2017-1947

In the United States Court of Appeals for the Federal Circuit

ANACOR PHARMACEUTICALS, INC.,

Appellant-Patent Owner,

v.

JOSEPH MATAL,

Acting Undersecretary of Commerce for Intellectual Property and Interim Director of the United States Patent & Trademark Office,

Intervenor.

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2015-01776

BRIEF OF APPELLANT-PATENT OWNER

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CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, Counsel for the Appellant-Patent Owner Anacor Pharmaceuticals, Inc. certifies the following:

1. The full name of every party or amicus represented by me is:

Anacor Pharmaceuticals, Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Sandoz Inc. was a real party in interest in IPR2015-01776 under 37 C.F.R. § 42.8(b)(1), but Sandoz Inc. is not represented by me.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Pfizer Inc.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

Covington & Burling LLP: Enrique D. Longton, Jeffrey B. Elikan, George F. Pappas, Christopher K. Eppich, Paul J. Berman.

Date: August 4, 2017

Respectfully Submitted:

/s/ Michael N. Kennedy
Michael N. Kennedy

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STATEMENT OF RELATED CASES

Counsel for Anacor Pharmaceuticals, Inc. are not aware of any other cases pending in this or any other court that will directly affect, or be directly affected by, this Court's decision in this appeal.

TABLE OF ABBREVIATIONS

’621 patent	U.S. Patent Number 7,582,621
Anacor	Anacor Pharmaceuticals, Inc. (Appellant-Patent Owner)
APA	Administrative Procedure Act
Austin	Int’l Pat. Appl. No. PCT/GB95/01206, to Peter William Austin *et al*. (filed May 26, 1995) (Ex. 1002)
Board	Patent Trial and Appeal Board
Brehove	U.S. Pat. Appl. No. 10/077,521, to James Edward Brehove (filed Feb. 15, 2002) (Ex. 1003)
CFAD	Coalition for Affordable Drugs X LLC (Petitioner)
FDA	U.S. Food and Drug Administration
Freeman	Int’l Pat. Appl. No. PCT/US02/23252, to Amihay Freeman *et al*. (filed Jul. 23, 2002) (Ex. 1004)
FWD	Final Written Decision
MIC	minimum inhibitory concentration
PBA	phenyl boronic acid
POSA	person of ordinary skill in the art
PTO	U.S. Patent and Trademark Office

JURISDICTIONAL STATEMENT

The Board had jurisdiction over IPR2015-01776 pursuant to 35 U.S.C. § 311 and 37 C.F.R. § 42.3. The Board filed its FWD regarding the patentability of the '621 patent on February 23, 2017. Anacor timely appealed on April 24, 2017. This Court has jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

STATEMENT OF THE ISSUES ON APPEAL

The single claim at issue on this appeal is drawn to a method of using a compound named tavaborole to treat *tinea unguium*, the most common form of a nail infection known as onychomycosis. *Tinea unguium* is caused by a family of fungi called dermatophytes. The parties agree that Petitioner's primary reference, *Austin*, is silent about the activity of tavaborole's class of compounds against dermatophytes. The Board nonetheless found that *Austin* could be combined with references disclosing different classes of compounds (*Brehove* and *Freeman*) to arrive at the claimed invention, based on an assertion that the various compounds at issue had "similar functional activity" and a POSA's alleged knowledge that a compound's activity against the yeast *C. albicans*, as disclosed in *Austin*, provides a reasonable expectation of activity against the dermatophytes that cause *tinea unguium*. The issues on appeal are:

1. Whether the Board provided Anacor with notice of, and adequate opportunity to respond to, the outcome-determinative argument that because activity

against *C. albicans* is predictive of activity against dermatophytes, the disclosure of activity against *C. albicans* in *Austin* would have provided a POSA with a reasonable expectation of successfully treating dermatophytes.

2. Whether the Board improperly shifted onto Anacor the burden of disproving essential factual premises of its obviousness finding, namely that (i) *C. albicans* activity provides a reasonable expectation of dermatophyte activity, and (ii) *Austin* and *Freeman* disclose similar functional activities because activity against *C. albicans* is closely related to activity against a different yeast, *C. parapsilosis*.

3A. Whether the Board's obviousness theory—that a POSA would have had a motivation to combine references disclosing structurally dissimilar compounds, and a reasonable expectation of success in doing so, based on some structural similarity between the compounds and a "similar functional activity"—lacks a rational underpinning.

3B. Whether the Board lacked substantial evidence in support of its factual findings that (i) the benzoxaboroles of *Austin* share a meaningful structural similarity with the compounds of either *Brehove* or *Freeman*, (ii) the compounds of *Austin* and *Freeman* disclose an overlapping functional activity, and (iii) a POSA would have expected *Austin*'s benzoxaboroles to have activity against dermatophytes based on *Freeman*'s disclosure of activity for phenyl boronic acid and pentafluorophenyl boronic acid.

INTRODUCTION

After the obviousness theory on which trial was actually instituted was decisively refuted, the Board "change[d] theories midstream," without providing Anacor with notice of the new obviousness theory or an adequate opportunity to respond to that theory. The Board then applied its new theory to invalidate Claim 6 based on obviousness combinations that were not in the Petition. Thus, Anacor's patent rights were extinguished without the due process and fairness to which Anacor was entitled.

At institution, the Board described Petitioner's argument for Ground 1 as follows: "both *Austin* and *Brehove* disclose [a class of compounds called] boron heterocycles, and … a person of ordinary skill in the art would have expected that compounds that share structural features would likely share functional features … ." Appx320; *see also* Appx323 (describing a similar argument for Ground 2). Invalidating Claim 6 requires looking beyond *Austin* because the compounds in that reference are tested only against a yeast called *C. albicans*, not a dermatophyte as required by Claim 6. Thus, the Petition asserted that a POSA would have expected the compounds of *Austin* to have activity against dermatophytes (as in Claim 6), allegedly like the compounds of either *Brehove* or *Freeman*, based on structural similarities among the compounds disclosed in the three references.

Anacor prepared its defense based on the Petition's theory. During a two-day cross examination, Petitioner's chemistry expert admitted that significant structural differences exist between *Austin*'s benzoxaboroles and the compounds of either *Brehove* or *Freeman*. Petitioner's formulation expert, Dr. Murthy, discredited his own structural similarity arguments with the acknowledgment that he is not a chemist. Appx5263. Meanwhile, Anacor's chemistry expert, Dr. Reider, presented evidence showing meaningful differences between the compounds in the asserted references, and also demonstrated why a POSA would have expected even small structural differences to result in unpredictable biological changes. This unpredictability, in turn, would defeat any notion that there would be a reasonable expectation of success in combining *Austin* with either *Brehove* or *Freeman*.

Having seen the essential premise of the Petition's obviousness theory destroyed, Petitioner began shifting to a new theory. Proving Claim 6 obvious requires showing a reasonable expectation of success that tavaborole (one of the multitude of compounds disclosed in *Austin*) would treat onychomycosis caused by a dermatophyte. The Petition attempted to show this through *Brehove* and *Freeman*. Petitioner's Reply, by contrast, argued that a reasonable expectation of success was established by combining (a) *Austin*'s disclosure that tavaborole had activity against a yeast, *C. albicans*, which rarely even causes onychomycosis; and (b) references not even cited in the Petition, *Segal* and *Mertin*, which the Reply argued established

that activity against dermatophytes could be predicted by observed activity against yeasts. This was essentially a new obviousness combination outside the grounds on which trial was instituted.

The FWD turned on the Reply's new argument. The Board found that *Austin*'s own disclosure of activity against *C. albicans* was sufficient for a POSA to predict activity against dermatophytes. But every piece of evidence cited by the Board in accepting the new argument was presented with Anacor's Response or Petitioner's Reply, not the Petition. The Board never revealed to Anacor that it would consider the new argument, let alone use it to decide the fate of Claim 6. The Board's decision, therefore, violates Anacor's due process and APA procedural rights by failing to provide both notice of the outcome-determinative argument and an adequate opportunity to respond. (*See* Part I below.)

The Board compounded its error by shifting the burden of persuasion onto Anacor with respect to key aspects of the obviousness inquiry. (*See* Part II below.) For example, Petitioner's new obviousness argument cited a handful of examples of other antifungals with similar activity against both dermatophytes and *C. albicans*. Petitioner never addressed how these unrelated antifungals are relevant to the question of whether a POSA would have expected *Austin*'s compounds to have activity against dermatophytes. Despite a total lack of evidence related to tavaborole, the Board accepted Petitioner's argument and effectively shifted onto Anacor the

burden of proving that tavaborole would be expected to behave differently against dermatophytes than Petitioner's isolated examples.

The Board also shifted onto Anacor the burden of proving that *Austin* and *Freeman* do not disclose "similar functional activity." Despite the acknowledged structural differences between the classes of compounds of *Austin* and *Freeman*, the Board found that a POSA would have been motivated to combine the references with a reasonable expectation of success because *Austin*'s compounds possess activity against *C. albicans* while *Freeman*'s compounds allegedly possess activity against *C. parapsilosis.* The Board accepted as fact that these represent similar functional activities, even though Petitioner presented no evidence on the issue, and the Board faulted Anacor for the sufficiency of its evidence to the contrary. But the burden of proof was Petitioner's, and Anacor should not be punished for the absence of evidence in record.

Not only is there a lack of evidence that *Austin* and *Freeman* disclose "similar functional activity," but the FWD lacks substantial evidence that *Austin*'s benzoxaboroles are structurally similar to *Brehove*'s dioxaborinanes or *Freeman*'s boronic acids. (*See* Part III below.) Although these classes of compounds all contain boron atoms, Petitioner's chemistry expert conceded that the structures are different, and even explained why a POSA would have expected the compounds of *Austin* and *Freeman* to have different biological activities as a result of their structural

differences. Moreover, the FWD lacks substantial evidence that *Freeman* would have provided a reasonable expectation of success that *Austin*'s compounds would have activity against dermatophytes because one of the two compounds Petitioner identified as relevant from *Freeman* does not have any activity against dermatophytes. When the evidence is taken as a whole, it is clear that a POSA would not have had a motivation to combine the asserted references or a reasonable expectation of success in doing so.

The Board's decision for Claim 6 should be reversed for any one of these reasons.

STATEMENT OF THE CASE

U.S. Patent No. 7,582,621 ("the '621 Patent") claims methods of treating infections in animals comprising administering a therapeutically effective amount of the compound "tavaborole" (1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole). The '621 Patent claims priority to a provisional application filed on February 16, 2005. At issue in this appeal is the patentability of Claim 6 of the '621 Patent. This claim narrows the method of treating "an infection" with tavaborole from independent Claim 1 to a method of treating "*tinea unguium*," which is the most common form of "onychomycosis."

I. Claim 6 of the '621 patent claims a method of treating onychomycosis, which is a fungal infection of the nail.

Onychomycosis refers to a fungal infection of the nail plate or nail bed. Appx6286. Onychomycosis can occur in either fingernails or toenails, and it is "characterized by the thickening of the nail, discoloration, separation of the nail plate from the nail bed, accumulation of subungual debris, nail plate dystrophy, and nail brittleness." Appx6289–90. *Tinea unguium* is onychomycosis caused by dermatophytes. Appx71; Appx1219.

A. Onychomycosis is primarily caused by dermatophytes, not yeasts such as those disclosed in Petitioner's primary reference.

Dermatophytes are a class of fungi responsible for 90% to 95% of onychomycosis cases. Appx1558; Appx6288. Dermatophytes are uniquely successful at colonizing nails because they contain an enzyme called keratinase, which breaks down the major protein component of nails (*i.e.*, keratin) for nutrients. Appx6286–88; Appx6301. The dermatophytes most often responsible for *tinea unguium* are *Trichophyton* ("*T.*") *rubrum*, *T. mentagrophytes*, *T. tonsurans*, and *Epidermophyton floccosum*. Appx6288–89.

Candida albicans is a yeast disclosed in *Austin* and *Brehove*, not a dermatophyte. *C. albicans* is responsible for less than 5% of onychomycosis cases. Appx6291–92 (citing Ex. 2049 (3.2%), Ex. 2027 (1–2%), Ex. 2066 (5.4%), Ex. 2059 (0% in toenail onychomycosis), Ex. 2067 (0% in toenail onychomycosis), Ex. 2039

(7%)). Petitioner's topical formulation expert, Dr. Murthy, initially argued that *C. albicans* is "the most common pathogen associated with onychomycosis." Appx1211 (citing Ex. 1003 (*Brehove*) at ¶ 18). However, Dr. Murthy later agreed that "*T. rubrum* is by far the most common pathogen causing onychomycosis." Appx5229; *see also* Appx5230; Appx10189 (Dr. Murthy admitting that mycology is not his expertise).

Dermatophytes and *C. albicans* have enzymatic differences that not only cause them to behave differently, but also potentially present different targets for pharmaceuticals. For example, *C. albicans* does not produce keratinase, and thus, is less capable of penetrating the nail than dermatophytes. Appx6300–01. Also unlike dermatophytes, *C. albicans* produces a number of different enzymatic virulence factors, such as phospholipases to break down cell membranes and allow *C. albicans* to invade systemically and disseminate via the blood. Appx6300. The different enzymatic virulence factors in dermatophytes and *C. albicans* usually cause these classes of fungi to infect different parts of the body. Appx6300–01.

C. parapsilosis is the only yeast tested in *Freeman*. It is part of the normal flora of the body as the major colonizer of the hands and subungual regions of healthy adults. Appx6293–94. Anacor's mycology expert Dr. Ghannoum presented evidence that *C. parapsilosis* is merely a contaminant, and not a cause of onychomycosis, because it normally lives in the subungual areas of healthy adults.

Id. (citing Ex. 2049 and Ex. 2069). Petitioner's expert, Dr. Murthy does not disagree that *C. parapsilosis* is the major colonizer of healthy hands. *See* Appx1751; Appx5230.

The record shows that dermatophytes and yeasts have many differences due to the genetic dissimilarities between them. *See, e.g.*, Appx6298–6300. In fact, dermatophytes and yeasts "diverge at the taxonomic level of class"—the same taxonomic level within the Kingdom Animalia at which mammals and fish diverge. *Id*. The genetic differences between dermatophytes and yeasts, such as *C. albicans*, cause these microorganisms to exhibit different "morphologies, macroscopic and microscopic appearances, rates of growth, and biochemical characteristics." *Id*.

Dermatophytes and yeasts also have different sensitivities to antifungal compounds. The only mycologist in this case, Dr. Ghannoum, concluded that "a 2005 POSA could not have predicted the activity of a compound against dermatophytes based on the activity against a different fungal microorganism, such as a yeast." Appx6318. Dr. Ghannoum provided the example of ketoconazole, which "has potent antifungal activity against *C. albicans* but has poor activity against the *Trichophyton* spp. *T. rubrum* and *T. mentagrophytes*." *Id*. (citing Ex. 2105).

B. The record here demonstrates the lack of guidance in the prior art concerning the possible use of boron-containing compounds to treat onychomycosis.

The compound recited in Claim 6, tavaborole, as well as the various compounds disclosed in the asserted references, contain boron atoms. Boron-containing compounds rarely appear in medicinal chemistry literature. Indeed, most examples of boron-containing compounds tested in animals resulted in unacceptable toxicities. *See* Appx239–42, and citations therein; Appx6223–26, and citations therein. Until the approval of Anacor's KERYDIN® product, only one other boron-containing drug was on the market. VELCADE®, which is a boronic acid and not a benzoxaborole, had been approved for refractory multiple myeloma, a serious form of cancer. Appx4392; Appx6230. As is fairly common with cancer drugs, VELCADE® exhibited severe side effects, including peripheral neuropathy and major organ toxicities. *Id*. Consequently, little was known about the biological properties of any boron-containing compound.

Tavaborole is from a class of compounds called "benzoxaboroles," which had never been tested in any animals as of 2005. Consequently, the relevant biological properties, such as nail penetration, stability, efficacy, and even solubility, had not been reported for any member of this class of compounds. To identify benzoxaboroles in the prior art, one must venture into prior art concerning biocides for industrial applications. *See* Appx378–79. One example is the "*Austin*" reference

(Int'l Pat. Appl. No. PCT/GB95/01206, Ex. 1002), which disclosed that tavaborole kills a handful of industrially relevant fungi, including *C. albicans*. Appx1067, Example 64. *Austin* does not disclose the use of its benzoxaboroles in animals, and instead shows that its compounds are useful as plastic preservatives. Appx1070–71.

The "*Brehove*" reference (U.S. Pat. Appl. No. 10/077,521, Ex. 1003) discloses an apparently unsuccessful attempt to develop a boron-containing pharmaceutical. In this reference, an individual attempted to treat onychomycosis caused by *C. albicans* using the active ingredients in a fuel additive called BioBor. Appx1081. These compounds are boron-containing dioxaborinanes. *Id*. *Brehove* does not disclose the use of its dioxaborinanes against any microorganism other than *C. albicans*. Appx1083–84; *see also* Appx29.

The final reference upon which trial was instituted, "*Freeman*", (Int'l Pat. Appl. No. PCT/US02/23252, Ex. 1004) also discloses an attempt to develop a boron-containing compound, in this case a boronic acid, as an onychomycosis treatment. This reference, unlike *Brehove*, does not test its compounds against *C. albicans*. *See* Appx1099. *Freeman* also discloses no *in vivo* tests—it reports nothing more than the potency of its compounds in Petri dishes. *See id*. Two compounds in *Freeman* are relevant to this case: phenyl boronic acid ("PBA") and pentafluorophenyl boronic acid. The former compound displayed activity against dermatophytes when

tested at very high concentrations, and the latter displayed "no effect" against dermatophytes. *Id*.

II. Proceedings before the Board.

On August 20, 2015, the Coalition for Affordable Drugs X LLC ("Petitioner") filed a petition for *inter partes* review ("IPR") of all claims in the '621 Patent.[1] The Petition argued three Grounds of obviousness based on *Austin* as the primary reference. The Board instituted IPR No. IPR2015-01776 on February 23, 2016 on two of the Grounds: (1) *Austin* in combination with *Brehove*, and (2) *Austin* in combination with *Freeman*. Anacor filed its Patent Owner Response on June 6, 2016, and Petitioner filed its Reply on August 24, 2016. Following oral argument, the Board's FWD on February 23, 2017, found the claims of the '621 Patent obvious over either combination of references. Anacor appeals the Board's decision in IPR2015-01776 with respect to Claim 6 of the '621 Patent.

