01789 U.S. PTO
021606

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UTILITY PATENT APPLICATION TRANSMITTAL

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

Attorney Docket No.	64507-5014-US
First Inventor	BAKER, Stephen J.
Title	BORON-CONTAINING SMALL MOLECULES
Express Mail Label No.	EV553729231US

3013 U.S. PTO
11/357687
021606

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

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 111]
   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* 12]
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

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

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

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. 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, 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.**

1-SF/7343079.1

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FEE TRANSMITTAL
For FY 2005

☒ Applicant claims small entity status. See 37 CFR 1.27

Total Amount of Payment ($) 1100.00

Complete if Known	
Application Number	Not Yet Assigned
Filing Date	February 16, 2006
First Named Investor	Baker, Stephen J.
Examiner Name	Not Yet Assigned
Art Unit	Not Yet Assigned
Attorney Docket No.	64507-5014-US

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

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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	500
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 ($)		Fee Paid ($)
39	- 20 or HP =	19	x	25	=	475

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

Multiple Dependent Claims	
Fee ($1)	Fee Paid ($1)

Indep. Claims		Extra Claims		Fee ($)		Fee Paid ($)
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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 (415) 442-1304
Name (Print/Type)	Todd Esker		Date February 16, 2006

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CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 2 of 558

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SUBMITTED BY

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Name (Print/Type)	Todd Esker		Date February 16, 2006

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Attorney Docket No.: 064507-5014 US

PATENT APPLICATION

BORON-CONTAINING SMALL MOLECULES

Inventor(s):

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Assignee: Anacor Pharmaceuticals
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Entity: Small

Todd Esker
Reg. No. 46,690

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San Francisco
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Fax 415 442-1001

AS FILED WITH THE USPTO ON FEBRUARY 16, 2006

BORON-CONTAINING SMALL MOLECULES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application 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 ketoconozole typically requires administration of 200 to 400 mg/day for 6 months before any significant therapeutic benefit is realized. Such long term, high dose systemic therapy can have significant adverse effects. For example, ketoconozole 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

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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 female patients or those 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, but the films are not occlusive. 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

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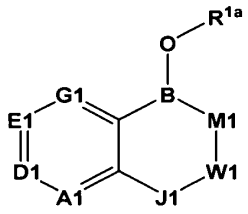
impermeability of pharmaceutical agents through the skin. However, the thin stratum corneum layer of the skin, which is about 10 to 15 cells thick and is formed naturally by cells migrating toward the skin surface from the basal layer, has been easier to penetrate than nails. Moreover, known penetration 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.

SUMMARY OF THE INVENTION

[0011] 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, 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 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

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heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. J1 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, OH, NH_2, SH, 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. W1 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, OH, NH_2, SH, 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. A1 is a member selected from CR^{9a} and N. D1 is a member selected from CR^{10a} and N. E1 is a member selected from CR^{11a} and N. G1 is a member selected from CR^{12a} and N. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OH, NH_2, SH, 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 (A1 + D1 + E1 + G1) 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. The aspect has the proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, then R^{9a} is not halogen, methyl, ethyl, or optionally joined with R^{10a} to a form 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

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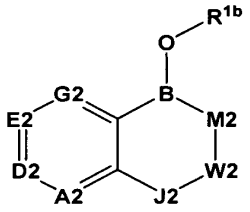
ring; and R^{12a} is not halogen. The aspect has the further proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, then neither R^{6a} nor R^{7a} are halophenyl. The aspect has the further proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, and R^{9a}, R^{10a} and R^{11a} are H, then R^{6a}, R^{7a} and R^{12a} are not H. The aspect has the further proviso that when M1 is oxygen wherein n1 is 1, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 0, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 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 W1 is not C=O (carbonyl). The aspect has the further proviso that when M1 is oxygen, W1 is CR^{5a}, J1 is CR^{8a}, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 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.

[0012] In a second aspect, the invention provides a pharmaceutical formulation comprising (a) a pharmaceutically acceptable excipient; and (b) a compound having a structure according to Formula II:



(II)

wherein B is boron. R^{1b} is a member selected from a negative charge, a salt counterion, 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. M2 is a member selected from oxygen, sulfur and NR^{2b}. R^{2b} 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. J2 is a member selected from $(CR^{3b}R^{4b})_{n2}$ and CR^{5b}. R^{3b}, R^{4b}, and R^{5b} are members independently selected from H, OH, NH_2, SH, substituted or unsubstituted

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alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The index n2 is an integer selected from 0 to 2. W2 is a member selected from C=O (carbonyl), $(CR^{6b}R^{7b})_{m2}$ and CR^{8b}. R^{6b}, R^{7b}, and R^{8b} are members independently selected from H, OH, NH_2, SH, 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 m2 is an integer selected from 0 and 1. A2 is a member selected from CR^{9b} and N. D2 is a member selected from CR^{10b} and N. E2 is a member selected from CR^{11b} and N. G2 is a member selected from CR^{12b} and N. R^{9b}, R^{10b}, R^{11b} and R^{12b} are members independently selected from H, OH, NH_2, SH, 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 (A2 + D2 + E2 + G2) is an integer selected from 0 to 3. A member selected from R^{3b}, R^{4b} and R^{5b} and a member selected from R^{6b}, R^{7b} and R^{8b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{3b} and R^{4b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{6b} and R^{7b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{9b} and R^{10b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{10b} and R^{11b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{11b} and R^{12b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

[0013] In another aspect, the invention provides a method of killing a microorganism, comprising contacting the microorganism with a therpeutically effective amount of a compound of the invention.

[0014] In another aspect, the invention provides a method of inhibiting microorganism growth, comprising contacting the microorganism with a therpeutically effective amount of a compound of the invention.

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[0015] In another aspect, the invention provides a method of treating an infection in an animal, comprising administering to the animal a therpeutically effective amount of a compound of the invention.

[0016] In another aspect, the invention provides a method of preventing an infection in an animal, comprising administering to the animal a therpeutically effective amount of a compound of the invention.

[0017] In another aspect, the invention provides a method of treating a systemic infection or an ungual or periungual infection in a human, comprising administering to the animal a therpeutically effective amount of a compound of the invention.

[0018] In another aspect, the invention provides a method of treating onychomycosis in a human, comprising administering to the animal a therpeutically effective amount of a compound of the invention.

[0019] In another aspect, the invention provides a method of synthesizing a compound of the invention.

[0020] In another aspect, the invention provides a method of delivering a compound from the dorsal layer of the nail plate to the nail bed. The method comprises contacting said cell with a compound capable of penetrating the nail plate, under conditions sufficient to penetrate said nail plate, and thereby delivering the compound. 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 has a water solubility between about 0.1 mg/mL and 1.0 g/mL octanol/saturated water.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] **FIG. 1** is a table of minimum inhibitory concentration (MIC) data of CBO against various fungi.

[0022] **FIG. 2A** displays minimum inhibitory concentration (MIC) for **C10**, ciclopirox, terbinafine, fluconazole and itraconazole (comparator drugs) against 19 test strains of fungi.

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[0023] **FIG. 2B** displays minimum fungicidal concentration (MFC) for **C10**, ciclopirox, terbinafine and itraconazole (comparator drugs) against 2 test strains of fungi.

[0024] **FIG. 3** displays a comparison of Normalized **C10** and Ciclopirox Equivalent in Each Part of Nail Plate Samples after 14-day Treatment.

[0025] **FIG. 4** displays a comparison of **C10** and Ciclopirox Equivalent in Cotton Ball Supporting Bed Samples after 14-day Treatment.

[0026] **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.

[0027] **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.

[0028] **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*.

[0029] **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*.

[0030] **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*.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions and Abbreviations

[0031] The abbreviations used herein generally have their conventional meaning within the chemical and biological arts.

[0032] "Compound of the invention," as used herein refers to the compounds discussed herein, pharmaceutically acceptable salts and prodrugs of these compounds.

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[0033] MIC, or minimum inhibitory concentration, is the point where compound stops more than 90% of cell growth relative to an untreated control.

[0034] 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 $-OCH_2-$.

[0035] 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.

[0036] "Moiety" refers to the radical of a molecule that is attached to another moiety.

[0037] 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.

[0038] 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".

[0039] 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 –

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$CH_2CH_2CH_2CH_2$-, 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.

[0040] 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.

[0041] 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 $-R'C(O)_2-$.

[0042] 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

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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.

[0043] 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.

[0044] 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, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0045] 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

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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).

[0046] 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.

[0047] 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).

[0048] 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', -

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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, -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.

[0049] 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)-, -$S(O)_2$-, -$S(O)_2$NR'- 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 –$S(O)_2$NR'-. The substituents R, R', R" and R"' are preferably independently selected from hydrogen or substituted or unsubstituted (C_1-C_6)alkyl.

[0050] "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"

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further includes a ring system comprising more than one "ring", wherein each "ring" is independently defined as above.

[0051] 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).

[0052] 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.

[0053] 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.

[0054] "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.

[0055] "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.

[0056] 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

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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.

[0057] 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.

[0058] 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.

[0059] 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.

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[0060] 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.

[0061] 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.

[0062] 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.

[0063] "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.

[0064] 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

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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.

[0065] 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.

[0066] The term "excipients" is conventionally known to mean carriers, diluents and/or vehicles used in formulating drug compositions effective for the desired use.

[0067] 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.

[0068] 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

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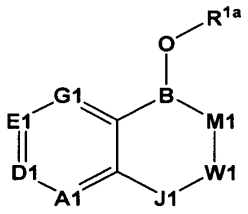
other application of a composition. The stratum corneum acts as a barrier and few pharmaceutical agents are able to penetrate intact skin. In contrast, the epidermis and dermis are permeable to many solutes and absorption of drugs therefore occurs more readily through skin, nail, hair, claw or hoof that 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.

II. Introduction

[0069] 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

[0070] 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, 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 a member selected from oxygen, sulfur and NR^{2a}. R^{2a} is a member

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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. J1 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, OH, NH_2, SH, 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. W1 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, OH, NH_2, SH, 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. A1 is a member selected from CR^{9a} and N. D1 is a member selected from CR^{10a} and N. E1 is a member selected from CR^{11a} and N. G1 is a member selected from CR^{12a} and N. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OH, NH_2, SH, 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 (A1 + D1 + E1 + G1) 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. The aspect has the proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, then R^{9a} is not halogen, methyl, ethyl, or optionally joined with R^{10a} to a form phenyl ring; R^{10a} is not unsubstituted

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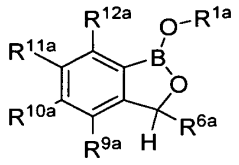
phenoxy, $C(CH_3)_3$, halogen, CF_3, methoxy, ethoxy, or optionally joined with R^{9a} to form a phenyl ring; R^{11a} is not halogen or optionally joined with R^{10a} to form a phenyl ring; and R^{12a} is not halogen. The aspect has the further proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, then neither R^{6a} nor R^{7a} are halophenyl. The aspect has the further proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, and R^{9a}, R^{10a} and R^{11a} are H, then R^{6a}, R^{7a} and R^{12a} are not H. The aspect has the further proviso that when M1 is oxygen wherein n1 is 1, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 0, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 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 W1 is not C=O (carbonyl). The aspect has the further proviso that when M1 is oxygen, W1 is CR^{5a}, J1 is CR^{8a}, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 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.

[0071] In an exemplary embodiment, the compound has a structure according to Formula (Ia):



(Ia)

wherein B is boron. R^{1a} is a member selected from a negative charge, a salt counterion, 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^{6a} are members independently selected from H, OH, NH_2, SH, 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}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OH, NH_2, SH, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

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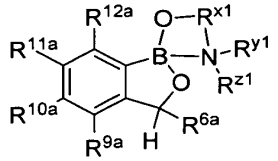
unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{9a} and R^{10a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{10a} and R^{11a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 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. This embodiment has the proviso that R^{9a} is not halogen, methyl, ethyl, or optionally joined with R^{10a} to form a 4 to 7 membered ring. This embodiment has the proviso that R^{10a} is not unsubstituted phenoxy, $C(CH_3)_3$, halogen, CF_3, methoxy, ethoxy, optionally joined with R^{9a} to form a 4 to 7 membered ring, or optionally joined with R^{11a} to form a 4 to 7 membered ring. This embodiment has the proviso that R^{11a} is not halogen or optionally joined with R^{10a} to form a 4 to 7 membered ring. This embodiment has the proviso that R^{12a} is not halogen.

[0072] In an exemplary embodiment, the compound has a structure according to Formula (Ib):



(Ib)

wherein B is boron. R^{x1} is a member selected from substituted or unsubstituted C_1-C_5 alkyl, substituted or unsubstituted C_1-C_5 heteroalkyl. R^{y1} and R^{z1} 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^{6a} are members independently selected from H, OH, NH_2, SH, 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}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OH, NH_2, SH, 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^{11a} and R^{12a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. This embodiment has the proviso that when R^{9a}, R^{11a} and R^{12a}

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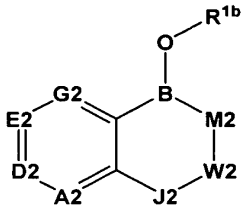
are H, R^{10a} is not H, halogen, unsubstituted phenoxy or t-butyl. This embodiment has the further proviso that when R^{9a} is H, R^{10a} and R^{11a} together with the atoms to which they are attached, are not joined to form a phenyl ring. This embodiment has the further proviso that when R^{11a} is H, R^{9a} and R^{10a} together with the atoms to which they are attached, are not joined to form a phenyl ring.

[0073] In another aspect, the invention provides a compound having a structure according to Formula II:



(II)

wherein B is boron. R^{1b} is a member selected from a negative charge, a salt counterion, 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. M2 is a member selected from oxygen, sulfur and NR^{2b}. R^{2b} 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. J2 is a member selected from $(CR^{3b}R^{4b})_{n2}$ and CR^{5b}. R^{3b}, R^{4b}, and R^{5b} are members independently selected from H, OH, NH_2, SH, 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 n2 is an integer selected from 0 to 2. W2 is a member selected from C=O (carbonyl), $(CR^{6b}R^{7b})_{m2}$ and CR^{8b}. R^{6b}, R^{7b}, and R^{8b} are members independently selected from H, OH, NH_2, SH, 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 m2 is an integer selected from 0 and 1. A2 is a member selected from CR^{9b} and N. D2 is a member selected from CR^{10b} and N. E2 is a member selected from CR^{11b} and N. G2

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is a member selected from CR^{12b} and N. R^{9b}, R^{10b}, R^{11b} and R^{12b} are members independently selected from H, OH, NH_2, SH, 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 (A2 + D2 + E2 + G2) is an integer selected from 0 to 3. A member selected from R^{3b}, R^{4b} and R^{5b} and a member selected from R^{6b}, R^{7b} and R^{8b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{3b} and R^{4b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{6b} and R^{7b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{9b} and R^{10b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{10b} and R^{11b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{11b} and R^{12b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

[0074] In an exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E is CR^{11b}, G is CR^{12b}, then R^{9b} is not a member selected from halogen, methyl, ethyl, or optionally joined with R^{10b} to a form phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_n$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_m$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{10b} is not a member selected from unsubstituted phenoxy, $C(CH_3)_3$, halogen, CF_3, methoxy, ethoxy, or optionally joined with R^{9b} to form a phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_n$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{11b} is not a member selected from halogen or optionally joined with R^{10b} to form a phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{12b} is not halogen. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen,

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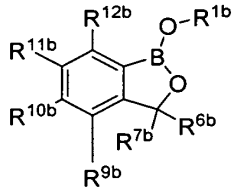
W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{6b} is not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{7b} is not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{6b} and R^{7b} are not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, and R^{9b}, R^{10b} and R^{11b} are H, then R^{6b}, R^{7b} and R^{12b} are not H. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen wherein n2 is 1, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 0, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, R^{9b} is H, R^{10b} is H, R^{11b} is H, R^{6b} is H, R^{7b} is H, R^{12b} is H, then W2 is not C=O (carbonyl). In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is CR^{5b}, J2 is CR^{8b}, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, R^{6b}, R^{7b}, R^{9b}, R^{10b}, R^{11b} and R^{12b} are H, then R^{5b} and R^{8b}, together with the atoms to which they are attached, do not form a phenyl ring.

[0075] In an exemplary embodiment, the compound with a structure according to Formula (IIa):



(IIa).

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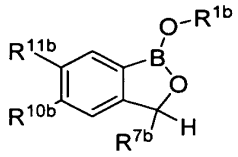
[0076] In another exemplary embodiment, the compound has a structure according to Formula (IIb):

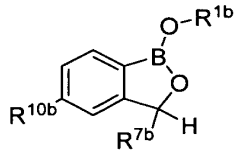


(IIb)

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.

[0077] In another exemplary embodiment, R^{1b} is a member selected from a negative charge, H and a salt counterion. In another exemplary embodiment, R^{10b} and R^{11b} are H. In another exemplary embodiment, 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, R^{10b} and R^{11b} are members independently selected from fluoro, chloro, methyl, cyano, methoxy, hydroxymethyl, and p-cyanophenyl. In another exemplary embodiment, 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, 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, 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.

[0078] In another exemplary embodiment, the compound has a structure according to Formula (IIc):



(IIc)

wherein R^{10b} is a member selected from H, halogen, CN and substituted or

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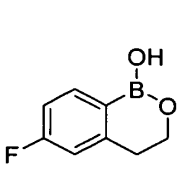
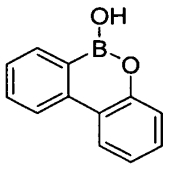
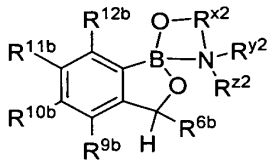
unsubstituted C_{1-4} alkyl. In another exemplary embodiment, the compound has a formulation which is a member selected from:



; and


.

[0079] In another exemplary embodiment, the compound has a structure according to Formula (IId):



(IId)

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.

[0080] The compounds of Formulae (I) or (II) can form a hydrate with water, solvates with alcohols such as methanol, ethanol, propanol, and the like; adducts with amino compounds, such as ammonia, methylamine, ethylamine, and the like; adducts with acids, such as formic acid, acetic acid and the like; complexes with ethanolamine, quinoline, amino acids, and the like.

Preparation of boron-containing small molecules

[0081] 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.

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[0082] 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^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} can be used to refer to the corresponding symbols in Formulae (I) or (II). For example, the symbol A can refer to A1 of Formula (I), or A2 of Formula (II), subject to the provisos of each Formula.

Preparation Strategy #1

[0083] 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.

[0084] 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.

[0085] 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.

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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 to 48 h.

[0086] 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, 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 40 °C, and is complete in 1 to 48 h.

[0087] 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.

[0088] 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, or isopropylmagnesium chloride 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

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-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. After the addition of trialkyl borate, the reaction is allowed to warm to room temperature, which is typically between 15 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.

[0089] In Step 5, the protecting group of compound 5 is removed under acidic conditions to give compound of Formulae (I) and (II). 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 and 40 °C; reaction completion times range from 0.5 to 48 h.

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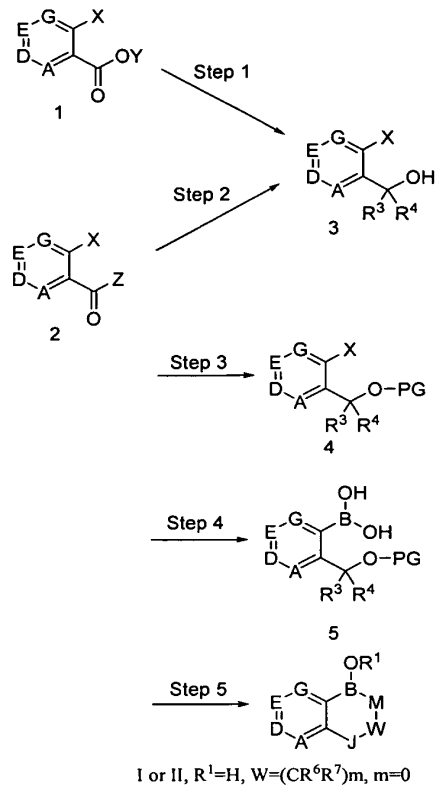
Scheme 1



Preparation Strategy #2

[0090] 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

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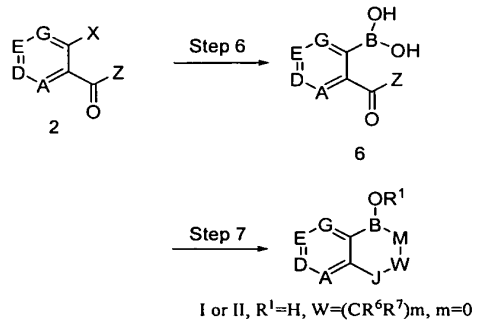
compound 2. Suitable solvents include *N,N*-dimethylformamide, dimethylsufoxide, tetrahydrofuran, 1,4-dioxane, toluene, combinations thereof and the like. Reaction temperatures range from 20 °C to the boiling point of the solvent used; preferably between 50 and 150 °C; reaction completion times range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

[0091] 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.

[0092] In Step 7, the carbonyl group of compound 6 is treated with a reducing agent in an appropriate solvent to give a compound of Formulae (I) and (II). 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



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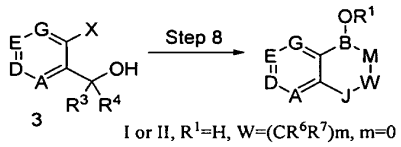
Preparation Strategy #3

[0093] In Scheme 3, Step 8, compounds of Formulae (I) and (II) 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



Preparation Strategy #4

[0094] 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.

[0095] 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

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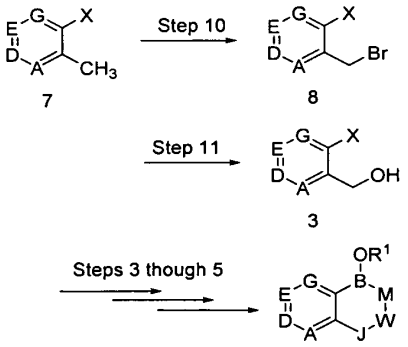
compound 8. Suitable solvents include tetrahydrofuran, 1,4-dioxane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, dimethylsulfoxide, combinations thereof and the like. Reaction temperatures range from 20 °C to the boiling point of the solvent used; preferably between 50 and 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.

[0096] Steps 3 through 5 convert compound 3 into a compound of Formulae (I) and (II).

Scheme 4



Preparation Strategy #5

[0097] 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

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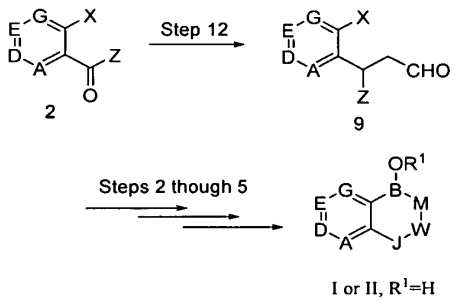
from 1 to 5 equivalents relative to compound 2. Suitable solvents include tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, ether, toluene, hexane, *N,N*-dimethylformamide, combinations thereof and the like. Reaction temperatures range from 0 °C to the boiling point of the solvent used; preferably between 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.

[0098] Steps 2 through 5 convert compound 9 into a compound of Formulae (I) and (II).

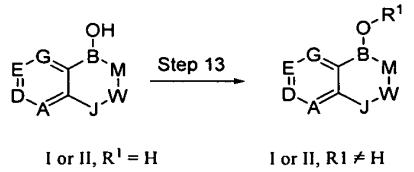
Scheme 5



Preparation Strategy #6

[0099] 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



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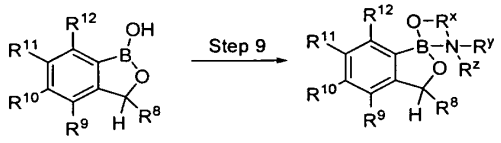
Preparation Strategy #7

[0100] In Scheme 7, compound (Ia) is converted into its aminoalcohol complex (Ib). Compound (Ia) is treated with $HOR^{1}NR^{1a}R^{1b}$. 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

[0101] The compounds of Formulae (I) or (II) can be converted into hydrates and solvates by methods similar to those described above.

IV. Methods of Inhibiting Microorganism Growth or Killing Microorganisms

[0102] 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 according to Formulae (I) or (II). 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.

[0103] 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,

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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.

[0104] 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

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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*; *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*.

[0105] 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.

[0106] 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

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

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Virus Category	Pertinent Human Infections
	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)

[0107] 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.*

V. Methods of Treating or Preventing Infections

[0108] In another aspect, the invention provides a method of treating or preventing an infection, or both. 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 of the invention is according to Formulae (I) or (II). 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

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embodiment, the infection is a member selected from a systemic infection, a cutaneous infection, and an ungual or periungual infection.

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

[0109] 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 the compound of the invention, sufficient to treat or prevent said infection. In another exemplary embodiment, the method includes administering the compound 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.

V. a) 1) ***Onychomycosis***

[0110] 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.

[0111] 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.

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[0112] 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.

[0113] In an exemplary embodiment, the invention provides a method of treating or preventing onychomycosis. The method includes administering to the animal a therapeutically effective amount of 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 having a structure according to Formula (IIb). In another exemplary embodiment, R^{1b} is H. In another exemplary embodiment, R^{10b} and R^{11b} are H. In another exemplary embodiment, 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, R^{10b} and R^{11b} are members independently selected from fluoro, chloro, methyl, cyano, methoxy, hydroxymethyl, and p-cyanophenyl. In another exemplary embodiment, R^{1b} is H; R^{7b} is H; R^{10b} is F and R^{11b} are H. In another exemplary embodiment, R^{11b} and R^{12b}, along with the atoms to which they are attached, are joined to form a phenyl group.

V. a) 2) ***<u>Other Unugal and Periungual Infections</u>***

[0114] In an exemplary embodiment, the invention provides a method of treating or preventing an ungual or periungual infection in a mammal. This method comprising administering to the mammal a therapeutically effective amount of a

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compound of the invention, thereby treating or preventing the ungual or periungual infection. In an exemplary embodiment, the ungual or periungual 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), 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.

[0115] 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.

[0116] 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.

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

[0117] 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 or transdermal.

[0118] In an exemplary embodiment, the infection is systemic and is a member selected from candidiasis, aspergillosis, coccidioidomycosis, cryptococcosis,

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histoplasmosis, blastomycosis, paracoccidioidomycosis, zygomycosis, phaeohyphomycosis and rhinosporidiosis.

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

[0119] 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.

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

[0120] 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.

VI. ***Methods of Nail Penetration***

[0121] 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.

[0122] 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 and/or preferentially bound to keratin that the drug is rendered inactive.

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[0123] 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.

[0124] 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.

[0125] 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.

[0126] 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.

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[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

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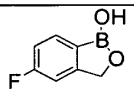
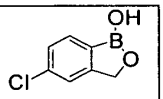
[0132] In an exemplary embodiment, the present invention provides compounds with a log P selected from a range above, with a water solubility selected from a range above, that are still able to penetrate the nail plate.

[0133] 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.

[0134] 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

[0135] 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

[0136] Compound 3 below is an example of a compound similar in molecular weight to ciclopirox, and like ciclopirox, penetrates the nail plate poorly.

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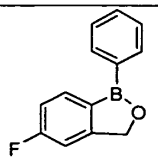
Structure:	 (compound **3**)
Formula:	$C_{13}H_{10}BFO$
Molecular weight (Da):	212.03
Plasma protein binding (%):	100
cLogP:	3.55
Water solubility (μg/mL):	not determined

[0137] In a preferred embodiment the topical formulations including a compound of Formulae (I) or (II) described structurally above 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.

[0138] This invention is still further directed to methods for treating a viral infection mediated at least in part by dermatophytes, *Trichophyton*, *Microsporum* or *Epidermophyton* species, or a yeast-like fungi including *Candida* species, in mammals, which methods comprise administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral 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.

[0139] 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.

[0140] 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.

VII. Pharmaceutical Formulations

[0141] In another aspect, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; and (b) a compound of the

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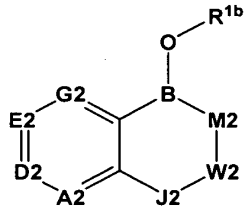
invention. In another aspect, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; and (b) a compound having a structure according to Formula (I), (Ia), (Ib), (Ic), or (Id). In another aspect, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; and (b) a compound which has a structure according to Formula (II), (IIa), (IIb), (IIc), (IId).

[0142] 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 II:



(II)

wherein B is boron. R^{1b} is a member selected from a negative charge, a salt counterion, 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. M2 is a member selected from oxygen, sulfur and NR^{2b}. R^{2b} 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. J2 is a member selected from $(CR^{3b}R^{4b})_{n2}$ and CR^{5b}. R^{3b}, R^{4b}, and R^{5b} are members independently selected from H, OH, NH_2, SH, 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 n2 is an integer selected from 0 to 2. W2 is a member selected from C=O (carbonyl), $(CR^{6b}R^{7b})_{m2}$ and CR^{8b}. R^{6b}, R^{7b}, and R^{8b} are members independently selected from H, OH, NH_2, SH, 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 m2 is an

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integer selected from 0 and 1. A2 is a member selected from CR^{9b} and N. D2 is a member selected from CR^{10b} and N. E2 is a member selected from CR^{11b} and N. G2 is a member selected from CR^{12b} and N. R^{9b}, R^{10b}, R^{11b} and R^{12b} are members independently selected from H, OH, NH_2, SH, 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 (A2 + D2 + E2 + G2) is an integer selected from 0 to 3. A member selected from R^{3b}, R^{4b} and R^{5b} and a member selected from R^{6b}, R^{7b} and R^{8b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{3b} and R^{4b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{6b} and R^{7b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{9b} and R^{10b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{10b} and R^{11b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{11b} and R^{12b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

[0143] In an exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E is CR^{11b}, G is CR^{12b}, then R^{9b} is not a member selected from halogen, methyl, ethyl, or optionally joined with R^{10b} to a form phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_n$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_m$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{10b} is not a member selected from unsubstituted phenoxy, $C(CH_3)_3$, halogen, CF_3, methoxy, ethoxy, or optionally joined with R^{9b} to form a phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_n$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{11b} is not a member selected from halogen or optionally joined with R^{10b} to form a phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2

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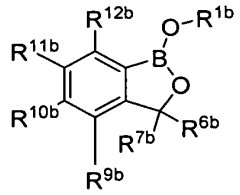
is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{12b} is not halogen. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{6b} is not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{7b} is not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{6b} and R^{7b} are not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, and R^{9b}, R^{10b} and R^{11b} are H, then R^{6b}, R^{7b} and R^{12b} are not H. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen wherein n2 is 1, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 0, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, R^{9b} is H, R^{10b} is H, R^{11b} is H, R^{6b} is H, R^{7b} is H, R^{12b} is H, then W2 is not C=O (carbonyl). In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is CR^{5b}, J2 is CR^{8b}, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, R^{6b}, R^{7b}, R^{9b}, R^{10b}, R^{11b} and R^{12b} are H, then R^{5b} and R^{8b}, together with the atoms to which they are attached, do not form a phenyl ring.

[0144] In an exemplary embodiment, the pharmaceutical formulation has a compound with a structure according to Formula (IIa):



(IIa).

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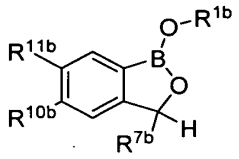
[0145] In another exemplary embodiment, the pharmaceutical formulation has a compound with a structure according to Formula (IIb):

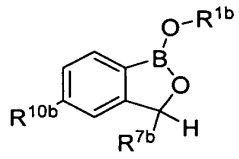


(IIb)

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.

[0146] In another exemplary embodiment, R^{1b} is a member selected from a negative charge, H and a salt counterion. In another exemplary embodiment, R^{10b} and R^{11b} are H. In another exemplary embodiment, 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, R^{10b} and R^{11b} are members independently selected from fluoro, chloro, methyl, cyano, methoxy, hydroxymethyl, and p-cyanophenyl. In another exemplary embodiment, 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, 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, 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.

[0147] In another exemplary embodiment, the pharmaceutical formulation has a compound with a structure according to Formula (IIc):



(IIc)

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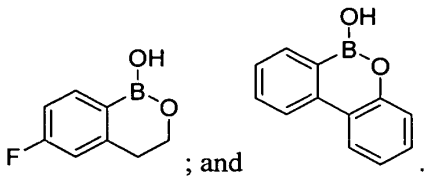
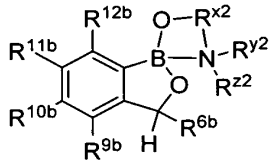
wherein R^{10b} is a member selected from H, halogen, CN and substituted or unsubstituted C_{1-4} alkyl. In another exemplary embodiment, the compound has a formulation which is a member selected from:



; and .

[0148] In another exemplary embodiment, the pharmaceutical formulation has a compound with a structure according to Formula (IId):



(IId)

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.

[0149] 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).

[0150] 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,

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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.

[0151] 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.

[0152] 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.

[0153] 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.

[0154] 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

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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.

[0155] 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.

[0156] 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.

[0157] 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

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the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0158] 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.

[0159] 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.

[0160] 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.

[0161] 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

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feed or drinking water. The composition can also added as a food or drink supplement for humans.

[0162] 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.

[0163] 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.

[0164] 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.

[0165] 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.

[0166] 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).

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[0167] 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).

[0168] 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.

VII. a) Topical formulations

[0169] In a preferred embodiment, the methods of the invention can be used employed through the topical application of the compounds described herein.

[0170] 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.

[0171] 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

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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.

[0172] 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.

[0173] 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.

[0174] 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;

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again, reference may be had to Remington: The Science and Practice of Pharmacy, supra, for further information.

[0175] 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.

[0176] 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.

[0177] 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.

[0178] 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),

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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.

[0179] 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.

[0180] 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%).

[0181] 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).

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[0182] 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.

[0183] 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).

[0184] 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%.

[0185] 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.

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[0186] 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%.

[0187] 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.

[0188] 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.

[0189] 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).

[0190] 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.

[0191] 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-

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increasing agent. These materials are available from Noveon Chemicals, Cleveland, OH.

[0192] 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.

[0193] 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.

[0194] 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

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solvent to an excellent solvent will decrease the maximum solubility for the blend compared with the maximum solubility in the excellent solvent.

[0195] 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 Formula (I) of Formula (II). 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 Formula (I) of Formula (II). 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.

[0196] 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.

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[0197] 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.

[0198] 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.

[0199] 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.

[0200] 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.

[0201] In an exemplary embodiment, the pharmaceutical formulation is a lacquer. Please see Remington's, supra, for more information on the production of lacquers.

[0202] 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

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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

[0203] 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.

[0204] Anti-inflammatory agents include, but are not limited to, bisabolol, mentholatum, dapsone, aloe, hydrocortisone, and the like.

[0205] 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.

[0206] 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.

[0207] 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).

[0208] 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.

[0209] Agents that are effective to control or modify keratinization, including without limitation: tretinoin, tazarotene, and adapalene.

[0210] The compositions comprising an compound/active agent of Formula (I) of Formula (II), 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,

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claw or hoof. Alternatively, any one of the topically applied active agents may also be delivered systemically by transdermal routes.

[0211] 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

[0212] 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).

[0213] 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

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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

[0214] 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.

[0215] 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.

[0216] 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 $mg/m^2/day$.

[0217] 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.

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Preferably, the compound is present at a level of about 0.1-3.0 wt%, more preferably, about 1.0 wt%.

[0218] 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

[0219] 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

[0220] 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

[0221] Exemplary compounds of structure **3** prepared by the method above are provided below.

1.2.a 2-Bromo-5-chlorobenzyl Alcohol

[0222] ^{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

[0223] ^{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).

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EXAMPLE 2

Preparation of 3 from 2

2.1. Reduction of Aldehyde

[0224] 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

[0225] Exemplary compounds of structure **3** prepared by the method above are provided below.

2.2.a 2-Bromo-5-(4-cyanophenoxy)benzyl Alcohol

[0226] ^{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

[0227] ^{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

[0228] 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

[0229] ^{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).

[0230] 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-

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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

[0231] 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

[0232] Exemplary compounds of structure **4** prepared by the method above are provided below.

3.2.a 2-Bromo-5-chloro-l-(methoxymethoxymethyl)benzene

[0233] ^{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

[0234] ^{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

[0235] ^{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

[0236] ^{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).

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3.2.e *2-Bromo-5-cyano-1-(methoxymethoxymethyl)benzene*

[0237] ^{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*

[0238] ^{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*

[0239] ^{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*

[0240] ^{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*

[0241] ^{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*

[0242] ^{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*

[0243] ^{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).

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3.2.1 2-Bromo-5-phenoxy-1-(methoxymethoxymethyl)benzene

[0244] ^{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).

[0245] 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

[0246] 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**.

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4.2 Results

[0247] Analytical data for exemplary compounds of structure **I** are provided below.

4.2.a 5-Chloro-1,3-dihydro-1 -hydroxy-2,1-benzoxaborole **(C1)**

[0248] 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 **(C2)**

[0249] 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-Fluoro-1,3-dihydro-1-hydroxy-3-methyl-2,1-benzoxaborole **(C3)**

[0250] ^{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 **(C4)**

[0251] ^{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 **(C5)**

[0252] ^{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 **(C6)**

[0253] ^{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 **(C7)**

[0254] 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.

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4.2.h *1,3-Dihydro-1-hydroxy-5-methyl-2,1-benzoxaborole* **(C8)**

[0255] 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* **(C9)**

[0256] 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* **(C10)**

[0257] 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* **(C11)**

[0258] 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.l *7-Hydroxy-2,1-oxaborolano[5,4-c]pyridine* **(C12)**

[0259] ^{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.

4.2.m *1,3-Dihydro-6-fluoro-1-hydroxy-2,1-benzoxaborole* **(C13)**

[0260] 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* **(C14)**

[0261] 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.

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4.2.o *3-Benzyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole* **(C15)**

[0262] 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* **(C16)**

[0263] ^{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* **(C17)**

[0264] ^{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* **(C18)**

[0265] 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* **(C19)**

[0266] 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* **(C20)**

[0267] 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* **(C21)**

[0268] 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.

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4.2.v *5-(4-Cyanobenzyloxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole* **(C22)**

[0269] ^{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* **(C23)**

[0270] ^{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* **(C24)**

[0271] ^{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* **(C25)**

[0272] ^{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* **(C26)**

[0273] ^{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* **(C27)**

[0274] ^{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* **(C28)**

[0275] 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.

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4.2.ac *6-(4-trifluoromethoxyphenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole* **(C29)**

[0276] 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* **(C30)**

[0277] 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* **(C31)**

[0278] 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* **(C32)**

[0279] 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* **(C33)**

[0280] 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* **(C34)**

[0281] ^{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.

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4.2.ai *5-Trifluoromethyl-1,3-dihydro-1-hydroxy-2,1-benzoxaborole* **(C35)**

[0282] 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* **(C36)**

[0283] 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.

[0284] ^{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* **(C37)**

[0285] For coupling between 3-fluorobenzonitrile and substituted phenol to give starting material 2: Li, F. *et al.*, *Organic Letters* (2003), 5(12), 2169-2171.

[0286] ^{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-hydroxy-2,1-benzoxaborole* **(C38)**

[0287] 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%).

[0288] ^{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-5-[4-(tetrazole-1-yl)phenoxy]-2,1-benzoxaborole* **(C39)**

[0289] 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.

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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%).

[0290] ^{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

[0291] 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

[0292] Analytical data for exemplary compounds of structure **I** are provided below.

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5.2.a *1,3-Dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole* **(C10)**

[0293] 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*

[0294] 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*

[0295] 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)**

[0296] 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*

[0297] 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**.

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7.2 Results

[0298] 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)**

[0299] Analytical data for this compound is listed in 4.2.j.

EXAMPLE 8

Preparation of 8 from 7

8.1 Bromination

[0300] 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

[0301] 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**.

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9.2 Results

[0302] Exemplary compounds of structure **3** prepared by the method above are provided below.

9.2.a 2-Bromo-5-cyanobenzyl Alcohol

[0303] ^{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).

[0304] 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

[0305] 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

[0306] 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.

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EXAMPLE 12

Preparation of Ib from Ia

12.1 Reaction

[0307] To a solution of **Ia** in toluene was added amino alcohol and the participated solid was collected to give **Ib**.

12.2 Results

[0308] (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 **(C40)**

[0309] ^{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

[0310] Compounds of the present invention can be administered to a patient using a therapeutically effective amount of a compound of Formulae (I) or (II) 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. 20% propylene glycol; 70% ethanol; 10% compound of invention;
2. 70% ethanol; 20% poly(vinyl methyl ether-alt-maleic acid monobutyl ester); 10% 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.

[0311] 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.

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EXAMPLE 14

Antifungal MIC Testing

[0312] All MIC testing followed the National Committee for Clinical Laboratory Standards (NCCLS) guidelines for antimicrobial testing of yeasts 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

[0313] 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).

[0314] 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

[0315] **(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*

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(*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

[0316] **(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.

[0317] 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

[0318] 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 AN2690 against 2

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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

[0319] The solubility, room temperature stability and Log P of **C10** was determined by the following methodology.

Reagents and Standards:

[0320] 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

[0321] 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

[0322] **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

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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

[0323] **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

[0324] 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

[0325] 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.

[0326] 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:

[0327] As shown in Table 17A the solubility of **C10** in both octanol and water is very good over the concentration range tested.

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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

[0328] 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

[0329] 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	

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EXAMPLE 18

Determination of Penetration of C10 into the Human Nail

[0330] 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

[0331] 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.

[0332] 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

[0333] 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:

[0334] 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).

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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

[0335] 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.

[0336] 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

[0337] A Teflon one-chamber diffusion cell (PermeGear, Inc., Hellertown, PA) was used to hold each nail. To approximate physiological conditions, a small cotton

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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

[0338] 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

[0339] 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.

[0340] The powdered nail samples were collected into a glass scintillation vial and weighted. Aliquots of 5.0 mL Packard soluene-350 (Packard Instrument

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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.

[0341] 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

[0342] 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

[0343] 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

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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.

Terminology

[0344] *Ventral / intermediate center*: Powdered nail sample 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).

[0345] *Dorsal / intermediate center*: Immediate area of dosed site.

[0346] *Remainder nail*: The remaining part of the nail that has not been dosed.

[0347] *Supporting bed*: 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.

[0348] *Surfacing washing*: Ethanol (or other organic solvents) and soap/water washing on the surface of the dosed site.

[0349] *Ring*: A plastic ring placed on the top of the nail plate to prevent leakage from the dose site onto rest of the nail plate or inside of the cell chamber.

[0350] *Cell washing*: Ethanol (or other organic solvents) and soap / water wash of the inside of the diffusion cell.

RESULTS

Characteristics of Nail Samples

[0351] 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

[0352] **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 ($p \leq 0.002$).

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C10 and Ciclopirox Equivalent in Cotton Ball Nail Supporting Bed

[0353] **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

[0354] 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

[0355] 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.

[0356] 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

[0357] 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.

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[0358] The following materials were used in these experiments. These materials were used without any modifications.

[0359] 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

[0360] 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

[0361] **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.

[0362] 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

[0363] 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.

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[0364] 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.

[0365] 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.

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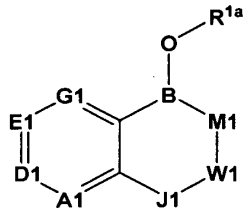
WHAT IS CLAIMED IS:

1. 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, 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 a member selected from oxygen, sulfur and NR^{2a};

wherein

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;

J1 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, 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

n1 is an integer selected from 0 to 2;

W1 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, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted

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or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

m1 is an integer selected from 0 and 1;

A1 is a member selected from CR^{9a} and N;

D1 is a member selected from CR^{10a} and N;

E1 is a member selected from CR^{11a} and N;

G1 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, OH, NH_2, SH, 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 (A1 + D1 + E1 + G1) is an integer selected from 0 to 3;

wherein

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;

with the proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, then R^{9a} is not halogen, methyl, ethyl, or optionally joined

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with R^{10a} to a form 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;

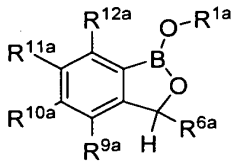
with the further proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, then neither R^{6a} nor R^{7a} are halophenyl;

with the further proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, and R^{9a}, R^{10a} and R^{11a} are H, then R^{6a}, R^{7a} and R^{12a} are not H;

with the further proviso that when M1 is oxygen n1 is 1, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 0, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 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 W1 is not C=O (carbonyl);

with the further proviso that when M1 is oxygen, W1 is CR^{5a}, n1 is 1, J1 is CR^{8a}, m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 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.

2. The compound of claim **1**, having a structure according to Formula (Ia):



(Ia)

wherein

R^{9a}, R^{10a}, R^{11a} and R^{12a} 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; and

wherein

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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; and

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

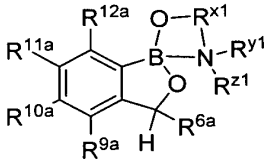
with the proviso that R^{9a} is not halogen, methyl, ethyl, or optionally joined with R^{10a} to form a 4 to 7 membered ring;

with the proviso that R^{10a} is not unsubstituted phenoxy, $C(CH_3)_3$, halogen, CF_3, methoxy, ethoxy, optionally joined with R^9 to form a 4 to 7 membered ring, or optionally joined with R^{11} to form a 4 to 7 membered ring;

with the proviso that R^{11a} is not halogen or optionally joined with R^{10} to form a 4 to 7 membered ring;

with the proviso that R^{12a} is not halogen.

3. The compound of claim **2**, having a structure according to Formula (Ib):



(Ib)

wherein

B is boron;

R^{x1} is a member selected from substituted or unsubstituted C_1-C_5 alkyl, substituted or unsubstituted C_1-C_5 heteroalkyl;

R^{y1} and R^{z1} 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^{6a} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,

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substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; and

R^{9a}, R^{10a}, R^{11a} and R^{12a} 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; and

wherein

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

with the proviso that when R^{9a}, R^{11a} and R^{12a} are H, R^{10a} is not H, halogen, unsubstituted phenoxy or t-butyl

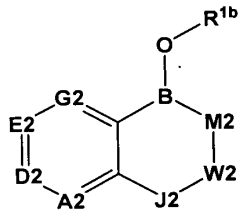
with the further proviso that when R^{9a} is H, R^{10a} and R^{11a} together with the atoms to which they are attached, are not joined to form a phenyl ring;

with the further proviso that when R^{11a} is H, R^{9a} and R^{10a} together with the atoms to which they are attached, are not joined to form a phenyl ring.

4. A pharmaceutical formulation comprising:

(a) a pharmaceutically acceptable excipient; and

(b) a compound having a structure according to Formula II:



(II)

wherein

B is boron;

R^{1b} is a member selected from a negative charge, a salt counterion, 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;

M2 is a member selected from oxygen, sulfur and NR^{2b}

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wherein

R^{2b} 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;

J2 is a member selected from $(CR^{3b}R^{4b})_{n2}$ and CR^{5b}

wherein

R^{3b}, R^{4b}, and R^{5b} are members independently selected from H, OH, NH_2, SH, 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;

n2 is an integer selected from 0 to 2;

W2 is a member selected from C=O (carbonyl), $(CR^{6b}R^{7b})_{m2}$ and CR^{8b}

wherein

R^{6b}, R^{7b}, and R^{8b} are members independently selected from H, OH, NH_2, SH, 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;

m2 is an integer selected from 0 and 1;

A2 is a member selected from CR^{9b} and N;

D2 is a member selected from CR^{10b} and N;

E2 is a member selected from CR^{11b} and N;

G2 is a member selected from CR^{12b} and N;

wherein

R^{9b}, R^{10b}, R^{11b} and R^{12b} are members independently selected from H, OH, NH_2, SH, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or

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unsubstituted heteroaryl;

the combination of nitrogens (A2 + D2 + E2 + G2) is an integer selected from 0 to 3;

a member selected from R^{3b}, R^{4b} and R^{5b} and a member selected from R^{6b}, R^{7b} and R^{8b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

R^{3b} and R^{4b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

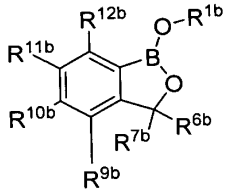
R^{6b} and R^{7b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring;

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

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

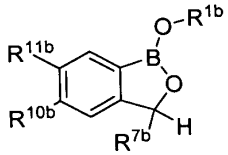
R^{11b} and R^{12b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

5. The pharmaceutical formulation of claim **4**, wherein said compound has a structure according to Formula (IIa):



(IIa).

6. The pharmaceutical formulation of claim **4**, wherein said compound has a structure according to Formula (IIb):



(IIb)

wherein

R^{7b} is a member selected from H, methyl, ethyl and phenyl;

R^{10b} is a member selected from H, halogen, substituted or unsubstituted phenoxy, substituted or unsubstituted phenylalkyloxy, substituted or

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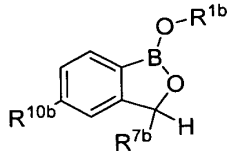
unsubstituted phenylthio and substituted or unsubstituted phenylalkylthio; and

R^{11b} is a member selected from H, OH, methyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenylalkyloxy, substituted or unsubstituted phenylthio and substituted or unsubstituted phenylalkylthio.

7. The pharmaceutical formulation of claim **4**, wherein said compound has a structure according to Formula (IIc):

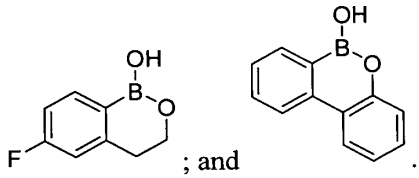


(IIc)

wherein

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

8. The pharmaceutical formulation of claim **4**, wherein said compound has a structure which is a member selected from:



; and .

9. The pharmaceutical formulation of claim **6**, wherein R^{1b} is a member selected from a negative charge, H and a salt counterion.

10. The pharmaceutical formulation of claim **9**, wherein R^{10b} and R^{11b} are H.

11. The pharmaceutical formulation of claim **6**, 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.

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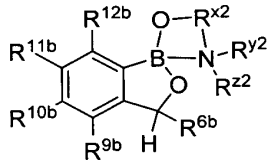
12. The pharmaceutical formulation of claim **6**, wherein R^{10b} and R^{11b} are members independently selected from fluoro, chloro, methyl, cyano, methoxy, hydroxymethyl, and p-cyanophenyl.

13. The pharmaceutical formulation of claim **6**, 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.

14. The pharmaceutical formulation of claim **6**, 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.

15. The pharmaceutical formulation of claim **4**, wherein R^{11b} and R^{12b}, along with the atoms to which they are attached, are joined to form a phenyl group.

16. The pharmaceutical formulation of claim **4**, wherein said compound has a structure according to Formula (IId):



(IId)

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.

17. The pharmaceutical formulation of claim **4**, wherein said excipient is a pharmaceutically acceptable topical carrier.

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18. The pharmaceutical formulation of claim **4**, wherein said compound is present in said pharmaceutical formulation in a concentration of from about 1% to about 10%.

19. 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 **1**.

20. The method of claim **19**, wherein said microorganism is a fungus.

21. The method of claim **19**, 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.

22. The method of claim **19**, wherein said fungus is a member selected from dermatophytes, *Trichophyton*, *Microsporum*, *Epidermophyton* and yeast-like fungi.

23. 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 **4**.

24. The method of claim **23**, wherein said microorganism is a fungus.

25. The method of claim **23**, 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,

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Scopulariopsis species, *Alternaria* species, *Penicillium* species, *Phialophora* species, *Rhizopus* species, *Scedosporium* species and *Zygomycetes* class.

26. The method of claim **23**, wherein said fungus is a member selected from dermatophytes, *Trichophyton*, *Microsporum*, *Epidermophyton* and yeast-like fungi.

27. 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 **1**.

28. The method of claim **27**, wherein said infection is a member selected from a systemic infection, a cutaneous infection, and an ungual or periungual infection.

29. The method of claim **27**, 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.

30. The method of claim **27**, wherein said infection is onychomycosis.

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31. The method of claim **27**, wherein said animal is a member selected from a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey.

32. A method of treating or preventing an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of the pharmaceutical formulation according to claim **4**.

33. The method of claim **32**, wherein said infection is a member selected from a systemic infection and an ungual or periungual infection.

34. The method of claim **32**, 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.

35. The method of claim **32**, wherein said infection is onychomycosis.

36. The method of claim **32**, wherein said animal is a member selected from a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey.

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37. A method for synthesizing the compound of claim **1**.

38. A method for synthesizing the pharmaceutical formulation of claim **4**.

39. A method of delivering a compound from the dorsal layer of the nail plate to the nail bed, said method comprising:

contacting said cell with a compound capable of penetrating the nail plate,

under conditions sufficient to penetrate said nail plate,

wherein

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 octanol/saturated water

thereby delivering said compound.

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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	

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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		

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

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

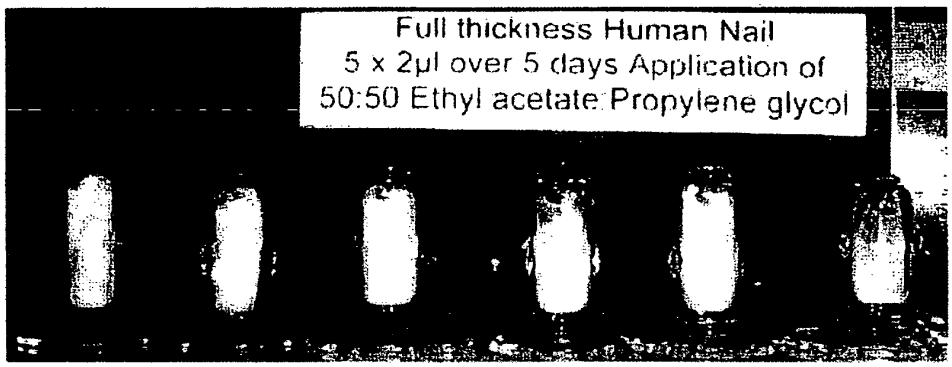

Full thickness Human Nail
5 x 2µl over 5 days Application of
50:50 Ethyl acetate:Propylene glycol

FIGURE 6

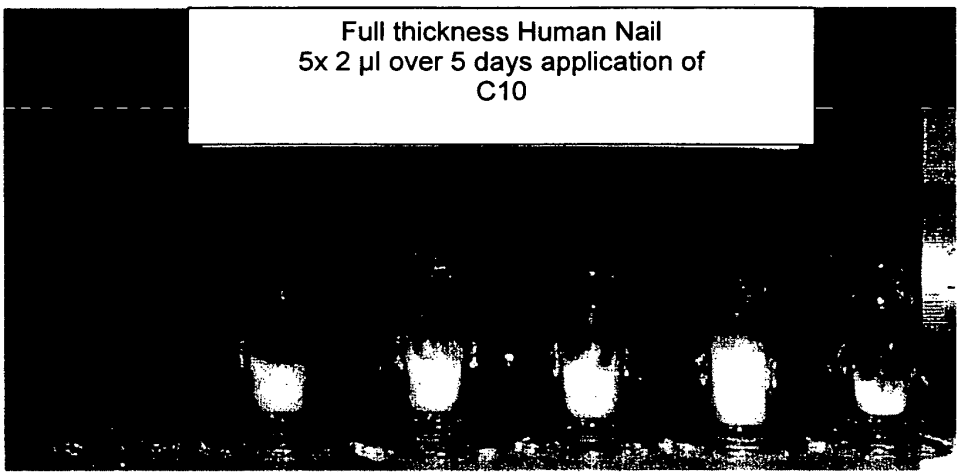

Full thickness Human Nail
5x 2 µl over 5 days application of
C10

FIGURE 7

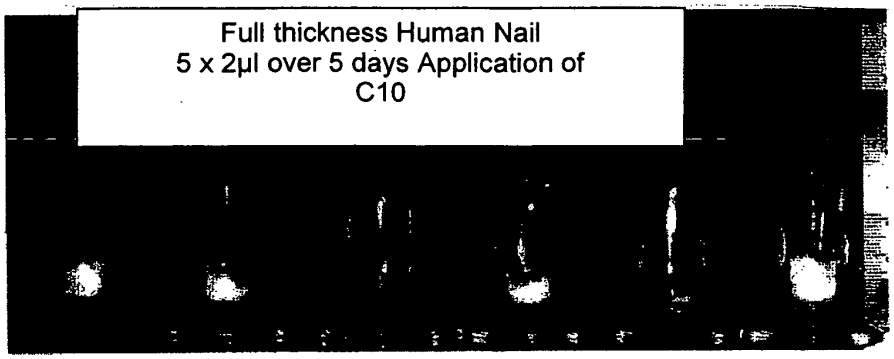

Full thickness Human Nail
5 x 2µl over 5 days Application of
C10

FIGURE 8

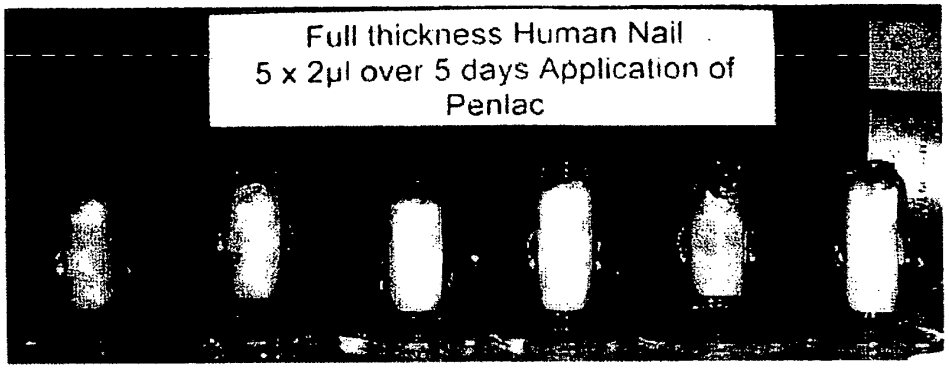
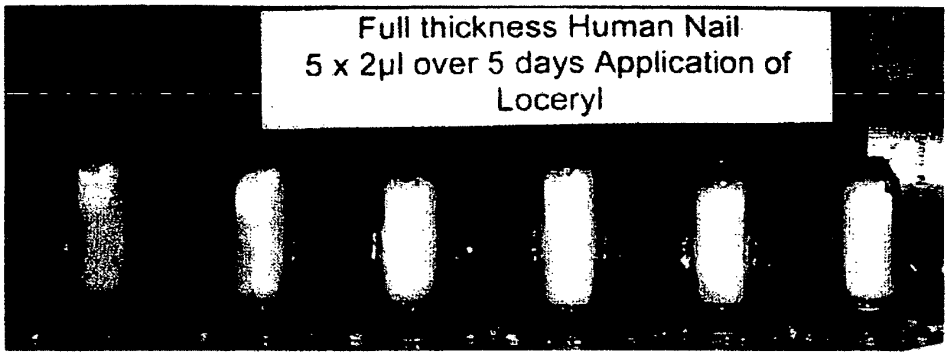

Full thickness Human Nail
5 x 2µl over 5 days Application of
Penlac

FIGURE 9


Full thickness Human Nail
5 x 2µl over 5 days Application of
Loceryl

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875 Effective December 8, 2004

Application or Docket Number: 11357687

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	$200
TOTAL CLAIMS (37 CFR 1.16(i))	39 minus 20 =	* 19	X$ 25 =	475.00	OR	X$50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	* 0	X100 =			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).			125.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			+180=			+360=	
			TOTAL	1100.00		TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	X$ 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	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT B	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.

