanover, MD, USA), followed by purification using the Wizard®SV gel and PCR Clean-Up system (Promega, Madison WI USA). The purified DNA fragments were ligated into pRS315 digested with *Bam*H I (Fermantas, Hanover MD USA) using T4 DNA ligase (Fermantas, Hanover MD USA). The ligation mixture was dialyzed against water using the VSWP 0025 filters (Millipore, Billerica, MA, USA) before it was electroporated into *Escherichia coli E.cloni* SUPREME cells (Lucigen, Middleton, WI, USA) following the protocol of the manufacturer. Transformants were plated out on LB plates with 200 µg/ml carbinicillin and incubated overnight at 37°C. The transformants were pooled and the plasmid DNA was isolated using Qiagen miniprep

kit (Valencia, CA, USA). The plasmid library was transformed into *S. cerevisiae* (Gietz, RD *et al.*, *Methods in Enzymology* **305**: 87-96 (2002)).

40.3g Sequencing

[0665] All sequencing was performed by Sequetech Corporation (Mountain View, CA USA).

40.3g(1) Mapping mutations

[0666] To further map the mutations to specific domains in CDC60, the following three pairs of primers were used 5' gcgaaaagaaacctaacgcatattc 3' and 5'ctatcgtgatccatacaagcttgac 3', 5' cgatagacaatccggtgaaggtgttac 3' and 5' catcccaaggcaatctggtacctaacc 3', and 5' gaaaaatacttagttgagtctttatca 3' and 5' caccatgaggcatcttgaaatattctc 3'.

40.3h Cloning and over-expressing wild type CDC60 in S. cerevisiae

[0667] A 4.0kb *Bam*H I-*Sal* I DNA fragment containing the entire CDC60 open reading frame (ORF) and 700bp of upstream sequence was amplified using KOD DNA polymerase, *S. cerevisiae* genomic DNA (Novagen, Madison, WI, USA), and the primers GAG GGA TCC GGT TAG TTT TAG TTC GCG AGT GAC CTG and GAG GTC GAC GAT TTC TGG TTG CTG TTT ATT GAT CTT (Operon , Alameda, CA, USA). This DNA fragment was then cloned into the 2 μM multi-copy plasmid pRS425, and transformed into *S. cerevisiae* ATCC201388 (Gietz, RD *et al.*, *Methods in Enzymology* **305**: 87-96 (2002)).

40.4 Results and Discussions

40.4a Isolation of resistant mutants

[0668] From 5 x 10^9 cells, 600 spontaneous **C10** resistant mutants were isolated, which makes the frequency of resistance 1.2 x 10^{-7} at 4 x MIC. Similar frequencies of resistance were obtained for 8x and 16x MIC. We also used EMS to isolate **C10** resistance mutants. Use of EMS increased the mutagenic frequency by 4,000 fold. The MICs of 8 spontaneous mutants and 3 EMS generated mutants were tested. All the mutants showed an 8 to 64-fold increase in resistance to **C10** (Table 1).

Table 1. MICs of Spontaneous and EMS induced **C10** mutants

S. cerevisiae Haploid Strains	MIC (μg/mL)	
	Cerulenin	**C10**
ATCC201388	1	0.5
(A)	0.5	4
(B)	0.5	16
(C)	0.5	16
(D)	0.5	32
(E)	0.5	16
(F)	0.5	32
(G)	0.5	32
(H)	0.5	32
(I)	1	32
(J)	1	32
(K)	1	32

40.4b ***C10*** *resistant mutations do not confer resistance to other antifungals*

[0669] To further characterize these resistant mutants, three **C10** resistant mutants were tested against various antifungal agents with known mechanisms of action. The **C10** resistant mutants did not show any resistance to these compounds (Table 2), which suggests that **C10** acts very differently from these antifungal agents.

Table 2. **C10** mutants are not resistant to other antifungals

Antifungal Agents	MIC (μg/mL)			
	ATCC201388	(C)	(G)	(H)
C10	0.5	16	16	16
Amphotericin B	0.125	0.125	0.125	0.125
Cyclohexamide	<0.06	<0.06	<0.06	<0.06
Cerulenin	0.5	0.5	0.5	0.5
Itraconazole	0.125	0.125	0.125	0.125
Aculeacin A	4	4	4	4
Ciclopririox	0.5	0.5	0.5	0.5
Terbinafine	4	4	4	4
Nikkomycin Z	64	64	64	64
Tunicamycin	8	8	8	8

*40.4c Resistance to **C10** is dominant*

[0670] In order to identify the gene that gives rise to **C10** resistance, it was first determined whether the mutation was either dominant or recessive. The parental *S. cerevisiae* strain and three mutants were selected and mated with *S. cerevisiae* ATCC 200901. The MIC of the diploids generated from the **C10** mutants were found to be 64-fold greater than the diploid generated from the parental strain (Table 3), which suggests that the mutations are dominant, and therefore, plasmid libraries were constructed from these three haploid **C10** resistant mutants.

Table 3. **C10** mutants are dominant

Diploid (mutant strain/ATCC200901)	MIC (μg/mL) **C10**
ATCC201388/ATCC200901	0.5
(C)/ATCC200901	32
(G)/ATCC200901	32
(H)/ATCC200901	32

*40.4d The CDC60 gene confers resistance to **C10***

[0671] Plasmid libraries from the three mutants were transformed into *S. cerevisiae* ATCC201388 and selected on SDM minus leucine agar with 1 μg/mL of **C10**. Plasmid DNA was isolated from **C10** resistant transformants and electroporated into *E. coli* 10G cells. The plasmid DNAs from the resulting *E. coli* carbenicillin resistant transformants were then transformed into *S. cerevisiae* ATCC201388 to confirm that the plasmids bore the gene for **C10** resistance. One plasmid from each library that

conferred **C10** resistance was sequenced and analyzed using a BLASTN search against the *S. cerevisiae* genome database (http://seq.yeastgenome.org/cgi-bin/nph-blast2sgd). The CDC60 gene was the only open reading frame identified in the cloned inserts from two plasmids derived from two of the plasmid libraries. Two genes were revealed, CDC60 and PET20, in the cloned insert from the remaining plasmid library. This suggests that these **C10** resistant mutations are located in the CDC60 gene, which encodes for the cytoplasmic leucyl-tRNA synthètase. CDC60 (leucyl tRNA synthetase) is one of 20 essential aminoacyl-tRNA synthetases (ARS) that attach amino acids to the 2' or 3' end of tRNAs.

*40.4e **C10** resistance mutations reside in the editing domain of CDC60*

[0672] DNA sequence analysis of the plasmids derived from the three mutants showed that there was a single amino acid substitution in CDC60 from each of the three mutants (Table 4). An additional eight mutants were analyzed by amplifying CDC60 by colony PCR and transforming the resulting product into *S. cerevisiae* ATCC201388. All transformants were resistant to **C10** and subsequent sequence analysis showed that all of them contained a single amino acid change within the editing domain of CDC60 (Table 4). The function of the ARS is to charge the correct tRNA with the correct amino acid. In leucyl-tRNA synthetases the active site for the editing mechanism is located in a separate domain, which is called the connective polypeptide 1(CP1), from the synthetic active site (Schmidt E. *et al*, *Biochemistry* **34(35)**:11204-10 (1995)). All of the amino acid substitutions from 11 mutants were located in this CP1 domain, demonstrating a link between the editing function of the enzyme and inhibitory activity of **C10**.

40.4f Over-expression of wild type CDC60 in S. cerevisiae

[0673] Since all 11 **C10** resistant mutants have single amino acid substitutions in the editing domain of leucyl-tRNA synthetase (Table 4), it strongly suggests that CDC60 is the target for **C10**. If leucyl-tRNA synthetase is the target, increasing the copies of CDC60 should increase resistance to **C10**. To test this hypothesis, the wild type CDC60 gene was cloned onto a multi-copy plasmid pRS425, and transformed into *S. cerevisiae* ATCC201388. As shown in Table 5, the MIC for this strain is eight times higher than the same strain bearing pRS425.

Table 4. Amino acid (AA) substitutions in **C10** resistant mutants

Resistant mutants	AA substitution in CDC60
(H)	T314M
(G)	L315V
(K)	T319I
(C)	C326F
(E)	C326R
(D)	G405V
(A)	N415D
(I)	S416L
(J)	D487N
(F)	D487G
(B)	R316I

Table 5. CDC60 overexpression increases **C10** resistance

	MIC (μg/mL)	
Compound	pRS425 Plasmid control	CDC60 on pRS425 (20 copies)
Fluconazole	2	2
1	0.125	1

EXAMPLE 41

[0674] Experiments to isolate mutant leucyl tRNA transferase molecules that were also resistant to **C10**.

[0675] The haploid wild type *Saccharomyces cerevisiae* strain ATCC 201388 (MATa his3Δ1 leu2Δ 0 met5Δ 0 ura3Δ 0) was used for selection of clones showing resistance to **C10**.

[0676] Mutations in the leucyl tRNA transferase were isolated in two ways. In one set of experiments, EMS was used as a chemical mutagenic agent. 2.5mL of an overnight culture was washed 2x with 50mM potassium phosphate buffer, pH 7.0, and resuspended in 10 mL of the buffer to reach approximately $5x10^7$ cells/ml. 300μL EMS (Alfa Aesar, Ward Hill, MA) was added to the cells, which were then incubated for 30 min at 30°C with shaking. The mutagenesis process was halted with the addition of 10% (w/v) sodium thiosulfate (Sigma-Aldrich, St. Louis, MO, USA). At the end of the mutagenesis cycle, the cells were washed 2x with water and then plated out on YPD agar plates containing **C10**.

[0677] In the second method, spontaneous mutant clones were isolated from YPD plates containing large concentrations of **C10**. Wild type haploid *S. cerevisiae* strain ATCC201388 (MATa his3Δ1 leu2Δ 0 met5Δ 0 ura3Δ 0) was grown overnight in Difco YPD broth (1% yeast extract, 2% Bacto Peptone, 2% glucose) at 30°C to reach ~ $1.0x10^8$ cells/ml. Cells were concentrated 10x in YPD broth, and 100μL was plated out onto each of 30 YPD agar (Difco YPD broth+1.5% Bacto agar) plates containing 1.6, 3.2, 6.4μg/ml **C10** (equivalent to 4x,8x, and 16x minimal inhibitory concentration of **C10**). Resistant mutants appeared after 2 days of incubation at 30°C. Frequency of resistance was determined by counting the number of the mutants, and the total number of cells.

[0678] The minimal inhibitory concentration (MIC) test was performed using NCCLS protocol. Yeast mating experiment was conducted following the procedure in *Methods in Enzymology* by Guthrie, C etc.

[0679] The genomic plasmid library for each clone was constructed using the yeast-*E.coli* shuttle vector pRS315 and transformed into *S. cerevisiae* ATCC201388. Transformants were selected on synthetic defined media with 0.2ug/ml **C10** minus leucine. All sequencing work was done by Sequeteq. Blast search was performed using *Saccharomyces* genome database. Yeast Transformation was carried out using LiAc/PEG method. Over-expression of CDC60 construct was made by using *S. cerevisiae* genomic DNA, and two primers 5'GAGGGATCCGGTTAGT TTTAGTTCGCGAGTGACC TG 3', 5'GAGGTCGACGATTTCTGGTTGCT GTTTATTGATCTT 3'.

[0680] A total of 23 **C10** resistant mutants were isolated from *S. cerevisiae*. All mutants were dominant and had 8-64 fold increased resistance to **C10** over wildtype in the minimal inhibitory concentration test. Further characterization of these mutants showed that they were not cross resistant to any anti-fungal agents with known mechanism of action.

Determination of dominance/recessiveness

[0681] In order to identify the resistant gene in mutant strain, we first determined whether the mutation is dominant or recessive. The mutant was mated with a wild type strain with opposite mating type to make mutant diploid. There were two sets of genes in the resulting mutant diploid cells, one from resistant mutant, and the other

one from the **C10**-sensitive wild type. If the mutant diploid was resistant to **C10**, the muted gene was dominant. To map the mutation, we constructed a plasmid library from the mutant strain, and transformed the library into the **C10**-sensitive wild type strain to select for the resistant phenotype. If the mutant diploid was sensitive to **C10**, the muted gene would be identified as recessive. A12, F4, H4 was mated with a wild type strain, respectively, as control; the parental strain was also mated with the same strain. Minimal inhibitory concentrations of both wild type diploid and 3 mutant diploids are shown in Table 3. Compared to wild type diploid, all 3 mutant diploids were resistant to **C10**, indicating that the resistant mutation in these 3 mutants is dominant.

Genetic mapping of mutation

[0682] All the mutations in the 23 isolated **C10** resistant mutants were mapped to 11 residues in the editing domain of CDC60, the cytoplasmic leucyl-tRNA synthetase.

[0683] To identify the mutation in the resistant mutant, we constructed 3 plasmid genomic libraries from mutant A12, F4 and H4, respectively. Plasmids with random genomic DNA fragment insert, size from 4-10kb, were transformed back into parental wild type strain. Transformants with plasmids carrying resistant genes were selected on SDM-leu agar plates with addition of **C10**. Plasmids were then isolated and sent for sequencing. Nucleotide sequence of the insert was BLAST searched against *S. cerevisiae* genome database, and the results revealed that there was a single ORF present in the insert of both plasmids isolated from F4 and H4 plasmid library. This ORF was identified as CDC60, the cytoplasmic leucyl tRNA synthetase, one of the 20 essential cytoplasmic aminoacyl-tRNA synthetases in *S. cerevisiae* (there are 20 more in mitochondrial). In addition to CDC60, there was a second ORF pet20 present in the plasmid isolated from A12 plasmid library, which encoded the protein required for respiratory growth and stability of the mitochondrial genome. To confirm that the CDC60 from these 3 mutants conferred resistance to **C10**, we re-transformed the 3 plasmids back to parental wild type strain. Compared to the control transformation of the plasmid without CDC60, ones with CDC60 from A12, F4, H4 gave >1,000 more resistant colonies on YPD agar containing **C10**, confirming that CDC60 from the 3 mutant strains contributed to **C10** resistance.

Sequence in CDC60 from each of the mutants contains single amino acid substitution

[0684] In order to identify whether there were any amino acid substitutions, the whole ORF of CDC60 from resistant plasmids A12, F4, and H4 was sequenced. Comparing the sequence with wild type CDC60 showed that there was a single amino acid substitution in each of the 3 CDC60 (Table 4). In addition, sequence analysis of CDC60 from the rest of 20 resistant mutants showed that each contains a single amino acid change within CDC60. DNA PCR fragments containing each mutation were transform back into wild type strain. These transformations conferred resistance, indicating that the resistance of all the mutants was due to the single amino acid substitution in CDC60.

[0685] CDC60 (leucyl tRNA synthetase) is one of the aminoacyl-tRNA synthetases (ARS) that belong to a family of essential enzymes that attach amino acids to the 2', or 3' end of tRNAs, the charged tRNAs are then used in protein synthesis. The aminoacylation of tRNA is a two-step reaction: a) activation of amino acids with ATP by forming aminoacyl adenylates and b) transferring of the aminoacyl residue from the aminoacyl adenylate to the cognate tRNA substrate. The accuracy of aminoacylation depends on both the specific recognition of amino acids during their activations (coarse sieve) and the pre- or post transferring editing (fine sieve). Some of the ARS have evolved editing mechanism that specifically hydrolyzes structurally close related misactivated amino acids. Leucyl tRNA synthetase is one of such enzymes that can discriminate leucine from isoleucine, and valine. The region that carries out this editing function is called connective polypeptide 1(CP1), it's a large insertion that interrupts the active site between the third and fourth b strands of the Rossman fold. All of the 11 amino acid substitutions from 23 mutants were located in this CP1 region, suggesting that there might be a link between the editing function of the enzyme and inhibition activity of **C10**.

EXAMPLE 42

Assay for determining that C10 inhibits the editing domain of tRNA synthetase in a bacteria

[0686] This example sets forth a representative assay for determining whether a particular compound inhibits the editing domain of an ARS in a bacterium.

[0687] The [^{3}H]-isoleucine mischarged tRNAleu was synthesized by incubating 1 μM of *Saccharomyces cerevisiae* editing defective Cdc60p (C326F) in 500 μL of 50mM Tris-HCl (pH 8.0), 60mM $MgCl_2$, 4mM ATP, 1mM DTT, 0.02% (w/v) BSA, 4mg/mL crude *E.coli* tRNA tRNA (Roche), 0.1mM isoleucine and 5 mCi L-[4,5-3H]isoleucine (100Ci/mmole, GE Healthcare) and 20% (v/v) DMSO for 1 hour at 30°C. The reaction was stopped by adding 10 μL of 10% (v/v) acetic acid followed by two acidic phenol (Sigma) extractions. The mischarged tRNA in the top aqueous phase was removed and precipitated by adding two volumes of 96% (v/v) ethanol and incubating at -20°C for 30 minutes. The precipitate was pelleted by centrifugation at 13,200 xg for 30 minutes and the mischarged tRNA pellet was washed twice with 70% (v/v) ethanol and then resuspended in 50 mM potassium phosphate buffer pH 5.2.

[0688] The reaction was terminated after 2 hours incubation at 30°C by the addition of acetic acid to 0.17 % (v/v). The isoleucylated crude $tRNA^{Leu}$ was purified by extracting twice with acidic phenol-chloroform extractions (pH 4.3), followed by ethanol precipitation. The tRNA pellet was washed twice with 70% ethanol, dried and then resuspended in 50 mM potasium phosphate (pH 5.0) and stored at -20°C. An aliquot was precipitated with 10% (w/v) TCA to quantify ile-$tRNA^{Leu}$.

[0689] Post-transfer editing hydrolysis assays were carried out at 30°C in 50 mM Hepes (pH 8), 10 mM $MgCl_2$, 30mM KCl, with ^{3}H-isoleucine-tRNA crude (~0.3 μCi/mL). Each reaction was initiated by addition of the 150 nM enzyme. At each time point three 20 μL aliquots of the reaction mixture was added to 200 μL of 10% (w/v) TCA in a Millipore filter plate and precipitated for 20 minutes at 4°C. The precipitate was filtered and washed three times with 200 μL of 5% (w/v) TCA, then dried and 20 μL Supermix scintillation cocktail was added. The Millipore filter plates were counted in the MicroBeta Trilux. The IC_{50} was determined by the amount of inhibitor that inhibited 50% activity, 100% post-transfer editing was calculated by taking the activity of the no enzyme control from the wild-type enzyme activity.

[0690] Compare the minimal inhibitory concentration (MIC) of a *tolC Escherichia coli* strain bearing a pUC derived plasmid with and without an *leuS* gene insert.

[0691] If the MIC of the strain bearing the extra copies of *leuS* is greater than 2-fold more than the control strain then pour LB agar plates with four times the concentration of the MIC of the compound.

[0692] Plate 1 x 10^{10} *E. coli* on ten plates containing 4 x MIC of the compound. Incubate for 1-2 days at 37°C and pick ten colonies and restreak on 4 x MIC LB agar plates to confirm resistance.

[0693] Take one large colony from each of the ten *E. coli* resistant mutants and resuspend in 50 µL of PCR buffer.

[0694] Amplify the editing domain of CDC60 using a proof-reading PCR enzyme and the following primers, ggcaccgtggacgtacgacaacatcgc and gggaaacaccccagtcgcgcaggcgg.

[0695] Purify the 980 bp PCR product using either Qiagen or Promega PCR cleanup kits.

[0696] Sequence amplify the mutant DNA and compared it to wild-type. If the mutant DNA bears mutations in the editing domain the inhibitor affects leucyl-tRNA synthetase via the editing domain.

EXAMPLE 43

Assay for determining that C10 inhibits the editing domain of tRNA synthetase in a fungus

[0697] This example details an exemplary assay for determining whether a selected compound inhibits the editing domain of an ARS in a fungus.

[0698] The [^{3}H]-isoleucine mischarged tRNAleu was synthesized by incubating 1 µM of *Saccharomyces cerevisiae* editing defective Cdc60p (C326F) in 500 µL of 50mM Tris-HCl (pH 8.0), 60mM $MgCl_2$, 4mM ATP, 1mM DTT, 0.02% (w/v) BSA, 16 µM brewer's yeast tRNA (Roche), 0.1mM isoleucine and 5 mCi L-[4,5-3H]isoleucine (100Ci/mmole, GE Healthcare) and 20% (v/v) DMSO for 1 hour at 30°C. The reaction was stopped by adding 10 µL of 10% (v/v) acetic acid followed by two acidic phenol (Sigma) extractions. The mischarged tRNA in the top aqueous phase was removed and precipitated by adding two volumes of 96% (v/v) ethanol and incubating at -20°C for 30 minutes. The precipitate was pelleted by centrifugation at 13,200 xg for 30 minutes and the mischarged tRNA pellet was washed twice with

70% (v/v) ethanol and then resuspended in 50 mM potassium phosphate buffer pH 5.2.

[0699] The reaction was terminated after 2 hours incubation at 30°C by the addition of acetic acid to 0.17 % (v/v). The isoleucylated crude $tRNA^{Leu}$ was purified by extracting twice with acidic phenol-chloroform extractions (pH 4.3), followed by ethanol precipitation. The tRNA pellet was washed twice with 70% ethanol, dried and then resuspended in 50 mM potasium phosphate (pH 5.0) and stored at -20°C. An aliquot was precipitated with 10% (w/v) TCA to quantify ile-$tRNA^{Leu}$.

[0700] Post-transfer editing hydrolysis assays were carried out at 25°C in 50 mM Hepes (pH 7.5), 10 mM $MgCl_2$, 30mM KCl, with ^{3}H-isoleucine-tRNA crude (~0.3 μCi/mL). Each reaction was initiated by addition of the 150 nM enzyme. At each time point three 20 μL aliquots of the reaction mixture was added to 200 μL of 10% (w/v) TCA in a Millipore filter plate and precipitated for 20 min. at 4°C. The precipitate was filtered and washed three times with 200 μL of 5% (w/v) TCA, then dried and 20 μL Supermix scintillation cocktail was added. The Millipore filter plates were counted in the MicroBeta Trilux. The IC_{50} was determined by the amount of inhibitor that inhibited 50% activity, 100% activity was calculated by taking the activity of the no enzyme control from the wild-type enzyme post-transfer editing activity.

EXAMPLE 44

Equilibrium Dialysis

[0701] Equilibrium dialysis experiments were performed in 1x AARS buffer containing 50 mM Hepes-KOH (pH 8.0), 30 mM $MgCl_2$ and 30 mM KCl. Experiments were performed using 5k MWCO DispoEquilibrium Dialyzer apparatus (Harvard Apparatus, Holliston, MA). On one side of the dialysis membrane (side A), [methylene-^{14}C] **C10**, 2.04 GBq/ mmol (Amersham) was added at concentrations ranging from 1 to 200 μM in 20 μL. On the opposite side of the membrane (side B), 30 μM recombinant Cdc60p (*Saccharomyces cerevisiae* cytoplasmic LeuRS) and 10 mM AMP (adenosine 5'-monophosphate, Sigma) was added in 20 μL. Samples were incubated at room temperature (21°C) while shaking for 4.5 hrs to establish **C10** equilibrium across the membrane. At equilibrium, **C10** on each side of the dialysis membrane was quantified by scintillation counting using a Wallac MicroBeta Trilux

model 1450 liquid scintillation counter. The amount of **C10** bound to Cdc60p was determined by subtracting $[\mathbf{C10}]_A$ from $[\mathbf{C10}]_B$.

PPi exchange assay

[0702] The PPi exchange assay was performed in 1x AARS buffer containing 50 mM Hepes-KOH (pH 8.0), 30 mM $MgCl_2$ and 30 mM KCl supplemented with 2 mM ATP and [^{32}P] PPi (10^5 cpm/μmol), 2 mM leucine and 7 nM recombinant Cdc60p. Experiments were also performed in the presence or absence of **C10** (15 μM) and tRNA (16 μM). After a 20 minute incubation at 30°C, reactions were initiated by the addition of ATP. At various time intervals, 45μL of reaction mixture was added to 100 μL of 2% perchloric acid and 0.1 M $Na_4P_2O_7$ to quench the reaction. Radioactive ATP was then absorbed to activated charcoal by the addition of 30 μL of a 5% suspension of acid-washed Norit A. This mixture was filtered though GF/C glass filters and washed 2x with 200 μL of distilled water then 1x with 200 μL of 95% ethanol. Filters were dried and scintillation counted using a Wallac MicroBeta Trilux model 1450 liquid scintillation counter.

Synthesis of Tritiated Mischarged $tRNA_{leu}$

[0703] The [^{3}H]-isoleucine mischarged tRNAleu was synthesized by incubating 1 μM of *Saccharomyces cerevisiae* editing defective Cdc60p (C326F) in 500 μL of 50mM Tris-HCl (pH 8.0), 60mM $MgCl_2$, 4mM ATP, 1mM DTT, 0.02% (w/v) BSA, 16 μM brewer's yeast tRNA (Roche), 0.1mM isoleucine and 5 mCi L-[4,5-3H]isoleucine (100Ci/mmole, GE Healthcare) and 20% (v/v) DMSO for 1 hour at 30°C. The reaction was stopped by adding 10 μL of 10% (v/v) acetic acid followed by two acidic phenol (Sigma) extractions. The mischarged tRNA in the top aqueous phase was removed and precipitated by adding two volumes of 96% (v/v) ethanol and incubating at -20°C for 30 minutes. The precipitate was pelleted by centrifugation at 13,200 xg for 30 minutes and the mischarged tRNA pellet was washed twice with 70% (v/v) ethanol and then resuspended in 50 mM potassium phosphate buffer pH 5.2.

Post-transfer Editing Assay

[0704] The [^{3}H]-isoleucine mischarged tRNAleu substrate, 40nM, was added to 50mM Hepes-KOH pH 8.0, 30mM KCl, 30mM $MgCl_2$, 0.02% (w/v) BSA, 1mM DTT, 2.4 nM *S. cerevisiae* Cdc60p at 30°C to start the reaction and 20 μL aliquots,

taken at set time points, were added to ice cold 200 μL 10% (w/v) trichloroacetic acid (TCA). The TCA precipitates were washed twice with 200 μl ice cold 5% (w/v) TCA and filtered through a Multiscreen HTS HA filter (Millipore). Optiphase (Perkin Elmer) scintillation cocktail was added to the filters and the TCA precipitate was counted in a Wallac MicroBeta Trilux model 1450 liquid scintillation counter.

EXAMPLE 45

Assay for determining that compounds inhibit ARS synthesis activity.

[0705] Aminoacylation assays were perfomed to determine the rate of net leucine/$tRNA^{Leu}$ synthesis by leucyl tRNA synthetase. Experiments were performed in 500 ul reaction mixtures containing1x AARS buffer (50 mM Hepes-KOH (pH 8.0), 30 mM $MgCl_2$ and 30 mM KCl) supplemented with 20 uM [14C]-leucine (Perkin-Elmer, 11.32 GBq/mmol.), 16 uM crude yeast tRNA, 0.02 % BSA, 1 mM dithiothreitol, 2 nM recombinant yeast LeuRS (CDC60) and 2 mM ATP. Reactions were performed at 30 deg Celsius. At time zero reactions were started by the addition of ATP. At various time intervals, 20 ul aliquots were added to 150 ul of 10% trichloroacetic acid (TCA) within a single well of a 96-well nitrocelluse membrane filterplate (Millipore Multiscreen HTS, MSHAN4B50). Each well was then washed 3x with 100 ul of 5% TCA. Filterplates were then dried under a heat lamp and the precipitated [14C]-leucine/$tRNA^{Leu}$ complexes were quantified by liquid scintillation counting using a Wallac MicroBeta Trilux model 1450 liquid scintillation counter. The inhibitory effects of boron-containing compounds, was determined by addition of up to a 100 uM of the compound in the reaction mixture for 20 minutes prior to the addition of ATP.

EXAMPLE 46

Test Article and Dosage Formulation

[0706] **C10** (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole), 5-fluoro-1,3-dihydro-1- phenyl-2,1-benzoxaborole, **C1** (5-chloro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole), and 5-fluoro-1,3-dihydro-1-(3-hydroxymethylphenyl)-2,1-benzoxaborole were obtained from Anacor Pharmaceuticals, Inc. (Palo Alto, CA). [^{14}C]-**C10** was synthesized by Amersham Biosciences UK Limited (Buckinghamshire HP& 9NA, UK) radiochemical purity and specific activity of >99.3% and 55 mCi/mmol, respectively.

[0707] Penlac™ nail lacquer (ciclopirox 8% topical solution) was manufactured by Dermik (Berwyn, PA). [^{14}C]-Ciclopirox (pyridinone-6-(^{14}C)-ciclopirox) was synthesized by PerkinElmer Life and Analytical Sciences (Boston, MA). The radiochemical purity and specific activity of the chemical was >95% and 12.5 mCi/mmol, respectively.

Experiment 1: Screening Four Oxaborole Compounds

[0708] **C10**, 5-fluoro-1,3-dihydro-1- phenyl-2,1-benzoxaborole, **C1**, and 5-fluoro-1,3-dihydro-1-(3-hydroxymethylphenyl)-2,1-benzoxaborole, formulated at 10%w/v in ethanol, were tested. A single aliquot (10 µl) of each formulation was dosed to the top of human nail plates using the nail penetration procedure described below, and allowed to stand for 3-days. The dosed area was washed, and then the cotton ball bed supporting the nail and the nail samples were collected at the end of the incubation period, stored at 4 °C and analyzed for drug using LC/MS/MS.

Experiment 2: Effect of Vehicle on **C10** Nail Penetration

[0709] The following formulations, all containing 10% **C10** were tested. Formulation A: 70% ethanol, 20% poly (vinyl methyl ether alt maleic acid monobutyl ester (v/v); Formulation B: 6% ethanol, 14% water, 15% poly (2-hydroxyethyl methacrylate), 5% dibutyl sebacate (v/v); Formulation C: 55% ethanol, 15% ethyl acetate, 15% poly (vinyl acetate), 5% dibutyl sebacate (v/v); Formulation D: 20%propylene glycol, 70% ethanol (v/v). Using the nail penetration procedure described below, aliquots (10 µL) of the dose formulations were applied to human nail plates once per day for 14 days with a daily wash before dosing. The cotton ball bed supporting the nail was collected from each cell chamber and replaced with a new one at day 5, 10, and 15 after the first dose. The nail samples were collected at the end of the 14-day dose period, stored at 4 °C and analyzed for drug by LC/MS/MS.

Experiment 3: Penetration of **C10** following a 14-day multiple dose treatment

[0710] Two test articles, **C10**, 10% in propylene glycol and ethanol (1:4, v/v) and ciclopirox, 8% in Penlac™ nail lacquer were compared for their penetration rate into and through the human nail plate. Trace amounts of carbon-14 radiolabelled **C10** and ciclopirox were added to their respective formulations the day before the first dose. Using the nail penetration procedure described below, aliquots (10 µl) of the dose formulations were applied to human nail plates once per day for 14 days with a

washing before each dose. The cotton ball bed supporting the nail was collected from each cell chamber and replaced with a new one every 72 hours after the first dose (days 3, 6, 9, 12, and 15). The nail samples were collected at the 14-day dose period. The radioactivity of all samples was analyzed and compared.

Nail Penetration Procedure

[0711] Details of the nail incubation have been previously described [9, 10]. Briefly, a healthy finger nail plate was mounted in a one-chamber diffusion cell (Figure 1, Permegear, Inc., Hellertown, PA) with the nail surface (top center) open to the air and the inner surface in contact with a small cotton ball acting as a supporting nail bed. The supporting cotton ball under the nail was wetted by normal saline providing moisture for the nail plate, and the degree of hydration was monitored and controlled during the experiment. The incubation period started 24 hours prior to the first dose, and ended 24 hours after the final dose. Aliquots (10 μL) were applied to the surface of the nail plate once daily.

[0712] Dosed surface area washing was conducted at the end of incubation period (for single dose study), or each morning before dosing starting on the second day (multiple dose study). The dosed surface area of the nail was washed with cotton tips in a cycle, as follows: two times with ethanol, then with 50% Ivory® liquid soap (Procter & Gamble, Cincinnati, Ohio), then two times with distilled water. The washing samples from each cycle were pooled and the radioactivity was measured. After completion of the dosing and the incubation phase, the nail plate was transferred to a cutting holder for sampling. Under the controlled humidity and temperature, we did not observe any abnormal situations such as the nail plate color change, hydration changes, or fungal growth during the 14-day dosing period. The nail plate was secured in position so that the outer dorsal-dosed surface faced the holder. The cutting holder was moved to bring the plate surface just barely in contact with the cutter tip. The drill was then started and a fine adjustment moved the stage toward the cutter tip, removing a powder sample from the nail. In this way, a hole approximately 0.3-0.4mm in depth and 7.9 mm in diameter was drilled in each nail, enabling the harvest of powder sample from the center of each nail's ventral surface. These samples are referred to as samples taken from the "ventral/intermediate nail plate center". Then the nail outside the dosing area (and also the sampling area) was cut away and saved as the "remainder nail plate". The layer above the powder sampling

area was also saved as "the dorsal/intermediate center". All the nail plate samples were individually collected into a glass scintillation vial and weighed.

Quantitative Analysis of Oxaboroles

[0713] LC/MS/MS (API3000, Applied Biosystems, Foster City, CA) was used to quantitate the amounts of non-radiolabeled oxaboroles, **C10**, 5-fluoro-1,3-dihydro-1-phenyl-2,1-benzoxaborole, **C1**, and 5-fluoro-1,3-dihydro-1-(3-hydroxymethylphenyl)-2,1-benzoxaborole in samples from the nail penetration studies. For the cotton ball analysis eleven calibration standards were prepared fresh in normal saline. A volume of 100 µL of each standard was spiked onto a fresh cotton ball with final calibration standard concentrations of 0, 2.5, 5, 10, 20, 40, 80, 160, 320, 640, 1280, and 2560 µg/mL. Acetonitrile (Burdick & Jackson, Muskegon, MI) containing the internal standard p-nitrophenol (PNP) was added to all cotton balls. The cotton ball samples and any residual solvent were transferred to centrifuge filter tubes. After centrifugation, the filtrate from the cotton ball samples was transferred to autosampler vials and analyzed by LC/MS/MS. For the ciclopirox samples, the filtrate was first derivatized with dimethylsulfate according to a previously described method before analysis by LC/MS/MS (Myoung and Choi, 2003). Samples with calculated concentrations above the highest calibration standard were diluted 10- or 20-fold with acetonitrile containing internal standard p-Nitrophenol (TCI America, Portland, OR). For the nail analysis, two separate calibration curves were prepared, one for nail powder analysis and one for top of the nail analysis. Each curve contained eleven calibration standards. Standards were first prepared in dimethylsulfoxide. A volume of 10 µL of each standard was spiked onto keratin powder (6.5 mg for nail powder curve and 17 mg for top of the nail curve). Nail samples were digested with 1N NaOH overnight at 45 °C. The next morning, before extraction with methylenechloride, the pH of the samples was adjusted to pH 3. After extraction, the organic layer was transferred and evaporated. Samples were reconstituted in acetonitrile and analyzed by LC/MS/MS using an Eclipse XDB-C18 5 µm, 2.1 x 50 mm column (Agilent, Wilmington, DE) and a gradient mobile phase from 5 mM ammonium acetate and acetonitrile.

Radioactivity Measurement

[0714] All radioactivity measurements were conducted with a Model 1500 Liquid Scintillation Counter (Packard Instrument Company, Downer Grove, IL). The

counter was audited for accuracy using sealed samples of quenched and unquenched standards as detailed by the instrument manual. The ^{14}C counting efficiency is equal to or greater than 95%. All nail samples pre-treated with Packard soluene-350 were incubated at 40°C for 48 hours followed by the addition of 10 mL scintillation cocktail (HIONIC-FLUOR, Packard Instrument Company, Meriden, CT). Other samples (standard dose, surface washing, and bedding material) were mixed directly with Universal ES scintillation cocktail (ICN Biomedicals, Costa Mesa, CA). Background control and test samples were counted for radioactivity for 3 minutes each.

Calculations and Data Analysis

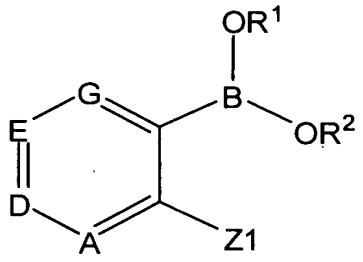
[0715] Quantitation of non-radioactive compounds was based on peak area ratios of compound to internal standard. The method of regression for the calibration curves was selected based on the best fit. Linear and quadratic regression was used with 1/x or 1/x squared weighting. All integrations were performed using Analyst version 1.3 (Applied Biosystems, Foster City, CA). The concentrations of compound in the cotton balls were converted to absolute amounts by taking the sample volume of 100 µl into account. The amount of compound in the nail powder and top of the nail were adjusted for their respective weights and reported in µg/mg.

[0716] The individual and mean (± S.E.) amount of test chemical equivalent in nail, bedding material, and wash samples are presented as dpm, µCi, percent administered dose, and mg equivalent at each time point. The concentration of ^{14}C-labeled test chemicals were calculated from the value based on the specific activity of each [^{14}C]-labeled test chemical. The information of concentration of non-labeled test chemical in the topical formulation was obtained from the manufacturers. The total concentration of test chemical equivalent is the sum of the concentration of ^{14}C-labeled test chemical and the concentration of non-labeled test chemical. The value of the total amount of test chemical equivalent in each nail sample was calculated from those values based on the radioactivity of the sample and the ratio of total mg test chemical equivalent and radioactivity of the test chemical. The data was further normalized by dividing by the weight of the sample. Statistical significant of nail samples from every two groups was analyzed by student t-test.