A. The Petition argued that a POSA would have extrapolated the properties described in either *Brehove* or *Freeman* to the compounds of *Austin* based on the compounds' alleged structural similarities.

In both grounds, Petitioner argued a reasonable expectation of successfully achieving the invention of Claim 6 because, in its view, "a person of ordinary skill in the art would have expected that 5-fluoro benzoxaborole [*i.e.*, tavaborole from

[1] Petitioner also filed two other petitions against the claims of a related patent covering formulations of tavaborole. The resulting IPR2015-01780 and IPR2015-01785 are not at issue here.

Austin], which shares similar structural features with the compounds of *Brehove*, would likely share similar functional features as well." Appx136; *see also* Appx150–51 ("A person of ordinary skill in the art would have expected that 5-fluoro benzoxaborole [*i.e.*, tavaborole from *Austin*], which shares similar structural features with the compounds of *Freeman*, would likely share similar functional features as well."). Indeed, the Petition's claim charts for Claim 6 only point to language from *Brehove* or *Freeman*, and do not cite any passage from *Austin*. *See* Appx142–43, Appx156.

The Petition also cited "share[d] functional activity" as support for a POSA's motivation to combine and reasonable expectation of success. Appx137; Appx151. Although Petitioner does not define "functional activity," it uses the term as a synonym for "biological property." For the combination of *Austin* and *Brehove*, Petitioner identified only one overlapping biological property: the compounds in both references inhibit *C. albicans*. Appx137. Petitioner also argued that the compounds of *Austin* and *Freeman* disclose overlapping functional activity, but the Petition does not explain what that activity is, besides "the inhibition of fungus responsible for onychomycosis." Appx151.

B. The Board found the compounds of *Austin, Brehove* and *Freeman* to be structurally dissimilar.

As explained above, the Petition's obviousness theories were based on the proposition that the asserted references could be combined because they all disclose

boron-containing compounds having structural similarity. The Board, however, made a key factual finding that negates this premise. Specifically, the Board noted that *Austin*'s benzoxaboroles, such as tavaborole, are structurally dissimilar from the compounds of either *Brehove* or *Freeman*.

For example, the Board "acknowledge[d] Patent Owner's argument that small structural changes can cause different biological actions and activities." Appx21 (citing Appx408–09 and Appx6220–22). In addition, the Board noted that Petitioner's chemistry expert Dr. Kahl "agrees that there are obviously structural differences between the dioxaborinanes of *Brehove* and the benzoxaboroles of *Austin*." Appx21. The Board also "agree[d] there are structural differences" between the compounds of *Austin* and *Freeman*. Appx39. These findings negate a key pillar of the Petition's obviousness arguments.

C. The Board found a reasonable expectation of successfully treating dermatophytes only by departing from the Petitioner's original obviousness theory.

Given that the Board disagreed with Petitioner's premise that structural similarity provided the basis to combine *Austin*, *Brehove* and *Freeman*, it is not surprising that the Board ended up invalidating Claim 6 by pivoting to an argument appearing nowhere in the Petition. The Board noted that "[i]t is undisputed that neither *Austin* nor *Brehove* expressly teaches whether the disclosed compounds exhibit any activity against dermatophytes." Appx29. Regardless, the Board found

that *Austin*'s disclosure that tavaborole has activity against an industrial strain of *C. albicans* was sufficient to provide a reasonable expectation of activity against clinically relevant dermatophytes. Appx29–30.

The outcome-determinative argument that activity against *C. albicans* alone would have provided a POSA with a reasonable expectation of successfully treating dermatophytes was first presented in Petitioner's Reply. Appx771–72; *see also* Appx10234–36 (Murthy Reply Dep. Tr.) (Petitioner's formulation expert stating that Petitioner was aware of the argument prior to the Petition but only argued it in the Reply). The Board did not inform the parties prior to the FWD that it would allow Petitioner's new argument.[2]

In its FWD, the Board determined that "the weight of the evidence favors Petitioner's argument" that *Austin*'s disclosure of activity against *C. albicans* would have provided a reasonable expectation of activity against dermatophytes. Appx30. In support of its conclusion, the Board cited references that surfaced for the first time in Petitioner's Reply (*i.e.*, (i) *Mertin* (Ex. 1065), (ii) the Murthy Decl. (Ex. 1044), and (iii) the deposition transcript of Anacor's mycology expert Dr. Ghannoum (Ex. 1046)) and from Anacor's Response (*i.e.*, (i) *Segal* (Ex. 2050), (ii) *Nimura* (Ex.

[2] Anacor asked for authorization to file a motion to strike the new argument and evidence, but the Board only allowed Anacor to file a short listing of improper new arguments from Petitioner's Reply. *See* Appx815 (citing Appx10314–15).

2105), and (iii) Dr. Ghannoum's Declaration (Ex. 2035)). *Id*. None of the cited evidence in the FWD was filed with the Petition.

For Ground 2 (*Austin* + *Freeman*), the Board incorporated its findings from Ground 1, including the key finding that *Austin*'s disclosure of activity against an industrial strain of *C. albicans* is predictive of activity against clinically relevant dermatophytes. Appx37. The Board asserted, "For similar reasons stated above with respect to the challenge over *Austin* and *Brehove*, we determine that the weight of the evidence supports Petitioner's argument that a person of ordinary skill in the art would have combined *Austin* and *Freeman* to achieve the claimed invention with a reasonable expectation of success." Appx39.

SUMMARY OF THE ARGUMENT

1. The Petitioner and the Board "change[d] theories midstream" without notifying Anacor of the new outcome-determinative issue in the case, and without providing Anacor an opportunity to respond to the new theory with arguments and evidence. *See SAS Inst., Inc. v. ComplementSoft, LLC*, 825 F.3d 1341, 1351 (Fed. Cir. 2016) (quoting *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1080 (Fed. Cir. 2015)); *In re NuVasive, Inc.*, 841 F.3d 966, 971 (Fed. Cir. 2016). The Petition alleged that *Austin* disclosed the structure of tavaborole and drew on a secondary reference, either *Brehove* or *Freeman*, as disclosing activity of structurally similar compounds against dermatophytes. Appx142–43, Appx156. The Board instituted

trial on this theory. Consequently, Anacor built its defense around the argument that the compounds of *Austin*, *Brehove* and *Freeman* are, in fact, not structurally similar. And Anacor made out this defense—by the time of the FWD, Petitioner's expert had admitted that the compounds of *Austin* are structurally different from the compounds of either *Brehove* or *Freeman*. But that no longer mattered. The Board ended up concluding that an expectation of activity against dermatophytes is shown, not by the secondary references the Petition asserted, but by *Austin* itself. The Board applied a theory that first surfaced in Petitioner's Reply that activity against an industrial strain of *C. albicans*, which *Austin* discloses, provides all the information a POSA would have needed for a reasonable expectation of successfully treating clinically relevant dermatophytes. Every piece of evidence supporting this theory in the FWD was absent from the Petition. Based on due process and APA notice guarantees, the FWD is fatally flawed because Anacor never had notice of or an adequate opportunity to respond to the new outcome-determinative argument.

2. Not only did the Board provide inadequate notice of its new theory of obviousness, but the Board also improperly shifted the burden of persuasion for the new theory onto Anacor. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–76 (Fed. Cir. 2016). Petitioner had the burden to demonstrate that a POSA would have reasonably expected tavaborole to have activity against dermatophytes. The Board accepted Petitioner's argument based on two unrelated antifungal

compounds, amorolfine and terbinafine, and one sentence from Petitioner's Reply that "[d]ermatophytes are usually more sensitive towards antimycotics than yeasts." *See* Appx30. The Board did not require Petitioner to show that tavaborole would be expected to behave like amorolfine or terbinafine, or even that tavaborole would have been expected to kill fungi according to one of the known antifungal mechanisms. Instead, the Board improperly shifted onto Anacor the burden of proving that Petitioner's limited evidence for other compounds would not apply to tavaborole.

The Board also improperly shifted onto Anacor the burden of proving that the compounds of *Austin* and *Freeman* do not disclose an overlapping biological property—*i.e.*, a "similar functional activity." The Board found that a POSA would have been motivated to combine *Austin* and *Freeman* with a reasonable expectation of success because the compounds in these references have some structural similarities and "similar functional activity against *Candida* species." But *Austin* and *Freeman* disclose activity against different microorganisms: *C. albicans* and *C. parapsilosis*, respectively. The Board did not consider whether Petitioner proved that a POSA would have viewed activities against these different species of *Candida* as equivalent, but rather, faulted Anacor for failing to prove that they are different. As with the previous example, Petitioner had the burden of persuasion, and the Board erred by shifting the burden onto Anacor.

3. The Board's theory of obviousness lacks a rational underpinning because there is no scientific explanation for why a POSA would ignore significant structural dissimilarities between the compounds of the asserted references on the basis of one overlapping biological property.

In addition, at least three of the Board's essential factual findings are not supported by substantial evidence. First, the evidence of record does not show that the compounds of *Austin* share any meaningful structural similarities with the compounds of either *Brehove* or *Freeman*. To the contrary, the parties' experts agree that *Austin*'s benzoxaboroles are structurally dissimilar from *Brehove*'s dioxaborinanes and *Freeman*'s boronic acids. Petitioner's chemistry expert even explained why the different structures of *Austin*'s benzoxaboroles and *Freeman*'s boronic acids would have led a POSA to expect ***different*** biological activities. Despite this, the Board found a motivation to combine the asserted references, and a reasonable expectation of success in doing so, based on some shared structural similarity. The Board does not identify that similarity, but its citations indicate that the similarity is the fact that all references disclose "boron-based compounds," by which it likely means that all of these compounds contain boron atoms. If this is indeed the structural similarity, substantial evidence does not show why a POSA would expect all "boron-based compounds" to behave similarly just because they all contain a boron atom.

Second, the record does not show that *Austin* and *Freeman* possess "similar functional activity." The Board alleged that the overlapping activities disclosed in these references would have contributed to a motivation to combine the references with a reasonable expectation of success. But no evidence shows that *Austin*'s disclosure of activity against an industrial strain of *C. albicans* and *Freeman*'s disclosure of activity against *C. parapsilosis* are "similar functional activities."

Third, even if a POSA were to combine *Austin* and *Freeman* under Ground 2, the evidence does not show that *Freeman*'s disclosure would have provided a reasonable expectation of successfully treating dermatophytes with tavaborole. The Petition argued that a POSA would have had a reasonable expectation from *Freeman* based on two compounds: PBA and pentafluorophenyl boronic acid. But *Freeman* shows that the latter compound has no activity against dermatophytes. The Board ignored the portion of Anacor's response that describes this evidence.

STANDARD OF REVIEW

This Court reviews the Board's conclusions of law *de novo*. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). Under the APA, whether the Board provided notice and an adequate opportunity to respond to a new argument is a question of law subject to *de novo* review. *In re NuVasive*, 841 F.3d at 970.

The Board's fact finding is reviewed for substantial evidence. *In re Gartside*, 203 F.3d at 1313. "Substantial evidence review involves examination of the record

as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *Id*. at 1312. Conclusory statements do not satisfy the standard, and instead, "the Board must point to some concrete evidence in the record … ." *In re Beasley*, 117 F. App'x 739, 744 (Fed. Cir. 2004). Otherwise, "the process of appellate review for substantial evidence on the record [would be] a meaningless exercise." *Id.*

ARGUMENT

I. The FWD should be reversed for failing to provide adequate notice of the arguments and evidence on which the FWD is based.

In essence, Claim 6 was invalidated based on a different combination of prior art (*Austin* + *Segal* + *Mertin*) than the combinations presented by the Petition (*Austin* + *Brehove* and *Austin* + *Freeman*). For this reason alone, the FWD must be reversed.

The Board must provide a patent owner in an IPR with "'notice of and a fair opportunity to meet the grounds of rejection,' based on due-process and APA guarantees." *In re NuVasive*, 841 F.3d at 971 (quoting *Belden*, 805 F.3d at 1080). The APA's notice provisions mandate "the Board must timely inform a patent owner of 'the matters of fact and law asserted,' give the patent owner an 'opportunity' for the 'submission and consideration of facts' and 'arguments,' and permit the patent owner 'to submit rebuttal evidence, and to conduct such cross-examination as may be required for a full and true disclosure of facts.'" *Rovalma S.A. v. Bohler-Edelstahl GmbH & Co. KG*, 856 F.3d 1019, 1029 (Fed. Cir. 2017) (quoting 5 U.S.C. §§

554(b)(3), (c), 556(d)) (citing *SAS Inst.*, 825 F.3d at 1351; *Dell Inc. v. Acceleron, LLC*, 818 F.3d 1293, 1301 (Fed. Cir. 2016); *Belden*, 805 F.3d at 1080). Thus, during an IPR, the Board "may not change theories midstream without giving respondents reasonable notice of the change and the opportunity to present argument under the new theory." *SAS Inst.*, 825 F.3d at 1351 (quoting *Belden*, 805 F.3d at 1080).

An IPR petition provides a patent owner with the notice required by due process and the APA. *See* 35 U.S.C. § 312(a)(3) ("the petition identifies, in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim"). Indeed, a petitioner has the burden of making out a *prima facie* case of unpatentability in its petition. *See In re Magnum Oil Tools*, 829 F.3d at 1375–76. "[I]f a petition fails to state its challenge with particularity—or if the Patent Office institutes review on claims or grounds not raised in the petition—the patent owner is forced to shoot into the dark." *Cuozzo Speed Techs., LLC v. Lee*, 136 S.Ct. 2131, 2154 (2016) (Thomas, J., concurring).

A petitioner's reply serves a different purpose: responding to the patent owner's defenses. 37 C.F.R. § 42.23(b) ("A reply may only respond to arguments raised in the corresponding opposition, patent owner preliminary response or patent owner response."). Due process and the APA require, however, that new arguments cannot be raised in the reply without the patent owner having an adequate

opportunity to respond with evidence and arguments. *In re NuVasive*, 841 F.3d at 973; *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016).

Here, the Board allowed Petitioner to assert a new theory of obviousness that was not presented in the petition. Appx30; Appx39. The Board even acknowledged that Petitioner does not mention the outcome-determinative argument for Claim 6—that activity against *C. albicans* alone would have provided a POSA with a reasonable expectation of success against dermatophytes—until its Reply. *See* Appx2 n.1; *see also* Appx815 (citing Appx10314–15). In addition, all the evidence proffered to support the new theory of obviousness was also missing from the Petition. *See* Appx 9. Thus, the Board violated due process and the APA by failing to provide Anacor with notice of the new obviousness theory or a fair opportunity to address it. *See In re NuVasive*, 841 F.3d at 971.

A. The outcome-determinative argument in the Board's obviousness analysis for Claim 6 was not in the Petition.

It is not enough under the APA for the Board to identify the references asserted against the claims. Rather, the parties must be aware of, and have an opportunity to respond to, the legal argument that ultimately decides the case. *See SAS Inst.*, 825 F.3d at 1351; *In re NuVasive*, 841 F.3d at 973.

The recent *In re NuVasive* decision is especially instructive here. There, an IPR petition argued that a claimed spinal fusion implant would have been obvious

because two prior-art references together disclosed crucial claim limitations. 841 F.3d at 969. Specifically, the SVS-PR (or Telemon) reference disclosed a spinal fusion implant whose length is at least 2.5 times its width while the Michelson reference disclosed an implant with a length greater than 40 mm. *In re NuVasive*, 841 F.3d at 969. The patent owner responded that neither reference taught an implant that was both longer than 40 mm and had a length at least 2.5 times its width. The petitioner's reply, however, identified a new portion of the Michelson reference as disclosing a spinal fusion implant whose length is at least 2.5 times its width, in addition to its original assertion that Michelson also disclosed an implant with a length greater than 40 mm. *Id*. So in effect, the petitioner's reply in *In re NuVasive* changed the ground of obviousness from the combination of SVS-PR and Michelson to the ground of Michelson alone, because SVS-PR was no longer necessary to the overall obviousness analysis. *See id*. In response to this shift, the patent owner requested leave to file a motion to strike the new ground of invalidity, filed observations on cross-examination of the new argument, and objected to the new theory during the oral argument. *Id*. at 970, 973. Regardless, the Board adopted the reasoning of the petitioner's reply to find the claims obvious. *Id*. This Court vacated the Board's decision in *In re NuVasive* for failing to provide the patent owner with both notice of the new obviousness argument based on Michelson alone and an adequate opportunity to respond to it. *Id*. at 972. Notably, the only response to the

new argument granted to patent owner—observations on cross-examination of petitioner's experts—were found not to be an adequate substitute for presenting arguments and evidence. *Id.*

The facts here are nearly identical to those from *In re NuVasive*. The Petition argued that *Austin* disclosed the claimed structure of tavaborole, while either *Brehove* (Ground 1) or *Freeman* (Ground 2) disclosed Claim 6's requirement of treating dermatophytes. Appx142–43, Appx156. The Board instituted IPR on those grounds. Appx320–21, Appx323. Anacor's Response pointed out that, contrary to Petitioner's assertions, neither *Brehove* nor *Freeman* discloses activity against dermatophytes. Appx410, Appx424–26. As in *In re NuVasive*, Petitioner's Reply did not argue that the *prima facie* case of obviousness presented in the Petition was correct. Rather, Petitioner changed the source of the alleged disclosure of activity against dermatophytes, and asserted in its Reply that a POSA would have understood from *Austin*'s disclosure, in view of the teachings of *Mertin* and *Segal*, that the reported activity against *C. albicans* also indicates effectiveness against dermatophytes. Appx771–72; *see also* Appx778 ("*Austin* discloses the activity of tavaborole, not *Freeman*"). And beyond even the facts of *In re NuVasive*, Petitioner was fully aware of its new argument before it filed the Petition, but chose not to advance it until much later. *See* Appx10234–36 (Dr. Murthy admitting that he told Petitioner about this argument before he filed his first declaration).

Anacor tried to protect itself from this ambush. In response to Petitioner's new argument, Anacor sought authorization to file a motion to strike, Appx10313, filed an identification of new arguments in Petitioner's Reply, Appx814–16, filed observations on cross-examination of the new argument, Appx842–44 & Appx847–49, and asked during the oral hearing that this new argument be given no weight, Appx985. In the FWD, the Board agreed with Anacor's Response that *Brehove* does ***not*** disclose treating dermatophytes, but just as in *In re NuVasive*, the Board adopted Petitioner's new Reply argument and ruled that Claim 6 of the '621 Patent is obvious due to the alleged relationship between activities against *C. albicans* and dermatophytes. *See* Appx29; *see also* Appx39 (applying the reasoning from Ground 1 to Ground 2).