This collection of information is required by 37 CFR 1.16. 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, 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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FEE RECORD SHEET

02/23/2006 HDEMESS1 00000041 500310 11357687

01 FC:2011 150.00 DA
02 FC:2111 250.00 DA
03 FC:2311 100.00 DA
04 FC:2202 475.00 DA
05 FC:2081 125.00 DA

PTO-1556
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*U.S. Government Printing Office: 2002 — 466-267/69033

Application Data Sheet

Application Information

Application number::	
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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-US
Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	
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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

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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::	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

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

Foreign Priority Information

Country::	Application number::	Filing Date::

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::

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
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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/357,687	02/16/2006	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ 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		(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))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

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

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

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

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

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

Legal Instrument Examiner:
/TARA J. WITCHER/

This collection of information is required by 37 CFR 1.16. 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, 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.**

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/357,687	02/16/2006	Stephen J. Baker	64507-5014-US

CONFIRMATION NO. 4964

043850
MORGAN, LEWIS & BOCKIUS LLP (SF)
2 PALO ALTO SQUARE
3000 El Camino Real, Suite 700
PALO ALTO, CA 94306

FORMALITIES LETTER

Date Mailed: 04/03/2006

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

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

• To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$65** for a Small Entity

- **$65** Surcharge.

Replies should be mailed to: Mail Stop Missing Parts

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

A copy of this notice MUST be returned with the reply.

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199, or 1-800-972-6382
PART 3 - OFFICE COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/357,687	02/16/2006	Stephen J. Baker	64507-5014-US

CONFIRMATION NO. 4964

043850
MORGAN, LEWIS & BOCKIUS LLP (SF)
2 PALO ALTO SQUARE
3000 El Camino Real, Suite 700
PALO ALTO, CA 94306

FORMALITIES LETTER

Date Mailed: 04/03/2006

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

07/03/2006 LWONDIM1 00000040 500310 11357687
01 FC:2051 65.00 DA

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

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

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$65** for a Small Entity

- **$65** Surcharge.

Replies should be mailed to: Mail Stop Missing Parts

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

A copy of this notice MUST be returned with the reply.

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199, or 1-800-972-6382
PART 2 - COPY TO BE RETURNED WITH RESPONSE

OIPE JAP62
JUN 30 2006
PATENT & TRADEMARK OFFICE

PTO/SB/21 (08-03)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	11/357,687
Filing Date	February 16, 2006
First Named Inventor	Baker, Stephen J.
Art Unit	1626
Examiner Name	Not Yet Assigned
Total Number of Pages in This Submission	
Attorney Docket Number	64507-5014-US

ENCLOSURES *(Check all that apply)*

- ☒ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☒ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☒ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s)
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below)*:
  - Return postcard
  - Declaration
  - Supplemental Application Data Sheet
  - Copy of Filing Receipt
  - Power of Attorney
  - 3.73(b) Statement and copy of Assignment
  - Copy of Notice to File Missing Parts

Remarks

The Commissioner is authorized to charge any additional fees to Deposit Account 50-0310.

Please issue corrected filing receipt.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual	Morgan, Lewis & Bockius LLP Jeffry S. Mann, Ph.D. Reg. No. 42,837
Signature	
Date	June 27, 2006

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Kathryn A. Degliantoni		
Signature		Date	June 27, 2006

1-SF/7377949.1

OIPE JAP62 JUN 30 2006 PATENT & TRADEMARK OFFICE

PTO/SB/17 (10-03)

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

CONFIRMATION NO. 4964

TOTAL AMOUNT OF PAYMENT ($) 125.00

Complete if Known	
Application Number	11/357,687
Filing Date	February 16, 2006
First Named Inventor	Baker, Stephen J.
Examiner Name	Not Yet Assigned
Art Unit	1626
Attorney Docket No.	64507-5014-US

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 50-0310

Deposit Account Name: Morgan, Lewis & Bockius LLP

The Director is authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1011	300	2011	150	Utility filing fee	
1002	350	2002	175	Design filing fee	
1003	550	2003	275	Plant filing fee	
1004	790	2004	395	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	
	500		250	Utility Search Fee	
	200		100	Utility Examination Fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims	Fee from below	Fee Paid
Total Claims		-20 =		X25 =	
Independent Claims		-3 =		X100 =	
Multiple Dependent				X =	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	50	2202	25	Claims in excess of 20
1201	200	2201	100	Independent claims in excess of 3
1203	360	2203	180	Multiple dependent claim, if not paid
1204	88	2204	44	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	65
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	120	2251	60	Extension for reply within first month	60
1252	450	2252	225	Extension for reply within second month	
1253	1,020	2253	510	Extension for reply within third month	
1254	1,590	2254	795	Extension for reply within fourth month	
1255	2,160	2255	1,080	Extension for reply within fifth month	
1401	500	2401	250	Notice of Appeal	
1402	500	2402	250	Filing a brief in support of an appeal	
1403	1,000	2403	500	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	500	2452	250	Petition to revive – unavoidable	
1453	1,500	2453	750	Petition to revive – unintentional	
1501	1,400	2501	700	Utility issue fee (or reissue)	
1502	800	2502	400	Design issue fee	
1503	1,100	2503	550	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Petitions related to provisional applications	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
1081	250	2081	125	Utility Application Size Fee – for each additional 50 sheets that exceeds 100 sheets	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($)125

SUBMITTED BY *Complete (if applicable)*

Name (Print/Type)	Jeffry S. Mann, Ph.D.	Registration No. (Attorney/Agent)	42,837	Telephone	(415) 442-1119
Signature				Date	June 27, 2006

1-SF/7377944.1

OIPE IAP62
JUN 30 2006
PATENT & TRADEMARK OFFICE

PTO/SB/22 (12-04)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2005** *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) 64507-5014-US
Application Number 11/357,687	Filed 02/16/2006
For BORON-CONTAINING SMALL MOLECULES	
Art Unit 1626	Examiner N/A

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))	$120	$60	$ 60
☐	Two months (37 CFR 1.17(a)(2))	$450	$225	$
☐	Three months (37 CFR 1.17(a)(3))	$1020	$510	$
☐	Four months (37 CFR 1.17(a)(4))	$1590	$795	$
☐	Five months (37 CFR 1.17(a)(5))	$2160	$1080	$

☑ 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. I have enclosed a duplicate copy of this sheet.

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.

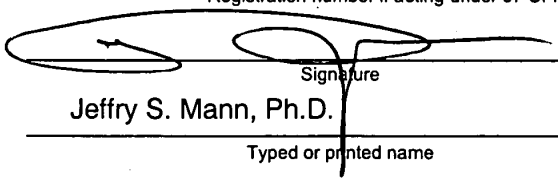
I am the

☐ 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 _____

☑ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 42,837



Signature — June 27, 2006 (Date)

Jeffry S. Mann, Ph.D. (Typed or printed name) — 415-442-1119 (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 pg. in duplicate forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 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.**

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

07/03/2006 LWONDIM1 00000040 500310 11357687
02 FC:2251 60.00 DA

OIPE
JUN 30 2006
PATENT & TRADEMARK OFFICE

Attorney Docket No.:
Client Ref. No.: **64507-5014-US**

PTO/SB/01A (10-00)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title: BORON-CONTAINING SMALL MOLECULES

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

This declaration is directed to:

☐ The attached application, or

☒ Application No. **11/357,687**, filed on **February 16, 2006**,

☐ as amended on _____ (if applicable);

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

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

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

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

FULL NAME OF INVENTOR(S)

Inventor 1 Stephen J. Baker Date: April 28th 2006
Signature: _____ Citizen of: Great Britain

Inventor 2 Tsutomu Akama Date: 4/28/06
Signature: _____ Citizen of: Japan

Inventor 3 Carolyn Bellinger-Kawahara Date: 4/28/06
Signature: _____ Citizen of: United States

Inventor 4 Vincent S. Hernandez Date: 4/28/06
Signature: _____ Citizen of: United States

☒ Additional inventors are being named on 1 additional form(s) attached hereto.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76) – ADDITIONAL INVENTOR(S)
Supplemental Sheet
(Total of 2 forms are submitted.)

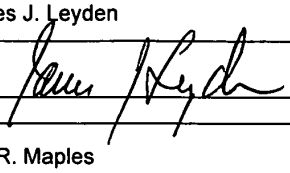
FULL NAME OF INVENTOR(S)

Inventor 5:	Karin M. Hold	Date:	4/28/06
Signature:		Citizen of:	United States
Inventor 6:	James J. Leydon	Date:	
Signature:		Citizen of:	United States
Inventor 7:	Kirk R. Maples	Date:	4/28/06
Signature:	Kirk R. Maples	Citizen of:	United States
Inventor 8:	Jacob J. Plattner	Date:	4/28/06
Signature:	Jacob J. Plattner	Citizen of:	United States
Inventor 9:	Virginia Sanders	Date:	4/28/06.
Signature:	Virginia Sanders	Citizen of:	United States
Inventor 10:	Yong-Kang Zhang	Date:	4-28-2006
Signature:	Yongkang Zhang	Citizen of:	United States

Burden Hour Statement: This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is used by the public to file (and the PTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This form is estimated to take 1 minute to complete. This time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 148 of 558

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76) – ADDITIONAL INVENTOR(S)
Supplemental Sheet
(Total of 2 forms are submitted.)

FULL NAME OF INVENTOR(S)			
Inventor 5:	Karin M. Hold	Date:	
Signature:		Citizen of:	United States
Inventor 6:	James J. Leyden	Date:	6/19/06
Signature:		Citizen of:	United States
Inventor 7:	Kirk R. Maples	Date:	
Signature:		Citizen of:	United States
Inventor 8:	Jacob J. Plattner	Date:	
Signature:		Citizen of:	United States
Inventor 9:	Virginia Sanders	Date:	
Signature:		Citizen of:	United States
Inventor 10:	Yong-Kang Zhang	Date:	
Signature:		Citizen of:	United States

Burden Hour Statement: This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is used by the public to file (and the PTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This form is estimated to take 1 minute to complete. This time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 149 of 558

Application Data Sheet

Application Information

Application number::	11/357,687
Filing Date::	February 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-US
Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	
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

Applicant Authority Type::	Inventor
Primary Citizenship Country::	Great Britain
Status::	Full Capacity
Given Name::	Stephen
Middle Name::	J.
Family Name::	Baker
Name Suffix::	
City of Residence::	Mountain View
State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	1568 Begen Avenue
City of Mailing Address::	Mountain View
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	94040

Applicant Authority Type::	Inventor
Primary Citizenship Country::	Japan
Status::	Full Capacity
Given Name::	Tsutomu
Middle Name::	
Family Name::	Akama
Name Suffix::	
City of Residence::	Sunnyvale
State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	832 Azure Street
City of Mailing Address::	Sunnyvale
State or Province of mailing address::	CA
Country of mailing address::	US

Postal or Zip Code of mailing address::	94087

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Carolyn ~~Carole~~
Middle Name::	
Family Name::	Bellinger-Kawahara
Name Suffix::	
City of Residence::	Redwood City
State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	15 Landa Lane
City of Mailing Address::	Redwood City
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	94061

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Vincent
Middle Name::	S.
Family Name::	Hernandez
Name Suffix::	
City of Residence::	Watsonville
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
Status::	Full Capacity
Given Name::	Karin
Middle Name::	M.
Family Name::	Hold
Name Suffix::	
City of Residence::	Belmont
State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	1908 Valdez Avenue
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::	US
Status::	Full Capacity
Given Name::	James
Middle Name::	J.
Family Name::	Leyden ~~Leydon~~
Name Suffix::	
City of Residence::	Malvern
State or Province of Residence::	PA
Country of Residence::	US
Street of Mailing Address::	319 Applebrook Drive
City of Mailing Address::	Malvern

State or Province of mailing address::	PA
Country of mailing address::	US
Postal or Zip Code of mailing address::	19355

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Kirk
Middle Name::	R.
Family Name::	Maples
Name Suffix::	
City of Residence::	San Jose
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
Street of Mailing Address::	1016 Amito Avenue

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::	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::	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

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

Foreign Priority Information

Country::	Application number::	Filing Date::

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::

Please type a plus sign (+) inside this box → [+]

PTO/SB/81 (02-01)
Approved for use through 10/31/2002. OMB 0651-0035
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POWER OF ATTORNEY OR AUTHORIZATION OF AGENT		
	Application Number	11/357,687
	Filing Date	February 16, 2006
	First Named Inventor	Baker, Stephen J.
	Title	Boron-Containing Small Molecules
	Group Art Unit	1626
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	64507-5014-US

I hereby appoint:

☒ Practitioners at Customer Number 43850 → *Place Customer Number Bar Code Label here*

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please change the correspondence address for the above-identified application to:

☐ The above-mentioned Customer Number.

OR

☐ Firm *or* Individual Name					
Address					
City		State		ZIP	
Country					
Telephone		Fax			

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).

SIGNATURE of Applicant or Assignee of Record

Name	Lucy O. Day, Chief Financial Officer, Anacor Pharmaceuticals, Inc.
Signature	
Date	6/19/2006

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.

Burden Hour Statement: This form is estimated to take 3 minutes to complete. Time will vary depending upon the needs of the individual case. Any Comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

1-SF/7134106.1

JUN 30 2006 PATENT & TRADEMARK OFFICE

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Attorney Docket No. 064507-5014-US

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Stephen J. Baker, Tsutomu Akama, Carolyn Bellinger-Kawahara, Vincent S. Hernandez, Karin M. Hold, James J. Leydon, Kirk R. Maples, Jacob J. Platner, Virginia Sanders, Yong-Kang Zhang

Application No./Patent No.: 11/357,687 Filed/Issue Date: February 16, 2006

Entitled: BORON-CONTAINING SMALL MOLECULES

Anacor Pharmaceuticals, Inc., a Delaware corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of an undivided part interest

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

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

OR

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

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

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

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

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

☐ Copies of assignments or other documents in the chain of title are attached.

[**NOTE**: A separate copy (i.e., the original assignment document or a true copy of the original document) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.8]

The undersigned (whose title is supplied below) is empowered to sign this statement on behalf of the assignee.

6/19/2006
Date

Signature

Lucy O. Day
Typed or printed name

Chief Financial Officer
Title

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

COPY AS SENT TO THE USPTO FOR RECORDATION

Attorney Docket No.: 64507-5014-US

ASSIGNMENT OF PATENT APPLICATION

JOINT

WHEREAS, Stephen J. Baker of 1568 Begen Avenue, Mountain View, CA, 94040; Tsutomu Akama of 832 Azure Street, Sunnyvale, CA, 94087; Carolyn Bellinger-Kawahara of 15 Landa Lane, Redwood City, CA, 94061; Vincent S. Hernandez of 287 Gilchrist Lane, Watsonville, CA, 95076; Karin M. Hold of 1908 Valdez Avenue, Belmont, CA, 94002; James J. Leyden of 319 Applebrook Drive, Malvern, CA, 19355; Kirk R. Maples of 1195 San Moritz Drive, San Jose, CA 95132; Jacob J. Plattner of 1016 Amito Avenue, Berkeley, CA 94705; Virginia Sanders of 2895 Harrison Street, Apt. 4, San Francisco, CA, 94110; and Yong-Kang Zhang of 5151 Westmont Avenue, San Jose, CA, 95130, hereinafter referred to as "Assignors," are the inventors of the invention described and set forth in the below-identified patent application:

Title of Invention:	BORON-CONTAINING SMALL MOLECULES
Filing Date:	February 16, 2006
Application No.:	11/357,687; and

WHEREAS, Anacor Pharmaceuticals, Inc., located at 1060 East Meadow Circle, Palo Alto, CA 94303, hereinafter referred to as "ASSIGNEE," is desirous of acquiring an interest in the invention and application and in any U.S. Letters Patent and Registrations which may be granted on any patent application claiming priority from the same;

For good and valuable consideration, receipt of which is hereby acknowledged by Assignors, Assignors have assigned, and by these presents does assign to Assignee all right, title and interest in and to the invention and application and to all foreign counterparts (including patent, utility model and industrial designs), and in and to any Letters Patent and Registrations which may hereafter be granted on any patent application claiming priority from the same in the United States and all countries throughout the world, and to claim the priority from the application as provided by the Paris Convention. The right, title and interest is to be held and enjoyed by Assignee and Assignee's successors and assigns as fully and exclusively as it would have been held and enjoyed by Assignors had this Assignment not been made, for the full term of any Letters Patent and Registrations which may be granted thereon, or of any division, renewal, continuation in whole or in part, substitution, conversion, reissue, prolongation or extension thereof.

Assignors further agree that Assignors will, without charge to Assignee, but at Assignee's expense, (a) cooperate with Assignee in the prosecution of U.S. Patent applications and foreign counterparts on the invention and any improvements, (b) execute, verify, acknowledge and deliver all such further papers, including applications and instruments of transfer, and (c) perform such other acts as Assignee lawfully may request to obtain or maintain Letters Patent and Registrations for the invention and improvements in any and all countries, and to vest title thereto in Assignee, or Assignee's successors and assigns.

Assignors hereby authorize and request Morgan, Lewis & Bockius LLP, One Market, Spear Street Tower, San Francisco, CA 94105, to insert herein above the application number and filing date of said application when known.

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 159 of 558

IN TESTIMONY WHEREOF, Assignors have signed his/her names on the dates indicated.

Dated: April 28th 2006

STEPHEN J. BAKER

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006, before me, Donielle M. Equite personally appeared STEPHEN J. BAKER, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

NOTARY PUBLIC

My ~~Commission Expires:~~ July 12, 2006

Dated: 4/28/06

TSUTOMU AKAMA

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006, before me, Donielle M. Equite personally appeared TSUTOMU AKAMA, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 160 of 558

Dated: 4/28/06

Carolyn Bellinger-Kawahara
CAROLYN BELLINGER-KAWAHARA

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared CAROLYN BELLINGER-KAWAHARA, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

~~WITNESS my hand and official seal.~~

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: 4/28/06

VINCENT S. HERNANDEZ

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared VINCENT S. HERNANDEZ, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 161 of 558

Dated: 4/28/06

KARIN M. HOLD

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

On April 28, 2006 before me, Donielle M. Equite personally appeared KARIN M. HOLD, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that ~~he~~/she executed the same in ~~his~~/her authorized capacity, and that by ~~his~~/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: _____

JAMES J. LEYDON

STATE OF)
) ss.
COUNTY OF)

On _____, before me, _____ personally appeared JAMES J. LEYDON, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: _____

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 162 of 558

Dated: _____

_____
KARIN M. HOLD

STATE OF CALIFORNIA)
) ss.
COUNTY OF)

On _____, before me, _____ personally appeared KARIN M. HOLD, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

_____
NOTARY PUBLIC

My Commission Expires: _____

Dated: 6/19/06

_____
JAMES J. LEYDEN

STATE OF)
) ss.
COUNTY OF)

On _____, before me, _____ personally appeared JAMES J. LEYDEN, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

_____
NOTARY PUBLIC

My Commission Expires: _____

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 163 of 558

Dated: 4/28/06

KIRK R. MAPLES

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M Equite personally appeared KIRK R. MAPLES, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: April 28, 2006

JACOB J. PLATTNER

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared JACOB J. PLATTNER, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 164 of 558

Dated: 4/28/06

Virginia Sanders
VIRGINIA SANDERS

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared VIRGINIA SANDERS, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: 4-28-2006

Yongkang Zhang
YONG-KANG ZHANG

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared YONG-KANG ZHANG, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 165 of 558

64507 5014...
JJM

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APPL NO.	FILING OR 371 (c) DATE	ART UNIT	FIL FEE REC'D	ATTY.DOCKET NO	DRAWINGS	TOT CLMS	IND CLMS
11/357,687	02/16/2006	1626	1100	64507-5014-US	12	39	3

CONFIRMATION NO. 4964

043850
MORGAN, LEWIS & BOCKIUS LLP (SF)
2 PALO ALTO SQUARE
3000 El Camino Real, Suite 700
PALO ALTO, CA 94306

OIPE JAP62
JUN 30 2006
PATENT & TRADEMARK OFFICE

FILING RECEIPT

OC000000018434221

NO DOCKETING REQUIRED

Date Mailed: 04/03/2006

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Stephen J. Baker, Mountain View, CA;
Tsutomu Akama, Sunnyvale, CA;
Carole Bellinger-Kawahara, Redwood City, CA; Carolyn
Vincent S. Hernandez, Watsonville, CA;
Karin M. Hold, Belmont, CA;
James J. Leydon, Malvern, PA; Leyden
Kirk R. Maples, San Jose, CA;
Jacob J. Plattner, Berkeley, CA;
Virginia Sanders, San Francisco, CA;
Yong-Kang Zhang, San Jose, CA;

Assignment For Published Patent Application

Anacor Pharmaceuticals, Palo Alto, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 60/654,060 02/16/2005

Foreign Applications

If Required, Foreign Filing License Granted: 03/30/2006

The country code and number of your priority application, to be used for filing abroad under the Paris

Convention, is US11/357,687

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

Boron-containing small molecules

Preliminary Class

514

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On May 3, 2007

MORGAN, LEWIS & BOCKIUS LLP

By: Kathy Degliantoni

PATENT

Attorney Docket No.: 64507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4964
Stephen J. Baker, *et al.*	Examiner: Balasubramanian, V.
Application No.: 11/357,687	Art Unit: 1626
Filed: February 16, 2006	INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97 and §1.98
For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

Commissioner for Patents
P.O. Box 1450
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Sir:

The references cited on attached form PTO/SB/8A are being called to the attention of the Examiner. Copies of the references are enclosed. It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

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CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 169 of 558

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Respectfully submitted,

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/357,687
Filing Date	February 16, 2006
First Named Inventor	Baker, Stephen J.
Art Unit	1626
Examiner Name	Balasubramanian, V.
Attorney Docket Number	64507-5014-US

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)	

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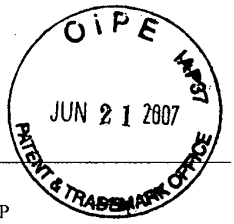

PATENT
Attorney Docket No.: 64507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4964
Stephen J. Baker, *et al.*	Examiner: Balasubramanian, V.
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For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

Commissioner for Patents
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Sir:

The references cited on attached form PTO/SB/8A are being called to the attention of the Examiner. Copies of the references are enclosed. Also enclosed is a copy of the Search/Examination report corresponding to the International Application No. PCT/US06/05542. It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

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CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 172 of 558

Applicant believes that no fee is required for submission of this statement, since it is being submitted within three months of the date that the International Search Report was mailed. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 50-0310. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

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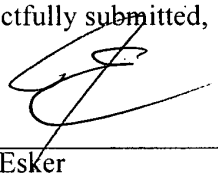

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 1

Complete if Known	
Application Number	11/440,839
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U.S. PATENT DOCUMENTS+

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

NON PATENT LITERATURE DOCUMENTS

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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(54) Title: HYDROLYTICALLY-RESISTANT BORON-CONTAINING THERAPEUTICS AND METHODS OF USE

(57) Abstract: Compositions and methods of use of borole derivatives, including benzoxaboroles, benzazaboroles and benzthiaboroles, as therapeutic agents for treatment of diseases caused by bacteria or viruses are disclosed, as well as methods for synthesis of said agents and compositions thereof.

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HYDROLYTICALLY-RESISTANT BORON-CONTAINING THERAPEUTICS AND METHODS OF USE

This application claims priority of U.S. Provisional Application Serial No. 60/478,921, filed 16 June 2003, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel compounds and compositions which have selective therapeutic activities, processes for making such compounds, synthetic intermediates employed in these processes and a method for treating human or other mammal in need of medical treatments.

BACKGROUND OF THE INVENTION

Many advances in medicine in the 20th century have been due to the discovery of new classes of small molecular weight effectors for various therapeutic needs. Herein we disclose the diverse, but selective pharmacologically active boron-containing entities.

One hallmark of the modern era of medicine has been the decline in morbidity and mortality associated with bacterial and fungal infections.

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However, misuse of conventional antibiotics and natural selection of the infectious bacterial population has resulted in the development of varying degrees of drug resistance by most bacterial infectious agents to most antibiotic agents. In severe cases, such as MRSA (Multidrug-Resistant StaphA), one or only a few antibiotics are currently effective. In addition, the existence of immunodeficiency syndromes results in additional incidences of opportunistic infections requiring intensive antibiotic treatment.

Viruses are implicated in a variety of animal and human disease. Numerous approaches have been proposed to combat these pathogens which include, but are not limited to herpesviruses 1 and 2 (HSV-1 and HSV-2), influenza viruses A, B and C, parainfluenza viruses 1-4, syncytial virus, Epstein-Barr virus, rhinoviruses, human immunodeficiency viruses (HIV), polioviruses, coxsackieviruses, echoviruses, rubella virus, varicella-zoster virus, neurodermatropic virus, variola virus, cytomegalovirus, hepatitis A, B and C viruses, papoviruses, rabies virus, yellow fever virus, dengue virus, West Nile virus and SARS virus.

One approach in the development of antiviral compounds has been to identify compounds which interfere with the normal viral metabolism and replication in infected host cells. During the screening of new borinic ester compounds, we have found that certain of these compounds show antiviral activity in cell culture assay systems. Many existing compounds currently in use for treating viral diseases are subject to resistance mechanisms, are expensive to make, do not adequately treat patients or have adverse side effects. Therefore, there is a continuing need for new compounds which act to kill viruses, to inhibit viral replication or to block the pathogenic action of viruses.

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

Boron containing compounds have received increasing attention as therapeutic agents over the past few years as technology in organic synthesis has expanded to include this atom. [Boron Therapeutics on the horizon,

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Groziak, M.P.; American Journal of Therapeutics (2001) 8, 321-328] The most notable boron containing therapeutic is the boronic acid bortezomib which was recently launched for the treatment of multiple myeloma. This breakthrough demonstrates the feasibility of using boron containing compounds as pharmaceutical agents. Boron containing compounds have been shown to have various biological activities including herbicides [Organic boron compounds as herbicides. Barnsley, G.E.; Eaton, J.K.; Airs, R.S.; (1957), DE 1016978 19571003], boron neutron capture therapy [Molecular Design and Synthesis of B-10 Carriers for Neutron Capture Therapy. Yamamoto, Y.; Pure Appl. Chem., (1991) 63, 423-426], serine protease inhibition [Borinic acid inhibitors as probes of the factors involved in binding at the active sites of subtilisin Carlsberg and α-chymotrypsin. Simpelkamp, J.; Jones, J.B.; Bioorganic & Medicinal Chemistry Letters, (1992), 2(11), 1391-4], [Design, Synthesis and Biological Evaluation of Selective Boron-containing Thrombin Inhibitors. Weinand, A.; Ehrhardt, C.; Metternich, R.; Tapparelli, C.; Bioorganic and Medicinal Chemistry, (1999), 7, 1295-1307], acetylcholinesterase inhibition [New, specific and reversible bifunctional alkylborinic acid inhibitor of acetylcholinesterase. Koehler, K.A.; Hess, G.P.; Biochemistry (1974), 13, 5345-50] and as antibacterial agents [Boron-Containing Antibacterial Agents: Effects on Growth and Morphology of Bacteria Under Various Culture Conditions. Bailey, P.J.; Cousins, G.; Snow, G.A.; and White, A.J.; Antimicrobial Agents and Chemotherapy, (1980), 17, 549-553]. The boron containing compounds with antibacterial activity can be sub-divided into two main classes, the diazaborinines, which have been known since the 1960's, and dithienylborinic acid complexes. This latter class has been expanded to include many different diarylborinic acid complexes with potent antibacterial activity [Preparation of diarylborinic acid esters as DNA methyl transferase inhibitors. Benkovic, S.J.; Shapiro, L.; Baker, S.J.; Wahnon, D.C.; Wall, M.; Shier, V.K.; Scott, C.P.; Baboval, J.; PCT Int. Appl. (2002), WO 2002044184]. Synthetic developments described in Benkovic et al. enabled creation of a much more diverse class of unsymmetrical di-substituted borinic acid complexes not possible before.

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Thus, there continues to be a need in the medical arts for novel, more effective, antibiotic compounds, especially for treating infectious diseases, that are resistant to currently available therapies.

BRIEF SUMMARY OF THE INVENTION

In one aspect, the present invention relates to therapeutic compounds, which are boron-containing. These compounds include structures that encompass benzoxaboroles, benzazaboroles, benzthiaboroles and related analogs.

These compounds are also provided as pharmaceutical compositions that can be administered to an animal, most preferably a human, for treatment of a disease having either bacterial, fungal or viral etiology, most preferably a human, in an immunologically compromised or debilitated state of health.

In preferred embodiments, the compounds of the invention are those having the structures given by Formula 1, with preferred substituents as disclosed herein.

The invention also provides methods for preparing these therapeutic compounds and pharmaceutical compositions thereof, and methods of using said compounds therapeutically. Kits and packaged embodiments of these compounds and pharmaceutical compositions of the invention are also contemplated.

The invention also relates to methods of treating various medical conditions, using the compounds disclosed herein.

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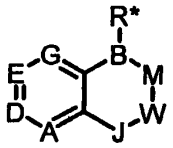
DETAILED DESCRIPTION OF THE INVENTION

This invention provides therapeutic agents, and specifically antibacterial, antifungal, or antiviral compounds, useful in treating and/or preventing conditions due to these pathogens.

The invention comprises a compound having the following structures



Formula 1

wherein B is boron, M is selected from oxygen, sulfur and NR**

wherein R* is selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 – C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

wherein R** is H, alkyl, alkyloxy, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

and wherein A is CH, CR^1, or N

and wherein D is CH, CR^2, or N

and wherein E is CH, CR^3, or N

and wherein G is CH, CR^4, or N

and the combination of nitrogens (A + D + E + G) is 0-3

and wherein J is $(CH_2)_n$ (n = 0 to 2) or CHR^5

and wherein W is $(CH_2)_m$ (m = 0 to 1), C=O (carbonyl) or CHR^6

wherein R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of hydrogen, haloalkyl, alkyl, cycloalkyl, $(CH_2)_pOH$ (p =

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1 to 3), halogen, CHO, CH=NOH, CO_2H, CO_2-alkyl, S-alkyl, SO_2-alkyl, S-aryl, $(CH_2)_qNR^{18}R^{19}$ (wherein R^{18} and R^{19} are independently selected from hydrogen, alkyl, and alkanoyl)(q = 0 to 2), alkoxy, CF_3, SCF_3, NO_2, SO_3H, OH, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, fused substituted or unsubstituted aryl, fused substituted or unsubstituted heteroaryl,

wherein R^5 is selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 – C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

wherein R^6 is selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 – C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

including salts thereof, especially all pharmaceutically acceptable salts.

In preferred embodiments of Formula 1, M is oxygen, or M is sulfur, or M is NR**. Further preferred embodiments of any of these three are any of the following.

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted alkyl (C_1 - C_4).

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted cycloalkyl (C_3 – C_7).

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted alkenyl. In a further preferred embodiment thereof, the substituted alkenyl has the structure

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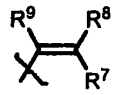
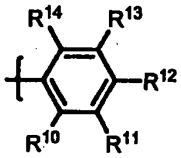


wherein R^7, R^8, and R^9 are each independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_rOH$ (where r = 1 to 3), $CH_2NR^{20}R^{21}$ (wherein R^{20} and R^{21} are independently selected from hydrogen and alkyl), CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted alkynyl. In a further preferred embodiment thereof the substituted alkynyl has the structure

wherein R^7 is defined as before.

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted aryl. In a further preferred embodiment thereof the substituted aryl has the structure



wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, 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, $(CH_2)_tNR^{22}R^{23}$ (wherein R^{20} and R^{21} are independently selected from hydrogen, alkyl, and alkanoyl)(t = 0 to 2),

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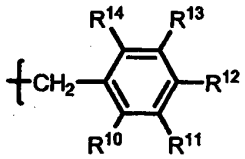
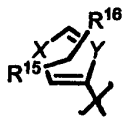
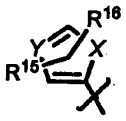
SO_2NH_2, $OCH_2CH_2NH_2$, $OCH_2CH_2NHalkyl$, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, or alkyl substituted oxazolidin-2-yl.

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted aralkyl. In a further preferred embodiment thereof the substituted aralkyl has the structure



wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are defined as before.

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted heteroaryl. In a further preferred embodiment thereof the heteroaryl has the structure

 or 

wherein X = CH=CH, N=CH, NR^{17} (wherein R^{17} = H, alkyl, aryl or benzyl), O, or S

and wherein Y = CH or N

and wherein R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_uOH$ (where u = 1, 2 or 3), $(CH_2)_vNR^{24}R^{25}$ (wherein R^{24} and R^{25} 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 and NO_2.

The structures of the invention also permit solvent interactions that may afford structures (Formula 1B) that include atoms derived from the solvent

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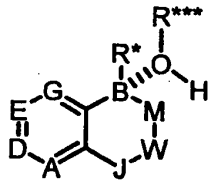
encountered by the compounds of the invention during synthetic manipulations and therapeutic uses. Structures 1B arise from formation of a dative bond between the solvent(s) with the Lewis acidic boron center. Thus, such solvent complexes 1B could be stable entities with comparative bioactivities. Such structures are expressly contemplated by the present invention where R*** is H or alkyl.



Formula 1B

As used herein, the following terms have the stated meaning:

By "alkyl", "lower alkyl", and "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "alkanoyl" in the present invention is meant straight or branched chain alkanoyl groups having 1-6 carbon atoms, such as, acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, isobutanoyl, 3-methylbutanoyl, and 4-methylpentanoyl.

By "alkoxy", "lower alkoxy", and "C_1-C_6 alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

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By "cycloalkyl", e.g., C_3-C_7 cycloalkyl, in the present invention is meant cycloalkyl groups having 3-7 atoms such as, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. In the C_3-C_7 cycloalkyl groups, preferably in the C_5-C_7 cycloalkyl groups, one or two of the carbon atoms forming the ring can optionally be replaced with a hetero atom, such as sulfur, oxygen or nitrogen. Examples of such groups are piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, imidazolidinyl, oxazolidinyl, perhydroazepinyl, perhydrooxazapinyl, oxepanyl, perhydrooxepanyl, tetrahydrofuranyl, and tetrahydropyranyl. C_3 and C_4 cycloalkyl groups having a member replaced by nitrogen or oxygen include aziridinyl, azetidinyl, oxetanyl; and oxiranyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which is optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy. Preferred aryl groups include phenyl and naphthyl, each of which is optionally substituted as defined herein.

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Such heteroaryl groups include, for example, thienyl, furanyl, thiazolyl, imidazolyl, (is)oxazolyl, pyridyl, pyrimidinyl, (iso)quinolinyl, napthyridinyl, benzimidazolyl, and benzoxazolyl. Preferred heteroaryls are thiazolyl, pyrimidinyl, preferably pyrimidin-2-yl, and pyridyl. Other preferred heteroaryl groups include 1-imidazolyl, 2-thienyl, 1-(or 2-)quinolinyl, 1-(or 2-) isoquinolinyl, 1-(or 2-)tetrahydroisoquinolinyl, and 2-(or 3-)furanyl.

The invention also provides embodiments of the compounds disclosed herein as pharmaceutical compositions. The pharmaceutical compositions of

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the present invention can be manufactured in a manner that is itself known, *e.g.*, by means of a conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, hydroxyethanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, $HOOC-(CH_2)_n-CH_3$ where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and functional equivalents. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

For injection, the compounds of the invention can be formulated in appropriate aqueous solutions, such as physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal and transcutaneous administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries,

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suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). 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.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions can take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.*, gelatin

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for use in an inhaler, can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension can also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use. The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic

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materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system can be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system can be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components can be varied: for example, other low-toxicity nonpolar surfactants can be used instead of polysorbate 80; the fraction size of polyethylene glycol can be varied; other biocompatible polymers can replace polyethylene glycol, *e.g.* polyvinyl pyrrolidone; and other sugars or polysaccharides can substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds can be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethyl sulfoxide also can be employed, although usually at the cost of greater toxicity. 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. Sustained-release capsules can, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the

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therapeutic reagent, additional strategies for protein and nucleic acid stabilization can be employed.

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

The compounds of the invention can be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, phosphoric, hydrobromic, sulfinic, formic, toluenesulfonic, methanesulfonic, nitic, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, $HOOC-(CH_2)_n-CH_3$ where n is 0-4, and the like. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

Pharmaceutical compositions of the compounds of the present invention can be formulated and administered through a variety of means, including systemic, localized, or topical administration. Techniques for formulation and administration can be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA. The mode of administration can be selected to maximize delivery to a desired target site in the body. Suitable routes of administration can, for example, include oral, rectal, transmucosal, transcutaneous, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal,

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direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

Alternatively, one can administer the compound in a local rather than systemic manner, for example, *via* injection of the compound directly into a specific tissue, often in a depot or sustained release formulation.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

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.

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.

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For administration to animals, the drug or a pharmaceutical composition containing the drug may also be added to the animal feed or drinking water. It will be convenient to formulate animal feed and drinking water products with a predetermined dose of the drug so that the animal takes in an appropriate quantity of the drug along with its diet. It will also be convenient to add a premix containing the drug to the feed or drinking water approximately immediately prior to consumption by the animal.

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, 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 Oravcová *et al.* (1996, *J. Chromat. B* 677: 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 Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

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 LD_{50} (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

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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).

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 100 - 2000 mg/day. Stated in terms of patient body surface areas, usual dosages range from 50 - 910 mg/m^2/day. Usual average plasma levels should be maintained within 0.1-1000 μM. In cases of local administration or selective uptake, the effective local concentration of the compound cannot be related to plasma concentration.

The compounds of the invention are useful as antibiotics for the treatment of diseases of both animals and humans, including but not limited to actinomycosis, anthrax, bacterial dysentery, botulism, brucellosis, cellulitis, cholera, conjunctivitis, cystitis, diphtheria, bacterial endocarditis, epiglottitis, gangerene, gastroenteritis, glanders, gonorrhea, Legionnaire's disease, leptospirosis, bacterial meningitis, plague, bacterial pneumonia, *otitis media*, puerperal sepsis, pyronephritis, rheumatic fever, Rocky Mountain spotted fever, scarlet fever, sinusitis, streptococcal pharyngitis, syphilis, tetanus, toxic shock syndrome, tuberculosis, tularemia, typhoid fever, typhus, and pertussis.

The compounds of the invention comprise a novel class of selective therapeutics. As antibacterial therapeutics, they inhibit medically-important bacterial species include gram-positive bacteria, including cocci such as *Staphylococcus* species and *Streptococcus* species; acid-fast bacterium, including *Mycobacterium* species; bacilli, including *Bacillus* species, *Corynebacterium* species (also Propionibacterium) and *Clostridium* species; filamentous bacteria, including *Actinomyces* species and *Streptomyces*

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species; gram-negative bacteria, including cocci such as *Neisseria* species and *Acinetobacter* 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.

Specific bacterial species that are targets for the antibiotics of the invention include *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 baumannii*; *Corynebacterium diphtheria*; *Clostridium perfringens*; *Clostridium botulinum*; *Clostridium tetani*; *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*.

Medically-relevant fungal and yeast species that provide appropriate targets for the antifungal activity of the inhibitors of this invention include *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Trichophyton mentagrophytes*, *Microsporium canis*, Aspergillus spp., *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Cocciodiodes immitis*, *Histoplasma capsulatum*, *Paracoccidiodes brasiliensis* and *Phycomycetes* spp.

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The compounds of the invention are useful as antivirals for the treatment of diseases of both animals and humans, including but not limited to hepatitis A – C, yellow fever, respiratory syncytial virus, influenza, human immunodeficiency virus 1 and 2, adenoviruses, Norwalk virus, herpes simplex virus 1 and 2, cytomegalovirus (HCMV), varicella zoster, Epstein-Barr virus, and herpes viruses.

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

In carrying out the procedures of the present invention it is of course to be understood that reference to particular buffers, media, reagents, cells, culture conditions and the like are not intended to be limiting, but are to be read so as to include all related materials that one of ordinary skill in the art would recognize as being of interest or value in the particular context in which that discussion is presented. For example, it is often possible to substitute one buffer system or culture medium for another and still achieve similar, if not identical, results. Those skill in the art will have sufficient knowledge of such systems and methodologies so as to be able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

The invention is described in more detail in the following non-limiting examples. It is to be understood that these methods and examples in no way limit the invention to the embodiments described herein and that other embodiments and uses will no doubt suggest themselves to those skilled in the art.

The compounds of this invention are evaluated for their antibacterial activity as per the guidelines and procedures prescribed by the National Committee for Clinical Laboratory Standards (NCCLS) (cf., NCCLS Document M7-A3, 1993 –Antimicrobial Susceptibility Testing).

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Protocol for MIC Determination

A useful protocol for MIC determination is as follows:

1. Approximately 2.5 mg of the compounds to be tested was weighed into cryovials.

2. 5 mg/ml stock solutions were made by adding DMSO to the samples accordingly.

3. 256 µg/ml working solutions were made by using the 5 mg/ml stock solutions and adding sterile distilled water accordingly.

4. A Beckman 2000 Automated Workstation was programmed to load 96 well plates with broth and compounds as follows:

-100 µl of the appropriate broth was added to columns 1-11
-200 µl of the appropriate broth was added to column 12
-100 µl of compounds at the 256 µg/ml working solution were added to column 1 (one compound per row)
-Two-fold serial dilutions were done from column 1 to 10
-Column 11 served as the growth control

5. The 10 organism panel was plated from stock vials stored at -80°C and incubated for 24 hours at 34°C. The organisms were then sub-cultured and incubated for 24 hours at 34°C.

-The inoculums were first prepared in sterile distilled water with a target of 0.09-0.11 absorbance at 620 nm wavelength
-A 1/100 dilution was made into the appropriate broth
-100 µl of broth with organism was added to columns 1-11
-Column 12 served as the blank control

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6. The completed 96 well plates were incubated for 24 hours at 34°C. The 96 well plates were then read using a Beckman Automated Plate Reader at 650 nm wavelength. The MIC was determined through calculations involving the growth control (column 11) and blank control (column 12).

Calculations

The absorbance readings from the Biomek Automated Plate Reader are used to determine the percent inhibition for each test well. The formula used is as follows:

$$\% \text{ Inhibition} = [\ 1 - (ABS_{test} - ABS_{blank}) / (ABS_{mean\ growth} - ABS_{blank})\ ] \times 100\%$$

ABS_{test}: Absorbance of the test well
ABS_{blank}: Absorbance of the blank well in the same row as the test well (column 12)
$ABS_{mean\ growth}$: Mean absorbance of the growth control wells (column 11)

The minimum inhibitory concentration (MIC) is found at the lowest concentration of compound where percent inhibition is greater than or equal to 80%.

These procedures were used to obtain the representative microbiological data for the compounds 10 to 19 shown in Table 1 as MIC (Minimum Inhibitory Concentration) with the values expressed as micrograms per ml.

The compounds of this invention are evaluated for their antiviral activity as per the guidelines and procedures prescribed.

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Protocols for Antiviral Determination

Yellow Fever (YFV) antiviral assay was performed with HeLa cells which were used in order to allow for a 7 day assay endpoint. HeLa cells were passaged in T-75 flasks. On the day preceding the assay, the cells were trypsinized, pelleted, counted and resuspended at $1x10^4$ / well in tissue culture medium in 96-well flat bottom tissue culture plates in a volume of 100 µl per well. One day following plating of cells, the wells were washed and the medium was replaced with complete medium (2% serum) containing various concentrations of test compound diluted in medium in a half-log series. A pretitered aliquot of 17D strain YFV virus was removed from the freezer (-80°C) just before each experiment. The virus was diluted into tissue culture medium such that the amount of virus added to each well would give complete cell killing at 7 days post-infection.

HepG2 2.15 Antiviral Evaluation Assay - HepG2 2.2.15 cells, which produce HBV ayw1 strain, were plated in 96-well collagencoated microtiter plates at a density of $2.5x10^4$/well with DMEM medium supplemented with 2% fetal bovine serum. One day following plating of cells, the wells were washed and the medium was replaced with complete medium containing the test compound diluted in the medium in a half-log series.

The medium was replaced once with the fresh medium containing the freshly diluted compound three days post the initial addition of the lamivudine, a positive control compound. Cell viability was determined using CellTiter 96® Reagent (Promega, Madison, WI) according to the manufacturer's protocol, using a Vmax plate reader (Molecular Devices, Sunnyvale, CA). The mixture is metabolized by the mitochondrial enzymes of metabolically active cells to a soluble formazan product, allowing the rapid quantitative analysis of cell numbers. The media was removed and replaced with 100 µl of fresh media and 10 µl of Cell Titer 96.. Plates were reincubated for 4 hours at 37° C and read spectrophotometrically at 490

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and 650 nm with a Molecular Devices Vmax plate reader. Percent cell viability of compound treated wells compared to no compound controls was calculated using an in-house computer program which graphs the percent reduction in viral cytopathic effects and the cell numbers at each drug concentration relative to control values. The program interpolates the inhibitory concentration of drug that reduces cytopathic effects by 50% (IC50) and the toxic concentration that kills 50% of cells (TC50).

HCV RNA Replicon Antiviral Evaluation Protocol

The cell line ET (luc-ubi-neo/ET), a new HCV RNA replicon that contains a stable luciferase (LUC) reporter, was used. The composition of the replicon is shown diagrammatically above (ref, Krieger, N., V. Lohmann, and R. Bartenschlager. 2001. Enhancement of hepatitis C virus RNA replicon replication by cell culture-adaptive mutations. J. Virol. **75:4614-4624**). The HCV RNA replicon ET contains the 5' NTR (IRES) of HCV (5') which drives the production of a firefly luciferase (Luc), ubiquitin (Ubiq), and neomycin phosphotransferase (Neo) fusion protein. Ubiquitin cleavage releases the LUC and Neo genes. The EMCV IRES element (E-I) controls the translation of the HCV structural proteins NS3-NS5.

The NS3 protein cleaves the HCV polyprotein to release the mature NS3, NS4A, NS4B, NS5A and NS5B proteins that are required for HCV replication. At the 3' end of the replicon is the authentic 3' NTR of HCV. The LUC reporter is used as an indirect measure of HCV replication. The activity of the LUC reporter is directly proportional to HCV RNA levels and positive control antiviral compounds behave comparably using either LUC

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or RNA endpoints. The use of the LUC endpoint is more economical than HCV RNA and can be used for high-throughput applications to screen libraries of compounds.

The HCV RNA replicon antiviral evaluation assay examines the effects of compounds at five half-log concentrations each. Human interferon alpha-2b is included in each run as a positive control compound. Subconfluent cultures of the ET line are plated out into 96-well plates that are dedicated for the analysis of cell numbers (cytotoxicity) or antiviral activity and the next day drugs are added to the appropriate wells. Cells are processed 72 hr later when the cells are still subconfluent. Compound IC50 and IC90 values are derived from HCV RNA levels assessed as either HCV RNA replicon-derived LUC activity or as HCV RNA using TaqMan RT-PCR. Compound TC50 and TC90 values are calculated using a colorimetric assay as an indicator of cell numbers and cytotoxicity when the LUC assay system is employed, while ribosomal (rRNA) levels determined via TaqMan RTPCR are used as an indication of cell numbers in the RNA-based assay. Compound TI50 and TI90 values are calculated from spreadsheets.

ANTIBACTERIAL ACTIVITY

Representative antibacterial data for the compounds 11 to 24 are shown in Table 1. The antibacterial activity of ciprofloxacin, cloxacillin, imipenem, ceftriaxone, meropenem, erythromycin and penicilling G, pertinent antibacterial-specific biological standards, are included as positive controls.

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Table 1. Antibacterial Profile Against Select Gram-positive and Gram-negative Pathogens

Exam	A	D	E	G	R*	M	N	*S. aureus* ATCC 29213	*S. epidermidis* ATCC 12228	*S. pneumoniae* ATCC 6301	*E. faecalis* ATCC 29212	*E. faecium* CT-36
11	CH	C-F	CH	CH	3-ClC$_6$H$_4$	O	1	<0.125	1	8	32	32
12	CH	CH	CH	CH	3-ClC$_6$H$_4$	O	1	0.5	2	8	16	16
13	CH	C-Cl	CH	CH	3-FC$_6$H$_4$	O	1	<0.125	0.25	4	16	8
14	CH	CH	CH	CH	3-NCC$_6$H$_4$	O	1	0.25	2	2	32	16
15	CH	CH	C-F	CH	3-ClC$_6$H$_4$	O	1	0.5	2	4	16	8
16	CH	CH	CH	CH	3-ClC$_6$H$_4$	O	CMe_2	0.5	2	8	16	16
17	CH	CH	CH	CH	4-ClC$_6$H$_4$	O	1	2	2	4	16	16
18	CH	CH	CH	CH	4-NCC$_6$H$_4$	O	1	2	2	4	32	32
19	CH	C-F	CH	CH	4-NCC$_6$H$_4$	O	1	8	16	16	>64	>64
20	CH	C-F	CH	CH	3-NCC$_6$H$_4$	O	1	1	16	8	64	64
21	CH	CH	C-F	CH	3-NCC$_6$H$_4$	O	1	8	16	8	64	64
22	CH	C-OMe	C-OMe	CH	3-ClC$_6$H$_4$	O	1	4	16	8	>64	64
23	CH	CH	CH	CH	3-ClC$_6$H$_4$	O	2	2	8	8	16	16
24	CH	CH	CH	CH	3-FC$_6$H$_4$	O	2	4	8	16	32	32
Ciprofloxacin								0.125	0.125	0.5	0.5	64
Oxacillin								0.125	0.25	0.125	16	64
Imipenem								0.125	0.125	0.125	1	64
Ceftriaxone								2	1	0.125	64	64
Erythromycin								0.5	0.5	NA	2	NA
Pen G								0.5	16	0.125	1	32

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BENZOXABOROLE ANTIVIRALS

This procedure was used to obtain the results in the following tables. Representative antiviral data for the compounds 11 to 22 are shown in Tables 2 and 3. The antiviral activity of interferon and lamividine, pertinent viral-specific biological standards, are included as positive controls.

Table 2. *In vitro* Antiviral Activity

	Anti-Yellow Fever Activity			Anti-Hepatitis B Activity		
Compound	IC50 (μM)	TC50 (μM)	Antiviral Index	IC50 (μM)	TC50 (μM)	Antiviral Index
11	0.65	4.14	6.38	2.47	3.20	1.30
13	1.39	6.22	4.48	NA	NA	NA
14	0.44	6.53	14.91	NA	NA	NA
15	1.19	6.60	5.53	NA	NA	NA
17	1.56	6.42	4.11	NA	NA	NA
18	0.74	6.60	8.91	NA	NA	NA
19	NA	17.1	NA	NA	NA	NA
20	1.62	21.0	12.98	NA	NA	NA
21	2.36	15.8	6.72	NA	NA	NA
22	NA	21.1	NA	NA	NA	NA
IFN-alpha	3.20 IU	>1000 IU	>312.5	NA	NA	NA
lamivudine	NA	NA	NA	0.0093	>1.0	>107.5

Table 3. *In vitro* Anti-Hepatitis Activity (Replicon Assay)

Compound	IC50 (μM)	TC50 (μM)	Selectivity Index
11	12.96	1.29	1.5
12	30.6	12.7	2.4
13	3.93	0.37	11
14	2.86	1.14	2.5
15	6.01	0.54	11
17	8.59	0.26	33
18	1.94	NA	NA
19	3.73	0.27	14
20	19.53	5.99	3.2
21	5.48	0.69	7.9
IFN-alpha2b	>5.00 (IU/ml)	0.08 (IU/ml)	>62.5

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BORON-CONTAINING THERAPEUTICS

The synthesis of the compounds of the invention is accomplished in several formats. Scheme #1 demonstrates an efficient synthesis of the benzoxaboroles, with broad range of substituents, including analogs (M = O, S, NR**) and the larger ring analogs. This is in contrast to the procedure of Haynes and Snyder [J. Org. Chem., 29, pp.3229 - 3233 (1964) which is limited in scope. Intermediate 1, after transmetallation by either Grignard exchange (isopropylmagnesium bromide) or an organolithium (preferably *sec*-butyllithium or *tert*-butyllithium), is reacted with a trialkyl borate. Subsequent acidic hydrolysis affords an intermediates boronic acid 2. Conversion of 2 to the ethylene glycol boronate 3 is achieved in high yields. Other diols such as 1,2-propanediol, 1,3-propanediol, 1,2-butanediol, 1,3-butanediol, 1,4-butanediol, or pinacol alcohol can be employed. Boronate esters 3 are reacted with the appropriate organometallic donor of substituent R*, followed by acidic hydrolysis to afford the desired benzoxaboroles 5.

While we demonstrate the use of the methoxymethyl (MOM) protecting group in the examples, other suitable protecting groups can be employed; exemplary are trialkylsilyl, alkyldiarylsilyl, tetrahydropyranyl, trialkylsilylalkoxy, trityl and substituted trityls, and tert-butyl.

The corresponding benzoazaboroles 7 and benzothiaboroles 9 were similarly obtained from suitably protected precursors.

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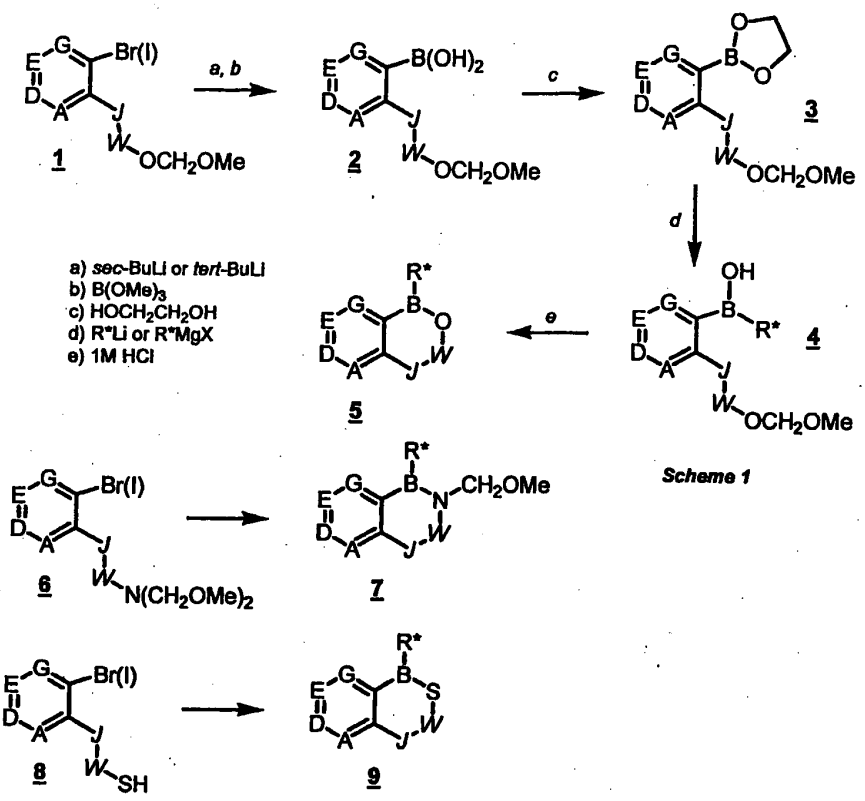

Scheme 1

In certain situations, compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, *i.e.*, optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

Representative compounds of the present invention include, but are not limited to the compounds disclosed herein and their pharmaceutically acceptable acid and base addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained

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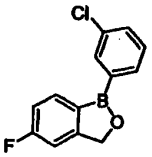
by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. In a preferred embodiment, the compounds of the invention comprise any of compounds 11 – 24 (Tables 1 to 3), and variants thereof.

The present invention also encompasses the acylated prodrugs of the compounds of the invention. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the inventive compounds.

EXAMPLES

Proton NMR are recorded on Varian AS 400 spectrometer and chemical shifts are reported as δ (ppm) down field from tetramethylsilane. Mass spectra are determined on Micromass Quattro II.