[0717] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A compound having a structure according to the following formula:

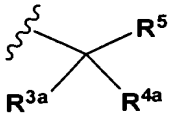


in which

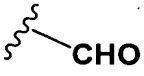
R^1 and R^2 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

wherein R^1 and R^2, together with the atoms to which they are attached, can be optionally joined to form a 4- to 7- membered ring;

Z1 is a member selected from



and



wherein

R^{3a} and R^{4a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R^5 is a member selected from halogen and OR^8

wherein

R^8 is a member selected from H, substituted or unsubstituted

alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

A is a member selected from CR^{9a} and N;

D is a member selected from CR^{10a} and N;

E is a member selected from CR^{11a} and N;

G is a member selected from CR^{12a} and N;

wherein

R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R^*$, $-S(O)_2NR^*R^{**}$, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

wherein each R* and R** are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

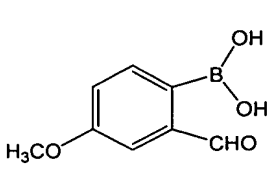
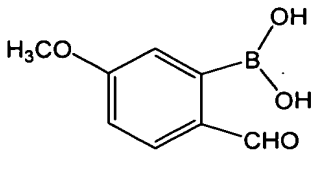
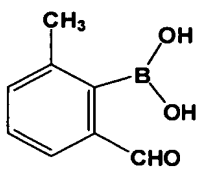
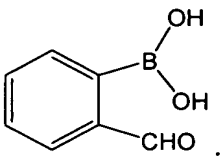
wherein R^{9a} and R^{10a}, along with the atoms to which they are attached, are optionally joined to form a ring;

wherein R^{10a} and R^{11a}, along with the atoms to which they are attached, are optionally joined to form a ring;

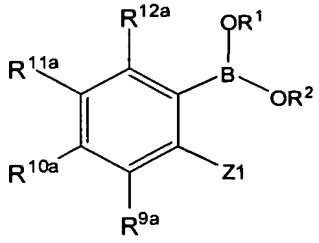
wherein R^{11a} and R^{12a}, along with the atoms to which they are attached, are optionally joined to form a ring;

the combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3

with the proviso that the compound is not a member selected from:




and  .

2. The compound of claim **1**, wherein said compound has a structure according to Formula (IX)



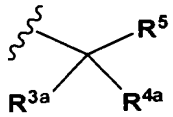
(IX).

3. The compound of claim **1**, wherein said R^1 and R^2 are each members independently selected from H, substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted butyl, substituted or unsubstituted t-butyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl

and wherein R^1 and R^2, together with the atoms to which they are joined, can optionally form a member selected from substituted or unsubstituted dioxaborolane, substituted or unsubstituted dioxaborinane and substituted or unsubstituted dioxaborepane.

4. The compound of claim **3**, wherein said R^1 and R^2, together with the atoms to which they are joined, form a member selected from dioxaborolane, substituted or unsubstituted tetramethyldioxaborolane, substituted or unsubstituted phenyldioxaborolane, dioxaborinane, dimethyldioxaborinane and dioxaborepane.

5. The compound of claim **1**, wherein Z1 is a member selected from



and R^5 is a member selected from substituted or unsubstituted methoxy, substituted or unsubstituted ethoxy, substituted or unsubstituted methoxymethoxy, substituted or

unsubstituted ethoxyethoxy and substituted or unsubstituted tetrahydro-2H-pyran-2-yloxy.

6. The compound according to claim **1**, wherein said R^{3a} is H and R^{4a} is a member selected from methyl, ethyl, propyl, butyl, phenyl, benzyl and cyano.

7. The compound according to claim **1**, wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted

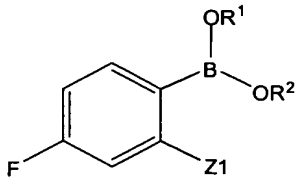
pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl.

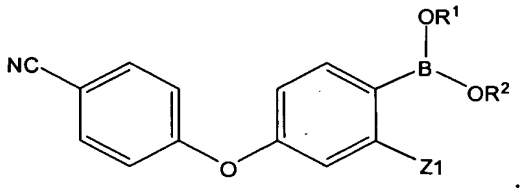
8. The compound according to claim **1**, wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-

fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

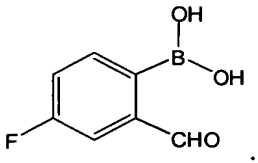
9. The compound according to claim **8**, wherein R^{9a} is H and R^{12a} is H.

10. The compound according to claim **9**, wherein said compound is a member selected from



and


11. The compound according to claim **10**, wherein said compound is a member selected from



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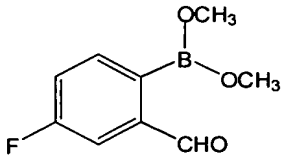

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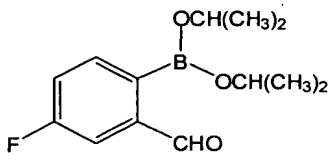

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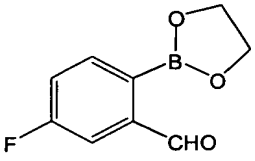

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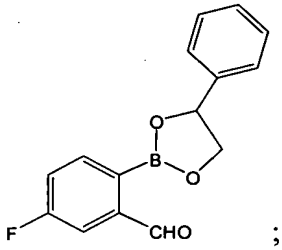

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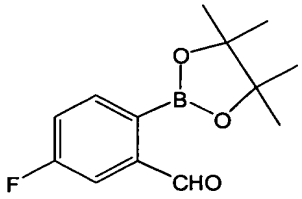

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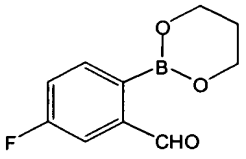

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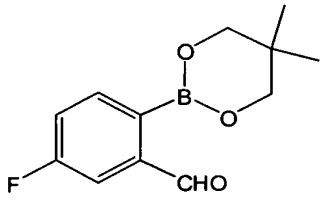

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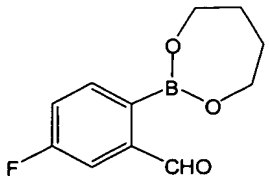

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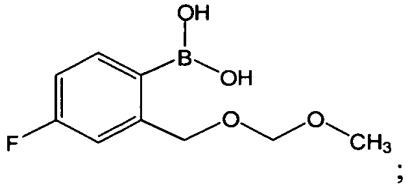

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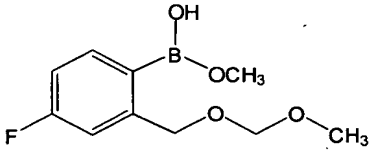

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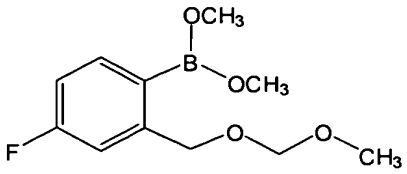
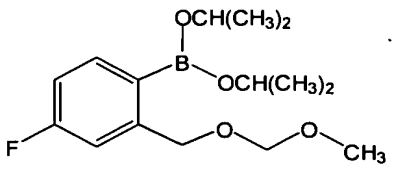
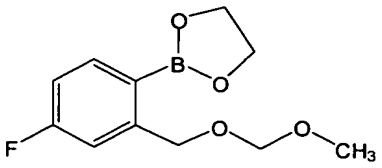
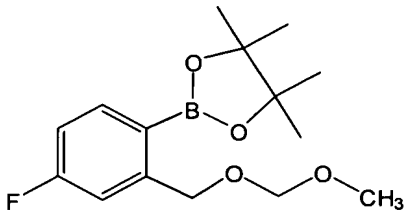
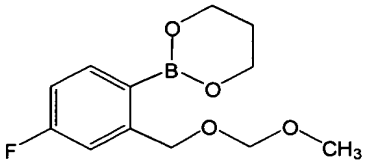
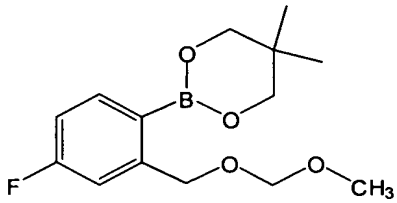
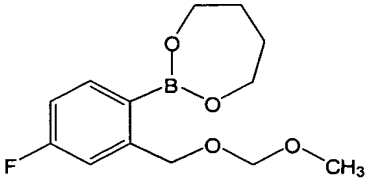
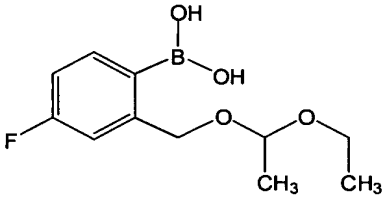
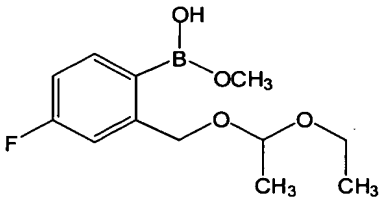
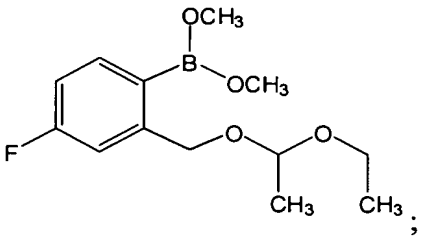
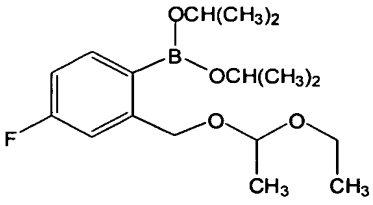
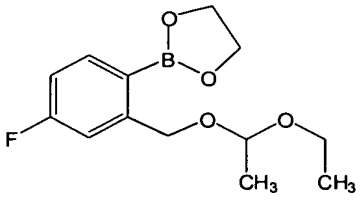
7  ;  ;

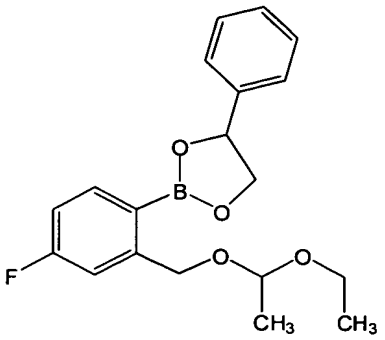
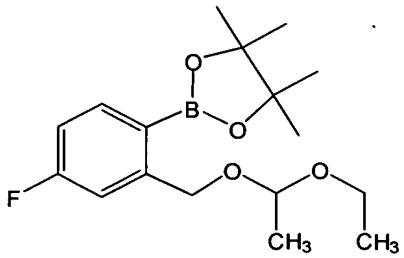
8  ;  ;

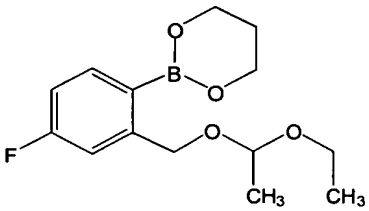
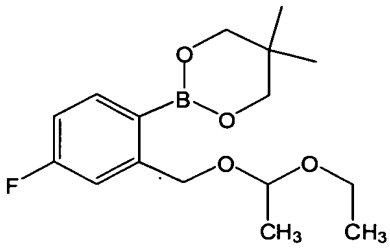
9  ;  ;

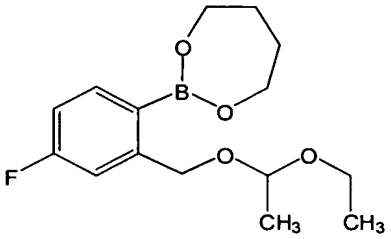
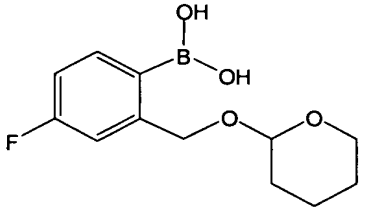
10  ;  ;

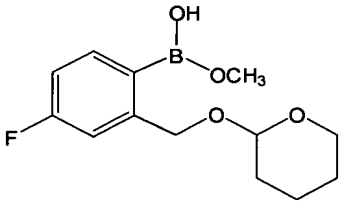
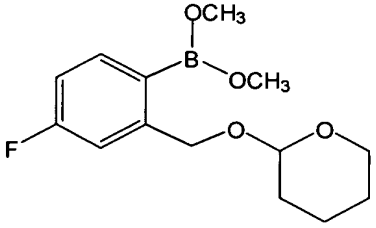
11  ;  ;

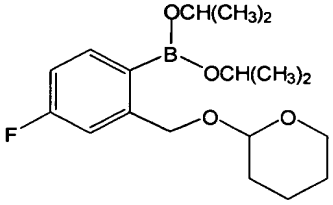
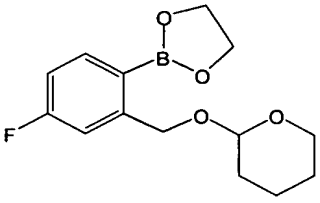
12  ;  ;

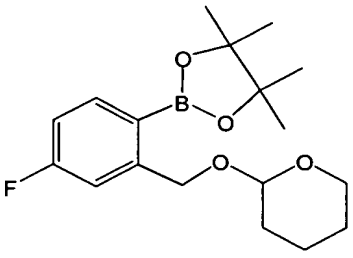
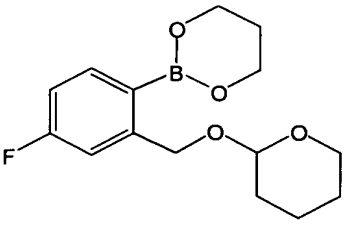
13  ;  ;

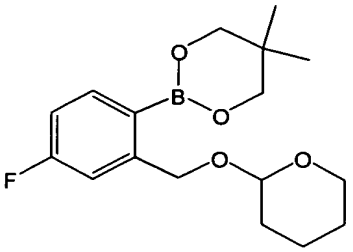
14  ;  ;

15  ;  ;

16  ;  ;

17  ;  ;

18  ;  ;



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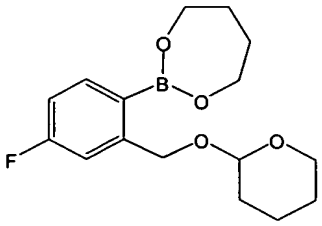
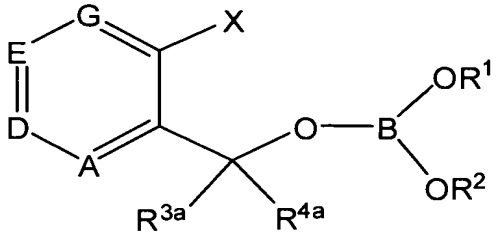


12. A compound having a structure according to the following formula:



in which

R^1 and R^2 are each members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

wherein R^1 and R^2, along with the atoms to which they are attached, are optionally joined to form a ring;

R^{3a} and R^{4a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; and

X is a member selected from bromo, iodo, triflate and diazo;

A is a member selected from CR^{9a} and N;

D is a member selected from CR^{10a} and N;

E is a member selected from CR^{11a} and N;

G is a member selected from CR^{12a} and N;

wherein

R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R$*, $-S(O)_2$NR*R**,

nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

wherein each R* and R** are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

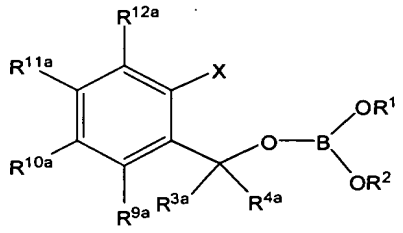
wherein R^{9a} and R^{10a}, along with the atoms to which they are attached, are optionally joined to form a ring;

wherein R^{10a} and R^{11a}, along with the atoms to which they are attached, are optionally joined to form a ring;

wherein R^{11a} and R^{12a}, along with the atoms to which they are attached, are optionally joined to form a ring;

the combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3.

13. The compound of claim **12**, wherein said compound has a structure according to Formula (Xa)



(Xa).

14. The compound according to claim **12**, wherein said R^1 and R^2 are each members independently selected from H, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, phenyl and benzyl

and wherein R^1 and R^2, together with the atoms to which they are joined, can optionally form a member selected from substituted or unsubstituted substituted or unsubstituted dioxaborolane, substituted or unsubstituted dioxaborinane, and substituted or unsubstituted dioxaborepane.

15. The compound according to claim **12**, wherein X is a member selected from iodo and bromo.

16. The compound according to claim **12**, wherein said R^{3a} and R^{4a} are each members independently selected from H, methyl, ethyl, propyl, butyl, phenyl, benzyl and cyano.

17. The compound according to claim **12**, wherein said R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino,

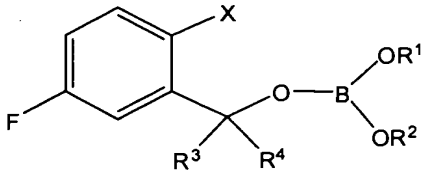
substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl.

18. The compound according to claim **12**, wherein said R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-

cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

19. The compound according to claim **18**, wherein R^{9a} is H and R^{12a} is H.

20. The compound according to claim **19**, wherein said compound has a structure which is a member selected from



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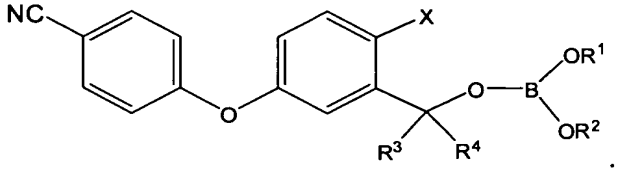
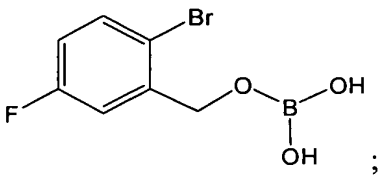


21. The compound according to claim **20**, wherein said compound has a structure which is a member selected from



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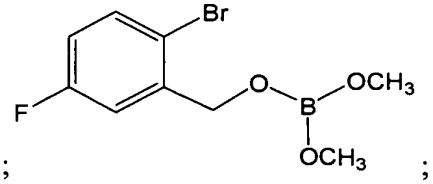

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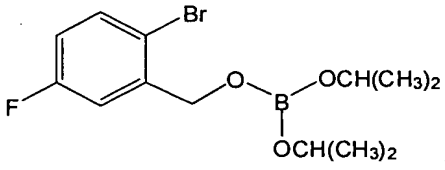

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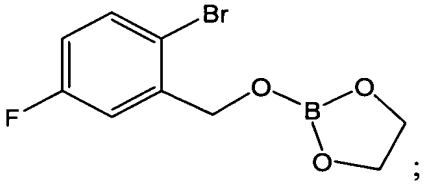

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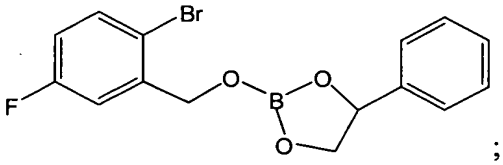

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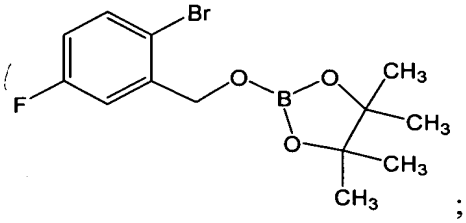

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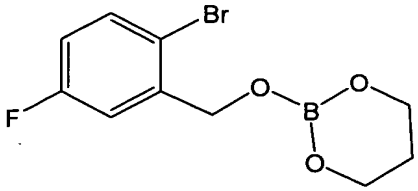

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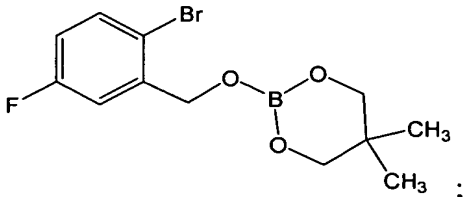

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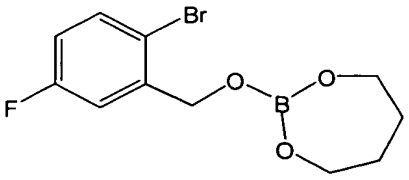

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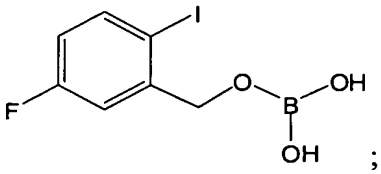

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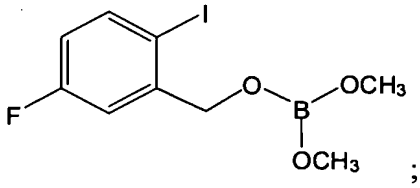
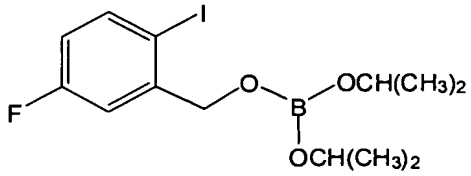
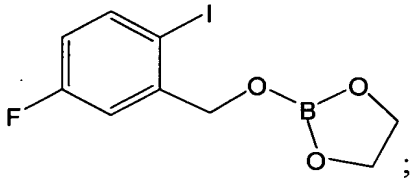
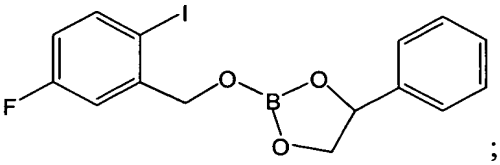
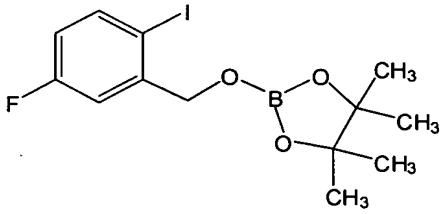
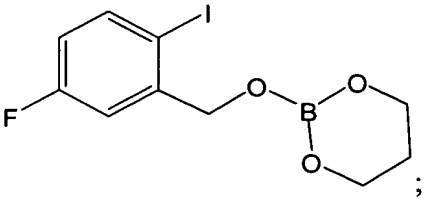
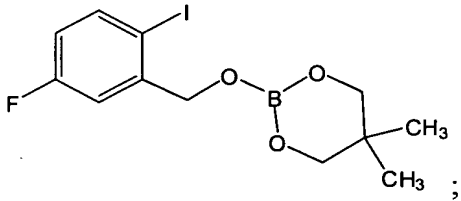
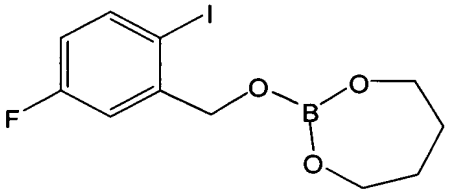
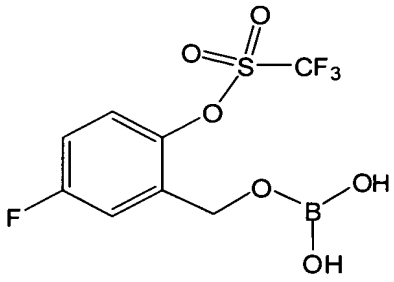
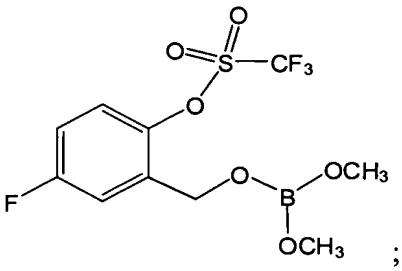
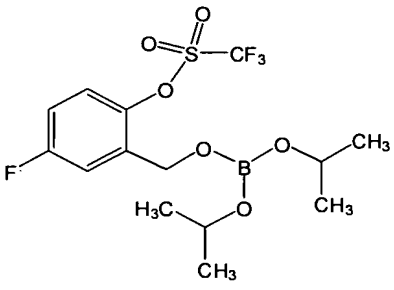
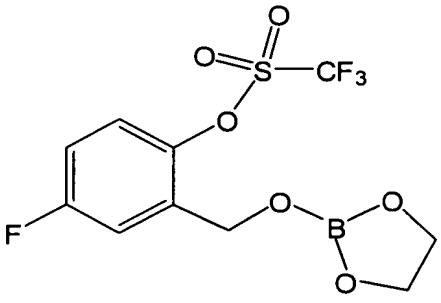
8  ;  ;

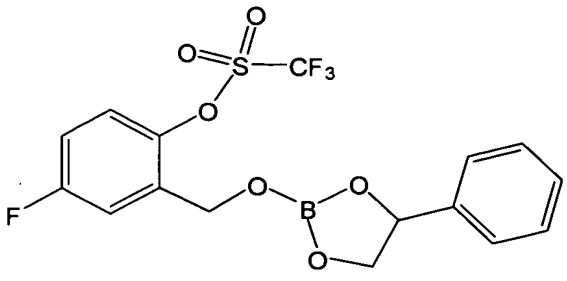
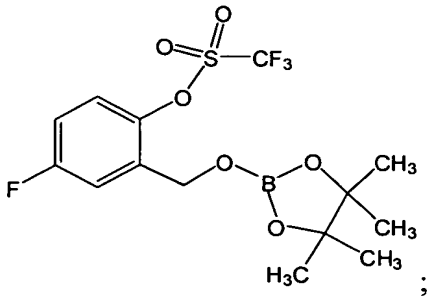
9  ;  ;

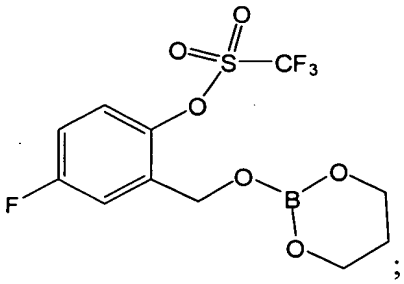
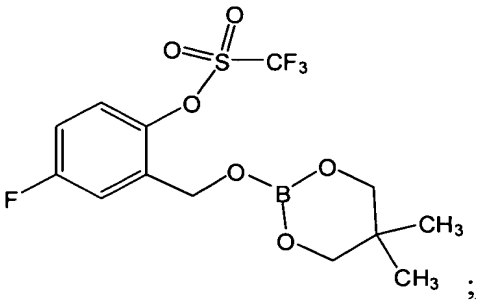
10  ;  ;

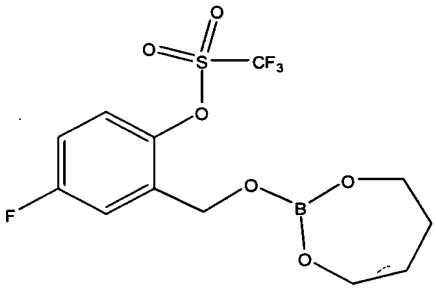
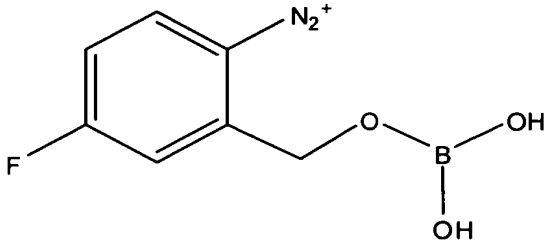
11  ;  ;

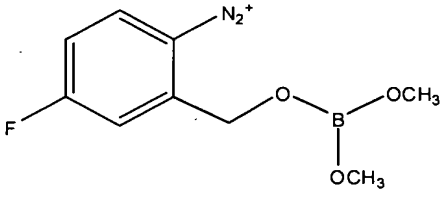
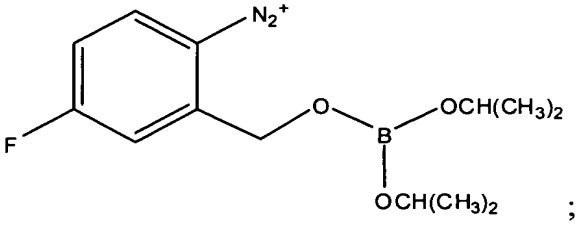
12  ;  ;

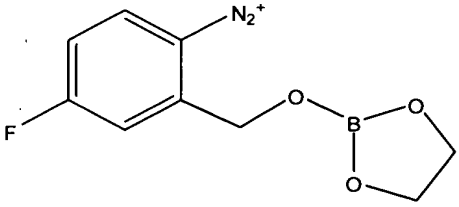
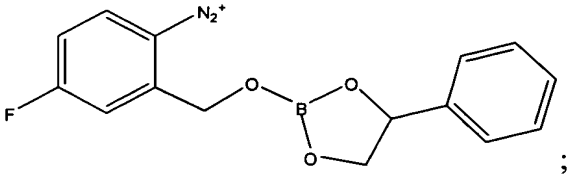
13  ;  ;

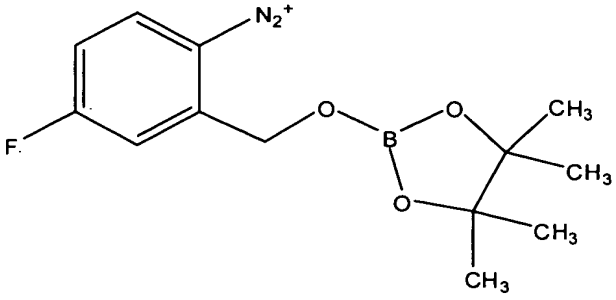
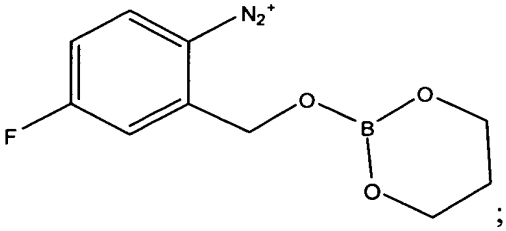
14  ;  ;

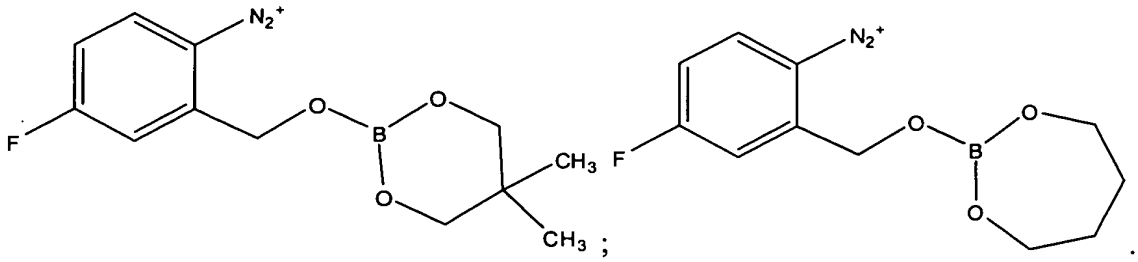
15  ;  ;

16  ;  ;

17  ;  ;

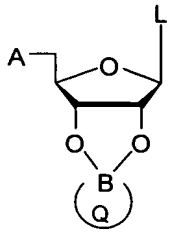
18  ;  ;

19  ;  ;



;

22. A compound having a structure according to the following formula:

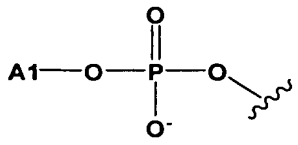


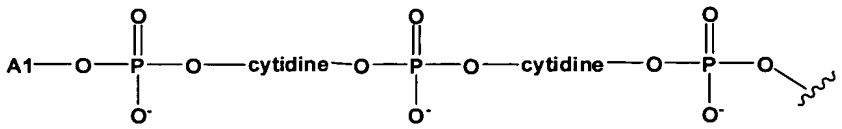
wherein

B is boron;

L is a member selected from OR^7, substituted or unsubstituted purine, substituted or unsubstituted pyrimidine, substituted or unsubstituted pyridine and substituted or unsubstituted imidazole;

wherein R^7 is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

A is a member selected from OH, substituted or unsubstituted monophosphate, substituted or unsubstituted diphosphate, substituted or unsubstituted triphosphate,  , and



;

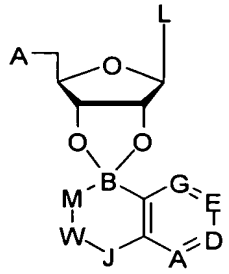
wherein

A1 is a nucleic acid sequence which comprises between 1 and 100 nucleotides;

Q is a member selected from substituted or unsubstituted heterocycloalkyl and substituted or unsubstituted heteroaryl; and

said Q comprises said boron and at least one oxygen.

23. The compound according to claim **22**, wherein said compound has a structure according to the following formula:



M is a member selected from O and S

J is a member selected from $(CR^{3a}R^{4a})_{n1}$ and CR^{5a}

wherein

R^{3a}, R^{4a}, and R^{5a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

n1 is an integer selected from 0 to 2;

W is a member selected from C=O (carbonyl), $(CR^{6a}R^{7a})_m$ and CR^{8a};

wherein

R^{6a}, R^{7a}, and R^{8a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, and substituted or unsubstituted heteroaryl;

m is an integer selected from 0 and 1;

A is a member selected from CR^{9a} and N;

D is a member selected from CR^{10a} and N;

E is a member selected from CR^{11a} and N;

G is a member selected from CR^{12a} and N;

wherein

R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, -$S(O)_2$R*, -$S(O)_2$NR*R**, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

wherein each R* and R** are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

the combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3;

a member selected from R^{3a}, R^{4a} and R^{5a} and a member selected from R^{6a}, R^{7a} and R^{8a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{3a} and R^{4a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

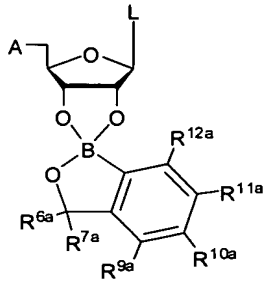
R^{6a} and R^{7a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{9a} and R^{10a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

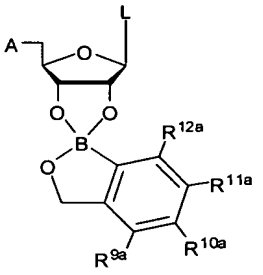
R^{10a} and R^{11a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{11a} and R^{12a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

24. The compound according to claim **22** wherein said compound has a structure according to the following formula:



25. The compound according to claim **22**, wherein said compound has a structure according to the following formula:



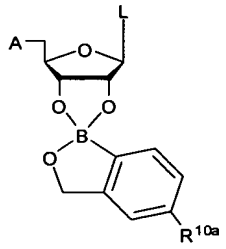
26. The compound according to claim **22**, wherein said R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted

benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl.

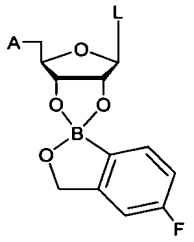
27. The compound according to claim **22**, wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-

indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

28. The compound according to claim **27**, wherein said compound has a structure according to



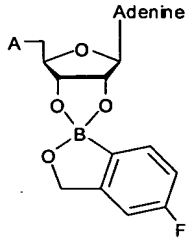
29. The compound according to claim **28**, wherein said compound has a structure according to the following formula:

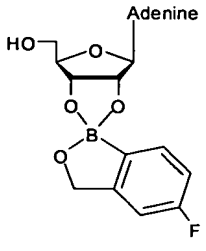


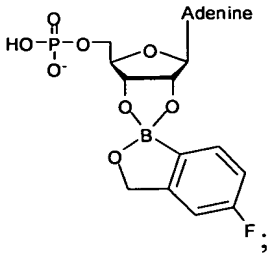
30. The compound according to claim **22**, wherein said L is a member selected from substituted or unsubstituted adenine, substituted or unsubstituted guanine, substituted or unsubstituted cytidine, substituted or unsubstituted uracil, and substituted or unsubstituted thymine.

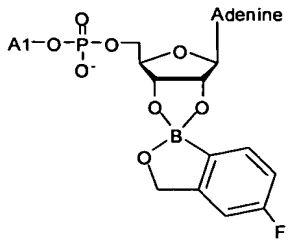
31. The compound according to claim **30**, wherein L is adenine.

32. The compound according to claim **31**, wherein the structure is a member selected from

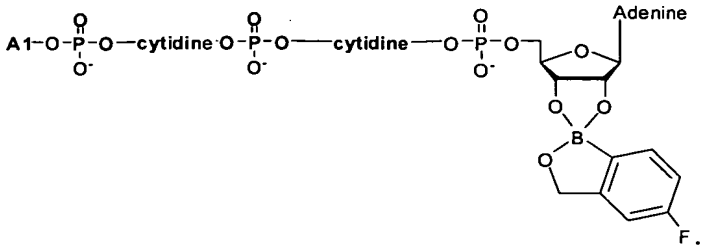


;


;


;


and



33. The compound according to claim **32**, wherein said A1 is the nucleic acid sequence for a tRNA, or a portion of a tRNA, and said t-RNA has a sequence which is a member selected from SEQ ID NO 18-62.

34. The compound according to claim **33**, wherein said tRNA, or the portion of a tRNA, is a leucyl tRNA.

35. The compound of claim **22**, further comprising a tRNA synthetase, wherein said compound is noncovalently attached to the editing domain of said tRNA synthetase.

36. The compound of claim **22**, wherein said compound is present in a microorganism, with the proviso that the microorganism is not a member selected from *Saccharomyces cerevisiae*, *Aspergillus niger*, *Pseudomonas aeruginosa*, *Staphlococcus aureus*, *Aureobasidium pullulans*, *Fusarium solani*, *Penicillium pinophilum*, *Scopulariopsis brevicaulis*, *Streptoverticillium waksmanii*, *Alternaria alternata*, *Cladosporium herbarum*, *Phoma violacea*, *Stemphylium dentriticum*, *Candida albicans*, *Escherichia coli*, and *Gliocladium roseum*.

37. The compound of claim **22**, wherein said compound is present is a fungus, with the proviso that the fungus is not a member selected from

Saccharomyces cerevisiae, *Aspergillus niger*, *Aureobasidium pullulans*, *Fusarium solani*, *Pepicillium pinophylum*, *Scopulariopsis brevicaulis*, *Alternaria alternata*, *Cladosporium herbarum*, *Phoma violacea*, *Stemphylium dentriticum*, *Candida albicans* and *Gliocladium roseum*.

38. The compound of claim **22**, wherein said compound is present in a member selected from a dermatophyte, *Trichophyton* spp., *Microsporum* spp., *Epidermophyton* spp., and yeast-like fungi.

39. The compound of claim **36**, wherein said microorganism is a member selected from *Trichophyton* spp..

40. The compound of claim **39**, wherein said microorganism is a member selected from *T. rubrum* and *T. menagrophytes*.