In short, Anacor was under the mistaken impression that the Board would only consider whether *Brehove* or *Freeman* disclosed activity against dermatophytes. *See* Appx142–43, Appx156. Without notice, Anacor did not have an opportunity to adequately respond to the new argument with its own argument and evidence. *In re NuVasive*, 841 F.3d at 973. Thus, the Board denied Anacor its procedural right to due process and APA notice guarantees.

B. The Board's analysis of Claim 6 relied entirely on evidence that was not in the Petition.

The Board's inadequate notice of the outcome-determinative argument for Claim 6 is highlighted by the fact that the FWD does not cite a single reference from

the Petition in support of the alleged relationship between *C. albicans* activity and dermatophyte activity.

A petition must make a *prima facie* case of obviousness, and in doing so, provide the patent owner with notice of the evidence asserted against the challenged claims. *See In re Magnum Oil Tools*, 829 F.3d at 1375–76; *Intelligent Bio-Systems*, 821 F.3d at 1369. The PTO also requires a petitioner's reply to respond to previous arguments and evidence; it is not an opportunity to present a new theory of unpatentability. 37 C.F.R. § 42.23(b). Consequently,

> It is of the utmost importance that petitioners in the IPR proceedings adhere to ***the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim.***' … Unlike district court litigation—where parties have greater freedom to revise and develop their arguments over time and in response to newly discovered material—the expedited nature of IPRs brings with it an obligation for petitioners to make their case in their petition to institute.

Intelligent Bio-Systems, 821 F.3d at 1369 (quoting 35 U.S.C. § 312(a)(3)) (emphasis added).

In *Intelligent Bio-Systems*, the petition argued that a POSA would have been motivated to combine the Zavgorodny and Tsien references because the azidomethyl group disclosed in Zavgorodny satisfies Tsien's requirement of a protecting group that can be quantitatively removed under mild conditions. *Id.* at 1368, 1369. The patent owner's response presented evidence that a POSA would

have expected only 60–80% removal of Zavgorodny's azidomethyl groups under the disclosed conditions. *Id*. In its reply, the petitioner cited new references not in the Petition to argue that a POSA would have considered Zavgorodny as a starting point for the routine development of mild conditions for quantitative removal of azidomethyl group. *Id*.

This Court affirmed the Board's rejection of the new evidence cited in the petitioner's reply as a violation of 37 C.F.R. § 42.23(b). *Intelligent Bio-Systems*, 821 F.3d at 1369–70 (noting that "[petitioner] chose which grounds of invalidity to assert in its petition and it chose not to assert this new one"). In support of this conclusion, the Court emphasized the PTO's own guidance: "Examples of indications that a new issue has been raised in a reply include ***new evidence necessary to make out a* prima facie *case for the … unpatentability of an original … claim, and new evidence that could have been presented in a prior filing***." *Id*. (quoting Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,767 (Aug. 14, 2012)) (emphasis added).

This is precisely the sort of improper new evidence that the Board relied on here to invalidate Claim 6. *See* Appx30. For example, in analyzing "the weight of the evidence," the Board cites only references and declarations that entered the case

in either the Patent Owner Response[3] or the Petitioner's Reply.[4] *See* Appx30. Thus, Petitioner could not have made a *prima facie* case for its new argument in the Petition because all of the supporting evidence came later. As in *Intelligent Bio-Systems*, Petitioner's "new evidence [that is] necessary to make out a *prima facie* case" violates 37 C.F.R. § 42.23(b)'s requirements for a proper reply. 821 F.3d at 1370.

II. The FWD should be reversed for improperly shifting the burden of proving nonobviousness onto Anacor.

"In an *inter partes* review … the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence." 35 U.S.C. § 316(e). The *In re Magnum Oil Tools* decision confirms that the burden of proving every aspect of obviousness rests squarely on the petitioner and never shifts to the patent owner. 829 F.3d at 1376. "This is especially true, where the only issues to be considered are what the prior art discloses, whether there would have been a motivation to combine the prior art, and whether that combination would render the patented claims obvious." *Id*.

The Board improperly shifts the burden of persuasion onto a patent owner when it accepts a petitioner's obviousness position without requiring the petitioner

[3] The cited references from the Patent Owner Response include *Segal* (Appx6995–7005), *Nimura* (Appx7989–98), and paragraph 64 of Dr. Ghannoum's Declaration in support of the Patent Owner Response (Appx6318).

[4] The cited references from the Petitioner's Reply include *Mertin* (Appx3605–12), paragraph 91 of Dr. Murthy's Declaration in support of Petitioner's Reply (Appx1755–56), and an excerpt from the deposition of Dr. Ghannoum (Appx2181).

to articulate some reasoning for each step of the argument. *See Intellectual Ventures II LLC v. Ericsson Inc.*, --- Fed. App'x ----, 2017 WL 1380616, at *6 (Fed. Cir. Apr. 18, 2017) (citing *In re Magnum Oil Tools*, 829 F.3d at 1379). For example, the petitioner in *In re Magnum Oil Tools* asserted two grounds of obviousness based on two primary references, each combined with the same secondary references. 829 F.3d at 1372. The petition presented arguments and evidence related to the first ground and incorporated that argument by reference to the second ground. *Id*. The Board instituted IPR based only on the second ground, and ultimately found the challenged claims unpatentable. *Id.* at 1373. This Court reversed the Board for accepting the petitioner's incorporated argument without an explanation for "why borrowing the rationale for combining the first set of references equally applies to the second set … ." *Id*. at 1379. The Court concluded, "Where, as here, it is clear that the Board did not require the petitioner to support its claim of obviousness by a preponderance of the evidence, we must reverse." *Id*. at 1378–79.

The Board here improperly shifted the burden of proving Claim 6's nonobviousness onto Anacor. In at least two respects, the Board's conclusions rested not on the Petitioner's presentation of evidence in support of an argument, but rather on whether Anacor sufficiently ***disproved*** that argument.

A. The Board improperly required Anacor to prove that tavaborole's activity against *C. albicans* does not provide a reasonable expectation of activity against dermatophytes.

The Board found Claim 6 obvious based on the newly presented argument in Petitioner's Reply that a POSA would have reasonably expected tavaborole to possess activity against clinically relevant dermatophytes because *Austin* discloses the compound's activity against industrial strains of *C. albicans*. Appx30–31, Appx39. The Board found that "the weight of the evidence" favored Petitioner's position that a POSA "would have had a reasonable expectation that a compound with activity against *C. albicans* would also have activity against dermatophytes." Appx30, Appx31. But this is the wrong question. Petitioner had the burden of proving that a POSA would have expected ***tavaborole*** to have similar activity against both *C. albicans* and dermatophytes, and Petitioner never made this showing.

The record provides no basis to conclude that tavaborole's activity against dermatophytes would be expected. The record shows that at least seven different biological mechanisms of action were known for existing antifungals in 2005. Appx6305–11. Petitioner's expert Dr. Murthy testified that there are exceptions to his assertion that activity against *C. albicans* predicts dermatophyte activity (Appx1757) but "[i]t's hard to predict exceptions." Appx10236. Despite this record, the Board did not require proof from Petitioner of which mechanism of action would have been expected for tavaborole, which mechanisms kill both dermatophytes and

C. albicans, or even of whether tavaborole is more like ketoconazole (which is more active against *C. albicans*) or the tertiary amine antifungals (which may be more active in dermatophytes).

The limited evidence on this point cited by the Board relates to compounds other than tavaborole, which do not contain boron. First, the Board cited two examples of tertiary amine antifungals, amorolfine and terbinafine, which are active against both *C. albicans* and dermatophytes. Appx30. The Board accepted these examples in isolation and did not require proof that a POSA would have considered the activity of either amorolfine or terbinafine to correlate with the activity of tavaborole. *See id*. Second, the Board relied on the statement "[d]ermatophytes are usually more sensitive towards antimycotics than yeasts" that appeared only in a reference identified in Petitioner's Reply. *Id*. The Board did not consider the exceptions to the statement, did not explain why the statement might apply to tavaborole, and did not consider whether the statement applies to all yeasts, including *C. albicans*. The Board simply acceded to Petitioner's position without considering tavaborole.

Thus, the Board erred under *In re Magnum Oil Tools* because it assumes Petitioner's position without supporting evidence. *See* 829 F.3d at 1379. Consequently, the Board improperly shifted the burden of persuasion onto Anacor, and the Board's decision should be reversed for this reason. *See id.*

B. The Board improperly required Anacor to prove that potency against *C. parapsilosis* is unrelated to potency against *C. albicans*.

The Board also inappropriately shifted the burden of proving that the compounds of *Austin* and *Freeman* possess "similar functional activities." The Board found Claim 6 obvious under Ground 2 because it was "persuaded that a person of ordinary skill in the art would have had a reason to combine [*Austin* and *Freeman*] in light of the structural similarities (i.e., both are boron heterocycles) ***and the similar functional activity against*** **Candida** ***species***." Appx39 (emphasis added). Under the Board's reasoning, the compounds of *Austin* and *Freeman* possess some "structural differences," but a POSA would still have had a motivation to combine the references with a reasonable expectation of success because *Austin*'s disclosure that benzoxaboroles have activity against an industrial strain of *C. albicans* is essentially equivalent to *Freeman*'s disclosure of activity against *C. parapsilosis*. Appx39, Appx40–41. However, the FWD cites no prior-art evidence supporting the position that these two activities are in any way similar. *See* Appx41. There was no such evidence in the record.

The Petition and the Reply do not even use the word *parapsilosis*, and simply argue, "A person of ordinary skill in the art would have expected the 5-fluoro benzoxaborole [of *Austin*], which shares functional activity with the compounds of *Freeman* (the inhibition of fungus responsible for onychomycosis), would likely have had other activities in common as well, i.e., the inhibition of additional fungi

responsible for onychomycosis." Appx151 (citing Ex. 1008 (Murthy Decl.) ¶ 133). The cited passage from the Murthy Declaration is also a conclusory assertion using nearly identical language. *See* Appx1237. In any event, Dr. Murthy is not a mycologist. Appx5230 ("Mycology is not my expertise.").

In fact, Anacor showed that *C. parapsilosis* is not "a fungus responsible for onychomycosis." Appx6293–94 (a POSA would have understood that *C. parapsilosis* is a common contaminant and not a causative agent of onychomycosis); *see also* Appx412–13. Dr. Ghannoum also presented the *Nguyen* reference (Ex. 2096), which shows that at least one drug, in this case fluconazole, is active against certain species of *Candida* but has no activity against certain others. Appx6311–12. Dr. Ghannoum, the only mycologist to testify in the case, concluded that the "antifungal activity of individual compounds is complex and unpredictable." Appx6312.

In the face of Dr. Ghannoum's testimony, the FWD cites the '621 Patent itself for the proposition that *C. parapsilosis* is a target organism of the claimed invention. Appx41. The Board cannot rely on the disclosure of the '621 Patent to show what a POSA would have known at the time of the invention. *W.L. Gore Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the

insidious effect of hindsight syndrome wherein that which only the inventor taught is used against its teacher.").

The Board also cites ***Anacor's*** allegedly unpersuasive response to a question during oral argument to discredit Dr. Ghannoum. Appx41 ("[Anacor's response] does not answer the question of whether a person of ordinary skill in the art would have expected a compound that is active against one species of *Candida* to be active against another species of *Candida*."). But it was not Anacor's burden to answer that question; it was Petitioner's. *See In re Magnum Oil Tools*, 829 F.3d at 1379. With no evidence in the record showing that activity against *C. albicans* and activity against *C. parapsilosis* are "similar functional activities," the Board improperly shifted the burden onto Anacor to disprove the relationship. Just as in *In re Magnum Oil Tools*, the FWD here is also tainted by an improper burden shift, and it should be reversed. *See id*.

III. The FWD should be reversed because the Board's obviousness theory lacks a rational underpinning and is not supported by substantial evidence.

"[T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). With pharmaceutical innovations, structural similarities and differences between prior-art compounds typically drive the analysis of a POSA's motivation to combine

references and reasonable expectation of success in doing so. *See, e.g.*, *In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985) ("When chemical compounds have very close structural similarities and similar utilities, without more a *prima facie* case may be made.") (quotations and citations omitted).

The law's focus on chemical structure makes scientific sense. Medicinal chemistry is guided by the principle that structure begets function, and thus, it follows that a POSA may expect similarly shaped compounds to have similar pharmacologies. The record in this case supports the traditional view of medicinal chemistry that a compound must have a precise structure to interact with a biological target, just like "the interaction between a lock and key." Appx6209. The compound's structure also directly influences numerous other properties, such as solubility and metabolic stability, which also contribute to the overall efficacy of the compound. *See* Appx6209–10, Appx6220–22. Consequently, there is a rational underpinning for determining obviousness based on structural similarities. *See Daiichi Sankyo Co, Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010) ("obviousness under the third *Graham* factor frequently turns on the structural similarities and differences between the compounds claimed and those in the prior art").

The Board's obviousness analysis in this case is dramatically different, as it begins with the acknowledgment that the benzoxaboroles of *Austin* are ***structurally***

dissimilar from the compounds disclosed in both *Brehove* and *Freeman*. *See* Appx21 ("Dr. Kahl agrees that there are obviously structural differences"); Appx39 ("we agree there are structural differences"). Nevertheless, according to the Board, a POSA will be motivated to combine references disclosing structurally dissimilar compounds, and will have a reasonable expectation of success in doing so, as long as the compounds display some structural similarity and one "similar functional activity." Appx39; *see also* Appx21–22. This theory lacks a "rational underpinning" under *KSR* because the Board has not, and cannot, explain the fundamental scientific principles at its core.

For example, the Board does not delimit the extent of structural similarity that is necessary under this theory. As described below, the Board hints that the structural similarity in this case is the presence of boron atoms, but if so, the Board fails to explain why a single atom in common would have contributed to an expectation of similar antifungal activity. In addition, one is left to guess how a "similar functional activity," in this case activity against *Candida* species, would lead a POSA to ignore the clear structural dissimilarities that would typically guide a medicinal chemist's analysis. Without a scientific rationale, the Board's reliance on one "similar functional activity" despite significant structural differences lacks a rational underpinning, and the Board's conclusion of obviousness is legally erroneous under *KSR* as a result. *See* 550 U.S. at 418.

Moreover, the Board does not apply its flawed theory properly because substantial evidence does not support a number of the Board's factual findings. First, the record does not contain substantial evidence that the compounds of *Austin*, *Brehove* and *Freeman* possess a meaningful structural similarity. Second, the record is devoid of evidence for Ground 2 that the compounds of *Austin* and *Freeman* have an overlapping biological property—*i.e.*, a "similar functional activity." Third, even if a POSA were to combine *Austin* and *Freeman* as Petitioner suggested, substantial evidence does not show why a POSA would have reasonably expected *Austin*'s benzoxaboroles to have activity against dermatophytes when one of the two allegedly similar compounds from *Freeman* is inactive against dermatophytes. Thus, not only does the FWD fail to provide a rational underpinning for its theory of obviousness, it also fails to present substantial evidence in support of its key factual findings. For either reason, the Board should be reversed.

A. Substantial evidence does not support the conclusion that the compounds of *Austin* are "structurally similar" to the compounds of *Brehove* and *Freeman*.

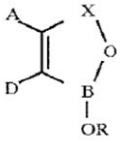
The Board maintains that relevant structural similarities exist between the compounds of *Austin*, *Brehove*, and *Freeman*. *See* Appx21, Appx39. This assertion is not supported by substantial evidence. Instead, the evidence of record overwhelmingly supports the opposite conclusion that the compounds are structurally dissimilar. In addition, the record demonstrates that a POSA would have

expected the structural differences to result in significant biological and chemical differences between the compounds of *Austin*, *Brehove* and *Freeman*. Since the Board counters this evidence with nothing more than conclusory statements and factual inaccuracies, the Board's decision is not supported by substantial evidence and should be reversed.

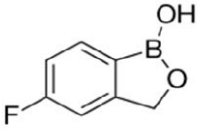
1. Petitioner did not disagree that the compounds of *Austin* possess structural differences from the compounds of *Brehove* and *Freeman*.

A simple comparison illustrates that the benzoxaboroles of *Austin* possess numerous structural differences from either *Brehove*'s dioxaborinanes or *Freeman*'s boronic acids.

Compounds disclosed in Austin

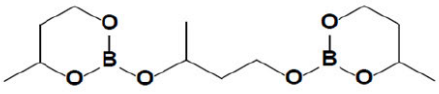


general structure of the compounds in Austin. *See* Ex. 1002 at 2:5–9.

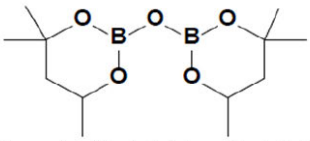


tavaborole: one of millions of preferred benzoxaboroles. *See* Ex. 1002 at 3:40–4:10; Pet. at 17.

Compounds disclosed in Brehove



2,2'-(1-methyltrimethylene dioxy)bis-(4-methyl-1,3,2-dioxaborinane)



2,2'-oxybis(4,4,6-trimethyl-1,3,2-dioxaborinane)

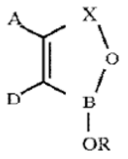
See Ex. 1003 at ¶ [0017]; Pet. at 19.

Appx265.

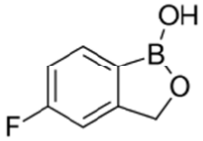
It is undisputed that *Austin*'s benzoxaboroles belong to an entirely different class of compounds than *Brehove*'s dioxaborinanes. Appx408–09. Patent Owner's

expert, Dr. Reider, enumerated numerous structural differences that distinguish benzoxaboroles from dioxaborinanes, including a carbon-boron bond, fewer oxygen atoms bound to the boron atom, a five-membered boron-containing ring instead of a six-membered ring, and the presence of a flat and unusually stable aromatic ring. Appx6258–60, Appx6191. Petitioner's chemistry expert, Dr. Kahl, agreed that the compounds of *Austin* and *Brehove* are "obviously not structurally similar." Appx5986; *see also* Appx5985 (agreeing that a POSA in 2005 would consider the structures to be different); Appx10054–55, Appx10082 (confirming that Kahl Dep. exhibits 42 and 43 are the dioxaborinanes of *Brehove*, and Kahl Dep. exhibit 70 is tavaborole).