1-(3-Chlorophenyl)-5-fluoro-1,3-dihydrobenzo[c][1,2]oxaborole (11)



a) *2-(3-Chlorophenyl)-[1,3,2]-dioxaborolane*: 3-Chlorophenylboronic acid (3.041g, 19.4mmol) was dissolved in 75 mL of dry THF under N_2. Ethylene glycol (1.323g, 21.3mmol) was added and the solution refluxed for 18 hours. The solution was allowed to cool and the THF removed under vacuum. The residue was further dried under high vacuum (<1mmHg) with occasional heating to remove excess ethylene glycol and THF. This gave pure *2-(3-*

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chlorophenyl)-[1,3,2]-dioxaborolane (3.55g, 100%) as a brown oil that solidified upon cooling in the freezer: ^{1}H NMR δ 4.39 (s,4H), 7.32 (t,1H), 7.44 (ddd,1H), 7.67 (d,1H), 7.78 (d,1H).

b) *2-Bromo-5-fluorobenzyl alcohol*: 2-Bromo-5-fluorobenzaldehyde (2.05g, 10.1mmol) was dissolved in 20 mL of warm absolute ethanol. Upon cooling to room temperature, sodium borohydride (0.19g, 5.0mmol) was slowly added to the ethanol solution. The solution was stirred at room temperature for 18 hours. 1 mL of H_2O was added to the solution and the ethanol removed under vacuum. The white residue was then partitioned between 30 mL of H_2O and 50 mL of diethyl ether. The ether was separated and the aqueous solution extracted twice more with ether (2 X 50mL). The ether extracts were combined, dried with $MgSO_4$, filtered and evaporated to give pure *2-bromo-5-fluorobenzyl alcohol* as a white solid (1.98g, 96%): ^{1}H NMR δ1.98 (t,1H), 4.72 (d,2H), 6.89 (dt,1H), 7.27 (dd,1H), 7.48 (dd,1H).

c) *1-Bromo-4-fluoro-2-((methoxymethoxy)methyl)benzene*: Sodium hydride (60% dispersion in mineral oil, 0.225g, 5.6mmol) was placed in a 250mL round bottom flask under N_2. The NaH was washed with dry hexanes (5mL). The hexanes were removed via cannula, and the process repeated twice (2 x 5mL). The NaH was dried under vacuum until a free flowing powder resulted and placed under N_2. (2-Bromo-5-fluorophenyl)methanol (0.97g, 4.7mmol) was dissolved in 20mL of dry THF and added dropwise to the solid NaH. Once H_2 evolution had ceased, the solution was refluxed for 1.5 hours. The solution was allowed to cool to room temperature then cooled to 0°C in an ice bath. Chloromethyl methyl ether (0.36mL, 4.2mmol) was then added and the solution allowed to warm to room temperature. The solution was stirred at room temperature for 18 hours then filtered through a 1 cm column of Celite. The Celite was washed with THF (2 x 10mL). The THF filtrates were combined and evaporated under vacuum to give pure *1-bromo-4-fluoro-2-((methoxymethoxy)methyl)benzene* as an oil (1.05g, 99%): ^{1}H NMR δ 3.49 (s,3H), 4.63 (s,2H), 4.78(s,2H), 6.88 (dt,1H), 7.26 (dd,1H), 7.49 (dd,1H).

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d) *(3-Chlorophenyl)(4'-fluoro-(2'-(methoxymethoxy)methyl)phenyl)borinic acid*: 1-Bromo-4-fluoro-2-((methoxymethoxy)methyl)benzene (1.06g, 4.2mmol) was dissolved in 50mL of dry THF under N_2 and cooled to -78°C. *t*-BuLi (1.7M in pentane)(5.3mL, 9.0mmol) was slowly added to the solution. After stirring for 10 minutes at -78°C, 2-(3-chlorophenyl)-[1,3,2]-dioxaborolane in 10mL of dry THF was added and the solution stirred for a further 0.5 hours. The solution was then allowed to warm to room temperature and stirred for 18 hours. The THF was removed under vacuum and the residue partitioned between 40 ml of H_2O and 80mL of diethyl ether. The solution was vigorously stirred for several minutes then neutralized (pH7) with 6N HCl. The ether was separated and the aqueous solution extracted again with ether (2 x 80mL). The ether extracts were combined, dried with $MgSO_4$, filtered and evaporated to give a yellow oil (1.22g). ^{1}H NMR of the product shows that the desired borinic acid was formed. This was used for the next step without purification.

Note: The borinic acid could be purified by flash column chromatography on silica gel using 3:1 hexanes: ethyl acetate as eluent. However, this leads to significant loss of desired product. Subsequent reactions showed that purification at this step was not necessary. ^{1}H NMR δ 3.45 (s,3H), 4.65 (s,2H), 4.66(s,2H), 7.06-7.12 (2H), 7.34 (t,1H), 7.44 (ddd,1H), 7.52 (dd,1H), 7.63 (td,1H), 7.73 (d,1H), 8.00 (s,1H).

e) 1-(3-Chlorophenyl)-5-fluoro-1,3-dihydrobenzo[c][1,2]oxaborole: The MOM protected borinic acid (0.70g, 2.3mmol) was dissolved in 46mL of THF and 4 mL of concentrated HCl. The solution was stirred at room temperature for 12 hours. 10 mL of H_2O was then added and the THF removed under vacuum. This gave a solid suspension. The solid was filtered under vacuum and washed with water (10mL) then with hexanes (5mL) and dried. This gave titled compound as a white solid (0.334g, 59%): ^{1}H NMR δ 5.38 (s,2H), 7.14-7.19 (2H), 7.43 (t,1H), 7.52 (td,1H), 8.00 (d,1H), 8.08 (d,1H), 8.13 (dd,1H);

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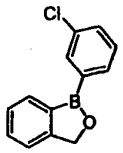
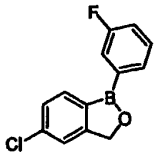
MS(ES⁻) 247.08, 249.03 (3:1); HPLC [ret. Time (% area)] 14.346 min (97.1%).

1-(3-Chlorophenyl)-1,3-dihydrobenzo[*c*][1,2]oxaborole (12)



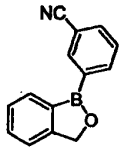
This was prepared as per the procedure in Example 11, from 2-(3-chlorophenyl)-[1,3,2]-dioxaborolane and 1-bromo-2-((methoxymethoxy)methyl)benzene to afford white crystalline product.

5-Chloro-1-(3-Fluorophenyl)-1,3-dihydrobenzo[*c*]-[1,2]oxaborole (13)



This was prepared as per the procedure in Example 11, from 2-(3-fluorophenyl)-[1,3,2]-dioxaborolane and 1-bromo-4-chloro-2-((methoxymethoxy)methyl)-benzene to afford white crystalline product.

3-(Benzo[*c*][1,2]oxaborol-1(3H)-yl)benzonitrile (14)



This was prepared as per the procedure in Example 11, from 2-(3-cyanophenyl)-[1,3,2]-dioxaborolane and 1-bromo-2-((methoxymethoxy)methyl)benzene to afford white crystalline product.

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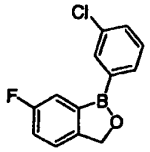
1-(3-Chlorophenyl)-6-fluoro-1,3-dihydrobenzo[*c*][1,2]oxaborole (15)



a) *2-Bromo-4-fluorobenzyl alcohol:* 2-Bromo-4-fluorobenzoic acid (7.908g, 36.1mmol) was dissolved in 50 mL of dry THF under N_2 and cooled to 0°C. BH_3-THF (1M in THF) (72mL, 72mmol) was added dropwise with stirring. Once the vigorous effervescence had subsided, the solution was stirred for a further 0.5 hours at 0°C then allowed to warm to room temperature. The solution was stirred at room temperature for 18 hours. The THF was removed under vacuum and the residue dissolved in CH_2Cl_2 (100mL). Methanol was slowly added to the solution until no bubbling could be observed and the solution was stirred for a further 15 minutes. The solvents were removed under vacuum and the residue re-dissolved in methanol (100mL). The solution was stirred for 10 minutes then the solvent was removed under vacuum. The residue was further dried for several hours under high vacuum (<1mmHg). This gave pure *2-bromo-4-fluorobenzyl alcohol* as a pale yellow solid (7.33g, 99%): ^{1}H NMR δ 1.99 (s,1H), 4.72 (s,3H), 7.05 (dt,1H), 7.31 (dd,1H), 7.46 (dd,1H).

b) *2-Bromo-4-fluoro-1-((methoxymethoxy)methyl)benzene*: Sodium hydride (60% dispersion in mineral oil, 0.39g, 9.7mmol) was placed in a 250mL round bottom flask under N_2. The NaH was washed with dry hexanes (5mL). The hexanes were removed via cannula, and the process repeated twice (2 x 5mL). The NaH was dried under vacuum until a free flowing powder resulted and placed under N_2. (2-Bromo-4-fluorophenyl)methanol (1.61g, 7.8mmol) was dissolved in 30mL of dry THF and added dropwise to the solid NaH. Once H_2 evolution had ceased, the solution was refluxed for 1 hour. The solution was allowed to cool to room temperature then cooled to 0°C in an ice bath. Chloromethyl methyl ether (0.6mL, 7.9mmol) was then added and the solution allowed to warm to room temperature. The solution was stirred at

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room temperature for 18 hours then filtered through a 1.5 cm column of Celite. The Celite was washed with THF (2 x 10mL). The THF filtrates were combined and evaporated under vacuum to give pure *2-bromo-4-fluoro-1-((methoxymethoxy)methyl)benzene* as an oil (1.700g, 87%): ^{1}H NMR δ 3.43 (s,3H), 4.63 (s,2H), 4.75 (s,2H), 7.04 (dt,1H), 7.31 (dd,1H), 7.46 (dd,1H).

d) *(3-Chlorophenyl)(5'-fluoro-(2'-(methoxymethoxy)methyl)phenyl)borinic acid*: 2-Bromo-4-fluoro-1-((methoxymethoxy)methyl)benzene (1.70g, 6.8mmol) was dissolved in 50mL of dry THF under N_2 and cooled to -78°C. *t*-BuLi (1.7M in pentane)(8.5mL, 14.5mmol) was slowly added to the solution. After stirring for 15 minutes at -78°C, 2-(3-chlorophenyl)-[1,3,2]-dioxaborolane in 10mL of dry THF was added and the solution stirred for a further 0.5 hours. The solution was then allowed to warm to room temperature and stirred for 18 hours. The THF was removed under vacuum and the residue partitioned between 50mL of H_2O and 80mL of diethyl ether. The solution was vigorously stirred for several minutes then neutralized (pH = 7) with 6N HCl. The ether was separated and the aqueous solution extracted again with ether (2 x 50mL). The ether extracts were combined, dried with $MgSO_4$, filtered and evaporated to give an orange oil (2.27g). ^{1}H NMR of the product showed that the desired borinic acid was formed. This was used for the next step without purification.

e) *1-(3-Chlorophenyl)-6-fluoro-1,3-dihydrobenzo[c][1,2]oxaborole*: The crude MOM protected borinic acid (2.27g) was dissolved in 46mL of THF and 4 mL of concentrated HCl. The solution was stirred at room temperature for 12 hours. 10 mL of H_2O was then added and the THF removed under vacuum. The aqueous solution was extracted with diethyl ether (3 x 50mL). The ether extracts were combined and washed with brine until neutral. The ether was dried with $MgSO_4$, filtered and evaporated to give an orange oil. The crude product was purified by column chromatography on silica gel using 5:1 hexanes: ethyl acetate as eluent. After removal of the solvents, titled compound (Rf = 0.63) was obtained as a white solid (0.515g, 2.1mmol. 33%;

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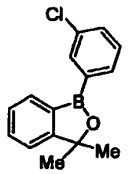
two steps): ^{1}H NMR δ 5.39 (s,2H), 7.24-7.29 (2H), 7.42-7.48 (2H), 7.53 (ddd,1H), 7.78 (dd,1H), 7.99 (d,1H), 8.07 (d,1H); MS(ES$^-$) 290.95, 292.97 (3:1) [Note: M$^-$ + formic acid]; HPLC [ret. Time (% area)] 14.162 min (97.6%).

1-(3-Chlorophenyl)-1,3-dihydro-3,3-dimethylbenzo[c][1,2]oxaborole (16)



a) *2-(2-Bromophenyl)propan-2-ol*: Methyl-2-bromobenzoate (3.403g, 15.8mmol) was dissolved in 50 mL of dry THF under N_2 and cooled to 0°C. Methyl magnesium iodide (3M in diethyl ether) (11mL, 33mmol) was added and the solution allowed to warm to room temperature followed by reflux for 1 hour. 50 mL of saturated ammonium chloride was added and the solution filtered under vacuum. The separated solids were washed with THF. The THF filtrates were combined and the solvent was removed under vacuum. The residue was partitioned between 40 mL of H_2O and 60 mL of diethyl ether with stirring. The ether was separated and the aqueous solution was extracted twice more with ether (2 x 60 mL). The ether extracts were combined and washed with brine until neutral. The ether was dried with $MgSO_4$, filtered and evaporated to give a yellow oil. The crude product was purified by column chromatography on silica gel using $CHCl_3$ as eluent. After removal of the solvent, pure *2-(2-bromo-phenyl)propan-2-ol* (Rf = 0.33) was obtained as a yellow oil (2.55g, 75%): ^{1}H NMR δ 1.75 (s,6H), 2.79 (s,1H), 7.10 (dt,1H), 7.30 (dt,1H), 7.58 (dd,1H), 7.66 (dd,1H).

b) *1-Bromo-2-(2-(methoxymethoxy)propan-2-yl)benzene*: Sodium hydride (60% dispersion in mineral oil, 0.576g, 14.4mmol) was placed in a 250mL round bottom flask under N_2. The NaH was washed with dry hexanes (10mL). The hexanes were removed via cannula, and the process repeated twice (2 x 10mL). The NaH was dried under vacuum until a free flowing powder resulted and placed under N_2. 2-(2-bromophenyl)propan-2-ol (2.55g, 11.8mmol) was

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dissolved in 50mL of dry THF and added dropwise to the solid NaH. Once H_2 evolution had ceased, the solution was refluxed for 1.5 hours. The solution was allowed to cool to room temperature then cooled to 0°C in an ice bath. Chloromethyl methyl ether (0.82mL, 10.8mmol) was then added and the solution allowed to warm to room temperature. The solution was stirred at room temperature for 18 hours then filtered through a 1 cm column of Celite. The Celite was washed with THF (2 x 15mL). The THF filtrates were combined and evaporated under vacuum to give a brown oil. The crude product was purified by column chromatography on silica gel using 2:1 hexanes: ethyl acetate as eluent. After removal of the solvents, pure *1-bromo-2-(2-(methoxymethoxy)propan-2-yl)benzene* (Rf = 0.82) was obtained as a yellow oil (1.70g, 55%): ^{1}H NMR δ 1.77 (s,6H), 3.14 (s,3H), 4.62 (s,2H), 7.10 (dt,1H), 7.28 (dt,1H), 7.50 (dd,1H), 7.62 (dd,1H).

c) *(3-Chlorophenyl)(2-(2-(methoxymethoxy)propan-2-yl)phenylborinic acid*: 2-Bromo-2-(2-(methoxymethoxy)propan-2-yl)benzene (1.700g, 6.5mmol) was dissolved in 50mL of dry THF under N_2 and cooled to -78°C. *t*-BuLi (1.7M in pentane)(8.4mL, 14.3mmol) was slowly added to the solution. After stirring for 15 minutes at -78°C, 2-(3-chlorophenyl)-[1,3,2]dioxaborolane in 10mL of dry THF was added and the solution stirred for a further 0.5 hours. The solution was then allowed to warm to room temperature and stirred for 18 hours. The THF was removed under vacuum and the residue partitioned between 50mL of H_2O and 80mL of diethyl ether. The solution was vigorously stirred for several minutes then neutralized (pH7) with 6N HCl. The ether was separated and the aqueous solution extracted again with ether (2 x 50mL). The combined ether extracts were combined, dried with $MgSO_4$, filtered and evaporated to give an orange oil (2.13g). The crude product was purified by column chromatography on silica gel using 3:1 hexanes: ethyl acetate as eluent. After removal of the solvents, pure borinic acid (Rf = 0.80) was obtained as a yellow oil (0.87g, 42%): ^{1}H NMR δ 1.61 (s,6H), 3.39 (s,3H), 4.57 (s,2H), 7.19-7.55 (5H), 8.02-8.11 (3H).

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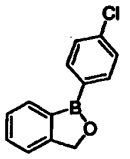
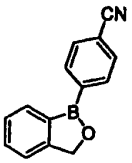
e) *1-(3-Chlorophenyl)-1,3-dihydro-3,3-dimethylbenzo[c][1,2]oxaborole*: The crude MOM protected borinic acid (0.87g, 2.7mmol) was dissolved in 46mL of THF and 4 mL of concentrated HCl. The solution was stirred at room temperature for 12 hours. 10 mL of H_2O was then added and the THF removed under vacuum. The aqueous solution was extracted with diethyl ether (3 x 60mL). The ether extracts were combined and washed with brine until neutral. The ether was dried with $MgSO_4$, filtered and evaporated to give a yellow oil. The crude product was purified by column chromatography on silica gel using 5:1 hexanes: ethyl acetate as eluent. After removal of the solvents, titled compound (Rf = 0.67) was obtained as a yellow oil (0.29g, 41%): ^{1}H NMR δ 1.64 (s,6H), 7.37 (d,1H), 7.40-7.45 (2H), 7.48-7.55 (2H), 8.03 (td,1H), 8.07-8.11 (2H); MS(ES$^-$) 301.01, 303.02 (3:1) [Note: M$^-$ + formic acid] ; HPLC [ret. Time (% area)] 15.847 min (92.2%).

1-(4-Chlorophenyl)-1,3-dihydrobenzo[*c*][1,2]oxaborole (17)



This was prepared as per the procedure in Example 11, from 2-(4-chlorophenyl)-[1,3,2]-dioxaborolane and 1-bromo-2-((methoxymethoxy)methyl)benzene to afford white crystalline product.

4-(Benzo[*c*][1,2]oxaborol-1(3H)-yl)benzonitrile (18)



This was prepared as per the procedure in Example 11, from 2-(4-cyanophenyl)-[1,3,2]-dioxaborolane and 1-bromo-2-((methoxymethoxy)methyl)-benzene to afford white crystalline product.

4-(5-Fluorobenzo[*c*][1,2]oxaborol-1(3H)-yl)benzonitrile (19)

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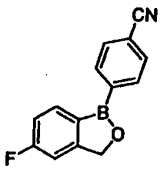
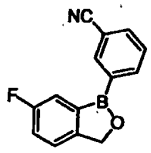


This was prepared as per the procedure in Example 11, from 2-(4-cyanophenyl)-[1,3,2]-dioxaborolane and 1-bromo-4-fluoro-2-((methoxymethoxy)methyl)benzene to afford white crystalline product.

3-(5-Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)benzonitrile (20)

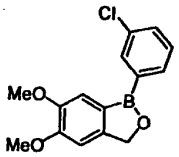
This was prepared as per the procedure in Example 11, from 2-(3-cyanophenyl)-[1,3,2]-dioxaborolane and 1-bromo-4-fluoro-2-((methoxymethoxy)methyl)benzene to afford white crystalline product.

3-(6-Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)benzonitrile (21)



This was prepared as per the procedure in Example 11, from 2-(3-cyanophenyl)-[1,3,2]-dioxaborolane and 1-bromo-5-fluoro-2-((methoxymethoxy)methyl)benzene to afford white crystalline product.

1-(3-Cyanophenyl)-5,6-dimethoxy-1,3-dihydrobenzo[c][1,2]-oxaborole (22)



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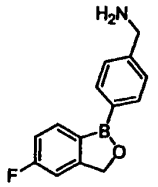
This was prepared as per the procedure in Example 11, from 2-(3-chlorophenyl)-[1,3,2]-dioxaborolane and 1-bromo-4,5-dimethoxy-2-((methoxymethoxy)methyl)-benzene to afford white crystalline product.

(4-(5-(Fluorobenzo[c][1,2]oxaborol-1(3*H*)-yl)phenylmethanamine (23)



a) *N,N-Bis(methoxymethyl)-4-bromobenzylamine*: To a solution of 4-bromobenzylamine hydrochloride (4.54 g, 20.0 mmol) in methanol (200 mL) were added 37% formaldehyde (25 mL) and potassium carbonate (4.28 g, 31.0 mmol), and the mixture was stirred at room temperature for overnight. The mixture was concentrated under reduced pressure to a third of volume. 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 *N,N-bis(methoxymethyl)-4-bromobenzylamine* (5.45 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 6H), 3.94 (s, 4H), 4.20 (s, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H).

b) *1-Bromo-4-fluoro-2-((methoxymethoxy)methyl)benzene*: To a solution of 2-bromo-5-fluorobenzoic acid (10.3 g, 45.3 g) in tetrahydrofuran (50 mL) was added borane-tetrahydrofuran complex (1M in tetrahydrofuran; 92 mL) at 0 °C under nitrogen atmosphere, and the mixture was stirred at room temperature overnight. Water was carefully added, and the mixture was concentrated under reduced pressure to about 50 mL. 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 2-bromo-5-fluorobenzyl alcohol, which was converted into its methoxymethyl ether in a similar manner to Example11, step (a) to afford *1-bromo-4-fluoro-2-((methoxymethoxy)methyl)benzene* (9.64

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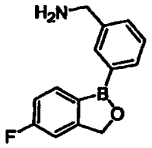
g, 85% in 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (s, 3H), 4.62 (s, 2H), 4.78 (s, 2H), 6.88 (td, *J* = 8.5, 3.2 Hz, 1H), 7.25 (dd, *J* = 9.6, 3.1 Hz, 1H), 7.48 (dd, *J* = 8.8, 5.3 Hz, 1H).

c) *5-Fluoro-2-(methoxymethoxymethyl)phenyl]-[1,3,2]-dioxaborolane:* This was obtained from the above intermediate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 3H), 4.36 (s, 4H), 4.76 (s, 2H), 4.87 (s, 2H), 6.96 (td, *J* = 8.2, 2.6 Hz, 1H), 7.26 (dd, *J* = 10.6, 2.6 Hz, 1H), 7.83 (dd, *J* = 8.2, 6.4 Hz, 1H).

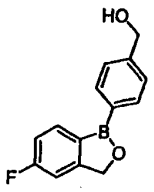
d) *(4-(5-(Fluorobenzo[c][1,2]oxaborol-1(3H)-yl)phenylmethanamine*: The title compound was obtained from *N,N*-bis(methoxymethyl)-4-bromobenzylamine and 5-fluoro-2-[(methoxymethoxymethyl)phenyl]-[1,3,2]-dioxaboralane: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.72 (s, 2H), 5.29 (s, 2H), 7.15 (m, 1H), 7.3-7.5 (m, 3H), 7.96 (d, *J* = 7.6 Hz, 1H), 8.11 (dd, *J* = 8.2, 5.9 Hz, 1H): ESI-MS *m/z* 242 (positive); $C_{14}H_{13}BFNO$ = 241.

(3-(5-(Fluorobenzo[*c*][1,2]oxaborol-1(3*H*)-yl)-phenylmethanamine (24)



The title compound was obtained from 3-bromobenzylamine hydrochloride in a similar sequence as Example 23: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.74 (s, 2H), 5.32 (s, 2H), 7.1-7.5 (m, 4H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.98 (s, 1H), 8.12 (dd, *J* = 8.2, 5.9 Hz, 1H): ESI-MS *m/z* 242 (positive); $C_{14}H_{13}BFNO$ = 241.

(4-(5-(Fluorobenzo[*c*][1,2]oxaborol-1(3*H*)-yl)phenyl)methanol (25)



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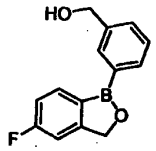
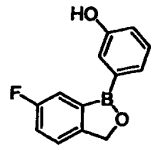
The title compound was obtained from 4-bromobenzyl alcohol in a similar sequence described in Examples 11 and 23: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.56 (d, J = 5.0 Hz, 2H), 5.25 (t, J = 5.6 Hz, 1H), 5.37 (s, 2H), 7.26 (m, 1H), 7.4-7.5 (m, 3H), 8.05 (d, J = 7.9 Hz, 1H), 8.22 (dd, J = 8.2, 5.9 Hz, 1H): ESI-MS m/z 241 (negative); $C_{14}H_{12}BFO_2$ = 242.

(3-(5-(Fluorobenzo[*c*][1,2]oxaborol-1(3*H*)-yl)phenyl)methanol (26)



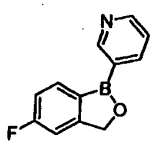
The title compound was obtained from 3-bromobenzyl alcohol in a sequence similar to Examples 11 and 23: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.57 (d, J = 5.6 Hz, 2H), 5.22 (t, J = 5.6 Hz, 1H), 5.37 (s, 2H), 7.26 (m, 1H), 7.4-7.5 (m, 3H), 8.03 (s, 1H), 8.20 (dd, J = 8.2, 5.9 Hz, 1H): ESI-MS m/z 241 (negative); $C_{14}H_{12}BFO_2$ = 242.

3-(6-Fluorobenzo[*c*][1,2]oxaborol-1(3*H*)-yl)phenol (27)



The title compound was obtained from 3-bromophenol and 2-bromo-4-fluorobenzoic acid in a similar manner to Examples 11 and 23: ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.30 (s, 2H), 6.89 (d, J = 8.2 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 8.9 Hz, 1H), 7.41 (s, 1H), 7.45 (d, J = 7.0 Hz, 1H), 7.55 (dd, J = 8.4, 4.9 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 9.31 (s, 1H): ESI-MS m/z 227 (negative); $C_{13}H_{10}BFO_2$ = 228.

3-(5-Fluorobenzo[*c*][1,2]oxaborol-1(3*H*)-yl)pyridine (28)



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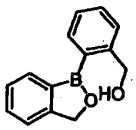
To a solution of 3-bromopyridine (731 mg, 4.63 mmol) in tetrahydrofuran was added isopropylmagnesium chloride (1 mol/L; 2.3 mL) at room temperature under nitrogen atmosphere, and the mixture was stirred for 1 h. To the mixture was added 5-fluoro-2-[(methoxymethoxymethyl)phenyl]-[1,3,2]-dioxaborolane obtained in Example 23, step (c) (1.11 g, 4.63 mmol) in tetrahydrofuran (4 mL), and the mixture was stirred at room temperature for overnight. Water was added and the pH was adjusted to pH7 with 1M hydrochloric acid. Then the mixture was extracted with ethyl acetate. The solvent was removed under reduced pressure, and the residue was dissolved in tetrahydrofuran (30 mL). To the mixture was added 1M hydrochloric acid (10 mL), and the mixture was refluxed for overnight. The pH was adjusted to 7 with saturated sodium bicarbonate 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 recrystallized from diisopropyl ether to afford the title compound (76 mg, 7.7%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.94 (s, 2H), 6.9-7.1 (m, 2H), 7.36 (br s, 1H), 7.66 (dd, J = 6.7, 5.3 Hz, 1H), 8.19 (d, J = 6.7 Hz, 1H), 8.24 (br s, 1H), 8.64 (d, J = 5.3 Hz, 1H): ESI-MS m/z 214 (positive); $C_{12}H_9BFNO$ = 213.

(2-(Benzo[*c*][1,2]oxaborol-1(3*H*)-yl)phenyl)methanol (29)



a) *1-Bromo-2-((methoxymethoxy)methyl)benzene*: To solution of 2-bromobenzyl alcohol (10.0 g, 53.5 mmol) and diisopropylethylamine (11 mL, 64 mmol) in dichloromethane (150 mL) was added chloromethyl methyl ether (4.5 mL, 59 mmol) at 0 °C under nitrogen atmosphere, and the mixture was stirred at room temperature for 15 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

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pressure, and the residue was purified by silica gel column chromatography (12:1 hexane/ethyl acetate) to give *1-bromo-2-((methoxymethoxy)methyl)benzene* (11.7 g, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 3H), 4.67 (s, 2H), 4.77 (s, 2H), 7.16 (td, *J* = 7.9, 1.8 Hz, 1H), 7.32 (td, *J* = 7.3, 1.2 Hz, 1H), 7.49 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.55 (dd, *J* = 8.2, 1.2 Hz, 1H).

b) *2-[(Methoxymethoxy)methyl]phenylboronic acid:* 1-Bromo-2-(methoxymethoxy)methylbenzene (2.50 g, 10.8 mmol) in tetrahydrofuran (25 mL) was added *sec*-butyllithium (1.4 mol/L in cyclohexane; 9.3 mL) at –78°C under nitrogen atmosphere. After stirring for 15 min, trimethyl borate (2.5 mL, 22 mol) was added dropwise, and the mixture was stirred at room temperature for 16 h. Water and 1M hydrochloric acid were 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 (2:1 hexane/ethyl acetate) to give desired boronic acid (1.47 g, 69%).

c) *2-[(Methoxymethoxymethyl)pheny]-[1,3,2]-dioxaborolane:* Mixture of 2-[(methoxymethoxy)methyl]phenylboronic acid (1.47 g, 7.50 mmol), ethylene glycol (466 mg, 7.50 mmol), and toluene (50 mL) was heated at reflux in a Dean-Stark apparatus for 3 h. The solvent was removed under reduced pressure to give desired boronate ester (1.59 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 3H), 4.37 (s, 4H), 4.75 (s, 2H), 4.87 (s, 2H), 7.30 (td, *J* = 7.3, 2.1 Hz, 1H), 7.4-7.5 (m, 2H), 7.84 (d, *J* = 7.9 Hz, 1H).

d) *Bis[2-(methoxymethoxymethyl)phenyl]borinic acid*: A solution of 1-bromo-2-((methoxymethoxy)methyl)benzene obtained in step (a) (1.65 g, 7.16 mmol) in tetrahydrofuran (14 mL) was added *sec*-butyllithium (1.4M in cyclohexane; 6.2 mL) at –78 °C under nitrogen atmosphere. After stirring for 15 min, a solution of 2-[(Methoxymethoxymethyl)pheny]-[1,3,2]-dioxaborolane obtained in step (c) (1.59 g, 7.16 mmol) in tetrahydrofuran (7 mL) was added, and the mixture

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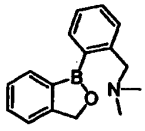
was stirred at room temperature for 1 h. Water and 1M hydrochloric acid were added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford desired borinic acid (1.82 g, 77%).

e) *(2-(Benzo[c][1,2]oxaborol-1(3H)-yl)phenyl)methanol*: To a solution of the above compound (1.38 g, 4.18 mmol) in tetrahydrofuran (60 mL) was added 1M hydrochloric acid (20 mL), and the mixture was refluxed for 5 h. The mixture was concentrated under reduced pressure to about half volume. The precipitates formed were collected by filtration to afford the title compound (610 mg, 65%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.98 (s, 4H), 7.1-7.4 (m, 8H); ESI-MS *m/z* 223 (negative); $C_{14}H_{13}BO_2$ = 224

(2-(Benzo[*c*][1,2]oxaborol-1(3*H*)-yl)phenyl)-N,N-dimethylmethanamine (30)



To a solution of (2-(benzo[*c*][1,2]oxaborol-1(3*H*)-yl)phenyl)methanol (300 mg, 1.34 mmol) in dichloromethane (10 mL) were added sequentially triethylamine (0.373 mL, 2.7 mmol) and methanesulfonyl chloride (0.125 mL, 1.60 mmol) at 0 °C. After stirring for 30 min, dimethylamine (2M in tetrahydrofuran; 3 mL) was added, and the mixture was sirred for another 30 min. 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 (1:2 hexane/ethyl acetate) followed by recrystallization from diisopropyl ether/hexane to give the title compound (185 mg, 55%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.41 (s, 3H), 4.09 (br d, *J* = 8.5 Hz, 2H), 4.87 (d, *J* = 13.2 Hz, 1H), 5.05 (d, *J* = 13.2 Hz, 1H), 7.0-7.3 (m, 8H); ESI-MS *m/z* 252 (positive); $C_{16}H_{18}BNO$ = 251

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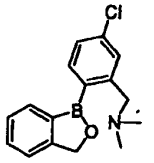
(2-(Benzo[*c*][1,2]oxaborol-1(3*H*)-yl)-5-chlorophenyl)-N,N-dimethylmethanamine (31)



a) *2-Bromo-5-chlorobenzyl bromide*: A mixture of 2-bromo-5-chlorotoluene (12.0 g, 56.6 mmol), *N*-bromosuccinimide (11.1 g, 62.3 mmol), and 2,2'-azobisiso-butyronitrile (464 mg, 2.83 mmol) in carbon tetrachloride (220 mL) was stirred at 50 °C, 60 °C, 70 °C, and reflux for 30 min each. After cooling down to room temperature, 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 afford *2-bromo-5-chlorobenzyl bromide* (17.1 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53 (s, 2H), 7.15 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.45 (d, *J* = 2.3 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H).

b) *1-Bromo-2-(dimethylamino)methyl-4-chlorobenzene*: To a solution of the above compound (5.00 g, 17.6 mmol) in tetrahydrofuran (10 mL) was added dimethylamine (2M in tetrahydrofuran; 20 mL), and the mixture was stirred at room temperature for 2 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 *1-bromo-2-(dimethylamino)methyl-4-chlorobenzene* (2.32 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 6H), 3.48 (s, 2H), 7.09 (dd, *J* = 7.9, 2.6 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 2.6 Hz, 1H).

c) *(2-(Benzo[c][1,2]oxaborol-1(3H)-yl)-5-chlorophenyl)-N,N-dimethylmethanamine* To a solution of 1-bromo-2-(dimethylamino)methyl-4-chlorobenzene (1.00 g, 4.02 mmol) in tetrahydrofuran (8 mL) was added *sec*-butyllithium (1.4M in cyclo-hexane; 3.6 mL) at –78 °C under nitrogen

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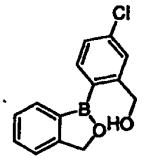
atmosphere. After stirring for 15 min, to the mixture was added 2-[(methoxymethoxymethyl)phenyl]-[1,3,2]dioxa-borolane (892 mg, 4.02 mmol) in tetrahydrofuran (4 mL), and the mixture was stirred for overnight while warming up to room temperature. Water was added, and the mixture was washed with ethyl acetate. The pH was adjusted to pH7 with 1M hydrochloric acid, 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 residue was dissolved in tetrahydrofuran (60 mL) and 1 mol/L hydrochloric acid (20 mL) was added. The mixture was refluxed for 2 h. After cooling down to room temperature, water and saturated sodium bicarbonate were 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 (2:3 to 1:2 hexane/ethyl acetate) followed by trituration with diisopropyl ether to give the title compound (356 mg, 31% in 2 steps): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3H), 2.41 (s, 3H), 4.10 (d, J = 3.8 Hz, 2H), 4.88 (d, J = 14.1 Hz, 1H), 5.05 (d, J = 14.1 Hz, 1H), 7.0-7.3 (m, 7H): ESI-MS m/z 288, 286 (positive); $C_{16}H_{17}B^{35}ClNO$ = 285

(2-(Benzo[*c*][1,2]oxaborol-1(3*H*)-yl)-5-chlorophenyl)methanol (32)



a) *2-Bromo-5-chlorobenzyl alcohol*: Solution of 2-bromo-5-chlorobenzyl bromide (12.1 g, 42.6 mmol), sodium acetate (16.4 g, 200 mmol), and dimethylformamide (120 mL) was stirred at 70 °C for overnight. After cooling down to room temperature, 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 dissolved in methanol (160 mL). To the mixture was

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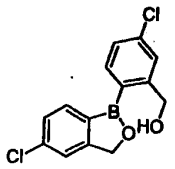
added 1M sodium hydroxide (40 mL), and the mixture was refluxed for 2h. The mixture was concentrated under reduced pressure to about half volume. Then water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was triturated with hexane to give desired alcohol (5.00 g, 53% in 2 steps): ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.47 (d, J = 5.6 Hz, 2H), 5.57 (t, J = 5.6 Hz, 1H), 7.26 (dd, J = 8.5, 2.9 Hz, 1H), 7.50 (d, J = 2.6 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H).

b) *1-Bromo-4-chloro-2((methoxymethoxy)methyl)benzene*: The above alcohol was converted into its methoxymethyl ether in the similar manner to Example 11, step (a) to afford *1-bromo-4-chloro-2-((methoxymethoxy)methyl)benzene*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (s, 3H), 4.62 (s, 2H), 4.77 (s, 2H), 7.13 (dd, J = 8.5, 2.6 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 2.6 Hz, 1H).

c) *(2-(Benzo[c][1,2]oxaborol-1(3H)-yl)-5-chlorophenyl)methanol:* Title compound was obtained from the above intermediate (b) and 2-[(methoxymethoxy-methyl)phenyl]-[1,3,2]-dioxaborolane: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.92 (s, 2H), 5.00 (s, 2H), 7.1-7.4 (m, 7H): ESI-MS *m/z* 259, 257 (negative); $C_{14}H_{12}B^{35}ClO_2$ = 258.

(5-Chloro-2-(5-chlorobenzo[c][1,2]oxaborol-1(3*H*)-yl)phenyl)methanol (33)



a) *Bis[4-chloro-2-(methoxymethoxymethyl)phenyl]borinic acid*: To a solution of 1-bromo-4-chloro-2-((methoxymethoxy)methyl)benzene (3.62 g, 13.6 mmol) in tetrahydrofuran (27 mL) was added *sec*-butyllithium (1.4 mol/L in cyclohexane; 12 mL) at – 78 °C under nitrogen atmosphere. After stirring for

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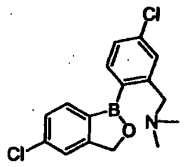
15 min, to the mixture was added trimethyl borate (706 mg, 6.8 mmol) in tetrahydrofuran (5 mL) and the mixture was stirred at room temperature for overnight. Water and 1 mol/L hydrochloric acid were added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried on anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (3:1~2:1 hexane/ethyl acetate) to give desired acid (880 mg, 32%).

b) *(5-Chloro-2-(5-chlorobenzo[c][1,2]oxaborol-1(3H)-yl)phenyl)methanol:* The title compound was obtained from the above compound in a similar manner to Example 11, step (e) after purification by silica gel column chromatography (9:1 chloroform/methanol): ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.93 (s, 4H), 7.18 (m, 4H), 7.32 (m, 2H): ESI-MS *m/z* 295, 293, 291 (negative); $C_{14}H_{11}B^{35}Cl_2O_2$ = 292.

(5-Chloro-2-(5-chlorobenzo[c][1,2]oxaborol-1(3*H*)-yl)phenyl-N,N-dimethyl-methanamine (34)



Title compound was obtained from (5-chloro-2-(5-chlorobenzo[*c*]-[1,2]oxaborol-1(3*H*)-yl)phenyl)methanol: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.26 (s, 3H), 2.42 (s, 3H), 4.11 (d, *J* = 2.9 Hz, 2H), 4.86 (d, *J* = 14.7 Hz, 1H), 5.03 (d, *J* = 14.3 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.1-7.2 (m, 3H), 7.2-7.3 (m, 2H): ESI-MS *m/z* 324, 322, 320 (positive); $C_{16}H_{16}B^{35}Cl_2NO$ = 319.

1-(4-chloro-2-methoxyphenyl)-1,3-dihydrobenzo[c][1,2]benzoxaborole (35)

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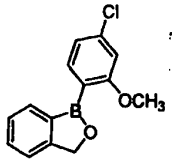

a) *4-Chloro-2-methoxyphenylboronic acid ethylene glycol ester*: To a solution of 2-bromo-5-chloroanisole (4.43 g, 20 mmol) in dry THF (100 mL) at -78°C was added dropwise t-BuLi (14.1 mL, 1.7 M, 23.97 mmol). The mixture was stirred for 10 min at -78°C and trimethyl borate (2.23 mL, 20 mmol) was added. The cooling bath was removed and the mixture was stirred for 30 min from -78°C to room temperature and then for 3 h with a water bath. Hydrochloric acid (6N, 8 mL) and brine were added. The mixture was extracted with ethyl acetate, dried and evaporated to give 4-chloro-2-methoxyphenylboronic acid as a brown solid (3.33 g, 17.88 mmol) in 89.4% yield. This boronic acid was mixed with ethylene glycol (1.1 g, 17.88 mmol) and toluene (150 mL). The mixture was refluxed for 2 h under N_2 with the help of a Dean-Stark trap to remove water generated. After being cooled to room temperature, the solution was transferred to another dry flask and rotary evaporated to provide 4-Chloro-2-methoxyphenylboronic acid ethylene glycol ester as a brown liquid (3.6 g, 16.97 mmol) in 84.8% yield.

b) *1-(4-chloro-2-methoxyphenyl)-1,3-dihydrobenzo[c][1,2]benzoxaborole*: To a solution of 2-(methoxymethoxymethyl) phenyl bromide (3.929 g, 17 mmol), which was obtained as described in Example 11(a), in dry THF (150-200 mL) at -78°C was added dropwise t-BuLi (12 mL, 1.7 M, 20.4 mmol). The mixture was stirred for 10 min at -78°C and a solution of 4-chloro-2-methoxyphenylboronic acid ethylene glycol ester (3.6 g, 17 mmol) in THF (30 mL) was added resulting in a viscous mixture. The cooling bath was removed and the mixture was stirred for 30 min from -78°C to room temperature and then for 3 h with a water bath. Hydrochloric acid (6N, 12 mL) was added and the mixture was stirred briefly for 5 min. The aqueous layer was removed and the THF layer was rotary evaporated. The residue was mixed with THF (50 mL), methanol (50 mL) and 6N HCl (50 mL) giving a homogeneous solution

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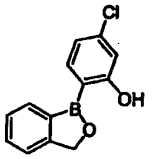
that was stirred for 30 min at room temperature. Organic solvents were rotary evaporated and the residue was extracted with ethyl acetate (3 × 80 mL). The combined ethyl acetate solution was washed with brine, dried and evaporated. The residue was purified by flash column chromatography eluted with a mixed solvent of hexanes and ethyl acetate (6:1, v/v) to provide 1,3-dihydro-1-(4-chloro-2-methoxyphenyl)-2,1-benzoxaborole as a white solid (AN-2551, 2.63 g, 10.17 mmol) in 59.8% yield. M.p. 66-68°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.05 (dm, J = 7.2 Hz, 1H), 7.80 (dd, J_1 = 7.8 Hz, J_2 = 2.1 Hz, 1H), 7.52-7.50 (m, 2H), 7.40-7.36 (m, 1H), 7.15-7.13 (m, 1H), 7.06 (dt, J_1 = 8.1 Hz, J_2 = 2.1 Hz, 1H), 5.34 (s, 2H) and 3.904 & 3.898 (s & s, 3H) ppm.

2-(Benzo[*c*][1,2]oxaboral-1(3H)-yl)-5-chlorophenol (36)



To a solution of 1,3-dihydro-1-(4-chloro-2-methoxyphenyl)-2,1-benzoxaborole as a white solid (AN-2551, 0.5 g, 1.93 mmol) in anhydrous methylene chloride (25 mL) at -78°C was added dropwise a solution of boron tribromide in methylene chloride (1.0 M, 1.93 mL, 1.93 mmol) under nitrogen. The mixture was stirred at -78°C for 1 h and at room temperature for 4 h. Then the reaction flask was re-cooled to -78°C and methanol (10 mL) was added. The reaction mixture was warmed to room temperature and 6N HCl (2 mL) was added. The mixture was evaporated to give a residue that was mixed with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue was purified by flash column chromatography eluted with a mixed solvent of hexanes and ethyl acetate (4:1, v/v) to provide the desired compound 1,3-dihydro-1-(4-chloro-2-hydroxyphenyl)-2,1-benzoxaborole as a white solid (0.32 g, 1.31 mmol) in 67.8% yield. M.p. 96-98°C; ^{1}H NMR (MeOH-d_4, 300 MHz): δ 8.19 (d, J = 7.5 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.52-7.51 (m, 2H), 7.43-7.38 (m, 1H), 6.96-6.91 (m, 1H), 6.89-6.88 (m, 1H) and 5.41 (s, 2H) ppm.

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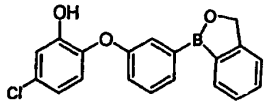
2-(3-(Benzo[*c*][1.2]oxaborol-1(3H)-yl)phenoxy)-5-chlorophenol (37)



a) *3-(4-Chloro-2-methoxyphenoxy)phenyl bromide*: To a three-necked flask equipped with a thermometer, a condenser-topped Dean-Stark trap and a rubber septa were added 4-chloro-2-methoxyphenol (10 g, 63.05 mmol), 1,3-dibromobenzene (14.88 g, 63.05 mmol), copper powder (0.4 g, 6.3 mmol) and potassium hydroxide (5 g, 75.7 mmol). Under nitrogen atmosphere, the mixture was stirred and heated slowly to 220-230°C and kept at this temperature for 1 h. After being cooled to room temperature, methylene chloride was added and the mixture was filtered. The filtrate was washed with 10% NaOH (2 × 200 mL), dried and evaporated. The residue was purified by flash column chromatography over silica gel eluted with a mixed solvent of hexanes and EtOAc (6:1, v/v) to provide 3-(4-chloro-2-methoxyphenoxy)phenyl bromide as a liquid-solid mixed form (3.09 g, 9.85 mmol) in 15.6% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.29-7.20 (m, 3H), 7.12 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.05-7.00 (m, 2H), 6.85-6.81 (m, 1H) and 3.75 (s, 3H) ppm.

b) *3-(4-Chloro-2-hydroxyphenoxy)phenyl bromide*: The demethylation procedure used in Example 37 was adapted for the synthesis of 3-(4-chloro-2-hydroxyphenoxy)phenyl bromide from 3-(4-chloro-2-methoxyphenoxy)phenyl bromide. The crude product was purified by flash column chromatography eluted with a mixed solvent of hexanes and EtOAc (6:1, v/v) to give 3-(4-chloro-2-hydroxyphenoxy)phenyl bromide as a white solid in 100% yield. M.p. 63-65°C; MS (ESI, negative): m/z = 299 (M-1); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.21 (s, 1H), 7.28-7.19 (m, 2H), 7.05 (d, J = 9.0 Hz, 1H), 6.99-6.97 (m, 2H) and 6.89-6.82 (m, 2H) ppm.

c) *3-(4-Chloro-2-methoxymethoxyphenoxy)phenyl bromide*: The methoxymethyl protection procedure used in Example 11(a) was adapted for

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the synthesis of 3-(4-chloro-2-methoxymethoxyphenoxy)phenyl bromide from 3-(4-chloro-2-hydroxyphenoxy)phenyl bromide. The crude product was purified by flash column chromatography eluted with a mixed solvent of hexanes and ethyl acetate (5:1, v/v) to afford 3-(4-chloro-2-methoxymethoxyphenoxy)phenyl bromide as a colorless oil in 84.5% yield. ^{1}H-NMR (DMSO-d_6, 300 MHz): δ 7.33-7.01 (m, 6H), 6.89-6.85 (m, 1H), 5.18 (s, 2H) and 3.21 (s, 3H) ppm.

d): *2-(3-(Benzo[c][1.2]oxaborol-1(3H)-yl)phenoxy)-5-chlorophenol* The procedure used for the preparation of Example 36 from 2-(methoxymethoxy)methylphenyl bromide and 4-chloro-2-methoxyphenylboronic acid ethylene glycol ester was adapted for the synthesis of the title compound from 3-(4-chloro-2-methoxymethoxyphenoxy)phenyl bromide and 2-[(methoxy-methoxy)methyl]phenylboronic acid ethylene glycol ester. The crude product was purified by flash column chromatography over silica gel eluted with a mixed solvent of hexanes and EtOAc (4:1, v/v). The solid obtained was washed with n-pentane and hexanes (50:50, v/v) to give 1,3-dihydro-1-[3-(4-chloro-2-hydroxyphenoxy) phenyl]-2,1-benzoxaborole as a white solid in 28.5% yield. M.p. 115-117°C; ^{1}H NMR (MeOH-d_4, 300 MHz): δ 8.05 (d, J = 7.2 Hz, 1H), 7.85 (d, J = 6.9 Hz, 1H), 7.64 (d, J = 2.1 Hz, 1H), 7.52 (d, J = 3.9 Hz, 2H), 7.47-7.38 (m, 2H), 7.11 (dd, J_1 = 8.1 Hz, J_2 = 2.1 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 6.83 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H) and 5.35 (s, 2H) ppm. The title compound can alternatively be prepared by lithium exchange of 3-(4-chloro-2-methoxyphenoxy)phenyl bromide and then reacting with 2-[(methoxymethoxy)methyl]phenylboronic acid ethylene glycol ester to give the corresponding methylated analogue of the title compound. Demethylation of this analogue can generate the desired title compound.

4-((3-(5-Fluorobenzo[*c*][1,2]oxaborol-1(3*H*)-yl)phenyl)methyl)morpholine (38)

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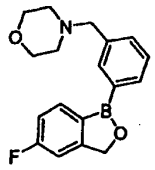
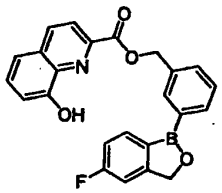


The title compound was obtained from (3-(5-(fluorobenzo[*c*][1,2]oxaborol-1(3*H*)-yl)phenyl)methanol obtained in Example 27 and morpholine. It was dissolved in ether and treated solution of 0.25M fumaric acid in methanol. The solvent was removed under reduced pressure and the residue was triturated with diisopropyl ether to afford the title compound as fumarate salt: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.41 (m, 4H), 3.57 (m, 4H), 5.33 (s, 2H), 6.60 (s, 1H), 7.23 (t, J = 9.1 Hz, 1H), 7.3-7.5 (m, 3H), 7.94 (m, 2H), 8.12 (dd, J = 7.6, 6.5 Hz, 1H): ESI-MS *m/z* 312 (positive); $C_{18}H_{19}BFNO_2$ = 311.

(3-(5-Fluorobenzo[*c*][1,2]oxaborol-1(3*H*)-yl]phenyl)-methyl 8-hydroxy-quinoline-2-carboxylate (39)



A mixture of (3-(5-(fluorobenzo[*c*][1,2]oxaborol-1(3*H*)-yl)-phenyl)methanol from Example 27 (100 mg, 0.413 mmol), 8-hydroxyquinoline-2-carboxylic acid (156 mg, 0.826 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (159 mg, 0.826 mmol), 1-hydroxybenzotriazole (112 mg, 0.826 mmol), and 4-*N*,*N*-dimethylaminopyridine (101 mg, 0.826 mmol) in dimethylformamide (3 mL) 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 purified by silica gel column chromatography (1:1 hexane/ethyl acetate) followed by recrystallization from ethyl acetate/hexane to give the title compound (92 mg, 54%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.34 (s, 2H), 5.54 (s, 2H), 7.1-7.2 (m, 2H), 7.36 (dd, J = 9.6, 2.0 Hz, 1H), 7.4-7.6 (m, 3H), 7.67 (d, J = 7.6 Hz, 1H), 8.01 (d, J = 7.3 Hz,

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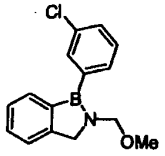
1H), 8.1-8.2 (m, 3H), 8.47 (d, J = 8.5 Hz, 1H), 10.0 (s, 1H): ESI-MS *m/z* 414 (positive), 412 (negative); $C_{24}H_{17}BFNO_4$ = 413.

1-(3-Chlorophenyl)-2,3-dihydro-2-(methoxymethy)-1H-benzo[c][1,2]aza-borole (40)



a) *N,N-Bis(methoxymethyl)-2-bromobenzylamine*: A solution of 2-bromobenzyl-amine hydrochloride (4.85 g, 20.7 mmol) in methanol (200 mL) was added 37% formaldehyde (25 mL) and potassium carbonate (4.28 g, 31.0 mmol), and the mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure to a third of volume. 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 *N,N-bis(methoxymethyl)-2-bromobenzylamine* (5.76 g, quant): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.28 (s, 6H), 4.11 (s, 2H), 4.26 (s, 4H), 7.12 (td, J = 7.6, 1.8 Hz, 1H), 7.28 (td, J = 7.3, 0.9 Hz, 1H), 7.43 (dd, J = 7.6, 1.8 Hz, 1H), 7.55 (dd, J = 7.9, 1.2 Hz, 1H).

b) *3-Chlorophenyl 2-[N,N-bis(methoxymethyl)aminomethyl]phenylborinic acid*: To a solution of the above compound (2.74 g, 10.0 mmol) in tetrahydrofuran (20 mL) was added *sec*-butyllithium (1.4 mol/L in cyclohexane; 10 mL) at – 78 °C under nitrogen atmosphere. After stirring for 15 min, to the mixture was added 3-chlorophenyl-[1,3,2]-dioxaborolane (1.82 g, 10.0 mmol) in tetrahydrofuran (8 mL), and the mixture was stirred at room temperature for 2 h. Water and 1M hydro-chloric acid were 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

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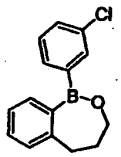
pressure to afford *3-chlorophenyl 2-[N,N-bis(methoxymethyl)aminomethyl]phenylborinic acid* (2.57 g, 77%).

c) *1-(3-Chlorophenyl)-2,3-dihydro-2-(methoxymethy)-1H-benzo[c][1,2]azaborole*: To a solution of the above compound (1.00 g, 4.18 mmol) in ethanol (27 mL) was added conc. hydrochloric acid (3 mL), and the mixture was refluxed for overnight. Saturated sodium bicarbonate was added and the mixture was extracted with ethyl aceate. 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 (9:1 chloroform/methanol) to give the title compound (550 mg, 68%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.03 (s, 3H), 3.9-4.2 (m, 2H), 5.94 (br s, 2H), 7.0-7.3 (m, 7H).

1-(3-Chlorophenyl)-1,3,4,5-tetrahydrobenzo-[c][1,2]-oxaborepine (41)



a) *3-(2-Bromophenyl)propan-1-ol*: 3-(2-Bromophenyl)propionic acid (4.989g, 21.8mmol) was dissolved in 50 mL of dry THF under N_2 and cooled to 0°C. BH_3-THF (1M in THF) (40mL, 40mmol) was added dropwise with stirring. Once the vigorous effervescence had subsided, the solution was stirred for a further 0.5 hours at 0°C then allowed to warm to room temperature. The solution was stirred at room temperature for 18 hours. The THF was removed under vacuum and the residue dissolved in CH_2Cl_2 (100mL). Methanol was slowly added to the solution until no bubbling could be observed and the solution was stirred for a further 15 minutes. The solvents were removed under vacuum and the residue re-dissolved in methanol (100mL). The solution was stirred for 10 minutes then the solvent was removed under vacuum. The residue was further dried for several hours under high vacuum

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(<1mmHg). This gave pure *3-(2-bromophenyl)-propan-1-ol* as a yellow oil (4.54g, 97%): ^{1}H NMR δ 1.90 (tt,2H), 2.84 (t,2H), 3.71 (t,2H), 7.06 (m,1H), 7.24 (m,2H), 7.53 (d,1H).

b) *1-Bromo-2-(2-(methoxymethoxy)propyl)benzene*: 3-(2-Bromophenyl)propan-1-ol (2.123g, 9.9mmol) was dissolved in 50mL of CH_2Cl_2 at room temperature under N_2. Diisopropylethylamine (1.9mL, 10.9mmol) and chloromethyl methyl ether (0.82mL, 10.8mmol) were then added and the solution was stirred at room temperature for 18 hours. The reaction mixture was poured into a separatory funnel and extracted with H_2O (2 x 20 mL) followed by brine (1 x 20 mL). The CH_2Cl_2 was dried with $MgSO_4$, filtered and evaporated under vacuum to give pure *1-bromo-2-(2-(methoxymethoxy)propyl)benzene* as a yellow oil (2.45g, 96%): ^{1}H NMR δ 1.92 (tt,2H), 2.83 (t,2H), 3.39 (s,3H), 3.58 (t,2H), 4.65 (s,2H), 7.06 (m,1H), 7.24 (m,2H), 7.53 (d,1H).

c) *1-(3-Chlorophenyl)-1,3,4,5-tetrahydrobenzo[c][1,2]oxaborepine*: 2-Bromo-2-(3-methoxymethoxypropyl)benzene (1.212g, 4.7mmol) was dissolved in 50mL of dry THF under N_2 and cooled to -78°C. *t*-BuLi (1.7M in pentane)(6.0mL, 10.2mmol) was slowly added to the solution. After stirring for 15 minutes at -78°C, 2-(3-chloro-phenyl)-[1,3,2]dioxaborolane was added and the solution stirred for a further 0.5 hours. The solution was then allowed to warm to room temperature and stirred for 18 hours. 5 ml of concentrated HCl was then added and the solution stirred at room temperature for a further 24 hours. 10 mL of H_2O was then added and the THF removed under vacuum. The aqueous solution was extracted with diethyl ether (3 x 50mL). The ether extracts were combined and washed with brine until neutral. The ether was dried with $MgSO_4$, filtered and evaporated to give an orange oil. The crude product was purified by column chromatography on silica gel using 5:1 hexanes: ethyl acetate as eluent. After removal of the solvents, titled compound (Rf = 0.82) was obtained as a yellow oil (0.480g, 40%): ^{1}H NMR δ 2.18 (tt,2H), 2.81 (t,2H), 4.11 (t,2H), 7.24 (d,1H), 7.29-7.36 (2H), 7.40-7.49

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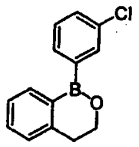
(3H), 7.73 (td,1H), 7.84 (m,1H); MS(ES$^-$) no molecular ion observed; HPLC [ret. Time (% area)] 15.573 min (96.9%).