41. The compound of claim **22**, wherein said compound is present in a human or an animal.

42. The compound of claim **41**, wherein said compound is present in a microoganism which is present in a nail component of a human or a nail, hoof, or horn component of an animal.

43. The compound of claim **22**, wherein said compound is present in a member selected from a dermatophyte, *Trichophyton* spp., *Microsporum* spp., *Epidermophyton* spp., and yeast-like fungi.

44. The compound of claim **36**, wherein said microorganism is a member selected from *Trichophyton* species.

45. The compound of claim **44**, wherein said microorganism is a member selected from *T. rubrum* and *T. menagrophytes*.

46. A method of killing or inhibiting growth of a microorganism present in a human nail component, wherein said human nail component comprises a nail plate, said method comprising:

contacting a dorsal layer of the nail plate with a compound capable of penetrating the nail plate and contacting said microorganism, under conditions sufficient for said compound to penetrate said nail plate, wherein

said compound has an MIC of less than 16 μg/mL against said microorganism;

said compound has a molecular weight of between about 100 and about 200 Da;

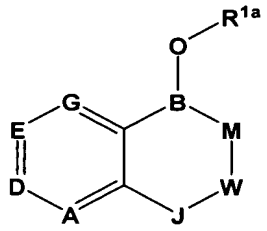
said compound has a log P value of between about 1.0 and about 2.6;

said compound has a water solubility greater than about 0.1 mg/mL

thereby killing or inhibiting the growth of said microorganism.

47. The method of claim **46**, wherein said compound comprises a boron-containing compound.

48. The method of claim **46**, wherein said compound has a structure according to the following formula:



(I)

wherein B is boron;

R^{1a} is a member selected from a negative charge, a salt counterion, H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

M is a member selected from oxygen, sulfur and NR^{2a};

R^{2a} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

J is a member selected from $(CR^{3a}R^{4a})_{n1}$ and CR^{5a};

R^{3a}, R^{4a}, and R^{5a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

n1 is an integer selected from 0 to 2;

W is a member selected from C=O (carbonyl), $(CR^{6a}R^{7a})_{m1}$ and CR^{8a};

R^{6a}, R^{7a}, and R^{8a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

m1 is an integer selected from 0 and 1;

A is a member selected from CR^{9a} and N;

D is a member selected from CR^{10a} and N;

E is a member selected from CR^{11a} and N;

G is a member selected from CR^{12a} and N;

wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R^*$, $-S(O)_2NR^*R^{**}$, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

the combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3;

each R* and R** are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

a member selected from R^{3a}, R^{4a} and R^{5a} and a member selected from R^{6a}, R^{7a} and R^{8a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{3a} and R^{4a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{6a} and R^{7a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{9a} and R^{10a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{10a} and R^{11a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{11a} and R^{12a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

49. The method according to claim **48**, wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino,

substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl.

50. The method according to claim **48**, wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-

yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

51. The method according to claim **49**, wherein R^{9a} is H and R^{12a} is H.

52. The method according to claim **48**, wherein said compound is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

53. A method of treating a disease caused by a microorganism present in a human nail component, wherein said human nail component comprises a nail plate, said method comprising:

contacting a dorsal layer of the nail plate with a compound capable of penetrating the nail plate and contacting said microorganism, under conditions sufficient for said compound to penetrate said nail plate and to treat said disease,

wherein

said compound has an MIC of less than 16 μg/mL against said microorganism;

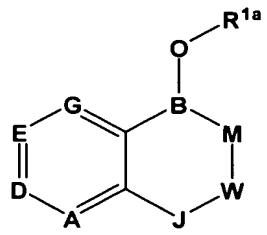
said compound has a molecular weight of between about 100 and about 200 Da;

said compound has a log P value of between about 1.0 and about 2.6;

said compound has a water solubility greater than about 0.1 mg/mL

thereby treating said disease.

54. The method of claim **53**, wherein said compound has a structure according to the following formula:



(I)

wherein B is boron;

R^{1a} is a member selected from a negative charge, a salt counterion, H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

M is a member selected from oxygen, sulfur and NR^{2a};

R^{2a} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

J is a member selected from $(CR^{3a}R^{4a})_{n1}$ and CR^{5a};

R^{3a}, R^{4a}, and R^{5a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

n1 is an integer selected from 0 to 2;

W is a member selected from C=O (carbonyl), $(CR^{6a}R^{7a})_{m1}$ and CR^{8a};

R^{6a}, R^{7a}, and R^{8a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

m1 is an integer selected from 0 and 1;

A is a member selected from CR^{9a} and N;

D is a member selected from CR^{10a} and N;

E is a member selected from CR^{11a} and N;

G is a member selected from CR^{12a} and N;

wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, -$S(O)_2$R*, -$S(O)_2$NR*R**, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

the combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3;

each R* and R** are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

a member selected from R^{3a}, R^{4a} and R^{5a} and a member selected from R^{6a}, R^{7a} and R^{8a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{3a} and R^{4a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{6a} and R^{7a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{9a} and R^{10a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{10a} and R^{11a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{11a} and R^{12a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

55. The method according to claim **54**, wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or

unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl.

56. The method according to claim **54**, wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl)

phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

57. The method according to claim **55**, wherein R^{9a} is H and R^{12a} is H.

58. The method according to claim **54**, wherein said compound is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

59. A method of delivering a compound from the dorsal layer of the nail plate to the nail bed, said method comprising:

contacting said dorsal layer of the nail plate with a compound capable of penetrating the nail plate, under conditions sufficient to penetrate said nail plate,

wherein

said compound has an efficacy coefficient above 10

thereby delivering said compound.

60. The method of claim **59**, wherein said compound comprises boron.

61. A method of treating a disease caused by a microorganism present in a human nail component, wherein said human nail component comprises a nail plate, said method comprising:

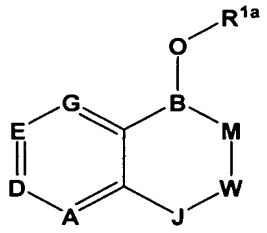
contacting a dorsal layer of the nail plate with a compound capable of penetrating the nail plate and contacting said microorganism, under conditions sufficient for said compound to penetrate said nail plate and to treat said disease;

wherein

said compound has an efficacy coefficient above 10

thereby treating said disease.

62. The method of claim **61**, wherein said compound has a structure according to the following formula:



(I)

wherein B is boron;

R^{1a} is a member selected from a negative charge, a salt counterion, H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

M is a member selected from oxygen, sulfur and NR^{2a};

R^{2a} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

J is a member selected from $(CR^{3a}R^{4a})_{n1}$ and CR^{5a};

R^{3a}, R^{4a}, and R^{5a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

n1 is an integer selected from 0 to 2;

W is a member selected from C=O (carbonyl), $(CR^{6a}R^{7a})_{m1}$ and CR^{8a};

R^{6a}, R^{7a}, and R^{8a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

m1 is an integer selected from 0 and 1;

A is a member selected from CR^{9a} and N;

D is a member selected from CR^{10a} and N;

E is a member selected from CR^{11a} and N;

G is a member selected from CR^{12a} and N;

wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R^*$, $-S(O)_2NR^*R^{**}$, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

the combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3;

each R* and R** are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

a member selected from R^{3a}, R^{4a} and R^{5a} and a member selected from R^{6a}, R^{7a} and R^{8a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{3a} and R^{4a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{6a} and R^{7a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{9a} and R^{10a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{10a} and R^{11a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{11a} and R^{12a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

63. The method according to claim **62**, wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or

unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino, substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl.

64. The method according to claim **62**, wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-

cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

65. The method according to claim **63**, wherein R^{9a} is H and R^{12a} is H.

66. The method according to claim **66**, wherein said compound is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

67. A formulation comprising:

(a) a compound which is a member selected from a boron-containing compound, a 2'-amino ribofuranose-containing compound, a 3'-amino ribofuranose-containing compound, and combinations thereof; and

(b) a keratin containing component which is a member selected from a human nail unit, skin and hair

wherein the compound of part (a) contacts the component of part (b).

68. The formulation of claim **67**, wherein said keratin containing component is a nail plate of the human nail unit.

69. The formulation of claim **67**, wherein said keratin containing component is a nail bed of the human nail unit.

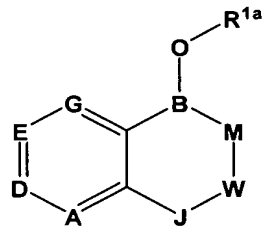
70. The formulation of claim **67**, wherein said compound is present in said formulation at a concentration which is a member selected from about 0.001%, 0.01%, about 0.05%, about 0.1%, about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%.

71. The formulation of claim **67**, wherein said keratin-containing component is present in said formulation at a concentration which is a member selected from about 99.999%, about 99.99%, about 99.95%, about 99.90%, about 99.5%, about 99.0%, about 98.5%, about 98.0%, about 97.5% and about 97%.

72. The formulation of claim **67**, wherein said compound is a boron-containing compound.

73. The formulation of claim **72**, wherein said boron-containing compound is a member selected from a cyclic boronic ester and a cyclic borinic ester.

74. The formulation of claim **67**, wherein said compound has a structure according to the following formula:



(I)

wherein B is boron;

R^{1a} is a member selected from a negative charge, a salt counterion, H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

M is a member selected from oxygen, sulfur and NR^{2a};

R^{2a} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

J is a member selected from $(CR^{3a}R^{4a})_{n1}$ and CR^{5a};

R^{3a}, R^{4a}, and R^{5a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and

substituted or unsubstituted heteroaryl;

n1 is an integer selected from 0 to 2;

W is a member selected from C=O (carbonyl), $(CR^{6a}R^{7a})_{m1}$ and CR^{8a};

R^{6a}, R^{7a}, and R^{8a} are members independently selected from H, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

m1 is an integer selected from 0 and 1;

A is a member selected from CR^{9a} and N;

D is a member selected from CR^{10a} and N;

E is a member selected from CR^{11a} and N;

G is a member selected from CR^{12a} and N;

wherein R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, $-S(O)_2R^*$, $-S(O)_2NR^*R^{**}$, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

the combination of nitrogens (A + D + E + G) is an integer selected from 0 to 3;

each R* and R** are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

a member selected from R^{3a}, R^{4a} and R^{5a} and a member selected from R^{6a}, R^{7a} and R^{8a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{3a} and R^{4a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{6a} and R^{7a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{9a} and R^{10a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{10a} and R^{11a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{11a} and R^{12a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

75. The formulation according to claim **74**, wherein said R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, halogen, cyano, nitro, substituted or unsubstituted methoxy, substituted or unsubstituted methyl, substituted or unsubstituted ethoxy, substituted or unsubstituted ethyl, trifluoromethyl, substituted or unsubstituted hydroxymethyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyloxy, substituted or unsubstituted phenyl methoxy, substituted or unsubstituted thiophenyloxy, substituted or unsubstituted pyridinyloxy, substituted or unsubstituted pyrimidinyloxy, substituted or unsubstituted benzylfuran, substituted or unsubstituted methylthio, substituted or unsubstituted mercaptomethyl, substituted or unsubstituted mercaptoalkyl, substituted or unsubstituted phenylthio, substituted or unsubstituted thiophenylthio, substituted or unsubstituted phenyl methylthio, substituted or unsubstituted pyridinylthio, substituted or unsubstituted pyrimidinylthio, substituted or unsubstituted benzylthiofuranyl, substituted or unsubstituted phenylsulfonyl, substituted or unsubstituted benzylsulfonyl, substituted or unsubstituted phenylmethylsulfonyl, substituted or unsubstituted thiophenylsulfonyl, substituted or unsubstituted pyridinylsulfonyl, substituted or unsubstituted pyrimidinylsulfonyl, substituted or unsubstituted sulfonamidyl, substituted or unsubstituted phenylsulfinyl, substituted or unsubstituted benzylsulfinyl, substituted or unsubstituted phenylmethylsulfinyl, substituted or unsubstituted thiophenylsulfinyl, substituted or unsubstituted pyridinylsulfinyl, substituted or unsubstituted pyrimidinylsulfinyl, substituted or unsubstituted amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted trifluoromethylamino, substituted or unsubstituted aminomethyl, substituted or unsubstituted alkylaminomethyl, substituted or unsubstituted dialkylaminomethyl, substituted or unsubstituted arylaminomethyl, substituted or unsubstituted benzylamino, substituted or unsubstituted phenylamino,

substituted or unsubstituted thiophenylamino, substituted or unsubstituted pyridinylamino, substituted or unsubstituted pyrimidinylamino, substituted or unsubstituted indolyl, substituted or unsubstituted morpholino, substituted or unsubstituted alkylamido, substituted or unsubstituted arylamido, substituted or unsubstituted ureido, substituted or unsubstituted carbamoyl, and substituted or unsubstituted piperizinyl.

76. The formulation according to claim **74**, wherein said R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, fluoro, chloro, bromo, nitro, cyano, amino, methyl, hydroxylmethyl, trifluoromethyl, methoxy, trifluoromethyoxy, ethyl, diethylcarbamoyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidinyl, piperizino, piperizinyl, piperizinocarbonyl, piperizinylcarbonyl, carboxyl, 1-tetrazolyl, 1-ethoxycarbonylmethoxy, carboxymethoxy, thiophenyl, 3-(butylcarbonyl) phenylmethoxy, 1H-tetrazol-5-yl, 1-ethoxycarbonylmethyloxy-, 1-ethoxycarbonylmethyl-, 1-ethoxycarbonyl-, carboxymethoxy-, thiophen-2-yl, thiophen-2-ylthio-, thiophen-3-yl, thiophen-3-ylthio, 4-fluorophenylthio, butylcarbonylphenylmethoxy, butylcarbonylphenylmethyl, butylcarbonylmethyl, 1-(piperidin-1-yl)carbonyl)methyl, 1-(piperidin-1-yl)carbonyl)methoxy, 1-(piperidin-2-yl)carbonyl)methoxy, 1-(piperidin-3-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methoxy, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)methyl, 1-(4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl, 1-4-(pyrimidin-2-yl)piperazin-1-yl, 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl), 1-(4-(pyridin-2-yl)piperazin-1-yl)carbonylmethyl, (1-(4-(pyridin-2-yl)piperazin-1-yl)carbonyl)-methoxy), 1-(4-(pyridin-2-yl)piperazin-1-yl, 1H-indol-1-yl, morpholino-, morpholinyl, morpholinocarbonyl, morpholinylcarbonyl, phenylureido, phenylcarbamoyl, acetamido, 3-(phenylthio)-1H-indol-1-yl, 3-(2-cyanoethylthio)-1H-indol-1-yl, benzylamino, 5-methoxy-3-(phenylthio)-1H-indol-1-yl, 5-methoxy-3-(2-cyanoethylthio)-1H-indol-1-yl)), 5-chloro-1H-indol-1-yl, 5-chloro-3-(2-cyanoethylthio)-1H-indol-1-yl)), dibenzylamino, benzylamino, 5-chloro-3-(phenylthio)-1H-indol-1-yl)), 4-(1H-tetrazol-5-yl)phenoxy, 4-(1H-tetrazol-5-yl)phenyl, 4-(1H-tetrazol-5-yl)phenylthio, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 2-cyanophenylthio, 3-cyanophenylthio, 4-cyanophenylthio, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2-cyanobenzyloxy, 3-cyanobenzyloxy, 4-

cyanobenzyloxy, 2-chlorobenzyloxy, 3-chlorobenzyloxy, 4-chlorobenzyloxy, 2-fluorobenzyloxy, 3-fluorobenzyloxy, and 4-fluorobenzyloxy.

77. The formulation according to claim **75**, wherein R^{9a} is H and R^{12a} is H.

78. The formulation of claim **74**, wherein said boron-containing compound is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

79. A method of inhibiting conversion of a tRNA molecule into a charged tRNA molecule, said method comprising:

contacting a tRNA synthetase with a compound effective to inhibit activity of an editing domain of said tRNA synthetase, under conditions sufficient to inhibit said activity, thereby inhibiting said conversion

wherein said compound comprises a member selected from a cyclic boronic ester, cyclic borinic ester, 2'-amino ribofuranose moiety and a 3'-amino ribofuranose moiety.

80. The method of claim **79** wherein inhibition occurs within a microorganism.

81. The method of claim **80** wherein said microorganism is a member selected from a bacteria, fungus, yeast, and parasite.

82. The method of claim **79** wherein said tRNA synthetase is a member selected from a mitochondrial tRNA synthetase and a cytoplasmic tRNA synthetase.

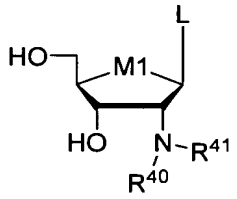
83. The method of claim **82** wherein said tRNA synthetase is a member selected from alanyl tRNA synthetase, isoleucyl tRNA synthetase, leucyl tRNA synthetase, methionyl tRNA synthetase, lysyl tRNA synthetase, phenylalanyl tRNA synthetase, prolyl tRNA synthetase, threonyl tRNA synthetase and valyl tRNA synthetase.

84. The method of claim **79**, wherein said compound has a $K_{D,\ synthesis}$ of greater than 100 μM against a synthetic domain of said tRNA synthetase.

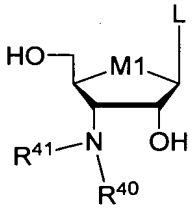
85. The method of claim **84**, wherein the ratio of a minimum concentration of said compound inhibiting said editing domain to a minimum concentration of said compound inhibiting said synthetic domain of said tRNA synthetase, represented as $K_{D,\ edit}/K_{D,\ synthesis}$, is less than one.

86. The method of claim **85**, wherein said $K_{D,\ edit}/K_{D,\ synthesis}$ of said compound is a member selected from less than 0.5, less than 0.1 and less than 0.05.

87. The method of claim **79**, wherein said 2'-amino ribofuranose moiety has a structure according to the following formula:



and said 3'-amino ribofuranose moiety has a structure according to the following formula:



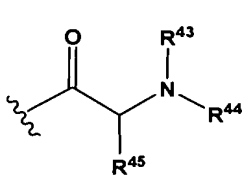
wherein

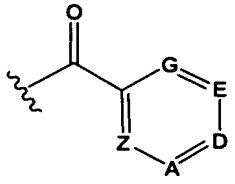
L is a member selected from substituted or unsubstituted purine, substituted or unsubstituted pyrimidine, substituted or unsubstituted pyridine, substituted or unsubstituted imidazole;

M1 is a member selected from O and S;

R^{40} and R^{41} are members independently selected from H, aralkyl, substituted aralkyl, $(CH_2)_sOH$, CO_2H, CO_2alkyl, $C(O)NH_2$, C(O)NHalkyl, $CON(alkyl)_2$, $C(O)R^{42}$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, $(CH_2)_tNR^{26}R^{27}$, SO_2NH_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, alkyl substituted oxazolidin-2-yl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,



and


wherein

R^{26} and R^{27} are independently selected from hydrogen, alkyl, and alkanoyl;

t is an integer selected from 0 to 2;

s is an integer selected from 1 to 3;

R^{42} is a member selected from H, haloalkyl, aralkyl, substituted aralkyl, $(CH_2)_rOH$, OH, $CH_2NR^{26}R^{27}$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

wherein

r is an integer selected from 1 to 6; and

R^{43}, R^{44}, and R^{45} are each members independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

88. The method of claim **80**, wherein said microorganism is an etiologic agent of onychomycosis.

89. The method of claim **80**, wherein said microorganism is a member selected from a dermatophyte, *Trichophyton* spp., *Microsporum* spp., *Epidermophyton* spp., and yeast-like fungi.

90. The method of claim **89**, wherein said microorganism is a member selected from *Trichophyton* species.

91. The method of claim **90**, wherein said microorganism is a member selected from *T. rubrum* and *T. menagrophytes*.

92. The method of claim **79** wherein said compound inhibits post-transfer editing of an improperly charged tRNA by said tRNA synthetase.

93. A method for killing a microorganism or inhibiting the growth of a microorganism in a human or animal, comprising contacting said microorganism with an amount of a pharmaceutical formulation effective to inhibit activity of an editing domain of a tRNA synthetase of said microorganism.

94. The method of claim **93**, wherein said pharmaceutical formulation comprises a member selected from a cyclic boronic ester, cyclic borinic ester, 2'-amino ribofuranose moiety and a 3'-amino ribofuranose moiety.

95. The method of claim **93**, wherein said microorganism is a member selected from bacteria, fungus, yeast and parasite.

96. The method of claim **95**, wherein said fungus is a member selected from *Candida* species, *Trichophyton* species, *Microsporium* species, *Aspergillus* species, *Cryptococcus* species, *Blastomyces* species, *Cocciodiodes* species, *Histoplasma* species, *Paracoccidiodes* species, *Phycomycetes* species, *Malassezia* species, *Fusarium* species, *Epidermophyton* species, *Scytalidium* species, *Scopulariopsis* species, *Alternaria* species, *Penicillium* species, *Phialophora* species, *Rhizopus* species, *Scedosporium* species and *Zygomycetes* class.

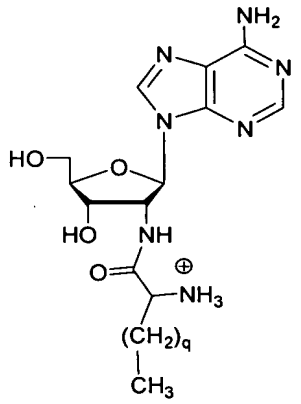
97. The method of claim **93**, wherein said microorganism is an etiologic agent of onychomycosis.

98. The method of claim **93**, wherein said pharmaceutical fomulation is present in a member selected from a dermatophyte, *Trichophyton* spp., *Microsporum* spp., *Epidermophyton* spp., and yeast-like fungi.

99. The method of claim **98**, wherein said microorganism is a member selected from *Trichophyton* species.

100. The method of claim **99**, wherein said microorganism is a member selected from *T. rubrum* and *T. menagrophytes*.

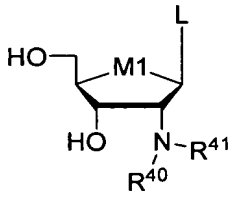
101. The method of claim **93**, with the proviso that said pharmaceutical formulation does not comprise a structure according to the formula:



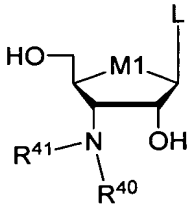
wherein q is an integer selected from 1 to 5.

102. The method of claim **93**, wherein said pharmaceutical formulation comprises a member selected from a 2'-amino ribofuranose moiety and a 3'-amino ribofuranose moiety.

103. The method of claim **102**, wherein said 2'-amino ribofuranose moiety has a structure according to the following formula:



and said 3'-amino ribofuranose moiety has a structure according to the following formula:

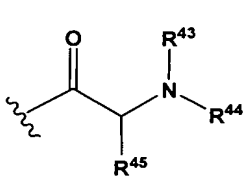


wherein

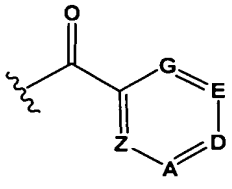
L is a member selected from substituted or unsubstituted purine, substituted or unsubstituted pyrimidine, substituted or unsubstituted pyridine and substituted or unsubstituted imidazole;

M1 is a member selected from O and S;

R^{40} and R^{41} are members independently selected from H, aralkyl, substituted aralkyl, $(CH_2)_sOH$, CO_2H, CO_2alkyl, $C(O)NH_2$, C(O)NHalkyl, $CON(alkyl)_2$, $C(O)R^{42}$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, $(CH_2)_tNR^{26}R^{27}$, SO_2NH_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, alkyl substituted oxazolidin-2-yl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,



and



wherein

R^{26} and R^{27} are independently selected from hydrogen, alkyl, and alkanoyl;

t is an integer selected from 0 to 2;

s is an integer selected from 1 to 3;

R^{42} is a member selected from H, haloalkyl, aralkyl, substituted aralkyl, $(CH_2)_rOH$, OH, $CH_2NR^{26}R^{27}$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

wherein

r is an integer selected from 1 to 6; and

R^{43}, R^{44}, and R^{45} are each members independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

104. The method of claim **94**, wherein said cyclic boronic ester is 1;3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

105. A method of treating or preventing an infection by a microorganism in a human or animal, said method comprising:

administering to said human or animal an amount of a pharmaceutical formulation effective to inhibit activity of an editing domain of a tRNA synthetase of said microorganism.

106. The method of claim **105**, wherein said pharmaceutical formulation comprises a member selected from a cyclic boronic ester, cyclic borinic ester, 2'-amino ribofuranose moiety and a 3'-amino ribofuranose moiety.

107. The method of claim **105**, wherein said microorganism is a member selected from a bacteria, fungus, yeast and parasite.

108. The method of claim **105**, wherein said tRNA synthetase is a member selected from a mitochondrial tRNA synthetase and a cytoplasmic tRNA synthetase.

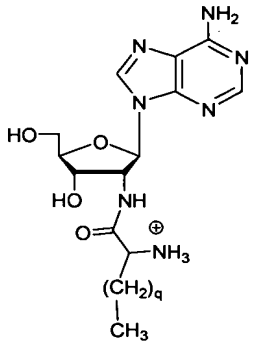
109. The method of claim **108**, wherein said tRNA synthetase is a member selected from alanyl tRNA synthetase, isoleucyl tRNA synthetase, leucyl tRNA synthetase, methionyl tRNA synthetase, lysyl tRNA synthetase, phenylalanyl tRNA synthetase, prolyl tRNA synthetase, threonyl tRNA synthetase and valyl tRNA synthetase.

110. The method of claim **105**, wherein said compound has a $K_{D,\ synthesis}$ of greater than 100 μM against a synthetic domain of said tRNA synthetase.

111. The method of claim **110**, wherein the ratio of a minimum concentration of said compound inhibiting said editing domain to a minimum concentration of said compound inhibiting a synthetic domain of said tRNA synthetase, represented as $K_{D,\ edit}/K_{D,\ synthesis}$, is less than one.

112. The method of claim **111**, wherein said $K_{D,\ edit}/K_{D,\ synthesis}$ of said compound is a member selected from less than 0.5, less than 0.1 and less than 0.05.

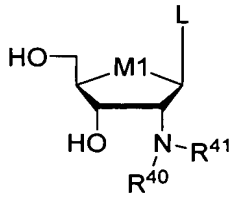
113. The method of claim **105**, with the proviso that said pharmaceutical formulation does not comprise a structure according to the formula:



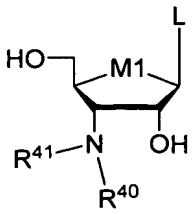
wherein q is an integer selected from 1 to 5.

114. The method of claim **106**, wherein said pharmaceutical formulation comprises a member selected from a 2'-amino ribofuranose moiety and a 3'-amino ribofuranose moiety.

115. The method of claim **114**, wherein said pharmaceutical formulation comprises a 2'-amino ribofuranose moiety, and said 2'-amino ribofuranose moiety has a structure according to the following formula:



and said 3'-amino ribofuranose moiety has a structure according to the following formula:

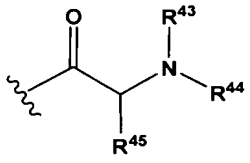


wherein

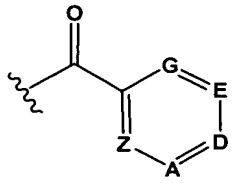
L is a member selected from substituted or unsubstituted purine, substituted or unsubstituted pyrimidine, substituted or unsubstituted pyridine and substituted or unsubstituted imidazole;

M1 is a member selected from O and S;

R^{40} and R^{41} are members independently selected from H, aralkyl, substituted aralkyl, $(CH_2)_sOH$, CO_2H, CO_2alkyl, $C(O)NH_2$, C(O)NHalkyl, $CON(alkyl)_2$, $C(O)R^{42}$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, $(CH_2)_tNR^{26}R^{27}$, SO_2NH_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, alkyl substituted oxazolidin-2-yl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,



and



wherein

R^{26} and R^{27} are independently selected from hydrogen, alkyl, and alkanoyl;

t is an integer selected from 0 to 2;

s is an integer selected from 1 to 3;

R^{42} is a member selected from H, haloalkyl, aralkyl, substituted aralkyl, $(CH_2)_rOH$, OH, $CH_2NR^{26}R^{27}$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

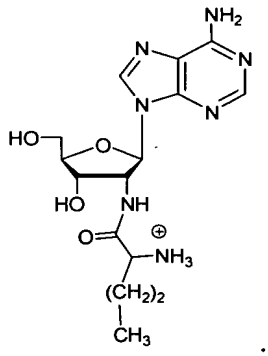
cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

wherein

r is an integer selected from 1 to 6; and

R^{43}, R^{44}, and R^{45} are each members independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

116. The method of claim **115**, wherein said pharmaceutical formulation comprises a 2'-amino ribofuranose moiety, and said 2'-amino ribofuranose moiety has a structure according to the following formula:



117. The method of claim **106**, wherein said cyclic boronic ester is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

118. The method of claim **105**, wherein said infection is a member selected from a systemic infection, an ungual infection, a periungual infection, a subungual infection and a cutaneous infection.

119. The method of claim **105**, wherein said infection is onychomycosis.

120. The method of claim **105**, wherein said infection is a member selected from chloronychia, paronychias, erysipeloid, onychorrhexis, gonorrhea, swimming-pool granuloma, larva migrans, leprosy, Orf nodule, milkers' nodules,

herpetic whitlow, acute bacterial perionyxis, chronic perionyxis, sporotrichosis, syphilis, tuberculosis verrucosa cutis, tularemia, tungiasis, peri- and subungual warts, zona, nail dystrophy (trachyonychia), dermatological diseases, psoriasis, pustular psoriasis, alopecia aerata, parakeratosis pustulosa, contact dermatosis, Reiter's syndrome, psoriasiform acral dermatitis, lichen planus, idiopathy atrophy in the nails, lichin nitidus, lichen striatus, inflammatory linear verrucous epidermal naevus (ILVEN), alopecia, pemphigus, bullous pemphigoid, acquired epidermolysis bullosa, Darier's disease, pityriasis rubra pilaris, palmoplantar keratoderma, contact eczema, polymorphic erythema, scabies, Bazex syndrome, systemic scleroderma, systemic lupus erythematosus, chronic lupus erythematosus, dermatomyositus, Sporotrichosis, Mycotic keratitis, Extension oculomycosis, Endogenous oculomycosis, Lobomycosis, Mycetoma, Piedra, Pityriasis versicolor, Tinea corporis, Tinea cruris, Tinea pedis, Tinea barbae, Tinea capitis, Tinea nigra, Otomycosis, Tinea favosa, Chromomycosis, and Tinea Imbricata.

121. A unit dosage formulation of an amount of a compound effective to inhibit conversion of a tRNA molecule into a charged tRNA molecule by a microorganism by inhibiting an editing domain of a tRNA synthetase.

122. The formulation of claim **121**, further comprising a pharmaceutically acceptable excipient.

123. The formulation of claim **121**, wherein said cell is a microbial cell.

124. The formulation of claim **121**, wherein said microorganism is a member selected from a bacteria, fungus, yeast, and parasite.

125. The formulation of claim **121**, wherein said tRNA synthetase is a member selected from a mitochondrial tRNA synthetase and a cytoplasmic tRNA synthetase.

126. The formulation of claim **125** wherein said tRNA synthetase is a member selected from alanyl tRNA synthetase, isoleucyl tRNA synthetase, leucyl tRNA synthetase, methionyl tRNA synthetase, lysyl tRNA synthetase, phenylalanyl

tRNA synthetase, prolyl tRNA synthetase, threonyl tRNA synthetase and valyl tRNA synthetase.

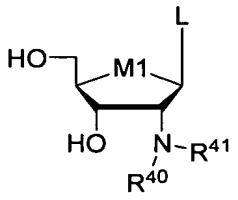
127. The formulation of claim **121**, wherein said compound has a $K_{D, synthesis}$ of greater than 100 μM against a synthetic domain of said tRNA synthetase.

128. The formulation of claim **127**, wherein the ratio of a minimum concentration of said compound inhibiting said editing domain to a minimum concentration of said compound inhibiting a synthetic domain of said tRNA synthetase, represented as $K_{D, edit}/K_{D, synthesis}$ is less than one.

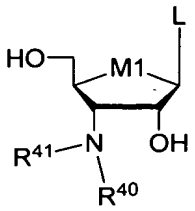
129. The formulation of claim **128**, wherein said $K_{D, edit}/K_{D, synthesis}$ of said formulation is a member selected from less than 0.5, less than 0.1 and less than 0.05.

130. The formulation of claim **121**, wherein said formulation comprises a compound which is a member selected from a cyclic boronic ester, a cyclic borinic ester, a 2'-amino ribofuranose moiety and a 3'-amino ribofuranose moiety.

131. The formulation of claim **130**, wherein said 2'-amino ribofuranose moiety has a structure according to the following formula:



and said 3'-amino ribofuranose moiety has a structure according to the following formula:

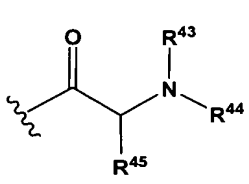


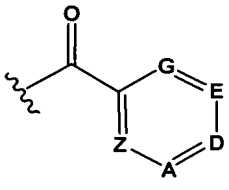
wherein

L is a member selected from substituted or unsubstituted purine, substituted or unsubstituted pyrimidine and substituted or unsubstituted pyridine;

M1 is a member selected from O and S;

R^{40} and R^{41} are members independently selected from H, aralkyl, substituted aralkyl, $(CH_2)_sOH$, CO_2H, CO_2alkyl, $C(O)NH_2$, C(O)NHalkyl, $CON(alkyl)_2$, $C(O)R^{42}$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, $(CH_2)_tNR^{26}R^{27}$, SO_2NH_2, $OCH_2CH_2NH_2$, $OCH_2CH_2NHalkyl$, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, alkyl substituted oxazolidin-2-yl, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,



and


wherein

R^{26} and R^{27} are independently selected from hydrogen, alkyl, and alkanoyl;

t is an integer selected from 0 to 2;

s is an integer selected from 1 to 3;

R^{42} is a member selected from H, haloalkyl, aralkyl, substituted aralkyl, $(CH_2)_rOH$, OH, $CH_2NR^{26}R^{27}$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

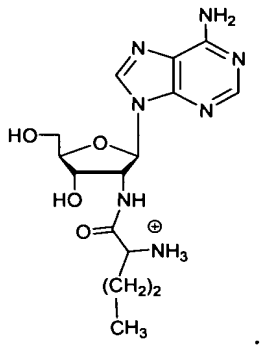
wherein

r is an integer selected from 1 to 6; and

R^{43}, R^{44}, and R^{45} are each members independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted

heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

132. The formulation of claim **131**, with the proviso that said compound does not have a structure according to the formula:



133. The formulation of claim **130**, wherein said cyclic boronic ester is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

134. The formulation of claim **121**, wherein said cell is a cell of an etiologic agent of onychomycosis.

135. The formulation of claim **121**, wherein said cell is a member selected from *Trychophyton* species.

136. The formulation of claim **121**, wherein said compound has a $K_{D,\ synthesis}$ of greater than 100 μM against a synthetic domain of said tRNA synthetase.

137. A method for identifying a compound which binds to an editing domain of a tRNA synthetase comprising:

a) contacting said editing domain with a test compound under conditions suitable for binding; and

b) detecting binding of said test compound to said editing domain.

138. The method of claim **137** wherein detecting binding of said compound comprises use of at least one detectable element, isotope, or chemical label attached to said compound.

139. The method of claim **138** wherein said element, isotope or chemical label is detected by a fluorescent, luminescent, radioactive, or absorbance readout.

140. The method of claim **137** wherein said contacting of said test compound with said editing domain also includes further contacting said test compound and said editing domain with a member selected from AMP and a molecule with a terminal adenosine.

141. The method of claim **137** wherein said tRNA synthetase is derived from a member selected from alanyl tRNA synthetase, isoleucyl tRNA synthetase, leucyl tRNA synthetase, methionyl tRNA synthetase, lysyl tRNA synthetase, phenylalanyl tRNA synthetase, prolyl tRNA synthetase, threonyl tRNA synthetase and valyl tRNA synthetase.

142. The method of claim **141** wherein said tRNA synthetase is derived from leucyl tRNA synthetase.

143. The method of claim **141** wherein said tRNA synthetase is derived from a mutated tRNA synthetase, wherein said mutated tRNA synthetase comprises amino acid mutations in an editing domain.

144. The method of claim **143** wherein said mutated tRNA synthetase comprises amino acid mutations in the editing domain as listed in Table 4.

145. The method of claim **137** wherein said editing domain of a tRNA synthetase comprises the amino acid sequence of SEQ ID NOS: 1-15.

146. A method for identifying a compound which binds to an editing domain of a tRNA synthetase, said assay comprising:

a) contacting said editing domain of a tRNA synthetase with said compound under conditions suitable for binding of said compound with said editing domain of a tRNA synthetase;

b) comparing a biological activity of said editing domain of a tRNA synthetase contacting said compound to said biological activity when

not contacting said compound; and

c) identifying said compound as binding to said editing domain of a tRNA synthetase if said biological activity of said editing domain of a tRNA synthetase is reduced when contacting said compound.

147. The method of claim **146** wherein said biological activity is hydrolysis of noncognate amino acid.

148. The method of claim **147** wherein said hydrolysis of said noncognate amino acid is detected through the use of one or more labels.

149. The method of claim **148** wherein said labels include a radiolabel, a fluorescent marker, an antibody, or a combination thereof.

150. The method of claim **148** wherein said labels can be detected using spectroscopy.

151. The method of claim **146** wherein said editing domain of a tRNA synthetase is derived from a member selected from alanyl tRNA synthetase, isoleucyl tRNA synthetase, leucyl tRNA synthetase, methionyl tRNA synthetase, lysyl tRNA synthetase, phenylalanyl tRNA synthetase, prolyl tRNA synthetase, threonyl tRNA synthetase and valyl tRNA synthetase.

152. The method of claim **151** wherein said editing domain of a tRNA synthetase is derived from leucyl tRNA synthetase.

153. A method of generating tRNA molecules with noncognate amino acid comprising:

a) creating or isolating a mutated tRNA synthetase with altered amino acid editing domains; and

b) contacting a tRNA molecule with said mutated tRNA synthetase and a noncognate amino acid.