Compounds disclosed in Austin

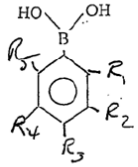


general structure of the compounds in Austin. *See* Ex. 1002 at 2:5–9.

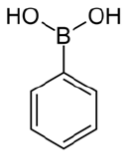


tavaborole: one of millions of preferred benzoxaboroles. *See* Ex. 1002 at 3:40–4:10; Pet. at 17.

Compounds disclosed in Freeman



general structure of the preferred compounds in Freeman. *See* Ex. 1004 at ¶ [0062].



phenyl boronic acid: the preferred compound in Freeman. *See* Ex. 1004 at ¶¶ [0028] & [0034]; Pet. at 44.

Appx280.

Similarly, the evidence of record shows that *Freeman*'s boronic acids belong to a different structural class of compounds than *Austin*'s benzoxaboroles. *See, e.g.*, Appx422–23. Benzoxaboroles differ from boronic acids at least because

benzoxaboroles possess a planar bicyclic ring structure instead of a monocyclic system, fewer B–OH groups, and a boron-containing heterocycle instead of an acyclic boron-containing group. Appx6268; Appx282. Again, Petitioner's chemistry expert and the Board agreed that the structures have differences. Appx6003–04 (also noting the different number of B–OH groups); Appx39 ("We agree there are structural differences").

2. The Board ignored evidence from both parties that a POSA would have expected structural differences between the compounds of *Austin*, *Brehove* and *Freeman* to cause those compounds to exhibit different biological activities.

The record shows that a POSA would have expected small structural changes to cause significant variation in chemical and biological properties. ***Petitioner's*** chemistry expert provided an ideal illustration of this point using the structural differences between the compounds of *Austin* and *Freeman*. Dr. Kahl contrasted the relative structural rigidity of *Austin*'s benzoxaboroles due to their boron-containing ring system with the acyclic boron-containing functional groups in *Freeman*'s boronic acids, and he concluded that a POSA would have therefore expected *Freeman*'s compounds to interact differently with biological molecules. Appx1692–93 ("The single boron-carbon bond [in *Freeman*'s compounds] allows the boron to rotate freely about the carbon bond. The ability of the B(OH)2 group to rotate freely around the boron-carbon bond allows the boron to take a greater number of potential configurations ***and therefor [sic] interact with a greater***

number of other molecules [than *Austin*'s compounds].") (emphasis added); *see also* Appx6268 (noting that the B–OH groups in *Freeman*'s compounds "can spin like a propeller in three-dimensional space," unlike *Austin*'s compounds). Dr. Kahl also explained that a POSA would have expected phenyl boronic acids, such as those in *Freeman,* to be more water soluble than the benzoxaboroles of *Austin* because benzoxaboroles possess fewer hydroxyl groups. Appx6008.

These explanations are wholly consistent with the evidence adduced by Anacor. *See, e.g.*, Appx6220–22 ("even small changes in the structure of a compound can drastically alter not only the compound's potency, but also other properties, including stability, solubility, selectivity, toxicity, absorption, distribution, metabolism, and excretion"). Anacor's chemistry expert, Dr. Reider, concluded that the substantial structural differences between the compounds of *Austin*, *Brehove* and *Freeman* would have led a POSA to expect "different functional properties such as pharmacokinetics, pharmacodynamics, water solubility, stability and nail permeability, to name a few." Appx6258–59, Appx 6268–69; *see also* Appx379.

3. The Board failed to show by substantial evidence that the compounds of *Austin, Brehove* and *Freeman* are "structurally similar."

The FWD concludes that, despite the significant structural differences described above, a POSA would have recognized some meaningful structural

similarity. The Board, however, never identifies that similarity and relies on conclusory assertions and factual inaccuracies to support its position. This is not substantial evidence. *See In re Gartside*, 203 F.3d at 1312 ("Substantial evidence is more than a mere scintilla.") (quotation omitted); *In re Beasley*, 117 F. App'x at 744 ("the Board must point to some concrete evidence in the record") (quotation omitted).

First, for the combination of *Austin* and *Brehove*, the Board simply states, "We are persuaded, however, by Dr. Murthy and Dr. Kahl's testimony that the combination of structural similarities *and* the similar fungicidal activity against *C. albicans* would have led a person of ordinary skill in the art to combine *Brehove*'s method of treating onychomycosis using *Austin*'s tavaborole instead of BioBor." Appx21 (emphasis in original) (citing Appx 1221–23 (Ex. 1008 (Murthy Decl.) ¶¶ 93–95); Appx1158 (Ex. 1006 (Kahl Decl.) ¶ 38); Appx1160 (Ex. 1006 (Kahl Decl.) ¶ 43)). But apart from the conclusory assertion of some structural similarities, the Board's decision does not actually identify a shared structural feature between the compounds of *Austin* and *Brehove* that supports its conclusion.

Second, the Board's support for its conclusion of structural similarities between the compounds of *Austin* and *Freeman* is factually incorrect. The Board states, "Although we agree there are structural differences, as above, we are persuaded that a person of ordinary skill in the art would have had a reason to

combine the references in light of the structural similarities (i.e., both are boron heterocycles) *and* the similar functional activity against *Candida* species." Appx39 (citing Appx148 (Petition at 46)) (emphasis in original). But *Freeman*'s compounds are not boron heterocycles, and no party has argued that they are. *See* Appx6268; Appx5152 (Dr. Kahl explaining that a phenyl boronic acid as in *Freeman* is not a heterocycle). Consequently, the Board's conclusion of structural similarities between *Austin*'s benzoxaboroles and *Freeman*'s boronic acids lacks any evidence, much less substantial evidence.

The Board's citations to the Petition and expert declarations do not overcome the dearth of evidence of structural similarities, because the cited passages of those documents are themselves conclusory. The only structural similarity disclosed in the citations is the fact that *Austin*'s benzoxaboroles, *Brehove*'s dioxaborinanes and *Freeman*'s boronic acids are all "boron-based compounds." Appx148 (Petition at 46); Appx 1221–23 (Ex. 1008 (Murthy Decl.) ¶¶ 93–95); Appx1158 (Ex. 1006 (Kahl Decl.) ¶ 38)[5]; *see also* Appx5748–49 (Petitioner's expert Dr. Kahl conceding that his use of the term "boron-based compounds" was "[p]robably a poor choice of words," and he really meant "boron-containing compounds"). None of the Board's

[5] The Board also cited paragraph 43 of the Kahl declaration (Appx1160) to support the argument that the compounds of *Austin* and *Brehove* are "structurally similar," but this paragraph is irrelevant because it describes *Freeman*'s compounds, not *Brehove*'s.

citations to the Petition or the declarations includes evidence, or even an explanation, for why a POSA would understand "boron-based compounds" to be structurally similar enough that the properties of one could be extrapolated to all members of the class. Indeed, no record evidence supports the notion that "boron-based compounds" all behave in a similar manner. To the contrary, the undisputed evidence shows that "there are many distinct classes of boron-containing compounds." Appx379 (citing Appx1155 (Ex. 1006 (Kahl Decl.) ¶ 30)); Appx1225 (Ex. 1008 (Murthy Decl.) ¶¶ 100–01); Appx5880–81 (Ex. 2033 (Kahl Dep. Tr.) at 250:24–251:9) (admitting there are 10–20 classes of organic boron-containing compounds); Appx6199–6203 (Ex. 2034 (Reider Decl.) ¶¶ 38–49)). As described above, a POSA would have understood that the different structural classes of boron-containing compounds behave differently. *See*, *e.g.*, Appx1692–93; Appx6199–6203.

Accordingly, substantial evidence from the record as a whole does not support the Board's finding of structural similarities between the compounds of *Austin*, *Brehove* and *Freeman*. This error is sufficient on its own for the Court to reverse the Board's decision, since it destroys the "structural similarity" prong of the Board's theory of obviousness. *See Duke Univ. v. BioMarin Pharm. Inc.*, --- F. App'x ----, 2017 WL 1458866, at *9, *10 (Fed. Cir. Apr. 25, 2017) (reversing an obviousness decision for lack of substantial evidence).

B. Substantial evidence does not support the conclusion that the compounds of *Austin* are "functionally similar" to the compounds of *Freeman*.

The second prong of the Board's two-part obviousness theory considers whether the proposed combination of references demonstrates a "similar functional activity." *See* Appx39. In Ground 2, the Board found that the overlapping biological property was "activity against *Candida* species." *Id*. The Board misapplied its obviousness theory because the record does not demonstrate that a POSA viewed *Austin*'s activity against *C. albicans* as similar, or even related, to *Freeman*'s activity against a different yeast, *C. parapsilosis*.

In fact, the record shows the opposite. The record shows no evidence that a POSA would have considered an activity against one *Candida* species as predictive of activity against a different *Candida* species.[6] Rather, Anacor presented evidence that the activity of different compounds is unpredictable, even between different *Candida* species. Appx6311–12. Anacor's mycology expert concluded that "antifungal activity of individual compounds is complex and unpredictable." *Id*. (citing Ex. 2090, Ex. 2096, Ex. 2097 and Ex. 2098).

The alleged "similar functional activity" played a vital role in the Board's analysis because it counteracted the admitted structural differences between the

[6] The Board's assumption of "similar functional activity" without evidence improperly shifts the burden of disproving the asserted relationship onto Anacor, as explained in Part II.B above.

compounds. Based on structural dissimilarities, a POSA would not have combined the references with a reasonable expectation that the different compounds would share properties. But despite this significance, the Board cited no support for the notion that *Austin* and *Freeman* actually disclose "similar functional activity," and the Board faulted Anacor for not disproving the relationship. Appx41. Substantial evidence does not support the Board's position when the record contains no evidence.

C. Substantial evidence does not support the conclusion that the combination of *Austin* and *Freeman* would provide a POSA with a reasonable expectation of successfully treating dermatophytes with tavaborole.

The Board's analysis of Claim 6 under Ground 2 begins with the misstatement that Anacor "does not separately address the dependent claims [such as Claim 6] with respect to this ground." Appx41. However, Anacor's Response expressly addresses a POSA's reasonable expectation based on the combination of *Austin* and *Freeman* that tavaborole would have no activity against dermatophytes, as recited in Claim 6. Appx426. As a result of this oversight, the Board apparently failed to consider evidence that undercuts the Board's conclusion that the combination of *Austin* and *Freeman* provides a reasonable expectation of successfully achieving the invention of Claim 6. When the evidence is considered as a whole, it is clear that substantial evidence does not support the conclusion that a POSA would have had a

reasonable expectation of activity against dermatophytes, even if the POSA were to combine *Austin* and *Freeman*.[7]

Both the Petition and Petitioner's expert Dr. Murthy conclude that a POSA "would have a reasonable expectation that 5-fluoro benzoxaborole [as disclosed by *Austin*] would have similar activity to PBA and pentafluorophenyl boronic acid [as disclosed by *Freeman*]." Appx1235; Appx149. Assuming that is true (which it is not), a POSA still would not have had a reasonable expectation of success because one of the identified comparison compounds—pentafluorophenyl boronic acid—is inactive against dermatophytes. *Freeman* makes clear that pentafluorophenyl boronic acid has "no effect" against the dermatophyte *T. rubrum* or any other microorganism. Appx1099. Similarly, PBA has activity at a concentration of 0.04M, but Petitioner's expert Dr. Murthy stated that he "would not be very optimistic" to develop an onychomycosis treatment with an MIC of 0.01M—4 times more potent than PBA in *Freeman*. Appx420–21; Appx5552–54.

[7] Because the Board found a reasonable expectation of success against dermatophytes based on *Austin*'s disclosure of activity against *C. albicans*, as described above and as argued in Petitioner's Reply at 23 (Appx778), it is unclear what limitation of Claim 6 *Freeman* allegedly discloses. To the extent the Board relied on *Freeman* for the limitation "a method of treating an infection in an animal," that factual finding also lacks substantial evidence because *Freeman*, like *Austin*, discloses no *in vivo* data. *See* Appx371 (citing Appx5304 (Ex. 2032 (Murthy Dep. Tr.) at 346:5–8); Appx422 (citing Appx6243–44 (Ex. 2034 (Reider Decl.) ¶ 137); Appx6266–67 (Ex. 2034 (Reider Decl.) ¶¶ 193–94)).

In its FWD, the Board does not consider Dr. Murthy's statement that he would not be very optimistic with a more potent compound than *Freeman*'s PBA because Dr. Murthy added the caveat that molecular size also plays a role in activity. Appx40. This reasoning only strengthens Anacor's point because Dr. Murthy maintains that low molecular weight predicts good nail penetration, but tavaborole is ***heavier*** than PBA. *See* Appx151 (citing Appx1237–38 (Ex. 1008 (Murthy Decl.) ¶ 134)). Thus, under Dr. Murthy's theory, heavier compounds are less likely to be effective because they are less likely to penetrate the nail. *See* Appx1237–38. Regardless, PBA is only one half of the evidence in the record. The other half is pentafluorophenyl boronic acid, but the Board failed to consider this compound. As Anacor's Response makes clear, *Freeman* discloses that pentafluorophenyl boronic acid has no effect against dermatophytes. Appx424–26.

Thus, when the evidence as a whole is considered, a POSA looking at the activities of PBA ***and*** pentafluorophenyl boronic acid in *Freeman*, as Petitioner argued, would have expected no more than a 50% chance that tavaborole has activity against dermatophytes. This is not substantial evidence, *see In re Gartside*, 203 F.3d at 1312, and the Board's decision otherwise should be reversed.

CONCLUSION

For the reasons above, the Court should reverse the Board's decision of invalidity, and remand the case to the Board for an entry of judgment upholding the patentability of Claim 6 of the '621 patent.[8]

Dated: August 4, 2017

Respectfully submitted,

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[8] On June 12, 2017, the Supreme Court granted certiorari in *Oil States Energy Servs., LLC v. Greene's Energy Grp., LLC* to consider the question of whether IPR proceedings violate the Constitution. No. 16-712, 2017 WL 2507340 (U.S. June 12, 2017). The FWD should also be reversed in the event that the Supreme Court finds IPR proceedings unconstitutional.

Addendum

Trials@uspto.gov Paper 70
571.272.7822 Entered: February 23, 2017

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 GRACE KARAFFA OBERMANN and MICHAEL P. TIERNEY, *Vice Chief Administrative Patent Judges*, and TINA E. HULSE, *Administrative Patent Judge*.

HULSE, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

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.").

On February 23, 2016, we instituted an *inter partes* review of claims 1–12 of the '621 patent on two grounds of obviousness. Paper 24 ("Dec. Inst."), 15. Patent Owner filed a Response to the Petition. Paper 32 ("PO Resp."). Petitioner filed a Reply to Patent Owner's Response. Paper 47 ("Pet. Reply").

Patent Owner filed a motion to exclude certain exhibits. Paper 57. Petitioner filed an opposition (Paper 63) and Patent Owner filed a reply (Paper 65). Pursuant to authorization from the Board, Patent Owner also filed an Identification of New Arguments and Evidence in Petitioner's Reply (Paper 53) and Petitioner filed a response (Paper 60).[1]

Patent Owner filed observations on the cross-examinations of Petitioner's declarants, Stephen B. Kahl, Ph.D. (Paper 55) and S. Narasimha Murthy, Ph.D. (Paper 56). Petitioner filed responses to Patent Owner's observations. Paper 61 (Kahl); Paper 62 (Murthy).

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[1] We do not find the arguments identified by Patent Owner to be impermissible new arguments and evidence in the Reply. Rather, we determine that the arguments were each in response to those set forth by Patent Owner in its Response, for the reasons stated by Petitioner. Paper 60, 1–3; 37 C.F.R. § 42.23(b) ("A reply may only respond to arguments raised in the corresponding opposition or patent owner response.").

An oral hearing was held on November 3, 2016, a transcript of which has been entered in the record. Paper 69 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–12 of the '521 patent are unpatentable.

A. Related Proceedings

Petitioner has filed concurrently two other petitions for *inter partes* review of the claims of related U.S. Patent No. 7,767,657 B2 in IPR2015-01780 and IPR2015-01785. Pet. 5.

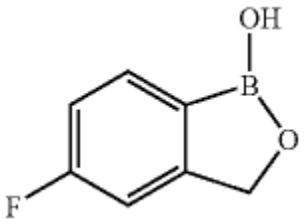
B. The '621 Patent

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 have 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. Moreover, 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.

Claims 2–4 and 10 depend directly or indirectly from claim 1 and further recite specific infections that are treated with the claimed method. Claims 5 and 7 depend from claim 1 and further recite specific animals that are treated,

including humans. Claims 8 and 9 depend from claim 1 and further recite the site of administration of the drug. And claims 11 and 12 are independent claims that are similar to claim 1, but recite a method of treating onychomycosis in a human (claim 11) and a method of inhibiting growth of a fungus in a human (claim 12).

D. Grounds of Unpatentability Instituted for Trial

We instituted trial based on the following grounds of unpatentability:

References	Basis	Claim(s) challenged
Austin[2] and Brehove[3]	§ 103	1–12
Austin and Freeman[4]	§ 103	1–12

II. ANALYSIS

A. Person of Ordinary Skill in the Art

The level of ordinary skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) and *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

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

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[2] Austin et al., WO 95/33754, published Dec. 14, 1995 (Ex. 1002).
[3] Brehove, US 2002/0165121 A1, published Nov. 7, 2002 (Ex. 1003).
[4] Freeman et al., WO 03/009689 A1, published Feb. 6, 2003 (Ex. 1004).

¶ 21; Ex. 1008 ¶ 34). Patent Owner asserts that a person of ordinary skill in the art would have "needed knowledge and experience in several areas: medicinal chemistry; the development of potential drug candidates suitable for treating onychomyosis; and in assessing, together with others, the toxicology, pharmacology, and clinical utility of such candidates, including parameters relating to transungual penetration." PO Resp. 21–22 (citing Ex. 2034 ¶ 108). Patent Owner further asserts that Petitioner's definition is incorrect because it excludes "necessary expertise in mycology and in clinical dermatology." *Id.* at 22.

