From the Test Tube to the Treatment Room

Fundamentals of Boron-containing Compounds and their Relevance to Dermatology

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ABSTRACT

The development of new drug classes and novel molecules that are brought to the marketplace has been a formidable challenge, especially for dermatologic drugs. The relative absence of new classes of antimicrobial agents is also readily apparent. Several barriers account for slow drug development, including regulatory changes, added study requirements, commercial pressures to bring drugs to market quickly by developing new generations of established compounds, and the greater potential for failure and higher financial risk when researching new drug classes. In addition, the return on investment is usually much lower with dermatologic drugs as compared to the potential revenue from "blockbuster" drugs for cardiovascular or gastrointestinal disease, hypercholesterolemia, and mood disorders. Nevertheless, some researchers are investigating new therapeutic platforms, one of which is boron-containing compounds. Boron-containing compounds offer a wide variety of potential applications in dermatology due to their unique physical and chemical properties, with several in formal phases of development. Tavaborole, a benzoxaborole compound, has been submitted to the United States Food and Drug Administration for approval for treatment of onychomycosis. This article provides a thorough overview of the history of boron-based compounds in medicine, their scientific rationale, physiochemical and pharmacologic properties, and modes of actions including therapeutic targets. A section dedicated to boron-based compounds in development for treatment of various skin disorders is also included.
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The lifeline of any medical discipline is the continued development of diagnostic tools and treatment approaches that improve therapeutic outcomes and the quality of life of affected patients. In the field of dermatology, where profits from new drug development are substantially lower than in other medical areas (i.e., cardiovascular disease, gastrointestinal disease, mood disorders), this lifeline must be sustained through continued commitment to quality research within large pharmaceutical companies, emerging smaller companies, academic centers, and from others who have the capacity to contribute to advances in clinically relevant research. In drug development, it is important that newer approaches provide true advantages over existing therapies, such as greater

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efficacy, more favorable safety profiles, improved pharmacokinetic characteristics, shorter durations of therapy, and lower potential for relapse. With topical therapies, tolerability, ease of application, and subjective assessment of the physical characteristics of the vehicle are also very important factors.

Unfortunately, the development of new drug compounds in dermatology has been relatively stagnant, especially with topical therapies and systemic agents other than biologics.[1,2] Three major contributing factors are the increased number and types of studies required during drug development, required changes in study designs, and challenges in defining quantitative endpoints that translate to clinical relevance, especially in some areas of dermatology research.[1] Other factors are limited knowledge of pathophysiology with many skin diseases, risk-benefit ratio considerations with many common skin diseases, increased generic drug intrusion, and the potential for return on investment.[1]

NEW TOPICAL COMPOUNDS IN DERMATOLOGY

From 1995 through November 2013, among the 37 new topical dermatologic products approved by the United States (US) Food and Drug administration (FDA), less than one-third (11) comprised new active ingredients.[2] These included topical retinoids (adapalene, tazarotene), calcineurin inhibitors (pimecrolimus), antifungal agents (luliconazole, butenafine), agents for rosacea (azelaic acid, brimonidine), and one agent for actinic keratosis (ingenol mebutate). Only one was a topical antibiotic (retapamulin). The remainder of the products in the topical therapy market were predominantly new vehicle formulations, combination therapy products, topical devices (501K-approved products), and a few older systemic compounds that were submitted later for FDA approval as topical products (i.e., tacrolimus, dapsone, mechlorethamine).[2] In a nutshell, most of the new topical products in dermatology over the past several years have been established compounds in new formulations, combination products, topical device (501K) products, or structural analogs of already existing compounds that often provide little or no therapeutic benefit as compared to their predecessor. Nevertheless, it is important to state that some of these new products, despite the absence of a new and novel compound as the active ingredient, may offer some definite advantages as compared to other available products within the same therapeutic class.