154. The method of claim **153** wherein said mutated tRNA synthetase contains one or more amino acid mutations in an editing domain.

155. The method of claim **153** wherein said mutated tRNA synthetase is unable to bind with 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

156. The method of claim **153** wherein said mutated tRNA synthetase is able to bind with 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

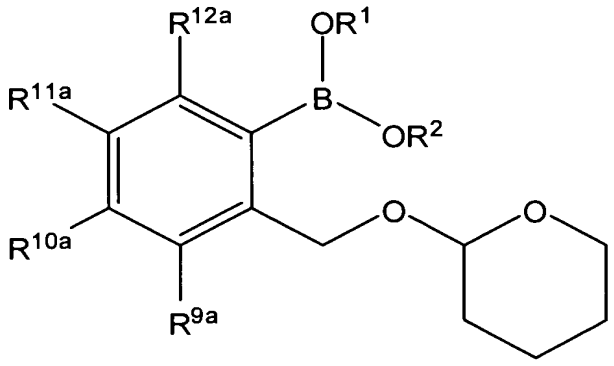
157. A composition that comprises one or more tRNA molecules attached to noncognate amino acids, wherein said tRNA molecules are synthesized using one or more mutated tRNA synthetases isolated from a microorganism or a cell line derived from a microorganism.

158. The composition of claim **157** wherein said microorganism is a fungus or a yeast.

159. The composition of claim **157** wherein said mutated tRNA synthetases contain amino acid mutations in their editing domains.

160. The composition of claim **157** wherein said mutated tRNA synthetases comprise point mutations in the editing domain as listed in Table 4.

161. A method of making a tetrahydropyran-containing boronic ester, said ester having a structure according to the following formula:



wherein

R^1 and R^2 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or

unsubstituted heteroaryl;

wherein R^1 and R^2, together with the atoms to which they are attached, can be optionally joined to form a 4- to 7- membered ring

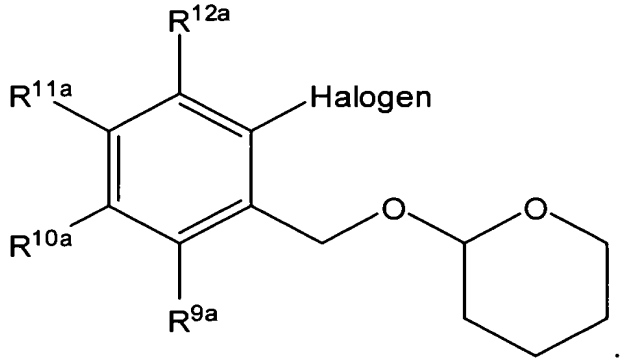
R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OR*, NR*R**, SR*, -S(O)R*, -$S(O)_2$R*, -$S(O)_2$NR*R**, nitro, halogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl

wherein

R* and R** is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

wherein said method comprises:

a) subjecting a first compound to Grignard or organolithium conditions, said first compound having a structure according to the following formula:



;

b) contacting the product of step a) with a borate ester

thereby forming said tetrahydropyran-containing boronic ester.

162. The method of claim **161**, wherein said halogen is a member selected from iodo and bromo.

163. The method of claim **161**, wherein said borate ester is a member selected from $B(OR^1)_2(OR^2)$, wherein R^1 and R^2

said R^1 and R^2 are each members independently selected from H, substituted

or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, substituted or unsubstituted isopropyl, substituted or unsubstituted butyl, substituted or unsubstituted t-butyl, substituted or unsubstituted phenyl and substituted or unsubstituted benzyl

and wherein R^1 and R^2, together with the atoms to which they are joined, can optionally form a member selected from substituted or unsubstituted dioxaborolane, substituted or unsubstituted dioxaborinane and substituted or unsubstituted dioxaborepane.

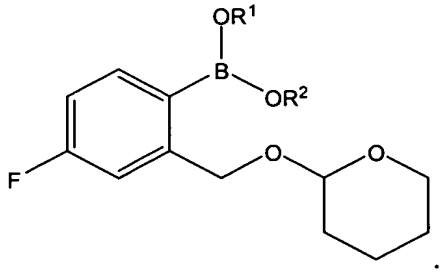
164. The method of claim **161**, wherein said borate ester is a member selected from $B(OR^1)_2(OR^2)$, wherein R^1 and R^2, together with the atoms to which they are joined, form a member selected from dioxaborolane, substituted or unsubstituted tetramethyldioxaborolane, substituted or unsubstituted phenyldioxaborolane, dioxaborinane, dimethyldioxaborinane and dioxaborepane.

165. The method of claim **161**, wherein said Grignard or organolithium conditions further comprise diisobutyl aluminum hydride.

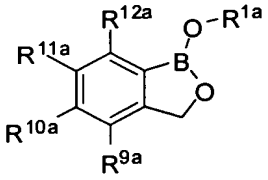
166. The method of claim **161**, wherein the temperature of the Grignard reaction does not exceed 35°C.

167. The method of claim **161**, wherein step (b) is performed at a temperature of from about -30°C to about -20°C.

168. The method of claim **161**, wherein said tetrahydropyran-containing boronic ester is

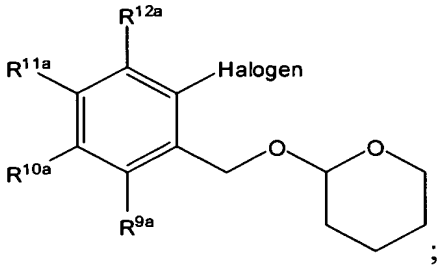


169. A method of making a compound having a structure according to the following formula



said method comprising:

a) subjecting a first compound to Grignard or organolithium conditions, said first compound having a structure according to the following formula:



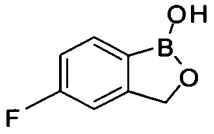
;

b) quenching said subjecting reaction with water and a organic acid, thereby forming said compound.

170. The method of claim **169**, wherein said organic acid is a member selected from acetic acid.

171. The method of claim **169**, wherein said quenching step is essentially not contacted with a strong acid.

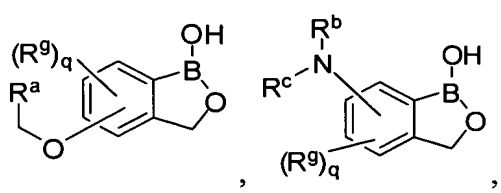
172. The method of claim **169**, wherein said compound is

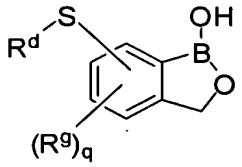
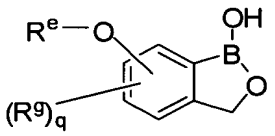
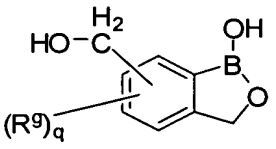


173. The method of claim **169** wherein said compound is purified by recrystallization from a recrystallization solvent, wherein said recrystallization solvent essentially does not contain acetonitrile.

174. The method of claim **173**, wherein said recrystallization solvent comprises toluene and heptane.

175. A compound having a structure which is a member selected from:



and

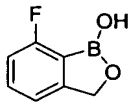
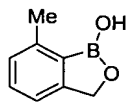
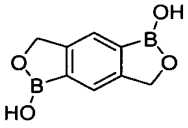
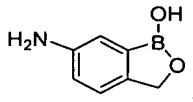
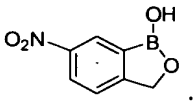
wherein

q is a number between 0 and 1;

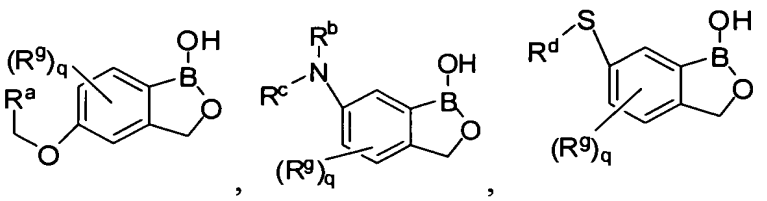
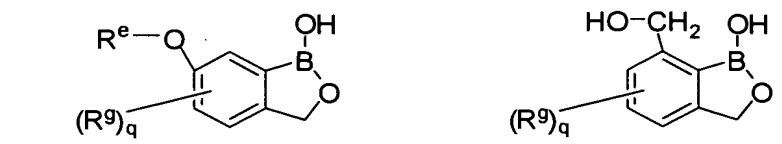
R^g is halogen;

R^a, R^b, R^c, R^d and R^e are members independently selected from a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

with the proviso that the compound is not a member selected from

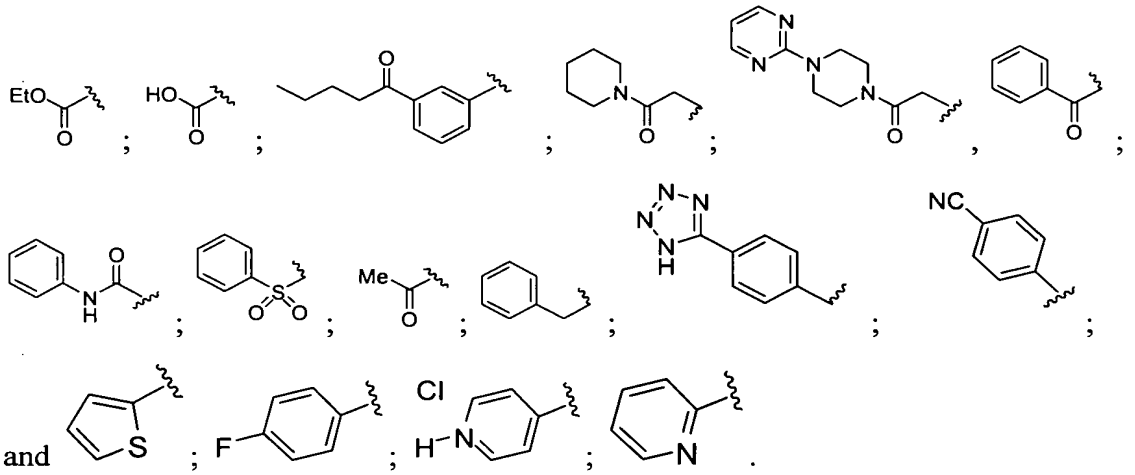






176. The compound according to claim **175**, wherein said structure is a member selected from:

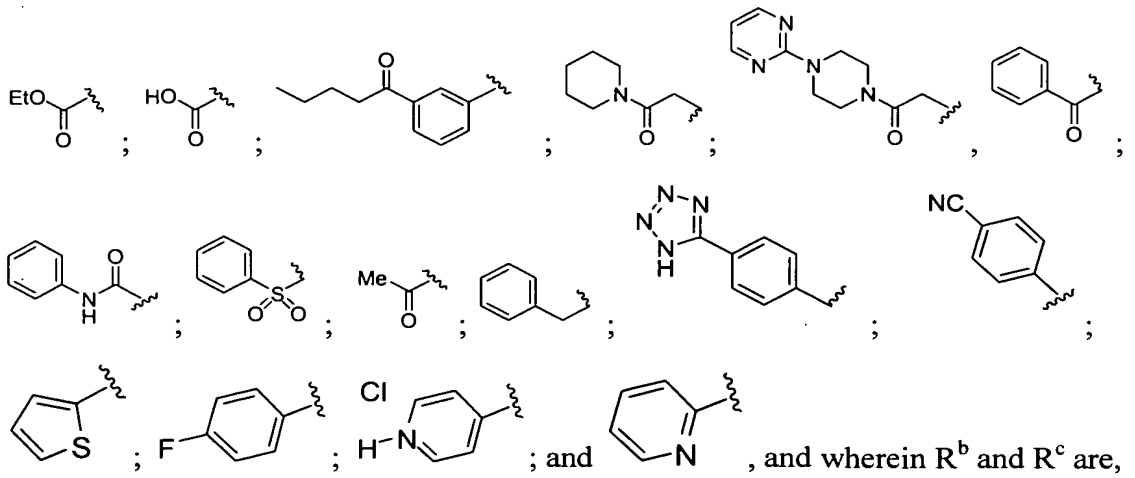
and .

177. The compound according to claim **175** or **176** wherein R^a, R^d and R^e are each members indepenently selected from:



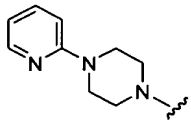
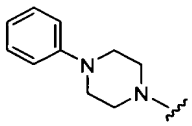
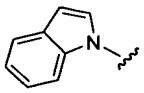
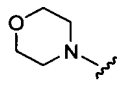
and .

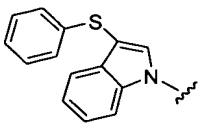
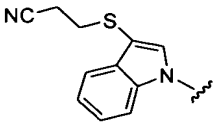
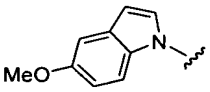
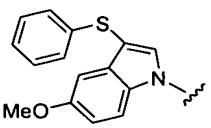
178. The compound according to claim **175** or **176** wherein R^b and R^c are members independently selected from H, methyl,

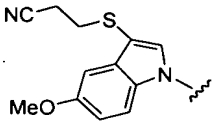
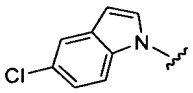
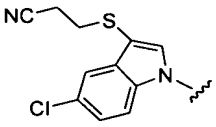
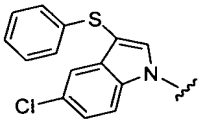


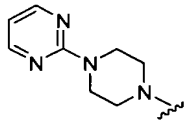
, and wherein R^b and R^c are,

together with the nitrogen to which they are attached, optionally joined to form a member selected from

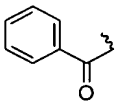
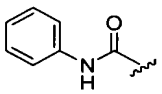
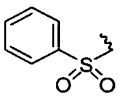
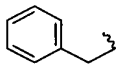
 ;  ;  ;  ;

 ;  ;  ;  ;

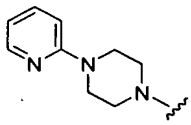
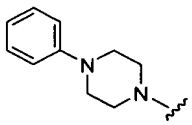
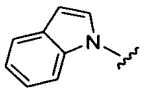
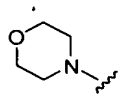
 ;  ;  ;  ;

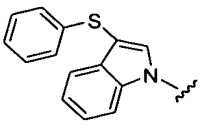
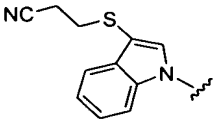
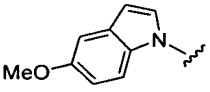
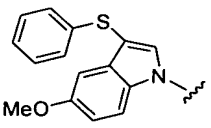
 and .

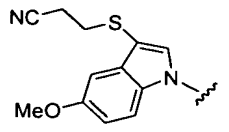
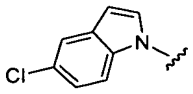
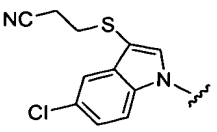
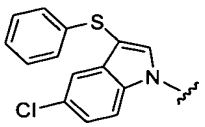
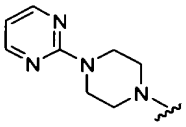
179. The compound according to claim **175**, wherein R^b is H and R^c is a member selected from

H, methyl,  ;  ;  ;  ; and  .

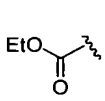
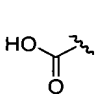
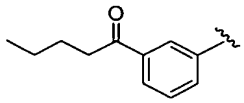
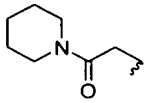
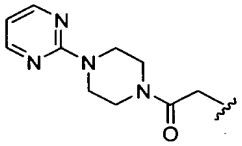
180. The compound according to claim **175**, wherein R^b and R^c are optionally joined to form a member selected from

 ;  ;  ;  ;

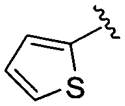
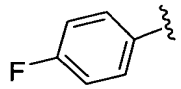
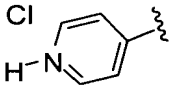
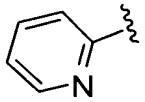
 ;  ;  ;  ;

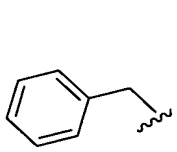
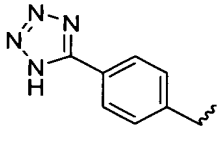
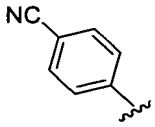
181. The compound according to claim **175**, wherein R^a is a member selected from

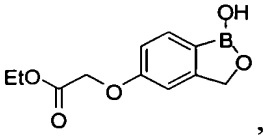
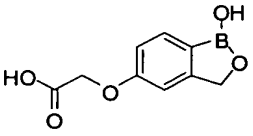
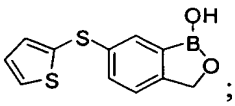
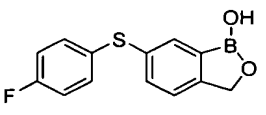
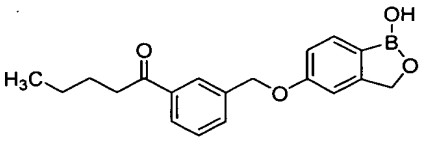
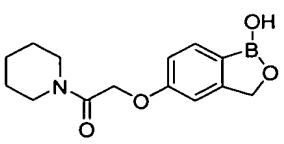
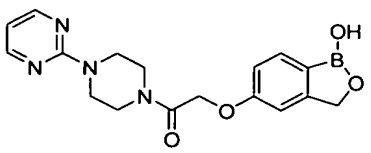
182. The compound according to claim **175**, wherein R^d is a member selected from

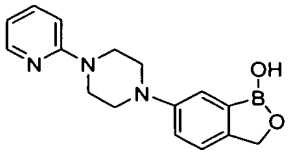
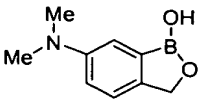
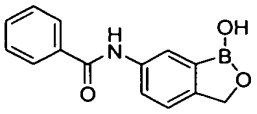
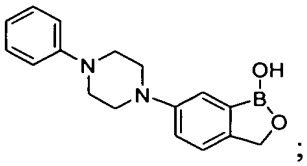





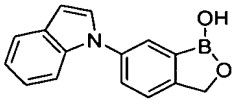
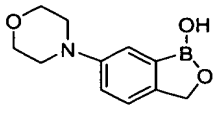
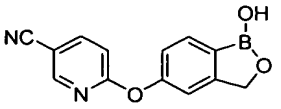
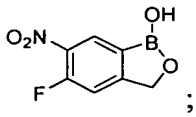
183. The compound according to claim **175**, wherein R^e is a member selected from

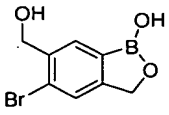
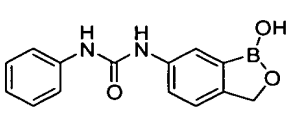
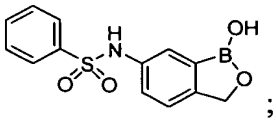
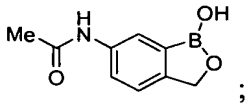




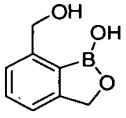
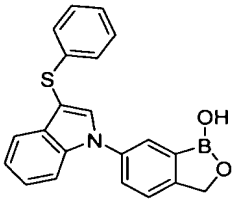
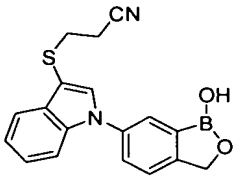
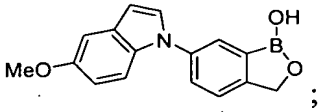
184. A compound having a structure which is a member selected from the following formulas:

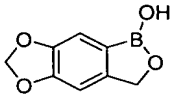
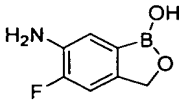
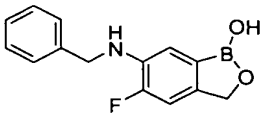
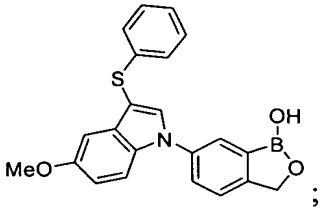








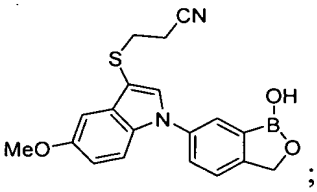
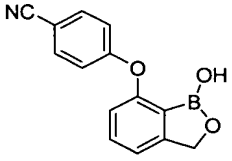
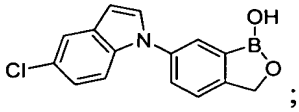
5  ;  ;  ;  ;

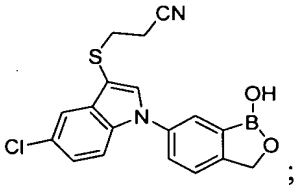
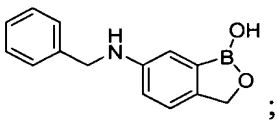
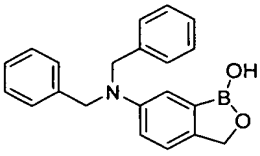
6  ;  ;  ;  ;

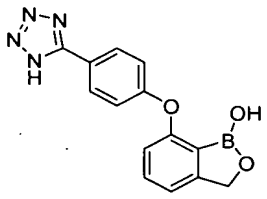
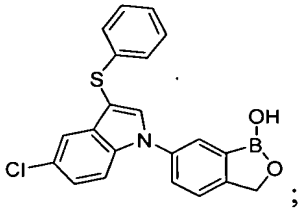
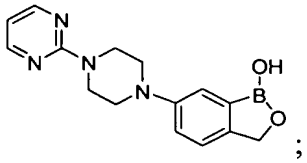
7  ;  ;  ;  ;

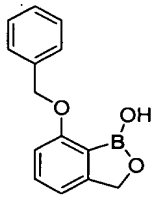
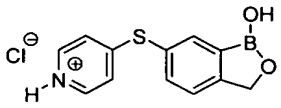
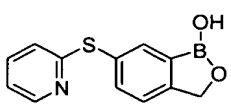
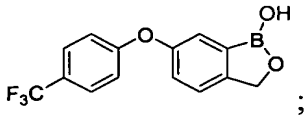
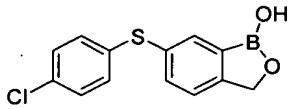
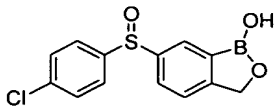
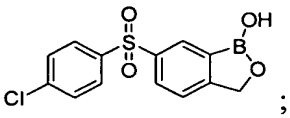
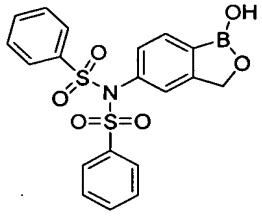
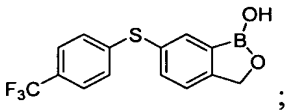
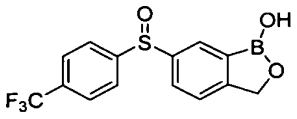
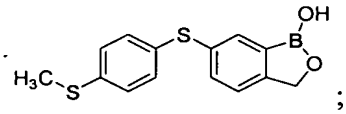
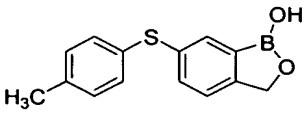
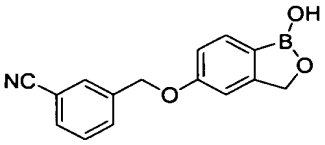
8  ;  ;  ;  ;

9  ;  ;  ;  ;

10  ;  ;  ;

11  ;  ;  ;

12  ;  ;  ;

185. A pharmaceutical formulation comprising:

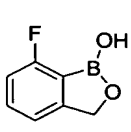
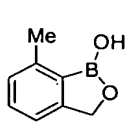
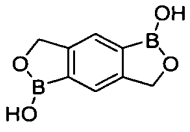
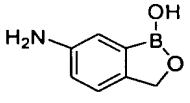
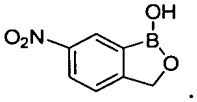
a) a pharmaceutically acceptable excipient;

b) the compound from claim **184**.

186. A pharmaceutical formulation comprising:

a) a pharmaceutically acceptable excipient;

b) a compound which is a member selected from

187. A method for killing a microorganism or inhibiting the growth of a microorganism, comprising contacting said microorganism with a therapeutically effective amount of a compound according to claim **186**.

188. A method for killing a microorganism or inhibiting the growth of a microorganism, comprising contacting said microorganism with a therapeutically

effective amount of a pharmaceutical formulation according to claim **185** or claim **186**.

189. A method of treating or preventing an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of the compound according to claim **184**.

190. A method of treating or preventing an infection in a human or an animal, said method comprising administering to the animal a therapeutically effective amount of a pharmaceutical formulation according to claim **185** or claim **186**.

191. A method for making the compound of claim **184**.

192. A method for making the pharmaceutical formulation of claim **185** or claim **186**.

BORON-CONTAINING SMALL MOLECULES

ABSTRACT OF THE DISCLOSURE

This invention relates to compounds useful for treating fungal infections, more specifically topical treatment of onychomycosis and/or cutaneous fungal infections. This invention is directed to compounds that are active against fungi and have properties that allow the compound, when placed in contact with a patient, to reach the particular part of the skin, nail, hair, claw or hoof infected by the fungus. In particular the present compounds have physiochemical properties that facilitate penetration of the nail plate.

FIGURE 1A

	MIC (ug/mL)							
	C. albicans ATCC 90028	C. albicans F56	C. neoformans F285	A. fumigatus ATCC 13073	T. mentagrophytes F311	S. cerevisiae ANA309	T. rubrum F296	T. rubrum F296 w/ 5% keratin
C1	1	2	2	1	2	0.5	1	1
C2	2	0.5	1	2	4		8	8
C3	16	32	32	16	16	4	32	
C4	64	64	> 64	32	32	8	32	
C5	4	8	2	2	4	0.25	4	
C6	8	16	8	16	16	64	16	
C7	> 64	> 64	> 64	> 64	32	4	64	
C8	2	2	8	2	4	2	8	
C9	> 64	> 64	> 64	> 64	64	>64	64	

FIGURE 1B

C10	0.5	0.5	0.25	0.25	≤0.5	<0.06	1	2
C11	32	32	32	32	2	2	4	
C12	256					>64		
C13	16					2	16	
C16	32					8	16	
C17	64	64	64	16	4	16	8	
C18						2		
C19						0.5	8	
C20						8		
C21						4		
C22						>64		
C23						>64		

FIGURE 1C

C24						16		
C25						>64		
C26						>64		
C27						>64		
C28						<0.06	4	
C31						8		

FIGURE 2A

EXAMPLE 2A

Fungus	Broth used	MIC (μg/mL)				
		(C10)	Ciclopirox	Terbinafine	Fluconazole	Itraconazole
A. fumigatus ATCC 13073	RPMI	0.25	nt	nt	>64	0.25
C. albicans ATCC 90028	RPMI	1	0.5	nt	0.25	≤ 0.12
C. albicans F56	RPMI	0.5	nt	nt	>64	0.25
C. glabrata ATCC 90030	RPMI + MOPs	≤ 0.5	≤ 0.5	64	nt	≤ 0.5
C. krusei ATCC 44507	RPMI + MOPs	1	≤ 0.5	64	nt	≤ 0.5
C. neoformans F285	RPMI	0.25	nt	nt	2	≤ 0.12
C. parapsilosis ATCC 22019	RPMI + MOPs	≤ 0.5	≤ 0.5	≤ 0.5	nt	≤ 0.5
C. tropicalis ATCC 13803	RPMI + MOPs	≤ 0.5	≤ 0.5	256	nt	1
E. floccosum ATCC 52066	RPMI + MOPs	≤ 0.5	≤ 0.5	≤ 0.5	nt	≤ 0.5
F. solani ATCC 36031	RPMI + MOPs	≤ 0.5	4	64	nt	>256
M. furfur ATCC 44344	Urea	1	≤ 0.5	2	nt	≤ 0.5
M. pachydermatis ATCC 96746	Urea	1	≤ 0.5	≤ 0.5	nt	≤ 0.5
M. sympodialis ATCC 44031	Urea	1	≤ 0.5	≤ 0.5	nt	≤ 0.5
M. audouinii ATCC 42558	RPMI + MOPs	2	1	≤ 0.5	nt	≤ 0.5
M. canis ATCC 10214	RPMI + MOPs	2	≤ 0.5	≤ 0.5	nt	≤ 0.5
M. gypseum ATCC 24103	RPMI + MOPs	2	≤ 0.5	≤ 0.5	nt	≤ 0.5
T. mentagrophytes F311	RPMI + MOPs	1	0.5	≤ 0.5	32	≤ 0.12
T. rubrum F296	RPMI + MOPs	1	1	≤ 0.5	1	≤ 0.12
T. rubrum F296	RPMI + MOPS + 5% keratin powder	2	1	nt	1	nt
T. tonsurans ATCC 28942	RPMI + MOPs	2	≤ 0.5	≤ 0.5	nt	≤ 0.5

nt = not tested

FIGURE 2B

EXAMPLE 2B

Fungus	Broth used*	MFC (μg/mL)			
		(C10)	Ciclopirox	Terbinafine	Itraconazole
T. mentagrophytes F311	RPMI + MOPs	16	1	≤ 0.5	4
T. rubrum F296	RPMI + MOPs	8	2	≤ 0.5	4

FIGURE 3

Nail Samples	Radioactivity as mg Equivalent/g Nail Samples		*P* value (*t*-test)
	Group A (**C10**)	Group C (Ciclopirox)	
Dorsal/intermediate center	25.65 ± 8.80	7.40 ± 3.47	0.0008
Ventral/intermediate center	20.46 ± 4.72	3.09 ± 2.07	0.0001
Remainder nail	26.06 ± 12.41	4.38 ± 2.73	0.0022

* The data represents the mean ± S.D. of each group (n = 6).

FIGURE 4

Sampling day	Radioactivity as mg Equivalent/Samples*		*P*-value (t-test)
	Group A (**C10**)	Group C (Ciclopirox)	
Day 3	0.0609 ± 0.0605	0.0011 ± 0.0020	0.0043
Day 6	0.1551 ± 0.1314	0.0013 ± 0.0027	0.0022
Day 9	0.3892 ± 0.3714	0.0018 ± 0.0030	0.0022
Day 12	0.6775 ± 0.6663	0.0014 ± 0.0019	0.0022
Day 15	0.9578 ± 0.6106	0.0033 ± 0.0041	0.0022
Total	2.2405 ± 1.7325	0.0089 ± 0.0131	0.0022

* The data represents the mean ± S.D. of each group (n = 6).

FIGURE 5

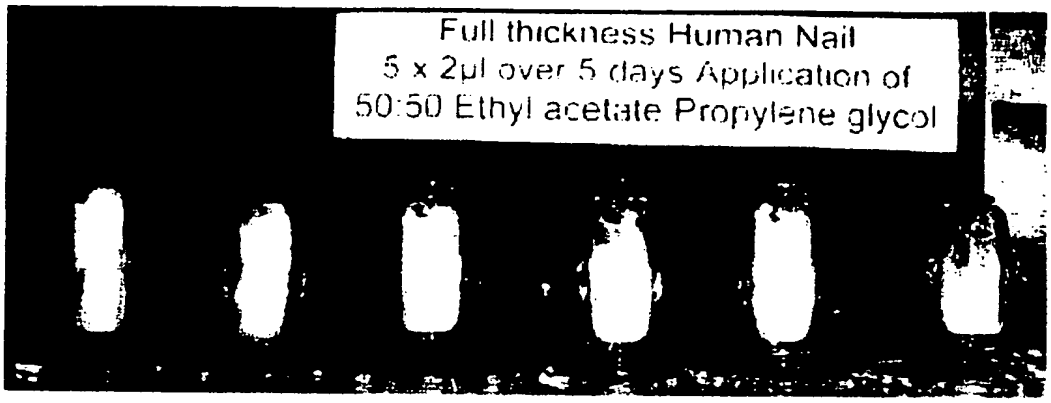

Full thickness Human Nail
5 x 2µl over 5 days Application of
50:50 Ethyl acetate Propylene glycol

FIGURE 6

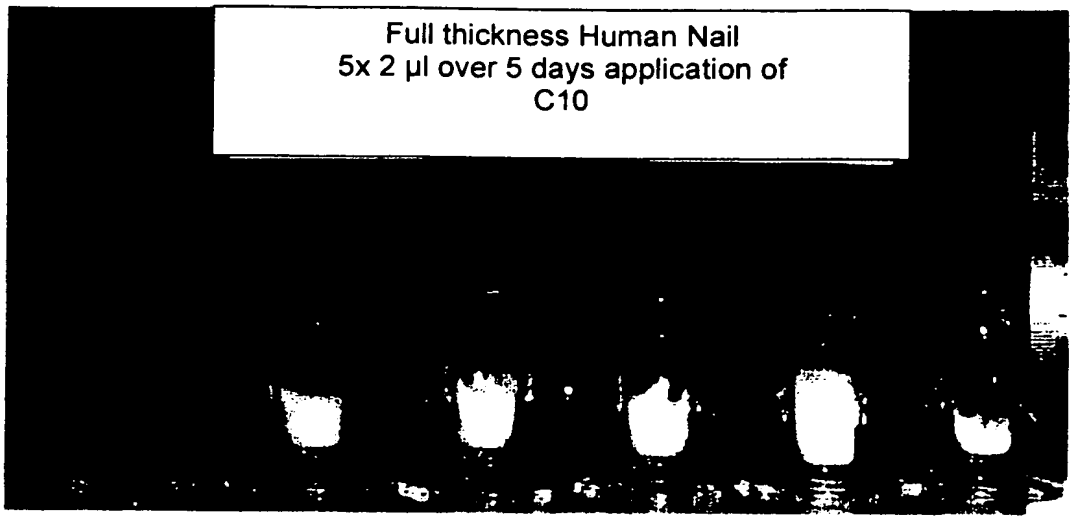

Full thickness Human Nail
5x 2 µl over 5 days application of
C10

FIGURE 7

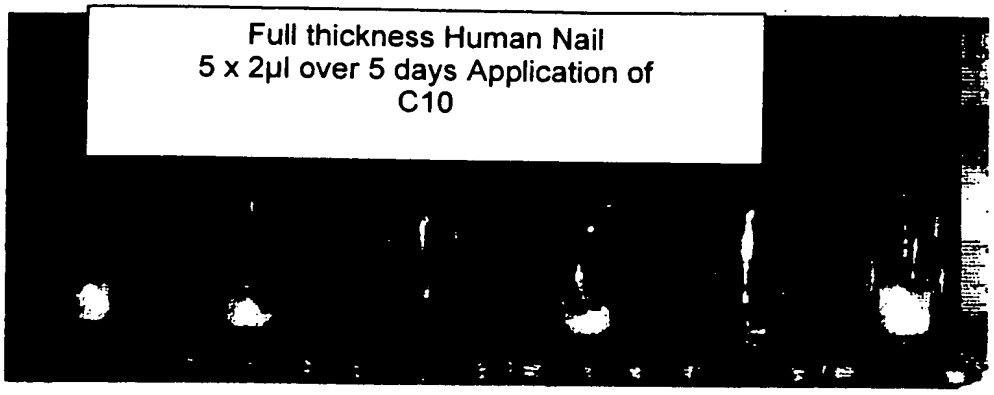

Full thickness Human Nail
5 x 2µl over 5 days Application of
C10

FIGURE 8

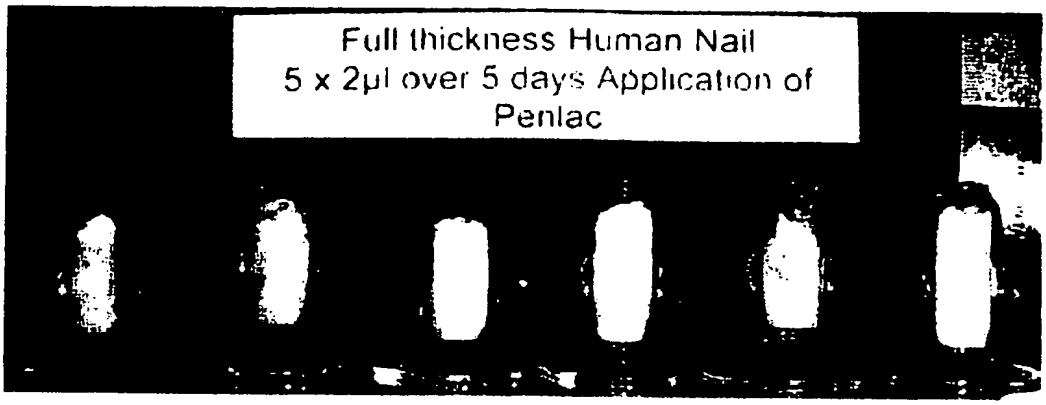

Full thickness Human Nail
5 x 2µl over 5 days Application of
Penlac

FIGURE 9

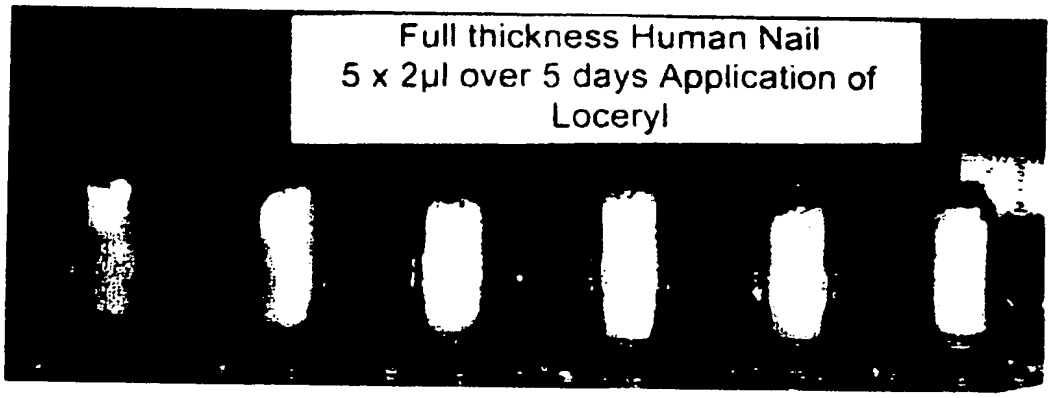

Full thickness Human Nail
5 x 2µl over 5 days Application of
Loceryl

Figure 10(1)

SUMMARY:

SEQ ID NO: 1–15	amino acid sequences of leucyl-tRNA synthetase editing domain
SEQ ID NO: 1	amino acid sequences of leucyl-tRNA synthetase editing domain from *S. cerivisiae*.
SEQ ID NO: 2	amino acid sequences of leucyl-tRNA synthetase editing domain from *S. cerivisiae* – overexpressed version
SEQ ID NO: 16–17	genomic sequences for tRNA-leu and tRNA-ile from *S. cerivisiae*.
SEQ ID NO: 18-62	tRNA sequences for tRNA-leu

A.