Based on the record presented, we hold that the cited prior art is representative of the level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "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)). The cited prior art is consistent with Petitioner's broader description of the level of ordinary skill in the art. We are not persuaded that additional experience in mycology, clinical dermatology, medicinal chemistry, the development of drug candidates for treating onychomycosis, and the assessment of the toxicology, pharmacology, and clinical utility of drug candidates is required, as Patent Owner suggests, as it is unclear as to why the claimed subject matter is beyond the abilities of someone that has Petitioner's proposed qualifications.

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);

Cuozzo Speed Techs., LLC v. Lee, 136 S. Ct. 2131, 2144–46 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). 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).

In our Decision to Institute, we determined 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." Dec. Inst. 6. Neither party contested this construction during trial. Accordingly, because nothing in the full record developed during trial persuades us to deviate from our prior construction, we adopt the construction for purposes of this Decision. For ease of reference, we refer to the claimed compound as "tavaborole" in this Decision.

1. "therapeutically effective amount"

Each of the claims of the '621 patent recites administering a "therapeutically effective amount of tavaborole." According to Petitioner, "therapeutically effective amount" means "an amount of the claimed compound needed to reach the desired therapeutic result." Pet. 12. Patent Owner asserts the claim phrase should be construed as expressly defined in the '621 patent specification: "'therapeutically effective' amount refers to the amount of drug needed to effect the desired therapeutic result." PO Resp. 25; Ex. 1001, 9:57–58.

Because the '621 patent specification defines the phrase with clarity, deliberateness, and precision, we determine the broadest reasonable interpretation of "therapeutically effective amount" is "the amount of drug needed to effect the desired therapeutic result." *See In re Paulsen*, 30 F.3d at 1480.

C. Credibility of Petitioner's Experts

As an initial matter, Patent Owner contends that we should not credit the testimony of Petitioner's declarants because they are not qualified to opine from the perspective of a person of ordinary skill in the art. PO Resp. 21–24. For the reasons that follow, we are not persuaded.

Petitioner relies on the testimony of two declarants: S. Narasimha Murthy, Ph.D. and Stephen Kahl, Ph.D. Both Dr. Murthy and Dr. Kahl provide their background and experience in their respective declarations, along with a curriculum vitae, which provides further detail regarding each declarant's experience. Ex. 1008 (Murthy) ¶¶ 4–8; Ex. 1009 (Murthy CV); Ex. 1006 (Kahl) ¶¶ 4–8; Ex. 1007 (Kahl CV). For example, Dr. Murthy has a Ph.D. in pharmaceutics, has been an assistant professor of pharmaceutics at various universities, and has received research grants relating to the topical administration of therapeutics, including ungual nail delivery, which has resulted in 85 publications in peer-reviewed journals. Ex. 1008 ¶¶ 4–8. Dr. Kahl has a Ph.D. in chemistry, is a professor in the department of pharmaceutical chemistry at the University of California, San Francisco, has served as an ad hoc reviewer for 20 journals, and has conducted research related to bioactive boron molecules that are specifically targeted to biological systems, which has resulted in over 65 publications in books and peer-reviewed journals. Ex. 1006 ¶¶ 4–8. Based on these qualifications, we

determine that the Drs. Murthy and Kahl are competent to opine on the matters in this proceeding.

Patent Owner contends that there are "huge holes" in the expertise of Petitioner's declarants. PO Resp. 23. For example, Patent Owner argues that Dr. Murthy's testimony should be disregarded because he allegedly conceded he is not a chemist. *Id.* We are persuaded by Dr. Murthy's testimony in response that, although he is not a synthetic chemist by profession, he is an expert in pharmaceutics with extensive coursework in various fields of chemistry. Ex. 1044 ¶ 10. Patent Owner also argues that neither declarant is a mycologist or has expertise in treating patients. PO Resp. 23. As explained above, we do not agree with Patent Owner's argument that a person of ordinary skill in the art is required to have expertise in mycology or clinical dermatology.

Thus, we are not persuaded by Patent Owner's argument that we should uphold the challenged claims because Petitioners' declarants are not qualified to opine from the perspective of a person of ordinary skill in the art in this proceeding. *Id.* at 24.

D. Principles of Law

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter 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 the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying

factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

We analyze the instituted grounds of unpatentability in accordance with the above-stated principles.

E. Obviousness over Austin and Brehove

Petitioner asserts that claims 1–12 are unpatentable as obvious over Austin and Brehove. Pet. 23–42. Petitioner relies on the Declarations of Stephen Kahl, Ph.D (Ex. 1006) and S. Narasimha Murthy, Ph.D. (Ex. 1008). Patent Owner opposes Petitioner's assertion, relying on the Declarations of Paul J. Reider, Ph.D. (Ex. 2034), Mahmoud A. Ghannoum, Ph.D., E.M.B.A. (Ex. 2035), Majella Lane, Ph.D. (Ex. 2036), and Howard I. Maibach, M.D., Ph.D. (Ex. 2037). PO Resp. 35–54. Based on the full trial record, we determine that Petitioner has established by a preponderance of the evidence that 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* ("*C. 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 *C. albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum* ("*T. rubrum*"), or *Epidermpophyton floccusum*. *Id.* ¶ 5. Brehove states that *C. 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 testing of the antifungal activity of S1 and S2 against *C. albicans* and in vivo treatment of patients with onychomycosis using S1 and S2. *Id.* ¶¶ 30–38.

3. Analysis

a. Whether Austin Is Analogous Art

Patent Owner first argues that Petitioner's arguments fail because Austin is not analogous art. PO Resp. 27–32. Prior art is analogous if it either (1) "is from the same field of endeavor, regardless of the problem addressed," or (2) "is reasonably pertinent to the particular problem with which the inventor is involved." *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1000 (Fed. Cir. 2016) (quoting *In re Clay*, 966 F.2d 656, 658–59 (Fed. Cir. 1992)). "A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1380–81 (Fed. Cir. 2007).

Patent Owner argues that medicinal chemists would not look to industrial biocides for pharmaceutical leads because the requirements for a useful biocide are different from the requirements for a useful drug. PO

Resp. 31 (citing Ex. 2034 ¶¶ 121–126). Patent Owner further asserts that a person of ordinary skill in the art would have sought out compounds with at least low in vivo toxicity, high in vivo activity against medicinally relevant targets, high selectivity, and chemical and metabolic stability. *Id.* Accordingly, Patent Owner contends that a person of ordinary skill in the art "would have learned from *Austin* that these characteristics are not relevant to an industrial biocide." *Id.* We are not persuaded.

Based on our review of the complete record, we find that Austin is reasonably pertinent to the particular problem the inventors sought to solve. Both the inventors and Austin sought to inhibit microorganisms, including *C. albicans*. Ex. 1001, 25:5–55; Ex. 1002, 33:7–38:2. Further, as noted by Petitioner, a person of ordinary skill in the art would have recognized that industrial fungicides may have therapeutic uses, including in some cases, topically treating a human for *C. albicans*. Pet. 15–17; *see, e.g.*, Ex. 1003 ¶¶ 14–15, 23, 30–38; Ex. 1021, 2:9–15, 3:12–16, 6:45–50; Ex. 1022, 1:18–26, 13:32–48; Ex. 1023, 1:25–40, 3:73–4:36; Ex. 1026, 12:52–54, 16:63–17:46; Ex. 1029, Abstract, 15:12–16:16. For example, Pfiffner[5] describes its antifungal compounds as suitable for combating fungi in agriculture and horticulture, but also as suitable for use in ointments where the active compound completely prevented the growth of *C. albicans* in vitro. Ex. 1026, 12:52–54, 17:9-46. As another example, Grier describes its compounds as suitable for the treatment of fungal infections caused by *C. albicans* and *T. rubrum*, as well as for industrial applications, such as mildew-proofing paint. Ex. 1022, 1:18–26, 13:32–48, 17:38–18:45.

[5] Albert Pfiffner, US 4,202,894, issued May 13, 1980 (Ex. 1026).

Moreover, Brehove describes the topical use of an industrial fungicide, BioBor, to treat onychomycosis "without skin irritation or noticeable side effects." Ex. 1003 ¶ 24; Ex. 1044 ¶¶ 50, 52. Brehove also notes that the materials safety data sheet of BioBor states, "Skin Contact: May cause slight to mild irritation. Prolonged or repeated contact may dry the skin and lead to irritation (i.e. dermatitis)." *Id.* ¶ 15. Patent Owner and its declarant assert that Brehove mischaracterizes the dangers associated with contacting the skin with BioBor based on the product label and other warnings in the safety data sheet to wear protective clothing and clean the skin if contact occurs. PO Resp. 32; Ex. 2034 ¶ 155. We do not find those other warnings identified by Dr. Reider to be inconsistent with or to outweigh the warning stated in Brehove that BioBor may cause skin irritation.

Thus, based on the record presented, we find that Austin logically would have commended itself to the problem facing the inventors of the '657 patent. *See Scientific Plastic Products, Inc. v. Biotage AB*, 766 F.3d 1355 (Fed. Cir. 2014); *see also In re ICON Health*, 496 F.3d at 1379–80 (holding that reference may be reasonably pertinent as analogous art where the matter it deals with logically would have commended itself to the inventor's attention).[6]

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[6] Petitioner points to a paper published in 2006 by the inventors of the '657 patent that published "their 'discovery' of a 'new' boron-containing compound (tavaborole) for the treatment of onychomycosis," and "also reported on the synthesis of benzoxaborole derivatives, including the 7-fluoro derivative," which was synthesized using a scheme disclosed in Austin. Reply 11–12 (citing Ex. 2157, 3, 6). Petitioner argues that the inventors' citation to Austin as a reference relied upon during the drug discovery process "prov[es] that a [person of ordinary skill in the art] would

b. Independent Claims

Petitioner provides a claim chart identifying where each limitation is taught in the cited references. Pet. 38–42. We have considered the claim chart and find that the combination of Austin and Brehove teaches each limitation of independent claims 1, 11, and 12. For example, regarding claim 1, Brehove teaches a method of treating an infection in an animal by disclosing that the invention relates to the treatment of human fingernails and toenails to cure or prevent the spread of nail infections such as onychomycosis, caused by bacteria, fungi and other pathogens. Ex. 1003 ¶ 3. Brehove also teaches administering a therapeutically effective amount of a pharmaceutical composition to the toenail of a patient suffering from onychomycosis in an amount sufficient to treat the infection. *Id.* ¶ 35. Finally, Austin teaches that tavaborole is effective against *C. albicans*. Ex. 1002, Abstract, 37 (Example 64).

Patent Owner argues that there is no basis to conclude that a person of ordinary skill in the art would have selected tavaborole from among the millions of compounds disclosed in Austin. PO Resp. 33–35. As Petitioner notes, however, Austin discloses tavaborole (i.e., 5-fluoro benzoxaborole) as a preferred fungicide. Pet. 27 (citing Ex. 1002, Abstract); Ex. 1006 ¶ 34; Ex. 1008 ¶ 61. Moreover, of the preferred compounds tested, tavaborole demonstrated the lowest Minimum Inhibitory Concentration ("MIC") tested

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find *Austin* directly relevant, and at minimum, analogous art." *Id.* at 11. Additionally, the examiner of the '621 patent application "also independently identified *Austin* in 2008 and rejected the pending claims over *Austin*." *Id.* at 12. Although we do not rely on the inventors' citation to Austin or the examiner's rejection over Austin in finding that Austin is analogous art, we note that both facts are consistent with our finding.

(5 ppm) against several pathogens, including *C. albicans*. Pet. 28; Ex. 1002, 37 (Table 9, Example 64); Ex. 1006 ¶ 34; Ex. 1008 ¶ 63. That is, tavaborole inhibited the growth of *C. albicans*—which is a cause of onychomycosis—at the lowest level of concentration. Ex. 1008 ¶¶ 63–64. Accordingly, evaluating Austin for all that it teaches, we determine that one of ordinary skill in the art would have recognized that tavaborole is a preferred fungicide for effectively inhibiting *C. albicans*, which causes onychomycosis.

Patent Owner contends that Petitioner's argument is flawed because Austin describes tens of thousands of structures as "preferred" and "particularly preferred," including the O-esters of 5- and 6-fluoro or bromo-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. PO Resp. 33–34 (citing Ex. 2034 ¶¶ 114, 148, 150); Ex. 1002, Abstract. Patent Owner also asserts that a person of ordinary skill in the art would not select tavaborole among the many disclosed compounds given that Table 8 identifies numerous benzoxaborole O-esters with the same MIC of 5 ppm as tavaborole. PO Resp. 34 (citing Ex. 1002, 5; Ex. 2034 ¶ 151).

We are not persuaded by Patent Owner's argument. Although Austin may encompass millions of compounds, Patent Owner's declarant, Dr. Reider, testifies that Austin disclosed test results for only sixteen compounds identified as "preferred compounds"—nine O-esters from Table 8 and seven simple benzoxaboroles, including tavaborole, from Table 9. Ex. 1048, 304:4–308:11. We are persuaded that a person of ordinary skill in the art would have looked to compounds in Table 9 over the O-esters of Table 8 because the Table 9 compounds have a lower molecular weight that is more likely to penetrate the nail. Pet. Reply 14–15; Ex. 1043 ¶¶ 10–11; Ex. 1044 ¶¶ 44–45.

During oral argument, Patent Owner argued that because almost all of the "particularly preferred" compounds of Table 8 have the lowest MIC for *C. albicans* and an average molecular weight of 219 Da, which is less than the molecular weights of the compounds of Brehove and Freeman, a person of ordinary skill in the art would turn to the compounds of Table 8, rather than Table 9, when reading Austin as a whole. Tr. 24:11–29:16. Even if true, we do not find Patent Owner's argument detracts from what Austin reasonably suggests to a person of ordinary skill in the art. *See Merck & Co. v. Biocraft Labs, Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the [prior art] discloses a multitude of effective combinations does not render any particular formulation less obvious."). In other words, that Austin also points to the compounds of Table 8 does not preclude a person of ordinary skill in the art from considering tavaborole when reading Austin as a whole. *See id.* ("[I]n a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'") (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)). This is particularly true where tavaborole has a lower molecular weight than the compounds of Table 8 and was the most effective against *C. albicans* of the preferred compounds in Table 9.

In sum, Austin teaches that tavaborole was known as a preferred fungicide that was effective against *C. albicans*. Although Austin describes a broad class of preferred compounds, Austin tested only sixteen of its preferred compounds where nine of the sixteen compounds were "O-esters" in Table 8 and seven of the sixteen compounds, including tavaborole, were listed in Table 9. Ex. 1002, Abstract, Tables 8 and 9; Ex. 1048, 304:4–308:11. Of the preferred compounds tested with the most potent activity,

tavaborole was the simplest and lowest molecular weight compound, which, as explained further below, is the most important factor in predicting whether a molecule will penetrate a nail plate. Ex. 1043 ¶¶ 10–11; Ex. 1044 ¶¶ 44–45. Accordingly, we find that a person of ordinary skill in the art would have chosen tavaborole as a potential candidate for treating onychomycosis. Pet. Reply 15; Ex. 1043 ¶¶ 10–11; Ex. 1044 ¶¶ 44–47.

Patent Owner also argues that neither reference discloses "administering to the animal [or human] a therapeutically effective amount of [tavaborole]," as required by each claim. PO Resp. 35–36. We are not persuaded. Patent Owner attacks each reference separately and does not acknowledge what the art fairly teaches in combination. *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (stating the prior art "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as whole"). Here, Austin and Brehove together suggest administering to a human a therapeutically effective amount of tavaborole.

The parties also dispute whether a person of ordinary skill in the art would have had a reason to combine Austin and Brehove to reach the claimed invention with a reasonable expectation of success. We determine that Petitioner has shown that it would.

In particular, we are persuaded by Petitioner's 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 response, Patent Owner first argues that an ordinary artisan would not have found Brehove credible and, therefore, would not have combined it with Austin with a reasonable expectation of success. PO Resp. 36–40. Specifically, Patent Owner criticizes Brehove for failing to provide further details regarding the in vivo tests and data described in Brehove. *Id.* at 37–39. For example, Patent Owner argues that Brehove does not confirm the clinical diagnosis of onychomycosis through laboratory analysis of the microorganisms causing the onychomycosis. *Id.* at 37. Nor does Brehove discuss the facts that, according to Patent Owner and its declarants, jet fuel additives have no relevance to onychomycosis, BioBor has safety warnings on its label and materials safety data sheet, and BioBor was shown to be ineffective in vitro in a different study. *Id.* at 37–38 (citing Ex. 2035 ¶¶ 26–27, 106–108, 113). Moreover, Patent Owner argues that Brehove inaccurately reports the toxicity of another boron-containing dioxaborinane called tolboxane, and is incorrect when it stated *C. albicans* is "the most common pathogen causing onychomycosis." *Id.* at 38–39. Finally, Patent Owner asserts that a person of ordinary skill in the art would have understood Brehove's examples to be prophetic and do not constitute data that would provide a reasonable expectation of success. *Id.* at 39–40.

We are not persuaded that a person of ordinary skill in the art would not have considered Brehove to be a credible reference. There is no requirement, as Patent Owner suggests, that Brehove provide details

regarding background tests, data, and long-term toxicity reports, to be credited as results by a person of ordinary skill in the art. *See* PO Resp. 37 (pointing to Dr. Murthy's testimony that he would ask for underlying data "if one of his graduate students were to hand him the *Brehove* disclosure as a draft academic paper") (citing Ex. 2032, 599:9–15). Brehove is a patent application that does not need to meet the standard of a peer-reviewed academic article. 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*, 874 F.2d at 807.

Having reviewed the complete record, we find that Brehove reasonably suggests administering Biobor to treat onychomycosis. We are persuaded by Dr. Murthy's testimony that it is reasonable to assume that where Brehove states a volunteer "has onychomycosis," that the volunteer was diagnosed before treatment. Ex. 1044 ¶ 51 (citing Ex. 1003 ¶¶ 34–38). Dr. Murthy explains why this belief is reasonable, stating Brehove describes symptoms in the patients that are associated with onychomycosis, such as detachment of the nail from the nail bed. *Id.* Similarly, we credit Dr. Murthy's testimony that where Brehove states the compositions "are effective in curing the onychomycosis without skin irritation and evidence side effects," he takes those statements to be true. *Id.* ¶ 52. Dr. Murthy's belief is reasonable in light of Brehove's description of the "clear zone in the treated nail," which is similar to observations made by others, including the inventors. *Id.* (citing Ex. 1003 ¶¶ 34–38; Ex. 1066, 2; Ex. 2001, 5; Ex. 2065, 943). As such, we are not persuaded that the alleged inaccuracies, unexplained data, and prophetic examples identified by Patent Owner (PO Resp. 37–39) detract from these teachings of Brehove.