New systemic compounds in dermatology. The release into the US marketplace of new FDA-approved systemic compounds administered orally or parenterally has been dominated by oncologic drugs (i.e., metastatic melanoma, basal cell carcinoma) and biologic agents used for psoriasis. Interestingly, many of the more recent major advances in systemic therapies introduced for dermatologic indications (primarily psoriasis) have been biologic agents administered by injection, and more are on the near-horizon. There has clearly been a conspicuous absence of newer oral therapy compounds in dermatology, with examples of more novel oral agents used commonly in dermatology being FDA approved 17 to 25+ years ago (i.e., acitretin [1997], cyclosporine [1995], acyclovir [1985], isotretinoin [1982]).[2–8] With the recent FDA recommendation that oral ketoconazole not be utilized for superficial cutaneous fungal infections due to safety concerns (hepatotoxicity), the armamentarium of oral antifungal agents used in dermatology has remained unchanged for more than two decades.[9,10] With regard to novel oral antibiotic development, only four new antibiotic classes have come to fruition since the early 1960s, most with limited impact.[3] In dermatology, other than penicillin derivatives, cephalosporins, and macrolides, the relative absence of new antibiotic compounds in the United States is exemplified by the fact that the more recent antibiotic classes that encompass agents that are sometimes used in dermatology in the United States are azalides (azithromycin [FDA approval 1991]), third-generation cephalosporins (cefdinir [FDA-approval 1997]), and, less commonly, quinolones (ciprofloxacin [FDA approval 1987]) and oxazolidinones (linezolid [FDA approval 2000]).[11]

Development of antimicrobial compounds. The limited development of new antimicrobial compounds has received widespread attention in the media and in publications within the medical, governmental, and lay public communities. This is especially due to the global emergence of multiresistant pathogens, especially bacteria, with increasing rates of antimicrobial resistance proving to be a very relevant clinical concern with both hospital-acquired and community-acquired infections.[3,11–14] Over time, fewer antibiotics are receiving FDA approval, with a conspicuous absence of new oral antibiotic classes or novel new-generation compounds available in dermatology. Within the more than $30 billion global antibiotic marketplace, most new antibiotics are based on structural modifications made to an antibiotic from a previous generation within the same antibiotic class (i.e., penicillin, cephalosporins, quinolones), an approach that is more expeditious and less complex than researching directions that require more time, effort, and financial support.[3,11,15] Development of systemic and topical antifungal compounds have also been relatively limited. In fact, the expansion of the topical antifungal category has primarily been through the addition of additional compounds within structural classes that already exist or with slight modification (i.e., imidazoles, allylamines, benzylamines) or new vehicle formulations.

New directions in drug development. Despite the challenges and realities that have seemed to retard the number of new drug compounds that are successfully developed and obtain FDA approval, there are continued efforts to develop new compounds and therapeutic classes. More attention is being placed on developing agents from a variety of organic, semi-synthetic, and synthetic sources ("scaffolds") that have not received adequate attention regarding their drug development potential and not simply through modifications of parent chemical moieties within drug classes that are already available.[3] In some cases, researchers have directed their focus on areas of drug

development that have been overlooked or where research has waned despite previous success.

Boron-based molecules in drug development. One category of compounds that has been relatively ignored for several years, and has received considerable attention more recently in drug development research, is boron-containing molecules.[16] There are a few reasons why researchers in pharmaceutical development have overlooked integrating boron into small molecules during chemical modification planning and drug screening. First, is the erroneous perception that incorporation of boron induces toxicity, a notion which has since been refuted by a good body of evidence.[16,17] Notably, boron is found in high concentrations in many natural foods (fruits, nuts, vegetables) and is commonly ingested daily by humans (0.3–4.2mg/day).[16] To add, boric acid, a major metabolite of the boronic acid functional group used in many boron-containing molecules, exhibits a favorable safety profile. Oral lethal dose (LD50) testing in rats shows that boric acid and table salt have very similar LD50 values (2660mg/kg and 3000mg/kg, respectively), and boric acid is a commonly used preservative in ophthalmological and vaginal products and is a major ingredient in a semi-solid squeezable toy for children.[16] To add, genetic toxicology studies have been completed with testing of four benzoxaboroles and one boronic acid ester, all five of which are currently in different phases of human drug development in preparation for FDA submission. All five boron-based molecules demonstrated no genetic toxicology liabilities, thus providing further evidence to support that many boron-based medicinal agents demonstrate favorable safety profiles to date.[17] A second reason relates to previous synthetic chemistry difficulties medicinal chemists encountered integrating boron into small molecules, a challenge that has been overcome by the introduction of new catalysts and other advances in synthetic organoboron chemistry.[16,17] Additional explanations regarding challenges to the incorporation of boron during drug development were related to manufacturing problems with diazoborine molecules. Finally, the over-reactivity/chemical instability of aliphatic boronic acid compounds also presented discovery and developmental challenges. Specifically, prior to the development of methods to alter interactive properties and stability characteristics, integration of boron into certain molecules was fraught with difficulties including a propensity to interact with moieties remote from the therapeutic target site (off-target binding) and/or susceptibility to oxidation and chemical degradation (deboration) with loss of biologic activity.[16,17]