1-(3-Chlorophenyl)-3,4-dihydro-1H-benzo[*c*][1,2]-oxaborinine (42)



a) *2-(3-Chlorophenyl)-[1,3,2]dioxaborolane*: 3-Chlorophenyl boronic acid (3.041g, 19.4mmol) was dissolved in 75 mL of dry THF under N_2. Ethylene glycol (1.323g, 21.3mmol) was added and the solution refluxed for 18 hours. The solution was allowed to cool and the THF removed under vacuum. The residue was further dried under high vacuum (<1mmHg) with occasional heating to remove excess ethylene glycol and THF. This gave pure *2-(3-chlorophenyl)-[1,3,2]dioxaborolane* (3.55g, 100%) as a brown oil that solidified upon cooling in the freezer: ^{1}H NMR δ 4.39 (s,4H), 7.32 (t,1H), 7.44 (ddd,1H), 7.67 (d,1H), 7.78 (d,1H).

b) *1-Bromo-2-(2-(methoxymethoxy)ethyl)benzene*: Sodium hydride (60% dispersion in mineral oil, 0.966g, 24.1mmol) was placed in a 250mL round bottom flask under N_2. The NaH was washed with dry hexanes (10mL). The hexanes were removed via cannula, and the process repeated twice (2 x 10mL). The NaH was dried under vacuum until a free flowing powder resulted and placed under N_2. 2-(2-bromophenyl)ethanol (4.016g, 20mmol) was dissolved in 60mL of dry THF and added dropwise to the solid NaH. Once H_2 evolution had ceased, the solution was refluxed for 1 hour. The solution was allowed to cool to room temperature then cooled to 0°C in an ice bath. Chloromethyl methyl ether (1.52mL, 20mmol) was then added and the solution allowed to warm to room temperature. The solution was stirred at room temperature for 18 hours then filtered through a 1.5 cm column of Celite. The Celite was washed with THF (2 x 15mL). The THF filtrates were combined and evaporated under vacuum to give pure methoxymethoxy ether

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as an oil (4.64g, 95%): ^{1}H NMR δ 3.06 (t,2H), 3.31 (s,3H), 3.78 (t,2H), 4.62 (s,2H), 7.08 (dt,1H), 7.26 (m,2H), 7.54 (dd,1H).

c) *(3-Chlorophenyl)(2'-(2-(methoxymethoxy)ethyl)phenyl)borinic acid*: 1-Bromo-2-(2-(methoxymethoxy)ethyl)benzene (2.21g, 9.0mmol) was dissolved in 50mL of dry THF under N_2 and cooled to -78°C. *t*-BuLi (1.7M in pentane)(11.7mL, 19.9mmol) was slowly added to the solution. After stirring for 15 minutes at -78°C, 2-(3-chlorophenyl)-[1,3,2]dioxaborolane in 10mL of dry THF was added and the solution stirred for a further 0.5 hours. The solution was then allowed to warm to room temperature and stirred for 18 hours. The THF was removed under vacuum and the residue partitioned between 50mL of H_2O and 80mL of diethyl ether. The solution was vigorously stirred for several minutes then neutralized (pH = 7) with 6N HCl. The ether was separated and the aqueous solution extracted again with ether (2 x 50mL). The ether extracts were combined, dried with $MgSO_4$, filtered and evaporated to give an orange oil (2.83g). ^{1}H NMR of the product showed that the desired borinic acid was formed. This was used for the next step without purification.

d) *1-(3-Chlorophenyl)-3,4-dihydro-1H-benzo[c][1,2]oxaborinine*: The crude MOM protected borinic acid (2.83g) was dissolved in 46mL of THF and 4 mL of concentrated HCl. The solution was stirred at room temperature for 12 hours. 10 mL of H_2O was then added and the THF removed under vacuum. The aqueous solution was extracted with diethyl ether (3 x 50mL). The ether extracts were combined and washed with brine until neutral. The ether was dried with $MgSO_4$, filtered and evaporated to give an orange oil (2.5g). The crude product was purified by column chromatography on silica gel using 5:1 hexanes: ethyl acetate as eluent. After removal of the solvents, pure product (Rf = 0.66) was obtained as a yellow oil (0.600g, 27%; two steps): 1H NMR δ 3.03 (t,2H), 4.35 (t,2H), 7.26 (d,1H), 7.32-7.39 (2H), 7.44-7.50 (2H), 7.75 (d,1H), 7.79 (d,1H), 7.85 (m,1H): MS(ES$^-$) 243.01; HPLC [ret. time(% area)] 14.623 min (96.8%).

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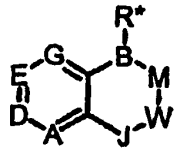
WHAT IS CLAIMED IS:

1. A compound having the structure of Formula 1



Formula 1

wherein B is boron, M is selected from oxygen, sulfur and NR^{**}

wherein R^* is selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 – C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

wherein R^{**} is H, alkyl, alkyloxy, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

and wherein A is CH, CR^1, or N

and wherein D is CH, CR^2, or N

and wherein E is CH, CR^3, or N

and wherein G is CH, CR^4, or N

and the combination of nitrogens (A + D + E + G) is 0-3

and wherein J is $(CH_2)_n$ (n = 0 to 2) or CHR^5

and wherein W is $(CH_2)_m$ (m = 0 to 1), C=O (carbonyl) or CHR^6

wherein R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of hydrogen, haloalkyl, alkyl, $(CH_2)_pOH$ (p = 1 to 3), halogen, CHO, CH = NOH, CO_2H, CO_2-alkyl, S-alkyl, SO_2-alkyl, S-aryl, $(CH_2)_qNR^{18}R^{19}$ (wherein R^{18} and R^{19} are independently selected from hydrogen, alkyl, and alkanoyl)(q = 0 to 2), alkoxy, CF_3, SCF_3, NO_2, SO_3H, OH, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, fused substituted or unsubstituted aryl, fused substituted or unsubstituted heteroaryl,

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wherein R^5 is selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 – C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

wherein R^6 is selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 – C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

including salts thereof, especially all pharmaceutically acceptable salts.

2. The compound of claim 1 wherein M is oxygen.

3. The compound of claim 1 wherein M is sulfur.

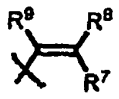
4. The compound of claim 1 wherein M is NR**.

5. The compound of claim I wherein R* is a substituted or unsubstituted alkyl (C_1 - C_4).

6. The compound of claim I wherein R* is a substituted or unsubstituted cycloalkyl (C_3 – C_7).

7. The compound of claim I wherein R* is a substituted or unsubstituted alkenyl.

8. The compound of claim 7 wherein said alkenyl has the structure



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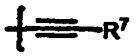
wherein R^7, R^8, and R^9 are each independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_rOH$ (where r I to 3), $CH_2NR^{20}R^{21}$ (wherein R^{2o} and R^{21} are independently selected from hydrogen and alkyl), CO_2H, CO_2alkyl, $CONH_2$, S- alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

9. The compound of claim 1 wherein R* is a substituted or unsubstituted alkynyl.

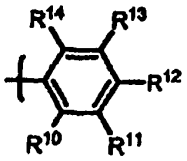
10. The compound of claim 9 wherein said alkynyl has the structure



wherein R^7 is selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_rOH$ (where r = I to 3), $CH_2NR^{20}R^{21}$ (wherein R^{20} and R^{21} 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 and NO_2.

11. The compound of claim I wherein R* is a substituted or unsubstituted aryl.

12. The compound of claim 11 wherein said aryl has the structure



wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_sOH$ (where s = I to 3), CO_2H, CO_2alkyl, $CONH_2$, CONHalkyl, $CON(alkyl)_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl,

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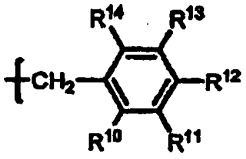
SO_3H, SCF_3, CN, halogen, CF_3, NO_2, $(CH_2)_tNR^{22}R^{23}$ (wherein R^{22} and R^{23} are independently selected from hydrogen, alkyl, and alkanoyl)(t = 0 to 2), SO_2NH_2, $OCH_2CH_2NH_2$, $OCH_2CH_2NHalkyl$, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, or alkyl substituted oxazolidin-2-yl.

13. The compound of claim 1 wherein R* is a substituted or unsubstituted aralkyl.

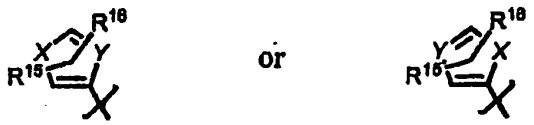
14. The compound of claim 13 wherein said aralkyl has the structure



wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, 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, $(CH_2)_tNR^{22}R^{23}$ (wherein R^{22} and R^{23} 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, or alkyl substituted oxazolidin-2-yl.

15. The compound of claim 1 wherein R* is a substituted or unsubstituted heteroaryl.

16. The compound of claim 15 wherein said heteroaryl has the structure



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wherein X = CH=CH, N=CH, NR^{17} (wherein R^{17} = H, alkyl, aryl or benzyl), O, or S

and wherein Y = CH or N

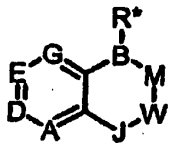
and wherein R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_uOH$ (where u = 1 to 3), $(CH_2)_vNR^{24}R^{25}$ (wherein R^{24} and R^{25} are independently selected from hydrogen alkyl 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 and NO_2.

17. A compound having the structure of compound 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24.

18. A composition comprising a compound of claim 1 in a pharmaceutically acceptable carrier.

19. A composition comprising a compound of claim 17 in a pharmaceutically acceptable carrier.

20. A method for inhibiting microbial growth comprising contacting a bacterium with a compound having the structure of Formula 1



Formula 1

wherein B is boron, M is selected from oxygen, sulfur and NR**

wherein R* is selected from substituted or unsubstituted alkyl ($C_1 - C_4$), substituted or unsubstituted cycloalkyl ($C_3 - C_7$), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

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wherein R** is H, alkyl, alkyloxy, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

and wherein A is CH, CR^1, or N

and wherein D is CH, CA^2, or N

and wherein E is CH, CR^3, or N

and wherein G is CH, CR^4, or N

and the combination of nitrogens (A + D + E + G) is 0-3

and wherein J is $(CH_2)_n$ (n = 0 to 2) or CHR^5

and wherein W is $(CH_2)_m$ (m =0 to 1), C=O (carbonyl) or CHR^6

wherein R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of hydrogen, haloalkyl, alkyl, $(CH_2)_p0H$ (p = 1 to 3), halogen, CHO, CH = NOH, CO_2H, $C0_2$-alkyl, S-alkyl, $S0_2$-alkyl, S-aryl, $(CH_2)_qNR^{18}R^{19}$ (wherein R^{18} and R^{19} are independently selected from hydrogen, alkyl, and alkanoyl) (q = 0 to 2), atkoxy, CF_3. SCF_3, NO_2, SO_3H, OH, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, fused substituted or unsubstituted aryl, fused substituted or unsubstituted heteroaryl,

wherein R^5 is selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 – C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

wherein R^6 is selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 – C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, including salts thereof, especially all pharmaceutically acceptable salts.

21. The method of claim 20 wherein M is oxygen.

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22. The method of claim 20 wherein M is sulfur.

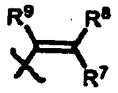
23. The method of claim 20 wherein M is NR**.

24. The method of claim 20 wherein R* is a substituted or unsubstituted alkyl ($C_1 - C_4$).

25. The method of claim 20 wherein R* is a substituted or unsubstituted cycloalkyl ($C_3 - C_7$).

26. The method of claim 20 wherein R* is a substituted or unsubstituted alkenyl.

27. The method of claim 26 wherein said alkenyl has the structure



wherein R^7, R^8, and R^9 are each independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_rOH$ (where r = I to 3), $CH_2NR^{20}R^{21}$ (wherein R^{20} and R^{21} 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 and NO_2.

28. The method of claim 20 wherein R* is a substituted or unsubstituted alkynyl.

29. The method of claim 28 wherein said alkynyl has the structure

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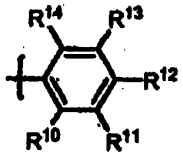
wherein R^7 is selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_rOH$ (where r = 1 to 3), $CH_2NR^{20}R^{21}$ (wherein R^{20} and R^{21} are independently selected from hydrogen and alkyl), CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

30. The method of claim 20 wherein R* is a substituted or unsubstituted aryl.

31. The method of claim 30 wherein said aryl has the structure



wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, 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, $(CH_2)_tNR^{22}R^{23}$ (wherein R^{22} and R^{23} 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, or alkyl substituted oxazolidin-2-yl.

32. The method of claim 20 wherein R* is a substituted or unsubstituted aralkyl.

33. The method of claim 32 wherein said aralkyl has the structure

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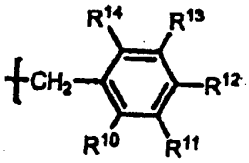

wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_sOH$ (where s = 1 to 3), CO_2H, CO_2alkyl, $CONH_2$, CONHalkyl, CON(alkyl)$_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, $(CH_2)_tNR^{22}R^{23}$ (wherein R^{22} and R^{22} 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, or alkyl substituted oxazolidin-2-yl.

34. The method of claim 20 wherein R* is a substituted or unsubstituted heteroaryl.

35. The method of claim 34 wherein said heteroaryl has the structure

 or 

wherein X = CH=CH, N=CH, NR^{17} (wherein R^{17} = H, alkyl, aryl or benzyl), O, or S

and wherein Y = CH or N

and wherein R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_uOH$ (where u = to 3), $(CH_2)_vNR^{24}R^{25}$ (wherein R^{24} and R^{25} are independently selected from hydrogen, alkyl and alkanoyl, v = 0 to 3), CO_2H, CO_2alkyl, $CONH_2$, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

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36. The method of claim 18 wherein said compound has the structure of compound 11, 12,13, 14,15, 16, 17, 18, 19, 20, 21, 22, 23 or 24.

37. The method of claim 18 wherein said contacting occurs *in vivo*.

38. A method for treating a microbial-caused disease in a patient afflicted therewith comprising administering to said patient a therapeutically effective amount of a compound of claim 1.

39. The method of claim 38 wherein said microbe is a bacterium.

40. The method of claim 39 wherein said bacterium is a gram positive bacterium.

41. The method of claim 40 wherein said gram positive bacterium is a member selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Bacillus* species, *Mycobacterium* species, *Corynebacterium* species (*Propionibacterium* species), *Clostridium* species, *Actinomyces* species, *Enterococcus* species, and *Streptomyces* species;

42. The method of claim 39 wherein said bacterium is a gram negative bacterium.

43. The method of claim 42 wherein said gram negative bacterium is a member selected from the group consisting of *Acinetobacter* species, *Neisseria* species, *Pseudomonas* species, *Brucella* species, *Agrobacterium* species, *Bordetella* species, *Escherichia* species, *Shigella* species, *Yersinia* species, *Salmonella* species, *Klebsiella* species, *Enterobacter* species, *Haemophilus* species, *Pasteurella* species, *Streptobacillus* species, spirochetal species, *Campylobacter* species, *Vibrio* species, and *Helicobacter* species.

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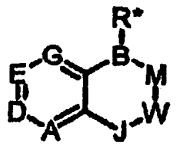
44. The method of claim 39 wherein said bacterium is a member selected from the group consisting of *Propionibacterium acnes*, *Staphylococcus aureus*; *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*; *Streptococcus pyogenes*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*; *Enterococcus faecalis*; *Enterococcus faecium*; *Bacillus anthracis*; *Mycobacterium avium-intracellulare*; *Mycobacterium tuberculosis*, *Acinetobacter baumanii*; *Corynebacterium diphtheria*; *Clostridium perfringens*; *Clostridium botulinum*; *Clostridium tetani*; *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 israelil*; *Rickettsia prowazekii*; *Rickettsia rickettsii*; *Chlamydia trachomatis*; *Chlamydia psittaci*; *Brucella abortus*; *Agrobacterium tumefaciens*; and *Francisella tularensis*.

45. The method of claim 38 wherein said compound has the structure of compound 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24.

46. A method for inhibiting viral multiplication comprising contacting a virus with a compound having the structure of Formula 1



Formula 1

wherein B is boron, M is selected from oxygen, sulfur or NR**

wherein R* is selected from substituted or unsubstituted alkyl ($C_1 - C_4$), substituted or unsubstituted cycloalkyl ($C_3 - C_7$), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

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wherein R** is H, alkyl, alkyloxy, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

and wherein A is CH, CR^1, or N

and wherein D is CH, CR^2, or N

and wherein E is CH, CR^3, or N

and wherein G is CH, CR^4, or N

and the combination of nitrogens (A + D + E + G) is 0-3 and wherein J is $(CH_2)_n$ (n = 0 to 2) or CHR^5

and wherein W is $(CH_2)_m$ (m = 0 to 1), C=O (carbonyl) or CHR^6

wherein R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of hydrogen, haloalkyl, alkyl, $(CH_2)_p$ OH (p = 1 to 3), halogen, CHO, CH=NOH, CO_2H, CO_2-alkyl, S-alkyl, SO_2-alkyl, S-aryl, $(CH_2)_qNR^{18}R^{19}$ (wherein R^{18} and R^{19} are independently selected from hydrogen, alkyl, and alkanoyl)(q = 0 to 2), alkoxy, CF_3, SCF_3, NO_2, SO_3H, OH, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, fused substituted or unsubstituted aryl, fused substituted or unsubstituted heteroaryl,

wherein R^5 is selected from substituted or unsubstituted alkyl ($C_1 - C_4$), substituted or unsubstituted cycloalkyl ($C_3 - C_7$), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

wherein R^6 is selected from substituted or unsubstituted alkyl ($C_1 - C_4$), substituted or unsubstituted cycloalkyl ($C_3 - C_7$), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

including salts thereof, especially all pharmaceutically acceptable salts.

47. The method of claim 46 wherein M is oxygen.

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48. The method of claim 46 wherein M is sulfur.

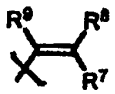
49. The method of claim 46 wherein M is NR**.

50. The method of claim 46 wherein R* is a substituted or unsubstituted alkyl ($C_1 - C_4$).

51. The method of claim 46 wherein R* is a substituted or unsubstituted cycloalkyl ($C_3 - C_7$).

52. The method of claim 46 wherein R* is a substituted or unsubstituted alkenyl.

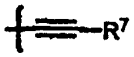
53. The method of claim 52 wherein said alkenyl has the structure



wherein R^7, R^8, and R^9 are each independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_rOH$ (where r = l to 3), $CH_2NR^{20}R^{21}$ (wherein R^{20} and R^{21} 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 and NO_2.

54. The method of claim 46 wherein R* is a substituted or unsubstituted alkynyl.

55. The method of claim 54 wherein said alkynyl has the structure



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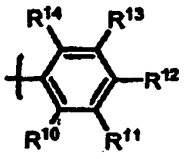
wherein R^7 is selected from the group consisting of nydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_rOH$ (where r = 1 to 3), $CH_2NR^{20}R^{21}$ (wherein R^{20} and R^{21} are independently selected from hydrogen and alkyl), CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

56. The method of claim 46 wherein R* is a substituted or unsubstituted aryl.

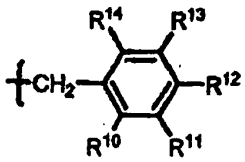
57. The method of claim 56 wherein said aryl has the structure



wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, 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, $(CH_2)_tNR^{22}R^{23}$ (wherein R^{22} and R^{23} 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, or alkyl substituted oxazolidin-2-yl.

58. The method of claim 46 wherein R* is a substituted or unsubstituted aralkyl.

59. The method of claim 58 wherein said aralkyl has the structure



SUBSTITUTE SHEET (RULE 26)

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wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, 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, $(CH_2)_tNR^{22}R^{23}$ (wherein R^{22} and R^{23} 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, or alkyl substituted oxazolidin-2-yl.

60. The method of claim 46 wherein R* is a substituted or unsubstituted heteroaryl.

61. The method of claim 60 wherein said heteroaryl has the structure

or


wherein X = CH=CH, N=CH, NR^{17} (wherein R^{17} = H, alkyl, aryl or benzyl), O, or S

and wherein Y = CH or N

and wherein R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_uOH$ (where u = 1 to 3), $(CH_2)_vNR^{24}R^{25}$ (wherein R^{24} and R^{25} 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 and NO_2.

62. The method of claim 46 wherein said compound has the structure of compound 11, 12,13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24.

63. The method of claim 46 wherein said contacting occurs *in vivo*.

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64. The method of claim 46 wherein said virus is a member selected from the group consisting of hepatitis A – B, yellow fever, respiratory syncytial virus, influenza, human immunodeficiency virus I and 2, adenoviruses, Norwalk virus, herpes simplex virus 1 and 2, cytomegalovirus (HCMV), varicella zoster, Epstein- Barr virus, and other herpes viruses.

65. A method for treating a viral-caused disease in a patient afflicted therewith comprising administering to said patient a therapeutically effective amount of a compound of claim 46.

66. The method of claim 65 wherein said virus is a member selected from the group consisting of hepatitis A – B, yellow fever, respiratory syncytial virus, influenza, human immunodeficiency virus 1 and 2, adenoviruses, Norwalk virus, herpes simplex virus 1 and 2, cytomegalovirus (HCMV), varicella zoster, Epstein- Barr virus, and other herpes viruses.

67. The method of claim 65 wherein said compound has the structure of compound 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24.

68. A method for synthesizing a compound of claim 1.

69. A method for synthesizing a compound of claim 17.

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PATENT

Attorney Docket No.: 64507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Stephen J. Baker, *et al*

Application No.: 11/357,687

Filed: February 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Examiner: SHIAO, Rei Tsang

Confirmation No. : 4964

Technology Center/Art Unit: 1626

STATUS INQUIRY

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

Sir:

Applicants request the status of the above-identified U.S. patent application. An Information Disclosure Statement was filed on June 19, 2007 and received by the PTO on June 21, 2007. The last communication we received from the PTO was an official Filing Receipt which was mailed on April 3, 2006.

Respectfully submitted,

Todd Esker
Reg. No. 46,690

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Electronic Acknowledgement Receipt

EFS ID:	2704166
Application Number:	11357687
International Application Number:	
Confirmation Number:	4964
Title of Invention:	Boron-containing small molecules
First Named Inventor/Applicant Name:	Stephen J. Baker
Customer Number:	43850
Filer:	Jeffry S. Mann
Filer Authorized By:	
Attorney Docket Number:	64507-5014-US
Receipt Date:	11-JAN-2008
Filing Date:	16-FEB-2006
Time Stamp:	13:52:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for status of Application	StatusInquiry.pdf	10573 9dce85bd36fcf55395e3a9e7a16db2261dbcee94	no	1
Warnings:					
Information:					

Total Files Size (in bytes):	10573

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

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

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/357,687	02/16/2006	Stephen J. Baker	64507-5014-US	4964

43850 7590 03/06/2008

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EXAMINER	
SHIAO, REI TSANG	
ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
03/06/2008	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)	
	11/357,687	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 *1* 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 *16 February 2006*.

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) *1-39* 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) _____ is/are rejected.

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

8)☒ Claim(s) *1-39* 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 _____ 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 _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-39 are pending in the application.

Election/Restriction

2. The Markush group set forth in the claims includes both independent and distinct inventions, and patentably distinct compounds (or species) within each invention. However, this application discloses and claims a plurality of patentably distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentably distinct compounds, also far too numerous to list individually. For these reasons provided below, restriction to one of the following Groups is required under 35 U.S.C. 121, wherein a Group is a set of patentably distinct inventions of a broad statutory category (e.g. Compounds, Methods of Use, Methods of Making, etc.):

I. Claims 1-2 and 4-18, in part, drawn to compounds/compositions of formula (I) or (Ia), wherein the variable A1 represents CR^{9a}, D1 represents CR^{10a}, E1 represents CR^{11a} and G1 represents CR^{12a} and R^{9a}, R^{10a}, R^{11a}, R^{12a} independently does not represents heteroaryl or heterocycloalkyl thereof, R^{9a}, R^{10a}, R^{11a}, R^{12a} independently is not substituted with heteroaryl or heterocycloalkyl thereof; the variable M1 represents oxygen thereof; the variable J1 represents $(CR^{3a}R^{4a})_{n1}$ and n1 is 0; the variables R^{1a}-R^{12a} independently does not represents heteroaryl or heterocycloalkyl thereof, R^{1a}-R^{12a} independently is not substituted with heteroaryl or

heterocycloalkyl thereof, any two of the variables R^{1a}-R^{12a} together with the atoms to which they are attached do not form a ring thereof, classified in class 514/549 with various subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose.

II. Claims 1, 3 and 4-18, in part, drawn to compounds/compositions of formula (I) or (Ib), wherein the variable A1 represents CR^{9a}, D1 represents CR^{10a}, E1 represents CR^{11a} and G1 represents CR^{12a} and R^{9a}, R^{10a}, R^{11a}, R^{12a} independently does not represents heteroaryl or heterocycloalkyl thereof, R^{9a}, R^{10a}, R^{11a}, R^{12a} independently is not substituted with heteroaryl or heterocycloalkyl thereof; the variable M1 represents oxygen thereof; the variable J1 represents $(CR^{3a}R^{4a})_{n1}$ and n1 is 0; the variables R^{1a}-R^{12a} independently does not represents heteroaryl or heterocycloalkyl thereof, R^{1a}-R^{12a} independently is not substituted with heteroaryl or heterocycloalkyl thereof, any two of the variables R^{1a}-R^{12a} together with the atoms to which they are attached do not form a ring thereof, classified in class 514/548/549 with various subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose.

III. Claims 1-18, in part, drawn to compounds/compositions of formula (I), containing compounds not encompassed in Groups I-II, classified in class

514/544/546/548/549 with various subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose. This group is subject further restriction if it is elected.

IV. Claims 19-26, drawn to methods of use (i.e., killing microorganism), classified in class 514/540/544/546/548/549 with various subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose. This group is subject further restriction if it is elected.

V. Claims 27-36, drawn to methods of use (i.e., treating infection), classified in class 514/540/544/546/548/549 with various subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose. This group is subject further restriction if it is elected.

VI. Claims 37-38, drawn to processes of making, classified in class 514/540/544/546/548/549 with various subclasses. If this group is elected, applicants are requested to elect a single species for the search purpose. This group is subject further restriction if it is elected.

VII. Claim 39, drawn to methods of use (i.e., delivering a compound), classified in class 514/540/544/546/548/549 with various subclasses. If

this group is elected, applicants are requested to elect a single species for the search purpose. This group is subject further restriction if it is elected.

In accordance with the decisions in ***In re Harnisch***, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and ***Ex parte Hozumi***, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984), restriction of a Markush group is proper where the compounds within the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility. In addition, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the other member(s) obvious under 35 U.S.C. 103.

Where an election of any one of Groups I-VII is made, an election of a single compound or species is further required. Moreover, an election of a single compound is further required including an exact definition of each substitution on the base molecule, i.e., the formula (I), wherein a single member at each substituent group or moiety is selected. For example, if a base molecule has a substituent group R^{1a}, wherein R^{1a} is recited to be hydrogen or alkyl, etc., then applicant must select a single substituent of R^{1a}, for example hydrogen and each subsequent variable position. Should applicant traverse on the ground that the compounds are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the compounds to be obvious

variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C 103(a) of the other.

All compounds falling outside the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to nonelected subject matter and will be withdrawn from consideration under 35 U.S.C. 121 and 37 C.F.R. 1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. The provisions of 35 U.S.C. 121 apply with regard to double patenting covering divisional applications.

Applicant is reminded that upon cancellation of claims to a non-elected invention, the inventors must be amended in compliance with 37C.F.R. 1.48(b) if one of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. 1.48(b) and by the fee required under 37CFR 1.17(i). If desired upon election of a single compound, applicants can review the claims and disclosure to determine the scope of the invention and can **set forth** a group of compounds which are so similar within the same inventive concept and reduction to practice. Markush claims must be provided with support in the disclosure for each member of the Markush group. See MPEP 608.01(p). Applicant should exercise caution in making a selection of a single

member for each substituent group on the base molecule to be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

Each invention set listed above is directed to or involves the use or making of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP 806.04, MPEP 808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over either of the other inventions, i.e. they are patentable over each other. Chemical structures which are similar are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrebuttable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holdings of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

The above Groups represent general areas wherein the inventions are independent and distinct, each from the other because of the following reasons:

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to

petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention. Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Advisory of Rejoinder

3. The following is a recitation of M.P.E.P. §821.04, Rejoinder:

> Where product and process claims drawn to independent and distinct inventions are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or process. See MPEP § 806.05(f) and § 806.05(h). The claims to the nonelected invention will be withdrawn from further consideration under 37 CFR 1.142. See MPEP § 809.02 (c) and § 821 through § 821.03. However, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined.
>
> Where product and process claims are presented in a single application and that application qualifies under the transitional restriction practice pursuant to 37 CFR 1.129(b), applicant may either (1) elect the invention to be searched and examined and pay the fee set forth in 37 CFR 1.17(s) and have the additional inventions searched and examined under 37 CFR 1.129(b)(2), or (2) elect the invention to be searched and examined and not pay the additional fee (37 CFR 1.129(b)(3)). Where no additional fee is paid, if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims which either depend from or include all the limitations of the allowable product will be rejoined. If applicant chooses to pay the fees to have the additional inventions searched and examined pursuant to 37 CFR 1.129(b)(2), even if the product is found allowable, applicant would not be entitled to a refund of the fees paid under 37 CFR 1.129(b) by arguing that the process claims could have been rejoined. 37 CFR 1.26 states that "money paid by actual mistake or in excess will be refunded, but a mere change of purpose after the payment of money...will not entitle a party to demand such a return..." The fees paid under 37 CFR 1.129(b) were not paid by actual mistake nor paid in excess, therefore, applicant would not be entitled to a refund.

> In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104 - 1.106. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action.

The following is a recitation from paragraph five, "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. §103(b)" (1184 TMOG 86(March 26, 1996)):

> "However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim **depends from or otherwise includes all the limitations of** an allowed product claim. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined." (emphasis added)

Therefore, in accordance with M.P.E.P. §821.04 and In re Ochiai, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of product claims with process claims commensurate in scope with the allowed product claims will occur following a finding that the product claims are allowable. Until, such time, a restriction between product claims and process claims is deemed proper. Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution to maintain either dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

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 Patent Examiner
Art Unit 1626

February 27, 2008

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
11/357,687	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	2/27/08
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Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/357,687	BAKER ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

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Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/357,687	BAKER ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
restriction	2/27/2008	R.S.

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BIB DATA SHEET

CONFIRMATION NO. 4964

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/357,687	02/16/2006 RULE	514	1626	64507-5014-US

APPLICANTS

Stephen J. Baker, Mountain View, CA;
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Kirk R. Maples, San Jose, CA;
Jacob J. Plattner, Berkeley, CA;
Virginia Sanders, San Francisco, CA;
Yong-Kang Zhang, San Jose, CA;

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

This appln claims benefit of 60/654,060 02/16/2005

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **

03/30/2006

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	12	39	3

ADDRESS

MORGAN, LEWIS & BOCKIUS LLP (SF)
2 PALO ALTO SQUARE
3000 El Camino Real, Suite 700
PALO ALTO, CA 94306
UNITED STATES

TITLE

Boron-containing small molecules

FILING FEE RECEIVED		
1165	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Electronic Patent Application Fee Transmittal

Application Number:	11357687
Filing Date:	16-Feb-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:	64507-5014-US
Filed as Small Entity	

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	3	25	75
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	2252	1	230	230
Miscellaneous:				
		Total in USD ($)		**305**

Electronic Acknowledgement Receipt	
EFS ID:	3418516
Application Number:	11357687
International Application Number:	
Confirmation Number:	4964
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:	64507-5014-US
Receipt Date:	06-JUN-2008
Filing Date:	16-FEB-2006
Time Stamp:	16:55:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$305
RAM confirmation Number	2096
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	Fee Worksheet (PTO-06)	Trans.pdf	268321 e6c00b352d397f4a8ffc758056be64c6e97aa233	no	1
Warnings:					
Information:					
2	Extension of Time	EOT.pdf	229997 f6eca9c1857ae829810fa45b420d169e3caa6c5b	no	1
Warnings:					
Information:					
3		RESPONSRR.pdf	760125 9ebf53558177573426 43c8b5fdf509ffabf24760	yes	7

Multipart Description/PDF files in .zip description

Document Description	Start	End
Response to Election / Restriction Filed	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	7

Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	8308 d9bc3a68b6348fc2e3b4ad326398363608abb659	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1266751		

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.

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: 6/6/08

Signed: C. Rubalcaba-Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4964
Stephen J. BAKER, *et al.*	Examiner: SHIAO, Rei Tsang
Application No.: 11/357,687	Art Unit: 1626
Filed: February 16, 2006	RESPONSE TO RESTRICTION REQUIREMENT
For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

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

Sir:

In response to the Restriction Requirement dated March 6, 2008, 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.

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Amendments to the Claims:

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

Listing of Claims:

1 **1.** (Cancelled).

1 **2.** (Cancelled).

1 **3.** (Cancelled).

1 **4.** (Cancelled).

1 **5.** (Cancelled).

1 **6.** (Cancelled).

1 7. (Cancelled).

1 **8.** (Cancelled).

1 **9.** (Cancelled).

1 **10.** (Cancelled).

1 **11.** (Cancelled).

1 **12.** (Cancelled).

1 **13.** (Cancelled).

1 **14.** (Cancelled).

1 **15.** (Cancelled).

1 **16.** (Cancelled).

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17. (Cancelled).

18. (Cancelled).

19. (Cancelled).

20. (Cancelled).

21. (Cancelled).

22. (Cancelled).

23. (Cancelled).

24. (Cancelled).

25. (Cancelled).

26. (Cancelled).

27. (Currently amended) A method of treating or preventing an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof or a prodrug thereof. ~~the compound according to claim 1~~.

28. (Original) The method of claim **27**, wherein said infection is a member selected from a systemic infection, a cutaneous infection, and an ungual or periungual infection.

29. (Original) The method of claim **27**, 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

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 278 of 558

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.

30. (Original) The method of claim **27**, wherein said infection is onychomycosis.

31. (Original) The method of claim **27**, wherein said animal is a member selected from a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey.

32. (Cancelled).

33. (Cancelled).

34. (Cancelled).

35. (Cancelled).

36. (Cancelled).

37. (Cancelled).

38. (Cancelled).

39. (Cancelled).

40. (New) The method of claim **30**, wherein said onychomycosis is *Tinea unguium*.

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41. (New) The method of claim **27**, wherein said method is a method of treating an infection in an animal.

42. (New) The method of claim **27**, wherein said animal is a human.

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REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-39 are filed in the original application. Claims 1-39 are subject to a Restriction Requirement. After entry of this Response, claims 27-31 and 40-42 are pending. Claims 40-42 are new. Claims 27-31 and 40-42 are elected for prosecution on the merits. Claim 27 is amended. No new matter has been added.

Claims 1-26 and 32-39 are cancelled without prejudice. Applicants reserve the right to pursue these claims in another application, such as a continuation or a divisional.

II. Support for the amended claims and new claims

Support for amended claim 27 is provided in paragraphs 15-18, 32, 108 and 257. Support for new claim 40 is provided in paragraph 110. Support for new claim 41 is provided in paragraph 15. Support for new claim 42 is provided in paragraph 108. No new matter has been added.

II. Response to the Restriction Requirement

The Examiner has restricted the pending claims into the following seven groups:

Group #	Claim Numbers
I.	portions of 1-2 and 4-18
II.	portions of 1, 3 and 4-18
III.	portions of 1-18
IV.	19-26
V.	27-36 (and new claims 40-42)
VI.	37-38
VII.	39

The claims are restricted into seven groups. Applicants elect Group V for prosecution on the merits. Each of claims 27-31 and 40-42 fall within Group V.

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a.) Election of Species

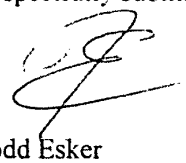
Applicants have been asked to elect one compound as a starting point from which the Examiner will search the prior art. Applicants elect 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

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,



Todd Esker
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1-SF/7711553.1

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 282 of 558

FEE TRANSMITTAL for FY 2007

Effective 10/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT | ($) 305

Complete if Known	
Application Number	11/357,687
Filing Date	02/16/2006
First Named Inventor	Stephen J. Baker
Examiner Name	SHIAO, Rei Tsang
Art Unit	1626
Attorney Docket No.	064507-5014-US

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 50-0310

Deposit Account Name: Morgan, Lewis & Bockius LLP

The Director is authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1011	310	2011	155	Utility filing fee	
	N/A	4011	75	E-file Utility filing fee	
1002	210	2002	105	Design filing fee	
1003	210	2003	105	Plant filing fee	
1004	310	2004	155	Reissue filing fee	
1005	210	2005	105	Provisional filing fee	
1111	510	2111	255	Utility Search Fee	
13411	210	2311	105	Utility Examination Fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below	Fee Paid
Total Claims	42	-39 =	3	X	25 =	75
Independent Claims		-3 =		X	=	
Multiple Dependent				X	=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	50	2202	25	Claims in excess of 20
1201	210	2201	105	Independent claims in excess of 3
1203	370	2203	185	Multiple dependent claim, if not paid
1204	210	2204	105	** Reissue independent claims over original patent
1205	50	2205	25	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	120	2251	60	Extension for reply within first month	
1252	460	2252	230	Extension for reply within second month	230
1253	1,050	2253	525	Extension for reply within third month	
1254	1,640	2254	820	Extension for reply within fourth month	
1255	2,230	2255	1,115	Extension for reply within fifth month	
1401	510	2401	255	Notice of Appeal	
1402	510	2402	255	Filing a brief in support of an appeal	
1403	1,030	2403	515	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	510	2452	255	Petition to revive – unavoidable	
1453	1,540	2453	770	Petition to revive – unintentional	
1501	1,440	2501	720	Utility issue fee (or reissue)	
1502	820	2502	410	Design issue fee	
1503	1,130	2503	565	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Petitions related to provisional applications	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	810	2809	405	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	810	2810	405	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	810	2801	405	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
1081	260	2081	130	Utility Application Size Fee – for each additional 50 sheets that exceeds 100 sheets	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($)230

SUBMITTED BY *Complete (if applicable)*

Name (Print/Type)	Todd Esker	Registration No. (Attorney/Agent)	46,690	Telephone	(415) 442-1000
Signature				Date	June 6, 2008

1-SF/7712415.1

PTO/SB/22 (01-08)
Doc Code: Approved for use through 01/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2008 *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) 064507-5014-US
Application Number 11/357,687	Filed 02/16/2006
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))	$120	$60	$____
☒	Two months (37 CFR 1.17(a)(2))	$460	$230	$230
☐	Three months (37 CFR 1.17(a)(3))	$1050	$525	$____
☐	Four months (37 CFR 1.17(a)(4))	$1640	$820	$____
☐	Five months (37 CFR 1.17(a)(5))	$2230	$1115	$____

☒ 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 500310. I have enclosed a duplicate copy of this sheet.

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 — June 6, 2008 — Date

Todd Esker — Typed or printed name — 415-442-1304 — 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.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 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.**

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

1-SF/7659282.1

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
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/357,687	02/16/2006	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ 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

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT	06/06/2008	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 39	= 0	X $25 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $105 =	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	

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

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

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

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

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

Legal Instrument Examiner:
/ROSA M. HOLLAND/

This collection of information is required by 37 CFR 1.16. 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, 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.**

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

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/357,687	02/16/2006	Stephen J. Baker	64507-5014-US	4964

43850 7590 08/26/2008

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	

MAIL DATE	DELIVERY MODE
08/26/2008	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)	
	11/357,687	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 *06 June 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) *27-31 and 40-42* 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) *27-31 and 40-42* 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 February 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 *5/07/07,6/21/07*.
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: 60/654,060 with a filing date 02/16/2005.

2. Amendment of claims 27, cancellation of claims 1-26 and 32-39, and addition of claims 40-42 in the amendment filed on June 06, 2008 is acknowledged. Claims 27-31 and 40-42 are pending in the application. No new matter is found. Since the newly added claims 40-42 are commensurate with the scope of the invention, claims 27-31 and 40-42 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 V claims 27-36 (now are 27-31 and 40-42) in the reply filed on June 06, 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 27-31 and 40-42 are pending in the application. The scope of the invention of the elected subject matter is as follows.

Claims 27-31 and 40-42 are drawn to methods of use using a compound 1, 3-dihydro-5-fluoro- 1-hydroxy-2, 1-benzoxaborole.

Claims 27-31 and 40-42 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.

5.1 Claims 27-31 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the instant compound for treating fungal infection, it does not reasonably provide enablement for using the instant compound for preventing infection, see claim 27. 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. Dependent claims 28-31 and 40-42 are also rejected along with claim 27 under 35 U.S.C. 112, first paragraph.

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 of claims 27-31 and 40-42 is drawn to intent methods of use using the instant compound for treating or preventing infection without limitation (I.e., no named infection), see claim 27.

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

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833,166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Adams et al. US 6,083,903 disclose similar boron compounds for treating HIV infection. Applicants are claiming intent methods of use using the instant compound effective to "treating or preventing infection" without limitation. As such, the specification fails to enable the skilled artisan to use the compounds of claims 27-31 and 40-42 effective to "treating or preventing infection" without limitation.

In addition, there is no established correlation between *in vitro* activity and accomplishing treatment of "treating or preventing disorders *in vitro* or *in vivo* "treating or preventing infection" without limitation, *in vivo*, and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success, and those skilled in the ad would not be able to use the instant compound since there is no description of an actual method wherein "treating or preventing infection" without limitation in a host is treated or prevented.

Hence, one of skill in the art is unable to fully predict possible results from the administration of the compounds of claims 27-31 and 40-42 due to the unpredictability of the "treating or preventing infection" without limitation. The treating or preventing infection" without limitation is known to have many obstacles that would prevent one of ordinary skill in the art from accepting treating or preventing regimen on its face.

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 the listing of exemplary assays of inhibiting fungal growth, , see Fig.1 - Fig.9 There are no *in vivo* working examples present for the prevention of infection by the administration of compounds of the instant invention.

The breadth of the claims

The breadth of the claims is methods of use using the instant compound effective to "treating or preventing infection" without limitation.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what "treating or preventing infection" without limitation would be benefited (i.e., prevented) by the administration of the instant compounds of the instant invention and would furthermore then have to determine which of the claimed methods of use would provide prevention of infection, if any.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to

determine which methods of use exhibit the desired pharmacological activity and which diseases would benefit from this activity. Thus, the specification fails to provide sufficient support of the broad use of the pharmaceutical compounds of the instant claims 27-31 and 40-42 for the “treating or preventing infection”. As a result necessitating one of skill to perform an exhaustive search for which “treating or preventing infection”, can be treated or prevented by what pharmaceutical compounds of the instant claims in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that “ a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation, with no assurance of success. This rejection can be overcome by incorporation of the limitation “fungal infection” into claim 27 and deletion of the limitation “preventing” from claim 27 respectively, would obviate the rejection.

5.2. Claims 27-31 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutically acceptable salts of the instant compound of claim 27, 1,3-dihydro-5-fluoro- 1-hydroxy-2,1-benzoxaborole, does not reasonably provide enablement for the prodrug of the instant compound of

claim 27, see claim 27. 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. Dependent claims 28-31 and 40-42 are also rejected along with claim 27 under 35 U.S.C. 112, first paragraph.

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. 1 12, 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.

The nature of the invention

The nature of the invention is the intent method of use using the compound of claim 27, i.e., 1,3-dihydro-5-fluoro- 1-hydroxy-2,1-benzoxaborole , their prodrugs or pharmaceutically acceptable salts thereof.

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

The state of the prior art is that pro-drugs are inactive substances that are converted to a drug within the body by enzymes or other chemicals. Prodrugs can be formed by various mechanisms and vary depending on the functional groups present in the parent compound, i.e. different prodrugs would arise from parent compounds containing varying functional groups, such as a carboxylic acid, ester, an alcohol or an amine, all of which would require differing mechanism.

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 the Compound of claim 27 and their pharmaceutically acceptable salts of the compounds. There is no data present in the instant specification for the preparation of constitutional prodrugs of the instant compound of claim 27.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include any prodrugs, i.e. any compound of claim 27 with various functional groups, no matter what the chain length and any covalently bonded compound that would release the active parent compound.

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

While the level of the skill in the pharmaceutical arts is high, it would require

undue experimentation of one of ordinary skill in the art to prepare any prodrug of claim 27 as instantly claimed since a pro-drug of the compounds of claim 27 can have varying functional groups in varying positions. It would also require undue experimentation to prepare any covalently bonded compound that would release the active parent drug since pro-drugs are formed by varying mechanisms and depend on the functional groups of the parent compound. The only guidance present in the instant specification is for the compounds of claim 27 and their pharmaceutically acceptable salts thereof. There is no guidance or working examples present for constitutional prodrugs of claim 27. Therefore, the claims lack enablement for all prodrugs of the compounds of claim 27. This rejection can be overcome by deleting the limitation “prodrug" from the instant claims.

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 27-31 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Austin et al. CAS: 124:234024 or see US 5,880,188 in view of fungicide: definition from Answre.com.

Applicants claim methods of use (i.e., treating infection) in an animal using 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, see claim 27.

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

Austin et al. disclose 5- and 6-fluoro or bromo-1,3-dihydro-1-hydroxy-2,1-benzoxaborole as fungicide for agriculture, see Austin et al. CAS: 124:234024.

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.

Fungicide: definition from Answre.com discloses fungicide can be used for agriculture or pharmaceutical industry, i.e., for human fungal infections. Austin et al. methods of use and teachings of fungicide: definition from Answre.com 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 27-31 and 40-42 prima facie obvious because one would be motivated to employ the methods of use of Austin et al. and teachings of fungicide: definition from Answre.com to obtain instant methods of use using 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole for treating infection (i.e., fungal infection) in animals. Dependent claims 28-31 and 40-42 are also rejected along with claim 27 under 35 U.S.C. 103(a).

The motivation to make the claimed compounds derived from the known compounds as fungicide of Austin et al. and teachings of Answre.com would possess similar activity (i.e., treating fungal infection) to that which is claimed in the reference.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with37 CFR 3.73(b).

Claim 27-31 and 40-42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 53-54 and 58 of Baker et al. co-pending application No. 11/505,591. Although the conflicting claims are not identical, they are not patentably distinct from each other and reasons are as follows.

Applicants claim methods of use (i.e., treating infection) using 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, see claims 27.

Baker et al. et al. '591 claim methods of use (i.e., treating microorganism) using compounds of formula (I) or s compound 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, see claim 54 or 58.

The difference between the instant claims and Baker et al. et al. is that the instant claims are using a compound 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, while Baker et al. using compound of formula (I) or a compound 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. Baker et al. methods of use inherently overlap with the instant invention.

One having ordinary skill in the art would find the instant claims 27-31 and 40-42 prima facie obvious **because** one would be motivated to employ the methods of use of BAker et al. '591 to obtain the instant methods of use using a compound 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole or its pharmaceutical salt .

The motivation to obtain the claimed catalyst derives from known Baker et al. methods of use would possess similar activity (i.e., treating fungus) to that which is claimed in the reference.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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 Patent Examiner
Art Unit 1626

August 21, 2008

Notice of References Cited	Application/Control No. 11/357,687	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-6,083,903	07-2000	Adams et al.	514/2
	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	fungicide: definition from Answre.com, 1998.
	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.

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BIB DATA SHEET

CONFIRMATION NO. 4964

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/357,687	02/16/2006 RULE	514	1626	64507-5014-US

APPLICANTS

Stephen J. Baker, Mountain View, CA;
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Virginia Sanders, San Francisco, CA;
Yong-Kang Zhang, San Jose, CA;

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

This appln claims benefit of 60/654,060 02/16/2005

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **

03/30/2006

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	12	~~39~~ 8	3

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

TITLE

Boron-containing small molecules

FILING FEE RECEIVED		
1240	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

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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	11/357,687
Filing Date	February 16, 2006
First Named Inventor	Baker, Stephen J.
Art Unit	1626
Examiner Name	~~Balasubramanian, V.~~ REitsang Shiao
Attorney Docket Number	64507-5014-US

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/ (08/20/2008)	Date Considered	

1-SF/7542387.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /RS/

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/357,687	BAKER ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/357,687	BAKER ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

SEARCHED			
Class	Subclass	Date	Examiner
514	64	8/21/2008	R.S.
558	288	8/21/2008	R.S.

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STN structure, inventor names	7/7/2008	R.S.
EAST class/subclass	8/21/2008	R.S.
PALM inventor names	8/21/2008	R.S.

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
11/357,687	BAKER ET AL.
Examiner	**Art Unit**
REI-TSANG SHIAO	1626

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
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Claim		Date
Final	Original	8/21/08
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/440,839
Filing Date	February 16, 2006
First Named Inventor	Baker, Stephen J.
Art Unit	1626
Confirmation No.	4964
Examiner Name	~~Balasubramanian, V.~~ REitsang Shiao
Attorney Docket Number	64507-5014-US

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/ (08/20/2008)	Date Considered	

1-SF/7564834.1 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /RS/

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	523	(514/64).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2008/08/21 14:05
L3	141	(558/288).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2008/08/21 14:06

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PATENT

Attorney Docket No.: 064507-5014-US00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Stephen J. BAKER, *et al.*

Application No.: 11/357,687

Filed: February 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Confirmation Number: 5739

Examiner: SHIAO, Rei Tsang

Technology Center/Art Unit: 1626

LETTER TO EXAMINER AND STATEMENT OF RELATEDNESS

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

Sir:

In view of *McKesson Information Solutions v. Bridge Medical* (Fed. Cir. 2007), Applicants wish to inform the Examiner (as required under MPEP 2001.06(b)) that this case is related to:

U.S. Application Serial No. **10/868,268**, filed **June 15, 2004**;

U.S. Application Serial No. **12/270,636**, filed **November 13, 2008**;

U.S. Application Serial No. **11/743,665**, filed **May 2, 2007**;

U.S. Application Serial No. **11/505,591**, filed **August 16, 2006**;

U.S. Application Serial No. **11/676,120**, filed **February 16, 2007**;

U.S. Application Serial No. **11/762,038**, filed **June 12, 2007**;

U.S. Application Serial No. **11/153,010**, filed **June 14, 2005**;

U.S. Application Serial No. **11/865,725**, filed **October 1, 2007**;

U.S. Application Serial No. **12/142,692**, filed **June 19, 2008**;

The Examiner is encouraged to review the art made of record, any Office Action, and any Notice of Allowance in the above-mentioned related application. Applicants assume that due to the ease of review on PAIR by the Examiner, Applicant need not submit copies of the individual Office Actions and/or Notices of Allowance. Applicants assume that the Examiner is aware that prosecution is ongoing in the above-referenced case, and that the Examiner will continue to evaluate this case as needed.

The Examiner is invited to contact the undersigned at (415) 442-1000.

Respectfully submitted,

Date: December 4, 2008

Todd Esker, Reg. No. 46,690

MORGAN, LEWIS & BOCKIUS LLP
One Market, Spear Street Tower
San Francisco, California 94105
(415) 442-1000

DB2/20925053.1

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 312 of 558

Electronic Acknowledgement Receipt

EFS ID:	4407336
Application Number:	11357687
International Application Number:	
Confirmation Number:	4964
Title of Invention:	Boron-containing small molecules
First Named Inventor/Applicant Name:	Stephen J. Baker
Customer Number:	43850
Filer:	Jeffry S. Mann
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4964
Stephen J. BAKER, *et al.*	Examiner: SHIAO, Rei Tsang
Application No.: 11/357,687	Art Unit: 1626
Filed: February 16, 2006	RESPONSE TO FIRST OFFICE ACTION
For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

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

Sir:

In response to the First Office Action dated August 26, 2008, 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 **4** of this paper.

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Amendments to the Claims:

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

Listing of Claims:

1. – 26. (Cancelled).

27. (Currently amended) A method of treating ~~or preventing~~ an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof ~~or a prodrug thereof~~., sufficient to treat said infection.

28. (Original) The method of claim **27**, wherein said infection is a member selected from a systemic infection, a cutaneous infection, and an ungual or periungual infection.

29. (Original) The method of claim **27**, 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.

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30. (Original) The method of claim **27**, wherein said infection is onychomycosis.

31. (Original) The method of claim **27**, wherein said animal is a member selected from a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey.

32. – 39. (Cancelled).

40. (Currently amended) The method of claim **30**, wherein said onychomycosis is ~~*Tinea unguium*~~ tinea unguium.

41. (Cancelled).

42. (Previously presented) The method of claim **27**, wherein said animal is a human.

43. (New) The method of claim **27**, wherein the administering is at a site which is a member selected from the skin, nail, hair, hoof and claw.

44. (New) The method of claim **43**, wherein said skin is the skin surrounding the nail, hair, hoof or claw.

45. (New) The method of claim **27**, wherein said infection is a fungal infection.

46. (New) A method of treating onychomycosis in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said onychomycosis.

47. (New) A method of inhibiting the growth of a fungus in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof.

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REMARKS/ARGUMENTS

I. Status of the Claims

After entry of this Response, claims 27-31, 40 and 42-47 are pending. Claims 1-26, 32-39 and 41 are cancelled without prejudice. Claims 43-47 are new. Claims 27-31 and 40 and 42-47 are currently presented. Claim 27 is amended. No new matter has been added.

II. Support for the amended claims and new claims

Claim 27 is amended to add the phrase "sufficient to treat said infection". Support for this amendment is provided in paragraph 108.

Support for new claim 43 is provided in paragraphs 108 and 109.

Support for new claim 44 is provided in paragraph 109.

Support for new claim 45 is provided in paragraphs 102, 103 and 108-116 and Fig. 2.

Support for new claim 46 is provided in paragraphs 108, 109 and 258.

Support for new claim 47 is provided in paragraphs 102, 103, 317, 320-323, 324-334, 335-371, 372-381.

No new matter has been added.

III. Response to the rejections

35 U.S.C. § 112, first paragraph, enablement (5.1)

Claims 27-31 and 40-42 are rejected for lacking enablement because the specification, while being enabling for using the compounds of claim 27 for treating fungal infections, allegedly does not reasonably provide enablement for using the compounds of claim 27 for preventing infection.

Solely to expedite prosecution, Applicants have amended claim 27 to remove the phrase 'or preventing'. Applicants reserve the right to pursue this subject matter in another application, such as a continuation or a divisional.

In light of this amendment, Applicants respectfully request withdrawal of the rejection.

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35 U.S.C. § 112, first paragraph, enablement (5.2)

Claims 27-31 and 40-42 are rejected for lacking enablement because the specification, while being enabling for pharmaceutically acceptable salts of the compounds of claim 27, allegedly does not reasonably provide enablement for prodrugs of the compounds of claim 27.

Solely to expedite prosecution, Applicants have amended claim 27 to remove the term 'or a prodrug thereof'. Applicants reserve the right to pursue this subject matter in another application, such as a continuation or a divisional.

In light of this amendment, Applicants respectfully request withdrawal of the rejection.

35 U.S.C. § 103(a)

Over Austin in view of Answers.com

Claims 27-31 and 40-42 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Austin et al., CAPlus Document No. 124:234024 (Accession No. 1996:181598) or US Patent 5,880,188 ("Austin") in view of "Fungicide," Answers.com. Reference to "Answers.com" herein refers to Exhibit A, showing the record accessed December 17, 2008, for "fungicide" on Answers.com.

Austin in view of Answers.com does not teach or suggest the invention as claimed. Austin 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

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> 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. Austin therefore is specifically directed to industrial uses of benzoxaboroles.

In contrast, claim 27 recites a method of treating an infection in an animal comprising administering to an animal a specific compound recited in the claim. 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, Answers.com, cited by the Examiner, 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. Austin, cited by the Examiner, teaches the use of oxaboroles in treating plastics and materials and in other industrial settings, and there is no

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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.

Answers.com thus does not provide a motivation to modify the teachings of Austin to use any particular oxaborole to treat an animal, and in fact teaches away from such modification. The Examiner has not established a prima facie case of obviousness. Withdrawal of the rejection is therefore respectfully requested.

Double Patenting

The Examiner has provisionally rejected claims 27-31 and 40-42 as allegedly being unpatentable over claims 53, 54 and 58 of Application No. 11/505,591 on the ground of nonstatutory obviousness-type double patenting. Claims 53, 54 and 58 have been canceled in Application No. 11/505,591, as shown in the accompanying restriction requirement response filed on December 3, 2008 (Exhibit B). As the claims at issue from Application No. 11/505,591 are no longer pending, Applicants respectfully request withdrawal of the rejection.

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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EXHIBIT A

Answers.com®

fungicide

Dictionary:

fungicide

(fŭn'jĭ-sīd', fŭng'gĭ-)

n.

A chemical substance that destroys or inhibits the growth of fungi.

fungicidal **fun'gi·cid'al** (-sīd'l) *adj.*
fungicidally **fun'gi·cid'al·ly** *adv.*

Encyclopedia of Public Health: Fungicides

Fungicides are a class of pesticides that are marketed specifically for the purpose of killing or inhibiting the growth of fungus. Fungus are defined under the Federal Insecticide, Fungicide, and Rodenticide Act as "any non-chlorophyllbearing thallophyte (that is, any non-chlorophyllbearing plant of a lower order than mosses and

Table 1

Classes of Fungicides, with Examples

Class of Fungicide	Examples
Substituted Benzenes	Chloroneb, chlorothalanil, Hexachlorobenzene, pentachloronitrobenzene
Thiocarbamates	Ferbam, metam sodium, thiram, ziram
Ethylene Bis Dithiocarbamates (EBDC's)	Mancozeb, maneb, nabam, zineb
Thiophthalimides	Captan, captafol, folpet
Copper compounds	
Organomercury compounds	Ethyl mercury, methyl mercury, phenyl mercuric acetate
Organotin compounds	Fentin, triphenyl tin
Cadmium compounds	
Miscellaneous organic fungicides	Benomyl, cyclohexamide, iprodione, metalaxyl, thiabendazole, triadimefon

SOURCE: Courtesy of author.

liverworts), as, for example, rust, smut, mildew, mold, yeast, and bacteria, except those on or in

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living man or other animals and those on or in processed food, beverages, or pharmaceuticals." Although the United States statutory definition excludes fungi that would grow on food, beverages, and pharmaceuticals, biologically these are fungi. Thus, in the United States, products designed to kill fungi are regulated by the U.S. Environmental Protection Agency as pesticides and/or by the Food and Drug Administration under food and drug law (a chemical may fall under the purview of both agencies).