SEQ ID NO: 1

TPQEYIGVKIEALEFADDAAKIIDSSSDLDKSKKFYFVAATLRPETMYGQTCCFVSPTI
EYGIFDAGDSYFITTERAFKNMSYQKLTPKRGFYKPIVTVPGKAFIGTKIHAPQSVYPE
LRILPMETVIATKGTGVVTCVPSNSPDDYITTKDLLHKPEYYGIKPEWIDHEIVPIMHTE
KYGDLTAKAIVEEKKIQSPKDKNLLAEAKKIAYKEDYYTGTMIYGPYKGEKVEQAKNK
VKADMIAAGEAFVYNEPESQDP

SEQ ID NO: 2

MTPQEYIGVKIEALEFADDAAKIIDSSSDLDKSKKFYFVAATLRPETMYGQTCCFVSPTI
EYGIFDAGDSYFITTERAFKNMSYQKLTPKRGFYKPIVTVPGKAFIGTKIHAPQSVYPE
LRILPMETVIATKGTGVVTCVPSNSPDDYITTKDLLHKPEYYGIKPEWIDHEIVPIMHTE
KYGDLTAKAIVEEKKIQSPKDKNLLAEAKKIAYKEDYYTGTMIYGPYKGEKVEQAKNK
VKADMIAAGEAFVYNEPESQDPQDPNSSSVDKLAAALEHHHHH

B.

SEQ ID NO: 3 G- E.coli crystal structure (185 amino acids) – tRNA synthetase editing domain

EGVEITFNVNDYDNTLTVYTTRPDTFMGCTYLAVAAGHPLAQKAAENNPELAAFIDECR
NTKVAEAEMATMEKKGVDTGFKAVHPLTGEEIPVWAANFVLMEYGTGAVMAVPGHD
QRDYEFASKYGLNIKPVILAADGSEPDLSQQALTEKGVLFNSGEFNGLDHEAAFNAIAD
KLTAMGVGERK

SEQ ID NO: 4 G+ Propionibacter acnes (185 aa) – tRNA synthetase editing domain

EGAYVDFTIDGHKEPVRVFTTRPDTLYGATFMVVAPDSALAQEIVSDEARPAFETYLDE
VKKKSEIERQATDHEKTGVPLGVEATNPVNGAKVPVWAGDYVLADYGTGAVMAVPA
HDQRDLDFARTYGIDVIPVIDTGEADPRESGVATTGDGVYQNSGFLNGIATKAEAIAKM
CEFLDEKGIGE

Figure 10(2)

SEQ ID NO: 5 from G- Pseudomonas aeruginosa (194 aa) – tRNA synthetase editing domain

GMEIGFPYDQASIGHAGQLKVFTTRPDTLMGATYVAVAAEHPLATQAAQNDPQLQAFI
DECKRGGVAEADIATQEKKGMATSLFVEHPLTGDKLPVWVANYVLMNYGEGAVMAV
PGHDERDFEFANKYGLPIRQVIAKVEGDDDFESSVWKEWYGAKDESVLTVNSGKYDNL
GYQAAFDAIGADLEAKGLGQAR

SEQ ID NO: 6 G+ Bacillus anthracis (183 aa) – tRNA synthetase editing domain
EGAEVHFNIDGTDEKFTVFTTRPDTLFGASYCVLAPEHALVADITTADQKEAVEAYINSV
KMKSDLERTELAKEKTGVFTGAYAVNPVNGEKLPIWIADYVLATYGTGAVMAVPAHD
ERDYEFASTFNLPMKEVVKGGDITKEAYTGDGAHVNSAFLDGLNKEEAIAKMIEWLEV
TSAGNQKV

SEQ ID NO: 7 from G+ Staphylococcus aureus (183 aa) – tRNA synthetase editing domain
EGAKVTFKIEQSDQNIEVFTTRPDTIYGTSFLVLSPEHPLVNEITTSDKEQEVKLYQNEA
SKKSDLERTDLAKEKTGVFTGTFAINPLSGDKLPIWIADYVLSTYGTGAVMAVPGHDER
DHEFATKFNLPIIEVIEGGEVQKYAYTGEGKHINSGELDGLENEAAISKAIELLESKGAGE
KKV

SEQ ID NO: 8 G+ Streptococcus pyogens (182 aa) – tRNA synthetase editing domain
GANVTFKVKDTDKNFTVFTTRPDTLFGATYAVLAPEHALVDAITTADQAEAVADYKRQ
ASLKSDLARTDLAKEKTGVWTGSYAINPVNGKEIPVWIADYVLASYGTGAIMAVPAHD
ERDWEFAKQFNLDIIPVLEGGNVEEAAFTEDGLHINSGFLDGLDKASAIAKMVEWLEAE
GVGNEKV

SEQ ID NO: 9 G+ Thermus thermophilus (187 aa) – tRNA synthetase editing domain
EGAEILFPVEGKEVRIPVFTTRPDTLFGATFLVLAPEHPLTLELAAPEKREEVLAYVEAA
KRKTEIERQAEGREKTGVFLGAYALNPATGERIPIWTADYVLFGYGTGAIMAVPAHDQR
DYEFARKFGLPIKKVIERPGEPLPEPLERAYEEPGIMVNSGPFDGTESEEGKRKVIAWLEE
KGLGKGR

SEQ ID NO: 10 Mycobacterium tuberculosis (186 aa) – tRNA synthetase editing domain
FEVDIEVFTTRPDTLFGATYLVLAPEHDLVDELVAASWPAGVNPLWTYGGGTPGEAIAA
YRRAMAAKSDLERQESREKTGVFVGSYAINPANGEPVPIFIADYVLAGYGTGAIMAVPG
HDQRDWDFARAFGLPIVEVIAGGNISESAYTGDGILVNSDYLNGMSVPAAKRAIVDRLE
SAGRGRARI

SEQ ID NO: 11 Candida albicans (251 aa) – tRNA synthetase editing domain
YVGIKIRLTDVAPQAQELFKKESLDVKENKVYLVAATLRPETMYGQTCCFVSPKIDYGV
FDAGNGDYFITTERAFKNMSFQNLTPKRGYYKPLFTINGKTLIGSRIDAPYAVNKNLRVL
PMETVLATKGTGVVTCVPSDSPDDFVTTRDLANKPEYYGIEKDWVQTDIVPIVHTEKYG
DKCAEFLVNDLKIQSPKDSVQLANAKELAYKEGFYNGTMLIGKYKGDKVEDAKPKVK
QDLIDEGLAFVYNEPE

Figure 10(3)

SEQ ID NO: 12 Aspergillus fumigatus (256 aa) – tRNA synthetase editing domain
YTAMKLQVKEWAPEIAELVKGKIEDDAKVYFVPATLRPETMYGQTCCFLGPKIKYGIFR
VKEKEYYIVTKRAAWNMAFQGIFFDSEHFPKTQDELPLVLEAPGSAFVGTLVNAPLSFH
TEGVRILPMEGVSATKGTGVVTSVPSDSPDDYATLVDLAKKPEYYGIKKEWAELEIFPLI
ETPTYGNLTAPTLVKKLKINSPKDVNQLAQAKELAYGEAYYKGTMLVGEFKGEPVSAA
KEKIRKSLYESGDAFPFADP

SEQ ID NO: 13 Trichophyton rubrum CP1 (256 aa) – tRNA synthetase editing domain
YTAMKLKVKEWSPKAKEIIQGKIEKDANVYFVPATLRPETMYGQTCCFVGPAISYGIFK
VKEKEYYVVTKRAAWNMAFQGIFFDVNNLPKSQDELPPVVEAPGSALIGTLVNAPLSFH
KEGVRILPMETVSANKGTGVVSCVPSDSPDDFATISDLAKKADYYGIQKEWAELEIHPLI
ETPTYGNLTAPALVKQLKINSPKDTVQLAQAKDLAYTEGFYKGKMLVGEFKGEPVQTA
KEKVRNSLIKSGDAFPFADP

SEQ ID NO: 14 Homo sapiens (253 aa) – tRNA synthetase editing domain
VGPQEYTLLKLKVLEPYPSKLSGLKGKNIFLVAATLRPETMFGQTNCWVRPDMKYIGFE
TVNGDIFICTQKAARNMSYQGFTKDNGVVPVVKELMGEEILGASLSAPLTSYKVIYVLP
MLTIKEDKGTGVVTSVPSDSPDDIAALRDLKKKQALRAKYGIRDDMVLPFEPVPVIEIPG
FGNLSAVTICDELKIQSQNDREKLAEAKEKIYLKGFYEGIMLVDGFKGQKVQDVKKTIQ
KKMIDAGDALIYMEPE

SEQ ID NO: 15 Trypanosoma brucei (259 aa) – tRNA synthetase editing domain
YTVVKLKVKNPLEQPALAPFSEIIGNRSVILPGATLRPETVIGQTNCWVSPNFSYMAYSIL
NGTGEEEIYIMTSRAARNLAYQNFTVNGKTGVDPSPLFEVDGAKLIGLPLSAPLCPYDTI
YTLPMQSIIETKGTGVVMSVPADSPDDYINYVQLVNKPDYRAKLGLKDEWVANKIVSLI
EVPGEMGRESAKYMCEKLKINGPNATDLLEEAKKVIYQAGFYQGVMIAGPFAGEKVSA
AKVKTVKLLEEQNAAIRYYEP

C.

SEQ ID NO: 16 *Saccharomyces cerevisiae* tRNA-Leu (genomic)
gggagtttgg ccgagtggtt taaggcgtca gatttaggct ctgatatctt cggatgcaag ggttcgaatc ccttagctct cacca

SEQ ID NO: 17 *Saccharomyces cerevisiae* tRNA-Ile (genomic)
gaaactataa ttcaattggt tagaatagta ttttgataag gtacaaatat aggttcaatccctgttagtt tcat

D.

SEQ ID NO: 18 *Saccharomyces cerevisiae* tRNA-Leu
G G U U G U U U G m^2G C ac^4C G A G C Gm G D C D A A G G C m_2^2G C C U G A Ψ U
m^5C A A m^1G C Ψ C A G G U A U C G U A A G A U G m^5C A A G A G T Ψ C G A A U C U
C U U A G C A A C C A C C A

Figure 10(4)

SEQ ID NO: 19 Haloferax Volcanii tRNA-Leu
G C G A G G G U A G C U A A fa^{7}d^{7}G U C A G G A A A A A G C m$_{2}^{2}$G G C G G A C U C A
A m^{1}G A Ψ C C G C U C C C G U A G G G G U Cm^{5}C G U G G G m^{1}Ψ Ψ Cm m^{1}I A A U C C
C U C C C C U C G C A C C A

SEQ ID NO: 20 Phage T4 tRNA-Leu
G C G A G A A s^{4}U G G U C A A A D U m^{2}G G D A A A G G C A C A G C A C U unkU A A
ms^{2}i^{6}A A Ψ G C U G C G G A A UGA U U U C C U U G U G G G T Ψ C G A G U C C C A C
U U C U C G C A C C A

SEQ ID NO: 21 Phage T5 tRNA-Leu
G G GG C U A U G C U G G A A C D Gm G D A G A C A A U A C G G C C U U A Gm^{6}A U
Ψ C C G U A G C U U A A A U G C G U G G G A G T Ψ C G A G U C U C C C U A G C C C
C A C C A

SEQ ID NO: 22 Bacillus Subtilis tRNA-Leu
GCGGG U G U G C G G G A A U D G G D A G A C C G G C U A G A U U C A Gm^{1}G A Ψ
C U A G G G U C U U U A U G G A C C U G A G G G T Ψ C A m^{1}A G U C C C U U C A C
C C G C A C C A

SEQ ID NO: 23 E.Coli tRNA-Leu
G C C C G G A s^{4}U G G U G GA A DC GmGD A G A CAC A AGGGA Ψ U unkA A A ms^{2}i^{6}A
A Ψ C C C U C G G C G U U C G C G C U G U G C G G G T Ψ C A A G U C C C G C U C C
G G G U A C C A

SEQ ID NO: 22 E.Coli tRNA-Leu2
GCGAA G G U G G C G G A A D D Gm G D A G A C G C G C U A G C U U C A G unkG Ψ
G Ψ U A G U G U C C U U A C G G A C G U G G G G G T Ψ C A A G U C C C C C C C C U
C G C A C C A

SEQ ID NO: 23 E.Coli tRNA-Leu3
GCCGA G G U G G U G G A A D D Gm G D A G A C A C G C U A C C U U G A G unkG Ψ
G G U A G U G C C C A A U A G G G C U U A C G G G T Ψ C A A G U C C C G U C C U C
G G U A C C A

SEQ ID NO: 24 Salmonella Typhi tRNA-Leu
GCGAA G G U G G C G G A A D D Gm G D A G A C G C G C U A G C U U C A G unkG Ψ
G Ψ U A G U G U C C U U A C G G A C G U G G G G G T Ψ C A A G U C C C C C C C C U
C G C A C C A

Figure 10(5)

SEQ ID NO: 25 Rhodospiril.Rub tRNA-Leu
GCCUU U G U A G C G G A A D G G D A A C G C G G C A G A C U C A A unkA A Ψ C U G C U U U G G U A A C C C A G G U G G U A G T Ψ C G A C U C U C C C C A A A G G C A C C A

SEQ ID NO: 26 Anacystis Nidulans tRNA-Leu
GGGCA A G U G G C G G A A U D G G D A G A C G C A G C A G A C U C A A unkA A Ψ C U G C C G C U A G C G A U A G U G U G U G G G T Ψ C G A G U C C C A C C U U G C C C A C C A

SEQ ID NO: 27 Anacystis Nidulans tRNA-Leu2
GCGGA A C U G G C G G A A U D G G D A G A C G C G C U A G A U U C A Gm^{1}G Ψ Ψ C U A G U G G U U U C A C G A C U G U C C G G G T Ψ C A A G U C C C G G G U U C C G C A C C A

SEQ ID NO: 28 Bacillus Stearo tRNA-Leu
G C C G A U G s^{4}U G G C G GA A UD G GC A Gm^{1}A C G C G C A C G A C U Cm A A ms^{2}i^{6}A A Ψ C G U G U G G G C U U U G C C C G U G U G G G T Ψ C G A C U C C C A C C A U C G G C A C C A

SEQ ID NO: 29 Glycine Max tRNA-Leu
GCCUU G G U G G U G A A A U Gm G D A G C C A C G C G A G A C U Cm A A unkA A Ψ C U C G U G C U A C A G A G C G U G G A G G T Ψ C G A G U C C U C U U C A A G G C A C C A

SEQ ID NO: 30 Glycine Max tRNA-Leu2
G G GG A U A U G G C G A A A U U Gm G D A G A C G C Ψ A C G G A C U Um A A unkA A Ψ C C G U C G A C U U A A G A A A U C A U G A G G G T Ψ C A A G U C C C U C U A U C C C C A C C A

SEQ ID NO: 31 Glycine Max tRNA-Leu3
GCCGC U A U G G U G A A A U U Gm GD A G A C A C G C U G C U C U U Am^{7}G m^{1}G A A G C A G U G C U A G A G C A U C U C G G T Ψ C G A G U C C G A G U A G C G G C A C C A

SEQ ID NO: 32 Phaseolus Vulgaris tRNA-Leu1
GGCUU G A U G G U G A A A U U Gm G D A G A C A C G C G A G A C U Cm A A unkA A U C U C G U G C U A A A G A G C G U G G A G G T Ψ C G A G U C C U C U U C A A G U C A C C A

Figure 10(6)

SEQ ID NO: 33 Phaseolus Vulgaris tRNA-Leu2
G G GG A U A U G G C G A A A U U Gm G D A G A C G C Ψ A C G G A C U unkU A A
unkA A Ψ C C G U C G A C U U A A U A A A U C A U G A G G G T Ψ C A A G U C C C U
C U A U C C C C A C C A

SEQ ID NO: 34 Phaseolus Vulgaris tRNA-Leu3
GCCGC U A U G G U G A A A U U Gm GD A G A C A C G C U G C U C U U Am^{7}G m^{1}G A
A G C A G U G C U A G A G C A U C U C G G T Ψ C G A G U C C G A G U A G C G G C A
C C A

SEQ ID NO: 35 Spinacia Oleracea tRNA-Leu
GCCGC U A U G G U G A A A U U Gm GD A G A C A C G C U G C U C U U Am^{7}G m^{1}G A
A G C A G U G C G A G A G C A U C U C G G T Ψ C G A G U C C G A G U A G C G G C A
C C A

SEQ ID NO: 36 Neurospora Crassa tRNA-Leu1
AUCCG A G U G A U G G A A D G G D A G A C A U A A C A U G C U unkU A A A A C A
U G U G G G C U U C A A G C U G U G A A G G T Ψ C A A G U C C U U C U U C G G A
U A C C A

SEQ ID NO: 37 Neurospora Crassa tRNA-Leu2
AUAGG U G U G C U G G A A D U G G D A G A C A G G U U C C G Ψ U U A Gm^{1}G C C
G G A A U G G U U U A A A A A C U G U A C A A G T Ψ C A A G U C U U G U C A U C
U A U A C C A

SEQ ID NO: 38 Saccharomyces Cer. tRNA-Leu
GCUAU U U U G G U G G A A D U G G D A G A C A Cm$_{2}$^{2}G A U A C Ψ C U cmnm^{5}U A A
m^{1}G A Ψ G U A U U A C U U U A C A G U A U G A A G G T Ψ C A A G U C C U U U A A
A U A G C A C C A

SEQ ID NO: 39 Solanum Tuberosum tRNA-Leu
G U C A G G A U G G C ac^{4}C G A G D Gm G D C acp^{3}U A A G G C m$_{2}$^{2}G C C A G A C U
unk A A m^{1}G U Ψ C U G G Um C U U C G U A A G A G G G m^{5}C G U G G G T Ψ C A m^{1}A
A U C C C A C U U C U G A C A C C A

SEQ ID NO: 40 Phaseolus Vulgaris tRNA-Leu1
G U C A G G A U G m^{2}G C ac^{4}C G A G D Gm G D C acp^{3}U A A G G C m$_{2}$^{2}G C C A G A C U
unk A A m^{1}G Ψ Ψ C U G G Um C U U C G A G A G A G G G m^{5}C G U G G G T Ψ C A m1A
A U C C C A C U U C U G A C A C C A

Figure 10(7)

SEQ ID NO: 41 Phaseolus Vulgaris tRNA-Leu2
G U C A G G A U G m^2G C ac^4C G A G D Gm G D C acp3U A A G G C m_2^2G C C A G A C U
unk A A m^1G Ψ Ψ C U G G Um C U U C G A A A G A G G G m^5C G U G G G T Ψ C A m^1A
A U C C C A C U U C U G A C A C C A

SEQ ID NO: 42 Phaseolus Vulgaris tRNA-Leu3
G A U A G U U U G m^2G C ac^4C G A G D Gm G D C acp3U A A G G C m_2^2G C C A G A Ψ U
unk A G m^1G C Ψ C U G G Um C C G A A A unk G G G m^5C G U G G G T Ψ C A m^1A A U C
C C A C A G C U G U C A C C A

SEQ ID NO: 43 Phaseolus Vulgaris tRNA-Leu4
G C U GG U U U G G C ac^4C G A G A Gm G D D A A G G C m_2^2G G A A G A C U unk A A
m^1G A Ψ C U U C Um G C A G U C A A C U G C G m^5C A U G G G T Ψ C G m^1A A C C C
C A U A G C C A G C A C C A

SEQ ID NO: 44 Rat Liver A tRNA-Leu1
C U U U U A U m^1A m^2GG A U A G A A G D A A U C C A Ψ U G G U C U U A Gm^1G A A
C C AA A A A C m^5C U U G G U G C A A C U C C A A A U A A A A G U A C C A

SEQ ID NO: 45 Candida Albicans tRNA-Leu
G A U A C G A U G G C ac^4C G A G D Gm G D D A A G G C m_2^2G A A G G A U G C A
Gm^{1}G Ψ Ψ C C U U U G G G C AUU G C C C G m^5C G C A G G T Ψ C G m^1A A C C C U G
C U C G U G U C G C C A

SEQ ID NO: 46 Saccharomyces Cer. tRNA-Leu1
G G U U G U U U G m^2G C ac^4C G A G C Gm G D C D A A G G C m_2^2G C C U G A Ψ U
m^5C A A m^1G C Ψ C A G G U A U C G U A A G A U G m^5C A A G A G T Ψ C G A A U C U
C U U A G C A A C C A C C A

SEQ ID NO: 47 Saccharomyces Cer. tRNA-Leu2
GG G A G U U U G m^2G C ac^4C G A G D Gm G D D D A A G G C m_2^2G Ψ C A G A Ψ U U A
Gm^{1}G C Ψ C U G A U A U C U U C G G A U G m^5C A A G G G T Ψ C G m^1A A U C C C U
U A G C U C U C A C C A

SEQ ID NO: 44 Saccharomyces Cer. tRNA-Leu3
G G A GG G U U G m^2G C ac^4C G A G D Gm G D C D A A G G C m_2^2G G C A G A Cm U U
A Am^{1}G A Ψ C U G U U G G A C GG U U G U C C Gm^{5}C G C G A G T Ψ C G m^1A A C C U
C G C A U C C U U C A C C A

SEQ ID NO: 45 Torulopsis Utilis tRNA-Leu
GGAUC U U U G m^2G C ac^4C G A G C Gm G D D U A A G G C m_2^2G C U C G A Cm U Cm
A A m^1G A Ψ C G A G U A U C G U A A G A U G m^5C A U G A G T Ψ C G m^1A A U C U C
A U A G G A U C C A C C A

Figure 10(8)

SEQ ID NO: 46 Candida Cylindra. tRNA-Leu
G G C C G U U U G m^2G C ac4C G A G D Gm G D C D A A G G C m_2^2G U C U G A Cm U Cm A A m^1G A Ψ C A G A Um C U C G U A A G A G G m^5C G U G U G T Ψ C G m^1A A C C A C A C A G C G G U C A C C A

SEQ ID NO: 47 Candida Cylindra. tRNA-Leu2
GGUUC U C U G G C ac^4C G A G D G G D C D A A G G C m_2^2G C A U G G Ψ U I A Gm^1G Ψ C C A U G U C U C U U C G G A G G m^5C G C G A G T Ψ C G m^1A A C C U C G C G G G A A U C A C C A

SEQ ID NO: 48 Candida Cylindra. tRNA-Leu3
GGCUC U C U G G C ac^4C G A G D G G D C D A A G G C m_2^2G C U A G G G U I A Gm^1G Ψ C C U A G U C U C U U C G G A G G m^5C G C G A G T Ψ C G m^1A A C C U C G C G G G A G U C A C C A

SEQ ID NO: 49 Phaseolus Vulgaris tRNA-Leu1
G U C A G G A U G m^2G C ac^4C G A G D G G D C ^{acp3U} A A G G C m_2^2G C C A G A C U unk A A ^{mIG} Ψ Ψ C U G G Um C U U C G A G A G A G G G m^5C G U G G G T Ψ C A m^1A A U C C C A C U U C U G A C A C C A

SEQ ID NO: 50 Phaseolus Vulgaris tRNA-Leu2
G U C A G G A U G m^2G C ac^4C G A G D G G D C acp3U A A G G C m_2^2G C C A G A C U unk A A m^1G Ψ Ψ C U G G Um C U U C G A A A G A G G G m^5C G U G G G T Ψ C A m^1A A U C C C A C U U C U G A C A C C A

SEQ ID NO: 51 Phaseolus Vulgaris tRNA-Leu3
G A U A G U U U G m^2G C ac^4C G A G D G G D C acp^3U A A G G C m_2^2G C C A G A Ψ U unk A G m^1G C Ψ C U G G Um C C G A A A unk G G G m^5C G U G G G U Ψ C A m^1A A U C C C A C A G C U G U C A C C A

SEQ ID NO: 52 Phaseolus Vulgaris tRNA-Leu4
G C U GG U U U G G C ac^4C G A G A G G D D A A G G C m_2^2G G A A G A C U unk A A m^1G A Ψ C U U C Um G C A G U C A A C U G C G m^5C A U G G G T Ψ C G m^1A A C C C C A U A G C C A G C A C C A

SEQ ID NO: 53 Solanum Tuberosum tRNA-Leu
G U C A G G A U G G C ac^4C G A G D G G D C acp^3U A A G G C m_2^2G C C A G A C U unk A A m^1G U Ψ C U G G Um C U U C G U A A G A G G G m^5C G U G G G T Ψ C A m^1A A U C C C A C U U C U G A C A C C A

Figure 10(9)

SEQ ID NO: 54 Cucumis Sativus tRNA-Leu
G U C A G G A U G m^2G C m^5C G A G D G G D C acp^3U A A G G C m_2^2G C C A G A C U
unkU A A m1G Ψ Ψ C U G G Um C C U C U A A G G A G G G m^5C G U G G G T Ψ C A
m^1A A U C C C A C U U C U G A C A C C A

SEQ ID NO: 55 Caenorhabdi.Eleg. tRNA-Leu
G G A G A G A U G G C ac^4C G A G C G G D C U A A G G C G C U G G U U U I A G G C
A C C A G U C C C U U C G G G G G C G U G G G T U C G A A U C C C A C U C U C U U
C A C C A

SEQ ID NO: 56 Mycoplasma Capric. tRNA- Leu2
C C C C A A G unkU G G C G G A A U A G G D A G m^1AC GC A U U GG A C U cmnm^{5}Um
A A m^6A A Ψ C C A A C G G G C U U A A U A U C C U G U G C C G G U Ψ C A A G U C
C G G C C U U G G G G A C C A

SEQ ID NO: 57 Mycoplasma Capric. tRNA- Leu1
GCCUU U U U G G C G G A A U D G G C A Gm1A C G C A U U A G A C U Cm A A m^6A
A Ψ C U A A C G A A GAA A U U C G U A U C G G U Ψ C G A A U C C G A U A A A G G
G C A C C A

SEQ ID NO: 58 Haloferax Volcanii YX tRNA- Leu5
G C G C G G G U A G C C A A fa7d7GU G GC C A A A GGCm_2^2G C A G C G C U mo^5U A
G m^1G A C G C U G U G G U G U A G A C C U U m^5C G C A G G m^1Ψ Ψ Cm G A A C C C
U G U C C C G C G C A C C A

SEQ ID NO: 59 Haloferax Volcanii YX tRNA- Leu4
GCGGG G G U G G C U G A fa^7d^7G C C A G G C C A A A A G C m^2G G C G G A C U U A
Am^{1}G A Ψ C C G C U C C C G U A G G G G U U C G C G A Gm^{1}Ψ Ψ Cm G A A U C U C G
U C C C C C G C A C C A

SEQ ID NO: 60 Haloferax Volcanii tRNA- Leu3
G C G U G G G U A G C C A A fa^7d^7G C C A G G C C A A C G G C m_2^2G C A G C G U U G
A Gm^{1}G G m^5CG C U G U C C U G U A G A G G U Cm^{5}C G C C G G m^1Ψ Ψ Cm m^1I A A U
C C G G U C C C A C G C A C C A

SEQ ID NO: 61 Haloferax Volcanii tRNA- Leu2
GCAGG G A U A G C C A Afa^7d^7G U C U G G C C A A C G G C m_2^2G C A G C G U U C A
Gm^{1}G G C G C U G U C U C A U A G G A G U C m^5C G C A G G m^1Ψ Ψ Cm m^1I A A U C C
U G C U C C C U G C A C C A

SEQ ID NO: 62 Haloferax Volcanii tRNA- Leu1
G C G A G G G U A G C U A A fa^7d^7G U C A G G A A A A A G C m_2^2G G C G G A C U C A
Am^{1}G A Ψ C C G C U C C C G U A G G G G U Cm5C G U G G G m^1Ψ Ψ Cm m^1I A A U C C
C U C C C C U C G C A C C A

FIGURE 11A

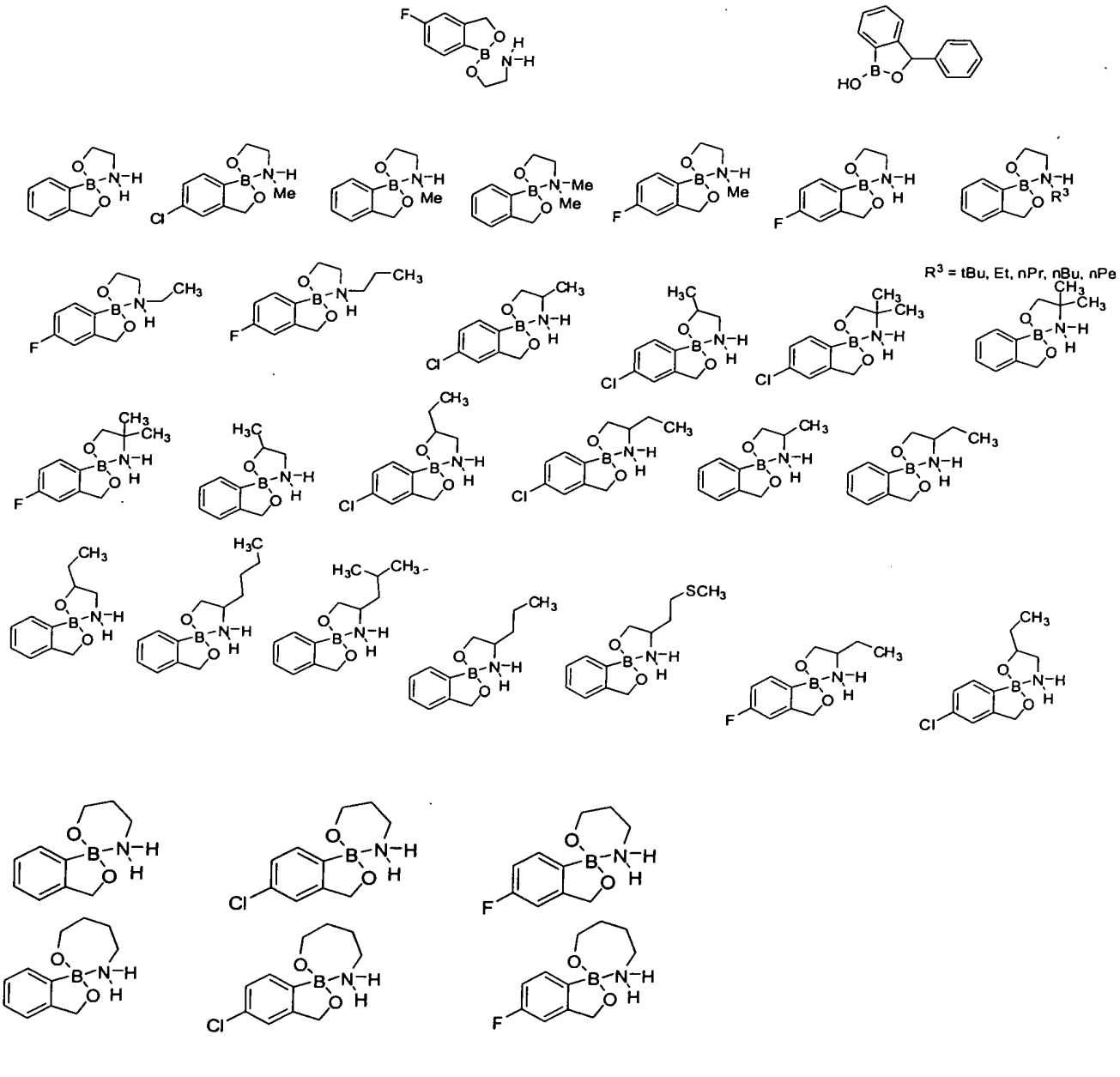


FIGURE 11B

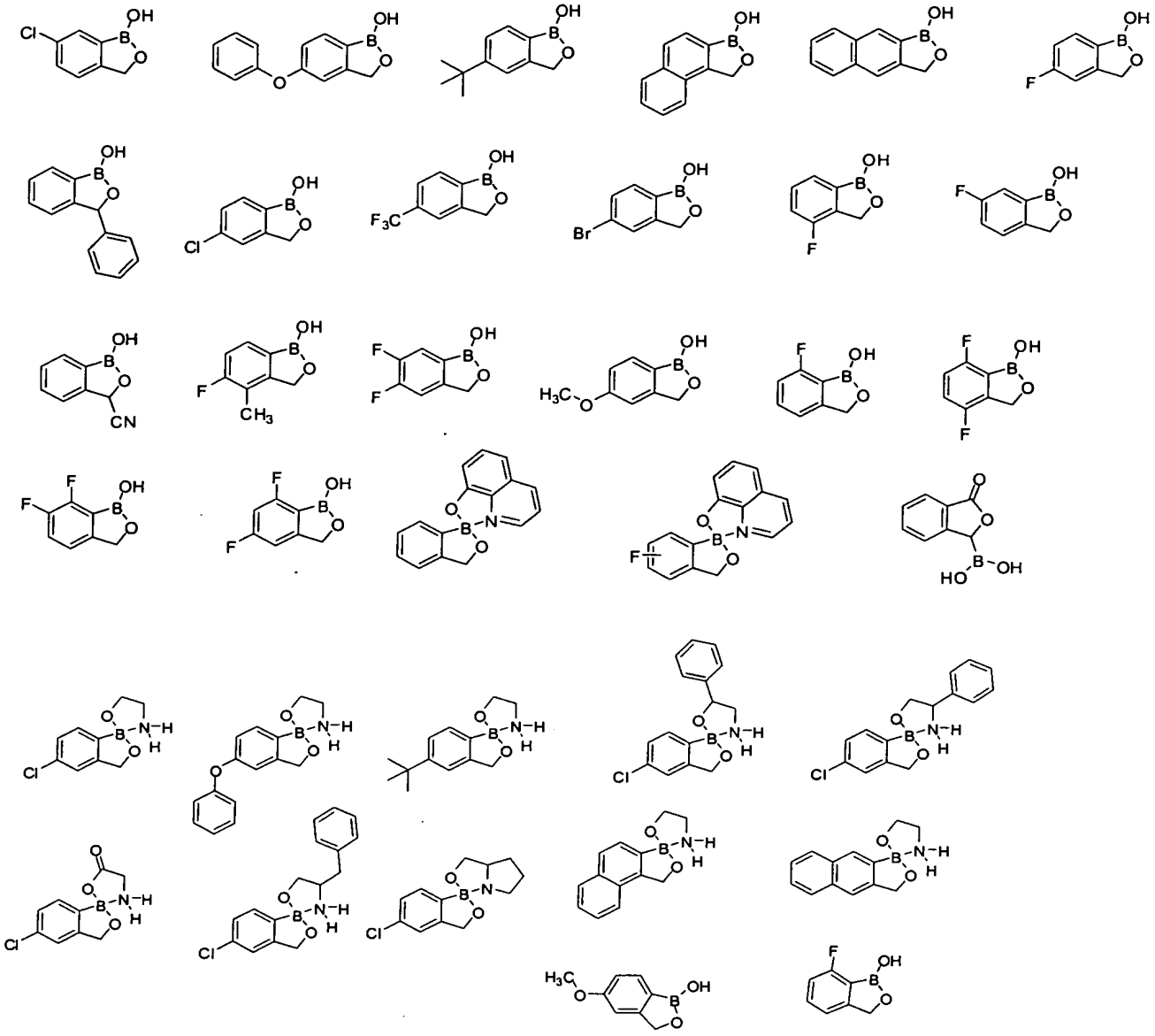


FIGURE 11C

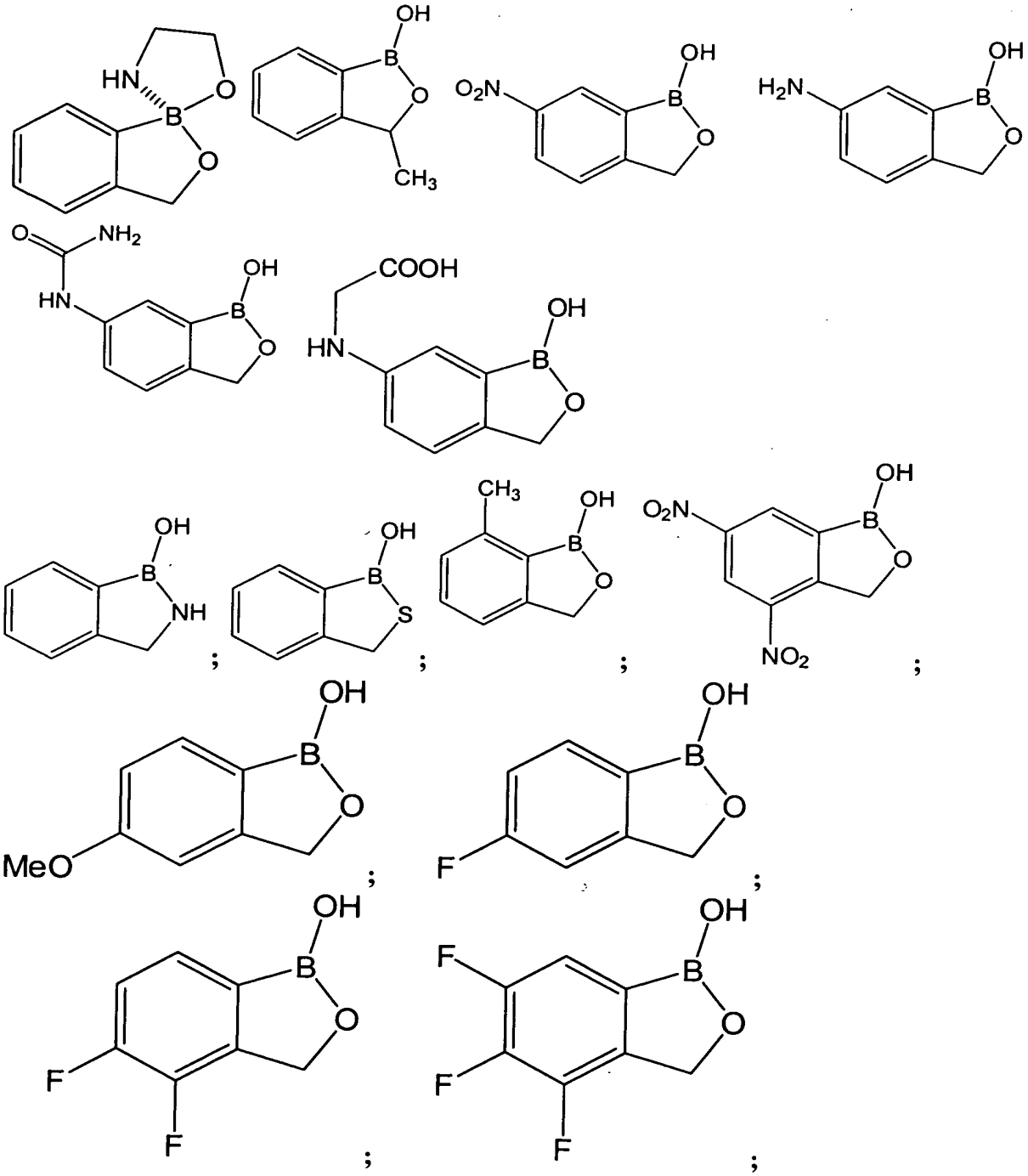
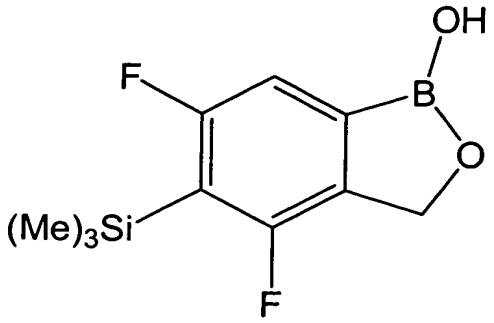
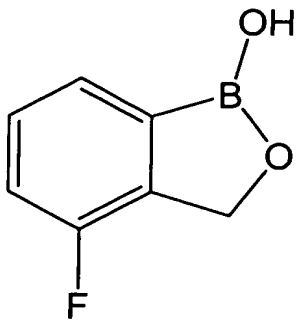