Nevertheless, some researchers noted important advantages that boron can provide as opposed to other atoms (i.e., nitrogen) when completing the process of molecular modification during drug synthesis. Molecular chemists modify molecules to augment or diminish specific properties observed with parent and sister molecules during the course of initial testing of pharmacological and pharmacodynamic properties. Integration of boron into the chemical structure has proven to be very helpful in producing agents that can bind and trap important functional groups involved in key pathophysiological pathways, especially target sites on specific enzymes.[16,18–20] New catalysts and novel methods to integrate boron into various organic molecules have expedited and expanded the development of new boron-containing compounds. The last decade has seen an emergence of several boron-containing molecules in drug development, with boron incorporated into most small molecules as a boronic acid group.[16,17] Various structural modifications related to how boron is integrated produces different structural classes of born-based molecules, with changes in specific physiochemical and pharmacological properties related to alterations in chemical structure.[16–24] The physiochemical and structural characteristics of boron that allow for its versatility and broad range of applications in medicinal chemistry and provide its capacity to trap key functional moieties leading to inhibition of important enzymes and other molecules are reviewed in Table 1.

The objective of this article is to introduce to the dermatological community an overview of the history of boron integration into drug development and explain the fundamental concepts that support relevant modes of action and clinical applications, including for dermatological disorders. Several boron-based molecules are in both early and later development stages including many for dermatological disorders, such as fungal infections, psoriasis, atopic dermatitis, and bacterial infections (Figure 1). Although the explanations here that pertain to organoboron medicinal chemistry may be a bit challenging for clinicians, most of whom may be far removed from benchtop chemistry research, an overall understanding of the general principles that relate to the modes of action of boron-based compounds will accelerate the ability to comprehend how these agents can be applied in the clinical setting when treating patients.

At this point, the two obvious questions about the role of boron in drug development are, *"What does boron actually do from a therapeutic standpoint?"* and *"What is its mode of action as a therapeutic agent?"* To properly address these questions, the first step is to recognize that incorporation of boron into a chemical compound is not related to one specific mechanism of action that boron provides. Rather, the physical, chemical, and structural properties unique to boron can often enhance specific activities of many different small molecules that cover a broad range of pharmacological modes of action, pharmacodynamic properties, and pharmacokinetic characteristics.[16–20] Ultimately, the potential therapeutic activity and clinical application of a given boron-containing compound depends on its target as boron serves within a given molecule to promote mimetic activity whereby there is adduct formation upon binding to a specific target site, usually within a key functional enzyme involved either directly or indirectly with important disease-related activity. This binding impairs the function of that target enzyme by trapping a binding site that normally plays a vital pathogenic role and rendering it inaccessible. There are different classes of boron-containing compounds with diverse activity profiles

TABLE 1. Why boron? Physiochemical and structural properties provided by boron that assist the medicinal chemist in developing boron-based molecules that exert modes of action with potential clinical relevance[16–24]