The benefits of fungicide use have been many. In agriculture, fungicides control pests that may rob water and nutrients from crop plants or may cause food spoilage as the products are brought to market. Fungicides may also prevent the growth of fungi that produce toxins, such as aflatoxins. Fungicides also have important industrial applications and are important in preserving the purity and safety of certain pharmaceutical agents.

In 1997 there were an estimated $0.8 billion in sales of fungicides in the United States, about 7 percent of the total pesticide market. In 1997, worldwide, 5.7 billion pounds of pesticides were used, of which 0.5 billion were fungicides. Of the1.2 billion pounds of conventional pesticides used in the United States in 1997, a total of 81 million pounds of fungicides were used; 79 percent of the use was in agriculture. Generally, the United States has experienced a downward trend in total fungicide use since 1970.

There are numerous classes of fungicides, with different modes of action as well as different potentials for adverse effect on health and the environment (see Table 1). 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.

Organic mercurials have caused severe acute and chronic toxicity. Worldwide, there have been a number of incidents of treated seed grain fed to people, with disastrous consequences in terms of acute poisoning and damage to fetuses. Phenyl mercuric acetate is no longer used as a paint preservative in the United States because it off-gases elemental mercury into the air, with the potential for causing toxicity to young children. Organotin compounds also have serious human toxicity and are very toxic to the environment; their use is banned or severely restricted in most of the world. Likewise, due to human toxicity concerns, cadmium is no longer used as a fungicide in the United States.

(SEE ALSO: *Mercury; Pesticides; Toxic Substances Control Act; Toxicology*)

Bibliography

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— *LYNN R. GOLDMAN*

Britannica Concise Encyclopedia: fungicide

Any toxin used to kill or inhibit growth of fungi (*see* fungus) that cause economic damage to crop

or ornamental plants (including rusts in cereals, blight in potatoes, mildew in fruits) or endanger the health of domestic animals or humans. Most are applied as sprays or dusts; seed fungicides are applied as a protective coating to seeds before germination. Copper compounds, especially copper sulfate mixed with lime and water (Bordeaux mixture), and sulfur have long been used for this purpose, but now synthetic organic compounds are commonly used. Many antifungal substances occur naturally in plant tissues.

For more information on fungicide, visit Britannica.com.

Architecture: fungicide

A substance that is poisonous to fungi; retards or prevents the growth of fungi.

Columbia Encyclopedia: fungicide
(fŭn'jəsīd', fŭng'gə-) , any substance used to destroy fungi. Some fungi are extremely damaging to crops (see diseases of plants), and others cause diseases in humans and other animals (see fungal infection).

Surface fungicides, which keep harmful fungi from penetrating the tissues of a plant, include inorganic and organic compounds. Sulfur compounds, long used on plants, have been supplemented for some time by other chemicals, especially by compounds of copper, such as Bordeaux mixture. After 1945, organic salts of iron, zinc, and mercury were synthesized as fungicides. Most post-1965 fungicides are systemic, acting directly on fungal cells. Antifungal drugs, such as miconazole and terbinafine, are used for human fungal infections.

Plant fungicides are usually applied by spraying or dusting, but some types are applied to seeds and soil for the destruction of vegetative spores. Fungicides used on wood, including creosote, prevent dry rot, and certain compounds are used to make fabrics resistant to mildews. Most agricultural fungicides are preventive; those applied after infection are called eradicant, or contact, fungicides.

In the United States, fungicides are governed by the 1972 federal Environmental Protection and Control Act. They must be registered with the Environmental Protection Agency and must conform to specifications. They must control the disease without injuring the plant and must leave no poisonous residue on edible crops. Antifungal drugs are approved by the Food and Drug Administration.

See also pesticide.

Veterinary Dictionary: fungicide

An agent that destroys fungi.

Gardener's Dictionary: fungicide

A compound that inhibits the growth of fungal organisms. Fungicides rarely kill fungi and are more useful as a preventive than as a cure.

Wikipedia: Fungicide

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Fungicides are chemical compounds or biological organisms used to kill or inhibit fungi or fungal spores. Fungi are capable of causing serious damage in agriculture, resulting in critical losses of yield, quality and profit. Although similar, oomycetes are not fungi. However, they use the same mechanisms to infect plants.[1] Consequently, in the study of plant disease (phytopathology), chemicals used to control oomycetes are also referred to as fungicides. As well as in agriculture, fungicides are used to fight fungal infections in animal tissue.

Fungicides can either be contact or systemic. A contact fungicide kills fungi when sprayed on its surface; a systemic fungicide has to be absorbed by the plant.

The majority of fungicides that can be bought retail are sold in a liquid form. The most common active ingredient is sulfur, running at 0.08% for the weaker concentrates, and has high as 0.5% for the more potent fungicides. In powdered form, the concentration is usually around 90%, and the product is very toxic.

Other active ingredients in different brands include neem oil, rosemary oil, jojoba oil, and the bacterium *Bacillus subtilis*.

Fungicide residues have been found on food for human consumption, mostly from post-harvest treatments.[2] Some fungicides are dangerous to human health, such as vinclozolin, which has now been removed from use.[3]

Contents

[hide]

Natural fungicides

Plants and other organisms over time have developed chemical defenses, (via natural selection), which give them an advantage against microorganisms such as fungi. Some of these compounds can be used as fungicides.

- Tea tree oil
- Cinnamaldehyde[4]
- Cinnamon essential oil[5]
- Jojoba oil is fungicide, and can be used for controlling mildew.[6]
- Neem oil
- Rosemary oil

Whole live or dead organisms that are efficient at killing or inhibiting fungi can sometimes be used as fungicides:

- The bacterium *Bacillus subtilis*
- Kelp (powdered dried kelp is fed to cattle to protect them from fungi in grass)

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Fungicide resistance

Pathogens respond to the use of fungicides by evolving resistance. In the field several mechanisms of resistance have been identified. The evolution of fungicide resistance can be gradual or sudden. In qualitative or discrete resistance a mutation (normally to a single gene) produces a race of a fungus with a high degree of resistance. Such resistant varieties also tend to show stability, persisting after the fungicide has been removed from the market. For example sugar beet leaf blotch remains resistant to azoles years after they were no longer used for control of the disease. This is because such mutations often have a high selection pressure when the fungicide is used, but there is low selection pressure to remove them in the absence of the fungicide.

In instances where resistance occurs more gradually a shift in sensitivity in the pathogen to the fungicide can be seen. Such resistance is polygenic - an accumulation of many mutation in different genes each having a small additive effect. This type of resistance is known as quantitative or continuous resistance. In this kind of resistance the pathogen population will revert back to a sensitive state if the fungicide is no longer applied.

Little is known about how variations in fungicide treatment affect the selection pressure to evolve resistance to that fungicide. Evidence shows that the doses that provide the most control of the disease also provide the largest selection pressure to acquire resistance, and that lower doses decreased the selection pressure.[7]

In some cases when a pathogen evolves resistance to one fungicide it automatically obtains resistance to others - a phenomenon known as cross resistance. These additional fungicides are normally of the same chemical family or have the same mode of action, or can be detoxified by the same mechanism. Sometimes negative cross resistance occurs, where resistance to one chemical class of fungicides leads to an increase in sensitivity to a different chemical class of fungicides. This has been seen with carbendazim and diethofencarb.

There are also recorded incidences of pathogens evolving multiple drug resistance - resistance to two chemically different fungicides by separate mutation events. For example *Botrytis cinerea* is resistant to both azoles and dicarboximide fungicides.

There are several routes by which pathogens can evolve fungicide resistance. The most common mechanism appears to be alternation of the target site, particular as a defence against single site of action fungicides. For example Black Sigatoka, an economically important pathogen of banana, is resistant to the QoI fungicides, due to a single nucleotide change resulting one amino acid (glycine) being replaced by another (alanine) in the target protein of the QoI fungicides, cytochrome b.[8] This presumably disrupts the binding of the fungicide to the protein, rendering the fungicide ineffective.

Upregulation of target genes can also render the fungicide ineffective. This is seen in DMI resistant strains of *Venturia inaequalis*.[9]

Resistance to fungicides can also be developed by efficient efflux of the fungicide out of the cell. *Septoria tritici* has developed multiple drug resistance using this mechanism. The pathogen had 5 ABC type transporters with overlapping substrate specificities that together work to effectively pump toxic chemicals out of the cell.[10]

In addiction to the mechanisms outlined above, fungi may also develop metabolic pathways that circumvent the target protein, or acquire enzymes that enable metabolism of the fungicide to a harmless substance.

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Fungicide resistance management

The fungicide resistance action committee (FRAC) has several recommended practices to try to avoid the development of fungicide resistance, especially in at-risk fungicides including *Strobilurins* such as azoxystrobin.

Products should not be used in isolation but rather as mixture, or alternate sprays, with another fungicide with a different mechanism of action. The likelihood of the pathogen developing resistance is greatly decreased by the fact that any resistant isolates to one fungicide will hopefully be killed by the other - in other words two mutations would be required rather than just one. The effectiveness of this technique can be demonstrated by Metalaxyl. When used as the sole product in Ireland to control potato blight (*Phytophthora infestans*) resistance developed within one growing season. However in countries like the UK where it was only ever marketed as a mixture resistance problems were not seen.

Fungicides should only be applied when absolutely necessary, especially if they are in an at-risk group. Lowering the amount of fungicide in the environment lowers the selection pressure for resistance to develop.

Manufacturers' doses should always be followed. These doses are normally designed to give the right balance between controlling the disease and limiting the risk of resistance development. Higher doses increase the selection pressure for single site mutations that confer resistance, as all strains but those that carry the mutation will be eliminated, and thus the resistant strain will propagate. Lower doses greatly increase the risk of polygenic resistance, as strains that are slightly less sensitive to the fungicide may survive.

It is also recommended that where possible fungicides are only used in a protective manner, rather than to try to cure already infected crops. Far fewer fungicides have curative/eradicative ability than protectant. Thus fungicide preparations advertised as having curative action may only have one active chemical; a single fungicide acting in isolation increases the risk of fungicide resistance.

It is better to use an integrative pest management approach to disease control, rather than relying on fungicides alone. This involves the use of resistant varieties and hygienic practises, such as the removal of potato discard piles and stubble on which the pathogen can overwinter, greatly reduce the titre of the pathogen and thus the risk of fungicide resistance development.

See also

- Antifungal drug
- List of fungicides
- Pesticide application
- Phytopathology
- Plant disease forecasting

External links

- Fungicide Resistance Action Group
- General Pesticide Information - National Pesticide Information Center

References

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This article needs additional citations for verification.
Please help improve this article by adding reliable references. Unsourced material may be challenged and removed. *(January 2008)*

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10. ^ Zwiers, L. H. *et al.* (2003) ABC transporters of the wheat pathogen Mycosphaerella graminicola function as protectants against biotic and xenobiotic toxic compounds *Molecular Genetics and Genomics* **269**:499-507

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EXHIBIT B

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Attorney Docket No.: 064507-5014-US01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Stephen J. BAKER, *et al.*

Application No.: 11/505,591

Filed: August 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Confirmation No.: 5739

Examiner: SHIAO, Rei Tsang

Art Unit: 1626

RESPONSE TO RESTRICTION REQUIREMENT

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

Sir:

In response to the Restriction Requirement dated July 3, 2008, 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.

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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. (Currently amended) A ~~unit dosage~~ 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.

~~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. – 192. (Cancelled).

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

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

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

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197. (New) 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. (New) 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. (New) 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. (New) 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. (New) 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. (New) 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. (New) The formulation of claim **121**, wherein said formulation is in a cosmetically effective amount.

204. (New) 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. (New) The formulation of claim **121**, wherein the microorganism is a fungus or a yeast.

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206. (New) 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. (New) 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. (New) 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. (New) The formulation of claim **205**, wherein said fungus or yeast is a dermatophyte.

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

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

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

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

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

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REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-192 are filed in the original application. Claims 1-192 are subject to a Restriction Requirement. After entry of this Response, claims 121, 193-214 are pending and elected for prosecution on the merits. Claims 193-214 are new. Claim 121 is amended. No new matter has been added.

Claims 1-120, 122-192 are cancelled without prejudice. Applicants reserve the right to pursue these claims in another application, such as a continuation or a divisional.

II. Support for the amended and new claims

Support for amended claim 121 is provided in paragraphs 279-280, 286, 326, 355, 367, 377-410, 465, and Example 46.

Support for new claim 193 is provided in paragraphs 374 and 379-383. Support for new claim 194 is provided in paragraph 374. Support for new claim 195 is provided in paragraphs 385-401 and 411-419. Support for new claims 196-200 is provided in paragraph 374. Support for new claim 201 is provided in paragraph 410. Support for new claim 202 is provided in paragraph 348. Support for claim 203 is provided in paragraph 423. Support for claim 204 is provided in paragraph 288. Support for new claims 205-209 are provided in paragraphs 280-281. Support for new claim 210 is provided in paragraph 289. Support for new claim 211 is provided in paragraph 286. Support for new claim 212 is provided in paragraphs 286-295. Support for new claim 213 is provided in paragraph 323. Support for new claim 214 is provided in paragraph 280.

No new matter has been added.

III. Response to the Restriction Requirement

The Examiner has restricted the pending claims into the following twenty groups:

Group #	Claim Numbers
I.	portions of 1-11
II.	portions of 1-11
III.	portions of 12-21

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IV.	portions of 12-21
V.	portions of 22-45
VI.	portions of 22-45
VII.	46-52
VIII.	53-60
IX.	61-78
X.	79-92
XI.	93-104
XII.	105-120
XIII.	121-136
XIV.	137-145
XV.	146-152
XVI.	153-160
XVII.	161-168
XVIII.	169-174
XIX.	175-186
XX.	187-192

Applicants elect Group XIII for prosecution on the merits. Each of claims 121, 193-213 fall within Group XIII.

a.) Election of Species

Applicants have been asked to elect one compound as a starting point from which the Examiner will search the prior art. Applicants elect 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.

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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,

Todd Esker
Reg. No. 46,690

MORGAN, LEWIS & BOCKIUS LLP
One Market, Spear Street Tower
San Francisco, CA 94105
Tel: 415-442-1000
Fax: 415-442-1001
DB2/20921328.1

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 338 of 558

PTO/SB/22 (12-08)
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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-US
Application Number 11/357,687	Filed 02/16/2006
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	$
☑	Two months (37 CFR 1.17(a)(2))	$490	$245	$ 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.

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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	01/23/2009 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.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 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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Electronic Patent Application Fee Transmittal

Application Number:	11357687
Filing Date:	16-Feb-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:	064507-5014US

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	2252	1	245	245

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Miscellaneous:				
			Total in USD ($)	**245**

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EFS ID:	4665595
Application Number:	11357687
International Application Number:	
Confirmation Number:	4964
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:	064507-5014US
Receipt Date:	23-JAN-2009
Filing Date:	16-FEB-2006
Time Stamp:	14:38:42
Application Type:	Utility under 35 USC 111(a)

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Payment Type	Deposit Account
Payment was successfully received in RAM	$245
RAM confirmation Number	9045
Deposit Account	500310
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	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	7	
	Rule 130, 131 or 132 Affidavits		8	15	
	Rule 130, 131 or 132 Affidavits		16	24	
Warnings:					
Information:					
2	Extension of Time	EOT.pdf	61249 849e1be1d27f1aa7741b7e30c9dcf31664b5f660	no	1
Warnings:					
Information:					
3	Fee Worksheet (PTO-06)	fee-info.pdf	30141 b77933fa88d7957caeaf8d20ab03082884d65990	no	2
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43850 7590 04/22/2009

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: 04/22/2009

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/357,687	02/16/2006	Stephen J. Baker	064507-5014US	4964

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	07/22/2009

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.

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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.

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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.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 345 of 558

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43850 7590 04/22/2009

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

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(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/357,687	02/16/2006	Stephen J. Baker	064507-5014US	4964

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	07/22/2009

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.**

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(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:

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❑ 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. _____

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/357,687	02/16/2006	Stephen J. Baker	064507-5014US	4964

43850 7590 04/22/2009

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: 04/22/2009

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 267 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 267 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.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 347 of 558

Notice of Allowability	Application No.	Applicant(s)	
	11/357,687	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 1/23/2009*.

2. ☒ The allowed claim(s) is/are *27-31, 40, and 42-47 , now are 1-12*.

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: 60/654,060 with a filing date 02/16/2005.

2. Amendment of claims 27 and 40, cancellation of claims 1-26 and 32-39, 41, and addition of claims 43-47 in the amendment filed on January 23, 2009 is acknowledged. Claims 27-31, 40, and 42-47 are pending in the application. No new matter is found. Since the newly added claims 43-47 are commensurate with the scope of the invention, claims 27-31, 40, and 42-47 are prosecuted in the case.

Reasons for Allowance

3. The rejection of claims 27-31, 40 and 42 under 35 U.S.C. 112, first paragraph has been overcome in the amendment filed on January 23, 2009.

4. Applicant's arguments regarding the rejection of claims 27-31, 40, and 42 under 35 U.S.C. 103(a) over Austin et al. '024 in view of Answre.com filed on January 23, 2009 have been fully considered and they are persuasive. Since Austin et al. '024 or Answre.com does not disclose the instant invention of methods of use for treating infection in an animal, therefor the instant invention is distinct from Austin et al. The rejection of claims 27-31, 40, and 42 under 35 U.S.C. 103(a) over Austin et al. '024 in view of Answre.com has been withdrawn herein. Since claim 41 has been canceled, the rejection of claim 41 under 35 U.S.C. 103(a) is obviated herein.

5. Since claims 53-54 and 58 of Baker et al. co-pending application No. 11/505,591 have been canceled, the provisional rejection of claims 27-31, 40, and 42 under the

obviousness-type double patenting over Baker et al. co-pending application No. 11/505,591 has been withdrawn herein.

6. Claims 27-31, 40, and 42-47 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 methods of use has not been found. Claims 27-31, 40, and 42-47 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

April 20, 2009

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	11/357,687	BAKER ET AL.	
	Examiner	Art Unit	
	REI-TSANG SHIAO	1626	

SEARCHED			
Class	Subclass	Date	Examiner
514	64	4/20/2009	R.S.
558	288	4/20/2009	R.S.

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	**64**	4/20/2009	**R.S.**
558	288	4/20/2009	R.S.

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
EAST class/subclass	4/20/2009	R.S.

Issue Classification	Application/Control No. 11/357,687	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		C	07	F	5	/04				/			
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)												
558	288					/				/			
						/				/			
						/				/			
						/				/			
						/				/			

(Assistant Examiner) (Date)	/Rei-tsang Shiao/ 4/20/2009 (Primary Examiner) (Date)	Total Claims Allowed: 12	
(Legal Instruments 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	5	31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
	4		34		64		94		124		154		184
	5		35		65		95		125		155		185
	6		36		66		96		126		156		186
	7		37		67		97		127		157		187
	8		38		68		98		128		158		188
	9		39		69		99		129		159		189
	10	6	40		70		100		130		160		190
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	14	9	44		74		104		134		164		194
	15	10	45		75		105		135		165		195
	16	11	46		76		106		136		166		196
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	21		51		81		111		141		171		201
	22		52		82		112		142		172		202
	23		53		83		113		143		173		203
	24		54		84		114		144		174		204
	25		55		85		115		145		175		205
	26		56		86		116		146		176		206
1	27		57		87		117		147		177		207
2	28		58		88		118		148		178		208
3	29		59		89		119		149		179		209
4	30		60		90		120		150		180		210

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Alexandria, Virginia 22313-1450
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BIB DATA SHEET

CONFIRMATION NO. 4964

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/357,687	02/16/2006 RULE	514	1626	064507-5014US

APPLICANTS

Stephen J. Baker, Mountain View, CA;
Tsutomu Akama, Sunnyvale, CA;
Carolyn Bellinger-Kawahara, Redwood City, CA;
Vincent S. Hernandez, Watsonville, CA;
Karin M. Hold, Belmont, CA;
James J. Leyden, Malvern, PA;
Kirk R. Maples, San Jose, CA;
Jacob J. Plattner, Berkeley, CA;
Virginia Sanders, San Francisco, CA;
Yong-Kang Zhang, San Jose, CA;

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

This appln claims benefit of 60/654,060 02/16/2005

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **

03/30/2006

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	12	~~39~~ 12	3

ADDRESS

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

TITLE

Boron-containing small molecules

FILING FEE RECEIVED		
1240	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	302	(514/64).CCLS.	USPAT; USOCR	OR	OFF	2009/04/20 11:35
L2	127	(558/288).CCLS.	USPAT; USOCR	OR	OFF	2009/04/20 11:35

4/20/2009 11:35:23 AM

PART B - FEE(S) TRANSMITTAL

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

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

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

43850 7590 04/22/2009

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.

Candida Rubalcaba-Rivera	(Depositor's name)
C. Rubalcaba-Rivera	(Signature)
07/21/2009	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/357,687	02/16/2006	Stephen J. Baker	064507-5014US	4964

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~~-~~ No	$755	$300	$0	$1055	07/22/2009

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 Morgan, Lewis &
2 Bockius, LLP
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)
Anacor Pharmaceuticals, Inc.	Palo Alto, CA

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

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☒ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid Issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 50-0310 (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 07/21/2009

Typed or printed name Todd Esker Registration No. 46,690

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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CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 356 of 558

Electronic Patent Application Fee Transmittal

Application Number:	11357687
Filing Date:	16-Feb-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:	064507-5014US

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:				
Utility Appl issue fee	1501	1	1510	1510
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1810**

Electronic Acknowledgement Receipt	
EFS ID:	5744760
Application Number:	11357687
International Application Number:	
Confirmation Number:	4964
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:	064507-5014US
Receipt Date:	21-JUL-2009
Filing Date:	16-FEB-2006
Time Stamp:	20:18:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1810
RAM confirmation Number	4841
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 1.19 (Document supply fees) Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)	

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	Issue Fee Payment (PTO-85B)	IssueFee.pdf	48654 ca90da3d2f634ee3166ba3dba2dabfbfaad8a224	no	1
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	31901 95b35c63e04a97742cf13b921911cfad907c8de5	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	80555		

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Bib Data Sheet

CONFIRMATION NO. 4964

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/357,687	02/16/2006 RULE	514	1626	064507-5014US

APPLICANTS

Stephen J. Baker, Mountain View, CA;
Tsutomu Akama, Sunnyvale, CA;
Carolyn Bellinger-Kawahara, Redwood City, CA;
Vincent S. Hernandez, Watsonville, CA;
Karin M. Hold, Belmont, CA;
James J. Leyden, Malvern, PA;
Kirk R. Maples, San Jose, CA;
Jacob J. Plattner, Berkeley, CA;
Virginia Sanders, San Francisco, CA;
Yong-Kang Zhang, San Jose, CA;

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

This appln claims benefit of 60/654,060 02/16/2005

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

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 03/30/2006

		STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
Foreign Priority claimed	☐ yes ☐ no	CA	12	39	3
35 USC 119 (a-d) conditions met	☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged	Examiner's Signature Initials				

ADDRESS
43850

TITLE

BORON-CONTAINING SMALL MOLECULES

FILING FEE RECEIVED		
1540	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/357,687	09/01/2009	7582621	064507-5014US	4964

43850 7590 08/12/2009

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 267 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.

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

Stephen J. Baker, Mountain View, CA;
Tsutomu Akama, Sunnyvale, CA;
Carolyn Bellinger-Kawahara, Redwood City, CA;
Vincent S. Hernandez, Watsonville, CA;
Karin M. Hold, Belmont, CA;
James J. Leyden, Malvern, PA;
Kirk R. Maples, San Jose, CA;
Jacob J. Plattner, Berkeley, CA;
Virginia Sanders, San Francisco, CA;
Yong-Kang Zhang, San Jose, CA;

PTO/SB/17p (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PETITION FEE
Under 37 CFR 1.17(f), (g) & (h)
TRANSMITTAL

(Fees are subject to annual revision)

Send completed form to: Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Application Number	11/357,687
Filing Date	February 16, 2006
First Named Inventor	BAKER, Stephen J.
Art Unit	1626
Examiner Name	SHIAO, Rei Tsang
Attorney Docket Number	064507-5014-US

Enclosed is a petition filed under 37 CFR 1.18(e) **that requires a processing fee (37 CFR 1.17(f), (g), or (h)). Payment of $** 200 **is enclosed.**

This form should be included with the above-mentioned petition and faxed or mailed to the Office using the appropriate Mail Stop (e.g., Mail Stop Petition), if applicable. *For transmittal of processing fees under 37 CFR 1.17(i), see form PTO/SB/17i.*

Payment of Fees (small entity amounts are NOT available for the petition fees)

☑ The Commissioner is hereby authorized to charge the following fees to Deposit Account No. 50-0310 :
☑ petition fee under 37 CFR 1.17(f), (g) or (h) ☑ any deficiency of fees and credit of any overpayments

☐ Check in the amount of $_____ is enclosed.

☐ Payment by credit card (Form PTO-2038 or equivalent enclosed). Do not provide credit card information on this form.

Petition Fees under 37 CFR 1.17(f): Fee $400 Fee Code 1462
For petitions filed under:
§ 1.36(a) - for revocation of a power of attorney by fewer than all applicants
§ 1.53(e) - to accord a filing date.
§ 1.57(a) - to accord a filing date.
§ 1.182 - for decision on a question not specifically provided for.
§ 1.183 - to suspend the rules.
§ 1.378(e) - for reconsideration of decision on petition refusing to accept delayed payment of maintenance fee in an expired patent.
§ 1.741(b) - to accord a filing date to an application under § 1.740 for extension of a patent term.

Petition Fees under 37 CFR 1.17(g): Fee $200 Fee Code 1463
For petitions filed under:
§ 1.12 - for access to an assignment record.
§ 1.14 - for access to an application.
§ 1.47 - for filing by other than all the inventors or a person not the inventor.
§ 1.59 - for expungement of information.
§ 1.103(a) - to suspend action in an application.
§ 1.136(b) - for review of a request for extension of time when the provisions of section 1.136(a) are not available.
§ 1.295 - for review of refusal to publish a statutory invention registration.
§ 1.296 - to withdraw a request for publication of a statutory invention registration filed on or after the date the notice of intent to publish issued.
§ 1.377 - for review of decision refusing to accept and record payment of a maintenance fee filed prior to expiration of a patent.
§ 1.550(c) - for patent owner requests for extension of time in ex parte reexamination proceedings.
§ 1.956 - for patent owner requests for extension of time in inter partes reexamination proceedings.
§ 5.12 - for expedited handling of a foreign filing license.
§ 5.15 - for changing the scope of a license.
§ 5.25 - for retroactive license.

Petition Fees under 37 CFR 1.17(h): Fee $130 Fee Code 1464
For petitions filed under:
§ 1.19(g) - to request documents in a form other than that provided in this part.
§ 1.84 - for accepting color drawings or photographs.
§ 1.91 - for entry of a model or exhibit.
§ 1.102(d) - to make an application special.
§ 1.138(c) - to expressly abandon an application to avoid publication.
§ 1.313 - to withdraw an application from issue.
§ 1.314 - to defer issuance of a patent.

Signature	September 25, 2009 (Date)
Todd W. Esker (Typed or printed name)	46,690 (Registration No., if applicable)

This collection of information is required by 37 CFR 1.17. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 5 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.**

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

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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: September 25, 2009

Signed: Jennifer C. Black

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4964
Stephen J. BAKER, *et al.*	Examiner: SHIAO, Rei Tsang
Patent No.: 7,582,621	Art Unit: 1626
Issued: September 1, 2009	PETITION FOR RECONSIDERATION OF PATENT TERM ADJUSTMENT UNDER 37 C.F.R. 1.705(d)
Issued from Application No.: 11/357,687	
Filed: February 16, 2006	
For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

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

Sir:

In response to the issuance of U.S. Pat. No. 7,582,621 on September 1, 2009, Applicants submit a petition for reconsideration of patent term adjustment (PTA). In this petition, Applicants request the addition of 197 (one hundred and ninty-seven) days to the patent term.

For your consideration, enclosed are the following:

1. Fee set forth under 1.18(e) (see Fee Transmittal Form);
2. Statement of the Facts Involved as described in 37 CFR 1.705(b); and
3. Copy of Patent Term Adjustment History (attached as Exhibit A)

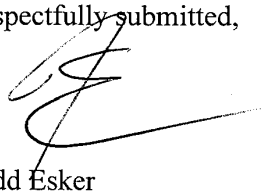
In view of the reasons set forth in the Statement of Facts, Applicants respectfully request that the patent term be corrected by adding 197 additional days to the term of the patent issuing from the above-identified application for a total of **464 (four hundred and sixty-four) days** to the term of U.S. Pat. No. 7,582,621.

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 364 of 558

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310.

If the Examiner believes a telephone conference would expedite this request for reconsideration, please telephone the undersigned at 415-442-1000.

Respectfully submitted,



Todd Esker
Reg. No. 46,690

MORGAN, LEWIS & BOCKIUS LLP
One Market, Spear Street Tower
San Francisco, CA 94105
Tel: 415-442-1000
Fax: 415-442-1001
DB2/21336942.1

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 365 of 558

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Dated: September 25, 2009

Signed: Jennifer C. Black

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4964
Stephen J. BAKER, *et al.*	Examiner: SHIAO, Rei Tsang
Patent No.: 7,582,621	Art Unit: 1626
Issued: September 1, 2009	STATEMENT UNDER 37 C.F.R. 1.705(b)(2)
Issued from Application No.: 11/357,687	
Filed: February 16, 2006	
For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

1. This statement is respectfully submitted in support of the Petition For Patent Term Adjustment Under 37 C.F.R. § 1.705(d) for the above-referenced patent. In view of the following, it is respectfully requested that Patentees be granted a final patent term adjustment of **464 days** and not 267 as calculated by the Patent Office.

37 C.F.R. § 1.705 (b)(2)(i)

2. The patent term adjustment shown on the Determination of Patent Term Adjustment Under 35 U.S.C. § 154(b) that was attached to the Notice of Allowance dated April 22, 2009, is 267 days. Applicants believe, based on their understanding of the rules governing patent term adjustment, that this determination is in error, due to the Office's improper interpretation of the PTA provisions as discussed in *Wyeth et al. v. Dudas*, No. 07-1492 (D.D.C. September 30, 2008). Specifically, the Office improperly limited PTA to either the PTA as calculated under 35 U.S.C. § 154(b)(1)(A) or as calculated under 35 U.S.C. § 154(b)(1)(B), but not both. 69 Fed. Reg. 34238 (June 21, 2004). However, as discussed in *Wyeth et al. v. Dudas*, the statute requires that PTA may comprise contributions from both 35 U.S.C. § 154(b)(1)(A)

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 366 of 558

and 35 U.S.C. § 154(b)(1)(B), and the Office's interpretation of the statute was erroneous to the extent that it considered any delays within the first three years after filing the application to "overlap" with delays under § 154(b)(1)(B) after three years from the filing of the application. According to the Court, no delay accumulated within the first three years after the filing date can be said to "overlap" with delays under §154(b)(1)(B), which by definition do not arise until after three years from the filing date. It is respectfully submitted that the correct patent term adjustment under 37 C.F.R. § 1.702, as calculated under the analysis of *Wyeth et al. v. Dudas*, is **464 days**.

37 C.F.R. § 1.705 (b)(2)(ii)

3. Applicants seek adjustment to the PTA based on the analysis laid out in *Wyeth et al. v. Dudas*, as contrasted with the Office's analysis laid out in 69 Fed. Reg. 34238 (June 21, 2004). Accordingly, the net PTA comprises accumulated PTA arising from both 35 U.S.C. § 154(b)(1)(A) and (B), excluding actual overlap (35 U.S.C. § 154(b)(2)(A)), and deducting any periods of time in which Applicants failed to engage in reasonable efforts to conclude prosecution (35 U.S.C. §154(b)(2)(C)).

A. Applicants do not presently dispute any aspect of the PTA determination other than the issue raised in *Wyeth et al. v. Dudas*. Accordingly, for the purposes of this request to modify PTA, Applicants accept the calculations provided by the USPTO on PAIR (a copy of which is attached as Exhibit A) indicating that there was a delay of 325 days by the USPTO (35 U.S.C. § 154(b)(1)(A)) in sending out the first action, and that Applicant subsequently incurred a delay of 58 days during the course of the prosecution (35 U.S.C. §154(b)(2)(C)). The resulting net PTA is 267 days, in agreement with the PTA provided on the Determination of Patent Term Adjustment Under 35 U.S.C. § 154(b) that was attached to the Notice of Allowance dated April 22, 2009.

B. With regard to the "three year guarantee" provisions of 37 C.F.R. §§ 1.702(b) and 1.703(b), the application was filed on February 16, 2006, and thus PTA began to accrue the day after February 16, 2009. The issuance of the patent on September 1, 2009 cut-off any further accumulation of PTA under 37 C.F.R. § 1.702(b). The period of February 16, 2006 through February 16, 2009 (inclusive) is 197 days (35 U.S.C. § 154(b)(1)(B)).

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 367 of 558

C. Under the analysis of *Wyeth et al. v. Dudas*, this 197 day period under 37 C.F.R. § 1.702(b) is added to the previously calculated 267 day period based on 37 C.F.R. § 1.702(a). However, the total examination delay must then be reduced by any actual overlap between the two delays. 37 C.F.R. § 1.703(f). Since Applicants' last communication to place the application in condition for allowance was on January 23, 2009, prior to the invocation of the delay under 35 U.S.C. §154(b)(1)(B) on February 16, 2009, there is no overlap between the two delays.

D. The resulting PTA is 267 + 197 = 464 days.

E. Accordingly, Applicants request that the calculated 267 day PTA be adjusted to **464 days**.

37 C.F.R. § 1.705 (b)(2)(iii)

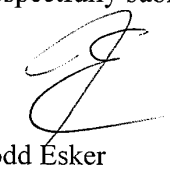
4. The present application is not subject to a Terminal Disclaimer.

37 C.F.R. § 1.705 (b)(2)(iv)

5. Circumstances set forth in 37 C.F.R. § 1.704 are described in Section 3(A) of this paper and in the attached printout of the Patent Term Adjustments tab from PAIR.

In view of the foregoing, it is respectfully requested that this Petition for Patent Term Adjustment Under 37 C.F.R. § 1.705(d) be favorably considered and that a corrected determination of Patent Term Adjustment be issued to reflect a PTA of **464** days.

Respectfully submitted,



Todd Esker
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Fax: 415-442-1001

DB2/21338317.1

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 368 of 558

EXHIBIT A

11/357,687	BORON-CONTAINING SMALL MOLECULES	09-22-2009::15:58:51

Patent Term Adjustments

Patent Term Adjustment (PTA) for Application Number: 11/357,687

Filing or 371(c) Date:	02-16-2006	USPTO Delay (PTO) Delay (days):	325
Issue Date of Patent:	09-01-2009	Three Years:	-
Pre-Issue Petitions (days):	+0	Applicant Delay (APPL) Delay (days):	58
Post-Issue Petitions (days):	+0	Total PTA (days):	267
USPTO Adjustment(days):	+0	Explanation Of Calculations	

Patent Term Adjustment History

Date	Contents Description	PTO(Days)	APPL(Days)
08-12-2009	PTA 36 Months		
09-01-2009	Patent Issue Date Used in PTA Calculation		
07-24-2009	Dispatch to FDC		
07-23-2009	Application Is Considered Ready for Issue		
07-21-2009	Issue Fee Payment Verified		
07-21-2009	Statement Filed Indicating a Loss of Entitlement to Small Entity Status		
07-21-2009	Issue Fee Payment Received		
04-22-2009	Mail Notice of Allowance		
04-21-2009	Document Verification		
04-21-2009	Notice of Allowance Data Verification Completed		
02-18-2009	Date Forwarded to Examiner		
01-23-2009	Response after Non-Final Action		58
01-23-2009	Request for Extension of Time - Granted		↑
12-05-2008	Miscellaneous Incoming Letter		↑
08-26-2008	Mail Non-Final Rejection		↑
08-25-2008	Non-Final Rejection		
06-21-2007	Information Disclosure Statement considered		
05-07-2007	Information Disclosure Statement considered		
06-30-2008	Date Forwarded to Examiner		
06-06-2008	Response to Election / Restriction Filed		
06-06-2008	Request for Extension of Time - Granted		
01-11-2008	Miscellaneous Incoming Letter		
03-06-2008	Mail Restriction Requirement	325	
02-28-2008	Requirement for Restriction / Election	↑	
06-21-2007	Information Disclosure Statement (IDS) Filed	↑	
06-21-2007	Information Disclosure Statement (IDS) Filed	↑	
05-07-2007	Information Disclosure Statement (IDS) Filed	↑	
05-07-2007	Information Disclosure Statement (IDS) Filed	↑	
03-22-2007	Case Docketed to Examiner in GAU	↑	
12-28-2006	IFW TSS Processing by Tech Center Complete	↑	

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 370 of 558

07-11-2006	Application Dispatched from OIPE	
07-11-2006	Application Is Now Complete	
06-30-2006	Additional Application Filing Fees	
06-30-2006	A statement by one or more inventors satisfying the requirement under 35 USC 115, Oath of the Applic	
04-03-2006	Notice Mailed--Application Incomplete--Filing Date Assigned	
03-27-2006	Cleared by L&R (LARS)	
03-20-2006	Referred to Level 2 (LARS) by OIPE CSR	
03-18-2006	IFW Scan & PACR Auto Security Review	
02-16-2006	Initial Exam Team nn	

Close Window

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 371 of 558

Electronic Patent Application Fee Transmittal

Application Number:	11357687
Filing Date:	16-Feb-2006
Title of Invention:	BORON-CONTAINING SMALL MOLECULES
First Named Inventor/Applicant Name:	Stephen J. Baker
Filer:	Jeffry S. Mann/Jennifer Black
Attorney Docket Number:	064507-5014US

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

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

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

Electronic Acknowledgement Receipt	
EFS ID:	6151753
Application Number:	11357687
International Application Number:	
Confirmation Number:	4964
Title of Invention:	BORON-CONTAINING SMALL MOLECULES
First Named Inventor/Applicant Name:	Stephen J. Baker
Customer Number:	43850
Filer:	Jeffry S. Mann/Jennifer Black
Filer Authorized By:	Jeffry S. Mann
Attorney Docket Number:	064507-5014US
Receipt Date:	25-SEP-2009
Filing Date:	16-FEB-2006
Time Stamp:	19:02:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$200
RAM confirmation Number	4839
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 1.20 (Post Issuance fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Patent Term Adjustment Petition	064507-5014US_Petition.pdf	334725 ea9d83341b52050f1be59729ff42ec4a4891c9e2	no	9
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	30379 a6eb2f513da93cc3879e892b6b2030d6980b8b9a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	365104		

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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APR 2 3 2010

OFFICE OF PETITIONS

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

In re Patent of Baker et al.	: DECISION ON REQUEST FOR
Patent No. 7,582,621	: RECONSIDERATION OF
Issue Date: September 1, 2009	: PATENT TERM ADJUSTMENT
Application No. 11/357,687	: AND NOTICE OF INTENT TO ISSUE
Filed: February 16, 2006	: CERTIFICATE OF CORRECTION
Atty. Docket No. 064507-5014US	:

This is a decision on the petition filed September 25, 2009, which is being treated as a petition under 37 CFR 1.705(d) requesting the patent term adjustment indicated on the above-identified patent be corrected to indicate that the term of the above-identified patent is extended or adjusted by four hundred sixty-four (464) days.

The petition to correct the patent term adjustment indicated on the above-identified patent to indicate that the term of the above-identified patent is extended or adjusted by four hundred sixty-four (464) days is **GRANTED**.

The Office acknowledges submission of the $200.00 fee set forth in 37 CFR 1.18(e). No additional fees are required.

The application is being forwarded to the Certificates of Correction Branch for issuance of a certificate of correction. The Office will issue a certificate of correction indicating that the term of the above-identified patent is extended or adjusted by **four hundred sixty-four (464)** days.

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

Shirene Willis Brantley

Shirene Willis Brantley
Senior Petitions Attorney
Office of Petitions

Enclosure: Copy of DRAFT Certificate of Correction

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT : 7,582,621 B2

DATED : **September 1, 2009** **DRAFT**

INVENTOR(S) : Baker et al.

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

On the cover page,

[*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 267 days

Delete the phrase "by 267 days" and insert – by 464 days--

CERTIFICATE OF ELECTRONIC TRANSMISSION

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Dated: 5/20/2010

Signed: C. Rubaleta Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:	Confirmation No.: 4964
Stephen J. BAKER, *et al.*	Examiner: SHIAO, Rei Tsang
Patent No.: 7,582,621	Art Unit: 1626
Issued: September 1, 2009	PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R § 1.324
Issued from Application No.: 11/357,687	
Filed: February 16, 2006	
For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

It is respectfully requested that a Certificate under 37 C.F.R. § 1.324 be issued to remove two inventors, Carolyn Bellinger-Kawahara and Kirk R. Maples, from the above-referenced patent. This request corrects errors in naming inventors that occurred without deceptive intention on the part of either Carolyn Bellinger-Kawahara or Kirk R. Maples.

Pursuant to 37 C.F.R. § 1.324(b)(2), statements from the currently named inventors, Stephen J. Baker, Tsutomu Akama, Vincent S. Hernandez, Karin M. Hold, James J. Leyden, Jacob J. Plattner, Virginia Sanders, Yong-Kang Zhang, Carolyn Bellinger-Kawahara, and Kirk R. Maples, agreeing to the change of inventorship, are attached hereto.

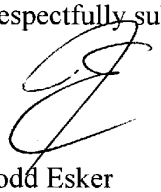
Anacor Pharmaceuticals, Inc. is the assignee of the entire interest of the above-referenced patent. Pursuant to 37 C.F.R. § 1.324(b)(3), a statement from Anacor

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 378 of 558

Pharmaceuticals, Inc. agreeing to the above-described change of inventorship for the above-referenced patent is enclosed.

The fee according to § 1.20(a) for submission of this Petition is estimated to be $130.00. A copy of this Petition is enclosed. Please charge all fees to Deposit Account No. 50-0310. If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310 (Order No. 064507-5014-US).

Respectfully submitted,



Todd Esker
Reg. No. 46,690

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Tel: 415-442-1000
Fax: 415-442-1001
E-mail: tesker@morganlewis.com

DB2/21404428.1

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 379 of 558

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Dated: 5/20/2010

Signed: C. Rubeleta-Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:

Stephen J. BAKER, *et al.*

Patent No.: 7,582,621

Issued: September 1, 2009

Issued from Application No.: 11/357,687

Filed: February 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Confirmation No.: 4964

Examiner: SHIAO, Rei Tsang

Art Unit: 1626

STATEMENT OF ANACOR PHARMACEUTICALS, INC, ASSIGNEE, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(3)

Anacor Pharmaceuticals, Inc. is the assignee of the above-referenced patent.

Anacor Pharmaceuticals, Inc. agrees that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

David Perry
Chief Executive Office, Anacor Pharmaceuticals

1020 East Meadow Circle
Palo Alto, CA 94303- 4230
Address of Anacor Pharmaceuticals

4/2/10
Date

Signature

DB2/21404700.1

CERTIFICATE OF ELECTRONIC TRANSMISSION

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Dated: 5/20/2010

Signed: C. Rubalcta - Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:

Stephen J. BAKER, *et al.*

Patent No.: 7,582,621

Issued: September 1, 2009

Issued from Application No.: 11/357,687

Filed: February 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Confirmation No.: 4964

Examiner: SHIAO, Rei Tsang

Art Unit: 1626

STATEMENT OF STEPHEN J. BAKER, INVENTOR, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(2)

I, Stephen Baker, agree that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

Stephen J. Baker
Name of Inventor

1568 Begen Avenue, Mountain View, CA 94040
Address of Inventor

3/25/10
Date

Signature of Inventor

DB2/21404688.1

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Dated: 5/20/2010

Signed: C. Rubeleba Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:

Stephen J. BAKER, *et al.*

Patent No.: 7,582,621

Issued: September 1, 2009

Issued from Application No.: 11/357,687

Filed: February 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Confirmation No.: 4964

Examiner: SHIAO, Rei Tsang

Art Unit: 1626

STATEMENT OF TSUTOMU AKAMA, INVENTOR, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(2)

I, Tsutomu Akama, agree that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

Tsutomu Akama
Name of Inventor

933 Berkshire Avenue, Sunnyvale, CA 94087
Address of Inventor

3/30/2010
Date

Signature of Inventor

DB2/21404691.1

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Signed: C. Rebaleta Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:	Confirmation No.: 4964
Stephen J. BAKER, *et al.*	Examiner: SHIAO, Rei Tsang
Patent No.: 7,582,621	Art Unit: 1626
Issued: September 1, 2009	STATEMENT OF VINCENT S. HERNANDEZ, INVENTOR, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(2)
Issued from Application No.: 11/357,687	
Filed: February 16, 2006	
For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

I, Vincent Hernandez, agree that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

Vincent S. Hernandez
Name of Inventor

287 Gilchrist Lane, Watsonville, CA 95076
Address of Inventor

3/30/10
Date

Signature of Inventor

DB2/21404692.1

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Dated: 5/20/2010

Signed: C. Rabaleta-Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:

Stephen J. BAKER, *et al.*

Patent No.: 7,582,621

Issued: September 1, 2009

Issued from Application No.: 11/357,687

Filed: February 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Confirmation No.: 4964

Examiner: SHIAO, Rei Tsang

Art Unit: 1626

STATEMENT OF KARIN M. HOLD, INVENTOR, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(2)

I, Karin Hold, agree that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

Karin M. Hold
Name of Inventor

2720 Wakefield Dr., Belmont, CA 94002
Address of Inventor

3/30/10
Date

Signature of Inventor

DB2/21404693.1

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Dated: 5/20/2010

Signed: C. Rubalcaba Rivera

Candida Rubalcaba-Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:

Stephen J. BAKER, *et al.*

Patent No.: 7,582,621

Issued: September 1, 2009

Issued from Application No.: 11/357,687

Filed: February 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Confirmation No.: 4964

Examiner: SHIAO, Rei Tsang

Art Unit: 1626

STATEMENT OF JAMES J. LEYDEN, INVENTOR, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(2)

I, James J. Leyden, agree that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

James J. Leyden
Name of Inventor

319 Applebrook Drive, Malvern, Pennsylvania 19355
Address of Inventor

5/13/10
Date

James Leyden
Signature of Inventor

DB2/21404694.1

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Dated: 5/20/2010

Signed: C. Rubalcaba Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:	Confirmation No.: 4964
Stephen J. BAKER, *et al.*	Examiner: SHIAO, Rei Tsang
Patent No.: 7,582,621	Art Unit: 1626
Issued: September 1, 2009	STATEMENT OF JACOB J. PLATTNER, INVENTOR, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(2)
Issued from Application No.: 11/357,687	
Filed: February 16, 2006	
For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

I, Jacob Plattner, agree that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

Jacob J. Plattner
Name of Inventor

119 Via Floreado Orinda, CA 94563
Address of Inventor

March 15, 2010
Date

Jacob J. Plattner
Signature of Inventor

DB2/21404695.1

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Dated: 5/20/2010

Signed: C. Rubulcta-Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:	Confirmation No.: 4964
Stephen J. BAKER, *et al.*	Examiner: SHIAO, Rei Tsang
Patent No.: 7,582,621	Art Unit: 1626
Issued: September 1, 2009	STATEMENT OF VIRGINIA SANDERS, INVENTOR, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(2)
Issued from Application No.: 11/357,687	
Filed: February 16, 2006	
For: BORON-CONTAINING SMALL MOLECULES	
Customer No.: 43850	

I, Virginia Sanders, agree that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

Virginia Sanders
Name of Inventor

2895 Harrison St, Apt 4, San Francisco, CA 94110
Address of Inventor

3-30-2010
Date

Virginia Sanders
Signature of Inventor

DB2/21404697.1

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Dated: 5/20/2010

Signed: C. Rebeleba-Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:

Stephen J. BAKER, *et al.*

Patent No.: 7,582,621

Issued: September 1, 2009

Issued from Application No.: 11/357,687

Filed: February 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Confirmation No.: 4964

Examiner: SHIAO, Rei Tsang

Art Unit: 1626

STATEMENT OF YONG-KANG ZHANG, INVENTOR, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(2)

I, Yong-Kang Zhang, agree that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

Yong-Kang Zhang
Name of Inventor

5151 Westmont Avenue, San Jose, CA 95130
Address of Inventor

3-30-2010
Date

Yongkang Zhang
Signature of Inventor

DB2/21404698.1

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: 5/20/2010

Signed: C. Rubalcaba-Rivera

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:

Stephen J. BAKER, *et al.*

Patent No.: 7,582,621

Issued: September 1, 2009

Issued from Application No.: 11/357,687

Filed: February 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Confirmation No.: 4964

Examiner: SHIAO, Rei Tsang

Art Unit: 1626

STATEMENT OF CAROLYN BELLINGER-KAWAHARA, CURRENTLY NAMED INVENTOR, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(2)

I, Carolyn Bellinger-Kawahara, agree that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

Carolyn Bellinger-Kawahara
Name of Currently Named Inventor

15 Landa Lane, Redwood City, CA 94061
Address of Currently Named Inventor

3/16/10
Date

Carolyn Bellinger-Kawahara
Signature of Currently Named Inventor

DB2/21514050.1

CERTIFICATE OF ELECTRONIC TRANSMISSION

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Dated: 5/20/2010

Signed: C. Rubalcaba

Attorney Docket No.: 064507-5014-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent to:

Stephen J. BAKER, *et al.*

Patent No.: 7,582,621

Issued: September 1, 2009

Issued from Application No.: 11/357,687

Filed: February 16, 2006

For: BORON-CONTAINING SMALL MOLECULES

Customer No.: 43850

Confirmation No.: 4964

Examiner: SHIAO, Rei Tsang

Art Unit: 1626

STATEMENT OF KIRK R. MAPLES, CURRENTLY NAMED INVENTOR, IN SUPPORT OF PETITION TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.324(b)(2)

I, Kirk Maples, agree that the inventorship of the above-referenced patent should be corrected to delete both Carolyn Bellinger-Kawahara and Kirk Maples as inventors.

IN TESTIMONY HEREOF, I have hereunto set my hand.

Kirk R. Maples
Name of Currently Named Inventor

1195 San Moritz Drive, San Jose, CA 95132
Address of Currently Named Inventor

3/18/10
Date

Kirk R Maples
Signature of Currently Named Inventor

DB2/21514066.1

Electronic Patent Application Fee Transmittal

Application Number:	11357687
Filing Date:	16-Feb-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:	064507-5014US

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Petition fee- 37 CFR 1.17(h) (Group III)	1464	1	130	130
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

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

Electronic Acknowledgement Receipt	
EFS ID:	7656745
Application Number:	11357687
International Application Number:	
Confirmation Number:	4964
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:	064507-5014US
Receipt Date:	20-MAY-2010
Filing Date:	16-FEB-2006
Time Stamp:	19:01:46
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	5179
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	Petition for review by the Office of Petitions.	Petition.pdf	35487 942716164c25af600158fc82e4b1305173563f5b	no	2
Warnings:					
Information:					
2	Consent of Assignee accompanying the declaration.	Statements.pdf	251445 b126e50b045e418d4666322cdb6b9cdb26597b24	no	11
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	30276 405a42dbf9431a8d03db02c8c753e7208bdfbc1b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	317208		

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,582,621 B2
APPLICATION NO. : 11/357687
DATED : September 1, 2009
INVENTOR(S) : Baker et al.

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

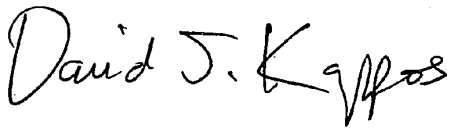
On the Title Page

Item [*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 267 days

Delete the phrase "by 267 days" and insert -- by 464 days --

Signed and Sealed this

First Day of June, 2010



David J. Kappos
Director of the United States Patent and Trademark Office

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. Box 1450
Alexandria, VA. 22313-1450
WWW.USPTO.GOV

David Perry
Anacor Pharmaceuticals
1020 East Meadow Circle

Palo Alto, CA 94303-4230

Date: December 30, 2011
Application No. 11/357,687
Filed: February 16, 2006
Subject: **BORON-CONTAINING SMALL MOLECULES**

ON PETITION
37 CFR 1.324

Receipt is acknowledged of the petition filed on May 20, 2010 under 37 CFR 1.324 for correction of inventorship. The petition has been **GRANTED**.

In view of the papers filed, it has been found that during the prosecution of the instant application a restriction was required and therefore, not all of the inventors contributed to the invention as now claimed. Accordingly, this application has been changed by the **deletion of the inventor Carolyn Bellinger-Kawahara and Kirk R. Maples.** The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Brandon Fetterolf
United States Patent and Trademark Office
Technology Center 1600
SPE, ART UNIT 1628
Remsen 5C09
571-272-2919

UNITED STATES PATENT AND TRADEMARK OFFICE
Certificate

Patent No. 7,582,621 B2 Patented: September 1, 2009

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

Accordingly, it is hereby certified that the correct inventorship of this patent is: Stephen J. Baker, Mountain View, CA (US); Tsutomu Akama, Sunnyvale, CA (US); Vincent S. Hernandez, Watsonville, CA (US); Karin M. Hold, Belmont, CA (US); James J. Leyden, Malvern, PA (US); Jacob J. Plattner, Berkeley, CA (US); Virginia Sanders, San Francisco, CA (US); and Yong-Kang Zhang, San Jose, CA (US).

Signed and Sealed this Sixteenth Day of July 2013.

BRANDON FETTEROLF
Supervisory Patent Examiner
Art Unit 1628
Technology Center 1600

IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICATION NUMBER : 11/357,687

PATENT NUMBER : 7,582,621

FILING DATE : February 16, 2006

ISSUE DATE : September 1, 2009

INVENTOR(S) : Baker *et al.*

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450
Mail Stop: Hatch-Waxman PTE

APPLICATION FOR EXTENSION OF THE TERM OF U.S. PATENT NO. 7,582,621 UNDER 35 U.S.C. § 156 FOR KERYDIN™ (TAVABOROLE) TOPICAL SOLUTION, 5%

Dear Ms. Till:

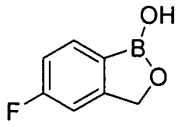
Pursuant to 35 U.S.C. § 156(d) and 37 C.F.R. §§ 1.710 *et seq.*, Anacor Pharmaceuticals, Inc. ("Anacor") hereby submits this application for an extension of the term of U.S. Patent No. 7,582,621 ("the '621 patent," attached as **Exhibit A**). The '621 patent, entitled BORON-CONTAINING SMALL MOLECULES, issued on September 1, 2009 to Stephen J. Baker, Tsutomu Akama, Carolyn Bellinger-Kawahara, Vincent S. Hernandez, Karin M. Hold, James J. Leyden, Kirk R. Maples, Jacob J. Plattner, Virginia Sanders, and Yong-Kang Zhang. Anacor is the marketing applicant for KERYDIN (tavaborole) topical solution, 5% ("KERYDIN product" or "KERYDIN"), which received marketing approval from the U.S. Food and Drug Administration ("FDA") on July 7, 2014. *See* KERYDIN product label attached as **Exhibit B** & KERYDIN approval letter attached as **Exhibit C**.

Anacor represents that it is the owner of the entire right, title, and interest in and to the '621 patent. Anacor is the owner of the '621 patent by virtue of an assignment by all named inventors, Stephen J. Baker, Tsutomu Akama, Carolyn Bellinger-Kawahara, Vincent S. Hernandez, Karin M. Hold, James J. Leyden, Kirk R. Maples, Jacob J. Plattner, Virginia Sanders, and Yong-Kang Zhang (recorded at Reel 017885, Frame Nos. 0979-0989). *See* Statement Under 37 C.F.R. § 3.73(b) and Assignment Record, attached as **Exhibit D**.

An extension of 408 days is requested based on the regulatory review period of the KERYDIN product as set forth below. The undersigned is authorized to represent Anacor in this application. *See* Power of Attorney (attached as **Exhibit E**).

Paragraphs (1) through (15) below correspond to paragraphs (1) through (15) of 37 C.F.R. § 1.740(a).

(1) The approved product is tavaborole, a 5% topical solution, and it is approved for marketing as KERYDIN for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes.* The chemical name for tavaborole is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, having the chemical formula $C_7H_6BFO_2$, a molecular weight of 151.93 and the following chemical structure:



See KERYDIN product label § 11.

KERYDIN for topical treatment contains the active ingredient, tavaborole 5% (w/w), in an alcohol-based solution. Each mL of KERYDIN contains 43.5 mg of tavaborole. Inactive ingredients include alcohol, edetate calcium disodium and propylene glycol. *See* KERYDIN product label, § 11.

The KERYDIN (tavaborole 5% topical solution) product is indicated for topical treatment of onychomycosis of the toenails and the recommended application of KERYDIN is to the entire toenail surface and under the tip of each toenail being treated, once daily for 48 weeks. *See* KERYDIN product label, § 2.