Patent Owner then argues that there would have been no reason to combine Austin and Brehove. PO Resp. 41–50. Specifically, Patent Owner contends that because Austin and Brehove concern structurally different compounds, a person of ordinary skill in the art "would not assume (without reliable tests) that data generated in connection with one class of compounds would be applicable to a different compound class." *Id.* at 41–42. Patent Owner also argues that neither reference provides guidance about treating onychomycosis caused by dermatophytes, which represents over 90% of onychomycosis cases. *Id.* at 43–47. Patent Owner further argues that because transungual penetration is difficult, and because Austin and Brehove do not provide any guidance on transungual penetration, a person of ordinary skill in the art would not have had a reason to combine the references or a reasonable expectation of success in doing so. *Id.* at 47–50.

Taken as a whole, the evidence of record persuades us that a person of ordinary skill in the art would have had a reason to combine Austin and Brehove. Petitioner's declarant, Dr. Kahl agrees that there are obviously structural differences between the dioxaborinanes of Brehove and the benzoxaboroles of Austin. Ex. 1043 ¶ 25. We are persuaded, however, by Dr. Murthy and Dr. Kahl's testimony that the combination of the structural similarities *and* the similar fungicidal activity against *C. albicans* would have led a person of ordinary skill in the art to combine Brehove's method of treating onychomycosis using Austin's tavaborole instead of BioBor. Ex. 1008 (Murthy) ¶¶ 93–95; Ex. 1006 (Kahl) ¶¶ 38, 43. We acknowledge Patent Owner's argument that small structural differences can cause different biological actions and activities. PO Resp. 41–42 (citing Ex. 2034 ¶ 90); *see also* Ex. 2034 ¶¶ 91–93. But we are persuaded that a person of ordinary skill in the art would have been less concerned about the possibility

of differences in biological function given Brehove and Austin's disclosure confirming that BioBor and tavaborole have similar fungicidal activity against *C. albicans*. In that regard, Austin's disclosure of tavaborole as a fungicide effective against *C. albicans* would have recommended its use for that purpose in treating onychomycosis. Of the seven preferred compounds tested in Austin's Table 9, tavaborole had the lowest tested anti-fungal activity against *C. albicans* and had the lowest molecular weight, which made it the first and best compound to select for treatment of onychomycosis. Ex. 1043 ¶¶ 10–11; Ex. 1044 ¶¶ 44–45.

We are also not persuaded that a person of ordinary skill in the art would not look to Austin because it only reports activity against *C. albicans*, which causes a very small percentage of onychomycosis cases. PO Resp. 43–47. Although dermatophytes cause about 90% of onychomycosis cases, the parties agree that onychomycosis can be caused by yeast (such as *C. albicans*). Ex. 1008 ¶ 49; Ex. 2035 ¶¶ 22, 28. We are not persuaded by Dr. Ghannoum's testimony that a person of ordinary skill in the art seeking to develop a formulation for the treatment of onychomycosis "would have been interested *only* in antifungal agents having demonstrated efficacy against dermatophytes, particularly *T. rubrum*, and efficacy only against *C. albicans* would have been inconsequential." Ex. 2035 ¶ 35 (emphasis added); *see also id.* ¶¶ 108–114. Brehove belies Dr. Ghannoum's assertion, as it relates to the treatment of onychomycosis and focuses on inhibiting *C. albicans* rather than the dermatophyte *T. rubrum*. Ex. 1003 ¶ 18 (describing the compositions of the invention as having "powerful potency against *Candida albicans*"). Accordingly, we are persuaded that Petitioner has shown sufficiently that a person of ordinary skill in the art would have had a reason

to combine Austin's tavaborole with Brehove's method of treating onychomycosis.

Patent Owner also argues that there would have been no reasonable expectation of success in combining Austin and Brehove. PO Resp. 47–52. In particular, Patent Owner contests Petitioner's argument that a person of ordinary skill in the art would have had a reasonable expectation that tavaborole would be an effective treatment because of its lower molecular weight, which would increase the likelihood of penetrating the nail barrier. *Id.* at 47–48. Patent Owner characterizes Petitioner's arguments as a "gross oversimplification of the many factors that govern whether a given compound will achieve effective penetration through the nail." *Id.* at 48. For example, Patent Owner asserts that a person of ordinary skill in the art would have recognized that a good candidate for transungual delivery would need to have a low affinity for keratin binding. *Id.* at 49 (citing Ex. 2036 ¶ 27). Because neither Austin nor Brehove provides any data on keratin binding, Patent Owner argues that a person of ordinary skill would not have identified tavaborole as a possible transungual candidate. *Id.* Moreover, Patent Owner argues that an ordinary artisan would not have expected the formulations described in Brehove to be effective in transungual delivery, particularly without information regarding the lipophilicity of tavaborole. *Id.* at 49–50 (citing Ex. 2036 ¶¶ 51–52).

Having considered the full trial record, we determine that Petitioner has shown that a person of ordinary skill in the art would have had a reasonable expectation of success in combining Austin and Brehove. Tavaborole has a molecular weight of 151.93 Da. Ex. 1008 ¶ 102. The parties agree the compounds in Brehove that were effective at treating onychomycosis are in the range of 260–290 Da. *Id.*; Tr. 26:1–3. Although

other factors such as lipophilicity, keratin binding, and potency of the compound may influence transungual drug delivery, we are persuaded by the well-supported testimony of Dr. Murthy that low molecular weight is the most important factor in predicting whether a molecule will penetrate the nail plate, and that the remaining factors described by Patent Owner's declarant, Dr. Lane, are of less importance, particularly with a low molecular weight and low MIC molecule such as tavaborole. Ex. 1008 ¶ 102; Ex. 1044 ¶¶ 63–64, 78–81. Dr. Murthy cites various references explaining that, "As expected, molecular size has an inverse relationship with penetration into the nail plate." Ex. 1008 ¶ 102 (citing Ex. 1028, "Murdan"); *see also* Ex. 1044 ¶ 68 (citing Ex. 1065, "Mertin", 3) ("There was a linear relationship with a negative slope between the permeability coefficient and the molecular weight for both the nail plate (generally lower P-values) and the hoof membrane."). Dr. Murthy's testimony is consistent with the specification of the provisional application to which the '621 patent claims priority, where the inventors state that "[c]ompounds with a molecular weight of less than 200 Da penetrate the nail plate in a manner superior to the commercially available treatment for onychomycosis." Ex. 1064 ¶ 6. Accordingly, we determine that a person of ordinary skill in the art would have had a reasonable expectation that administering tavaborole topically would penetrate the nail.

Patent Owner also asserts that concerns about tavaborole's toxicity preclude a reasonable expectation of success. PO Resp. 50–52. In light of the alleged "conventional wisdom" regarding boron's toxicity and without any evidence regarding tavaborole's safety in humans, Patent Owner contends that a person of ordinary skill in the art would have had no reasonable basis to believe tavaborole could be used as a pharmaceutical

formulation. *Id.* at 51. According to Patent Owner, this is particularly true where Austin teaches that tavaborole has a wider spectrum of activity against multiple organisms such as bacteria and algae in addition to fungi. *Id.* (citing Ex. 2034 ¶¶ 119, 124–125); *see also id.* at 7.

Although the parties have presented ample arguments and evidence conveying contrary opinions regarding the inherent toxicity of boron-containing compounds (Pet. 15–21; PO Resp. 7–15; Pet. Reply. 3–10), we find the weight of the evidence favors Petitioner. For example, we are persuaded by the 2001 review article by Groziak stating "boron-based agents [are] clearly visible on the therapeutic horizon," thereby suggesting such compounds are not inherently toxic. Ex. 1027,[7] Abstract. Groziak also states that "[b]oronic acids are fairly common and easily prepared synthetic organic compounds" and that no commercially available boronic acid has been found to be "unusually toxic" to date. *Id.* at 322. Patent Owner criticizes Petitioner for failing to report that Groziak also states that "one of the reasons boron has not been used is because it often forms complexes that are 'highly toxic to both bacteria and mammalian cells.'" PO Resp. 15 (citing Ex. 1027, Abstract, 321). But we disagree with Patent Owner's characterization of Groziak. Read in its entirety, Groziak states that one reason boron has been underutilized in therapeutic agents is because "very few boron-containing natural products are available to serve as an intellectual spark for medicinal chemists in their drug-design efforts, and to make matters worse, these turn out to be rather poor models." Ex. 1027, 321. The reason those boron-containing natural products are poor models is

[7] Michael P. Groziak, *Boron Therapeutics on the Horizon*, 8 AM. J. THERAPEUTICS 321–28 (2001) (Ex. 1027).

because they form complexes that are highly toxic to bacteria and mammalian cells. *Id.* Thus, Groziak does not state that all boron-containing compounds are highly toxic, as Patent Owner asserts; Groziak simply explains why it has been difficult for medicinal chemists to design drugs using natural boron-containing products as a model.

Moreover, we are persuaded by Dr. Kahl's testimony that many of the references cited by Patent Owner and Dr. Reider as demonstrating the toxicity of boron-containing compounds can be discounted because they (1) rely on discredited statements regarding toxicity in a 1984 article by Grassberger[8] (Ex. 2008), (2) are outdated papers that have been refuted by more recent research, or (3) relate to administering boron-containing compounds orally or intravenously, as opposed to topically, as indicated in Brehove. Ex. 1043 ¶¶ 12–26. We also note the inventors of the '621 patent published a review article in 2009 ("Baker"), citing mostly pre-2005 prior art, in which they concluded that "boron is not an inherently toxic element." Ex. 1056,[9] 1; Ex. 1043 ¶¶ 27–30. And, like Dr. Kahl, the inventors discredited Grassberger's assertions regarding boron toxicity:

> Grassberger *et al.* cautioned against the potential toxicity associated with this class and openly speculated that boron could be involved. However, no toxicity data were published and no proof (or testable hypothesis) that boron was the origin of toxicity was offered. A retrospective on Grassberger's work then misinterpreted these comments as proof that boron can not

[8] Grassberger et al., *Preparation and Antibacterial Activities of New 1,2,3-Diazaborine Derivatives and Analogues*, 27 J. Med. Chem. 947–953 (1984) (Ex. 2008).
[9] Baker et al., *Therapeutic Potential of Boron-Containing Compounds*, 1 FUTURE MED. CHEM. 1275–88 (2009) (Ex. 1056).

> be used clinically because of the "inherent toxicity of boron-containing compounds."

Ex. 1056, 3.

Moreover, boron's allegedly "promiscuous" behavior does not dissuade a person of ordinary skill in the art from considering boron-containing compounds generally, or tavaborole in particular. Onychomycosis has multiple causes, such as dermatophytes, yeast, and molds. Ex. 2035 ¶ 22. As such, we credit the testimony of Dr. Murthy that broad-spectrum activity would be preferred over limited-spectrum antifungals to treat the various potential causes of onychomycosis. Ex. 1044 ¶ 47 (citing Ex. 2070, 422 ("Griseofulvin['s] . . . effectiveness in onychomycosis proved a disappointment since its spectrum of activity is limited to dermatophytes only . . . .")).

Taken together, we determine that a person of ordinary skill in the art in 2005 would have understood that boron-containing compounds generally were not considered inherently toxic such that they would be excluded from consideration from topical therapeutic purposes.

Finally, Patent Owner argues that Freeman undermines Petitioner's argument that boron-containing compounds with similar structure share similar functional features. PO Resp. 53–54. According to Patent Owner, Freeman teaches that phenylboronic acids (PBAs) are ineffective at inhibiting microorganisms because the disclosed MICs of 3–10 mg/ml are thousands of times higher than the maximum acceptable concentrations for potential pharmaceutical products. PO Resp. 53 (citing Ex. 2035 ¶¶ 127–131). Thus, Patent Owner argues that, under Petitioner's theory of functional similarity, a person of ordinary skill in the art would have reasonably expected the dioxaborinanes to be ineffective for pharmaceutical

purposes. *Id.* at 53–54. To the extent we understand Patent Owner's argument, we are not persuaded. Brehove teaches that dioxaborinanes are effective in inhibiting *C. albicans* and treating onychomycosis. Ex. 1003 ¶¶ 33–38. And, as explained above, for an obviousness analysis, prior art may be relied on for all that it reasonably would have suggested to one of ordinary skill in the art. *Merck*, 874 F.2d at 807. Moreover, Petitioner's theory is not based on structural similarities alone. Petitioner's theory is based on the combination of structural similarity and functional similarity (i.e., both are active against *C. albicans*). Thus, we are not persuaded by Patent Owner's argument.

Accordingly, having considered the full trial record, we determine that the combination of Austin and Brehove teaches each limitation of independent claims 1, 11, and 12, and that a person of ordinary skill in the art would have had a reason to combine Austin and Brehove with a reasonable expectation of success.

c. Dependent Claims

For the reasons stated in the Petition and by Dr. Murthy, we are persuaded that the combination of Austin and Brehove teaches or suggests each limitation of dependent claims 2–10. *See* Pet. 39–42; Ex. 1008 ¶¶ 107–117. For the same reasons stated above, we determine that a person of ordinary skill in the art would have had a reason to combine Austin and Brehove with a reasonable expectation of success. In response, Patent Owner argues that, at a minimum, Petitioner has a complete failure of proof as to dependent claim 4, which is limited to treating onychomycosis, and dependent claim 6, which is further limited to treating tinea unguium (i.e., onychomycosis caused by a dermatophyte). PO Resp. 64. As explained above, however, we determine that Brehove teaches treating onychomycosis.

Thus, we reject Patent Owner's argument as to dependent claim 4. The question remains, however, whether the combination of Brehove and Austin teaches or suggests treating onychomycosis caused by a dermatophyte, as required by dependent claim 6. We determine that it does.

It is undisputed that neither Austin nor Brehove expressly teaches whether the disclosed compounds exhibit any activity against dermatophytes. The parties dispute centers on whether a person of ordinary skill in the art would have understood that the combination of Austin and Brehove teaches or suggests administering tavaborole to treat onychomycosis caused by a dermatophyte with a reasonable expectation of success.

Petitioner asserts that because both references disclose the inhibition of *C. albicans* by boron heterocycles, a person of ordinary skill in the art would have expected that tavaborole, which shares functional activity with the compounds of Brehove, would have shared other activities as well, "such as the inhibition of additional fungi responsible for onychomycosis." Pet. 35 (citing Ex. 1008 ¶ 101). Brehove discloses that onychomycosis is typically caused by *C. albicans* and *T. rubrum*, among others. Ex. 1003 ¶ 5. Brehove also teaches the effective treatment of patients suffering from onychomycosis. *Id.* ¶¶ 34–38. Thus, Dr. Murthy contends that the in vitro testing together with the effective treatment of onychomycosis would have led a person of ordinary skill in the art to reasonably assume that the boron-containing compounds were effective against both *C. albicans* and dermatophytes. Ex. 1044 ¶ 53. Patent Owner responds that a person of ordinary skill in the art could not have predicted activity against dermatophytes based on activity against a yeast such as *C. albicans*. PO Resp. 44 (citing Ex. 2035 ¶ 123).

We determine that the weight of the evidence favors Petitioner's argument. For example, a 1996 paper by Segal[10] shows that terbinafine, which is highly potent against dermatophytes, is also active (albeit less so) against *C. albicans*. Ex. 2050, 960. Patent Owner's declarant Dr. Ghannoum cites Nimura[11] to show that a person of ordinary skill in the art would have known that ketoconazole has potent antifungal activity against *C. albicans* but has poor activity against dermatophytes. Ex. 2035 ¶ 64. But, as confirmed by Dr. Murthy and Dr. Ghannoum, Nimura also teaches that amorolfine "exhibited potent antifungal activity against all fungal species tested," which included both *C. albicans* and *T. rubrum*. Ex. 2105, 175; *see also* Ex. 1044 ¶ 91; Ex. 1046, 101:5–14. Moreover, although it does not expressly identify *C. albicans* as the yeast tested, Mertin[12] teaches that "[d]ermatophytes are usually more sensitive towards antimycotics than yeasts." Ex. 1065, 6.

We note that conclusive proof of efficacy is not required to show obviousness. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."). As such, in light of the evidence of record, we determine that a

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[10] Segal et al., *Treatment of Candida Nail Infection with Terbinafine*, 35 J. AM. ACAD. DERMATOL. 958–61 (1996) (Ex. 2050).
[11] Nimura et al., *Comparison of In Vitro Antifungal Activities of Topical Antimycotics Launched in 1990s in Japan*, 18 Intl. J. Antimicrobial Agents 173–78 (2001) (Ex. 2105).
[12] Mertin & Lippold, *In-vitro Permeability of the Human Nail and of a Keratin Membrane from Bovine Hooves: Prediction of the Penetration Rate of Antimycotics Through the Nail Plate and Their Efficacy,* 49 J. Pharm. Pharmacol. 866–72 (1997) (Ex. 1065).

person of ordinary skill in the art would have had a reasonable expectation that a compound with activity against *C. albicans* would also have activity against dermatophytes, particularly given the teaching that dermatophytes are usually more sensitive to antimycotics than yeast.

Thus, having considered the full trial record, we determine that the combination of Austin and Brehove teaches each limitation of claims 2–10 and that a person of ordinary skill in the art would have had a reason to combine Austin and Brehove with a reasonable expectation of success.

d. Secondary Considerations of Nonobviousness

Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham*, 383 U.S. at 17–18. The totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the challenged claims would not have been obvious to one of ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984).

Patent Owner argues that the nonobviousness of the claims is supported by objective evidence of unexpected results, the satisfaction of a long-felt need, and industry praise. PO Resp. 60–64. As explained further below, we are not persuaded by Patent Owner's argument and evidence.

i. Unexpected Results

Patent Owner argues that a person of ordinary skill in the art would not have had any basis for an expectation of success, thereby making the success of tavaborole unexpected. Patent Owner asserts that the selective toxicity of tavaborole—i.e., its ability to kill the fungus but not be toxic to the human host—is over 1000-fold. PO Resp. 60 (citing Ex. 2035 ¶ 139). Dr. Ghannoum testifies that this is remarkable given the similarities between

fungal and human cells and the expectation in the art that the oxaboroles of Austin would be toxic. Ex. 2035 ¶ 139.