ACTIVITY RELATED TO MODE OF ACTION	RELATED BORON PROPERTY	POTENTIAL CLINICAL RELEVANCE
Capacity for covalent bond formation with many designated functional groups	Empty p-orbital (as compared to some other atoms [i.e., nitrogen]) promotes bond formation at target site on key protein; boron molecule acts as a mimic and locks up the key protein rendering it inactive/less active	Inhibit key target proteins (i.e., mostly hydrolase enzymes) involved in pathways involved in pathogenesis. Multiple examples (with targets): (1) Inhibition of phosphodiesterase-4 → reduced cytokine production in psoriasis/atopic dermatitis (2) Inhibition of leucyl *t*RNA synthetase → blocks protein synthesis in dermatophytes, *Candida albicans*, other fungi (3) Inhibition of β-lactamases → reduce resistance to antibiotic therapy
Incorporation of boron in a variety of structural classes of boron-based compounds	Successfully integrated into diazaborines, boronic acid enzyme inhibitors, benzoxaboroles, others; Some forms (benzoxaboroles) with dissociation constants (pKa) within physiologic pH range	Adaptabilty to variety of disease states depending on pharamacologic, pharmacokinetic, and pharmacodynamic properties needed; Different structural classes of boron-based compounds may be more or less adaptable to specific targets and disease states; pKa of boron-based molecule can be fine-tuned to weaken or strengthen interactive capacity
Boron can participate in bond formations other than covalent bonds (i.e., hydrogen bonds) and other forms of interaction (i.e., with metal ions)	Capability to interact with multiple types of functional groups at key target sites (protein kinases)	Adaptability to multiple important targets, which expands the list of potential disease states or microbial organisms that boron-based molecules can be developed to counteract
Boron can exist in several geometries depending on structural characteristics of the molecule	Can exist in tetrahedral and trigonal forms, which can affect binding affinity to target sites, inhibitor activity	Allows for potential to develop boron-based molecule with characteristics needed to more avidly interact with target site
Boron reactivity can be modulated to reduce off-target binding and improve selectivity for target site	Maintains binding ability when in cyclic form (i.e., benzoxaborole compounds); ability to exist in cyclic form enhances stability via geometric constraint	Allows for development of boron-based compounds that are more chemically stable than boronic acid molecules with balance between affinity and selectivity; benzoxaboroles exhibit utility with various types of targets (many unrelated to each other), which expands potential applications to many disease states and microbial organisms
Boron allows for many types of molecular alterations	Can maintain binding ability in many stereochemical and structural forms, which permits lipophilicity, polarity, other characteristics that are optimal in meeting specific drug development needs	Allows for modifications that change molecular size (weight), shape, hydrophilicity/lipophilicity, polarity, other characteristics → can produce compounds to meet pharmacokinetic demands to both reach anatomic site of action in host and bind the therapeutic target to lock up its activity. Example: development of tavaborole (formerly AN-2690) to produce a small, polar, water-soluble molecule to penetrate through nail plate and retain antifungal activity in presence of keratin

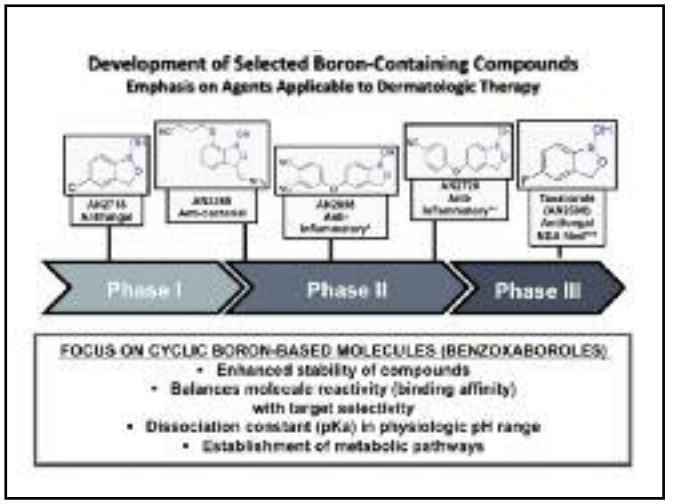

Figure 1. Boron-based compounds in dermatology: Timeline of progression in human drug development

* Benzoxaborole phosphodiesterase-4 (PDE-4) inhibitor of TNFα, IL-12, and IL-23 shown in research models in development for atopic dermatitis and psoriasis; greater *in vivo* potency and anti-inflammatory activity than AN2728 in animal models

** Benzoxaborole phosphodiesterase-4 (PDE-4) inhibitor of TNFα, IL-12, and IL-23 shown in research models in development for atopic dermatitis and psoriasis; lesser *in vivo* potency and anti-inflammatory activity than AN2898 in animal models; metabolism by hepatic enzymes evaluated