(2) Regulatory review of KERYDIN (tavaborole 5% topical solution) for topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes* occurred under section 505(b) of the Federal Food, Drug and Cosmetic Act, codified at 21 U.S.C. § 355(b).

(3) KERYDIN (tavaborole 5% topical solution) received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug and Cosmetic Act on July 7, 2014. It was approved for use in the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*.

(4) The only active ingredient of KERYDIN for topical treatment is tavaborole. Tavaborole, or any pharmaceutically acceptable salt thereof, has not previously been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act. KERYDIN was approved for use in the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes* pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act, codified at 21 U.S.C. § 355(b).

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. § 1.720(f). The last day on which this application could be submitted is September 4, 2014.

(6) The patent for which an extension is being sought is as follows:

Inventors: Stephen J. Baker, Tsutomu Akama, Vincent S. Hernandez, Karin M. Hold, James J. Leyden, Jacob J. Plattner, Virginia Sanders, and Yong-Kang Zhang (Inventorship corrected on July 16, 2013. *See* Exhibit A.)

Patent No.: 7,582,621

Issue date: September 1, 2009

Expiration: May 26, 2027 (includes 464 days of patent term adjustment)

(7) A copy of the '621 patent is attached hereto as Exhibit A.

(8) No terminal disclaimer or reexamination certificate has been issued. Fourth year maintenance fees have been paid, receipts for which are attached as **Exhibit F**. Certificates of correction that have been issued in connection with the '621 patent are attached hereto as part of Exhibit A.

(9) The '621 patent claims certain methods of using the KERYDIN product. Provided below are the applicable patent claims and the manner in which each claim reads on the method of using the approved product.

Claim 1:

Claim 1 reads as follows:

> 1. A method of treating an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said infection.

The KERYDIN product is tavaborole, a 5% topical solution. *See* KERYDIN product label, § 1. The chemical name for tavaborole is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. The KERYDIN product is indicated for the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*. *See* KERYDIN product label, §§ 1 & 11. *Trichophyton rubrum* and *Trichophyton mentagrophytes* are fungi, and the onset of onychomycosis due to these fungi constitutes a fungal infection. KERYDIN administered to patients in the amounts and manner described on the product label has been shown in clinical trials to be therapeutically effective in treating onychomycosis. *See* KERYDIN product label, ¶ 14. Claim 1 therefore reads on the approved use of the approved KERYDIN product.

Claim 2:

Claim 2 reads as follows:

> 2. The method of claim 1, wherein said infection is a member selected from a systemic infection, a cutaneous infection, and an ungual or periungual infection.

For the reasons described above, Claim 1 reads on the approved use of the approved KERYDIN product. Further, the KERYDIN product label indicates that KERYDIN is indicated for the treatment of onychomycosis of the toenails, which is an ungual or periungual infection. *See* KERYDIN label, § 1. Claim 2 therefore reads on the approved use of the approved KERYDIN product.

Claim 4:

Claim 4 reads as follows:

> 4. The method of claim 1, wherein said infection is onychomycosis.

For the reasons described above, Claim 1 reads on the approved use of the approved KERYDIN product. The KERYDIN product label specifically states that KERYDIN is indicated for the treatment of onychomycosis of the toenails. *See* KERYDIN label, § 1. Claim 4 therefore reads on the approved use of the approved KERYDIN product.

Claim 5:

Claim 5 reads as follows:

> 5. The method of claim 1, wherein said animal is a member selected from a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey.

For the reasons discussed above, Claim 1 reads on the approved use of the approved KERYDIN product. KERYDIN is indicated for the treatment of onychomycosis of the toenails in humans. Claim 5 therefore reads on the approved use of the approved KERYDIN product.

Claim 6:

Claim 6 reads as follows:

> 6. The method of claim 4, wherein said onychomycosis is tinea unguium.

For the reasons discussed above, Claim 4 reads on the approved use of the approved KERYDIN product. Tinea unguium is a type of onychomycosis caused by a dermatophyte, which includes *Trichophyton rubrum* and *Trichophyton mentagrophytes*. The approved KERYDIN product is indicated for the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*, and Claim 6 therefore reads on the approved use of the approved KERYDIN product.

Claim 7:

Claim 7 reads as follows:

> 7. The method of claim 1, wherein said animal is a human.

For the reasons discussed above, Claim 1 reads on the approved use of the approved KERYDIN product. KERYDIN is approved for the treatment of onychomycosis of the toenails in humans. Claim 7 therefore reads on the approved use of the approved KERYDIN product.

Claim 8:

Claim 8 reads as follows:

> 8. The method of claim 1, wherein the administering is at a site which is a member selected from the skin, nail, hair, hoof and claw.

For the reasons discussed above, Claim 1 reads on the approved use of the approved KERYDIN product. KERYDIN is approved for the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*. Section 2 of the approved product label instructs patients to apply KERYDIN to the affected toenails. Claim 8 therefore reads on the approved use of the approved KERYDIN product.

Claim 9:

Claim 9 reads as follows:

> 9. The method of claim 8, wherein said skin is the skin surrounding the nail, hair, hoof or claw.

For the reasons discussed above, Claim 8 reads on the approved use of the approved KERYDIN product. According to the approved product label, KERYDIN should be applied to the entire toenail surface and under the tip of each toenail being treated. *See* KERYDIN product label, § 2. Claim 9 therefore reads on the approved use of the approved KERYDIN product.

Claim 10 reads as follows:

> 10. The method of claim 1, wherein said infection is a fungal infection.

For the reasons discussed above, Claim 1 reads on the approved use of the approved KERYDIN product. KERYDIN is approved for the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*. *Trichophyton rubrum* and *Trichophyton mentagrophytes* are fungi, and the onset of onychomycosis due to these fungi constitutes a fungal infection. Claim 10 therefore reads on the approved use of the approved KERYDIN product.

Claim 11:

Claim 11 reads as follows:

> 11. A method of treating onychomycosis in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said onychomycosis.

The KERYDIN product is tavaborole, a 5% topical solution. *See* KERYDIN product label, § 1. The chemical name for tavaborole is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. The KERYDIN product is indicated for the treatment of a human having onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*. *See* KERYDIN product label, § 11. KERYDIN, when administered in the manner and amount specified in the product label, has been demonstrated in human clinical trials to be therapeutically effective in treating onychomycosis in humans. *See* the KERYDIN product label at § 14. Claim 11 therefore reads on the approved use of the approved KERYDIN product.

Claim 12:

Claim 12 reads as follows:

> 12. A method of inhibiting the growth of a fungus in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof.

The KERYDIN product is tavaborole, a 5% topical solution. The KERYDIN product is indicated for the treatment of humans having onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*. *See* KERYDIN product label, § 1. The chemical name for tavaborole is 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. *See* KERYDIN product label, § 11. *Trichophyton rubrum* and *Trichophyton mentagrophytes* are fungi, and the onset of onychomycosis due to these fungi constitutes a fungal infection. KERYDIN, when administered in the manner and amount specified in the product label, has been proven in human clinical trials to be therapeutically effective in inhibiting the growth of the fungi that cause onychomycosis. *See* KERYDIN product label at § 14. Claim 12 therefore reads on the approved use of the approved KERYDIN product.

(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are:

IND number:	71,206
IND effective date:	December 31, 2005
NDA number:	NDA 204427
NDA submission date:	July 26, 2013
NDA approval date:	July 7, 2014

(11) As a brief description of the significant activities undertaken by the marketing applicant Anacor during the applicable regulatory review period with respect to the approved KERYDIN product and the significant dates applicable to such activities, attached hereto is **Exhibit G**. Throughout the regulatory review period, Anacor conducted clinical trials and analyses of the KERYDIN product. Exhibit G provides a chronology of the IND No. 71,206 and NDA No. 204427, including significant communications with the FDA during the regulatory review period culminating with the approval of the KERYDIN product on July 7, 2014.

(12) In the opinion of the applicant, the '621 patent is eligible for patent term extension under 35 U.S.C. § 156. An extension of 408 days is claimed. The eligibility for and length of the claimed extension were determined as follows:

(a) 35 U.S.C. § 156(a)

The '621 patent claims methods of treatment using the approved KERYDIN product.

(b) 35 U.S.C. § 156(a)(1)

The term of the '621 patent is due to expire on May 26, 2027, and therefore has not expired before the submission of this application.

(c) 35 U.S.C. § 156(a)(2)

The term of the '621 patent has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3)

The application for extension is submitted by the owner of the '621 patent, Anacor.

(e) 35 U.S.C. § 156(a)(4)

The product (the active ingredient, including any salt or ester of the active ingredient) in the KERYDIN product has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A)

The permission for the commercial marketing or use of the KERYDIN product after the regulatory review period referred to in subsection (e) above is the first permitted commercial marketing or use of the product under section 505(b) of the Federal Food Drug and Cosmetic Act.

(g) 35 U.S.C. § 156(c)(4)

No patent has been extended under 35 U.S.C. § 156(e)(1) for the regulatory review period that forms the basis for this application for extension of the term of U.S. Patent No. 7,582,621.

The length of extension of the patent term of the '621 patent claimed by applicant is 408 days, until July 7, 2028. The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a)	2765	The number of days in the period beginning on the date an exemption under subsection (i) of section 505 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product (in other words the effective date of IND – here, December 31, 2005) and ending on the

		date the application (NDA) was initially submitted for such product under that subsection (July 26, 2013) (*see* 37 C.F.R. § 1.775(c)(1)).
(b)	347	The number of days in the period beginning on the date the application was initially submitted for the approved product under subsection (b) of section 505 of the Federal Food, Drug, and Cosmetic Act (July 26, 2013) and ending on the date such application was approved under such section (July 7, 2014) (*see* 37 C.F.R. § 1.775(c)(2)).
(c)	3112	The sum of (a) and (b). This is the regulatory review period. (37 C.F.R. § 1.775(c)).
(d)	1341	The number of days in the regulatory review period of (a) which were on and before the date on which the '621 patent issued. (37 C.F.R. § 1.775(d)(1)(i)).
(e)	1424	Subtract (d) from (a) for the days remaining in the regulatory review period of (a). (37 C.F.R. § 1.775(d)(1)(i)).
(f)	0	The number of days in the regulatory review period during which it is determined under 35 U.S.C. § 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence.[1] (37 C.F.R. § 1.775(d)(1)(ii)).
(g)	347	Subtract (f) from (b). (37 C.F.R. § 1.775(d)((1)(ii)).
(h)	1424	Subtract (f) from (e). (37 C.F.R. § 1.775(d)((1)(ii)).
(i)	712	Subtract from (h) one half of the days calculated in (h); half days will be ignored for the purposes of subtraction. (37 C.F.R. § 1.775(d)(1)(iii)).
(j)	1059	The sum of (g) and (i). (37 C.F.R. § 1.775(d)(1)(iii)).
(k)	05/26/2027	The original term of the '621 patent, shortened by any terminal disclaimer.
(l)	4/19/2030	The original term of the patent as shortened by any terminal disclaimer plus the number of days in (j). (37 C.F.R. § 1.775(d)(2)).
(m)	07/07/2028	The date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug and Cosmetic Act plus 14 years. (37 C.F.R. § 1.775(d)(3)).

[1] There has been no such determination. The applicant is not aware of a lack of diligence during the regulatory review period.

(n)	07/07/2028	The earlier of (l) and (m). (37 C.F.R. § 1.775(d)(4)).
(o)	05/26/2032	(k) plus 5 years. (37 C.F.R. § 1.775(d)(5)(i)).
(p)	07/07/2028	The earlier of (n) and (o). (37 C.F.R. § 1.775(d)(5)(ii)).

(13) The applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) Please charge the required fee ($1,120.00) pursuant to 37 C.F.R. § 1.20(j) for receiving and acting upon this Application for Patent Term Extension of the '621 patent to deposit account 03-1721.

(15) Please address inquiries and correspondence to the undersigned.

An original and two copies of these application papers are hereby submitted.

Respectfully submitted,

Dated: August 18, 2014

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(617) 248-4000 (facsimile)

EXHIBIT A

US007582621B2

(12) **United States Patent**
Baker et al.

(10) **Patent No.: US 7,582,621 B2**
(45) **Date of Patent: Sep. 1, 2009**

(54) **BORON-CONTAINING SMALL MOLECULES**

(75) Inventors: **Stephen J. Baker**, Mountain View, CA (US); **Tsutomu Akama**, Sunnyvale, CA (US); **Carolyn Bellinger-Kawahara**, Redwood City, CA (US); **Vincent S. Hernandez**, Watsonville, CA (US); **Karin M. Hold**, Belmont, CA (US); **James J. Leyden**, Malvern, PA (US); **Kirk R. Maples**, San Jose, CA (US); **Jacob J. Plattner**, Berkeley, CA (US); **Virginia Sanders**, San Francisco, CA (US); **Yong-Kang Zhang**, San Jose, CA (US)

(73) Assignee: **Anacor Pharmaceuticals, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 267 days.

(21) Appl. No.: **11/357,687**

(22) Filed: **Feb. 16, 2006**

(65) **Prior Publication Data**

US 2006/0234981 A1 Oct. 19, 2006

Related U.S. Application Data

(60) Provisional application No. 60/654,060, filed on Feb. 16, 2005.

(51) **Int. Cl.**
A61K 31/69 (2006.01)
C07F 5/04 (2006.01)

(52) **U.S. Cl.** **514/64**; 558/288

(58) **Field of Classification Search** 514/64; 558/288

See application file for complete search history.

(56) **References Cited**

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S. J. Baker, et al., "Progress on New Therapeutics for Fungal Nail Infections,"*Annual Reports in Medicinal Chemistry*, 40:323-335 (2005).

* cited by examiner

Primary Examiner—Rei-tsang Shiao
(74) *Attorney, Agent, or Firm*—Morgan, Lewis & Bockius, LLP

(57) **ABSTRACT**

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.

12 Claims, 12 Drawing Sheets

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		

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

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

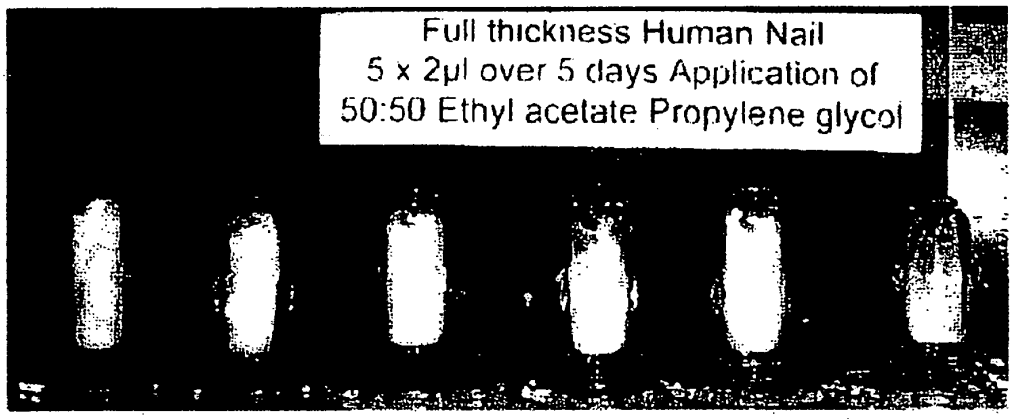

Full thickness Human Nail
5 x 2µl over 5 days Application of
50:50 Ethyl acetate Propylene glycol

FIGURE 6

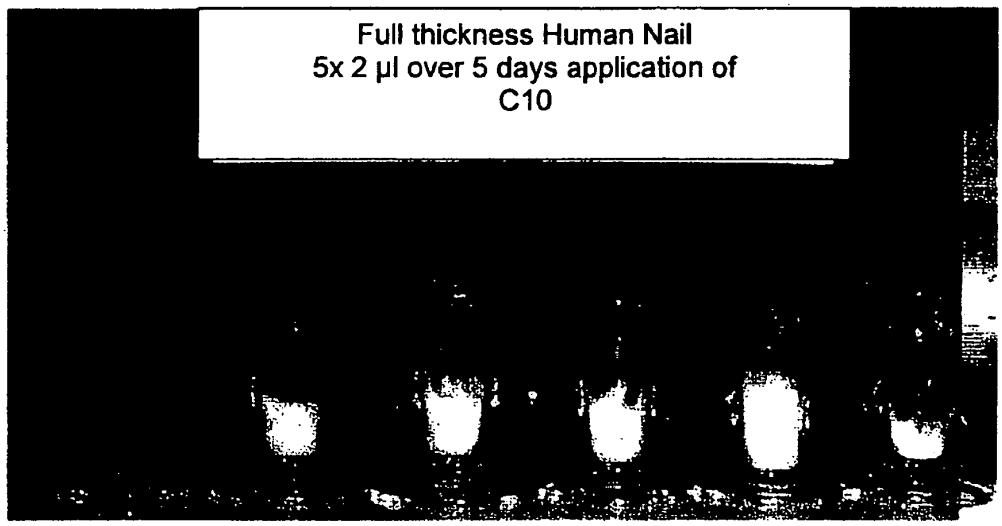

Full thickness Human Nail
5x 2 µl over 5 days application of
C10

FIGURE 7

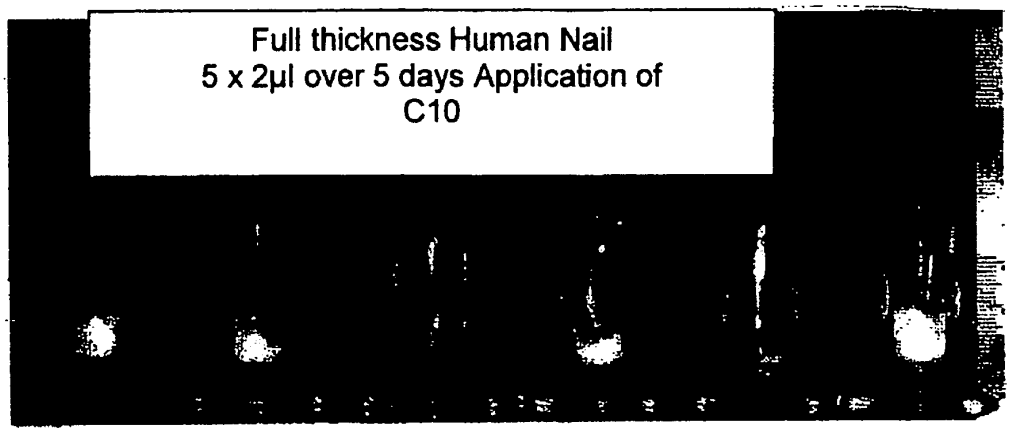

Full thickness Human Nail
5 x 2µl over 5 days Application of
C10

FIGURE 8

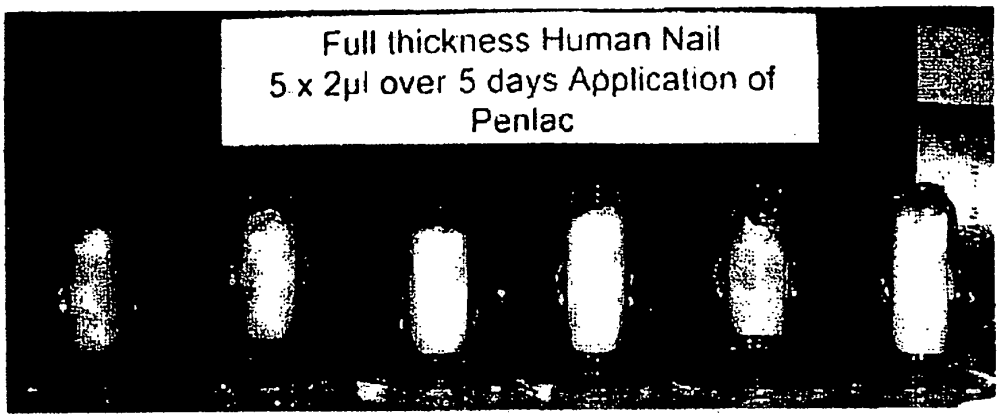
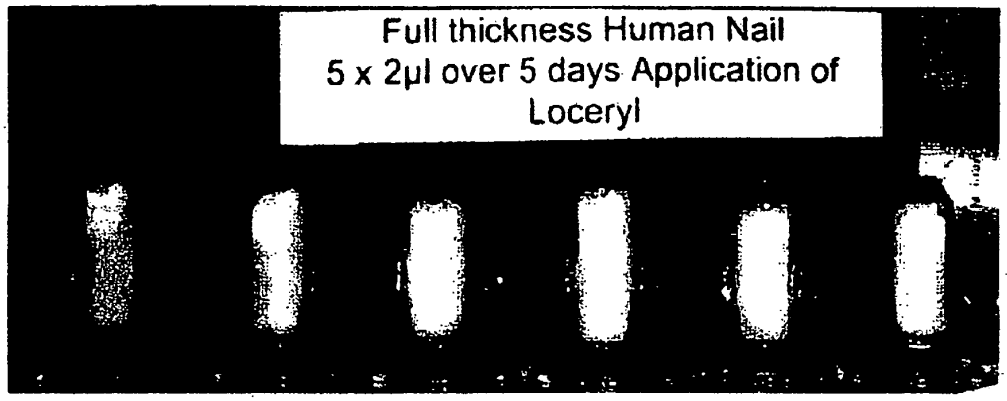

Full thickness Human Nail
5 x 2µl over 5 days Application of
Penlac

FIGURE 9


Full thickness Human Nail
5 x 2µl over 5 days Application of
Loceryl

BORON-CONTAINING SMALL MOLECULES

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is related to U.S. Provisional Patent Application 60/654,060 filed Feb. 16, 2005, which is incorporated by reference in its entirety for all purposes.

BACKGROUND FOR THE INVENTION

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.

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 ketoconozole typically requires administration of 200 to 400 mg/day for 6 months before any significant therapeutic benefit is realized. Such long term, high dose systemic therapy can have significant adverse effects. For example, ketoconozole 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.

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 female patients or those more sensitive to physical appearance. Generally, this type of treatment is not realistic for ruminants such as horses.

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.

Hydrophilic and hydrophobic film forming topical antifungal solutions have also been developed. These dosage forms provide improved contact between the drug and the nail, but the films are not occlusive. 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.

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.

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.

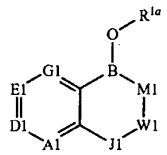
Antimicrobial compositions for controlling bacterial and fungal infections comprising a metal chelate of 8-hydroxyquinoline and an alkyl benzene sulfonic acid have been shown to be efficacious due to the increased ability of the oleophilic group to penetrate the lipoid layers of micro-cells. The compounds 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.

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.

SUMMARY OF THE INVENTION

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

(I)

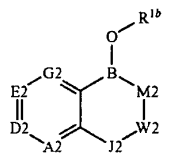


wherein B is boron. R^{1a} is a member selected from a negative charge, a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. M1 is 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 het-

eroaryl. J1 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, OH, NH_2, SH, 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. W1 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, OH, NH_2, SH, 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. A1 is a member selected from CR^{9a} and N. D1 is a member selected from CR^{10a} and N. E1 is a member selected from CR^{11a} and N. G1 is a member selected from CR^{12a} and N. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OH, NH_2, SH, 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 (A1+D1+E1+G1) 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. The aspect has the proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{11a}, E1 is CR^{11a}, G1 is CR^{12a}, then R^{9a} is not halogen, methyl, ethyl, or optionally joined with R^{10a} to a form 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. The aspect has the further proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, then neither R^{6a} nor R^{7a} are halophenyl. The aspect has the further proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 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. The aspect has the further proviso that when M1 is oxygen wherein n1 is 1, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 0, A1 is CR^{9a}, D1 is CR^{1a}, E1 is CR^{11a}, G1 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 W1 is not C=O (carbonyl). The aspect has the further proviso that when M1 is oxygen, W1 is CR^{5a}, J1 is CR^{8a}, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{2a}, 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.

In a second aspect, the invention provides a pharmaceutical formulation comprising (a) a pharmaceutically acceptable excipient; and (b) a compound having a structure according to Formula II:

(II)



wherein B is boron. R^{1b} is a member selected from a negative charge, a salt counterion, 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. M2 is a member selected from oxygen, sulfur and NR^{2b}. R^{2b} 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. J2 is a member selected from $(CR^{3b}R^{4b})_{n2}$ and CR^{5b}. R^{3b}, R^{4b}, and R^{5b} are members independently selected from H, OH, NH_2, SH, 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 n2 is an integer selected from 0 to 2. W2 is a member selected from C=O (carbonyl), $(CR^{6b}R^{7b})_{m2}$ and CR^{8b}. R^{6b}, R^{7b}, and R^{8b} are members independently selected from H, OH, NH_2, SH, 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 m2 is an integer selected from 0 and 1. A2 is a member selected from CR^{9b} and N. D2 is a member selected from CR^{10b} and N. E2 is a member selected from CR^{11b} and N. G2 is a member selected from CR^{12b} and N. R^{9b}, R^{10b}, R^{11b} and R^{12b} are members independently selected from H, OH, NH_2, SH, 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 (A2+D2+E2+G2) is an integer selected from 0 to 3. A member selected from R^{3b}, R^{4b} and R^{5b} and a member selected from R^{6b}, R^{7b} and R^{8b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{3b} and R^{4b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{6b} and R^{7b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{9b} and R^{10b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{10b} and R^{11b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{11b} and R^{12b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

In another aspect, the invention provides a method of killing a microorganism, comprising contacting the microorganism with a therapeutically effective amount of a compound of the invention.

In another aspect, the invention provides a method of inhibiting microorganism growth, comprising contacting the microorganism with a therapeutically effective amount of a compound of the invention.

In another aspect, the invention provides a method of treating an infection in an animal, comprising administering to the animal a therapeutically effective amount of a compound of the invention.

In another aspect, the invention provides a method of preventing an infection in an animal, comprising administering to the animal a therapeutically effective amount of a compound of the invention.

In another aspect, the invention provides a method of treating a systemic infection or an ungual or periungual infection in a human, comprising administering to the animal a therapeutically effective amount of a compound of the invention.

In another aspect, the invention provides a method of treating onychomycosis in a human, comprising administering to the animal a therapeutically effective amount of a compound of the invention.

In another aspect, the invention provides a method of synthesizing a compound of the invention.

In another aspect, the invention provides a method of delivering a compound from the dorsal layer of the nail plate to the nail bed. The method comprises contacting said cell with a compound capable of penetrating the nail plate, under conditions sufficient to penetrate said nail plate, and thereby delivering the compound. 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 has a water solubility between about 0.1 mg/mL and 1.0 g/mL octanol/saturated water.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a table of minimum inhibitory concentration (MIC) data of CBO against various fungi.

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

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

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

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

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.

FIG. **6** displays the results of a 40 μL/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.

FIG. **7** displays the results of a 40 μL/cm 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*.

FIG. **8** displays the results of a 40 μL/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*.

FIG. **9** displays the results of a 40 μL/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*.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions and Abbreviations

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

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

MIC, or minimum inhibitory concentration, is the point where compound stops more than 90% of cell growth relative to an untreated control.

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—.

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.

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

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.

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".

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.

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.

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 $—R'C(O)_2—$.

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.

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.

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, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

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).

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.

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'", $—NR"C(O)_2R'$, —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 $—NO_2$ 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).

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.

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)—, —$S(O)_2$—, —$S(O)_2$NR'— 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 —$S(O)_2$NR'—. The substituents R, R', R" and R'" are preferably independently selected from hydrogen or substituted or unsubstituted (C_1-C_6)alkyl.

"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.

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).

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.

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.

"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.

"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.

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.

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.

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.

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.

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.

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.

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.

"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.

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.

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.

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

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.

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.

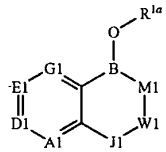
II. Introduction

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

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

(I)

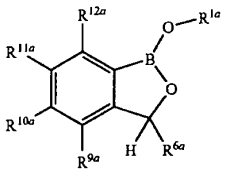


wherein B is boron. R^{1a} is a member selected from a negative charge, a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. M1 is 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. J1 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, OH, NH_2, SH, 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. W1 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, OH, NH_2, SH, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsub-

stituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. The index m1 is an integer selected from 0 and 1. A1 is a member selected from CR^{9a} and N. D1 is a member selected from CR^{10a} and N. E1 is a member selected from CR^{11a} and N. G1 is a member selected from CR^{12a} and N. R^{9a}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OH, NH_2, SH, 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 (A1+D1+E1+G1) 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. The aspect has the proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{1a}, G1 is CR^{12a}, then R^{9a} is not halogen, methyl, ethyl, or optionally joined with R^{10a} to a form 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. The aspect has the further proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, then neither R^{6a} nor R^{7a} are halophenyl. The aspect has the further proviso that when M1 is oxygen, W1 is a member selected from $(CR^{3a}R^{4a})_{n1}$, wherein n1 is 0, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 1, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 is CR^{12a}, and R^{9a}, R^{10a} and R^{11a} are H, then R^{6a}, R^{7a} and R^{12a} are not H. The aspect has the further proviso that when M1 is oxygen wherein n1 is 1, J1 is a member selected from $(CR^{6a}R^{7a})_{m1}$, wherein m1 is 0, A1 is CR^{9a}, D1 is CR^{10a}, E1 is CR^{11a}, G1 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 W1 is not C═O (carbonyl). The aspect has the further proviso that when M1 is oxygen, W1 is CR^{5a}, J1 is CR^{8a}, A1 is CR^{9a}, D1 is C^{10a}, E1 is CR^{11a}, G1 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.

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

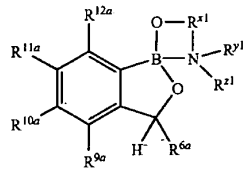
(Ia)



wherein B is boron. R^{1a} is a member selected from a negative charge, a salt counterion, 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^{6a} are members independently selected from H, OH, NH_2, SH, 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}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OH, NH_2, SH, 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}, 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. This embodiment has the proviso that R^{9a} is not halogen, methyl, ethyl, or optionally joined with R^{10a} to form a 4 to 7 membered ring. This embodiment has the proviso that R^{10a} is not unsubstituted phenoxy, $C(CH_3)_3$, halogen, CF_3, methoxy, ethoxy, optionally joined with R^{9a} to form a 4 to 7 membered ring, or optionally joined with R^{11a} to form a 4 to 7 membered ring. This embodiment has the proviso that R^{11a} is not halogen or optionally joined with R^{10a} to form a 4 to 7 membered ring. This embodiment has the proviso that R^{12a} is not halogen.

In an exemplary embodiment, the compound has a structure according to Formula (Ib):

(Ib)

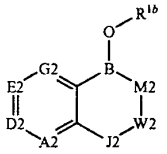


wherein B is boron. R^{x1} is a member selected from substituted or unsubstituted C_1-C_5 alkyl, substituted or unsubstituted C_1-C_5 heteroalkyl. R^{y1} and R^{z1} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. R^{6a} are members independently selected from H, OH, NH_2, SH, 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}, R^{10a}, R^{11a} and R^{12a} are members independently selected from H, OH, NH_2, SH, 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^{11a} and R^{12a}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. This embodiment has the proviso that when R^{9a}, R^{11a} and R^{12a} are H, R^{10a} is not H, halogen, unsubstituted phenoxy or t-butyl. This embodiment has the further proviso that when R^{9a} is H,

R^{10a} and R^{11a} together with the atoms to which they are attached, are not joined to form a phenyl ring. This embodiment has the further proviso that when R^{11a} is H, R^{9a} and R^{10a} together with the atoms to which they are attached, are not joined to form a phenyl ring.

In another aspect, the invention provides a compound having a structure according to Formula II:

(II)

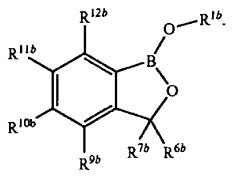


wherein B is boron. R^{1b} is a member selected from a negative charge, a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. M2 is a member selected from oxygen, sulfur and NR^{2b}. R^{2b} 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. J2 is a member selected from $(CR^{3b}R^{4b})_{n2}$ and CR^{5b}. R^{3b}, R^{4b}, and R^{5b} are members independently selected from H, OH, NH_2, SH, 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 n2 is an integer selected from 0 to 2. W2 is a member selected from C=O (carbonyl), $(CR^{6b}R^{7b})_{n2}$ and CR^{8b}. R^{6b}, R^{7b}, and R^{8b} are members independently selected from H, OH, NH_2, SH, 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 m2 is an integer selected from 0 and 1. A2 is a member selected from CR^{9b} and N. D2 is a member selected from CR^{10b} and N. E2 is a member selected from CR^{11b} and N. G2 is a member selected from CR^{12b} and N. R^{9b}, R^{10b}, R^{11b} and R^{12b} are members independently selected from H, OH, NH_2, SH, 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 (A2+D2+E2+G2) is an integer selected from 0 to 3. A member selected from R^{3b}, R^{4b} and R^{5b} and a member selected from R^{6b}, R^{7b} and R^{8b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{3b} and R^{4b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{6b} and R^{7b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{9b} and R^{10b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{10b} and R^{11b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{11b} and R^{12b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

In an exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{n2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E is CR^{11b}, G is CR^{12b}, then R^{9b} is not a member selected from halogen, methyl, ethyl, or optionally joined with R^{10b} to a form phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_n$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_m$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{11b} is not a member selected from unsubstituted phenoxy, $C(CH_3)_3$, halogen, CF_3, methoxy, ethoxy, or optionally joined with R^{9b} to form a phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{10b} is not a member selected from halogen or optionally joined with R^{10b} to form a phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4a})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12}, then R^{12b} is not halogen. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_2$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{6b} is not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{7b} is not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{6b} and R^{7b} are not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, and R^{9b}, R^{10b} and R^{11b} are H, then R^{6b}, R^{7b} and R^{12b} are not H. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen wherein n2 is 1, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, R^{9b} is H, R^{10b} is H, R^{11b} is H, R^{6b} is H, R^{7b} is H, R^{12b} is H, then W2 is not C=O (carbonyl). In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is CR^{5b}, J2 is CR^{8b}, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, R^{6b}, R^{7b}, R^{9b}, R^{10b}, R^{11b} and R^{12b} are H, then R^{5b} and R^{8b}, together with the atoms to which they are attached, do not form a phenyl ring.

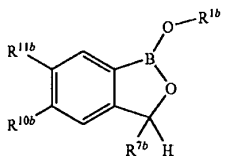
In an exemplary embodiment, the compound with a structure according to Formula (IIa):

(IIa)



In another exemplary embodiment, the compound has a structure according to Formula (IIb):

(IIb)

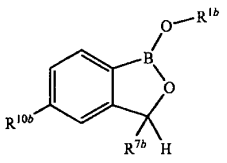


wherein R^{7b} is a member selected from H, methyl, ethyl and phenyl. R^{10b} is a member selected from H, OH, NH_2, SH, halogen, substituted or unsubstituted phenoxy, substituted or unsubstituted phenylalkyloxy, substituted or unsubstituted phenylthio and substituted or unsubstituted phenylalkylthio. 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.

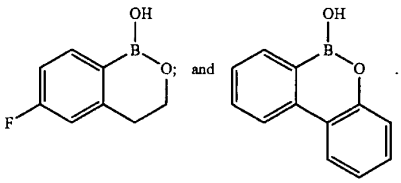
In another exemplary embodiment, R^{1b} is a member selected from a negative charge, H and a salt counterion. In another exemplary embodiment, R^{10b} and R^{11b} are H. In another exemplary embodiment, one member selected from R^{10b} and R^{11b} is H and the other member selected from R^{10b} and R^{11b} is a member selected from halo, methyl, cyano, methoxy, hydroxymethyl and p-cyanophenyloxy. In another exemplary embodiment, R^{10b} and R^{11b} are members independently selected from fluoro, chloro, methyl, cyano, methoxy, hydroxymethyl, and p-cyanophenyl. In another exemplary embodiment, 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, 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, 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.

In another exemplary embodiment, the compound has a structure according to Formula (IIc):

(IIc)

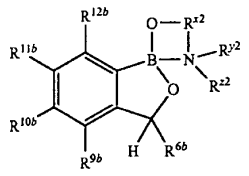


wherein R^{10b} is a member selected from H, halogen, CN and substituted or unsubstituted C_{1-4} alkyl. In another exemplary embodiment, the compound has a formulation which is a member selected from:



In another exemplary embodiment, the compound has a structure according to Formula (IId):

(IId)



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.

The compounds of Formulae (I) or (II) can form a hydrate with water, solvates with alcohols such as methanol, ethanol, propanol, and the like; adducts with amino compounds, such as ammonia, methylamine, ethylamine, and the like; adducts with acids, such as formic acid, acetic acid and the like; complexes with ethanolamine, quinoline, amino acids, and the like.

Preparation of Boron-Containing Small Molecules

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.

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^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} can be used to refer to the corresponding symbols in Formulae (I) or (II). For example, the symbol A can refer to A1 of Formula (I), or A2 of Formula (II), subject to the provisos of each Formula.

Preparation Strategy #1

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.

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-tetrahydro-

furan, 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.

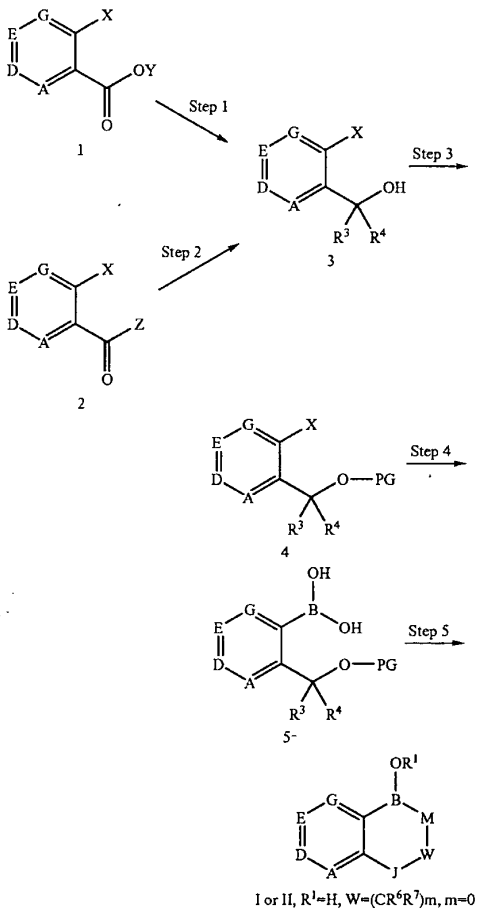
In Step 3, the hydroxyl group of compound 3 is protected with a protecting group which is stable under neutral or basic conditions. The protecting group is typically selected from methoxymethyl, ethoxyethyl, tetrahydropyran-2-yl, trimethylsilyl, tert-butyldimethylsilyl, tributylsilyl, combinations thereof 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 to 48 h.

In the case of tetrahydropyran-2-yl, compound 3 is treated with 1 to 3 equivalents of 3,4-dihydro-2H-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, 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 40° C., and is complete in 1 to 48 h.

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.

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, or isopropylmagnesium chloride 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. After the addition of trialkyl borate, the reaction is allowed to warm to room temperature, which is typically between 15 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.

In Step 5, the protecting group of compound 5 is removed under acidic conditions to give compound of Formulae (I) and (II). 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 and 40° C.; reaction completion times range from 0.5 to 48 h.



Preparation Strategy #2

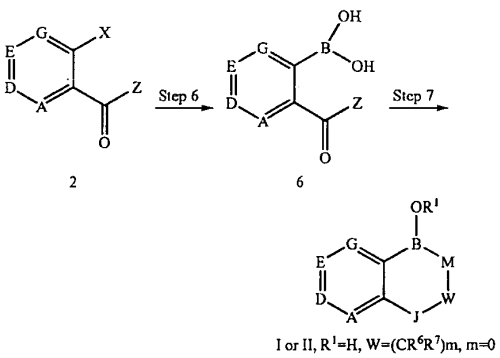
In Scheme 2, Step 6, compound 2 is converted into boronic acid (6) via a transition metal catalyzed cross-coupling reaction. Compound 2 is treated with 1 to 3 equivalents of bis (pinacolato)diboron or 4,4,5,5-tetramethyl-1,3,2-dioxaborolane in the presence of transition metal catalyst, with the use of appropriate ligand and base as necessary. Suitable transi-

tion 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, dimethylsulfoxide, 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.

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.

In Step 7, the carbonyl group of compound 6 is treated with a reducing agent in an appropriate solvent to give a compound of Formulae (I) and (II). 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



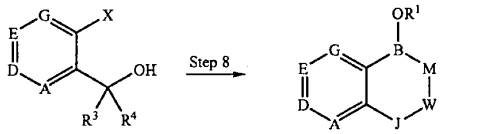
2 6

I or II, R^1=H, W=(CR^6R^7)m, m=0

Preparation Strategy #3

In Scheme 3, Step 8, compounds of Formulae (I) and (II) 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



3

I or II, R^1=H, W=(CR^6R^7)m, m=0

Preparation Strategy #4

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.

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.

Steps 3 through 5 convert compound 3 into a compound of Formulae (I) and (II).

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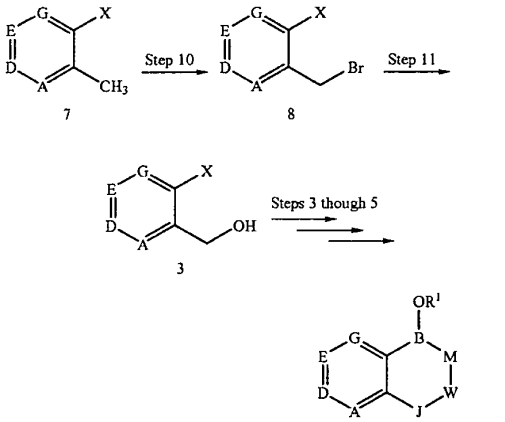
Scheme 4

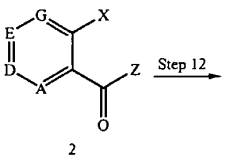


Preparation Strategy #5

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.

Steps 2 through 5 convert compound 9 into a compound of Formulae (I) and (II).

Scheme 5



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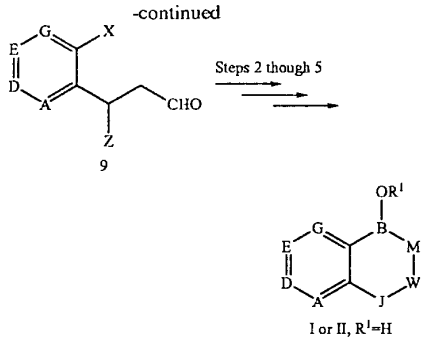
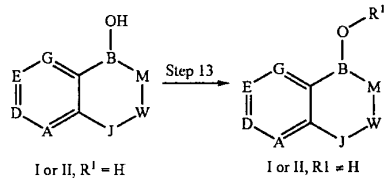


Preparation Strategy #6

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.

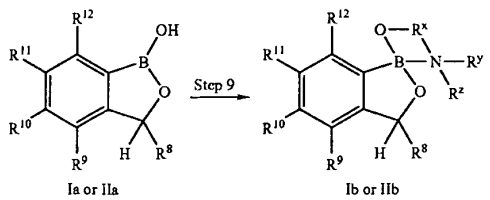
Scheme 6



Preparation Strategy #7

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



The compounds of Formulae (I) or (II) can be converted into hydrates and solvates by methods similar to those described above.

IV. Methods of Inhibiting Microorganism Growth or Killing Microorganisms

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 according to Formulae (I) or (II). 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.

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.

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; 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*.

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.

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	
Picornaviridae	Polio Human hepatitis A Human rhinovirus
Togaviridae and Flaviviridae	Rubella - German measles Yellow fever

TABLE A-continued

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

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.*

V. Methods of Treating or Preventing Infections

In another aspect, the invention provides a method of treating or preventing an infection, or both. 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 of the invention is according to Formulae (I) or (II). 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 or periungual infection.

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

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 the compound of the invention, sufficient to treat or prevent said infection. In another exemplary embodiment, the method includes administering the compound 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.

V. a) 1) Onychomycosis

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.

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.

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.

In an exemplary embodiment, the invention provides a method of treating or preventing onychomycosis. The method includes administering to the animal a therapeutically effective amount of a pharmaceutical formulation of the invention, sufficient to treat or prevent onychomycosis. In another exemplary embodiment, the method includes administering the

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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 having a structure according to Formula (IIb). In another exemplary embodiment, R^{1b} is H. In another exemplary embodiment, R^{10b} and R^{11b} are H. In another exemplary embodiment, 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, R^{10b} and R^{11b} are members independently selected from fluoro, chloro, methyl, cyano, methoxy, hydroxymethyl, and p-cyanophenyl. In another exemplary embodiment, R^{1b} is H; R^{7b} is H; R^{10b} is F and R^{11b} are H. In another exemplary embodiment, R^{11b} and R^{12b}, along with the atoms to which they are attached, are joined to form a phenyl group.

V. a) 2) Other Unugal and Periungual Infections

In an exemplary embodiment, the invention provides a method of treating or preventing an ungual or periungual infection in a mammal. This method comprising administering to the mammal 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 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), 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.

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.

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.

V. b) Methods of Treating Systemic Diseases

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 diseases can be oral, intravenous or transdermal.

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.

V. c) Methods of Treating Diseases Involving Viruses

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.

V. d) Methods of Treating Diseases Involving Parasites

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.

VI. Methods of Nail Penetration

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.

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 and/or preferentially bound to keratin that the drug is rendered inactive.

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.

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.

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.

Compounds with a molecular weight of less than 200 Da penetrate the nail plate in a manner superior to the commer-

cially 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.

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.

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.

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.

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.

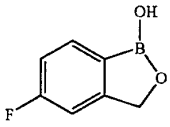
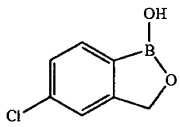
In an exemplary embodiment, the present invention provides compounds with a molecular weight selected from a range above, with a water solubility selected from a range above, that are still able to penetrate the nail plate.

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.

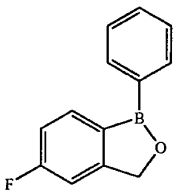
In an exemplary embodiment, the present invention provides compounds with a molecular weight selected from a range above, with a log P selected from a range above, and with a water solubility selected from a range above, that are still able to penetrate the nail plate.

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

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

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 (μ/mL):	not determined

In a preferred embodiment the topical formulations including a compound of Formulae (I) or (II) described structurally above 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.

This invention is still further directed to methods for treating a viral infection mediated at least in part by dermatophytes, *Trichophyton, Microsporum* or *Epidermophyton* species, or a yeast-like fungi including *Candida* species, in mammals, which methods comprise administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral 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.

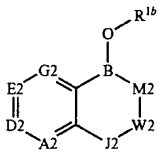
Compounds contemplated by the present invention may have broad spectrum antifungal activity and as such may be candidates for use against other cutaneous fungal infections.

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.

VII. Pharmaceutical Formulations

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 according to Formula (I), (Ia), (Ib), (Ic), or (Id). 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 Formula (II), (IIa), (IIb), (IIc), (IId).

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 II:



(II)

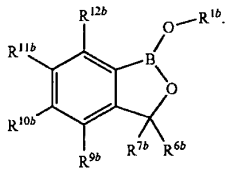
wherein B is boron. R^{1b} is a member selected from a negative charge, a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. M2 is a member selected from oxygen, sulfur and NR^{2b}. R^{2b} 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. J2 is a member selected from $(CR^{3b}R^{4b})_{n2}$ and CR^{5b}. R^{3b}, R^{4b}, and R^{5b} are members independently selected from H, OH, NH_2, SH, 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 n2 is an integer selected from 0 to 2. W2 is a member selected from C=O (carbonyl), $(CR^{6b}R^{7b})_{m2}$ and CR^{8b}. R^{6b}, R^{7b}, and R^{8b} are members independently selected from H, OH, NH_2, SH, 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 m2 is an integer selected from 0 and 1. A2 is a member selected from CR^{9b} and N. D2 is a member selected from CR^{10b} and N. E2 is a member selected from CR^{11b} and N. G2 is a member selected from CR^{12b} and N. R^{9b}, R^{10b}, R^{11b} and R^{12b} are members independently selected from H, OH, NH_2, SH, 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 (A2+D2+E2+G2) is an integer selected from 0 to 3. A member selected from R^{3b}, R^{4b} and R^{5b} and a member selected from R^{6b}, R^{7b} and R^{8b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{3b} and R^{4b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{6b} and R^{7b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{9b} and R^{10b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{10b} and R^{11b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring. R^{11b} and R^{12b}, together with the atoms to which they are attached, are optionally joined to form a 4 to 7 membered ring.

In an exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{n2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E is CR^{11b}, G is CR^{12b}, then R^{9b} is not a member selected from halogen, methyl, ethyl, or optionally joined with R^{10b} to a form phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_n$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_m$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{10b} is not a member selected from unsubstituted phenoxy, $C(CH_3)_3$, halogen, CF_3, methoxy, ethoxy, or optionally joined with R^{9b} to form a phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{11b} is not a member selected from halogen or optionally joined with R^{10b} to form a phenyl ring. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{12b}, G2 is CR^{12b}, then R^{12b} is not halogen. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{6b} is not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_2$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, then R^{7b} is not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_m$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{11b}, E2 is CR^{12b}, G2 is CR^{12}b, then R^{6b} and R^{7b} are not halophenyl. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is a member selected from $(CR^{3b}R^{4b})_{n2}$, wherein n2 is 0, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 1, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, and R^{9b}, R^{10b} and R^{11b} are H, then R^{6b}, R^{7b} and R^{12b} are not H. In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen wherein n2 is 1, J2 is a member selected from $(CR^{6b}R^{7b})_{m2}$, wherein m2 is 0, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is CR^{12b}, R^{9b} is H, R^{10b} is H, R^{11b} is H, R^{6b} is H, R^{7b} is H, R^{12b} is H, then W2 is not C=O (carbonyl). In another exemplary embodiment, the aspect has the proviso that when M2 is oxygen, W2 is CR^{5b}, J2 is CR^{8b}, A2 is CR^{9b}, D2 is CR^{10b}, E2 is CR^{11b}, G2 is

CR^{12b}, R^{6b}, R^{7b}, R^{9b}, R^{10b}, R^{11b} and R^{12b} are H, then R^{5b} and R^{8b}, together with the atoms to which they are attached, do not form a phenyl ring.

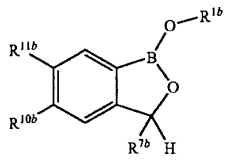
In an exemplary embodiment, the pharmaceutical formulation has a compound with a structure according to Formula (IIa):

(IIa)



In another exemplary embodiment, the pharmaceutical formulation has a compound with a structure according to Formula (IIb):

(IIb)

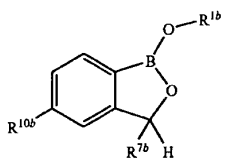


wherein R^{7b} is a member selected from H, methyl, ethyl and phenyl. R^{10b} is a member selected from H, OH, NH_2, SH, halogen, substituted or unsubstituted phenoxy, substituted or unsubstituted phenylalkyloxy, substituted or unsubstituted phenylthio and substituted or unsubstituted phenylalkylthio. 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.

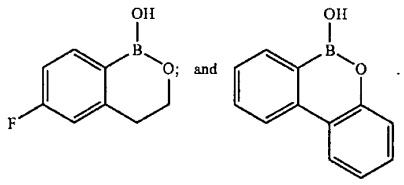
In another exemplary embodiment, R^{1b} is a member selected from a negative charge, H and a salt counterion. In another exemplary embodiment, R^{10b} and R^{11b} are H. In another exemplary embodiment, one member selected from R^{10b} and R^{11b} is H and the other member selected from R^{10b} and R^{11b} is a member selected from halo, methyl, cyano, methoxy, hydroxymethyl and p-cyanophenyloxy. In another exemplary embodiment, R^{10b} and R^{11b} are members independently selected from fluoro, chloro, methyl, cyano, methoxy, hydroxymethyl, and p-cyanophenyl. In another exemplary embodiment, 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, 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, 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.

In another exemplary embodiment, the pharmaceutical formulation has a compound with a structure according to Formula (IIc):

(IIc)

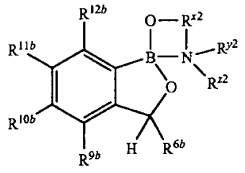


wherein R^{10b} is a member selected from H, halogen, CN and substituted or unsubstituted C_{1-4} alkyl. In another exemplary embodiment, the compound has a formulation which is a member selected from:



In another exemplary embodiment, the pharmaceutical formulation has a compound with a structure according to Formula (IId):

(IId)



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^{y2} 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 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).

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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).

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).

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.

VII. a) Topical Formulations

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

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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%).

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, N.J.).

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.

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, N.J.).

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%.

The topical pharmaceutical compositions may also comprise suitable preservatives. Preservatives are compounds added to a pharmaceutical formulation to act as an antimicrobial 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.

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%.

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.

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.

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, Calif.).

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.

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, Ohio.

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.

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.

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.

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 Formula (I) of Formula (II). 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 Formula (I) of Formula (II). 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.

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.

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.

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.

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.

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.

In an exemplary embodiment, the pharmaceutical formulation is a lacquer. Please see Remington's, supra, for more information on the production of lacquers.

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 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

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.

Anti-inflammatory agents include, but are not limited to, bisabolol, mentholatum, dapsone, aloe, hydrocortisone, and the like.

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.

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.

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).

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.

Agents that are effective to control or modify keratinization, including without limitation: tretinoin, tazarotene, and adapalene.

The compositions comprising an compound/active agent of Formula (I) of Formula (II), 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.

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

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. B*677: 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).

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

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.

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.

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 $mg/m^2/day$.

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 %.

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

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

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

Exemplary compounds of structure 3 prepared by the method above are provided below.

1.2.a 2-Bromo-5-chlorobenzyl Alcohol

^{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

^{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

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

Exemplary compounds of structure 3 prepared by the method above are provided below.

2.2.a 2-Bromo-5-(4-cyanophenoxy)benzyl Alcohol

^{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

^{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

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

^{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).

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

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

Exemplary compounds of structure 4 prepared by the method above are provided below.

3.2.a 2-Bromo-5-chloro-1-(methoxymethoxymethyl)benzene

^{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-[ ]-(methoxymethoxy)ethyl/benzene

^{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

^{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-(methoxymethoxym-ethyl)benzene

^{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

^{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).

3.2f 2-Bromo-5-methoxy-1-(methoxymethoxymethyl)benzene

^{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=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-(meth-oxymethoxy)ethane

^{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

^{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-(meth-oxymethoxymethyl)benzene

^{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.

3.2j 2-Bromo-5-(tert-butyldimethylsiloxy)-1-(meth-oxymethoxymethyl)benzene

^{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-(meth-oxymethoxymethyl)benzene

^{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.l 2-Bromo-5-phenoxy-1-(methoxymethoxymethyl)benzene

^{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).

Additional examples of compounds which can be produced by this method include 2-bromo-1-(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

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

Analytical data for exemplary compounds of structure I are provided below.

4.2.a 5-Chloro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (C1)

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 (C2)

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

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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-Fluoro-1,3-dihydro-1-hydroxy-3-methyl-2,1-benzoxaborole (C3)

^{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, 1H), 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 (C4)

^{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 (C5)

^{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 (C6)

^{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 (C7)

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, 3H) ppm.

4.2.h 1,3-Dihydro-1-hydroxy-5-methyl-2,1-benzoxaborole (C8)

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 (C9)

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 (C10)

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 (C11)

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=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.l 7-Hydroxy-2,1-oxaborolano[5,4-c]pyridine (C12)

^{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.

4.2.m 1,3-Dihydro-6-fluoro-1-hydroxy-2,1-benzoxaborole (C13)

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 (C14)

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 (C15)

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 (C16)

^{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 (C17)

^{1}H-NMR (300 MHz, DMSO-d_6) 8 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 (C18)

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 (C19)

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 (C20)

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 (C21)

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 (C22)

^{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 (C23)

^{1}H-NMR (300 MHz, DMSO-d_6) 6 (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 (C24)

^{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 (C25)

^{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 (C26)

^{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 (C27)

^{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 (C28)

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 (C29)

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 (C30)

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 (C31)

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 (C32)

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 (C33)

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 (C34)

^{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 (C35)

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 (C36)

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.

^{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 (C37)

For coupling between 3-fluorobenzonitrile and substituted phenol to give starting material 2: Li, F. et al., *Organic Letters* (2003), 5(12), 2169-2171.

^{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-hydroxy-2,1-benzoxaborole (C38)

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%).

^{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-5-[4-(tetrazole-1-yl)phenoxy]-2,1-benzoxaborole (C39)

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%).

^{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

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

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)

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

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

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)

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

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

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)

Analytical data for this compound is listed in 4.2.j.

Example 8

Preparation of 8 from 7

8.1 Bromination

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

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

Exemplary compounds of structure 3 prepared by the method above are provided below.

9.2.a 2-Bromo-5-cyanobenzyl Alcohol

^{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).

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

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 (×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

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

To a solution of Ia in toluene was added amino alcohol and the participated solid was collected to give Ib.

12.2 Results

(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 (C40)

^{1}H-NMR (300 MHz, DMSO-d_6) 6 (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

Compounds of the present invention can be administered to a patient using a therapeutically effective amount of a compound of Formulae (I) or (II) 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. 20% propylene glycol; 70% ethanol; 10% compound of invention;

2. 70% ethanol; 20% poly(vinyl methyl ether-alt-maleic acid monobutyl ester); 10% 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.

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

All MIC testing followed the National Committee for Clinical Laboratory Standards (NCCLS) guidelines for antimicrobial testing of yeasts 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

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).

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

(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

(C10) was obtained from Anacor Pharmaceuticals, Inc. (Palo Alto, Calif., 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.