We are not persuaded that Patent Owner has demonstrated that the selective toxicity of tavaborole was an unexpected result. In particular, based on Patent Owner's argument and Dr. Ghannoum's testimony, we are unable to ascertain that the results are unexpected. Specifically, Dr. Ghannoum testifies that a person of ordinary skill in the art would have understood that a new compound identified as a potential antifungal would have been expected to be toxic to host cells, unless proven otherwise. Ex. 2035 ¶ 139. Dr. Ghannoum, however, does not direct our attention to any credible evidence to support this proposition. For example, although Dr. Ghannoum cites Alley[13] (Ex. 2113) for its teaching of tavaborole selectivity, Alley does not mention this particular selectivity as surprising or unexpected but, at best, mentions that specific fungal inhibitors are "less common." Ex. 2113, 163 ("Although eukaryotic protein synthesis inhibitors are common . . ., specific fungal inhibitors are less common because of the similarity between the fungal and human enzymes involved in protein synthesis.").

Further, Dr. Ghannoum does not provide a sufficient explanation as to how this selectivity represents an alleged unexpected result in light of the closest prior art of record. That is, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever United States, Inc*., 441 F.3d 963, 970 (Fed. Cir. 2006) (*quoting In re Baxter Travenol*

[13] Alley et al., *Recent Progress on the Topical Therapy of Onychomycosis*, 16 EXPERT OPIN. INVESTIG. DRUGS 157–67 (2007) (Ex. 2113).

Labs., 952 F.2d 388, 392 (Fed. Cir. 1991)). Here, Patent Owner has not identified the closest prior art and has therefore not explained sufficiently why the 1000-fold selective toxicity was unexpected as compared to the closest prior art or the statistical and practical significance of the selectivity. Accordingly, we are not persuaded that Patent Owner's evidence of unexpected results supports the nonobviousness of the challenged claims or overcomes the evidence of obviousness presented by Petitioner.

ii. Long-Felt Need

"Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016). "[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem which were, before the invention, unsuccessful." *Tex. Instruments v. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). In particular, the evidence must show that the need was a persistent one that was recognized by those of ordinary skill in the art. *In re Gershon*, 372 F.2d 535, 539 (CCPA 1967).

Patent Owner argues that there has been a long-felt need for a safe and effective topical treatment for onychomycosis, particularly in light of the serious side effects of oral formulations. PO Resp. 61–62 (citing Ex. 2037 ¶¶ 37–47). According to Patent Owner, Penlac (ciclopirox) was the only topical treatment for onychomycosis that had been approved by the FDA as of 2005, but it was barely more effective than the placebo. *Id.* at 62 (citing Ex. 2037 ¶ 52–57). Patent Owner also contends that Loceryl was available abroad, but was insufficiently effective to gain approval in the United States and exhibited poor transungual penetration. *Id.* at 63 (citing Ex. 2037 ¶¶ 52,

58). Finally, Patent Owner asserts that many other attempts to develop topical onychomycosis treatments by other pharmaceutical companies had failed. *Id.* (citing Ex. 2037 ¶¶ 69–77).

Although Patent Owner contends Kerydin met the long-felt need for a safe and effective topical treatment for onychomycosis, Patent Owner does not provide persuasive evidence to support its contention. In particular, what is missing from Patent Owner's analysis is sufficient and credible evidence to show Kerydin is more effective than, for example, Penlac. Patent Owner criticizes Penlac for being barely more effective than the placebo, but does not say how much more effective Kerydin is. Without that evidence, we cannot ascertain whether Kerydin satisfied that long-felt but unmet need. Indeed, Petitioner notes that a 2016 article by Rosen suggests that Kerydin (tavaborole) has similar efficacy to Penlac (ciclopirox):

TABLE 3. Topical Antifungals: Efficacy in Phase III Pivotal Trials

Medication	Complete Cure Rates*
Ciclopirox 8%[12]	5.5% and 8.5%
Efinaconazole 10%[15]	15% and 18%
Tavaborole 10%[16]	7% and 9%

Regimens: All of these medications are approved for daily application for 48 weeks.

*Results of two phase III trials, respectively.

Ex. 2062,[14] 6. We recognize that the studies reported in Table 3 were not conducted using standardized protocols and that the authors stated "each

[14] Rosen et al., *Antifungal Drugs for Onychomycosis: Efficacy, Safety, and Mechanisms of Action*, 35 Seminars in Cutaneous Medicine and Surgery S51–S55 (2016) (Ex. 2062). We cite the page numbers provided by Patent Owner pursuant to 37 C.F.R. § 42.63(d)(2)(i).

medication must be considered on its own merits in determining which topical agent to choose for an individual patient." *Id.* But even with that limitation, when asked about the Table 3 data during oral argument, Patent Owner did not address the similarity of the cure rates between Kerydin (tavaborole) and Penlac (ciclopirox), or point us to any contrary data indicating that the efficacy of Kerydin was superior to Penlac. Tr. 44:11–45:6. Thus, it remains unclear to us whether Kerydin satisfied a long-felt but unmet need of providing a more effective topical treatment for onychomycosis.I love

Accordingly, we are not persuaded that Patent Owner's evidence of the satisfaction of a long-felt need supports the nonobviousness of the challenged claims or overcomes the evidence of obviousness presented by Petitioner.

iii. Industry Praise

Industry praise for an invention may provide evidence of non-obviousness where the industry praise is linked to the claimed invention. *See Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010); *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

Patent Owner asserts that KERYDIN has received industry praise directly related to the administration of tavaborole, as claimed in the '621 patent. PO Resp. 63–64. Patent Owner identifies several examples:

- A 2015 article stating, "[tavaborole] offers an important alternative to [previously] available topical antifungal therapies." (Ex. 2060 at 6189.) The article praised tavaborole's efficacy and "excellent safety profile," and described the emergence of tavaborole as "exciting." (*Id*. at 6188-89.)
- A 2016 article praising tavaborole's nail penetration for being "40-fold greater than that of ciclopirox after 14 days of

treatment." (Ex. 2061 at 27; Ex. 2037 (Maibach) ¶ 85; *see also* Ex. 2063 at 9 (touting tavaborole's improved nail penetration compared to ciclopirox).

- A 2016 article reported that the introduction of tavaborole, along with topical efinoconazole, "expanded the roster of medications available to more effectively manage onychomycosis in a wide range of patients, including those for whom comorbid conditions, concomitant medications, or patient preference limited the use of systemic antifungals." (Ex. 2062 at S53.)

PO Resp. 63–64; *see also* Ex. 2037 ¶¶ 81–88 (Dr. Maibach's testimony identifying and describing similar articles).

We are not persuaded that the evidence presented demonstrates industry praise for the invention, as opposed to praise for another alternative therapy for topical treatment of onychomycosis. The statements cited by Patent Owner that tavaborole offers "an important alternative" (Ex. 2060, 6189) and "expand[s] the roster of medications available" (Ex. 2062, 6) do not persuade us that the industry praised the claimed invention. Moreover, the statement praising tavaborole's improved nail penetration says little about whether tavaborole is more effective than ciclopirox. Indeed, as explained above, from the limited data we have on record, it appears the efficacy of the two drugs is similar.

Accordingly, we are not persuaded that Patent Owner's evidence of industry praise supports the nonobviousness of the challenged claims or overcomes the evidence of obviousness presented by Petitioner.

4. Conclusion as to Obviousness

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re Eli Lilly & Co.*, 902 F.2d 943, 945 (Fed. Cir. 1990) ("After a prima facie case of obviousness has been made and rebuttal evidence submitted, all the

evidence must be considered anew."). In doing so, we conclude that Petitioner has shown by a preponderance of the evidence that claims 1–12 are unpatentable as obvious over Austin and Brehove.

F. 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. PO Resp. 54–60. Having considered the full trial record, we determine that Petitioner has established by a preponderance of the evidence that 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 phenylboronic acid (PBA) and related boronic acid compounds that are used for treating fungal infections such as onychomycosis. Ex. 1004, Abstract, ¶ 1. Freeman identifies *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, PBAs "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 PBA. *Id.* ¶¶ 31–34. In particular, Freeman notes that PBA exhibited fungicidal effect on *T. rubrum* within a concentration range of 5-10 mg/ml. *Id.* ¶ 34. Freeman also notes that the compounds tested had a fungicidal effect on *Candida parapsilosis* at 10 mg/ml. *Id.*

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. Patent Owner again argues that Petitioner's assertions must fail because (1) Austin is not analogous art, (2) a person of ordinary skill in the art would have been concerned about the toxicity of boron-containing compounds, and (3) Austin provides no basis to choose tavaborole to treat fungal infections. PO Resp. 54–55. For the same reasons stated above, we are not persuaded by Patent Owner's arguments.

a. Independent Claims 1, 11, and 12

We are persuaded that the combination of Austin and Freeman teaches each limitation of independent claims 1, 11, and 12, for the reasons stated by Petitioner and Dr. Murthy. Pet. 51–52, 55–56. Patent Owner contends that the combination of Austin and Freeman does not disclose "administering to the animal [or human] a therapeutically effective amount of [tavaborole]." PO Resp. 55. We do not find Patent Owner's argument persuasive, as Freeman teaches that the present invention relates to methods for treating fungal infections such as onychomycosis. *See* Ex. 1004 ¶¶ 1, 22 ("It has now been discovered that phenyl boronic acid and derivatives thereof as well as related boronic acid compounds have fungicidal properties, and that these compounds are particularly useful in treating fungal infections [and] particularly useful in treating nail fungal infections.").

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).

For similar reasons stated above with respect to the challenge over Austin and Brehove, we determine that the weight of the evidence supports Petitioner's argument that a person of ordinary skill in the art would have combined Austin and Freeman to achieve the claimed invention with a reasonable expectation of success. Patent Owner asserts that a person of ordinary skill in the art would not combine Austin and Freeman with a reasonable expectation of success given the structural differences between tavaborole and PBAs. PO Resp. 55–56. Although we agree there are structural differences, as above, we are persuaded that a person of ordinary skill in the art would have had a reason to combine the references in light of the structural similarities (i.e., both are boron heterocycles) *and* the similar functional activity against *Candida* species. Pet. 46.

Patent Owner again argues that a person of ordinary skill in the art would have expected tavaborole to be toxic given reports of clinical studies showing para-fluoro PBA is highly toxic to mice. PO Resp. 57 (citing Ex. 2052, 311). For the same reasons stated above, we are not persuaded. And as noted by Petitioner, the studies in mice are directed to boron neutron capture therapy for cancer, which one would expect to be toxic. Pet. 23; Ex. 1043 ¶¶ 14–17. Moreover, the studies injected the compound

intraperitoneally into the mice, rather than topically. *See* Ex. 2052, 311 (stating the compound was "injected intraperitoneally"). Even Freeman recognizes that PBA "is considered harmful if swallowed," but still teaches administering the compound topically to treat fungal infections. Ex. 1004 ¶¶ 28–29. Thus, we are not persuaded that a person of ordinary skill in the art would have been dissuaded from combining Austin and Freeman because of toxicity concerns over PBAs.

Patent Owner also argues that Freeman reports fungicidal activity of PBAs at concentrations much higher than a person of ordinary skill in the art would have considered to be the upper concentration limits for potential pharmaceuticals. PO Resp. 57—58 (citing Ex. 2035 ¶¶ 127–31). Patent Owner further notes that Dr. Murthy admitted that Freeman teaches poor antifungal effectiveness for its PBAs. *Id.* at 58 (citing Ex. 2032, 594:9–595:4). To start, we disagree with Patent Owner's characterization of Dr. Murthy's testimony. The cited testimony did not specifically address Freeman. Rather, the line of questioning appears to begin with Patent Owner's hypothetical question, "How high is too high?" Ex. 2032, 592:18. Dr. Murthy answered, with the caveat that it depends on the molecular size. *Id.* at 592:23–24. Moreover, Dr. Murthy explained that a person of ordinary skill in the art would expect compounds with similar structure to exhibit a similar spectrum of activity against fungi, but not necessarily at the same concentration. *Id.* at 210:25–211:8.

We are persuaded that a person of ordinary skill in the art would have had a reason to modify Freeman to administer Austin's tavaborole instead of PBA in light of the similar chemical structure and the similar activity against *Candida* species. Patent Owner argues that a person of ordinary skill in the art would have known that *C. parapsilosis* is not a cause of onychomycosis

and is a contaminant normally found on the hands. Ex. 2035 ¶ 31. We note, however, that the '621 patent specification identifies *C. parapsilosis* as a target microorganism of the invention. Ex. 1001, 25:37. Moreover, at oral argument, when asked whether a person of ordinary skill in the art would have expected that a drug that is active against one species of *Candida* would not be active against another species of *Candida*, Patent Owner directed us to Dr. Ghannoum's declaration testifying that an ordinary artisan could not have predicted the activity of a compound against *dermatophytes* based on activity of a different fungal organism, such as a yeast. Tr. 31:14–32:5 (citing Ex. 2035 ¶ 64). That testimony does not answer the question of whether a person of ordinary skill in the art would have expected a compound that is active against one species of *Candida* to be active against another species of *Candida*. Thus, we are not persuaded by Dr. Ghannoum's testimony.

Accordingly, having considered the full trial record, we determine that the combination of Austin and Freeman teaches each limitation of independent claims 1, 11, and 12, and 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.

b. Dependent Claims

For the reasons stated in the Petition and by Dr. Murthy, we are persuaded that the combination of Austin and Freeman teaches or suggests each limitation of dependent claims 2–10. *See* Pet. 52–55; Ex. 1008 ¶¶ 138–146. Patent Owner does not separately address the dependent claims with respect to this ground. Accordingly, for the same reasons stated above, we also determine 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.

c. Conclusion as to Obviousness

Patent Owner makes no other specific arguments with respect to any other claims and the combination of Austin and Freeman. Accordingly, having considered the record as a whole—including the evidence of secondary considerations of nonobviousness, as explained above—we conclude that Petitioner has established by a preponderance of the evidence that claims 1–12 are unpatentable as obvious over Austin and Freeman.

III. PATENT OWNER'S MOTION TO EXCLUDE

The party moving to exclude evidence bears the burden of proving that it is entitled to the relief requested—namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

Patent Owner filed a Motion to Exclude Exhibits 1024, 1025, 1031, 1032, 1051, 1067, 1068, 1069, 1071, 1074, and 1075. Paper 57. We do not rely on any of the challenged exhibits in rendering this Decision. Accordingly, we dismiss Patent Owner's Motion to Exclude as moot.

IV. CONCLUSION

We conclude that Petitioner has shown by a preponderance of the evidence that claims 1–12 of the '621 patent are unpatentable.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–12 of the '621 patent are held unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude is *dismissed as moot*.

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2015-01776
Patent 7,582,621 B2

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(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**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 267 days.

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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.

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(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

CFAD Exhibit 1001

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

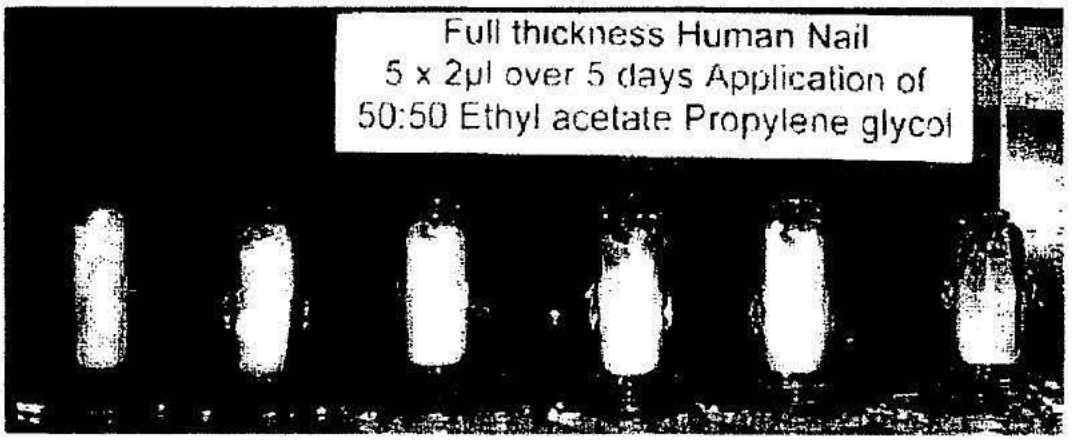

Full thickness Human Nail
5 x 2µl over 5 days Application of
50:50 Ethyl acetate Propylene glycol