HN
O
B
O
OH
B
O
CH3
O2N
OH
B
O
H2N
OH
B
O
O
NH2
HN
OH
B
O
COOH
HN
OH
B
O
OH
B
NH
OH
B
S
CH3
OH
B
O
O2N
OH
B
O
NO2
MeO
OH
B
O
F
OH
B
O
F
F
OH
B
O
F
F
OH
B
O
F
F

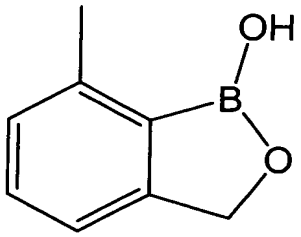
FIGURE 11D


OH
F
B
O
(Me)3Si
F

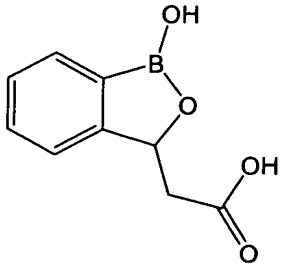
;


OH
B
O
F

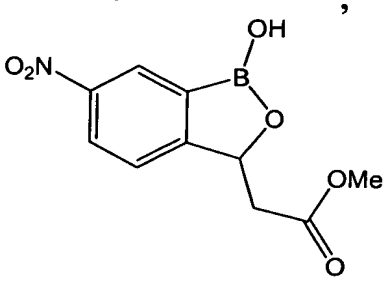
;


OH
B
O

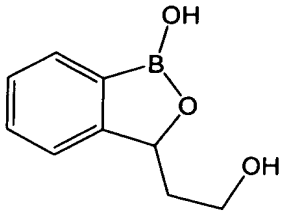
;


OH
B
O
OH
O

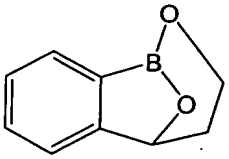
;


O2N
OH
B
O
OMe
O

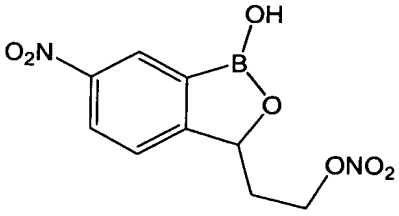
;


OH
B
O
OH

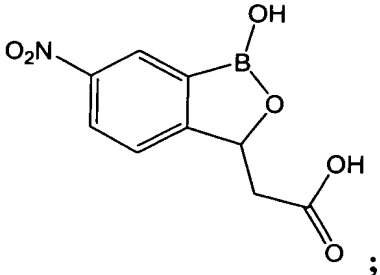
;


O
B
O

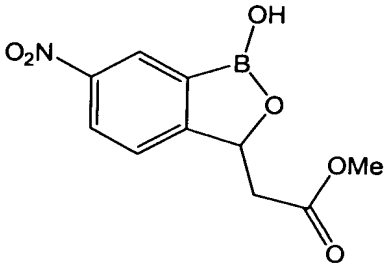
;


O2N
OH
B
O
ONO2

;


O2N
OH
B
O
OH
O

;


O2N
OH
B
O
OMe
O

;

FIGURE 11E

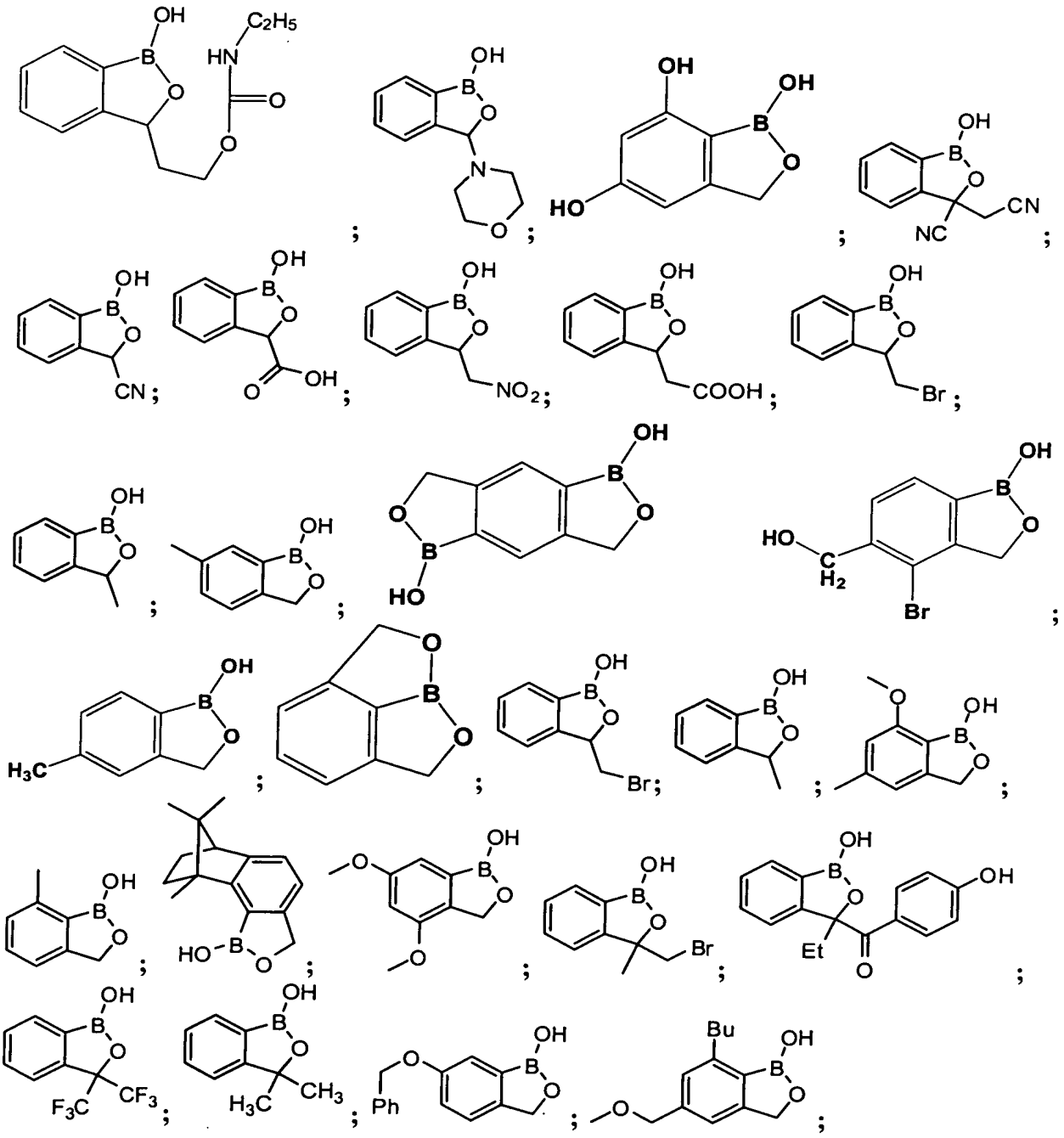


FIGURE 11F

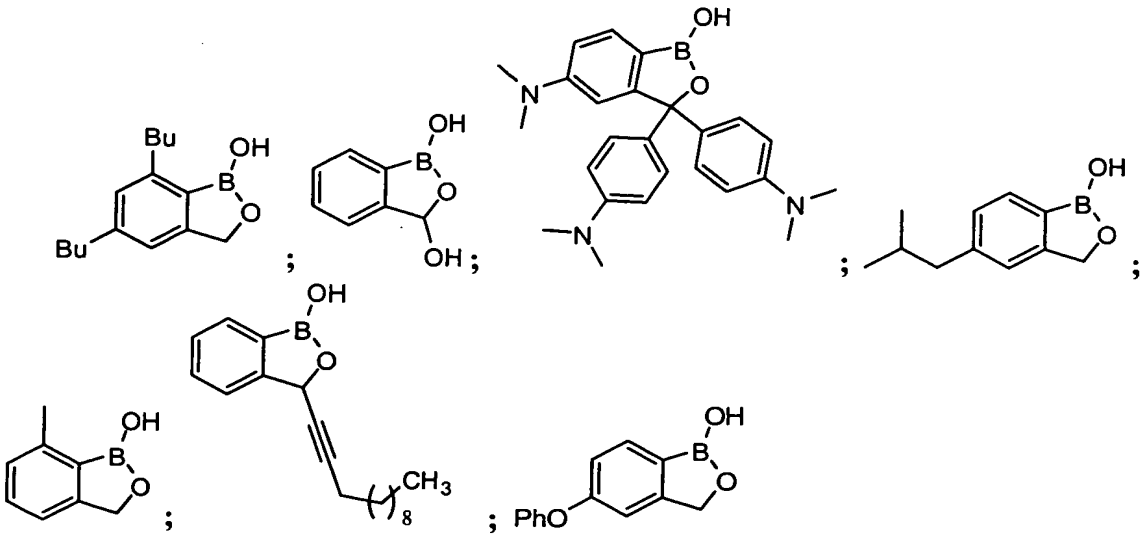


FIGURE 12A

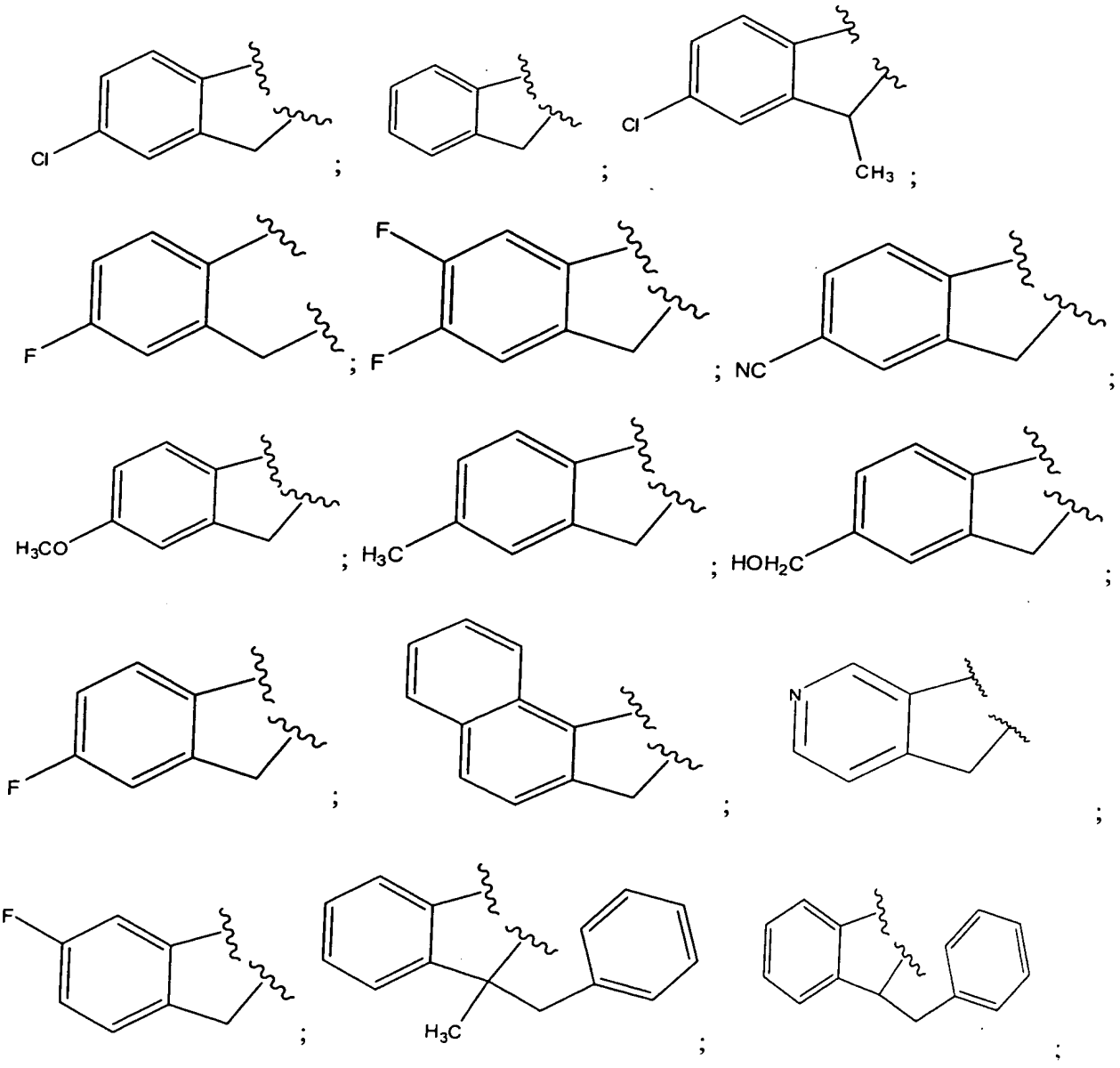


FIGURE 12B

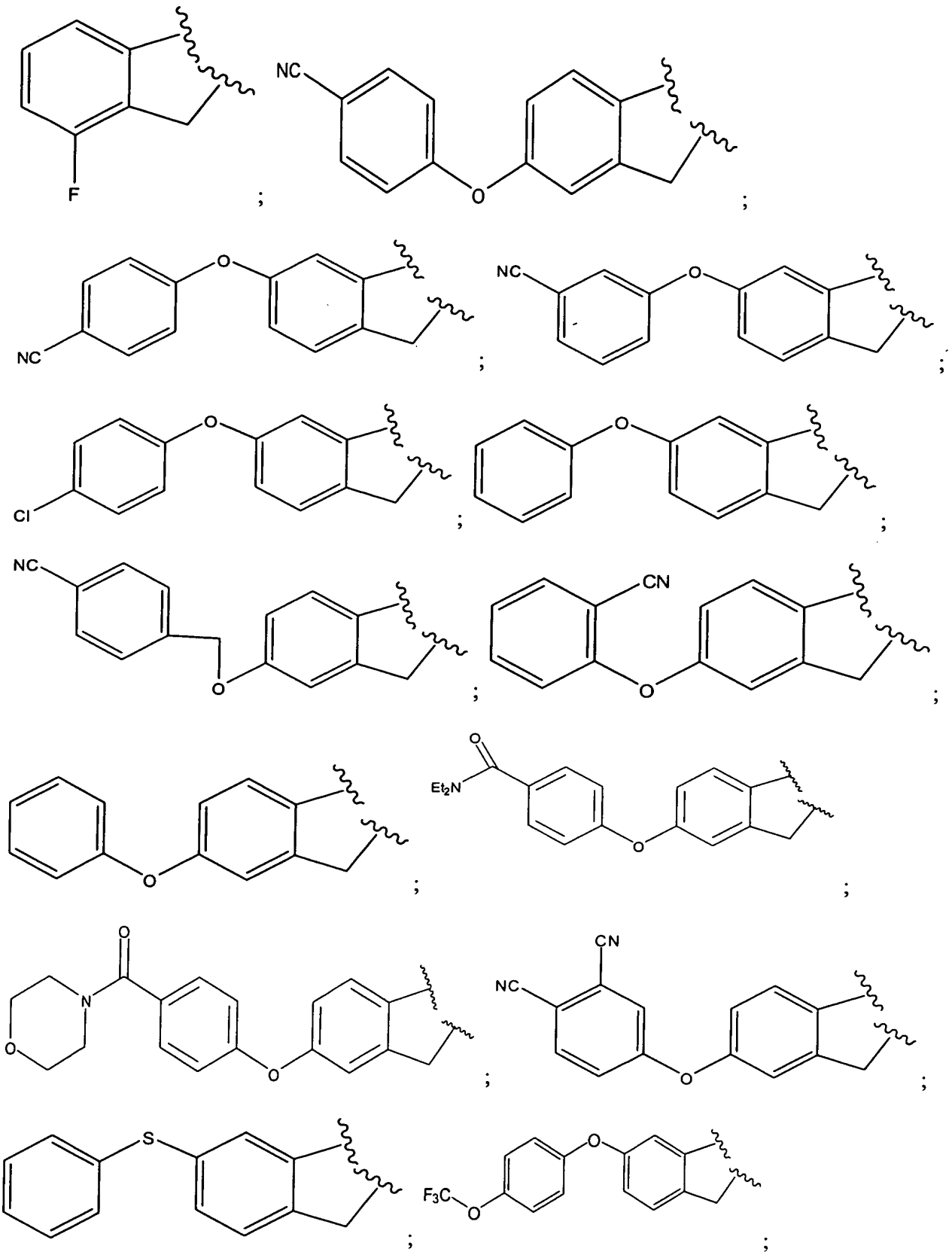


FIGURE 12C

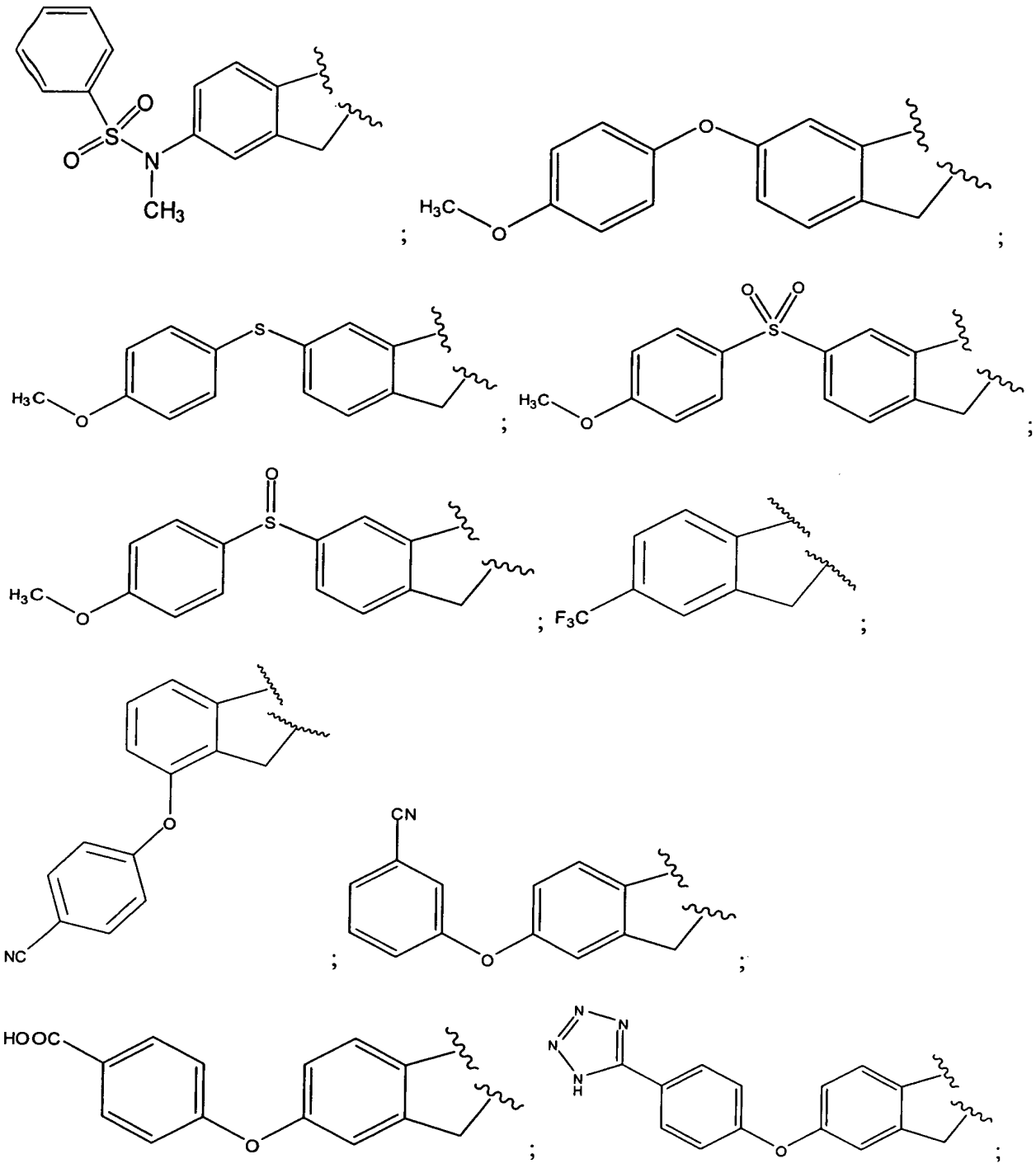


FIGURE 12D

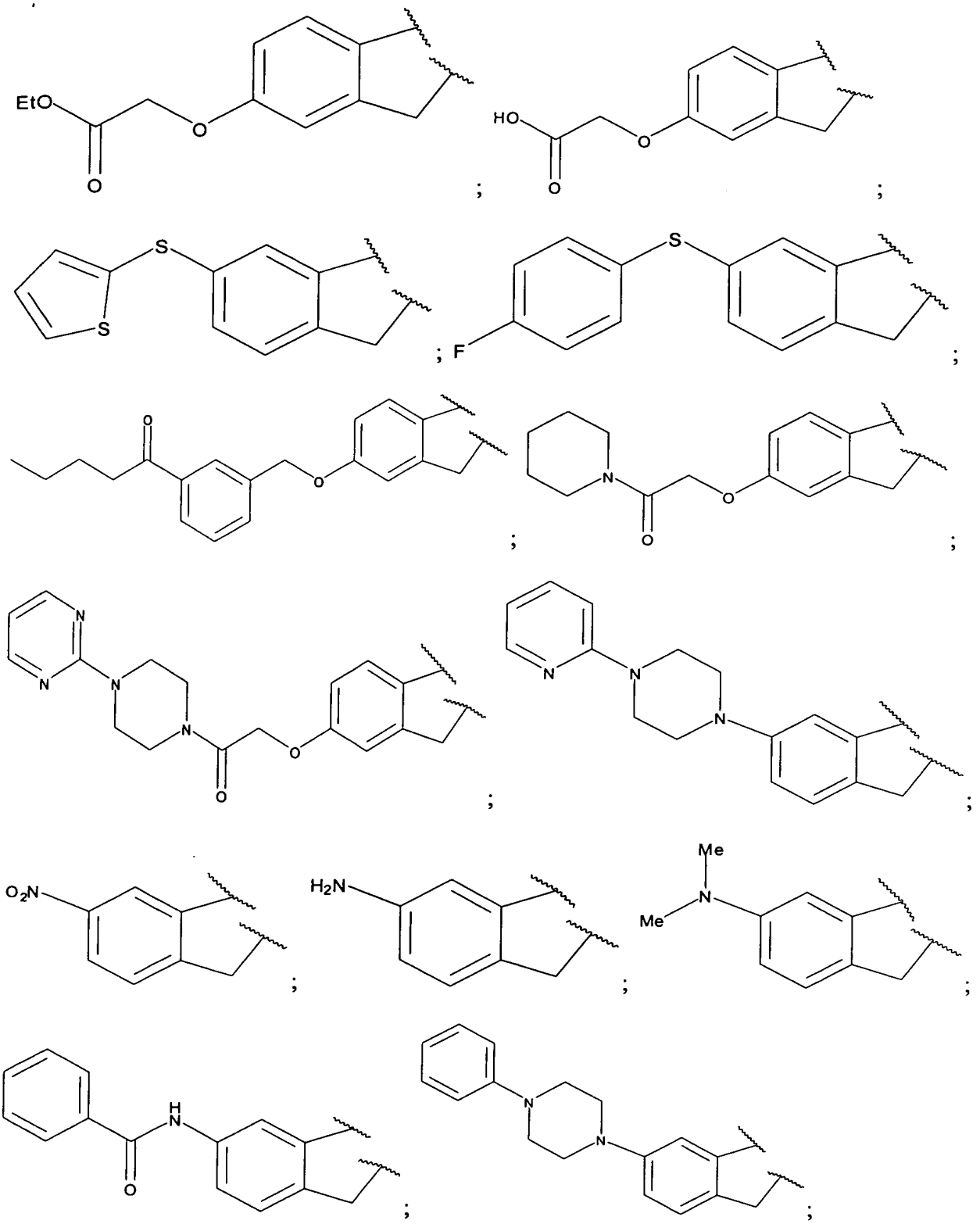


FIGURE 12E

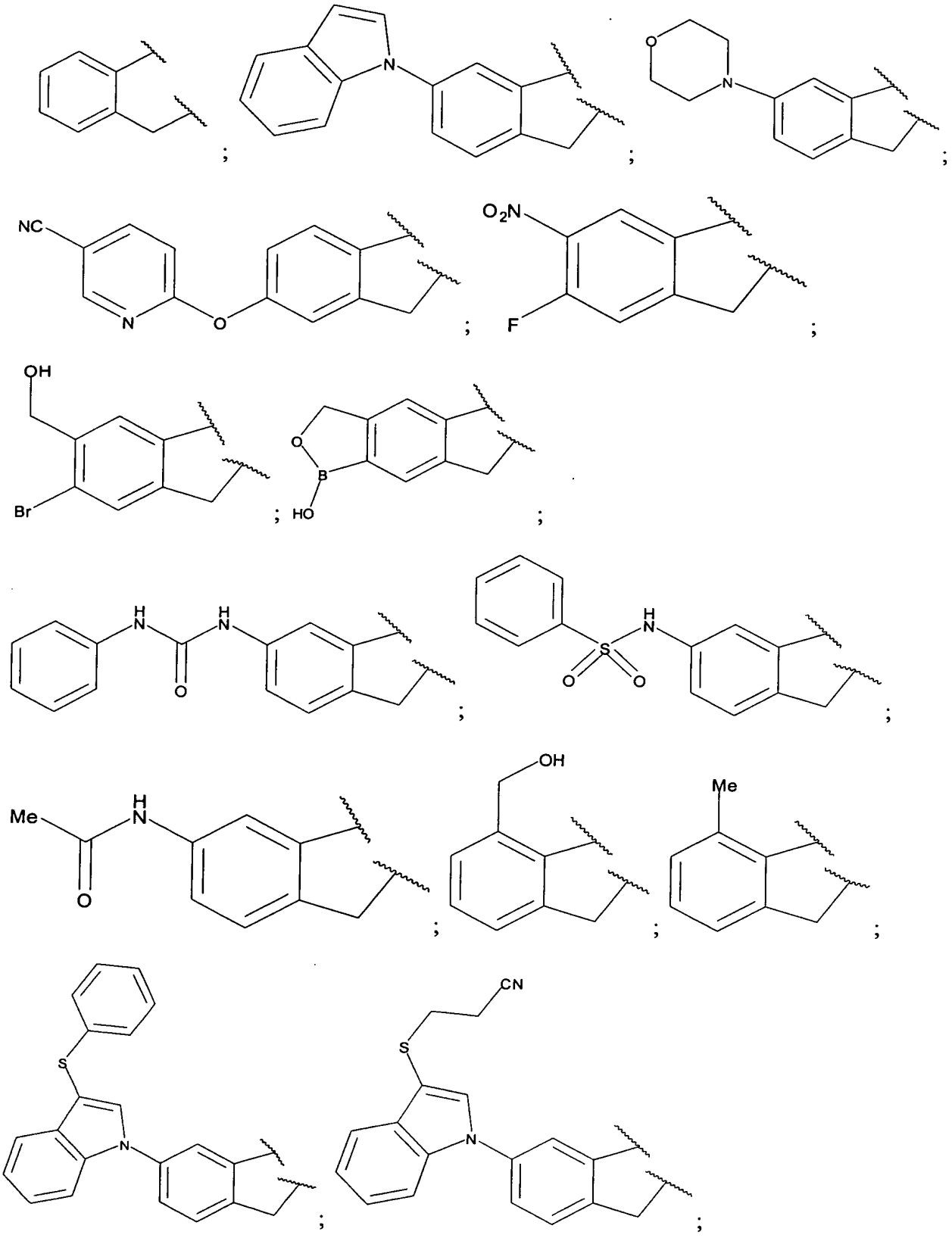


FIGURE 12F

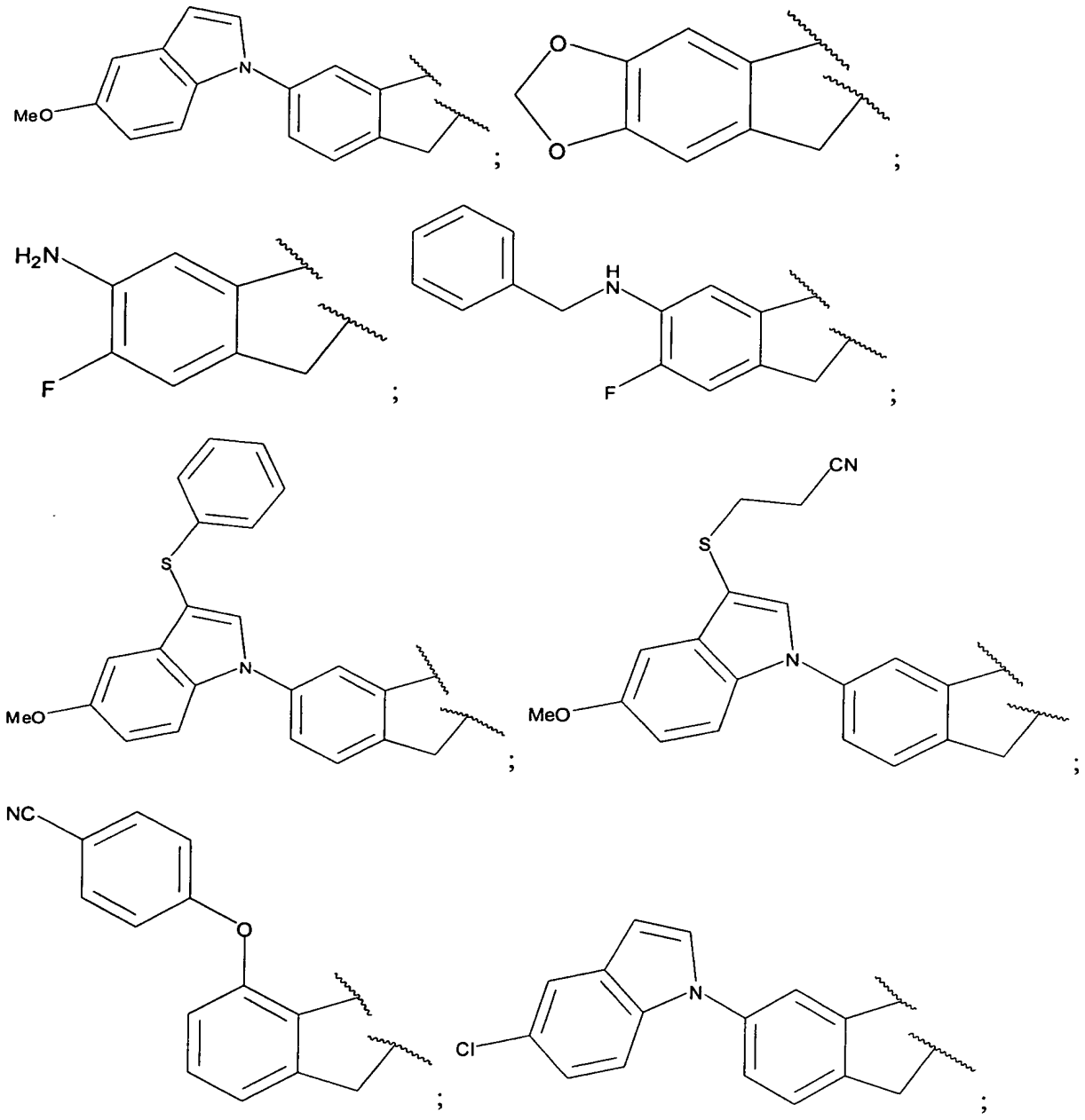
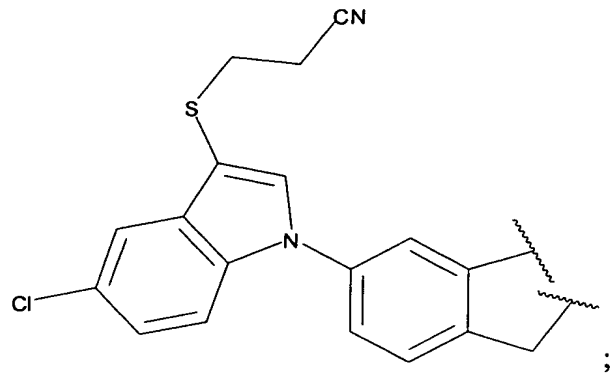


FIGURE 12G



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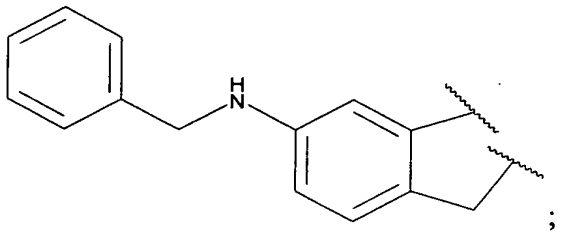

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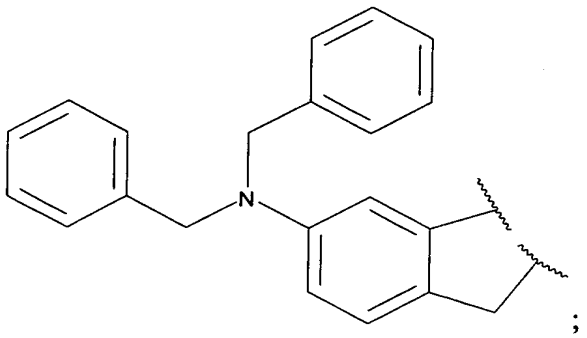

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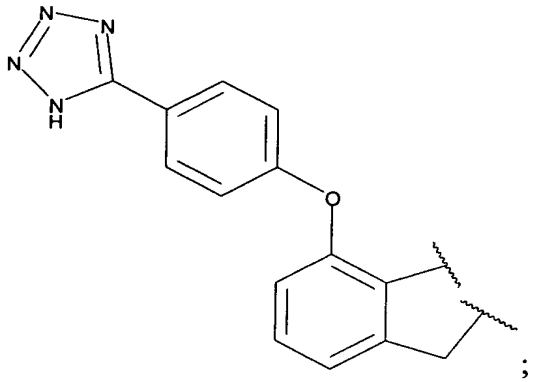

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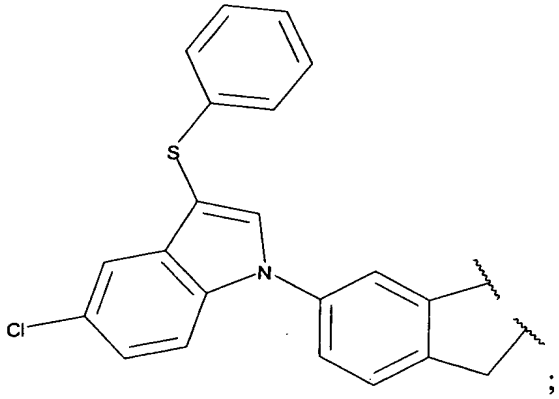

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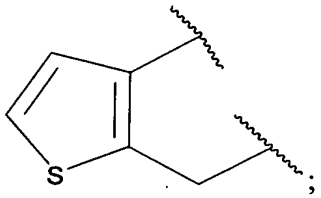

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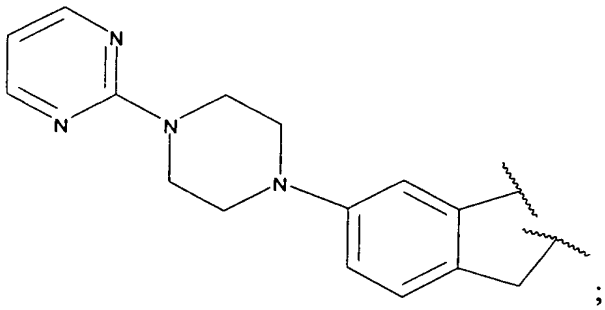