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 $0.5\text{-}2.5\times10^3$ cells/mL for yeasts or $0.4\text{-}5\times10^4$ 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

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 AN2690 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

The solubility, room temperature stability and Log P of C10 was determined by the following methodology.

Reagents and Standards:

Ethanol: 200 proof ACS Grade (EM Science, Gibbstown, N.J., USA); Octanol: Octyl alcohol (EM Science, Gibbstown, N.J., USA); Acetonitrile: HPLC Grade (Burdick & Jackson, Muskegon, Mich., USA); Ammonium Acetate: lot 3272X49621 (Mallinckrodt, Phillipsburg, N.J., USA); C10: lot A032-103 (Anacor Pharmaceuticals, Palo Alto, Calif., USA); p-Nitrophenol (PNP): lot OGNO1 (TCI America, Portland, Oreg., USA); Water: Deionized water (from Millipore systems, Billerica, Mass., USA)

Solubility

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

C10 (10 μL of 5000 μ/mL) at 2× 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

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

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 μL 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

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.

The partition coefficient (P) was calculated according to the equation detailed below:

$$P=[\text{Sample concentration}]_{octanol}/[\text{Sample concentration}]_{water}$$

$$\text{Log } P=\log_{10}(\text{partition coefficient})$$

Results:

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

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
1 h-1	1.26	108	1.93
1 h-2	1.21	103	1.93
1 h-3	1.05	115	2.04
24 h-1	1.27	104	1.91
24 h-2	1.17	109	1.97
24 h-3	1.28	99.0	1.89

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-0 h	82.5	3.72	115
Water-24 h	95.0	21.4	
Octanol-0 h	115	3.06	93
Octanol-24 h	107	6.11	

Example 18

Determination of Penetration of C10 into the Human Nail

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

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.

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 (×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

Healthy human finger nail plates were collected from adult human cadavers and stored in a closed container at 0-4° 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:

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	Group A			Group C		
Day	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

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:

tip wetted with absolute ethanol, then
tip wetted with absolute ethanol, then
tip wetted with 50% IVORY liquid soap, then
tip wetted with distilled water, then
final tip wetted with distilled water.

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

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

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

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.

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, Conn.) 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.

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

All radioactivity measurements were conducted with a Model 1500 Liquid Scintillation Counter (Packard Instrument Company, Downer Grove, Ill.). 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, Conn.). Other samples (standard dose, surface washing, and bedding material) were mixed directly with Universal ES scintillation cocktail (ICN Biomedicals, Costa Mesa, Calif.). Background control and test samples were counted for 3 minutes each for radioactivity.

Data Analysis

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 concentra-

tion 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.

Terminology

Ventral/intermediate center: Powdered nail sample 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).

Dorsal/intermediate center: Immediate area of dosed site.

Remainder nail: The remaining part of the nail that has not been dosed.

Supporting bed: 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.

Surfacing washing: Ethanol (or other organic solvents) and soap/water washing on the surface of the dosed site.

Ring: A plastic ring placed on the top of the nail plate to prevent leakage from the dose site onto rest of the nail plate or inside of the cell chamber.

Cell washing: Ethanol (or other organic solvents) and soap/water wash of the inside of the diffusion cell.

Results

Characteristics of Nail Samples

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

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 ($p \leqq 0.002$).

C10 and Ciclopirox Equivalent in Cotton Ball Nail Supporting Bed

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 ($p \leqq 0.004$). 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

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

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.

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 ($p \leqq 0.002$) than group C after a 14-day dosing period.

Example 19

Determination of Penetration of C10 into the Human Nail

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 Feb. 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.

The following materials were used in these experiments. These materials were used without any modifications.

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

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

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.

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

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.

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.

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 method of treating an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said infection.

2. The method of claim **1**, wherein said infection is a member selected from a systemic infection, a cutaneous infection, and an ungual or periungual infection.

3. The method of claim **1**, 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.

4. The method of claim **1**, wherein said infection is onychomycosis.

5. The method of claim **1**, wherein said animal is a member selected from a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey.

6. The method of claim **4**, wherein said onychomycosis is tinea unguium.

7. The method of claim **1**, wherein said animal is a human.

8. The method of claim **1**, wherein the administering is at a site which is a member selected from the skin, nail, hair, hoof and claw.

9. The method of claim **8**, wherein said skin is the skin surrounding the nail, hair, hoof or claw.

10. The method of claim **1**, wherein said infection is a fungal infection.

11. A method of treating onychomycosis in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said onychomycosis.

12. A method of inhibiting the growth of a fungus in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,582,621 B2
APPLICATION NO. : 11/357687
DATED : September 1, 2009
INVENTOR(S) : Baker et al.

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

On the Title Page

Item [*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 267 days

Delete the phrase "by 267 days" and insert -- by 464 days --

Signed and Sealed this

First Day of June, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
Certificate

Patent No. 7,582,621 B2 Patented: September 1, 2009

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

Accordingly, it is hereby certified that the correct inventorship of this patent is: Stephen J. Baker, Mountain View, CA (US); Tsutomu Akama, Sunnyvale, CA (US); Vincent S. Hernandez, Watsonville, CA (US); Karin M. Hold, Belmont, CA (US); James J. Leyden, Malvern, PA (US); Jacob J. Plattner, Berkeley, CA (US); Virginia Sanders, San Francisco, CA (US); and Yong-Kang Zhang, San Jose, CA (US).

Signed and Sealed this Sixteenth Day of July 2013.

BRANDON FETTEROLF
Supervisory Patent Examiner
Art Unit 1628
Technology Center 1600

EXHIBIT B

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KERYDIN safely and effectively. See full prescribing information for KERYDIN.

KERYDIN™ (tavaborole) topical solution, 5%
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------
KERYDIN is an oxaborole antifungal indicated for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*. (1)

----------DOSAGE AND ADMINISTRATION----------
- Apply KERYDIN to affected toenails once daily for 48 weeks. (2)
- KERYDIN should be applied to the entire toenail surface and under the tip of each toenail being treated. (2)
- For topical use only. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Solution, 5%. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
Common adverse reactions occurring in ≥1% in subjects treated with KERYDIN included application site exfoliation, ingrown toenail, application site erythema, and application site dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Anacor Pharmaceuticals at 1-844-4ANACOR [1-844-426-2267] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KERYDIN (tavaborole) topical solution, 5% is an oxaborole antifungal indicated for the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*.

2 DOSAGE AND ADMINISTRATION

Apply KERYDIN to affected toenails once daily for 48 weeks.
KERYDIN should be applied to the entire toenail surface and under the tip of each toenail being treated.
KERYDIN is for topical use only and not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

KERYDIN topical solution, 5% is a clear, colorless alcohol-based solution. Each milliliter of solution contains 43.5 mg (5% w/w) of tavaborole.

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two clinical trials, 791 subjects were treated with KERYDIN. The most commonly reported adverse reactions are listed below (Table 1).

Table 1: Adverse Reactions Occurring in ≥1% of KERYDIN Topical Solution, 5%-Treated Subjects and at a Greater Frequency than Observed with Vehicle

Preferred Term	KERYDIN N=791 n(%)	Vehicle N=395 n(%)
Application site exfoliation	21 (2.7%)	1 (0.3%)
Ingrown toenail	20 (2.5%)	1 (0.3%)
Application site erythema	13 (1.6%)	0 (0%)
Application site dermatitis	10 (1.3%)	0 (0%)

A cumulative irritancy study revealed the potential for KERYDIN to cause skin irritation. There was no evidence that KERYDIN causes contact sensitization.

7 DRUG INTERACTIONS

In vitro studies have shown that tavaborole, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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There are no adequate and well-controlled studies with KERYDIN in pregnant women. KERYDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted in rats and rabbits and a dermal embryofetal development study was conducted in rabbits.

Oral administration:
In an oral embryofetal development study in rats, oral doses of 30, 100, and 300 mg/kg/day tavaborole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal resorption and/or deaths) and drug-related skeletal malformations and variations suggestive of delayed development (i.e., a delay in ossification) were noted in fetuses at 300 mg/kg/day tavaborole [570 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No developmental toxicity was noted in rats at 100 mg/kg/day tavaborole (26 times the MRHD based on AUC comparisons).

In an oral embryofetal development study in rabbits, oral doses of 15, 50, and 150 mg/kg/day tavaborole were administered during the period of organogenesis (gestational days 7-19) to pregnant female rabbits. In the presence of maternal toxicity, excessive embryofetal mortality due to post-implantation loss was noted at 150 mg/kg/day tavaborole. No drug related malformations were noted in rabbits at 150 mg/kg/day tavaborole (155 times the MRHD based on AUC comparisons). No embryofetal mortality was noted in rabbits at 50 mg/kg/day tavaborole (16 times the MRHD based on AUC comparisons).

Topical administration:
In a dermal embryofetal development study in rabbits, topical doses of 1%, 5%, and 10% tavaborole solution were administered during the period of organogenesis (gestational days 6-28) to pregnant female rabbits. A dose dependent increase in dermal irritation at the treatment site was noted at 5% and 10% tavaborole solution. A decrease in fetal bodyweight was noted at 10% tavaborole solution. No drug related malformations were noted in rabbits at 10% tavaborole solution (36 times the MRHD based on AUC comparisons). No embryofetal toxicity was noted in rabbits at 5% tavaborole solution (26 times the MRHD based on AUC comparisons).

Nonteratogenic effects:
In an oral pre- and post-natal development study in rats, oral doses of 15, 60, and 100 mg/kg/day tavaborole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of minimal maternal toxicity, no embryofetal toxicity or effects on postnatal development were noted at 100 mg/kg/day (29 times the MRHD based on AUC comparisons).

8.3 Nursing Mothers
It is not known whether tavaborole is excreted in human milk following topical application of KERYDIN. Because many drugs are excreted in human milk, caution should be exercised when KERYDIN is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

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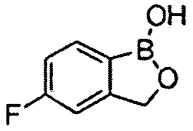
8.5 Geriatric Use

In clinical trials of 791 subjects who were exposed to KERYDIN, 19% were 65 years of age and over, while 4% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

KERYDIN (tavaborole) topical solution, 5% contains tavaborole, 5% (w/w) in a clear, colorless alcohol-based solution for topical use. The active ingredient, tavaborole, is an oxaborole antifungal with the chemical name of 5 fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. The chemical formula is $C_7H_6BFO_2$, the molecular weight is 151.93 and the structural formula is:



Tavaborole is a white to off-white powder. It is slightly soluble in water and freely soluble in ethanol and propylene glycol.

Each mL of KERYDIN contains 43.5 mg of tavaborole. Inactive ingredients include alcohol, edetate calcium disodium, and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

KERYDIN is an oxaborole antifungal [see *Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

At therapeutic doses, KERYDIN is not expected to prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

Tavaborole undergoes extensive metabolism. Renal excretion is the major route of elimination.

In a clinical pharmacology trial of six healthy adult male volunteers who received a single topical application of 5% ^{14}C-tavaborole solution, tavaborole conjugates and metabolites were shown to be excreted primarily in the urine.

The pharmacokinetics of tavaborole was investigated in 24 subjects with distal subungual onychomycosis involving at least 4 toenails (including at least 1 great toenail) following a single dose and a 2-week daily topical application of 200 µL of a 5% solution of tavaborole to all ten toenails and 2 mm of skin surrounding each toenail. Steady state was achieved after 14 days of dosing. After a single dose, the mean (± standard deviation) peak concentration (C_{max}) of tavaborole was 3.54 ± 2.26 ng/mL (n=21 with measurable concentrations, range 0.618-10.2 ng/mL, LLOQ=0.5 ng/mL), and the mean AUC_{last} was 44.4 ± 25.5 ng*hr/mL (n=21). After 2 weeks of daily dosing, the mean C_{max} was 5.17 ± 3.47 ng/mL (n=24, range 1.51-12.8 ng/mL), and the mean AUC_{τ} was 75.8 ± 44.5 ng*hr/mL.

12.4 Microbiology

Mechanism of Action

The mechanism of action of tavaborole is inhibition of fungal protein synthesis. Tavaborole inhibits protein synthesis by inhibition of an aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS).

Activity in vitro and in clinical infections

Tavaborole has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections *[see Indications and Usage (1)]:*

Trichophyton rubrum

Trichophyton mentagrophytes

Mechanism of Resistance

Trichophyton mentagrophytes and *Trichophyton rubrum* strains from isolates collected in the clinical trials have not demonstrated resistance following repeated exposure to tavaborole.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an oral carcinogenicity study in Sprague-Dawley rats, oral doses of 12.5, 25, and 50 mg/kg/day tavaborole were administered to rats once daily for 104 weeks. No drug related neoplastic findings were noted at oral doses up to 50 mg/kg/day tavaborole (14 times the MRHD based on AUC comparisons).

In a dermal carcinogenicity study in CD-1 mice, topical doses of 5%, 10%, and 15% tavaborole solution were administered to mice once daily for 104 weeks. No drug related neoplastic findings were noted at topical doses up to 15% tavaborole solution (89 times the MRHD based on AUC comparisons).

Tavaborole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

No effects on fertility were observed in male and female rats that were administered oral doses up to 300 mg/kg/day tavaborole (107 times the MRHD based on AUC comparisons) prior to and during early pregnancy.

14 CLINICAL STUDIES

The efficacy and safety of KERYDIN was evaluated in two multicenter, double-blind, randomized, vehicle-controlled trials. KERYDIN or vehicle was applied once daily for 48 weeks in subjects with 20% to 60% clinical involvement of the target toenail, without dermatophytomas or lunula (matrix) involvement.

A total of 1194 subjects (795 KERYDIN, 399 Vehicle) 18 to 88 years of age, 82% male, 84% white, participated in these two trials. Efficacy assessments were made at 52 weeks following a 48-week treatment period.

The Complete Cure efficacy endpoint included negative mycology (negative KOH wet mount and negative fungal culture) and Completely Clear Nail (no clinical evidence of onychomycosis as evidenced by a normal toenail plate, no onycholysis, and no subungual hyperkeratosis). Efficacy results from the two trials are summarized in Table 2.

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Table 2: Efficacy Outcomes

Efficacy Variable	Trial 1		Trial 2	
	KERYDIN N=399 n(%)	Vehicle N=194 n(%)	KERYDIN N=396 n(%)	Vehicle N=205 n(%)
Complete Cure[a]	26 (6.5%)	1 (0.5%)	36 (9.1%)	3 (1.5%)
Complete or Almost Complete Cure[b]	61 (15.3%)	3 (1.5%)	71 (17.9%)	8 (3.9%)
Mycologic Cure[c]	124 (31.1%)	14 (7.2%)	142 (35.9%)	25 (12.2%)

a. Complete cure defined as 0% clinical involvement of the target toenail plus negative KOH and negative culture.

b. Complete or almost complete cure defined as ≤10% affected target toenail area involved and negative KOH and culture.

c. Mycologic cure defined as negative KOH and negative culture.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

KERYDIN (tavaborole) topical solution, 5% is a clear, colorless solution supplied in a 12-mL amber glass bottle with a screw cap. At initial use, the screw cap is replaced with the dropper assembly.

KERYDIN (tavaborole) topical solution, 5% is supplied in the following presentation:

NDC 55724-111-11: One bottle containing 10 mL of solution with one glass pointed-tip dropper

16.2 Storage and Handling

Store at 20–25°C (68–77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].
CAUTION: Flammable. Keep away from heat and flame.
Discard product within 3 months after insertion of the dropper.
Keep bottle tightly closed. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

The patient should be told the following:

- Use KERYDIN as directed by a health care professional.
- KERYDIN is for external use only. Avoid contact with eyes, mouth, or vagina. Avoid contact with skin other than skin immediately surrounding the treated nail(s). Wipe away excess solution from surrounding skin.
- Clean and dry nails prior to KERYDIN use. KERYDIN should be applied to completely cover the nail surface and also applied under the tip of each nail being treated. Allow solution to dry following application.
- Inform a health care professional if the area of application shows signs of persistent irritation (for example, redness, itching, swelling).
- Forty-eight (48) weeks of daily application with tavaborole is considered the full treatment for toenail onychomycosis.
- Do not use KERYDIN for any disorder other than that for which it is prescribed.
- Product is flammable. Avoid use near heat or open flame.

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Manufactured for:
Anacor Pharmaceuticals, Inc.
1020 East Meadow Circle
Palo Alto, CA 94303

Issue: 07/2014

ANACOR PHARMACEUTICALS

KERYDIN™ is a trademark of Anacor Pharmaceuticals, Inc.
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U.S. Patent Nos. 7,767,657 and 7,582,621

PATIENT INFORMATION
KERYDIN™ (ker' i din)
(tavaborole) Topical Solution, 5%

Important information: KERYDIN is for use on toenails only. Do not use KERYDIN in your mouth, eyes, or vagina.

What is KERYDIN?

KERYDIN is a prescription medicine used to treat fungal infections of the toenails.
It is not known if KERYDIN is safe and effective in children.

What should I tell my healthcare provider before using KERYDIN?

Before using KERYDIN, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if KERYDIN can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if KERYDIN passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use KERYDIN?

See the "Instructions for Use" at the end of this Patient Information for detailed information about the right way to use KERYDIN.

- Use KERYDIN exactly as your healthcare provider tells you to use it.
- Apply KERYDIN to your affected toenails 1 time each day.
- KERYDIN is used for 48 weeks.

What should I avoid while using KERYDIN?

- Avoid getting KERYDIN on skin that is not surrounding the treated toenail.
- KERYDIN is flammable. Avoid heat and flame while applying KERYDIN to your toenail.

What are the possible side effects of KERYDIN?

KERYDIN may cause irritation at the treated site. The most common side effects include: skin peeling, ingrown toenail, redness, itching, and swelling. Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all of the possible side effects of KERYDIN.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KERYDIN?

- Store KERYDIN at room temperature, between 68°F to 77°F (20°C to 25°C).
- KERYDIN is flammable. Keep away from heat and flame.
- Keep the bottle tightly closed.
- Safely throw away KERYDIN after 3 months of inserting the dropper.

Keep KERYDIN and all medicines out of the reach of children.

General information about the safe and effective use of KERYDIN

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about KERYDIN that is written for health professionals. Do not use KERYDIN for a condition for which it was not prescribed. Do not give KERYDIN to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in KERYDIN?

Active ingredient: tavaborole
Inactive ingredients: alcohol, propylene glycol, and edetate calcium disodium

Manufactured for: Anacor Pharmaceuticals, Inc., 1020 East Meadow Circle, Palo Alto, CA, 94303
For more information, call 1-844-4ANACOR [1-844-426-2267] or go to www.kerydin.com.
This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 07/2014

Instructions for Use
KERYDIN™ (ker' i din)
(tavaborole) Topical Solution, 5%

Important information: KERYDIN is for use on toenails only. Do not use KERYDIN in your mouth, eyes, or vagina.

Read the Instructions for Use that comes with KERYDIN before you start using it. Talk to your healthcare provider if you have any questions.

How to apply KERYDIN:

Your toenails should be clean and dry before you apply KERYDIN.

Step 1: Before you apply KERYDIN to your affected toenail for the first time, remove the cap from the KERYDIN bottle **(See Figure A).** Throw away the cap.

Step 2: Remove the wrapping from the dropper that comes with KERYDIN. Insert the dropper into the KERYDIN bottle. **(See Figure B)**

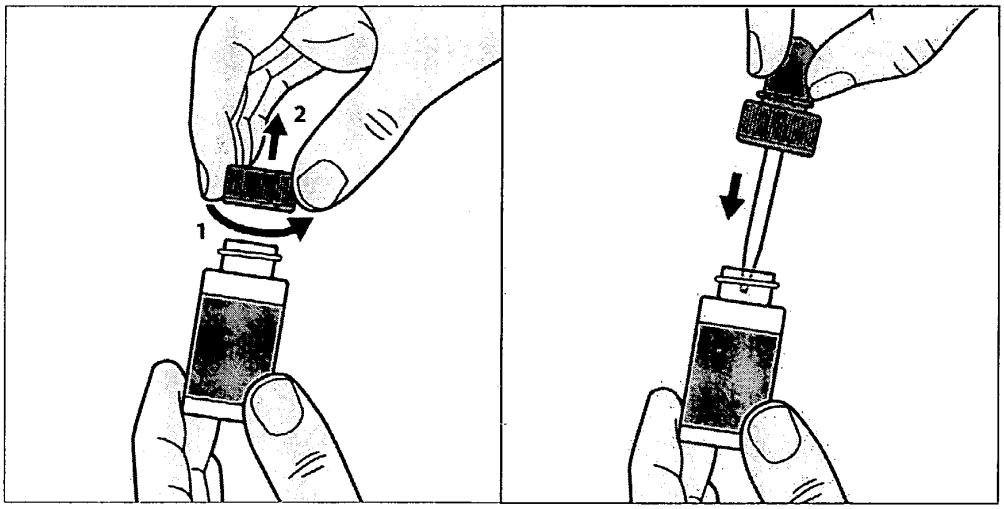

Figure A **Figure B**

Only apply KERYDIN using the provided dropper. Do not use the dropper for any other purpose.

Step 3: With the dropper inserted into the KERYDIN, squeeze the bulb and then release the bulb to draw KERYDIN into the dropper.

Step 4: Remove the dropper from the bottle and hold the dropper tip over your affected toenail.

Step 5: Slowly squeeze the bulb to apply KERYDIN to your toenail. Apply enough solution to completely cover your toenail. You may need to use more than one drop. **(See Figure C)**

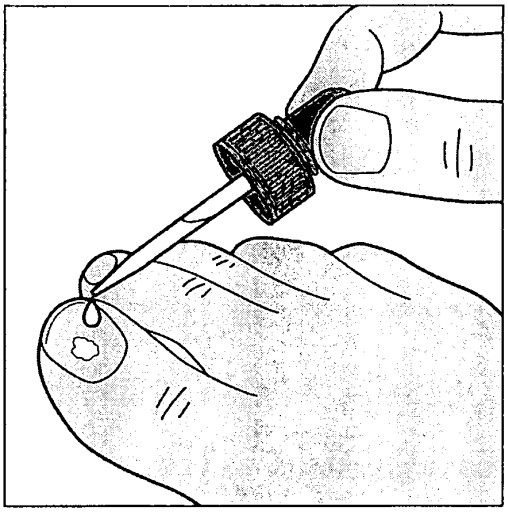

Figure C

Step 6: Use the dropper tip to gently spread KERYDIN to cover the entire toenail up to the edges of the toenail. **(See Figure D)**

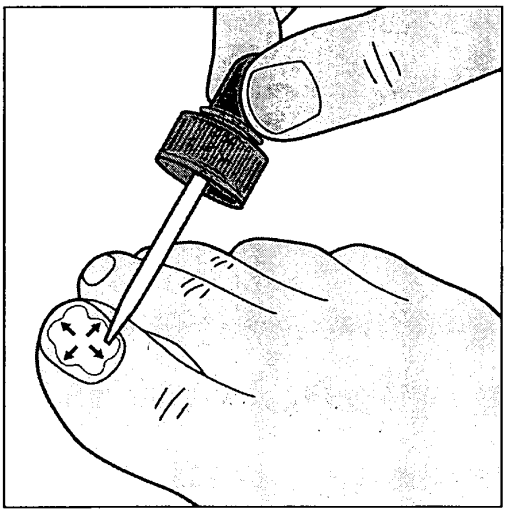

Figure D

Step 7: In addition to the top of the toenail, also apply KERYDIN under the tip of the toenail. Use the dropper tip to gently spread KERYDIN under the entire tip of the toenail. **(See Figures E and F)**

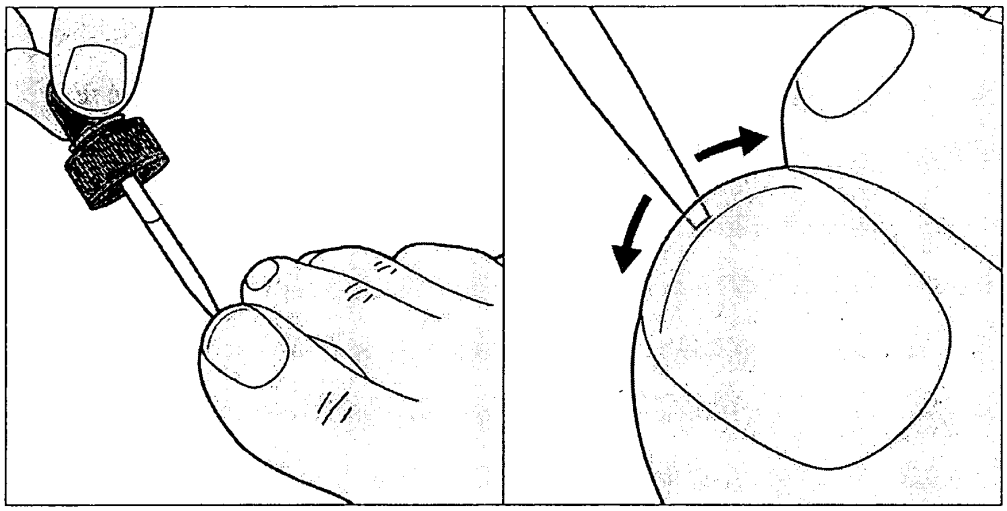

Figure E **Figure F**

Step 8: Repeat Steps 3 to 7 to apply KERYDIN to each affected toenail.

Step 9: Let the KERYDIN dry completely. This may take a couple of minutes.

If KERYDIN comes in contact with surrounding skin, use a tissue to wipe any excess solution from the surrounding skin. **Do not wipe KERYDIN off of your toenails.**

Step 10: After applying KERYDIN to your toenails, insert the dropper back into the bottle and screw it on tightly.

Step 11: Wash your hands with soap and water after applying KERYDIN.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for: Anacor Pharmaceuticals, Inc., 1020 East Meadow Circle, Palo Alto, CA, 94303

Issued: 07/2014

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EXHIBIT C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204427

NDA APPROVAL

Anacor Pharmaceuticals, Inc.
Attention: Carmen Rodriguez, MSc
Vice President, Regulatory Affairs and Quality
1020 East Meadow Circle
Palo Alto, CA 94309-4320

Dear Ms. Rodriguez:

Please refer to your New Drug Application (NDA) dated July 26, 2013, received July 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kerydin (tavaborole) topical solution, 5%.

We acknowledge receipt of your amendments dated August 9, 14 and 19, October 18, 23 and 30, November 18 and 25, and December 19 and 27, 2013: January 16, 21 and 31, April 1, 4 and 18, May 5, 13 and 20, and June 2, 11 and 23, 2014.

This new drug application provides for the use of Kerydin (tavaborole) topical solution, 5% for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes.*

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

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CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **"Final Printed Carton and Container Labels for approved NDA 204427."** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for (tavaborole) topical solution, 5% was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 11 years and 11 months because necessary studies are impossible or highly impracticable. This is because onychomycosis due to *Trichophyton rubrum* or *Trichophyton mentagrophytes* is not prevalent in the population younger than 12 years of age.

We are deferring submission of your pediatric study for ages 12 to 17 years and 11 months for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

PMR 2154-1 Pharmacokinetic/safety study of tavaborole topical solution, 5% in 40 pediatric subjects age 12 to 17 years and 11 months with onychomycosis of the toenails.

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Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions.

Final Protocol Submission:	12/2014
Study Completion:	12/2018
Final Report Submission:	06/2019

Submit the protocol(s) to your IND 071206, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

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If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, MD, MPH
Deputy Director (acting)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
07/07/2014

Reference ID: 3537640

EXHIBIT D

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

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Baker et al.

Application No./Patent No.: 11/357,687 Filed/Issue Date: February 16, 2006

Titled: BORON-CONTAINING SMALL MOLECULES

Anacor Pharmaceuticals, Inc. , a Corporation

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

states that it is:

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

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

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

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

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 017885, Frame 0979, or for which a copy therefore is attached.

OR

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

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

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

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

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

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

Signature — Date: 8/28/2014

Ryan Walsh — Chief IP & Litigation Counsel

Printed or Typed Name — Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. 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, 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.**

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

Privacy Act Statement

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

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

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

On this 26th day of August, 2014, I certify that the attached document is a true, exact, complete, and unaltered copy (12 pages) made by me from our files of a Certified Copy of an Assignment from the inventors to Anacor Pharmaceuticals, Inc.

Carmen Constantinescu
Notary Public
My Commission expires February 13, 2015

Carmen M. Constantinescu
Notary Public
Commonwealth of Massachusetts
My Commission Expires
February 13, 2015

6193882v1

A 7488680

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

August 04, 2014

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON JUNE 29, 2006.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

M. TARVER
Certifying Officer

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
Stephen J. Baker	04/28/2006
Tsutomu Akama	04/28/2006
Carolyn Bellinger-Kawahara	04/28/2006
Karin M. Hold	04/28/2006
James J. Leyden	06/19/2006
Kirk R. Maples	04/28/2006
Jacob J. Plattner	04/28/2006
Virginia Sanders	04/28/2006
Yong-Kang Zhang	04/28/2006
Vincent S. Hernandez	04/28/2006

RECEIVING PARTY DATA

Name:	Anacor Pharmaceuticals, Inc.
Street Address:	1060 East Meadow Circle
City:	Palo Alto
State/Country:	CALIFORNIA
Postal Code:	94303

CH $40.00 11357687

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	11357687

CORRESPONDENCE DATA

Fax Number: (650)843-4001
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 415-442-1749
Email: kdegliantoni@morganlewis.com
Correspondent Name: Jeffry S. Mann
Address Line 1: MLB, LLP, Two Palo Alto Square

Address Line 2:	3000 El Camino Real, Suite 700
Address Line 4:	Palo Alto, CALIFORNIA 94306

ATTORNEY DOCKET NUMBER:	64507-5014-US
NAME OF SUBMITTER:	Jeffry S. Mann

Total Attachments: 9
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source=A5014US#page8.tif
source=A5014US#page9.tif

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Attorney Docket No. 64507-5014-US

Form PTO-1595
(Rev. 10-02)
OMB No. 0651-0027 (exp. 5/31/2002)

Recordation Form Cover Sheet
PATENTS ONLY

U.S. Department of Commerce
U.S. Patent and Trademark Office

Tab settings ⇨⇨⇨ ▼ ▼ ▼ ▼ ▼ ▼ ▼

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof

1. Name of conveying party(ies):

Stephen J. Baker
Tsutomu Akama
Carolyn Bellinger-Kawahara

Additional name(s) of conveying party(ies) attached? ☒ Yes ☐ No.

2. Name and address of receiving party(ies)

Name: Anacor Pharmaceuticals, Inc.

Street Address: 1060 East Meadow Circle

City: Palo Alto State: CA ZIP: 94303

Additional name(s) and address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other:

Execution Dates: 04/28/06, 04/28/06, 04/28/06, 04/28/06, 04/28/06, 06/19/06, 04/28/06, 04/28/06, 04/28/06, and 04/28/06, respectively

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No(s): 11/357,687

B. Patent No(s):

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Jeffry S. Mann, Ph.D.
Morgan, Lewis & Bockius LLP
Two Palo Alto Square
3000 El Camino Real, Ste. 700
Palo Alto, CA 94306
Tel. (415) 442-1000
Direct Dial: (415) 442-1119
eFAX: (650) 843-4001
e-mail: jmann@morganlewis.com

6. Total number of applications and patents involved 1

7. Total fee (37 CFR 3.41): ~~\$40.00~~

☐ Enclosed

☒ Authorized to be charged to deposit account

8. Deposit account number: **50-0310**

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Jeffry S. Mann, Ph.D.
Name of Person Signing
Atty. Reg. No. 42,837

Signature

~~June~~ 27, 2006
Date

Total number of pages including cover sheet, attachments and documents: 9

Mail documents to be recorded with required cover sheet information to:
Mail Stop Assignment Recordation Services
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

1-SF/7385940.1

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 485 of 558

1. **Additional name(s) of conveying party(ies): (Continued from Page 1)**

Vincent S. Hernandez
Karin M. Hold
James J. Leyden
Kirk R. Maples
Jacob J. Plattner
Virginia Sanders
Yong-Kang Zhang

2. Additional name(s) and address(es) of receiving party(ies): (Continued from Page 1)

3. Additional application number(s) or patent number(s): (Continued from Page 1)

A. Patent Application No.(s)	B. Patent No.(s)

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 486 of 558

Attorney Docket No.: 64507-5014-US

ASSIGNMENT OF PATENT APPLICATION

JOINT

WHEREAS, Stephen J. Baker of 1568 Begen Avenue, Mountain View, CA, 94040; Tsutomu Akama of 832 Azure Street, Sunnyvale, CA, 94087; Carolyn Bellinger-Kawahara of 15 Landa Lane, Redwood City, CA, 94061; Vincent S. Hernandez of 287 Gilchrist Lane, Watsonville, CA, 95076; Karin M. Hold of 1908 Valdez Avenue, Belmont, CA, 94002; James J. Leyden of 319 Applebrook Drive, Malvern, CA, 19355; Kirk R. Maples of 1195 San Moritz Drive, San Jose, CA 95132; Jacob J. Plattner of 1016 Amito Avenue, Berkeley, CA 94705; Virginia Sanders of 2895 Harrison Street, Apt. 4, San Francisco, CA, 94110; and Yong-Kang Zhang of 5151 Westmont Avenue, San Jose, CA, 95130, hereinafter referred to as "Assignors," are the inventors of the invention described and set forth in the below-identified patent application:

Title of Invention:	BORON-CONTAINING SMALL MOLECULES
Filing Date:	February 16, 2006
Application No.:	11/357,687; and

WHEREAS, Anacor Pharmaceuticals, Inc., located at 1060 East Meadow Circle, Palo Alto, CA 94303, hereinafter referred to as "ASSIGNEE," is desirous of acquiring an interest in the invention and application and in any U.S. Letters Patent and Registrations which may be granted on any patent application claiming priority from the same;

For good and valuable consideration, receipt of which is hereby acknowledged by Assignors, Assignors have assigned, and by these presents does assign to Assignee all right, title and interest in and to the invention and application and to all foreign counterparts (including patent, utility model and industrial designs), and in and to any Letters Patent and Registrations which may hereafter be granted on any patent application claiming priority from the same in the United States and all countries throughout the world, and to claim the priority from the application as provided by the Paris Convention. The right, title and interest is to be held and enjoyed by Assignee and Assignee's successors and assigns as fully and exclusively as it would have been held and enjoyed by Assignors had this Assignment not been made, for the full term of any Letters Patent and Registrations which may be granted thereon, or of any division, renewal, continuation in whole or in part, substitution, conversion, reissue, prolongation or extension thereof.

Assignors further agree that Assignors will, without charge to Assignee, but at Assignee's expense, (a) cooperate with Assignee in the prosecution of U.S. Patent applications and foreign counterparts on the invention and any improvements, (b) execute, verify, acknowledge and deliver all such further papers, including applications and instruments of transfer, and (c) perform such other acts as Assignee lawfully may request to obtain or maintain Letters Patent and Registrations for the invention and improvements in any and all countries, and to vest title thereto in Assignee, or Assignee's successors and assigns.

Assignors hereby authorize and request Morgan, Lewis & Bockius LLP, One Market, Spear Street Tower, San Francisco, CA 94105, to insert herein above the application number and filing date of said application when known.

IN TESTIMONY WHEREOF, Assignors have signed his/her names on the dates indicated.

Dated: April 28th 2006

STEPHEN J. BAKER

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006, before me, Donielle M. Equite personally appeared STEPHEN J. BAKER, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

NOTARY PUBLIC

My ~~Commission Expires~~: July 12, 2007

Dated: 4/28/06

TSUTOMU AKAMA

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared TSUTOMU AKAMA, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 488 of 558

Dated: 4/28/06

CAROLYN BELLINGER-KAWAHARA

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared CAROLYN BELLINGER-KAWAHARA, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

~~WITNESS my hand and official seal.~~

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: 4/28/06

VINCENT S. HERNANDEZ

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared VINCENT S. HERNANDEZ, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 489 of 558

Dated: 4/28/06

KARIN M. HOLD

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared KARIN M. HOLD, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: _____

JAMES J. LEYDON

STATE OF)
) ss.
COUNTY OF)

On _____, before me, _____ personally appeared JAMES J. LEYDON, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: _____

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 490 of 558

Dated: _____

_____
KARIN M. HOLD

STATE OF CALIFORNIA)
) ss.
COUNTY OF)

On _____, before me, _____ personally appeared KARIN M. HOLD, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

_____
NOTARY PUBLIC

My Commission Expires: _____

Dated: 6/19/06

_____
JAMES J. LEYDEN

STATE OF)
) ss.
COUNTY OF)

On _____, before me, _____ personally appeared JAMES J. LEYDEN, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

_____
NOTARY PUBLIC

My Commission Expires: _____

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 491 of 558

Dated: 4/28/06

KIRK R. MAPLES

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared KIRK R. MAPLES, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: April 28, 2006

JACOB J. PLATTNER

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared JACOB J. PLATTNER, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 492 of 558

Dated: 4/28/06

Virginia Sanders
VIRGINIA SANDERS

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared VIRGINIA SANDERS, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: 4-28-2006

Yongkang Zhang
YONG-KANG ZHANG

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared YONG-KANG ZHANG, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

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EXHIBIT E

PTO/SB/81 (01-09)
Approved for use through 11/30/2011. OMB 0651-0035
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.

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	11/357,687
Filing Date	February 16, 2006
First Named Inventor	Baker, Stephen J.
Title	BORON-CONTAINING SMALL MOLECULES
Art Unit	1626
Examiner Name	Shiao, Rei Tsang
Attorney Docket Number	064507-5014US

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: **24280**

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

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

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature		Date	8/28/2014
Name	Ryan Walsh	Telephone	650-543-7531
Title and Company	Chief IP & Litigation Counsel - Anacor Pharmaceuticals, Inc.		

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.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 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.**

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

Privacy Act Statement

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

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

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

EXHIBIT F

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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Customer No 000000000 ISTMT DATE PRINTED 07/22/2014

MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 28
San Francisco CA 94105

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	ENTITY STATUS	ATTY DKT NUMBER
7582621	**$1,150.00**	**$0.00**	**10/22/12**	**11357687**	**09/01/09**	**02/16/06**	**04**	**LARGE**	**064507-5014US**

PTOL-439 (Rev. 09/2006)

EXHIBIT G

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IND 71,206: AN2690 Solution for Onychomycosis
FDA Communications Chronology

Date	Type of Communication	SSN	Description
4/23/2014	Submission	SN0150	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Study TAV-ONYC-206) Nadarajah
4/03/2014	Submission	SN0149	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Study TAV-ONYC-206) Youngswick, Noroyan, Marshall, Dodson
3/17/2014	Submission	SN0148	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Study TAV-ONYC-206) Caporusso, Brill, Sigal
3/10/2014	Submission	SN0147	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Study TAV-ONYC-206) Weisfeld, Ashton, Penny, Surprenant, Kasper, Dunne, Reyzelman
3/03/2014	Submission	SN0146	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Study TAV-ONYC-206) Agnew, Hori, Pollak
2/14/2014	Submission	SN0145	Protocol Amendment: New Protocol (TAV-ONYC-206) and New Investigator Information Amendment–Clinical (Updated IB) Information Amendment–CMC (Investigational Label)
11/27/2013	Submission	SN0144	ANNUAL REPORT INFORMATION AMENDMENT - CLINICAL - Final Clinical Study Reports for Study AN2690-ONYC-301 (report 002-CLN CL-008-01) and Study AN2690-ONYC-302 (report 002-CLN CL-009-01)
09/24/2013	Email	–	FDA Correspondence
09/16/2013	Call	–	Teleconference with FDA
09/13/2013	Letter	–	FDA Correspondence
07/24/2013	Submission	SN0143	INFORMATION AMENDMENT-CLINICAL- Final Clinical Study Report (002-CLN CL-007-01) For study AN2690-ONYC-103
07/18/2013	Call	–	Teleconference with FDA
07/18/2013	Submission	SN0142	INFORMATION AMENDMENT – PHARMACOLOGY/TOXICOLOGY: Final nonclinical Study Reports: 002-NCL-PP-017-01 & 002-NCL-PP-018-01
07/17/2013	Submission	SN0141	INFORMATION AMENDMENT- CLINICAL- Clinical Study Report Errata.
07/17/2013	Submission	SN0140	INFORMATION AMENDMENT – PHARMACOLOGY/TOXICOLOGY: Final Nonclinical Study Reports: 002-NCL-PK-069-01 & 002-NCL-PK-070-01
07/16/2013	Submission	SN0139	INFORMATION AMENDMENT – CLINICAL- Clinical Study Report Errata
07/03/2013	Submission	SN0138	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Updated Forms FDA-1572 for Study AN2690-ONYC-301 and AN2690-ONYC-302)
06/26/2013	Letter	–	FDA Correspondence
06/25/2013	Submission Sample	–	Electronic Submission Sample: eCTD. Submitted to agency from Omnicia.
06/17/2013	Email	–	FDA Correspondence
06/14/2013	Email	–	FDA Correspondence
06/14/2013	Letter	–	FDA Correspondence
06/13/2013	Telephone Call	—	Teleconference with FDA
06/10/2013	Email	–	FDA Correspondence
06/10/2013	Telephone Call	—	Teleconference with FDA
06/10/2013	Telephone Call	—	Teleconference with FDA
06/07/2013	Letter	—	FDA Correspondence
06/07/2013	Telephone Call	—	Teleconference with FDA
06/04/2013	Email	—	FDA Correspondence
06/03/2013	Email	—	FDA Correspondence
05/24/2013	Email	—	FDA Correspondence

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Date	Type of Communication	SSN	Description
05/24/2013	Submission	SN0137	GENERAL CORRESPONDENCE – Response to FDA Pre-Meeting communication
05/24/2013	Email	—	FDA Correspondence
05/23/2013	Email	—	FDA Correspondence
05/22/2013	Telephone Call	—	Teleconference with FDA
05/21/2013	Email	—	FDA Correspondence
05/21/2013	Email	—	FDA Correspondence
05/16/2013	Telephone Call	—	Teleconference with FDA
05/14/2013	Fax	—	FDA Correspondence
05/13/2013	Telephone Call	—	Teleconference with FDA
05/08/2013	Email	—	FDA Correspondence
05/03/2013	Letter	—	FDA Correspondence
04/24/2013	Submission	SN0136	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Updated Forms FDA 1572 for Study AN2690 ONYC 302)
04/18/2013	Letter	—	FDA Correspondence
04/18/2013	Email	—	FDA Correspondence
04/18/2013	Telephone Call	—	Teleconference with FDA
04/15/2013	Email	—	FDA Correspondence
04/12/2013	Email	—	FDA Correspondence
04/12/2013	Submission	SN0135	PRE-NDA MEETING BRIEFING BOOK
4/11/2013	Telephone Call	—	Teleconference with FDA
04/09/2013	Submission	SN0134	INFORMATION AMENDMENT – PHARMTOX: Amended Final Report 002-NCL-TX-071-02
04/04/2013	Letter	—	FDA Correspondence
04/01/2013	Letter	—	FDA Correspondence
03/29/2013	Email	—	FDA Correspondence
03/29/2013	Submission	SN0133	INFORMATION AMENDMENT – CLINICAL: Final TQT Clinical Study Report 002-CLN-CL-006-01
03/25/2013	Submission	SN0132	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Updated Forms FDA 1572 for Study AN2690-ONYC-302)
03/19/2013	Email	—	FDA Correspondence
03/19/2013	Email	—	FDA Correspondence
03/18/2013	Submission	SN0131	RECONSIDERATION OF PROPRIETARY NAME REVIEW – Primary Name: Tavanty™ (tavaborole)
03/08/2013	Email	—	FDA Correspondence
03/08/2013	Telephone	—	Teleconference with FDA
03/04/2013	Email	—	FDA Correspondence
02/28/2013	Email	—	FDA Correspondence
02/26/2013	Letter/Submission	N/A	FDA Correspondence
02/25/2013	Email	—	FDA Correspondence
02/20/2013	Submission	SN0130	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Updated Forms FDA 1572 for Studies AN2690 ONYC 301 and AN2690 ONYC 302)
02/15/2013	Submission	SN0129	INFORMATION AMENDMENT: PHARMACOLOGY/TOXICOLOGY
02/14/2013	Email	—	FDA Correspondence
02/14/2013	Letter	—	FDA Correspondence
02/12/2013	Letter	—	FDA Correspondence

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Date	Type of Communication	SSN	Description
02/07/2013	Submission	SN0128	TYPE B MEETING REQUEST- PRE-NDA MEETING
02/05/2013	Email	—	FDA Correspondence
02/04/2013	Letter	—	FDA Correspondence
02/04/2013	Email	—	FDA Correspondence
02/01/2013	Letter	—	FDA Correspondence
01/30/2013	Submission	SN0127	INFORMATION AMENDMENT - CLINICAL - SAP for Study AN2690-ONYC-302
01/22/2013	Submission	SN0126	INFORMATION AMENDMENT - CLINICAL - Version 3 of SAP for Study AN2690-ONYC-301
01/21/2013	Submission	SN0125	PROTOCOL AMENDMENT - NEW INVESTIGATOR (Updated Forms FDA 1572 for Studies AN2690 ONYC-301 and AN2690-ONYC-302)
01/04/2013	Call	—	Teleconference with FDA
12/20/2012	Submission	SN0124	PROTOCOL AMENDMENT - NEW INVESTIGATOR (Updated Forms FDA 1572 for Studies AN2690 ONYC-301 and AN2690-ONYC-302)
12/17/2012	Submission	SN0123	INFORMATION AMENDMENT - CLINICAL Statistical Analysis Plans for Studies AN2690-ONYC-102 and AN2690-ONYC-103
12/14/2012	Email	—	FDA Correspondence
12/13/2012	Email	—	FDA Correspondence
12/10/2012	Telephone Call	—	Teleconference with FDA
12/10/2012	Email	—	FDA Correspondence
12/05/2012	Letter	—	FDA Correspondence
12/04/2012	Letter	—	FDA Correspondence
12/04/2012	Call	—	Teleconference with FDA
12/04/2012	Email	—	FDA Correspondence
12/03/2012	Email	—	FDA Correspondence
11/30/2012	Submission	SN0122	Annual Report
11/28/2012	Submission	SN0121	INFO AMENDMENT - PHARM/TOX Candida MOA report (002-NCL-PP-016-01)
11/27/2012	Email	—	FDA Correspondence
11/27/2012	Submission	SN0120	PROTOCOL AMENDMENT - NEW INVESTIGATOR Updated Form FDA 1572 for Studies AN2690-ONYC-301 and AN2690-ONYC-302
11/27/2012	Submission	SN0119	General Correspondence Sponsor's Meeting Minutes of Pre-NDA meeting
11/20/2012	Email	–	FDA Correspondence
11/20/2012	Letter	—	FDA Correspondence
11/16/2012	Submission	SN0118	RESPONSE TO FDA REQUEST FOR INFORMATION INFORMATION AMENDMENT, Chemistry
11/16/2012	Submission	SN0117	FDA Request for Information: Pharmacology/Toxicology: Resubmission of SN0055 originally submitted by Schering-Plough on November 5, 2009
11/14/2012	Email	—	FDA Correspondence
11/14/2012	Email	—	FDA Correspondence
11/14/2012	Email	—	FDA Correspondence
11/14/2012	Email	—	FDA Correspondence
11/13/2012	Email	—	FDA Correspondence
11/13/2012	Email	—	FDA Correspondence
11/13/2012	Email	—	FDA Correspondence
11/12/2012	Email	—	FDA Correspondence

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Date	Type of Communication	SSN	Description
11/09/2012	Email	—	FDA Correspondence
11/09/2012	Email	—	FDA Correspondence
11/5/2012	Submission	SN0116	INFORMATION AMENDMENT - PHARMACOLOGY/TOXICOLOGY Final Study Report 002-NCL PP-015-01: "An Interlaboratory Study of Quality Control Isolates for the Testing of Tavaborole Against Dermatophytes"
10/24/2012	Submission	SN0115	PROTOCOL AMENDMENT – NEW INVESTIGATOR: Updated Form FDA 1572 for Studies AN2690-ONYC-301 and AN2690-ONYC-302
10/24/2012	Email	—	FDA Correspondence
09/28/2012	Submission	SN0114	PRE-NDA MEETING BRIEFING BOOK
09/26/2012	Submission	SN0113	INFORMATION AMENDMENT – CLINICAL: Version 2 of SAP for Studies AN2690-ONYC-301 and AN2690-ONYC-302
09/20/2012	Submission	SN0112	PROTOCOL AMENDMENT – NEW INVESTIGATOR: Updated Form FDA 1572 for Studies AN2690-ONYC-301 and AN2690-ONYC-302
09/14/2012	Submission	SN0111	PROTOCOL AMENDMENT – CHANGE IN PROTOCOL: AN2690-ONYC-301 and AN2690-ONYC-302
08/30/2012	Submission	SN0110	General Correspondence: Response To FDA Advice/Information Request Letter Dated August 15, 2012
8/23/2012	Letter	—	FDA Correspondence
08/09/2012	Submission	SN0109	PROTOCOL AMENDMENT – NEW INVESTIGATOR: Updated Form FDA 1572 for Study AN2690-ONYC-302
08/03/2012	Submission	SN0108	INFORMATION AMENDMENT – Pharmacology/Toxicology
08/02/2012	Submission	SN0107	PROPRIETARY NAME REVIEW – Primary Name: Tavantiv™ (tavaborole)
07/13/2012	Submission	SN0106	PROTOCOL AMENDMENT – CHANGE IN PROTOCOL: "A Randomized, Controlled Study to Evaluate the Sensitizing Potential and Cumulative Irritation Potential of AN2690 Topical Solution, 5% in Healthy Volunteers Using a Repeat Insult Patch Test and Cumulative Irritation Design" (Study AN2690-ONYC-103) INFORMATION AMENDMENT – CLINICAL: Revised Transfer of Obligations for Study AN2690-ONYC-103
07/10/2012	Submission	SN0105	PROTOCOL AMENDMENT – NEW INVESTIGATOR: Updated Form FDA 1572 for Studies AN2690-ONYC-301 and AN2690-ONYC-302
06/13/2012	Submission	SN0104	PROTOCOL AMENDMENT – NEW INVESTIGATOR: "A Randomized, Controlled Study to Evaluate the Sensitizing Potential and Cumulative Irritation Potential of AN2690 Topical Solution, 5% in Healthy Volunteers Using a Repeat Insult Patch Test and Cumulative Irritation Design" (Study AN2690-ONYC-103) INFORMATION AMENDMENT – CLINICAL: Transfer of Obligations for Study AN2690-ONYC-103
6/12/2012	Submission	SN0103	PROTOCOL AMENDMENT – REVISED PROTOCOL: "A Randomized, Crossover Study of the Effects of AN2690 on QT/QTc Intervals Compared to Vehicle and Moxifloxacin in Healthy Subjects" (Study AN2690-ONYC-102)"
6/6/2012	Submission	SN0102	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Updated Form 1572 for Studies AN2690-ONYC-301 and AN2690-ONYC-302)
6/1/2012	Letter	—	FDA Correspondence
6/1/2012	Email	—	FDA Correspondence
5/25/2012	Submission	SN0101	INFORMATION AMENDMENT – Chemistry, Manufacturing, and Controls and Clinical for Study AN2690-ONYC-102
5/18/2012	Email	—	FDA Correspondence
5/18/2012	Email	—	FDA Correspondence
5/10/2012	Email	—	FDA Correspondence
5/8/2012	Submission	SN0100	TYPE B MEETING REQUEST: PRE-NDA MEETING

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Date	Type of Communication	SSN	Description
4/26/2012 & 5/6/2012	Email	—	FDA Correspondence
5/4/2012	Submission	SN0099	PROTOCOL AMENDMENT – REVISED PROTOCOL: "A Randomized, Crossover Study of the Effects of AN2690 on QT/QTc Intervals Compared to Vehicle and Moxifloxacin in Healthy Subjects" (Study AN2690-ONYC-102)" (TQT)
5/2/2012	Submission	SN0098	PROTOCOL AMENDMENT – NEW INVESTIGATOR (Updated Form 1572 for Studies AN2690-ONYC-301 and AN2690-ONYC-302)
5/1/2012	Submission	SN0097	PROTOCOL AMENDMENT – NEW PROTOCOL (Study AN2690-ONYC-103 RIPT)
4/27/2012	Submission	SN0096	Information Amendment: CMC (CMC summary, sample drug labels, CoA) Information Amendment: Clinical (updated AN2690 IB)
4/25/2012	Letter	—	FDA Correspondence
4/17/2012	Submission	SN0095	Protocol Amendment: New Protocol (AN2690-ONYC-102 TQT) and New Investigator
3/27/2012	Submission	SN0094	Protocol Amendment: New Investigator (updated 1572s)
3/12/2012	Submission	SN0093	Information Amendment: Clinical
2/29/2012	Submission	SN0092	Protocol Amendment: New Investigator (updated 1572s)
2/29/2012	Email	—	FDA Correspondence
2/29/2012	Email/Official Correspondence	—	FDA Correspondence
2/28/2012	Email	—	FDA Correspondence
2/27 – 2/28/2012	Email	—	FDA Correspondence
2/24/2012	Email	—	FDA Correspondence
2/3/2012	Submission	SN0091	Protocol Amendment: New Investigator
2/1/2012	Email	—	FDA Correspondence
2/1/2012	Submission	SN0090	Type C Meeting Briefing Book Submission
1/4/2012	Email	—	FDA Correspondence
12/7/2011	Email	—	FDA Correspondence
12/7/2011	Submission	SN0089	General Correspondence: Type C Meeting Request
12/1/2011	Submission	SN0088	Protocol Amendment: New Investigator
11/30/2011	Submission	SN0087	Annual Report
11/3/2011	Email	—	FDA Correspondence
10/26/2011	Repeat Submission	SN0086	Resubmitted SN0086 due to submission being sent to incorrect address. Three IND binders were labeled with "REPLACEMENT SUBMISSION FOR INCORRECTLY ADDRESSED SN0086 SENT 19 OCT 2011". Previous submission was incorrectly sent to 9201 CORPORATE BLVD # 540 ATTN: STANKA KUKICH, MD; HFD540 ROCKVILLE MD 208503202 US.
10/19/2011	Submission	SN0086	Protocol Amendment: New Investigator
9/19/2011	Letter from FDA	—	FDA Correspondence
9/19/2011	Submission	SN0085	Protocol Amendment: New Investigator
9/13/2011	Email from FDA	—	FDA Correspondence
9/13/2011	Submission	SN0084	Information Amendment: Pharm/Tox
9/8/2011	Email to and from FDA	—	FDA Correspondence
8/12/2011	Submission	SN0083	Protocol Amendment: New Investigator
8/1/2011	Email to and from FDA	—	FDA Correspondence
6/29/2011	Submission	SN0082	Protocol Amendment: New Investigator

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Date	Type of Communication	SSN	Description
6/15/2011	Submission	SN0081b	Sent 3 desk copies of SN0081 to attention of Cristina Attinello
6/15/2011	Email to FDA	—	FDA Correspondence
6/15/2011	Email from FDA	—	FDA Correspondence
6/12/2011	Email to FDA	—	FDA Correspondence
6/10/2011	Submission	SN0081	Protocol Amendment: New Protocol and Info Amendment: Clinical
6/1/2011	Submission	SN0080	Protocol Amendment: New Investigator
5/9/2011	Email from FDA	—	FDA Correspondence
5/5/2011	Email to FDA	—	FDA Correspondence
5/3/2011	Submission	SN0079	Information Amendment: Pharmacology/Toxicology
4/25/2011	Submission	SN0078	Protocol Amendment: New Investigator
4/1/2011	Submission	SN0077	Protocol Amendment: New Investigator
3/17/2011	FDA Letter	—	FDA Correspondence
3/14/2011	Submission	SN0076	Info Amendment: CMC
2/28/2011	Submission	SN0075	Protocol Amendment: New Investigator
1/27/2011	Submission	SN0074	Protocol Amendment: New Investigator
1/19/2011	Submission	SN0073	Protocol Amendment: New Protocol
12/23/2010	Submission	SN0072	Response to FDA Request for Information
11/30/2010	Submission	SN0071	Annual Report and Info Amendment (Pharm Tox)
11/23/2010	FDA phone call	—	Teleconference with FDA
11/22/2010	FDA voice mail	—	Teleconference with FDA
11/19/2010	Submission	SN0070	Protocol Amendment, Info Amendment (CMC and Microbiology), and Gen'l Corresp. (Transfer of Sponsor Contact Information) Updated IB (August 27, 2010)
11/10/2010	FDA Letter	—	FDA Correspondence
11/2/2010	Submission	SSN0069	Gen'l Corresp. – Notice of intent to start Ph3 clinical study AN2690-ONYC-301
9/30/2010	Submission	SSN0068	Gen'l Corresp. – Reply to FDA's SPA response
9/13/2010	FDA Letter	—	FDA Correspondence
9/1/2010	Submission	SSN0067	Information Amendment – Clinical
8/10/2010	FDA Phone call	—	Teleconference with FDA
8/9/2010	Submission	SSN0066b	Sent 4 extra desk copies of SSN0066 to the attention of Christine Attinello
8/6/2010	Email from FDA	—	FDA Correspondence
8/3/2010	Submission	SSN0066	Request for SPA review of Phase 3 protocol
7/26/2010	Submission	SSN0065	Gen'l Corresp. – Response to Reviewers' Questions
7/22/2010	FDA Letter	—	FDA Correspondence
6/1/2010	Submission	SSN0064	Gen'l Corresp. – Transfer and Acceptance of IND Ownership
5/25/2010	Submission	SSN0063	Gen'l Corresp. – Transfer and Acceptance of IND Ownership
5/24/2010	Submission	SSN0062	Protocol Amendment: New Investigator