FIGURE 6

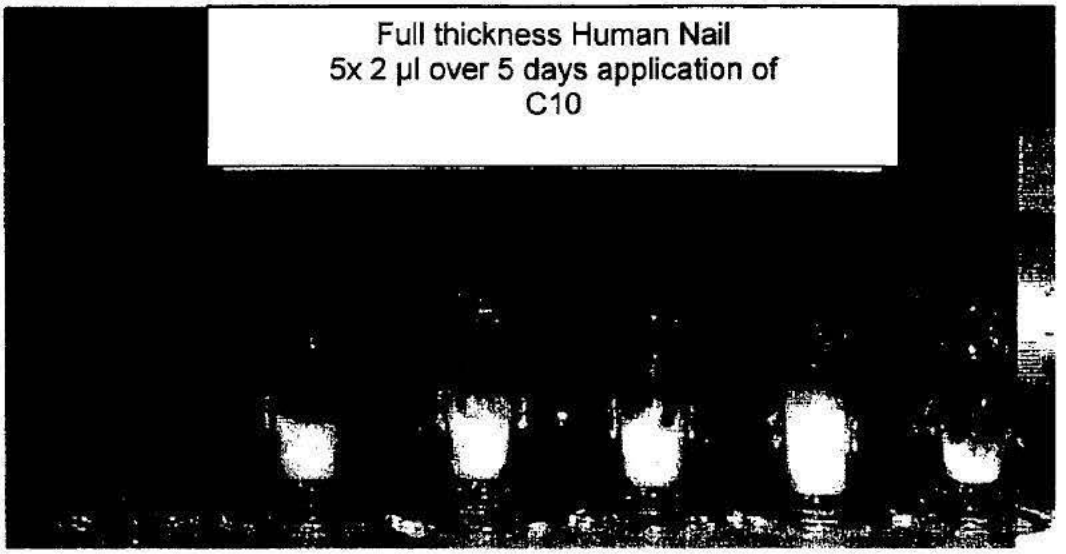

Full thickness Human Nail
5x 2 µl over 5 days application of
C10

FIGURE 7

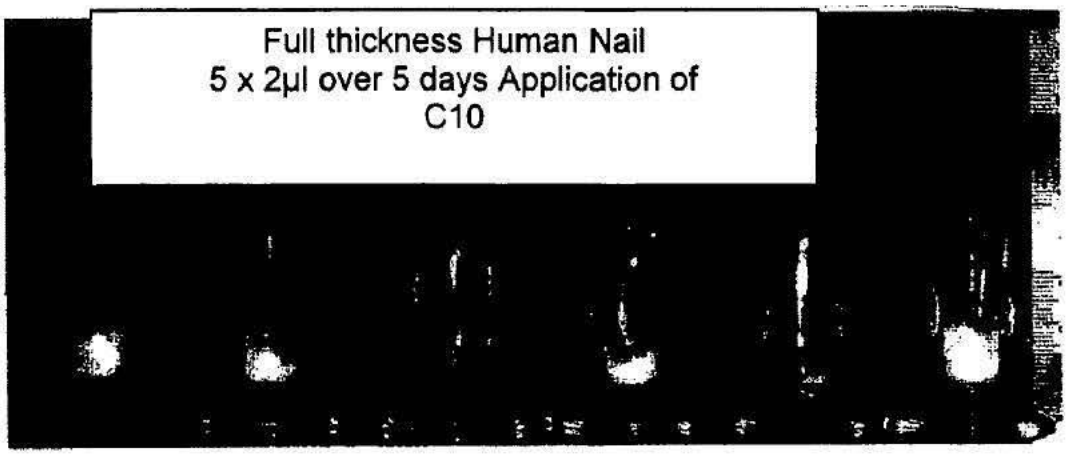

Full thickness Human Nail
5 x 2µl over 5 days Application of
C10

FIGURE 8

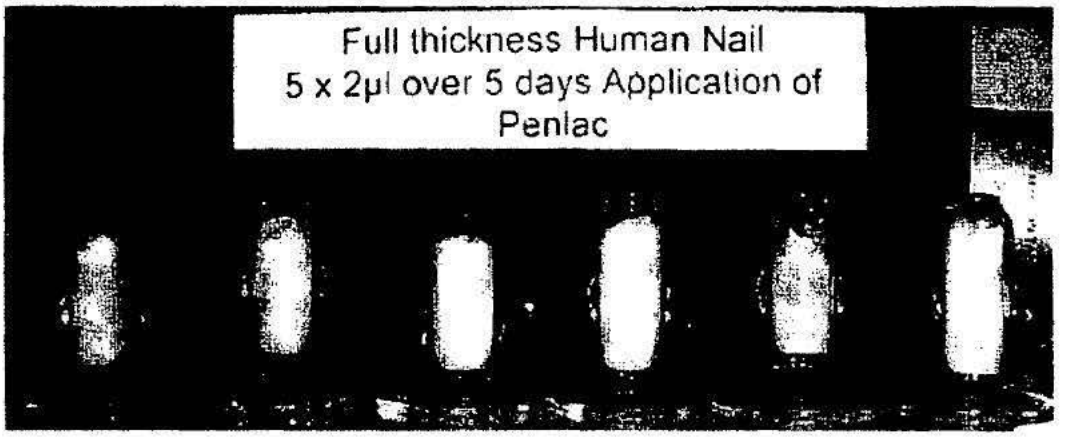
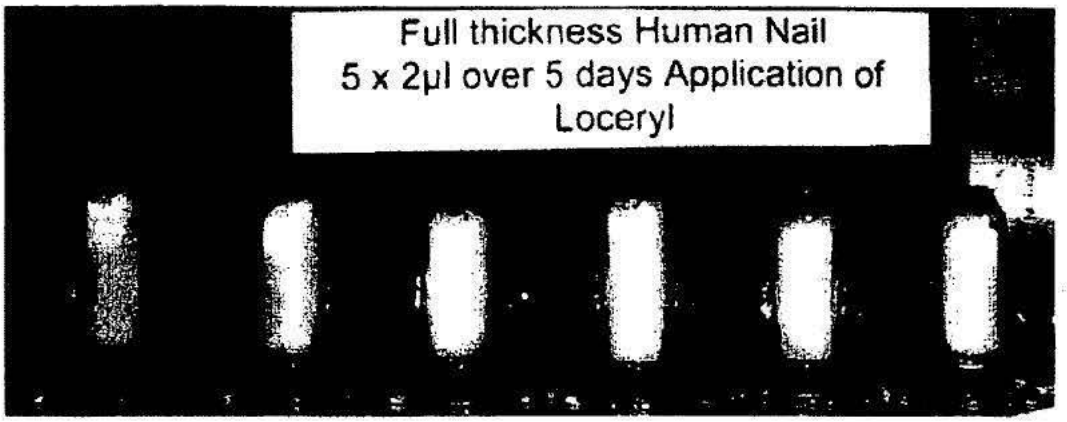

Full thickness Human Nail
5 x 2µl over 5 days Application of
Penlac

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.

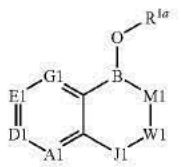
Antimicrobial compositions for controlling bacterial and fungal infections comprising a metal chelate of 8-hydroxyquinoline and an alkyl benzene sulfonic acid have been shown to be efficacious due to the increased ability of the oleophilic group to penetrate the lipoid layers of micro-cells. The compounds 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)

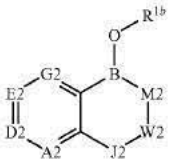


wherein B is boron. R^{1a} is a member selected from a negative charge, a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted 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. **2**A displays minimum inhibitory concentration (MIC) for C10, ciclopirox, terbinafine, fluconazole and itraconazole (comparator drugs) against 19 test strains of fungi.

FIG. **2**B 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 —$C(O)_2$R'— represents both —$C(O)_2$R'— 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"$C(O)_2$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).

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"$C(O)_2$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.

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.

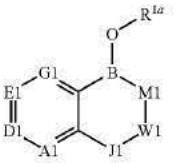
II. Introduction

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)

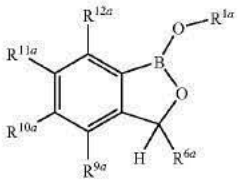


wherein B is boron. R^{1a} is a member selected from a negative charge, a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted 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):

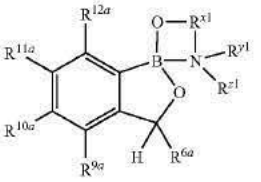
(Ia)



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)

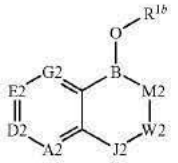


wherein B is boron. R^{x1} is a member selected from substituted or unsubstituted C_1-C_5 alkyl, substituted or unsubstituted C_1-C_5 heteroalkyl. R^{y1} and R^{z1} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or 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)

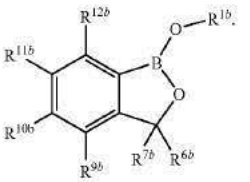


wherein B is boron. R^{1b} is a member selected from a negative charge, a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted 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 $(CR^{6b}R^{7b})_{n2}$, 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.

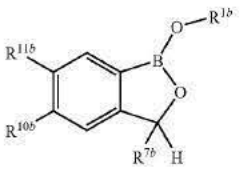
In an exemplary embodiment, the compound with a structure according to Formula (IIa):

(IIa)



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

(IIb)

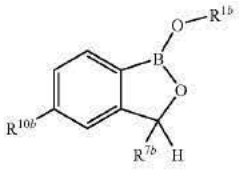


wherein R^{7b} is a member selected from H, methyl, ethyl and phenyl. R^{10b} is a member selected from H, OH, NH_2, SH, halogen, substituted or unsubstituted phenoxy, substituted or unsubstituted phenylalkyloxy, substituted or unsubstituted phenylthio and substituted or unsubstituted phenylalkylthio. 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.

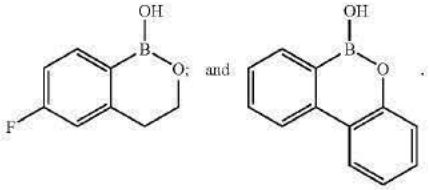
In another exemplary embodiment, R^{1b} is a member selected from a negative charge, H and a salt counterion. In another exemplary embodiment, R^{10b} and R^{11b} are H. In another exemplary embodiment, one member selected from R^{10b} and R^{11b} is H and the other member selected from R^{10b} and R^{11b} 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)

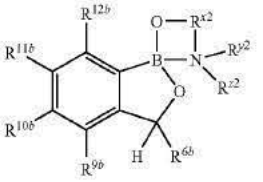


wherein R^{10b} is a member selected from H, halogen, CN and substituted or unsubstituted C_{1-4} alkyl. In another exemplary embodiment, the compound has a formulation which is a member selected from:



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.

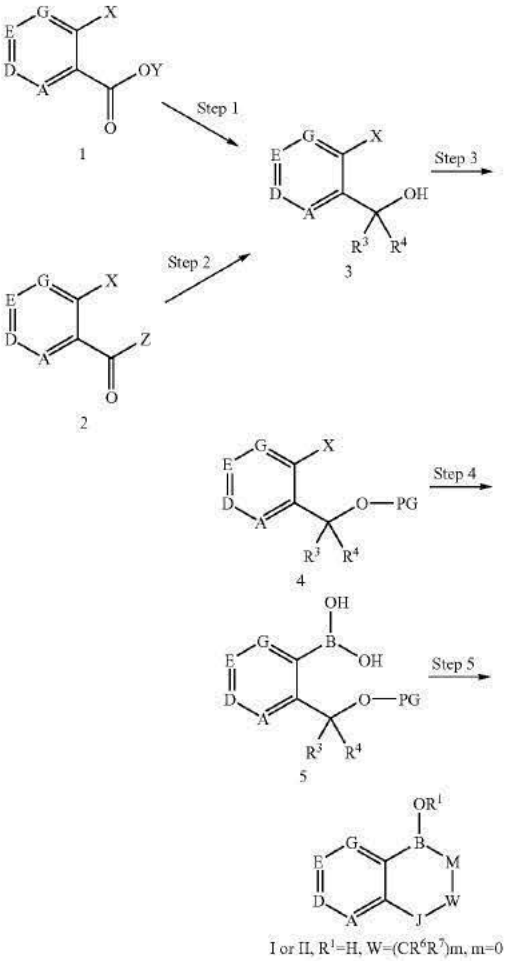
In Step 3, the hydroxyl group of compound 3 is protected with a protecting group which is stable under neutral or basic conditions. The protecting group is typically selected from methoxymethyl, ethoxyethyl, tetrahydropyran-2-yl, trimethylsilyl, tert-butyldimethylsilyl, tributylsilyl, combinations thereof 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

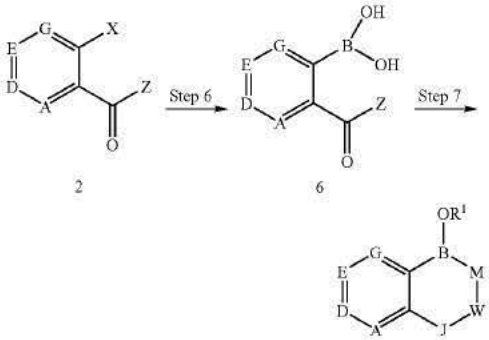
In Scheme 2, Step 6, compound 2 is converted into boronic acid (6) via a transition metal catalyzed cross-coupling reaction. Compound 2 is treated with 1 to 3 equivalents of bis (pinacolato)diboron or 4,4,5,5-tetramethyl-1,3,2-dioxaborolane in the presence of transition metal catalyst, with the use of 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.

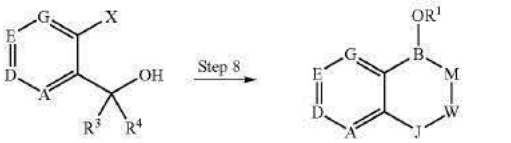
Scheme 2



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



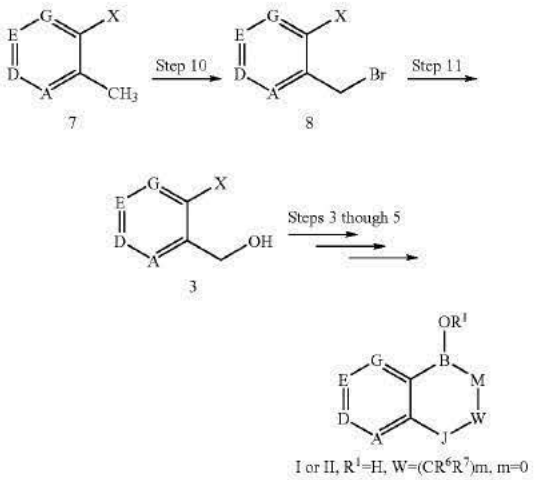
Preparation Strategy #4

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).

Scheme 4

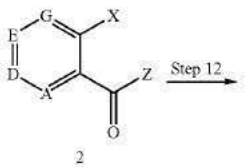


Preparation Strategy #5

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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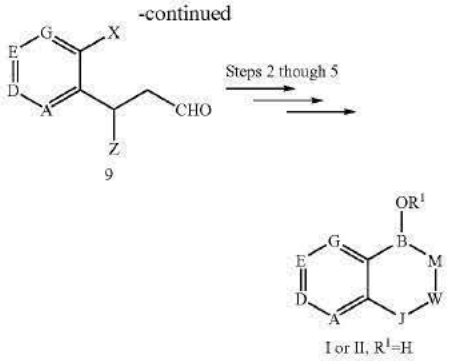
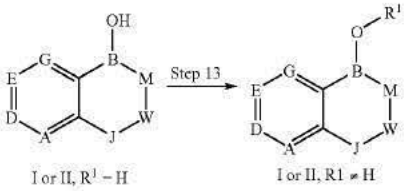


Preparation Strategy #6

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.

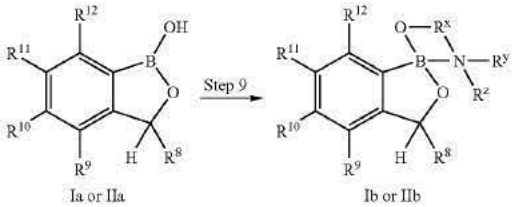
Scheme 6



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, *Phyconycetes* 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*), *Microsporun audouinii* (*M. audouinii*), *Microsporum canis* (*M. canis*), *Microsporum gypseum* (*M. gypseum*), *Paracoccidiodes brasiliensis* and *Phyconycetes* 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; Treponema 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, neuroderma-tropic 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
	Pneunovirus - 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 lymphocytetic choriomeningitis
Reoviridae	Retovirus
	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

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.

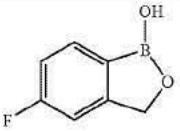
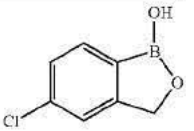
In an exemplary embodiment, the present invention provides compounds with a molecular weight selected from a range above, with a water solubility selected from a range above, that are still able to penetrate the nail plate.

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.

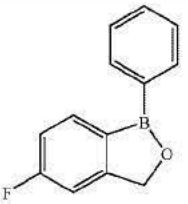
In an exemplary embodiment, the present invention provides compounds with a molecular weight selected from a range above, with a log P selected from a range above, and with a water solubility selected from a range above, that are still able to penetrate the nail plate.

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.

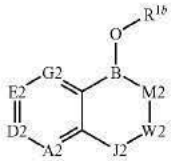
The methods provided in this aspect of the invention are useful in the penetration of nails and hoofs, as well as the treatment of ungual and periungual conditions.

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)



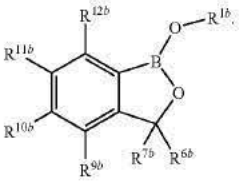
wherein B is boron. R^{1b} is a member selected from a negative charge, a salt counterion, H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted 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.

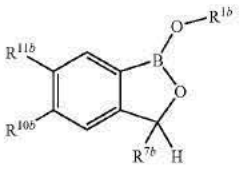
In an exemplary embodiment, the pharmaceutical formulation has a compound with a structure according to Formula (IIa):

(IIa)



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

(IIb)

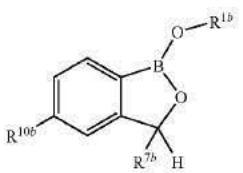


wherein R^{7b} is a member selected from H, methyl, ethyl and phenyl. R^{10b} is a member selected from H, OH, NH_2, SH, halogen, substituted or unsubstituted phenoxy, substituted or unsubstituted phenylalkyloxy, substituted or unsubstituted phenylthio and substituted or unsubstituted phenylalkylthio. 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.

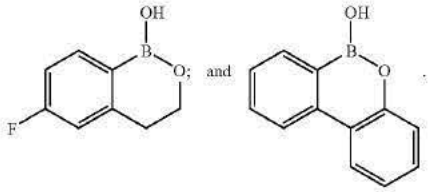
In another exemplary embodiment, R^{1b} is a member selected from a negative charge, H and a salt counterion. In another exemplary embodiment, R^{10b} and R^{11b} are H. In another exemplary embodiment, one member selected from R^{10b} and R^{11b} is H and the other member selected from R^{10b} and R^{11b} 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)

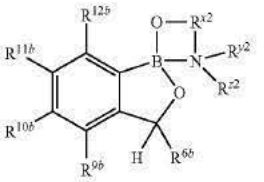


wherein R^{10b} is a member selected from H, halogen, CN and substituted or unsubstituted C_{1-4} alkyl. In another exemplary embodiment, the compound has a formulation which is a member selected from:



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

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 μL/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 μL/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

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that a copy of the foregoing Brief of Appellant-Patent Owner, including the Certificate of Interest and the Certificate of Compliance, was electronically filed on this 4th day of August 2017 with the Clerk of the U.S. Court of Appeals for the Federal Circuit using the CM/ECF system, which will serve via e-mail notice such filing on counsel registered as CM/ECF users.

/s/ Michael N. Kennedy
Michael N. Kennedy

Dated: August 4, 2017

CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitations of Fed. R. App. P. 32(a)(7)(B)(i) because this brief contains 11,380 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word using 14-point Times New Roman font.

/s/ Michael N. Kennedy
Michael N. Kennedy

Dated: August 4, 2017