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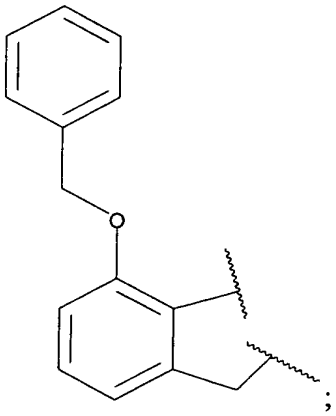

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FIGURE 12H

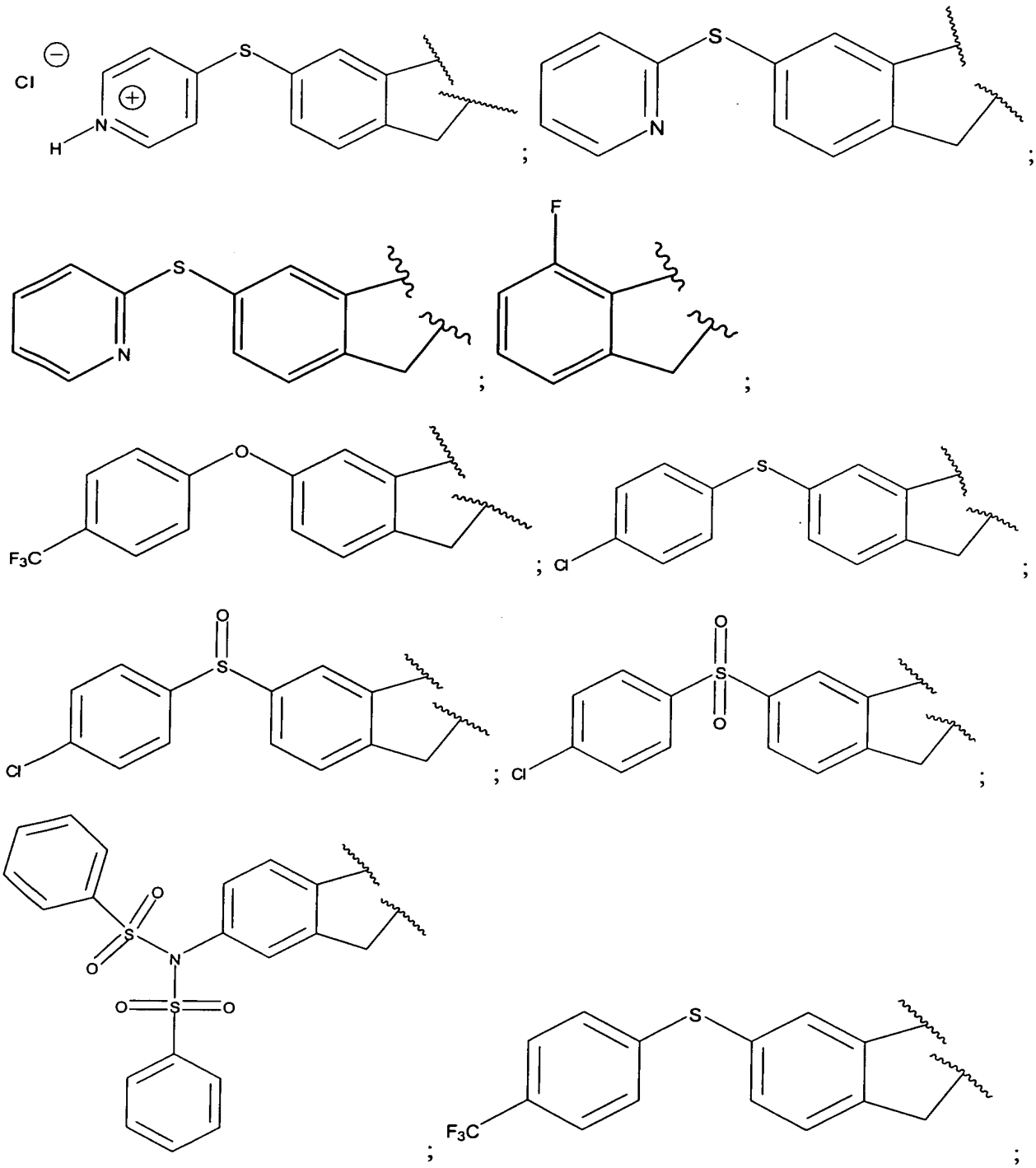
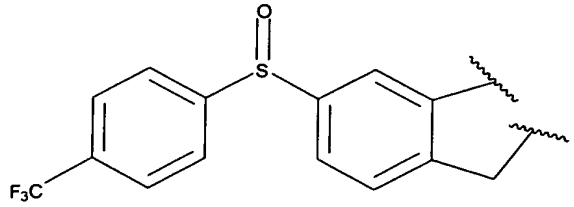


FIGURE 12I



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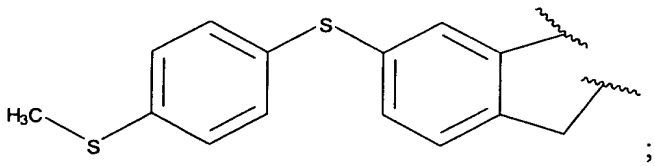

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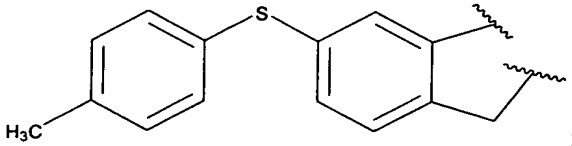
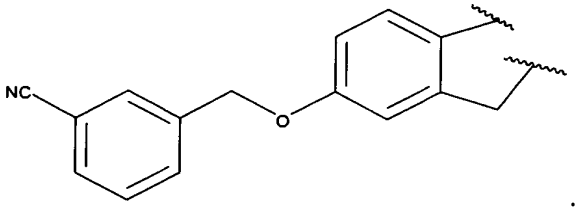


; and



.

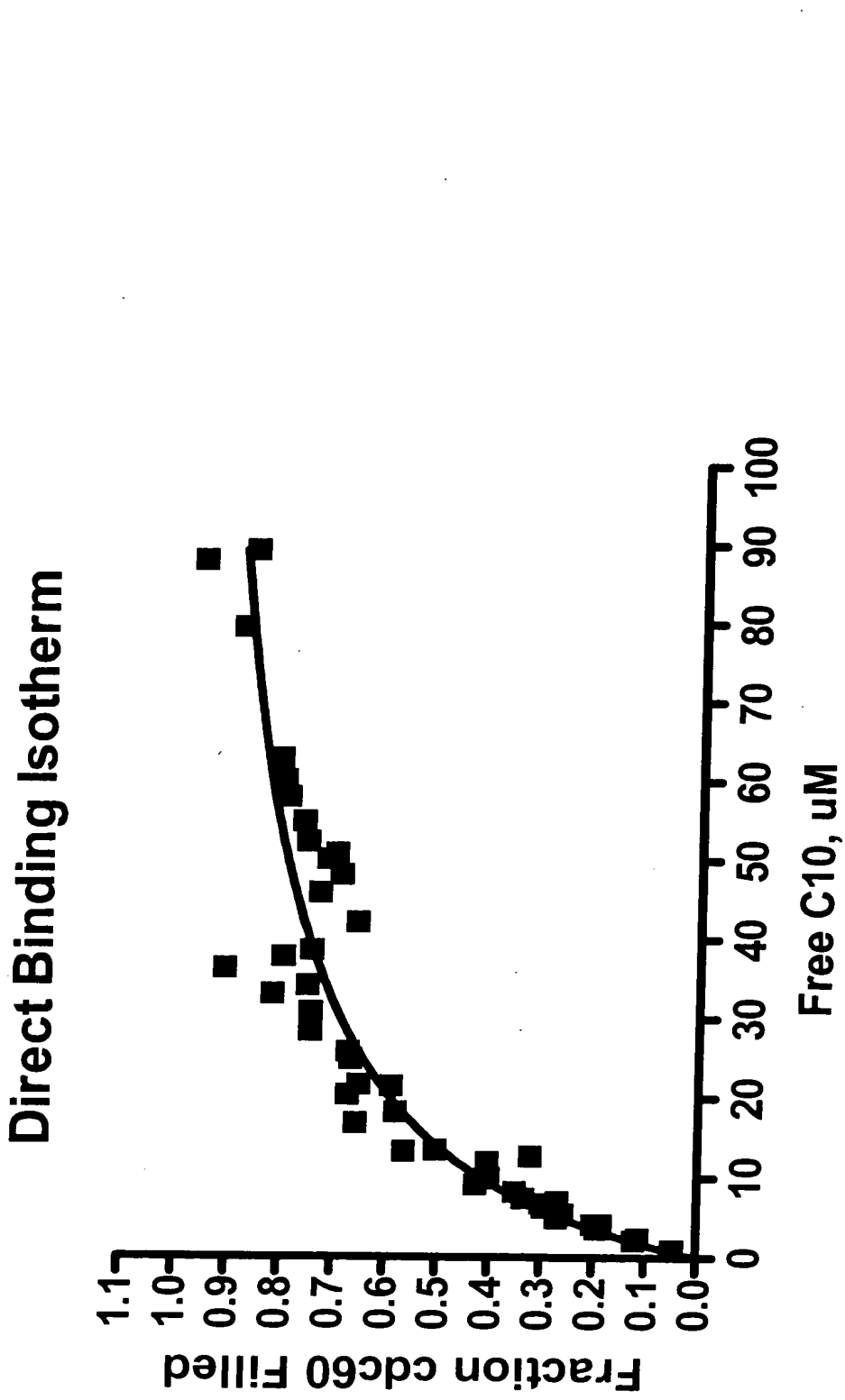
Percent cdc60 Bound with C10 at Equilibrium

Additive	Free [C10], µM	% cdc60 Occupied
20 mM ATP	27.5	44.0
5 mM ATP	30.1	29.9
2.5 mM ATP	39.1	7.7
0.5 mM ATP	34.8	7.4
0.1 mM ATP	36.8	-2.9
20 mM AMP	**33.3**	**59.0**
Nothing	42.6	-6.6

Assay conditions: 31 uM cdc60, 1 mM DTT, 0 mM Leucine, 0 mM tRNA, initial [C10] are 72 – 79 uM, pre-equilibrium. 1x AARS buffer

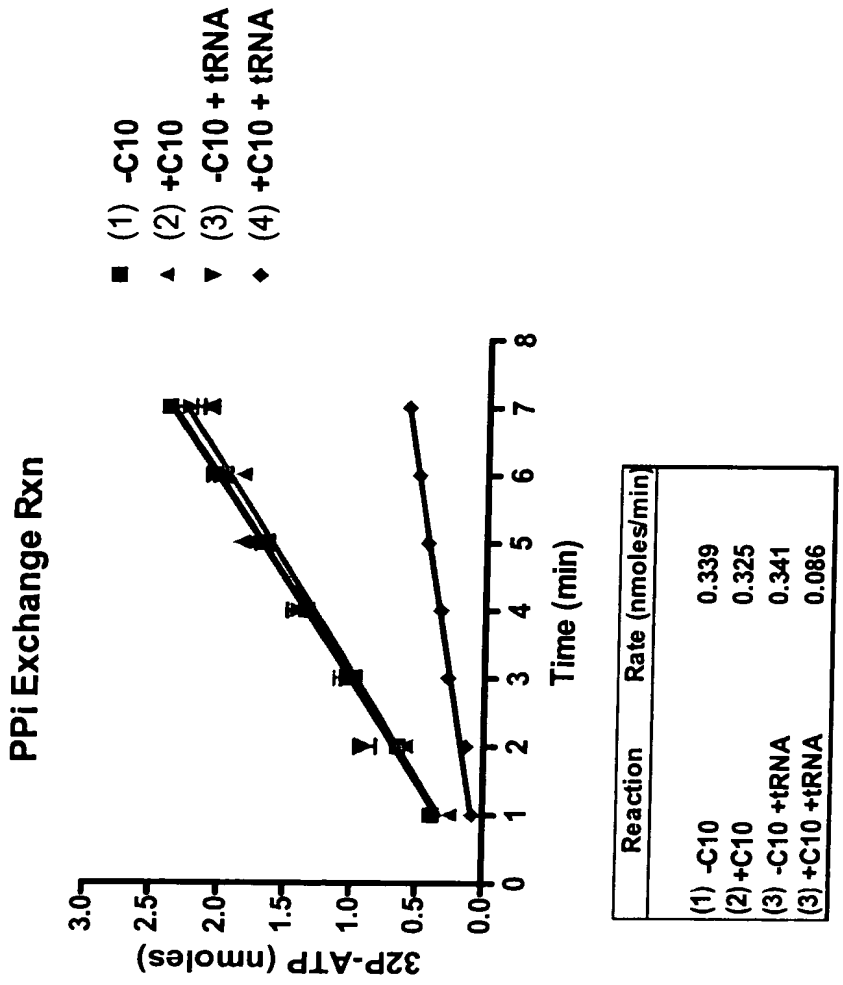
FIGURE 13

FIGURE 14



Assay conditions: 5 mM AMP, 27.3 uM cdc60, 1 mM DTT, 0 mM Leucine, 0 mM tRNA, initial [C10] are 2.5 – 200 uM, pre-equilibrium in 1x AARS buffer.

FIGURE 15



Reaction	Rate (nmoles/min)
(1) -C10	0.339
(2) +C10	0.325
(3) -C10 +tRNA	0.341
(3) +C10 +tRNA	0.086

7 nM cdc60, 16 uM tRNA, 2 mM ATP, 2 mM PPi, 2 mM Leu

FIGURE 16

C10 Inhibits LeuRS Aminoacylation of $tRNA^{leu}$

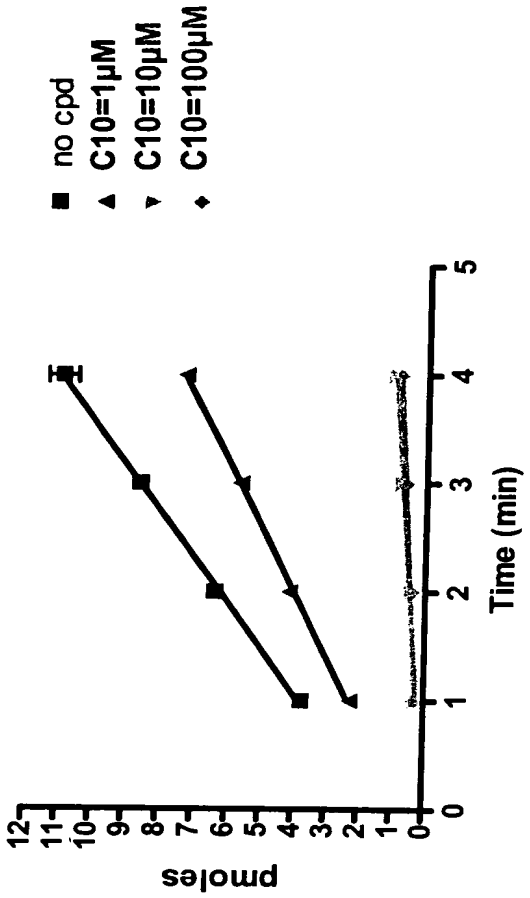


FIGURE 17

C10 inhibits post transfer editing (PTE) of *S. cerevisiae* CDC60

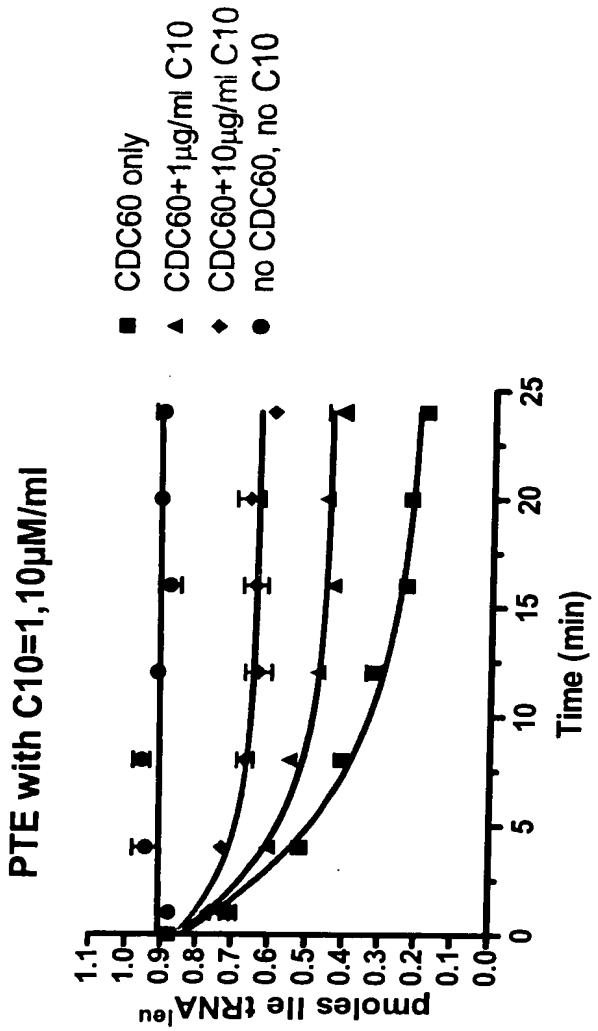


FIGURE 18A

5-chlorobenzo[c][1,2]oxaborol-1(3H)-ol, benzo[c][1,2]oxaborol-1(3H)-ol, 5-chloro-3-methylbenzo[c][1,2]oxaborol-1(3H)-ol, 6-fluoro-3,4-dihydrobenzo[c][1,2]oxaborinin-1-ol, 5,6-difluorobenzo[c][1,2]oxaborol-1(3H)-ol, 1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-5-carbonitrile, 5-methoxybenzo[c][1,2]oxaborol-1(3H)-ol, 5-methylbenzo[c][1,2]oxaborol-1(3H)-ol, 5-(hydroxymethyl)benzo[c][1,2]oxaborol-1(3H)-ol, 5-fluorobenzo[c][1,2]oxaborol-1(3H)-ol, naphtho[1,2-c][1,2]oxaborol-1(3H)-ol, 6-fluorobenzo[c][1,2]oxaborol-1(3H)-ol, 3-benzyl-3-methylbenzo[c][1,2]oxaborol-1(3H)-ol, 3-benzylbenzo[c][1,2]oxaborol-1(3H)-ol, 4-fluorobenzo[c][1,2]oxaborol-1(3H)-ol, *4-(1-*hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)benzonitril, 4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yloxy)benzonitrile, 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yloxy)benzonitrile, 6-(4-chlorophenoxy)benzo[c][1,2]oxaborol-1(3H)-ol, 6-phenoxybenzo[c][1,2]oxaborol-1(3H)-ol, 4-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)methyl)benzonitrile, 2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)benzonitrile, 5-phenoxybenzo[c][1,2]oxaborol-1(3H)-ol, N,N-diethyl-4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)benzamide, (4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)phenyl)(morpholino)methanone, 4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)phthalonitrile, 6-(phenylthio)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-(trifluoromethoxy)phenoxy)benzo[c][1,2]oxaborol-1(3H)-ol, N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)-N-methylbenzenesulfonamide, 6-(4-methoxyphenoxy)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-methoxyphenylthio)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-methoxyphenylsulfonyl)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-methoxyphenylsulfinyl)benzo[c][1,2]oxaborol-1(3H)-ol, 5-(trifluoromethyl)benzo[c][1,2]oxaborol-1(3H)-ol, 4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-4-yloxy)benzonitrile, 3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)benzonitrile, 4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)benzoic acid, 5-(4-(1H-tetrazol-5-yl)phenoxy)benzo[c][1,2]oxaborol-1(3H)-ol, 7-Hydroxy-2,1-oxaborolano[5,4-c]pyridine [[1,2]oxaborolo[3,4-c]pyridin-1(3H)-ol], Ethyl 2-(1-hydroxy-1,3-

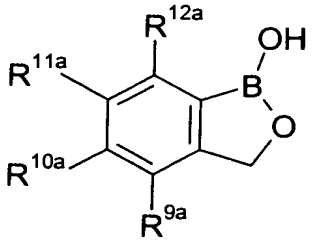
FIGURE 18B

dihydrobenzo[c][1,2]oxaborol-5-yloxy)acetate, 2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)acetic acid, 6-(thiophen-2-ylthio)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-fluorophenylthio)benzo[c][1,2]oxaborol-1(3H)-ol, 1-(3-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)methyl)phenyl)pentan-1-one, 2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)-1-(piperidin-1-yl)ethanone, 2-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)-1-(4-(pyrimidin-2-yl)piperazin-1-yl)ethanone, 6-(4-(pyridin-2-yl)piperazin-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol, 6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol, 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol, 6-(dimethylamino)benzo[c][1,2]oxaborol-1(3H)-ol, N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)benzamide, 6-(4-phenylpiperazin-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol, 6-morpholinobenzo[c][1,2]oxaborol-1(3H)-ol, 6-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)nicotinonitrile, 5-fluoro-6-nitrobenzo[c][1,2]oxaborol-1(3H)-ol, 5-bromo-6-(hydroxymethyl)benzo[c][1,2]oxaborol-1(3H)-ol, 3,7-dihydro-1,5-dihydroxy-1H,3H-benzo[1,2-c:4,5-c']bis[1,2]oxaborole, 1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-3-phenylurea, N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)benzenesulfonamide, N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)acetamide, 7-(hydroxymethyl)benzo[c][1,2]oxaborol-1(3H)-ol, 7-methylbenzo[c][1,2]oxaborol-1(3H)-ol, 6-(3-(phenylthio)-1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol, 3-(1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-3-ylthio)propanenitrile, 6-(5-methoxy-1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol, 6-amino-5-fluorobenzo[c][1,2]oxaborol-1(3H)-ol, 6-(benzylamino)-5-fluorobenzo[c][1,2]oxaborol-1(3H)-ol, 6-(5-methoxy-3-(phenylthio)-1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol, 3-(1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-5-methoxy-1H-indol-3-ylthio)propanenitrile, 4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yloxy)benzonitrile, 6-(5-chloro-1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol, 3-(5-chloro-1-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)-1H-indol-3-ylthio)propanenitrile, 6-(benzylamino)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(dibenzylamino)benzo[c][1,2]oxaborol-1(3H)-ol, 7-(4-(1H-tetrazol-5-

FIGURE 18C

yl)phenoxy)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(5-chloro-3-(phenylthio)-1H-indol-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol, 3,4-dihydro-1H-thieno[3,2-c][1,2]oxaborinin-1-ol, 6-(4-(pyrimidin-2-yl)piperazin-1-yl)benzo[c][1,2]oxaborol-1(3H)-ol, 7-(benzyloxy)benzo[c][1,2]oxaborol-1(3H)-ol, 4-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-ylthio)pyridinium chloride, 6-(pyridin-2-ylthio)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(pyridin-2-ylthio)benzo[c][1,2]oxaborol-1(3H)-ol, 7-fluorobenzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-(trifluoromethyl)phenoxybenzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-chlorophenylthio)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-chlorophenylsulfinyl)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-chlorophenylsulfonyl)benzo[c][1,2]oxaborol-1(3H)-ol, N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)-N-(phenylsulfonyl)benzenesulfonamide, 6-(4-(trifluoromethyl)phenylthio)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-(trifluoromethyl)phenylsulfinyl)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(4-(methylthio)phenylthio)benzo[c][1,2]oxaborol-1(3H)-ol, 6-(p-tolylthio)benzo[c][1,2]oxaborol-1(3H)-ol, and 3-((1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yloxy)methyl)benzonitrile.

FIGURE 19A



No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
1	F	H	H	H
2	H	F	H	H
3	H	H	F	H
4	H	H	H	F
5	F	F	H	H
6	H	F	F	H
7	H	H	F	F
8	F	H	F	H
9	H	F	H	F
10	F	H	H	F
11	H	F	F	F
12	F	H	F	F
13	F	F	H	F
14	F	F	F	H
15	F	F	F	F
16	Cl	H	H	H
17	H	Cl	H	H
18	H	H	Cl	H
19	H	H	H	Cl
20	Cl	Cl	H	H
21	H	Cl	Cl	H
22	H	H	Cl	Cl
23	Cl	H	Cl	H
24	H	Cl	H	Cl
25	Cl	H	H	Cl
26	H	Cl	Cl	Cl
27	Cl	H	Cl	Cl
28	Cl	Cl	H	Cl
29	Cl	Cl	Cl	H
30	Cl	Cl	Cl	Cl
31	Br	H	H	H

FIGURE 19B

No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
32	H	Br	H	H
33	H	H	Br	H
34	H	H	H	Br
35	Br	Br	H	H
36	H	Br	Br	H
37	H	H	Br	Br
38	Br	H	Br	H
39	H	Br	H	Br
40	Br	H	H	Br
41	H	Br	Br	Br
42	Br	H	Br	Br
43	Br	Br	H	Br
44	Br	Br	Br	H
45	Br	Br	Br	Br
46	-CN	H	H	H
47	H	-CN	H	H
48	H	H	-CN	H
49	H	H	H	-CN
50	-CN	-CN	H	H
51	H	-CN	-CN	H
52	H	H	-CN	-CN
53	-CN	H	-CN	H
54	H	-CN	H	-CN
55	-CN	H	H	-CN
56	H	-CN	-CN	-CN
57	-CN	H	-CN	-CN
58	-CN	-CN	H	-CN
59	-CN	-CN	-CN	H
60	-CN	-CN	-CN	-CN
61	-Me	H	H	H
62	H	-Me	H	H
63	H	H	-Me	H
64	H	H	H	-Me
65	-Me	-Me	H	H
66	H	-Me	-Me	H
67	H	H	-Me	-Me
68	-Me	H	-Me	H
69	H	-Me	H	-Me
70	-Me	H	H	-Me
71	H	-Me	-Me	-Me
72	-Me	H	-Me	-Me

FIGURE 19C

No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
73	-Me	-Me	H	-Me
74	-Me	-Me	-Me	H
75	-Me	-Me	-Me	-Me
76	$-CH_2OH$	H	H	H
77	H	$-CH_2OH$	H	H
78	H	H	$-CH_2OH$	H
79	H	H	H	$-CH_2OH$
80	$-CH_2OH$	$-CH_2OH$	H	H
81	H	$-CH_2OH$	$-CH_2OH$	H
82	H	H	$-CH_2OH$	$-CH_2OH$
83	$-CH_2OH$	H	$-CH_2OH$	H
84	H	$-CH_2OH$	H	$-CH_2OH$
85	$-CH_2OH$	H	H	$-CH_2OH$
86	H	$-CH_2OH$	$-CH_2OH$	$-CH_2OH$
87	$-CH_2OH$	H	$-CH_2OH$	$-CH_2OH$
88	$-CH_2OH$	$-CH_2OH$	H	$-CH_2OH$
89	$-CH_2OH$	$-CH_2OH$	$-CH_2OH$	H
90	$-CH_2OH$	$-CH_2OH$	$-CH_2OH$	$-CH_2OH$
91	-benzyl	H	H	H
92	H	-benzyl	H	H
93	H	H	-benzyl	H
94	H	H	H	-benzyl
95	-benzyl	-benzyl	H	H
96	H	-benzyl	-benzyl	H
97	H	H	-benzyl	-benzyl
98	-benzyl	H	-benzyl	H
99	H	-benzyl	H	-benzyl
100	-benzyl	H	H	-benzyl
101	H	-benzyl	-benzyl	-benzyl
102	-benzyl	H	-benzyl	-benzyl
103	-benzyl	-benzyl	H	-benzyl
104	-benzyl	-benzyl	-benzyl	H
105	-benzyl	-benzyl	-benzyl	-benzyl
106	-OMe	H	H	H
107	H	-OMe	H	H
108	H	H	-OMe	H
109	H	H	H	-OMe
110	-OMe	-OMe	H	H
111	H	-OMe	-OMe	H
112	H	H	-OMe	-OMe
113	-OMe	H	-OMe	H

FIGURE 19D

No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
114	-OMe	H	H	-OMe
115	H	-OMe	-OMe	-OMe
116	-OMe	H	-OMe	-OMe
117	-OMe	-OMe	H	-OMe
118	-OMe	-OMe	-OMe	H
119	-OMe	-OMe	-OMe	-OMe
120	-4-cyanophenoxy	H	H	H
121	H	-4-cyanophenoxy	H	H
122	H	H	-4-cyanophenoxy	H
123	H	H	H	-4-cyanophenoxy
124	-4-cyanophenoxy	-4-cyanophenoxy	H	H
125	H	-4-cyanophenoxy	-4-cyanophenoxy	H
126	H	H	-4-cyanophenoxy	-4-cyanophenoxy
127	-4-cyanophenoxy	H	-4-cyanophenoxy	H
128	H	-4-cyanophenoxy	H	-4-cyanophenoxy
129	-4-cyanophenoxy	H	H	-4-cyanophenoxy
130	H	-4-cyanophenoxy	-4-cyanophenoxy	-4-cyanophenoxy
131	-4-cyanophenoxy	H	-4-cyanophenoxy	-4-cyanophenoxy
132	-4-cyanophenoxy	-4-cyanophenoxy	H	-4-cyanophenoxy
133	-4-cyanophenoxy	-4-cyanophenoxy	-4-cyanophenoxy	H
134	-4-cyanophenoxy	-4-cyanophenoxy	-4-cyanophenoxy	-4-cyanophenoxy
135	-3-cyanophenoxy	H	H	H
136	H	-3-cyanophenoxy	H	H
137	H	H	-3-cyanophenoxy	H
138	H	H	H	-3-cyanophenoxy
139	-3-cyanophenoxy	-3-cyanophenoxy	H	H
140	H	-3-cyanophenoxy	-3-cyanophenoxy	H
141	H	H	-3-cyanophenoxy	-3-cyanophenoxy
142	-3-cyanophenoxy	H	-3-cyanophenoxy	H
143	H	-3-cyanophenoxy	H	-3-cyanophenoxy
144	-3-cyanophenoxy	H	H	-3-cyanophenoxy
145	H	-3-cyanophenoxy	-3-cyanophenoxy	-3-cyanophenoxy
146	-3-cyanophenoxy	H	-3-cyanophenoxy	-3-cyanophenoxy
147	-3-cyanophenoxy	-3-cyanophenoxy	H	-3-cyanophenoxy
148	-3-cyanophenoxy	-3-cyanophenoxy	-3-cyanophenoxy	H
149	-3-cyanophenoxy	-3-cyanophenoxy	-3-cyanophenoxy	-3-cyanophenoxy
150	-2-cyanophenoxy	H	H	H
151	H	-2-cyanophenoxy	H	H
152	H	H	-2-cyanophenoxy	H
153	H	H	H	-2-cyanophenoxy

FIGURE 19E

No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
154	-2-cyanophenoxy	-2-cyanophenoxy	H	H
155	H	-2-cyanophenoxy	-2-cyanophenoxy	H
156	H	H	-2-cyanophenoxy	-2-cyanophenoxy
157	-2-cyanophenoxy	H	-2-cyanophenoxy	H
158	H	-2-cyanophenoxy	H	-2-cyanophenoxy
159	-2-cyanophenoxy	H	H	-2-cyanophenoxy
160	H	-2-cyanophenoxy	-2-cyanophenoxy	-2-cyanophenoxy
161	-2-cyanophenoxy	H	-2-cyanophenoxy	-2-cyanophenoxy
162	-2-cyanophenoxy	-2-cyanophenoxy	H	-2-cyanophenoxy
163	-2-cyanophenoxy	-2-cyanophenoxy	-2-cyanophenoxy	H
164	-2-cyanophenoxy	-2-cyanophenoxy	-2-cyanophenoxy	-2-cyanophenoxy
165	-4-chlorophenoxy	H	H	H
166	H	-4-chlorophenoxy	H	H
167	H	H	-4-chlorophenoxy	H
168	H	H	H	-4-chlorophenoxy
169	-4-chlorophenoxy	-4-chlorophenoxy	H	H
170	H	-4-chlorophenoxy	-4-chlorophenoxy	H
171	H	H	-4-chlorophenoxy	-4-chlorophenoxy
172	-4-chlorophenoxy	H	-4-chlorophenoxy	H
173	H	-4-chlorophenoxy	H	-4-chlorophenoxy
174	-4-chlorophenoxy	H	H	-4-chlorophenoxy
175	H	-4-chlorophenoxy	-4-chlorophenoxy	-4-chlorophenoxy
176	-4-chlorophenoxy	H	-4-chlorophenoxy	-4-chlorophenoxy
177	-4-chlorophenoxy	-4-chlorophenoxy	H	-4-chlorophenoxy
178	-4-chlorophenoxy	-4-chlorophenoxy	-4-chlorophenoxy	H
179	-4-chlorophenoxy	-4-chlorophenoxy	-4-chlorophenoxy	-4-chlorophenoxy
180	-3-chlorophenoxy	H	H	H
181	H	-3-chlorophenoxy	H	H
182	H	H	-3-chlorophenoxy	H
183	H	H	H	-3-chlorophenoxy
184	-3-chlorophenoxy	-3-chlorophenoxy	H	H
185	H	-3-chlorophenoxy	-3-chlorophenoxy	H
186	H	H	-3-chlorophenoxy	-3-chlorophenoxy
187	-3-chlorophenoxy	H	-3-chlorophenoxy	H
188	H	-3-chlorophenoxy	H	-3-chlorophenoxy
189	-3-chlorophenoxy	H	H	-3-chlorophenoxy
190	H	-3-chlorophenoxy	-3-chlorophenoxy	-3-chlorophenoxy
191	-3-chlorophenoxy	H	-3-chlorophenoxy	-3-chlorophenoxy
192	-3-chlorophenoxy	-3-chlorophenoxy	H	-3-chlorophenoxy
193	-3-chlorophenoxy	-3-chlorophenoxy	-3-chlorophenoxy	H
194	-3-chlorophenoxy	-3-chlorophenoxy	-3-chlorophenoxy	-3-chlorophenoxy

FIGURE 19F

No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
195	-2-chlorophenoxy	H	H	H
196	H	-2-chlorophenoxy	H	H
197	H	H	-2-chlorophenoxy	H
198	H	H	H	-2-chlorophenoxy
199	-2-chlorophenoxy	-2-chlorophenoxy	H	H
200	H	-2-chlorophenoxy	-2-chlorophenoxy	H
201	H	H	-2-chlorophenoxy	-2-chlorophenoxy
202	-2-chlorophenoxy	H	-2-chlorophenoxy	H
203	H	-2-chlorophenoxy	H	-2-chlorophenoxy
204	-2-chlorophenoxy	H	H	-2-chlorophenoxy
205	H	-2-chlorophenoxy	-2-chlorophenoxy	-2-chlorophenoxy
206	-2-chlorophenoxy	H	-2-chlorophenoxy	-2-chlorophenoxy
207	-2-chlorophenoxy	-2-chlorophenoxy	H	-2-chlorophenoxy
208	-2-chlorophenoxy	-2-chlorophenoxy	-2-chlorophenoxy	H
209	-2-chlorophenoxy	-2-chlorophenoxy	-2-chlorophenoxy	-2-chlorophenoxy
210	-phenoxy	H	H	H
211	H	-phenoxy	H	H
212	H	H	-phenoxy	H
213	H	H	H	-phenoxy
214	-phenoxy	-phenoxy	H	H
215	H	-phenoxy	-phenoxy	H
216	H	H	-phenoxy	-phenoxy
217	-phenoxy	H	-phenoxy	H
218	H	-phenoxy	H	-phenoxy
219	-phenoxy	H	H	-phenoxy
220	H	-phenoxy	-phenoxy	-phenoxy
221	-phenoxy	H	-phenoxy	-phenoxy
222	-phenoxy	-phenoxy	H	-phenoxy
223	-phenoxy	-phenoxy	-phenoxy	H
224	-phenoxy	-phenoxy	-phenoxy	-phenoxy
225	-4-cyanophenylthio	H	H	H
226	H	-4-cyanophenylthio	H	H
227	H	H	-4-cyanophenylthio	H
228	H	H	H	-4-cyanophenylthio
229	-4-cyanophenylthio	-4-cyanophenylthio	H	H
230	H	-4-cyanophenylthio	-4-cyanophenylthio	H
231	H	H	-4-cyanophenylthio	-4-cyanophenylthio
232	-4-cyanophenylthio	H	-4-cyanophenylthio	H
233	H	-4-cyanophenylthio	H	-4-cyanophenylthio
234	-4-cyanophenylthio	H	H	-4-cyanophenylthio
235	H	-4-cyanophenylthio	-4-cyanophenylthio	-4-cyanophenylthio