*** Benzoxaborole inhibitor of amino-acyl (leucyl) *t*RNA synthetase with broad-spectrum antifungal activity and favorable nail plate penetration submitted to FDA for topical treatment of toenail onychomycosis

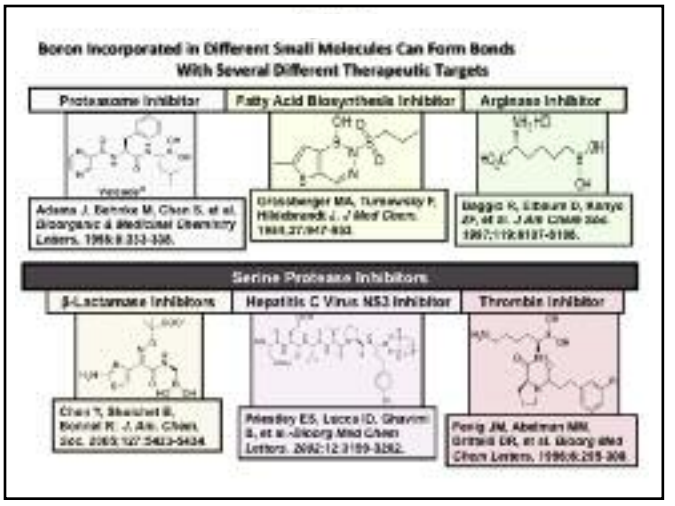

Figure 2. Incorporation of boron into different small molecules provides versatility of molecular interactions: Several potential therapeutic targets and applications for multiple disease states

and structure-activity relationships (SARs), with each directing its binding activity at a defined therapeutic target site involved with a specific disease state.[16–20] Therefore, there is potential for therapeutic application of boron-containing compounds in a wide variety of disease states, as a diverse group of therapeutic targets may be inhibited by individual boron-based compounds. Figure 2 shows selected boron-containing molecules and their respective therapeutic targets, all of which play major pathophysiological roles in specific disease states.

HISTORICAL OVERVIEW OF BORON-CONTAINING COMPOUNDS USED FOR MEDICINAL PURPOSES

A detailed account of the history of organoboron medicinal chemistry, the development of boron-containing small molecule SARs analysis, and the therapeutic applications of individual boron-based molecules is beyond the scope of this article and is reviewed in detail elsewhere.[16–24] However, some major developments that have occurred over time demonstrate the broad range of advances in organoboron medicinal chemistry and the wide variety of potential therapeutic applications that boron-based molecules can provide. The main categories of boron-containing molecules that have emerged from medical chemistry research are the diazoborines, boronic acid enzyme inhibitors, and benzoxaborole derivatives.[16,17] Figure 1 shows a timeline of some benzoxaborole-based small molecules that are currently in different phases of formal human drug development. Figure 2 depicts clinically relevant examples of boronic acid and diazoborine-based compounds.

Diazoborines. One of the earliest classes of boron-based compounds is the diazaborines, which were synthesized approximately five decades ago; however, the first publications describing their mechanisms of action and antimicrobial properties appeared in 1971.[16,25] This led to a research platform of diazoborine compounds that demonstrated activity against Gram-negative bacteria and *Mycobacterium tuberculosis* by targeting a specific enzyme (enoyl reductase [ENR]) involved in fatty acid biosynthesis.[16] Other diazoborine compounds based on activities evaluated to date include estrogen-like compounds.[16] Chemical manufacturing and control challenges can complicate the production of diazoborine compounds.

Boronic acid enzyme inhibitors. Boron-based compounds that incorporate boronic acid or a boronic functional group comprise many of the boron-based compounds that are being evaluated in drug development projects.[16,17] A major challenge with aliphatic boronic acid

TABLE 2. Boronic-based enzyme inhibitors: Correlation of activity with clinical relevance