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Date	Type of Communication	SSN	Description
5/19/2010	Submission	SSN0061	Information Amendment – Nonclinical Pharm/Tox
4/29/2010	Submission	SSN0060	Information Amendment – Nonclinical Pharm/Tox
4/20/2010	Submission	SSN0059	Information Amendment – Nonclinical Pharm/Tox
12/23/2010	Email from FDA	—	FDA Correspondence
12/20/2009	Submission	SSN0058	Information Amendment — Nonclinical Pharm/Tox
12/17/2009	Email from FDA	—	FDA Correspondence
11/29/2009	Submission	SSN0057	Annual Report for IND 71,206 for AN2690 Solution
11/18/2009	Submission	SSN0056	Information Amendment—Clinical
11/10/2009	FDA Letter	—	FDA Correspondence
11/5/2009	Submission	SSN0055	Gen'l Corresp. — Response to Reviewers' Questions
11/4/2009	Submission	SSN0054	Gen'l Corresp.
10/26/2009	Submission	SSN0053	Information Amendment – Toxicology
10/23/2009	Submission	SSN0052	Information Amendment—CMC
10/22/2009	Submission	SSN0051	Information Amendment – Toxicology
10/21/2009	FDA Letter	—	FDA Correspondence
10/14/2009	Submission	SSN0050	Protocol Amendment: Change in Protocol (P06118 amendment 2 and P06118 amendment 3)
9/23/2009	Submission	SSN0049	Gen'l Corresp. — End of Phase 2 Meeting Briefing Book
9/14/2009	Submission	SSN0048	Protocol Amendment: Change in Protocol (P05204)
9/11/2009	Submission	SSN0047	Information Amendment—Clinical
8/21/2009	Submission	SSN0046	Response to FDA request for Information
8/6/2009	Submission	SSN0045	Information Amendment – Clinical
7/2/2009	FDA Letter	—	FDA Correspondence
6/5/2009	Submission	SSN0044	Protocol Amendment: New Protocol (P06118 Amendment 1)
6/2/2009	Submission	SSN0043	Type B Meeting Request: End of Phase 2 Meeting
5/21/2009	Submission	SSN0042	Information Amendment—CMC
3/26/2009	FDA Letter	—	FDA Correspondence
3/30/2009	Submission	SSN0041	Information Amendment — Toxicology
3/10/2009	Submission	SSN0040	Information Amendment — Toxicology
2/10/2009	Submission	SSN0039	Information Amendment — Toxicology
1/27/2009	Submission	SSN0038	Protocol Amendment: Change in Protocol (P05577)
1/5/2009	Email from the FDA	—	FDA Correspondence
12/4/2008	Submission	SSN0037	Protocol Amendment: New Protocol (P05577) and Information Amendment — CMC
11/25/2008	Submission	SSN0036	Annual Report for Investigational New Drug (IND) Application Number 71,206 for AN2690 Solution
11/18/2008	Submission	SSN0035	Information Amendment—Clinical
11/13/2008	Submission	SSN0034	Transfer of Sponsor Contact Information (from Lisa Travis to Barbara Gunther).
9/8/2008	Email from the FDA	—	FDA Correspondence
8/22/2008	Submission	SSN0033	Gen'l Corresp. — Transfer and Acceptance of IND Ownership
8/15/2008	Letter to FDA		Acceptance of IND Ownership
8/13/2008	Email from the FDA	—	FDA Correspondence

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Date	Type of Communication	SSN	Description
8/13/2008	Telephone Report	—	Teleconference with FDA
8/12/2008	Telephone Report	—	Teleconference with FDA
8/12/2008	Fax from the FDA	—	FDA Correspondence
8/11/2008	Telephone Report	—	Teleconference with FDA
8/7/2008	Email to the FDA	—	FDA Correspondence
8/5/2008	Submission	SSN0032	Response to FDA request for Information
8/1/2008	Submission	SSN0031	Information Amendment—Clinical
7/10/2008	Submission	SSN0030	Gen'l Corresp. — End of Phase 2 Meeting Briefing Book
7/2/2008	Submission	SSN0029	Information Amendment—CMC
6/26/2008	Submission	SSN0028	Information Amendment—Clinical
6/5/2008	Submission	SSN0027	Information Amendment—Toxicology
4/2/2008	Submission	SSN0026	Type B Meeting Request: End of Phase 2 Meeting
1/7/2008	Email from FDA	—	FDA Correspondence
12/12/2007	Submission	SSN0025	Transfer of Sponsor Contact Information (from Todd Paporello to Lisa Travis
11/30/2007	Submission	SSN0024	Gen'l Corresp. — Request for Medical Review Team Comment on Phase 3 development plans
11/29/2007	Email to the FDA	—	FDA Correspondence
11/26/2007	Telephone Report	—	Teleconference with FDA
11/26/2007	Submission	SSN0023	Annual Report for Investigational New Drug (IND) Application Number 71,206 for AN2690 Solution
11/21/2007	Email to the FDA	—	FDA Correspondence
11/5/2007	FDA Fax (via SP)	—	FDA Correspondence
7/13/2007	Submission	SSN0022	Information Amendment—Clinical
6/29/2007	Email From FDA	—	FDA Correspondence
6/29/2007	FDA Letter	—	FDA Correspondence
6/8/2007	FDA Fax (via SP)	—	FDA Correspondence
6/5/2007	Email to the FDA	—	FDA Correspondence
5/23/2007	Submission	SSN0020	Final Clinical Report for AN2690-ONYC-101 "21-Day Cumulative Irritation Test"
5/15/2007	Submission	SSN0021	Additional End of Phase II Briefing Book requested by FDA, sent by Schering-Plough
5/14/2007	Email from FDA	—	FDA Correspondence
5/11/2007	Email to the FDA	—	FDA Correspondence
5/11/2007	Email to the FDA	—	FDA Correspondence
5/11/2007	Submission	SSN0020	End of Phase II Briefing Book submitted to the FDA by Schering-Plough
5/9/2007	Submission	SSN0019 (Designate SP as Agent)	Letter to the FDA appointing Schering-Plough as an agent for IND 71,206
5/9/2007	Fax to the FDA	—	FDA Correspondence
2/27/2007	Submission	SSN0018 (New Protocol)	New Protocol for Investigational New Drug (IND) Application Number 71,206 for AN2690 Vehicle Applied as a 7.5% Solution for the Treatment of Onychomycosis (AN2690-ONYC-205)
2/13/2007	Submission	SSN0017 (Annual Report)	Annual Report for Investigational New Drug (IND) Application Number 71,206 for AN2690 Solution
2/5/2007	FDA Letter	—	FDA Correspondence

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Date	Type of Communication	SSN	Description
1/24/2007	Submission	SSN0016 (New Protocol)	New Protocol for Investigational New Drug (IND) Application Number 71,206 for AN2690 Vehicle, 2.5%, 5% and 7.5% for the Treatment of Onychomycosis (AN2690-ONYC-101)
1/11/2007	Fax to the FDA	—	FDA Correspondence
12/21/2006	Submission	SSN0015 (Protocol Amendment)	Protocol Amendment 2 for the AN2690-ONYC-200A clinical trial.
12/19/2006	Submission	SSN0014 (Investigator's Info)	Form 1572s and signed curriculum vitae for each investigator that are involved in the AN2690-ONYC-200A and AN2690-ONYC-203 studies
11/29/2006	FDA Fax	—	FDA Correspondence
11/6/2006	Submission	SSN0013	Request for an end of Phase II Meeting with the FDA to discuss the development of AN2690 for the treatment of Onychomycosis.
11/6/2006	Fax to the FDA	—	FDA Correspondence
11/3/2006	Submission	SSN0012	Response to FDA Fax of 11/2/06 with answers to questions posed by the FDA regarding the CAC submission
11/3/2006	Fax to the FDA	—	FDA Correspondence
11/3/2006	Fax to the FDA	—	FDA Correspondence
10/31/2006	Fax from the FDA	—	FDA Correspondence
9/14/2006	Submission	SSN0011	Request that our study protocol for determining the carcinogenic potential of AN2690 following dermal application to mice for 2-years be evaluated by the Executive Carcinogenicity Assessment Committee (CAC)
9/14/2006	Fax to the FDA	—	FDA Correspondence
9/14/2006	Fax to the FDA	—	FDA Correspondence
8/28/2006	Submission	SSN0010	Finalized version of TX reports previously submitted as DRAFTS in Submission 0006 and additional TX reports that were recently finalized.
8/25/2006	Submission	SSN0009 (Response to FDA Reviewer Comments)	Response to the FDA's fax of 8/1/06 with comments on the Clinical Chemistry and Clinical Microbiology of AN2690.
8/24/2006	Telephone Report	—	Teleconference with FDA
8/17/2006	Fax to the FDA	—	FDA Correspondence
8/2/2006	Telephone Report	—	Teleconference with FDA
8/1/2006	Telephone Report	—	Teleconference with FDA
8/1/2006	FDA Fax	—	FDA Correspondence
6/19/2006	Submission	SSN0008 (Double Blind Protocol)	New Clinical Protocol, entitled "AN2690-ONYC-200A, A Randomized, Double-Blind, Vehicle-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Topically Applied AN2690 2.5%, 5.0%, and 7.5% Solutions vs. Vehicle for the Treatment of Adult Subjects with Onychomycosis of the Great Toenail" for Investigational New Drug (IND) Application Number 71,206 for AN2690 Solution.
6/16/2006	Submission	SSN0007	Response to Carcinogenicity Special Protocol Assessment Request - Final CAC Report
6/15/2006	FDA Fax	—	FDA Correspondence

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Date	Type of Communication	SSN	Description
6/9/2006	Submission	SSN0006 (Open Label Protocol)	New Clinical Protocol, entitled "An Open Label, Multi-Center Study to Evaluate the Safety and Efficacy of Topically Applied AN2690 1% and 5% Solutions for the Treatment of Adult Subjects with Onychomycosis of the Great Toenail" for Investigational New Drug (IND) Application Number 71,206 for AN2690 Solution
6/9/2006	Fax to the FDA	—	FDA Correspondence
5/19/2006	Telephone Report	—	Teleconference with FDA
5/12/2006	Fax to the FDA	—	FDA Correspondence
5/12/2006	Fax to the FDA	—	FDA Correspondence
5/11/2006	Submission	SSN0005	Request for Special Protocol Assessment: Two-Year Carcinogenicity Study of AN2690 Administered by the Oral Route in Rats
5/6/2006	Telephone Report	—	Teleconference with FDA
5/2/2006	Fax to the FDA	—	Kirk Maples sent fax to Kalyani Bhatt with letter of intent to submit carcinogenic assessment protocols for AN2690.
4/12/2006	Submission	SSN0004 (Revised Absorption Protocol)	Revised version of the absorption study clinical protocol submitted last December submitted to the FDA
3/30/2006	Submission	SSN0003 (Final Reports to Replace Draft Reports Submitted to the IND)	Final Reports to replace draft reports submitted to the initial IND.
3/12/2006	Telephone Report	—	FDA Correspondence
2/9/2006	Submission	SSN0002 (Pharm/Tox Reviewer's Comments)	Response to comments made by the FDA reviewers regarding the Pharmacology and Toxicology in the Initial IND Submission.
2/8/2006	Email to the FDA	—	FDA Correspondence
2/7/2006	FDA Letter	—	FDA Correspondence
12/31/2005	N/A	—	Effective Date of IND
12/27/2005	Submission	SSN0001 (Response to Comments from FDA Reviewers)	Response to comments made by the FDA reviewers in a letter from Kalyani Bhatt on 12/22/05.
12/27/2005	Fax to the FDA	—	FDA Correspondence
12/22/2005	FDA Fax	—	FDA Correspondence
12/22/2005	FDA Fax	—	FDA Correspondence
12/6/2005	Telephone Report	—	Teleconference with FDA
12/6/2005	Email to the FDA	—	FDA Correspondence
12/1/2005	Receipt	—	FDA Receives IND Submission

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Date	Type of Communication	SSN	Description
11/29/2005	Submission	SSN0000 (Original IND)	Investigational New Drug (IND) Application for AN2690 Solution. Title: "An Open-Label, Multiple-Dose Study of the Absorption and Systemic Pharmacokinetics of AN2690 Applied as a 7.5% Solution to All Toenails of Adult Patients with Moderate to Severe Onychomycosis of the Great Toenail".
11/22/2005	Telephone Report	—	Teleconference with FDA
11/3/2005	FDA Fax	—	FDA Correspondence
11/2/2005	FDA Letter	—	FDA Correspondence
10/28/2005	Submission		Export Authorization Letter, Mexico
9/30/2005	FDA Fax	—	Fax from with FDA: Draft Reviewer's Comments on Pre-IND Briefing Package Submitted on 8/31/05
8/31/2005	Submission	Pre-IND Briefing Book Package	A letter from KM was sent to Sandy Childs with the Briefing Package
7/5/2005	FDA Letter	—	FDA Correspondence
6/20/2005	Submission	Type B Pre-IND Meeting Request (2nd request)	Pre-IND Meeting request for AN2690 for Onychomycosis
6/16/2005	Telephone Report	—	Teleconference with FDA
5/25/2005	FDA Letter	—	FDA Correspondence
5/12/2005	Submission	Type B Pre-IND Mtg Request (1st request)	Pre-IND Meeting request for AN2690 for Onychomycosis (this request was later canceled by KM on 7/16/05)

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NDA 204427: AN2690 (Tavaborole) Solution for Onychomycosis
FDA Communications Chronology

Date	Type of Communication	SSN	Description
7/7/2014	Email	–	NDA APPROVAL Cristina Attinello from FDA sent a courtesy email copy of the NDA approval letter for KERYDIN to Carmen Rodriguez.
6/23/2014	Submission	SN0022	Revised Draft Labeling
6/23/2014	Telephone Contact	–	Teleconference with FDA
6/20/2014	Telephone Contact	–	Teleconference with FDA
6/20/2014	Email	–	FDA Correspondence
6/19/2014	Email	–	FDA Correspondence
6/18/2014	Telephone Call	–	Teleconference with FDA
6/11/2014	Submission	SN0021	Response to FDA Request Draft Labeling Document
6/11/2014	Email	–	FDA Correspondence
6/10/2014	Email	–	FDA Correspondence
6/6/2014	Email	–	FDA Correspondence
6/2/2014	Submission	SN0020	General Correspondence-Draft Labeling Discussion Topics
6/2/2014	Email	–	FDA Correspondence
5/30/2014	Email	–	FDA Correspondence
5/28/2014	Email	–	FDA Correspondence
5/27/2014	Telephone Call	–	Teleconference with FDA
5/23/2014	Email	–	FDA Correspondence
5/20/2014	Submission	SN0019	General Correspondence – Draft Labeling Discussion Topics
5/15/2014	Email	–	FDA Correspondence
5/15/2014	Email	-	FDA Correspondence
5/15/2014	Email	-	FDA Correspondence
5/14/2014	Email	-	FDA Correspondence
5/13/2014	Submission	SN0018	Amendment: Response to FDA Request: Revised Draft Proposed Labeling Documents
5/13/2014	Telephone Call	-	Teleconference with FDA
5/13/2014	Email	-	FDA Correspondence
5/12/2014	Email	-	FDA Correspondence
5/12/2014	Email	-	FDA Correspondence
05/05/2014	Submission	SN0017	Amendment: Response to FDA Request: Revised Draft Proposed Labeling Documents
5/5/2014	Email	-	FDA Correspondence
5/5/2014	Email	-	FDA Correspondence
5/1/2014	Email	-	FDA Correspondence
5/1/2014	Email	-	FDA Correspondence
4/30/2014	Email	-	FDA Correspondence
4/29/2014	Email	-	FDA Correspondence
4/25/2014	Email	-	FDA Correspondence
4/25/2014	Email	-	FDA Correspondence
4/24/2014	Email	-	FDA Correspondence

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Date	Type of Communication	SSN	Description
4/18/2014	Submission	SN0016	Amendment: Response to FDA Request-Revised Draft Proposed Labeling Documents
4/15/2014	Email	-	FDA Correspondence
4/14/2014	Email	-	FDA Correspondence
4/4/2014	Letter	-	FDA Correspondence
4/04/2014	Submission	SN0015	Amendment: Response to FDA Request-Revised Draft Proposed Labeling Documents
4/02/2014	Email	-	FDA Correspondence
4/01/2014	Submision	SN0014	Amendment, Response to FDA Request-Revised Draft Bottle and Carton Labels
4/01/2014	Email	-	FDA Correspondence
4/01/2014	Meeting	-	Conference with FDA
3/27/2014	Email	-	FDA Correspondence
3/26/2014	Letter	-	FDA Correspondence
3/25/2014	Email	-	FDA Correspondence
3/21/2014	Email	-	FDA Correspondence
3/19/2014	Letter	-	FDA Correspondence
3/10/2014	Email	-	FDA Correspondence
01/31/2014	Submission	SN0013	Amendment SN0013 – Response to FDA Request – Revised Draft Bottle and Carton Labels
01/30/2014	Phone Call	-	Teleconference with FDA
01/30/2014 (letter dated 01/23/2014)	Letter	-	FDA Correspondence
01/30/2014 (letter dated 01/23/2014)	Letter	-	FDA Correspondence
01/30/2014	Email	-	FDA Correspondence
01/29/2014	Phone Call	–	Teleconference with FDA
01/29/2014	Email	–	FDA Correspondence
01/29/2014	Email	–	FDA Correspondence
01/28/2014	Email	–	FDA Correspondence
01/23/2014	Email	–	FDA Correspondence
01/22/2014	Email	–	FDA Correspondence
01/21/2014	Submission	SN0012	Amendment SN0012 – Response to FDA Request – Revised Pediatric Study Plan
01/16/2014	Submission	SN0011	Amendment SN0011 – Response to FDA Request for Information for KERYDIN, the proposed proprietary name
01/15/2014	Voicemail	–	Teleconference with FDA
01/15/2014	Email	–	Cristina Attinello provided the FDA attendee list for the Mid Cycle Communication meeting on 1/15/2014.
01/15/2014	Teleconference	–	Teleconference with FDA
01/13/2014	Email	–	FDA Correspondence
01/09/2014	Email	–	FDA Correspondence
01/08/2014	Email	–	FDA Correspondence
12/27/2013	Submission	SN0010	Amendment SN0010 – Response to FDA Request for Information
12/24/2013	Letter	–	FDA Correspondence
12/20/2013	Letter	–	FDA Correspondence

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Date	Type of Communication	SSN	Description
12/20/2013	Submission	SN0009	Amendment SN0009 – Response to FDA Request for Revised CMC Documents
12/18/2013	Email	--	FDA Correspondence
12/12/2013	Email	--	FDA Correspondence
12/05/2013	Email	--	FDA Correspondence
12/04/2013	Email	--	FDA Correspondence
11/27/2013	Email	--	FDA Correspondence
11/27/2013	Email	--	FDA Correspondence
11/26/2013	Email	--	FDA Correspondence
11/25/2013	Submission	SN0008	Amendment SN0008 – 4-Month Safety Update Report
11/18/2013	Submission	SN0007	Amendment SN0007 – Response to CMC Requests for Information in 74-Day Letter
11/17/2013	Email	--	FDA Correspondence
11/13/2013	Letter	--	FDA Correspondence
11/12/2013	Email	--	FDA Correspondence
11/12/2013	Email/Phone	--	FDA Correspondence
11/05/2013	Email	--	FDA Correspondence
10/30/2013	Submission	SN0006	Amendment SN0006 – Request for Proprietary Name Review for KERYDIN
10/29/2013	Call	--	Teleconference with FDA
10/23/2013	Email	--	FDA Correspondence
10/23/2013	Submission	SN0005	Amendment SN0005 – Response to Request for Information
10/18/2013	Email	--	FDA Correspondence
10/18/2013	Submission	SN0004	Amendment SN0004 – Module 1 Response to Day 74 Letter
10/11/2013	Fax	--	FDA Correspondence
10/10/2013	Letter and Email	--	FDA Correspondence
10/10/2013	Letter and Email	--	FDA Correspondence
09/26/2013	Letter (Recd 10/02/2013)	--	FDA Correspondence
10/01/2013	Phone call	--	Teleconference with FDA
09/22/2013	Letter	--	FDA Correspondence
09/06/2013	Email	--	FDA Correspondence
08/22/2013	Phone Call	--	Teleconference with FDA
08/20/2013	Email	--	FDA Correspondence
08/19/2013	Email	--	FDA Correspondence
08/19/2013	Submission	SN0003	Amendment SN0003 – Resubmission of Module 3.2.S.2.2 Document
08/16/2013	Email	--	FDA Correspondence
08/16/2013	Email	--	FDA Correspondence
08/16/2013	Email	--	FDA Correspondence
08/16/2013	Email	--	FDA Correspondence
08/14/2013	Submission	SN0002	Amendment SN0002 – Module 1 Draft Labeling Documents
08/13/2013	Email	--	FDA Correspondence
08/12/2013	Email	--	FDA Correspondence
08/09/2013	Email	--	FDA Correspondence
08/09/2013	Submission	SN0001	Amendment SN0001 – Module 1 Financial Disclosure Information

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Date	Type of Communication	SSN	Description
08/09/2013	Email	--	FDA Correspondence
08/06/2013	Email	--	FDA Correspondence
08/01/2013	Email	--	FDA Correspondence
08/01/2013	Email	--	FDA Correspondence
07/31/2013	Email	--	FDA Correspondence
07/31/2013	Email	--	FDA Correspondence
07/26/2013	Email	--	FDA Correspondence
07/26/2013	Submission	0000	Submission of New Drug Application
07/19/2013	Email	--	FDA Correspondence
07/16/2013	Letter	--	FDA Correspondence

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614-248-4054
Telephone Number

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

1. Patent Term Extension Application 35 U.S.C. § 156, including Exhibits A through G (3 copies, 118 pages each);
2. Certificate of Express Mailing (1 page); and
3. Return Receipt Postcard (1 page).

5955300v1

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER		Docket Number: 064507-5014US	
Application Number 11/357,687	Filing Date February 16, 2006	Examiner Shiao, Rei Tsang	Art Unit 1626
Patent Number 7,582,621	Issue Date September 1, 2009	[redacted]	
Invention Title Boron-Containing Small Molecules		Inventor(s) Baker *et al.*	

Address to:
Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450
Mail Stop: Hatch-Waxman PTE

RECEIVED
AUG 29 2014
PATENT EXTENSION
OPLA

Dear Ms. Till:

PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C. § 156

Please find enclosed the following documents filed in connection with the above-referenced patent:

1. Application for Extension of Patent Term Under 35 U.S.C. § 156 (original and two copies);
2. Statement under 37 C.F.R. § 3.73(b) and Assignment Record; and
3. Power of Attorney by Owner of Entire Interest.

As set forth under 37 C.F.R. § 1.20(j), please charge the sum of $1,120.00 to Deposit Account No. 03-1721. Please charge any underpayment or any additional fees that may be required, or credit any overpayment, to Deposit Account No. 03-1721.

Respectfully submitted,

Dated: August 28, 2014

Andrea L.C. Reid, Reg. No. 47,902
Attorney for Anacor Pharmaceuticals, Inc.

Choate, Hall & Stewart LLP
2 International Place
Boston, MA 02110
(617) 248-5000 (telephone)
(212) 248-4000 (facsimile)

Customer No. 24280

06/10/2015 GARIAS 00000011 031721 11357687
Sale Ref: 00000014 DA#: 031721 11357687
01 FC:1457 1120.00 DA

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UNITED STATES PATENT AND TRADEMARK OFFICE

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

Office of Management
Food and Drug Administration
10001 New Hampshire Ave.,
Hillandale Campus RM 3180
Silver Spring, MD 20993

JUN 10 2015

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 7,582,621 was filed on August 29, 2014, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, KERYDIN® (tavaborole), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Associate Commissioner
for Patent Examination Policy

cc: Andrea L.C. Reid
Choate Hall & Stewart LLP
2 International Place
Boston, MA 02110

PTO/SB/81 (01-09)
Approved for use through 11/30/2011. OMB 0651-0035
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.

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	11/357,687
Filing Date	February 16, 2006
First Named Inventor	Baker, Stephen J.
Title	BORON-CONTAINING SMALL MOLECULES
Art Unit	1626
Examiner Name	Shiao, Rei Tsang
Attorney Docket Number	064587-5014US

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 24280

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

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

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature	/Ryan Walsh/	Date	7/29/2009
Name	Ryan Walsh	Telephone	650-543-7531
Title and Company	Chief IP & Litigation Counsel - Anacor Pharmaceuticals, Inc.		

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.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 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.**

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

Privacy Act Statement

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

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

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

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Baker et al.

Application No./Patent No.: 11/357,687 Filed/Issue Date: February 16, 2006

Titled: BORON-CONTAINING SMALL MOLECULES

Anacor Pharmaceuticals, Inc. , a Corporation

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

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

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

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

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

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 017685, Frame 0979, or for which a copy therefore is attached.

OR

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

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

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

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

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

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

Signature 4/28/2014 Date

Ryan Walsh Chief IP & Litigation Counsel

Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. 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, 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.**

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

Privacy Act Statement

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

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

On this 26th day of August, 2014, I certify that the attached document is a true, exact, complete, and unaltered copy (12 pages) made by me from our files of a Certified Copy of an Assignment from the inventors to Anacor Pharmaceuticals, Inc.

Carmen Constantinescu
Notary Public
My Commission expires February 13, 2015

Carmen M. Constantinescu
Notary Public
Commonwealth of Massachusetts
My Commission Expires
February 13, 2015

6193882v1

A 7488680

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

August 04, 2014

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON JUNE 29, 2006.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

M. TARVER
Certifying Officer

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
Stephen J. Baker	04/28/2006
Tsutomu Akama	04/28/2006
Carolyn Bellinger-Kawahara	04/28/2006
Karin M. Hold	04/28/2006
James J. Leyden	06/19/2006
Kirk R. Maples	04/28/2006
Jacob J. Plattner	04/28/2006
Virginia Sanders	04/28/2006
Yong-Kang Zhang	04/28/2006
Vincent S. Hernandez	04/28/2006

RECEIVING PARTY DATA

Name:	Anacor Pharmaceuticals, Inc.
Street Address:	1060 East Meadow Circle
City:	Palo Alto
State/Country:	CALIFORNIA
Postal Code:	94303

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	11357687

CH $40.00 11357687

CORRESPONDENCE DATA

Fax Number: (650)843-4001
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 415-442-1749
Email: kdegliantoni@morganlewis.com
Correspondent Name: Jeffry S. Mann
Address Line 1: MLB, LLP, Two Palo Alto Square

Address Line 2:	3000 El Camino Real, Suite 700
Address Line 4:	Palo Alto, CALIFORNIA 94306

ATTORNEY DOCKET NUMBER:	64507-5014-US
NAME OF SUBMITTER:	Jeffry S. Mann

Total Attachments: 9
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source=A5014US#page7.tif
source=A5014US#page8.tif
source=A5014US#page9.tif

Attorney Docket No. 64507-5014-US

Form PTO-1595
(Rev. 10-02)
OMB No. 0651-0027 (exp. 5/31/2002)

Recordation Form Cover Sheet
PATENTS ONLY

U.S. Department of Commerce
U.S. Patent and Trademark Office

Tab settings ⇨⇨⇨▼ ▼ ▼ ▼ ▼ ▼ ▼

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof

1. Name of conveying party(ies):

Stephen J. Baker
Tsutomu Akama
Carolyn Bellinger-Kawahara

Additional name(s) of conveying party(ies) attached? ☒ Yes ☐ No.

2. Name and address of receiving party(ies)

Name: Anacor Pharmaceuticals, Inc.

Street Address: 1060 East Meadow Circle

City: Palo Alto State: CA ZIP: 94303

Additional name(s) and address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other:

Execution Dates: 04/28/06, 04/28/06, 04/28/06, 04/28/06, 04/28/06, 06/19/06, 04/28/06, 04/28/06, 04/28/06, and 04/28/06, respectively

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No(s): 11/357,687

B. Patent No(s):

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Jeffry S. Mann, Ph.D.
Morgan, Lewis & Bockius LLP
Two Palo Alto Square
3000 El Camino Real, Ste. 700
Palo Alto, CA 94306
Tel. (415) 442-1000
Direct Dial: (415) 442-1119
eFAX: (650) 843-4001
e-mail: jmann@morganlewis.com

6. Total number of applications and patents involved 1

7. Total fee (37 CFR 3.41): ----------$40.00

☐ Enclosed

☒ Authorized to be charged to deposit account

8. Deposit account number: **50-0310**

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Jeffry S. Mann, Ph.D.
Name of Person Signing
Atty. Reg. No. 42,837

Signature

June 27, 2006
Date

Total number of pages including cover sheet, attachments and documents: 9

Mail documents to be recorded with required cover sheet information to:
Mail Stop Assignment Recordation Services
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

1-SF/7385940.1

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 527 of 558

1. **Additional name(s) of conveying party(ies): (Continued from Page 1)**

Vincent S. Hernandez
Karin M. Hold
James J. Leyden
Kirk R. Maples
Jacob J. Plattner
Virginia Sanders
Yong-Kang Zhang

2. Additional name(s) and address(es) of receiving party(ies): (Continued from Page 1)

3. Additional application number(s) or patent number(s): (Continued from Page 1)

A. Patent Application No.(s)

B. Patent No.(s)

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 528 of 558

Attorney Docket No.: 64507-5014-US

ASSIGNMENT OF PATENT APPLICATION

JOINT

WHEREAS, Stephen J. Baker of 1568 Begen Avenue, Mountain View, CA, 94040; Tsutomu Akama of 832 Azure Street, Sunnyvale, CA, 94087; Carolyn Bellinger-Kawahara of 15 Landa Lane, Redwood City, CA, 94061; Vincent S. Hernandez of 287 Gilchrist Lane, Watsonville, CA, 95076; Karin M. Hold of 1908 Valdez Avenue, Belmont, CA, 94002; James J. Leyden of 319 Applebrook Drive, Malvern, CA, 19355; Kirk R. Maples of 1195 San Moritz Drive, San Jose, CA 95132; Jacob J. Plattner of 1016 Amito Avenue, Berkeley, CA 94705; Virginia Sanders of 2895 Harrison Street, Apt. 4, San Francisco, CA, 94110; and Yong-Kang Zhang of 5151 Westmont Avenue, San Jose, CA, 95130, hereinafter referred to as "Assignors," are the inventors of the invention described and set forth in the below-identified patent application:

Title of Invention:	BORON-CONTAINING SMALL MOLECULES
Filing Date:	February 16, 2006
Application No.:	11/357,687; and

WHEREAS, Anacor Pharmaceuticals, Inc., located at 1060 East Meadow Circle, Palo Alto, CA 94303, hereinafter referred to as "ASSIGNEE," is desirous of acquiring an interest in the invention and application and in any U.S. Letters Patent and Registrations which may be granted on any patent application claiming priority from the same;

For good and valuable consideration, receipt of which is hereby acknowledged by Assignors, Assignors have assigned, and by these presents does assign to Assignee all right, title and interest in and to the invention and application and to all foreign counterparts (including patent, utility model and industrial designs), and in and to any Letters Patent and Registrations which may hereafter be granted on any patent application claiming priority from the same in the United States and all countries throughout the world, and to claim the priority from the application as provided by the Paris Convention. The right, title and interest is to be held and enjoyed by Assignee and Assignee's successors and assigns as fully and exclusively as it would have been held and enjoyed by Assignors had this Assignment not been made, for the full term of any Letters Patent and Registrations which may be granted thereon, or of any division, renewal, continuation in whole or in part, substitution, conversion, reissue, prolongation or extension thereof.

Assignors further agree that Assignors will, without charge to Assignee, but at Assignee's expense, (a) cooperate with Assignee in the prosecution of U.S. Patent applications and foreign counterparts on the invention and any improvements, (b) execute, verify, acknowledge and deliver all such further papers, including applications and instruments of transfer, and (c) perform such other acts as Assignee lawfully may request to obtain or maintain Letters Patent and Registrations for the invention and improvements in any and all countries, and to vest title thereto in Assignee, or Assignee's successors and assigns.

Assignors hereby authorize and request Morgan, Lewis & Bockius LLP, One Market, Spear Street Tower, San Francisco, CA 94105, to insert herein above the application number and filing date of said application when known.

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 529 of 558

IN TESTIMONY WHEREOF, Assignors have signed his/her names on the dates indicated.

Dated: April 28th 2006

STEPHEN J. BAKER

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared STEPHEN J. BAKER, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

NOTARY PUBLIC

My ~~Commission Expires:~~ July 12, 2006

Dated: 4/28/06

TSUTOMU AKAMA

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared TSUTOMU AKAMA, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

1-SF/7364295.1

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 530 of 558

Dated: 4/28/06

CAROLYN BELLINGER-KAWAHARA

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared CAROLYN BELLINGER-KAWAHARA, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that ~~he~~/she executed the same in ~~his~~/her authorized capacity, and that by ~~his~~/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

~~WITNESS my hand and official seal.~~

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: 4/28/06

VINCENT S. HERNANDEZ

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared VINCENT S. HERNANDEZ, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/~~she~~ executed the same in his/~~her~~ authorized capacity, and that by his/~~her~~ signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 531 of 558

Dated: 4/28/06

KARIN M. HOLD

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared KARIN M. HOLD, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: _____

JAMES J. LEYDON

STATE OF)
) ss.
COUNTY OF)

On _____, before me, _____ personally appeared JAMES J. LEYDON, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: _____

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 532 of 558

Dated: _____

_____
KARIN M. HOLD

STATE OF CALIFORNIA)
) ss.
COUNTY OF)

On _____, before me, _____ personally appeared KARIN M. HOLD, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

_____
NOTARY PUBLIC

My Commission Expires: _____

Dated: 6/19/06

_____
JAMES J. LEYDEN

STATE OF)
) ss.
COUNTY OF)

On _____, before me, _____ personally appeared JAMES J. LEYDEN, personally known to me (or proved to me on the basis of satisfactory evidence) to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

_____
NOTARY PUBLIC

My Commission Expires: _____

PATENT
REEL: 017855 FRAME: 0987

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 533 of 558

Dated: 4/28/06

KIRK R. MAPLES

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared KIRK R. MAPLES, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: April 28, 2006

JACOB J. PLATTNER

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared JACOB J. PLATTNER, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 534 of 558

Dated: 4/28/06

Virginia Sanders
VIRGINIA SANDERS

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared VIRGINIA SANDERS, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

Dated: 4-28-2006

Yongkang Zhang
YONG-KANG ZHANG

STATE OF CALIFORNIA)
) ss.
COUNTY OF Santa Clara)

On April 28, 2006 before me, Donielle M. Equite personally appeared YONG-KANG ZHANG, personally known to me ~~(or proved to me on the basis of satisfactory evidence)~~ to be the person whose name is subscribed to the within instrument, and acknowledged to me that he/she executed the same in his/her authorized capacity, and that by his/her signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

WITNESS my hand and official seal.

Donielle M. Equite
NOTARY PUBLIC

My Commission Expires: July 12, 2007

DONIELLE M. EQUITE
Commission # 1430053
Notary Public - California
Santa Clara County
My Comm. Expires Jul 12, 2007

1-SF/7364295.1

Attorney Docket No.: 2011549-0002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Baker *et al.*
Application No.: 11/357,687
Filed: February 16, 2006
Patent No.: 7,582,621
Issued: September 1, 2009
For: BORON-CONTAINING SMALL MOLECULES

Confirmation No.: 4964
Art Unit: 1626
Examiner: Shiao, Rei Tsang

TRANSMITTAL LETTER

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

Dear Commissioner:

Applicant submits herewith a Statement Under 37 CFR 3.73(b) and an executed Power of Attorney document in connection with the above-referenced patent.

The Statement and Power of Attorney are being re-submitted after previously being filed on August 28, 2014, with the Patent Term Extension Application filed under 35 U.S.C. § 156.

Applicant respectfully requests acknowledgement of the documents submitted herewith and acceptance of Power of Attorney.

Dated: September 14, 2015

Respectfully submitted,

/Kevin M. Henry/
Kevin M. Henry, PhD, JD
Registration No.: 65,647
CHOATE, HALL & STEWART LLP
Two International Place
Boston, Massachusetts 02110
(617) 248-5159
Attorney for Applicant

7010874v1

Electronic Acknowledgement Receipt

EFS ID:	23485271
Application Number:	11357687
International Application Number:	
Confirmation Number:	4964
Title of Invention:	BORON-CONTAINING SMALL MOLECULES
First Named Inventor/Applicant Name:	Stephen J. Baker
Customer Number:	43850
Filer:	Kevin M. Henry/Kayla Pitney
Filer Authorized By:	Kevin M. Henry
Attorney Docket Number:	064507-5014US
Receipt Date:	14-SEP-2015
Filing Date:	16-FEB-2006
Time Stamp:	16:40:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	2011549_0002_POA.pdf	644743 a98204dee009859fdfde86d456a5534738eda8c1	no	2
Warnings:					
Information:					

2	Assignee showing of ownership per 37 CFR 3.73	2011549_0002_ROA.pdf	1386515 1b348664b1ab0c994b03dcd21e09c28d0d2eae88	no	15
Warnings:					
Information:					
3	Transmittal Letter	2011549_0002_Transmittal.pdf	92041 3c29e3e43edf148e0be1d86db53e067507e574cf	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	2123299		

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/357,687	02/16/2006	Stephen J. Baker	064507-5014US

CONFIRMATION NO. 4964

24280
CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

POA ACCEPTANCE LETTER

OC000000077560710

Date Mailed: 09/22/2015

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/14/2015.

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

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/hachristian/

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/357,687	02/16/2006	Stephen J. Baker	064507-5014US

CONFIRMATION NO. 4964

43850
MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

POWER OF ATTORNEY NOTICE

OC000000077560637

Date Mailed: 09/22/2015

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/14/2015.

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

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/hachristian/

Department of Health and Human Services | Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Building # 51, Room 6250
Silver Spring, MD 20993-0002

OCT 1 5 2015

Re: KERYDIN
Patent No. 7,582,621
Docket No. FDA-2015-E-3488

The Honorable Michelle K. Lee
Under Secretary of Commerce for Intellectual Property
Director of the United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Director:

This is concerning the application for patent term extension for U.S. Patent No. 7,582,621 filed by Anacor Pharmaceuticals, Inc., under 35 U.S.C. 156. The human drug product claimed by the patent is KERYDIN (tavaborole), which was assigned new drug application (NDA) No. 204427.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. 156(f)(1).

The NDA was approved on July 7, 2014, which makes the submission of the patent term extension application on August 29, 2014, timely within the meaning of 35 U.S.C. 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Carol Bennett

for Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

cc: Andrea L.C. Reid
Choate, Hall & Stewart LLP
2 International Place
Boston, MA 02110

Trials@uspto.gov
571.272.7822

Paper No. 24
Entered: February 23, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS X LLC,
Petitioner,

v.

ANACOR PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2015-01776
Patent 7,582,621 B2

Before MICHAEL P. TIERNEY, GRACE KARAFFA OBERMANN, and TINA E. HULSE, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Coalition for Affordable Drugs X LLC ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–12 of U.S. Patent No. 7,582,621 B2 (Ex. 1001, "the '621 patent"). Paper 1 ("Pet."). Anacor Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 17 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the Petition and Preliminary Response, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–12. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

Petitioner has filed concurrently two other petitions for *inter partes* review of related U.S. Patent No. 7,767,657 B2 in IPR2015-01780 and IPR2015-01785. Pet. 5.

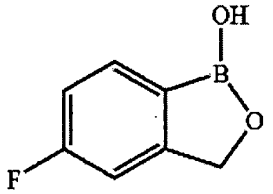
B. The '621 Patent

The '621 patent relates to boron-containing compounds useful for treating fungal infections, including infections of the nail and hoof known as ungual and/or periungual infections. Ex. 1001, Abstract, 1:12–13. One type of ungual and/or periungual fungal infection is onychomycosis. *Id.* at 1:15–17. According to the Specification, current treatment for ungual and/or periungual infections generally falls into three categories: systemic administration of medicine; surgical removal of the nail or hoof followed by

topical treatment of the exposed tissue; or topical application of medicine with bandages to keep the medication in place on the nail or hoof. *Id.* at 1:17–24.

Each of the approaches has major drawbacks. Systemic administration of medicine typically requires long-term, high-dose therapy, which can have significant adverse effects on, for example, the liver and testosterone levels. *Id.* at 1:28–45. Surgical treatment is painful and undesirable cosmetically (or not realistic for animals such as horses). *Id.* at 1:46–52. And topical dosage forms cannot keep the drug in contact with the infected area for therapeutically effective periods of time and, because of the composition of the nail, topical therapy for fungal infections have generally been ineffective. *Id.* at 1:53–2:11. Accordingly, the Specification states that "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." *Id.* at 2:36–39.

The '621 patent claims a method of treating an infection using 1,3-dihydro-5-fluoro-l-hydroxy-2, 1-benzoxaborole, which is referred to as either compound 1 (*see id.* at 32:10–17) or compound C10 (*see id.* at 51:55–61) in the Specification, and has the following chemical structure:



C. Illustrative Claim

Petitioner challenges claims 1–12 of the '621 patent. Claim 1 is illustrative and is reproduced below:

> 1. A method of treating an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-l-hydroxy-2, 1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said infection.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–12 of the '621 patent on the following grounds:

References	**Basis**	**Claim(s) challenged**
Austin[1] and Brehove[2]	§ 103	1–12
Austin and Freeman[3]	§ 103	1–12
Austin, Freeman, and Sun[4]	§ 103	9

Petitioner also relies on the Declarations of Stephen Kahl Ph.D. ("Kahl Decl.," Ex. 1006) and S. Narasimha Murthy Ph.D. ("Murthy Decl.," Ex. 1008).

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[1] Austin et al., WO 95/33754, published Dec. 14, 1995 (Ex. 1002).

[2] Brehove, US 2002/0165121 A1, published Nov. 7, 2002 (Ex. 1003).

[3] Freeman et al., WO 03/009689 A1, published Feb. 6, 2003 (Ex. 1004).

[4] Sun et al., US 6,042,845, issued Mar. 28, 2000 (Ex. 1005).

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II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art at the time the '621 patent was filed would have had an advanced degree (Master's or Ph.D.) or equivalent experience in chemistry, pharmacology, or biochemistry, and at least two years of experience with the research, development, or production of pharmaceuticals. Pet. 23 (citing Ex. 1006 ¶ 21; Ex. 1008 ¶ 34). Patent Owner largely agrees with Petitioner's definition, further adding that a skilled artisan must also have knowledge and experience with developing potential drugs candidates for treating onychomycosis and ungual and other infections. Prelim. Resp. 15–16.

We need not decide at this time whether one skilled in the art would have possessed the additional knowledge identified by Patent Owner for purposes of this Decision. Moreover, Patent Owner acknowledges that Petitioner's declarants purport to have experience in the additional fields (Prelim. Resp. 16), and the prior art itself is sufficient to demonstrate the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (holding the absence of specific findings on "level of skill in the art does not give rise to reversible error 'where the prior art itself reflects an appropriate level and a need for testimony is not shown'") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

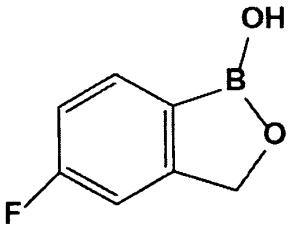
In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015),

CFAD v. Anacor, IPR2015-01776, CFAD EXHIBIT 1070 - Page 547 of 558

cert. granted sub nom. Cuozzo Speed Techs., LLC v. Lee, 84 U.S.L.W. 3218 (U.S. Jan. 15, 2016) (No. 15-446). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole"

Independent claims 1, 11, and 12 recite the compound 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole has the following structure:



The parties agree that the claimed compound may also be referred to as "5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole." Pet. 11; Prelim. Resp. 17–18. Patent Owner further notes that the claimed compound is also known as "tavaborole." Prelim. Resp. 18.

We determine that the broadest reasonable interpretation of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole includes "5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole" and "tavaborole." Accordingly, for ease of reference, we refer to the claimed compound as "tavaborole" in this Decision.

2. Remaining Claim Terms

At this stage of the proceeding, we determine that it is unnecessary to expressly construe the remaining claim terms for purposes of this Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

C. Obviousness over Austin and Brehove

Petitioner asserts that claims 1–12 are unpatentable as obvious over Austin and Brehove. Pet. 23–42. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 19–45. Based on the current record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing claims 1–12 are unpatentable as obvious over Austin and Brehove.

1. Austin (Ex. 1002)

Austin relates to the use of oxaboroles as industrial biocides, and especially as fungicides for the protection of plastic materials. Ex. 1002, Abstract. The Abstract further states that "[p]referred compounds are 5- and 6-fluoro or bromo-1,3-dihydro-1-hydroxy-2,1-benzoxaborole including O-esters thereof." *Id.* Austin notes that it has been found that compounds containing an oxaborole ring are "particularly effective against micro-organisms such as bacteria, algae, yeasts and particularly fungi, especially fungi which cause degradation of plastics materials." *Id.* at 1:35–38.

Along with a number of different preferred oxaboroles, Austin discloses tavaborole as Example 64, as well as the results of a study showing tavaborole has effective antifungal activity against five different fungi: *Aspergillus niger*, *Aureobasidium pullulans*, *Candida albicans*, *Gliocladium roseum*, and *Penicillium pinophylum*. *Id.* at 37 (Table 9).

2. Brehove (Ex. 1003)

Brehove relates to the topical treatment of nail infections such as onychomycosis caused by bacteria, fungi, and other pathogens. Ex. 1003 ¶ 3. Brehove explains that onychomycosis is a nail disease typically caused by *Candida albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, or *Epidermpophyton floccusum*. *Id.* ¶ 5. Brehove states that *Candida albicans* is the most common pathogen causing onychomycosis. *Id.* ¶ 18. Brehove teaches that to be effective for onychomycosis, the topical treatment should exhibit a powerful potency for pathogens, be permeable through the nail barrier, and be safe for patient use. *Id.* ¶ 6. According to Brehove, "[t]here exists a need in the art for a topical application that combines these traits in high degree." *Id.*

Brehove states that the "safety and non-toxicity of organo-boron compounds has been questioned." *Id.* ¶ 13. On the one hand, Brehove describes one reference that states that boron compounds are "very toxic," while on the other hand, Brehove describes references that found the toxicity of a certain boron-containing compound to be "very low" and another industrial fungicide compound called Biobor® JF to cause "mild irritation." *Id.* ¶¶ 14–15.

Biobor® JF contains a combination of 2,2'-(1-methyltrimethylene dioxy) bis-(4-methyl-1, 3, 2-dioxaborinane) (referred to by Brehove as "S1") and 2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane) (referred to by Brehove as "S2"). Ex. 1003 ¶¶ 15, 30. Brehove describes the results of both in vitro and in vivo testing of the antifungal activity of S1 and S2 against *Candida albicans*. *Id.* ¶¶ 30–38.

3. Analysis

Petitioner argues that claims 1–12 are unpatentable as obvious over the combination of Austin and Brehove. Through claim charts and Dr. Murthy's testimony, Petitioner asserts that the combination teaches each limitation of the claims. Pet. 38–42; Ex. 1008 ¶¶ 87–92, 107–15. Having reviewed the arguments and evidence, we are persuaded that Petitioner has shown sufficiently that each limitation of the challenged claims is taught by the combination of Austin and Brehove.

Petitioner then provides a detailed explanation supported by the testimony of its two declarants as to why a person of ordinary skill in the art would have administered Austin's tavaborole in Brehove's method of treating onychomycosis with a reasonable expectation of success. Pet. 31–38. Specifically, Petitioner asserts that a person of ordinary skill in the art would have combined Austin and Brehove because:

> (1) both references teach the use of boron-based compounds as fungicides; (2) both references also disclose the use of boron-based compounds to specifically inhibit *Candida albicans*, which is one of the fungi responsible for onychomycosis; and (3) *Austin* discloses boron-based compounds that have lower molecular weight than the successful compounds of *Brehove* and are therefore likely to effectively penetrate the nail barrier.

Pet. 31 (citing Ex. 1006 ¶¶ 33-34, 36; Ex. 1008 ¶¶ 86, 93-96, 116).

In its Preliminary Response, Patent Owner does not appear to challenge that the combination of references teaches each limitation of the claims. Instead, Patent Owner argues that Petitioner has failed to meet its burden to show that a person of ordinary skill in the art would have combined Austin and Brehove in the manner recited in the claims with a reasonable expectation of success.

First, Patent Owner argues that a skilled artisan would not have started with a compound selected from Austin because Austin discloses a biocide, which is a toxic poison designed to kill living organisms. Prelim. Resp. 21. The parties, however, dispute the toxicity of boron-containing compounds. For example, Petitioner's declarant, Dr. Kahl, testifies that "[b]oron-containing compounds are generally considered safe."[5] Ex. 1006 ¶ 30. And Brehove identifies at least one article that states that the toxicity of the dioxiborinane tested was "very low." Ex. 1003 ¶ 15. Thus, at this stage of the proceeding, we are persuaded that Petitioner has made a sufficient showing that a person of ordinary skill in the art would not have been dissuaded from starting with Austin because it teaches boron-containing compounds.

Patent Owner also argues that a person of ordinary skill in the art would not have selected tavaborole from the millions of compounds disclosed in Austin. Prelim. Resp. 23–29. It is well settled that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art. *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Here, Austin discloses 5-fluoro benzoxaboroles as preferred fungicides in the Abstract, and tavaborole is one of three preferred compounds tested that effectively inhibits *Candida albicans*, which is a cause of onychomycosis. Pet. 31–32 (citing Ex. 1006

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[5] We acknowledge Patent Owner's argument challenging Dr. Kahl's credibility regarding the toxicity of boron-containing compounds. Prelim. Resp. 4 (citing a paper by Dr. Kahl (Ex. 2002) allegedly emphasizing the toxicity of boron-containing compounds). At this stage of the proceeding, however, we decline to comment on this issue until the record has been developed further during trial.

¶¶ 34, 38; Ex. 1008 ¶¶ 61, 64, 67–71, 90). Accordingly, evaluating Austin for all that it teaches, we conclude on the present record that one of ordinary skill in the art would have recognized that tavaborole is a preferred fungicide for inhibiting *Candida albicans*, which is a cause of onychomycosis.

Patent Owner then asserts that Petitioner has not provided a credible reason to combine the tavaborole of Austin with the method of treating onychomycosis in Brehove with a reasonable expectation of success. Prelim. Resp. 29–38. Patent Owner argues that Brehove would not supply a reasonable expectation of success because a skilled artisan would not be convinced that dioxaborinanes are not toxic, particularly given the lack of data in Brehove. *Id.* at 30–32, 37–38. Patent Owner also argues that a skilled artisan would not combine the references given the structural differences between tavaborole and dioxaborinanes. *Id.* at 32–35. Petitioner, however, offers the testimony of its declarant, Dr. Murthy, who states that both Austin and Brehove disclose boron heterocycles, and that a person of ordinary skill in the art would have expected that compounds that share similar structural features would likely share similar functional features, such as the inhibition of additional fungi responsible for oncyhomycosis. Ex. 1008 ¶¶ 100-01. As to the lack of in vivo data in Brehove, we note the specificity of the examples and reported results of those examples. Ex. 1003 ¶¶ 34–38. Moreover, citing the examples, Dr. Murthy testifies that "the topical application of the [Brehove] compositions . . . effectively treated the onychomycosis with '[n]o skin irritation . . . and no [evidence of] side effects.'" Ex. 108 ¶ 71 (citing Ex. 1003 ¶¶ 22, 30, 34–38). Thus, although we acknowledge Patent Owner's arguments to the contrary, on this record and at this stage of the proceeding, we determine that Petitioner has set forth sufficient evidence to show that a person of

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ordinary skill in the art would have had a reason to apply Austin's tavaborole to Brehove's method of treating onychomycosis with a reasonable expectation of success. *See* Pet. 31–51.

Accordingly, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing claims 1–12 are unpatentable as obvious over Austin and Brehove.

D. Obviousness over Austin and Freeman

Petitioner argues that claims 1–12 are unpatentable as obvious over Austin and Freeman. Pet. 43–56. Patent Owner opposes. Prelim. Resp. 45–58. Based on the current record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing claims 1–12 are unpatentable over Austin and Freeman. We incorporate here our earlier findings and discussion regarding the disclosure of Austin.

1. Freeman (Ex. 1004)

Freeman discloses phenyl boronic acid and related boronic acid compounds that are used for treating fungal infections such as onychomycosis. Ex. 1004, Abstract, ¶ 1. Freeman identifies *Trichophyton rubrum* ("*T. rubrum*") as one of the most common dermatophyte causes of onychomycosis. *Id.* ¶ 8. Freeman also identifies non-dermatophytes, "especially *Candida Sp.*," as another cause of onychomycosis. *Id.* According to Freeman, phenyl boronic acids "have been found to be particularly useful in treating nail fungal infections." *Id.* ¶ 22.

Freeman also discloses results of in vitro testing of the fungicidal activity of phenyl boronic acid. *Id.* ¶¶ 31–34. In particular, Freeman notes that phenyl boronic acid exhibited fungicidal effect on *T. rubrum*. *Id.* ¶ 34. Freeman also notes that the compounds tested had a fungicidal effect on *Candida parapsylosis* at 10 mg/ml. *Id.*

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2. Analysis

Petitioner asserts that the combination of Austin and Freeman render the subject matter of claims 1–12 obvious. Pet. 43– 56. Through claim charts and Dr. Murthy's testimony, Petitioner asserts that the combination teaches each limitation of the claims. Pet. 51–56; Ex. 1008 ¶¶ 119–24, 138–46. Having reviewed the arguments and evidence, we are persuaded that Petitioner has shown sufficiently that each limitation of the challenged claims is taught by the combination of Austin and Freeman.

Petitioner also asserts that a person of ordinary skill in the art would have had a reason to combine Austin's tavaborole with Freeman's method of treating onychomycosis with a reasonable expectation of success. Pet. 45–51. Specifically, Petitioner asserts:

> (1) both references teach the use of boron-based compounds as fungicides; (2) both references disclose the use of boron-based compounds to specifically inhibit *Candida albicans* or *T. rubrum*, which are fungi responsible for onychomycosis; and (3) *Austin* discloses boron-based compounds that have structural similarity to *Freeman's* preferred compounds for treating and inhibiting onychomycosis in humans.

Id. at 45–46 (citing Ex. 1008 ¶¶ 65, 74, 77, 125–27). Patent Owner challenges Petitioner's assertions, making similar arguments as described above with the combination of Austin and Brehove.

For example, Patent Owner again argues that a person of ordinary skill in the art would not have selected tavaborole from Austin. Prelim. Resp. 46–47. Patent Owner also argues a person of ordinary skill in the art would not combine Austin and Freeman because a skilled artisan would expect Austin's benzoxaboroles to be toxic. *Id.* at 47–48. Finally, Patent Owner asserts that a person of ordinary skill in the art would not combine

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the references given the differences in structure and function of tavaborole and Freeman's phenyl boronic acid. *Id.* at 48–54.

For similar reasons stated above with respect to the challenge over Austin and Freeman, we determine that Petitioner has made a sufficient showing as to why a person of ordinary skill in the art would combine Austin and Freeman with a reasonable expectation of success. For example, in light of the dispute over the toxicity of boron-containing compounds, we are not persuaded, on this record, that the alleged toxicity of benzoxaboroles would deter a skilled artisan from looking to Austin and recognizing that tavaborole is a preferred fungicide for inhibiting *Candida albicans*. Moreover, although Austin describes the fungicidal activity against *Candida albicans* and Freeman describes the fungicidal activity against *T. rubrum*, Freeman also teaches that its compounds are effective against a different species of *Candida* (*Candida parapsylosis*). *See* Ex. 1004 ¶ 34. Petitioner's declarant, Dr. Murthy, explains that "*Freeman* links *Candida Sp.*, also a common target of *Austin* and *Brehove*, to onychomycosis and further recognizes, consistent with the knowledge of a [person of ordinary skill in the art] before February 16, 2005, that the 'dermatophyte species that most often causes onychomycosis in North America' includes 'T. rubrum.'" Ex. 1008 ¶ 74. Thus, Petitioner offers evidence to show that Austin and Freeman's disclosure of *Candida* as a cause of onychomycosis would give a skilled artisan a reason to combine the references.

Regarding the structural and functional similarities of the compounds, Dr. Murthy testifies that because tavaborole and the compounds of Freeman are boron-based cyclic compounds, a skilled artisan would expect the compounds to share functional features, such as the inhibition of additional fungi responsible for onychomycosis. *Id.* ¶¶ 132–33. Thus, while we

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acknowledge Patent Owner's arguments to the contrary, we are persuaded that Petitioner has set forth sufficient evidence at this stage of the proceeding to show that a person of ordinary skill in the art would have had a reason to combine Austin and Freeman with a reasonable expectation of success.

Accordingly, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing claims 1–12 are unpatentable as obvious over Austin and Freeman.

E. Remaining Challenge

Petitioner also asserts that claim 9 is unpatentable as obvious over Austin, Freeman, and Sun. Pet. 56–59. In light of our findings above with respect to Austin and Brehove and Austin and Freeman, we exercise our discretion not to institute an *inter partes* review on this ground. *See* 37 C.F.R. § 42.108(a).

III. CONCLUSION

We conclude that Petitioner has established a reasonable likelihood of prevailing on its assertions that claims 1–12 of the '621 patent are unpatentable as obvious.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim or the construction of any claim term.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted on the following grounds:

A. Claims 1–12 as obvious over Austin and Brehove; and

B. Claims 1–12 as obvious over Austin and Freeman;

FURTHER ORDERED that no other proposed grounds of unpatentability are authorized.

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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