FIGURE 19G

No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
236	-4-cyanophenylthio	H	-4-cyanophenylthio	-4-cyanophenylthio
237	-4-cyanophenylthio	-4-cyanophenylthio	H	-4-cyanophenylthio
238	-4-cyanophenylthio	-4-cyanophenylthio	-4-cyanophenylthio	H
239	-4-cyanophenylthio	-4-cyanophenylthio	-4-cyanophenylthio	-4-cyanophenylthio
240	-3-cyanophenylthio	H	H	H
241	H	3-cyanophenylthio	H	H
242	H	H	-3-cyanophenylthio	H
243	H	H	H	-3-cyanophenylthio
244	-3-cyanophenylthio	-3-cyanophenylthio	H	H
245	H	-3-cyanophenylthio	-3-cyanophenylthio	H
246	H	H	-3-cyanophenylthio	-3-cyanophenylthio
247	-3-cyanophenylthio	H	-3-cyanophenylthio	H
248	H	-3-cyanophenylthio	H	-3-cyanophenylthio
249	-3-cyanophenylthio	H	H	-3-cyanophenylthio
250	H	-3-cyanophenylthio	-3-cyanophenylthio	-3-cyanophenylthio
251	-3-cyanophenylthio	H	-3-cyanophenylthio	-3-cyanophenylthio
252	-3-cyanophenylthio	-3-cyanophenylthio	H	-3-cyanophenylthio
253	-3-cyanophenylthio	-3-cyanophenylthio	-3-cyanophenylthio	H
254	-3-cyanophenylthio	-3-cyanophenylthio	-3-cyanophenylthio	-3-cyanophenylthio
255	-2-cyanophenylthio	H	H	H
256	H	-2-cyanophenylthio	H	H
257	H	H	-2-cyanophenylthio	H
258	H	H	H	-2-cyanophenylthio
259	-2-cyanophenylthio	-2-cyanophenylthio	H	H
260	H	-2-cyanophenylthio	-2-cyanophenylthio	H
261	H	H	-2-cyanophenylthio	-2-cyanophenylthio
262	-2-cyanophenylthio	H	-2-cyanophenylthio	H
263	H	-2-cyanophenylthio	H	-2-cyanophenylthio
264	-2-cyanophenylthio	H	H	-2-cyanophenylthio
265	H	-2-cyanophenylthio	-2-cyanophenylthio	-2-cyanophenylthio
266	2-cyanophenylthio	H	-2-cyanophenylthio	-2-cyanophenylthio
267	2-cyanophenylthio	-2-cyanophenylthio	H	-2-cyanophenylthio
268	2-cyanophenylthio	-2-cyanophenylthio	-2-cyanophenylthio	H
269	2-cyanophenylthio	-2-cyanophenylthio	-2-cyanophenylthio	-2-cyanophenylthio
270	$-OCH_2C(O)OH$	H	H	H
271	H	$-OCH_2C(O)OH$	H	H
272	H	H	$-OCH_2C(O)OH$	H
273	H	H	H	$-OCH_2C(O)OH$
274	F	$-OCH_2C(O)OH$	H	H
275	H	$-OCH_2C(O)OH$	F	H

FIGURE 19H

No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
276	H	$-OCH_2C(O)OH$	H	F
277	F	$-OCH_2C(O)OH$	F	H
278	H	$-OCH_2C(O)OH$	F	F
279	F	$-OCH_2C(O)OH$	F	F
280	$-NMeS(O)_2Ph$	H	H	H
281	H	$-NMeS(O)_2Ph$	H	H
282	H	H	$-NMeS(O)_2Ph$	H
283	H	H	H	$-NMeS(O)_2Ph$
284	F	$-NMeS(O)_2Ph$	H	H
285	H	$-NMeS(O)_2Ph$	F	H
286	H	$-NMeS(O)_2Ph$	H	F
287	F	$-NMeS(O)_2Ph$	F	H
288	H	$-NMeS(O)_2Ph$	F	F
289	F	$-NMeS(O)_2Ph$	F	F
290	$-CH_2OH$	H	H	H
291	H	$-CH_2OH$	H	H
292	H	H	$-CH_2OH$	H
293	H	H	H	$-CH_2OH$
294	$-CH_2OH$	F	H	H
295	$-CH_2OH$	H	F	H
296	$-CH_2OH$	H	H	F
297	$-CH_2OH$	Cl	H	H
298	$-CH_2OH$	H	Cl	H
299	$-CH_2OH$	H	H	Cl
300	F	$-CH_2OH$	H	H
301	H	$-CH_2OH$	F	H
302	H	$-CH_2OH$	H	F
303	Cl	$-CH_2OH$	H	H
304	H	$-CH_2OH$	Cl	H
305	H	$-CH_2OH$	H	Cl
306	F	H	$-CH_2OH$	H
307	H	F	$-CH_2OH$	H
308	H	H	$-CH_2OH$	F
309	Cl	H	$-CH_2OH$	H
310	H	Cl	$-CH_2OH$	H
311	H	H	$-CH_2OH$	Cl
312	F	H	H	$-CH_2OH$
313	H	F	H	$-CH_2OH$
314	H	H	F	$-CH_2OH$
315	Cl	H	H	$-CH_2OH$
316	H	Cl	H	$-CH_2OH$

FIGURE 19I

No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
317	H	H	Cl	$-CH_2OH$
318	F	$-CH_2OH$	F	H
319	H	$-CH_2OH$	F	F
320	F	$-CH_2OH$	F	F
321	H	$-NH_2$	H	H
322	H	H	$-NH_2$	H
323	H	H	H	$-NH_2$
324	$-NH_2$	F	H	H
325	$-NH_2$	H	F	H
326	$-NH_2$	H	H	F
327	$-NH_2$	Cl	H	H
328	$-NH_2$	H	Cl	H
329	$-NH_2$	H	H	Cl
330	F	$-NH_2$	H	H
331	H	$-NH_2$	F	H
332	H	$-NH_2$	H	F
333	Cl	$-NH_2$	H	H
334	H	$-NH_2$	Cl	H
335	H	$-NH_2$	H	Cl
336	F	H	$-NH_2$	H
337	H	F	$-NH_2$	H
338	H	H	$-NH_2$	F
339	Cl	H	$-NH_2$	H
340	H	Cl	$-NH_2$	H
341	H	H	$-NH_2$	Cl
342	F	H	H	$-NH_2$
343	H	F	H	$-NH_2$
344	H	H	F	$-NH_2$
345	Cl	H	H	$-NH_2$
346	H	Cl	H	$-NH_2$
347	H	H	Cl	$-NH_2$
348	F	$-NH_2$	F	H
349	H	$-NH_2$	F	F
350	F	$-NH_2$	F	F
351	-O(4-CN-Ph)	H	H	H
352	H	-O(4-CN-Ph)	H	H
353	H	H	-O(4-CN-Ph)	H
354	H	H	H	-O(4-CN-Ph)
355	F	-O(4-CN-Ph)	H	H
356	H	-O(4-CN-Ph)	F	H
357	H	-O(4-CN-Ph)	H	F

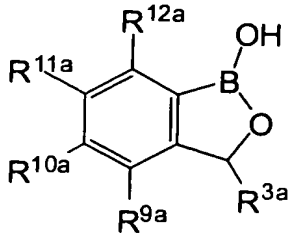
FIGURE 19J

No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
358	F	-O(4-CN-Ph)	F	H
359	H	-O(4-CN-Ph)	F	F
360	F	-O(4-CN-Ph)	F	F
361	3-(phenylthio)-1H-indol-1-yl	H	H	H
362	H	3-(phenylthio)-1H-indol-1-yl	H	H
363	H	H	3-(phenylthio)-1H-indol-1-yl	H
364	H	H	H	3-(phenylthio)-1H-indol-1-yl
365	F	3-(phenylthio)-1H-indol-1-yl	H	H
366	H	3-(phenylthio)-1H-indol-1-yl	F	H
367	H	3-(phenylthio)-1H-indol-1-yl	H	F
368	F	3-(phenylthio)-1H-indol-1-yl	F	H
369	H	3-(phenylthio)-1H-indol-1-yl	F	F
370	F	3-(phenylthio)-1H-indol-1-yl	F	F
371	dibenzylamino	H	H	H
372	H	dibenzylamino	H	H
373	H	H	dibenzylamino	H
374	H	H	H	dibenzylamino
375	F	dibenzylamino	H	H
376	H	dibenzylamino	F	H
377	H	dibenzylamino	H	F
378	F	dibenzylamino	F	H
379	H	dibenzylamino	F	F
380	F	dibenzylamino	F	F
381	$-S(O)_2$(4-Cl-Ph)	H	H	H
382	H	$-S(O)_2$(4-Cl-Ph)	H	H
383	H	H	$-S(O)_2$(4-Cl-Ph)	H
384	H	H	H	$-S(O)_2$(4-Cl-Ph)
385	F	$-S(O)_2$(4-Cl-Ph)	H	H
386	H	$-S(O)_2$(4-Cl-Ph)	F	H
387	H	$-S(O)_2$(4-Cl-Ph)	H	F
388	F	$-S(O)_2$(4-Cl-Ph)	F	H
389	H	$-S(O)_2$(4-Cl-Ph)	F	F
390	F	$-S(O)_2$(4-Cl-Ph)	F	F
391	-S(4-pyridyl)	H	H	H
392	H	-S(4-pyridyl)	H	H
393	H	H	-S(4-pyridyl)	H

FIGURE 19K

No.	R^{9a}	R^{10a}	R^{11a}	R^{12a}
394	H	H	H	-S(4-pyridyl)
395	F	-S(4-pyridyl)	H	H
396	H	-S(4-pyridyl)	F	H
397	H	-S(4-pyridyl)	H	F
398	F	-S(4-pyridyl)	F	H
399	H	-S(4-pyridyl)	F	F
400	F	-S(4-pyridyl)	F	F
401	$-NHCH_2Ph$	H	H	H
402	H	$-NHCH_2Ph$	H	H
403	H	H	$-NHCH_2Ph$	H
404	H	H	H	$-NHCH_2Ph$
405	F	$-NHCH_2Ph$	H	H
406	H	$-NHCH_2Ph$	F	H
407	H	$-NHCH_2Ph$	H	F
408	F	$-NHCH_2Ph$	F	H
409	H	$-NHCH_2Ph$	F	F
410	F	$-NHCH_2Ph$	F	F

FIGURE 20A



No.	R^{3a}	R^{9a}	R^{10a}	R^{11a}	R^{12a}
1	-CH_2Ph	F	H	H	H
2	-CH_2Ph	H	F	H	H
3	-CH_2Ph	H	H	F	H
4	-CH_2Ph	H	H	H	F
5	-CH_2Ph	F	F	H	H
6	-CH_2Ph	H	F	F	H
7	-CH_2Ph	H	H	F	F
8	-CH_2Ph	F	H	F	H
9	-CH_2Ph	H	F	H	F
10	-CH_2Ph	F	H	H	F
11	-CH_2Ph	H	F	F	F
12	-CH_2Ph	F	H	F	F
13	-CH_2Ph	F	F	H	F
14	-CH_2Ph	F	F	F	H
15	-CH_2Ph	F	F	F	F
16	-CH_2Ph	-$OCH_2C(O)OH$	H	H	H
17	-CH_2Ph	H	-$OCH_2C(O)OH$	H	H
18	-CH_2Ph	H	H	-$OCH_2C(O)OH$	H
19	-CH_2Ph	H	H	H	-$OCH_2C(O)OH$
20	-CH_2Ph	F	-$OCH_2C(O)OH$	H	H
21	-CH_2Ph	H	-$OCH_2C(O)OH$	F	H
22	-CH_2Ph	H	-$OCH_2C(O)OH$	H	F
23	-CH_2Ph	F	-$OCH_2C(O)OH$	F	H
24	-CH_2Ph	H	-$OCH_2C(O)OH$	F	F
25	-CH_2Ph	F	-$OCH_2C(O)OH$	F	F
26	-CH_2Ph	-$NMeS(O)_2Ph$	H	H	H
27	-CH_2Ph	H	-$NMeS(O)_2Ph$	H	H
28	-CH_2Ph	H	H	-$NMeS(O)_2Ph$	H
29	-CH_2Ph	H	H	H	-$NMeS(O)_2Ph$
30	-CH_2Ph	F	-$NMeS(O)_2Ph$	H	H
31	-CH_2Ph	H	-$NMeS(O)_2Ph$	F	H
32	-CH_2Ph	H	-$NMeS(O)_2Ph$	H	F
33	-CH_2Ph	F	-$NMeS(O)_2Ph$	F	H

FIGURE 20B

No.	R^{3a}	R^{9a}	R^{10a}	R^{11a}	R^{12a}
34	$-CH_2Ph$	H	$-NMeS(O)_2Ph$	F	F
35	$-CH_2Ph$	F	$-NMeS(O)_2Ph$	F	F
36	$-CH_2Ph$	H	$-CH_2OH$	H	H
37	$-CH_2Ph$	H	H	$-CH_2OH$	H
38	$-CH_2Ph$	H	H	H	$-CH_2OH$
39	$-CH_2Ph$	$-CH_2OH$	F	H	H
40	$-CH_2Ph$	$-CH_2OH$	H	F	H
41	$-CH_2Ph$	$-CH_2OH$	H	H	F
42	$-CH_2Ph$	$-CH_2OH$	Cl	H	H
43	$-CH_2Ph$	$-CH_2OH$	H	Cl	H
44	$-CH_2Ph$	$-CH_2OH$	H	H	Cl
45	$-CH_2Ph$	F	$-CH_2OH$	H	H
46	$-CH_2Ph$	H	$-CH_2OH$	F	H
47	$-CH_2Ph$	H	$-CH_2OH$	H	F
48	$-CH_2Ph$	Cl	$-CH_2OH$	H	H
49	$-CH_2Ph$	H	$-CH_2OH$	Cl	H
50	$-CH_2Ph$	H	$-CH_2OH$	H	Cl
51	$-CH_2Ph$	F	H	$-CH_2OH$	H
52	$-CH_2Ph$	H	F	$-CH_2OH$	H
53	$-CH_2Ph$	H	H	$-CH_2OH$	F
54	$-CH_2Ph$	Cl	H	$-CH_2OH$	H
55	$-CH_2Ph$	H	Cl	$-CH_2OH$	H
56	$-CH_2Ph$	H	H	$-CH_2OH$	Cl
57	$-CH_2Ph$	F	H	H	$-CH_2OH$
58	$-CH_2Ph$	H	F	H	$-CH_2OH$
59	$-CH_2Ph$	H	H	F	$-CH_2OH$
60	$-CH_2Ph$	Cl	H	H	$-CH_2OH$
61	$-CH_2Ph$	H	Cl	H	$-CH_2OH$
62	$-CH_2Ph$	H	H	Cl	$-CH_2OH$
63	$-CH_2Ph$	F	$-CH_2OH$	F	H
64	$-CH_2Ph$	H	$-CH_2OH$	F	F
65	$-CH_2Ph$	F	$-CH_2OH$	F	F
66	$-CH_2Ph$	H	$-NH_2$	H	H
67	$-CH_2Ph$	H	H	$-NH_2$	H
68	$-CH_2Ph$	H	H	H	$-NH_2$
69	$-CH_2Ph$	$-NH_2$	F	H	H
70	$-CH_2Ph$	$-NH_2$	H	F	H
71	$-CH_2Ph$	$-NH_2$	H	H	F
72	$-CH_2Ph$	$-NH_2$	Cl	H	H
73	$-CH_2Ph$	$-NH_2$	H	Cl	H
74	$-CH_2Ph$	$-NH_2$	H	H	Cl
75	$-CH_2Ph$	F	$-NH_2$	H	H

FIGURE 20C

No.	R^{3a}	R^{9a}	R^{10a}	R^{11a}	R^{12a}
76	$-CH_2Ph$	H	$-NH_2$	F	H
77	$-CH_2Ph$	H	$-NH_2$	H	F
78	$-CH_2Ph$	Cl	$-NH_2$	H	H
79	$-CH_2Ph$	H	$-NH_2$	Cl	H
80	$-CH_2Ph$	H	$-NH_2$	H	Cl
81	$-CH_2Ph$	F	H	$-NH_2$	H
82	$-CH_2Ph$	H	F	$-NH_2$	H
83	$-CH_2Ph$	H	H	$-NH_2$	F
84	$-CH_2Ph$	Cl	H	$-NH_2$	H
85	$-CH_2Ph$	H	Cl	$-NH_2$	H
86	$-CH_2Ph$	H	H	$-NH_2$	Cl
87	$-CH_2Ph$	F	H	H	$-NH_2$
88	$-CH_2Ph$	H	F	H	$-NH_2$
89	$-CH_2Ph$	H	H	F	$-NH_2$
90	$-CH_2Ph$	Cl	H	H	$-NH_2$
91	$-CH_2Ph$	H	Cl	H	$-NH_2$
92	$-CH_2Ph$	H	H	Cl	$-NH_2$
93	$-CH_2Ph$	F	$-NH_2$	F	H
94	$-CH_2Ph$	H	$-NH_2$	F	F
95	$-CH_2Ph$	F	$-NH_2$	F	F
96	$-CH_2Ph$	-O(4-CN-Ph)	H	H	H
97	$-CH_2Ph$	H	-O(4-CN-Ph)	H	H
98	$-CH_2Ph$	H	H	-O(4-CN-Ph)	H
99	$-CH_2Ph$	H	H	H	-O(4-CN-Ph)
100	$-CH_2Ph$	F	-O(4-CN-Ph)	H	H
101	$-CH_2Ph$	H	-O(4-CN-Ph)	F	H
102	$-CH_2Ph$	H	-O(4-CN-Ph)	H	F
103	$-CH_2Ph$	F	-O(4-CN-Ph)	F	H
104	$-CH_2Ph$	H	-O(4-CN-Ph)	F	F
105	$-CH_2Ph$	F	-O(4-CN-Ph)	F	F
106	$-CH_2Ph$	3-(phenylthio)-1H-indol-1-yl	H	H	H
107	$-CH_2Ph$	H	3-(phenylthio)-1H-indol-1-yl	H	H
108	$-CH_2Ph$	H	H	3-(phenylthio)-1H-indol-1-yl	H
109	$-CH_2Ph$	H	H	H	3-(phenylthio)-1H-indol-1-yl
110	$-CH_2Ph$	F	3-(phenylthio)-1H-indol-1-yl	H	H
111	$-CH_2Ph$	H	3-(phenylthio)-1H-indol-1-yl	F	H
112	$-CH_2Ph$	H	3-(phenylthio)-1H-indol-1-yl	H	F
113	$-CH_2Ph$	F	3-(phenylthio)-1H-indol-1-yl	F	H

FIGURE 20D

No.	R^{3a}	R^{9a}	R^{10a}	R^{11a}	R^{12a}
114	$-CH_2Ph$	H	3-(phenylthio)-1H-indol-1-yl	F	F
115	$-CH_2Ph$	F	3-(phenylthio)-1H-indol-1-yl	F	F
116	$-CH_2Ph$	dibenzylamino	H	H	H
117	$-CH_2Ph$	H	dibenzylamino	H	H
118	$-CH_2Ph$	H	H	dibenzylamino	H
119	$-CH_2Ph$	H	H	H	dibenzylamino
120	$-CH_2Ph$	F	dibenzylamino	H	H
121	$-CH_2Ph$	H	dibenzylamino	F	H
122	$-CH_2Ph$	H	dibenzylamino	H	F
123	$-CH_2Ph$	F	dibenzylamino	F	H
124	$-CH_2Ph$	H	dibenzylamino	F	F
125	$-CH_2Ph$	F	dibenzylamino	F	F
126	$-CH_2Ph$	$-S(O)_2$(4-Cl-Ph)	H	H	H
127	$-CH_2Ph$	H	$-S(O)_2$(4-Cl-Ph)	H	H
128	$-CH_2Ph$	H	H	$-S(O)_2$(4-Cl-Ph)	H
129	$-CH_2Ph$	H	H	H	$-S(O)_2$(4-Cl-Ph)
130	$-CH_2Ph$	F	$-S(O)_2$(4-Cl-Ph)	H	H
131	$-CH_2Ph$	H	$-S(O)_2$(4-Cl-Ph)	F	H
132	$-CH_2Ph$	H	$-S(O)_2$(4-Cl-Ph)	H	F
133	$-CH_2Ph$	F	$-S(O)_2$(4-Cl-Ph)	F	H
134	$-CH_2Ph$	H	$-S(O)_2$(4-Cl-Ph)	F	F
135	$-CH_2Ph$	F	$-S(O)_2$(4-Cl-Ph)	F	F
136	$-CH_2Ph$	-S(4-pyridyl)	H	H	H
137	$-CH_2Ph$	H	-S(4-pyridyl)	H	H
138	$-CH_2Ph$	H	H	-S(4-pyridyl)	H
139	$-CH_2Ph$	H	H	H	-S(4-pyridyl)
140	$-CH_2Ph$	F	-S(4-pyridyl)	H	H
141	$-CH_2Ph$	H	-S(4-pyridyl)	F	H
142	$-CH_2Ph$	H	-S(4-pyridyl)	H	F
143	$-CH_2Ph$	F	-S(4-pyridyl)	F	H
144	$-CH_2Ph$	H	-S(4-pyridyl)	F	F
145	$-CH_2Ph$	F	-S(4-pyridyl)	F	F
146	$-CH_2Ph$	$-NHCH_2Ph$	H	H	H
147	$-CH_2Ph$	H	$-NHCH_2Ph$	H	H
148	$-CH_2Ph$	H	H	$-NHCH_2Ph$	H
149	$-CH_2Ph$	H	H	H	$-NHCH_2Ph$
150	$-CH_2Ph$	F	$-NHCH_2Ph$	H	H
151	$-CH_2Ph$	H	$-NHCH_2Ph$	F	H
152	$-CH_2Ph$	H	$-NHCH_2Ph$	H	F
153	$-CH_2Ph$	F	$-NHCH_2Ph$	F	H
154	$-CH_2Ph$	H	$-NHCH_2Ph$	F	F

FIGURE 20E

No.	R^{3a}	R^{9a}	R^{10a}	R^{11a}	R^{12a}
155	$-CH_2Ph$	F	$-NHCH_2Ph$	F	F
156	Me	F	H	H	H
157	Me	H	F	H	H
158	Me	H	H	F	H
159	Me	H	H	H	F
160	Me	F	F	H	H
161	Me	H	F	F	H
162	Me	H	H	F	F
163	Me	F	H	F	H
164	Me	H	F	H	F
165	Me	F	H	H	F
166	Me	H	F	F	F
167	Me	F	H	F	F
168	Me	F	F	H	F
169	Me	F	F	F	H
170	Me	F	F	F	F
171	Me	$-OCH_2C(O)OH$	H	H	H
172	Me	H	$-OCH_2C(O)OH$	H	H
173	Me	H	H	$-OCH_2C(O)OH$	H
174	Me	H	H	H	$-OCH_2C(O)OH$
175	Me	F	$-OCH_2C(O)OH$	H	H
176	Me	H	$-OCH_2C(O)OH$	F	H
177	Me	H	$-OCH_2C(O)OH$	H	F
178	Me	F	$-OCH_2C(O)OH$	F	H
179	Me	H	$-OCH_2C(O)OH$	F	F
180	Me	F	$-OCH_2C(O)OH$	F	F
181	Me	$-NMeS(O)_2Ph$	H	H	H
182	Me	H	$-NMeS(O)_2Ph$	H	H
183	Me	H	H	$-NMeS(O)_2Ph$	H
184	Me	H	H	H	$-NMeS(O)_2Ph$
185	Me	F	$-NMeS(O)_2Ph$	H	H
186	Me	H	$-NMeS(O)_2Ph$	F	H
187	Me	H	$-NMeS(O)_2Ph$	H	F
188	Me	F	$-NMeS(O)_2Ph$	F	H
189	Me	H	$-NMeS(O)_2Ph$	F	F
190	Me	F	$-NMeS(O)_2Ph$	F	F
191	Me	H	$-CH_2OH$	H	H
192	Me	H	H	$-CH_2OH$	H
193	Me	H	H	H	$-CH_2OH$
194	Me	$-CH_2OH$	F	H	H
195	Me	$-CH_2OH$	H	F	H

FIGURE 20F

No.	R^{3a}	R^{9a}	R^{10a}	R^{11a}	R^{12a}
196	Me	$-CH_2OH$	H	H	F
197	Me	$-CH_2OH$	Cl	H	H
198	Me	$-CH_2OH$	H	Cl	H
199	Me	$-CH_2OH$	H	H	Cl
200	Me	F	$-CH_2OH$	H	H
201	Me	H	$-CH_2OH$	F	H
202	Me	H	$-CH_2OH$	H	F
203	Me	Cl	$-CH_2OH$	H	H
204	Me	H	$-CH_2OH$	Cl	H
205	Me	H	$-CH_2OH$	H	Cl
206	Me	F	H	$-CH_2OH$	H
207	Me	H	F	$-CH_2OH$	H
208	Me	H	H	$-CH_2OH$	F
209	Me	Cl	H	$-CH_2OH$	H
210	Me	H	Cl	$-CH_2OH$	H
211	Me	H	H	$-CH_2OH$	Cl
212	Me	F	H	H	$-CH_2OH$
213	Me	H	F	H	$-CH_2OH$
214	Me	H	H	F	$-CH_2OH$
215	Me	Cl	H	H	$-CH_2OH$
216	Me	H	Cl	H	$-CH_2OH$
217	Me	H	H	Cl	$-CH_2OH$
218	Me	F	$-CH_2OH$	F	H
219	Me	H	$-CH_2OH$	F	F
220	Me	F	$-CH_2OH$	F	F
221	Me	H	$-NH_2$	H	H
222	Me	H	H	$-NH_2$	H
223	Me	H	H	H	$-NH_2$
224	Me	$-NH_2$	F	H	H
225	Me	$-NH_2$	H	F	H
226	Me	$-NH_2$	H	H	F
227	Me	$-NH_2$	Cl	H	H
228	Me	$-NH_2$	H	Cl	H
229	Me	$-NH_2$	H	H	Cl
230	Me	F	$-NH_2$	H	H
231	Me	H	$-NH_2$	F	H
232	Me	H	$-NH_2$	H	F
233	Me	Cl	$-NH_2$	H	H
234	Me	H	$-NH_2$	Cl	H
235	Me	H	$-NH_2$	H	Cl
236	Me	F	H	$-NH_2$	H
237	Me	H	F	$-NH_2$	H

FIGURE 20G

No.	R^{3a}	R^{9a}	R^{10a}	R^{11a}	R^{12a}
238	Me	H	H	$-NH_2$	F
239	Me	Cl	H	$-NH_2$	H
240	Me	H	Cl	$-NH_2$	H
241	Me	H	H	$-NH_2$	Cl
242	Me	F	H	H	$-NH_2$
243	Me	H	F	H	$-NH_2$
244	Me	H	H	F	$-NH_2$
245	Me	Cl	H	H	$-NH_2$
246	Me	H	Cl	H	$-NH_2$
247	Me	H	H	Cl	$-NH_2$
248	Me	F	$-NH_2$	F	H
249	Me	H	$-NH_2$	F	F
250	Me	F	$-NH_2$	F	F
251	Me	-O(4-CN-Ph)	H	H	H
252	Me	H	-O(4-CN-Ph)	H	H
253	Me	H	H	-O(4-CN-Ph)	H
254	Me	H	H	H	-O(4-CN-Ph)
255	Me	F	-O(4-CN-Ph)	H	H
256	Me	H	-O(4-CN-Ph)	F	H
257	Me	H	-O(4-CN-Ph)	H	F
258	Me	F	-O(4-CN-Ph)	F	H
259	Me	H	-O(4-CN-Ph)	F	F
260	Me	F	-O(4-CN-Ph)	F	F
261	Me	3-(phenylthio)-1H-indol-1-yl	H	H	H
262	Me	H	3-(phenylthio)-1H-indol-1-yl	H	H
263	Me	H	H	3-(phenylthio)-1H-indol-1-yl	H
264	Me	H	H	H	3-(phenylthio)-1H-indol-1-yl
265	Me	F	3-(phenylthio)-1H-indol-1-yl	H	H
266	Me	H	3-(phenylthio)-1H-indol-1-yl	F	H
267	Me	H	3-(phenylthio)-1H-indol-1-yl	H	F
268	Me	F	3-(phenylthio)-1H-indol-1-yl	F	H
269	Me	H	3-(phenylthio)-1H-indol-1-yl	F	F
270	Me	F	3-(phenylthio)-1H-indol-1-yl	F	F
271	Me	dibenzylamino	H	H	H
272	Me	H	dibenzylamino	H	H
273	Me	H	H	dibenzylamino	H
274	Me	H	H	H	dibenzylamino

FIGURE 20H

No.	R^{3a}	R^{9a}	R^{10a}	R^{11a}	R^{12a}
275	Me	F	dibenzylamino	H	H
276	Me	H	dibenzylamino	F	H
277	Me	H	dibenzylamino	H	F
278	Me	F	dibenzylamino	F	H
279	Me	H	dibenzylamino	F	F
280	Me	F	dibenzylamino	F	F
281	Me	-S(O)$_2$(4-Cl-Ph)	H	H	H
282	Me	H	-S(O)$_2$(4-Cl-Ph)	H	H
283	Me	H	H	-S(O)$_2$(4-Cl-Ph)	H
284	Me	H	H	H	-S(O)$_2$(4-Cl-Ph)
285	Me	F	-S(O)$_2$(4-Cl-Ph)	H	H
286	Me	H	-S(O)$_2$(4-Cl-Ph)	F	H
287	Me	H	-S(O)$_2$(4-Cl-Ph)	H	F
288	Me	F	-S(O)$_2$(4-Cl-Ph)	F	H
289	Me	H	-S(O)$_2$(4-Cl-Ph)	F	F
290	Me	F	-S(O)$_2$(4-Cl-Ph)	F	F
291	Me	-S(4-pyridyl)	H	H	H
292	Me	H	-S(4-pyridyl)	H	H
293	Me	H	H	-S(4-pyridyl)	H
294	Me	H	H	H	-S(4-pyridyl)
295	Me	F	-S(4-pyridyl)	H	H
296	Me	H	-S(4-pyridyl)	F	H
297	Me	H	-S(4-pyridyl)	H	F
298	Me	F	-S(4-pyridyl)	F	H
299	Me	H	-S(4-pyridyl)	F	F
300	Me	F	-S(4-pyridyl)	F	F
301	Me	-NHCH$_2$Ph	H	H	H
302	Me	H	-NHCH$_2$Ph	H	H
303	Me	H	H	-NHCH$_2$Ph	H
304	Me	H	H	H	-NHCH$_2$Ph
305	Me	F	-NHCH$_2$Ph	H	H
306	Me	H	-NHCH$_2$Ph	F	H
307	Me	H	-NHCH$_2$Ph	H	F
308	Me	F	-NHCH$_2$Ph	F	H
309	Me	H	-NHCH$_2$Ph	F	F
310	Me	F	-NHCH$_2$Ph	F	F

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

SERIAL NO. | FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1ST AMENDMENT		AFTER 2ND AMENDMENT	
	IND	DEP	IND	DEP	IND	DEP
1		1				
2		1				
3		1				
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5	1					
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37	1					
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44						
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46	1					
47						
48						
49						
50						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

	IND	DEP	IND	DEP	IND	DEP
51						
52						
53	1					
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57	1					
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61	1					
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85		1				
86	1					
87		1				
88		2				
89		1				
90		2				
91		1				
92		2				
93						
94						
95						
96						
97						
98						
99						
100						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

PTO-1360 (Replacement only) (3/03)

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

SERIAL NO.	FILING DATE
APPLICANT(S)	

CLAIMS

	AS FILED		AFTER 1ST AMENDMENT		AFTER 2ND AMENDMENT	
	IND	DEP	IND	DEP	IND	DEP
1						
2						
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TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

	IND	DEP	IND	DEP	IND	DEP
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97						
98						
99						
100						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

PTO-1360 (Reproduction only) (3/03)

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

08/21/2006 MAHMED1 00000065 500310 11505591

01 FC:2011	150.00	DA
02 FC:2111	250.00	DA
03 FC:2311	100.00	DA
04 FC:2201	1800.00	DA
05 FC:2202	4425.00	DA

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 469-267/69033

PTO/SB/06 (12-04)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875 Effective December 8, 2004

Application or Docket Number: 09/505,591

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	150.00		N/A	300.00
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	$250		N/A	$500
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	$100		N/A	$200
TOTAL CLAIMS (37 CFR 1.16(i))	197 minus 20 =	* 177	X$ 25 =	4425	OR	X$50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	21 minus 3 =	* 18	X100 =	1800		X200 =	
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))			+180=			+360=	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	6,725		TOTAL	

APPLICATION AS AMENDED – PART II

1111

AMENDMENT A	(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))	*	Minus	**	=	X$ 25 =		OR	X$50 =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X100 =		OR	X200 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					+180=		OR	+360=	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

4, 11, 22, 146, 53, 59, 61, 67, 79, 121, 137, 146, 153, 157, 161, 169, 174, 184, 186

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X$ 25 =		OR	X$50 =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X100 =		OR	X200 =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					+180=		OR	+360=	
					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.

Application Data Sheet

Application Information

Application number::	
Filing Date::	August 16, 2006
Application Type::	Regular
Subject Matter::	Utility
Suggested classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R??::	
Number of CD disks::	
Number of copies of CDs::	
Sequence Submission::	
Computer Readable Form (CRF)?::	
Number of copies of CRF::	
Title::	BORON-CONTAINING SMALL MOLECULES
Attorney Docket Number::	64507-5014-US01
Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	63
Small Entity?::	YES
Latin name::	
Variety denomination name::	
Petition included?::	No
Petition Type::	
Licensed US Govt. Agency::	
Contract or Grant Numbers One::	
Secrecy Order in Parent Appl.::	No

Applicant Information

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Primary Citizenship Country::	Great Britain
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Postal or Zip Code of mailing address::	94040

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City of Mailing Address::	State College
State or Province of mailing address::	PA

Country of mailing address::	US
Postal or Zip Code of mailing address::	16803

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Family Name::	DiPierro
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City of Mailing Address::	Wadsworth
State or Province of mailing address::	IL
Country of mailing address::	US
Postal or Zip Code of mailing address::	60083

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
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Given Name::	Vincent
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Family Name::	Hernandez
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State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	287 Gilchrist Lane
City of Mailing Address::	Watsonville

State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	95076

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
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Name Suffix::	
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City of Mailing Address::	Belmont
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	94002

Applicant Authority Type::	Inventor
Primary Citizenship Country::	Canada
Status::	Full Capacity
Given Name::	Isaac
Middle Name::	
Family Name::	Kennedy
Name Suffix::	
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State or Province of Residence::	IL
Country of Residence::	US
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City of Mailing Address::	Bolingbrook
State or Province of mailing address::	IL
Country of mailing address::	US
Postal or Zip Code of mailing address::	60490

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Igor
Middle Name::	
Family Name::	Likhotvorik
Name Suffix::	
City of Residence::	Naperville
State or Province of Residence::	IL
Country of Residence::	US
Street of Mailing Address::	1124 Laurel Lane
City of Mailing Address::	Naperville
State or Province of mailing address::	IL
Country of mailing address::	US
Postal or Zip Code of mailing address::	60540

Applicant Authority Type::	Inventor
Primary Citizenship Country::	People's Republic of China
Status::	Full Capacity
Given Name::	Weimin
Middle Name::	
Family Name::	Mao
Name Suffix::	
City of Residence::	Sunnyvale
State or Province of Residence::	CA
Country of Residence::	US

Street of Mailing Address::	1154 West Olive Ave., #114
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State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	94086

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Kirk
Middle Name::	R.
Family Name::	Maples
Name Suffix::	
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State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	1195 San Moritz Drive
City of Mailing Address::	San Jose
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	95132

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Jacob
Middle Name::	J.
Family Name::	Plattner
Name Suffix::	
City of Residence::	Berkeley
State or Province of Residence::	CA

Country of Residence::	US
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City of Mailing Address::	Berkeley
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	94705

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Fernando
Middle Name::	
Family Name::	Rock
Name Suffix::	
City of Residence::	Los Altos
State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	1183 Lisa Lane
City of Mailing Address::	Los Altos
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	94024

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Virginia
Middle Name::	
Family Name::	Sanders
Name Suffix::	
City of Residence::	San Francisco

State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	2895 Harrison St., Apt. 4
City of Mailing Address::	San Francisco
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	94110

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Aaron
Middle Name::	M.
Family Name::	Stemphoski
Name Suffix::	
City of Residence::	Florence
State or Province of Residence::	SC
Country of Residence::	US
Street of Mailing Address::	736 Kitty Lane
City of Mailing Address::	Florence
State or Province of mailing address::	SC
Country of mailing address::	US
Postal or Zip Code of mailing address::	29501

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	George
Middle Name::	Petros
Family Name::	Yiannikouros
Name Suffix::	

City of Residence::	Florence
State or Province of Residence::	SC
Country of Residence::	US
Street of Mailing Address::	1864 Brigadoone Lane
City of Mailing Address::	Florence
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	29505

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Siead
Middle Name::	
Family Name::	Zegar
Name Suffix::	
City of Residence::	Orland Park
State or Province of Residence::	IL
Country of Residence::	US
Street of Mailing Address::	15124 Teebrook Drive
City of Mailing Address::	Orland Park
State or Province of mailing address::	IL
Country of mailing address::	US
Postal or Zip Code of mailing address::	60462

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Yong-Kang
Middle Name::	
Family Name::	Zhang

Name Suffix::	
City of Residence::	San Jose
State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	5151 Westmont Avenue
City of Mailing Address::	San Jose
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	95130

Applicant Authority Type::	Inventor
Primary Citizenship Country::	People's Republic of China
Status::	Full Capacity
Given Name::	Huchen
Middle Name::	
Family Name::	Zhou
Name Suffix::	
City of Residence::	Palo Alto
State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	3375 Alma St., Apt. 179
City of Mailing Address::	Palo Alto
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	94306

Correspondence Information

Correspondence Customer Number::	043850

Representative Information

Representative Customer Number:: 043850

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This application	*An application claiming the benefit under 35 USC 119(e)*	60/654,060	02/16/05
This application	Continuation-in-Part	11/357,687	02/16/06

Foreign Priority Information

Country::	Application number::	Filing Date::
WO	PCT/US2006/05542	02 February 2006

Assignee Information

Assignee Name::

Street of mailing address::

City of mailing address::

State or Province of mailing address::

Country of mailing address::

Postal or Zip Code of mailing address::

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

08/21/2006 MAHMED1 00000065 500310 11505591

01 FC:2011 150.00 DA
02 FC:2111 250.00 DA
03 FC:2311 100.00 DA
04 FC:2201 1800.00 DA
05 FC:2202 4425.00 DA

10/03/2006 BHABTEW 00000002 500310 11505591

01 FC:2081 750.00 DA

10/03/2006 BHABTEW 00000011 500310 11505591

01 FC:2203 180.00 DA

PTO-1556
(5/87)

*U.S. Government Printing Office: 2003 — 489-047/60033

PTO/SB/06 (12-04)
Approved for use through 7/31/2006. 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: 11,505,591

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))				150			300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))				250			500
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))				100			200
TOTAL CLAIMS (37 CFR 1.16(i))	197 minus 20 =	177	X$ 25	4425	OR	X$50	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	21 minus 3 =	* 18	X$100	1800		X$200	
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			750			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			180	180		360	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	7655		TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT A

	(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))	*	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))					180		OR	360	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	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))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T 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.