PATHOPHYSIOLOGICAL STATE/PROCESS	ACTIVITY OF BORON-BASED MOLECULE
Hepatitis C virus (HCV)	Boron promotes inhibition of HCV serine protease NS3/4A by trapping of designated hydroxyl functional group
β-lactamases (multiple)	SP inhibitor molecule with incorporated boron mimics a target site on the β-lactam ring; other structural variations with penicillin and cephalosporin side chains and with boron incorporated inhibit CTX-M β-lactamases
Hypercoagulable states	Anticoagulation via boronic acid analogs of lysine and arginine inhibit thrombin; phenylboronic acid derivatives reported to inhibit factor XIa
Superficial fungal infections	Benzoxaborole compounds inhibit fungal protein synthesis by adduct formation with the editing domain of leucyl-*t*RNA synthetase
Diabetes	Boron-based potent inhibitors of the SP enzyme dipeptidyl peptidase (DPP4) identified; DPP4 inactivates glucagon peptide-1 (GLP-1), a known stimulus for glucose-induced insulin biosynthesis; DPP4 inhibition a promising approach for diabetes
Atopic dermatitis/psoriasis	5-phenoxybenzoxaborole derivatives impair the function of the phosphodiesterase 4 enzyme and inhibit cytokine release (TNFα, INF-γ)

enzyme inhibitors is off target binding, which reduces their selectivity and potential effectiveness as therapeutic agents.[16,17] This adverse property, which is known to occur with this category of boron-based compounds, is due to their high level of chemical reactivity.

Boronic acid enzyme inhibitors have been developed that exert potent activity against key target sites on serine protease (SP) enzymes. In addition, boronic compounds inhibiting other enzymes are being pursued that target a variety of cutaneous infections and other disease states.[16] Examples are listed in Table 2.

The first therapeutic proteasome inhibitor to be tested in humans and now commercialized was bortezomib (Velcade, Millennium Pharmaceuticals, Inc.), a boronic acid-containing molecule FDA approved for treatment of relapsed multiple myeloma and mantle cell lymphoma.[16] The boron atom in bortezomib binds the catalytic site of the 26S proteasome with high affinity and specificity, with some patients demonstrating a highly favorable therapeutic response. Toxicities associated with botezomib temporarily dampened enthusiasm for further development of boron-based compounds; however, it was later determined that specific toxic effects were mechanism of action related and not due specifically to the presence of boron, and a second company providing bortezomib had manufactured some lots of the product with excessive amounts of the active compound above the acceptable range allowed based on the FDA-approved concentration for the product.[16,26]

Cyclic boron-based molecules (benzoxaboroles). Advances in the incorporation of boron-containing molecules in medicinal chemistry required that researchers depart from the traditional path of synthesizing and screening only boronic acid-based molecules.[16–20] This new approach led to the development of cyclicized boron-based molecules, such as oxaboroles and benzoxaboroles, the latter progressing to be a major platform for new drug development, including multiple compounds applicable to dermatology (discussed in more detail below). The integration of a boron ring into the cyclic structure allowed for greater stability, physiological availability to the requisite site of action, development of some compounds with dissociation constants (pKa) within physiological range of pH, and an optimized balance of molecule reactivity and target selectivity to reduce off-target interactions without significant loss of the desired therapeutic activity.[16–20] Through molecular modifications of certain benzoxaborole compounds, organoboron chemists are capable of producing small boron-based molecules that are highly stable, demonstrate effective target binding capacity and selectivity, and exhibit optimal physical properties that allow for access to the required anatomic site of the disease state. This was achieved with tavaborole (formerly AN2690), a benzoxaborole compound with a unique mode of action against dermatophytes and several other fungi (broad spectrum antifungal activity) and characteristics that allow for favorable penetration into and permeation through human nail plate and maintenance of antifungal activity in the presence of keratin.[27] Tavaborole was submitted to the FDA in 2013 for approval for the topical treatment of toenail onychomycosis.[27]

Benzoxaboroles have also been developed that inhibit phosphodiesterase-4 (PDE-4) (AN2728; AN2898) with various research studies demonstrating inhibition of various pro-inflammatory cytokines (potential application for psoriasis and atopic dermatitis), inhibition of leucyl-*t*RNA synthetase with activity against multiple fungal organisms (tavaborole; AN2718) and Gram-negative bacteria (AN3365), inhibition of HCV NS3 protease (potential application for hepatitis C infection), and antiprotozoal activity against *Trypanosoma brucei* (SCYX-7158; others).[16–20,28] The latter is a promising advance that may provide effective therapy for African sleeping sickness, a disorder that is endemic in Saharan Africa with tens of

TABLE 3. Boron-based compounds under evaluation for dermatologic uses

COMPOUND	POSSIBLE INDICATION	COMMENTS
Tavaborole (formerly AN2690) Mode of action: Inhibition of *t*RNA synthetase (good selectivity for fungal enzyme) → block protein synthesis	Topical treatment of toenail onychomycosis	Penetration through human fingernail plate in high concentrations with efficacy coefficient reaching 50x MIC after 14 days and high penetration through nail plate independent of vehicle (4 vehicles used).[27,29] Minimum inhibitory concentration (MIC) study performed with *Trichophyton rubrum* in the presence and absence of 5% powdered keratin showed no differences between groups in MIC → antifungal activity maintained in presence of keratin/keratin binding[27] – Broad-spectrum antifungal activity against *T. rubrum, T. mentagrophytes, Candida albicans*, other fungi[27] – Topical application once daily of 7.5% solution; associated with negligible plasma levels; rapid conversion to negative fungal culture (<4 weeks)[30] – *Ex vivo* antifungal activity (subunbgual) markedly superior to ciclopirox and amorolfine lacquers[27,31] – Obtains >200-fold greater subungual concentration compared to ciclopirox lacquer[31] – Reservoir effect after last dose with therapeutic levels present for at least 3 months (average level 161-fold higher than MIC and 20-fold higher than MFC)[32] – Efficacy and safety demonstrated in Phase 2 (187 patients) and Phase 3 (approximately 600 patients) trials[33,34]
AN2728 AN2898 Mode of action: Inhibition of phodsphodiesterase-4 (PDE4) → reduced production of pro-inflammatory cytokines → inhibition of inflammation	Psoriasis, atopic dermatitis (topical therapy)	– Both PDE4 inhibitors shown to inhibit release of TNFα, IL-23, and other cytokines in research models[35] – AN2898 (close analog) with augmented potency[35] – Both in 5% ointment demonstrated no irritation potential; preliminary testing showed improvement of psoriatic plaques[36] – Efficacy, tolerability, and safety demonstrated in Phase 2 study for atopic dermatitis with AN2728 2% ointment[37] – Ointment vehicle delivered the greatest quantity of AN2728 into and through skin (mouse skin)[38]

thousands of people infected annually and is associated with severe morbidity and death.[28]

BORON-CONTAINING COMPOUNDS UNDER DEVELOPMENT FOR DERMATOLOGIC INDICATIONS

Most of the boron-based molecules that are under development for indications related to dermatology fall under the benzoxaborole class of compounds. As discussed above, tavaborole has been submitted to the FDA for the topical treatment of onychomycosis with the New Drug Application (NDA) accepted by the agency as sufficiently complete for review and consideration for FDA approval (Business Wire press release, Anacor Pharmaceuticals, October 2013). Two PDE4 inhibitors are in the Phase II evaluation process with potential application for psoriasis and atopic dermatitis. Others are being evaluated as antibiotic or antifungal agents. Table 3 lists several compounds under evaluation for dermatological use with

accompanying information that has been reported on the activity and properties of these molecules.

CONCLUSION

Despite the slow development of new therapeutic drug classes and novel compounds in dermatology, some researchers are focusing on development of new compound scaffolds. Advances in technologies and other developments in medicinal chemistry, and the vision and scientific dedication to further evaluate previously overlooked or misunderstood classes of compounds, have opened up novel pathways of drug development research. Despite prior unfounded perceptions of potential toxicities, and with the availability of new advances in synthetic organoboron chemistry, research of boron-based medicinal compounds has re-emerged. The incorporation of boron into a wide variety of small molecules allows for interaction with several therapeutic target sites on key functional proteins.

This research approach has provided a platform of unique boron-based compounds with potential for therapeutic application in many different disease states. Many of these compounds are in progressive phases of clinical drug development for skin diseases including fungal infections, atopic dermatitis, and psoriasis. Tavaborole, a benzoxaborole compound, has been submitted under an NDA to the FDA for topical treatment of onychomycosis. This agent exhibits a unique mode of action, specifically the inhibition of the editing domain of leucyl-*t*RNA synthetase with good relative selectivity for the fungal enzyme. Tavaborole exhibits antifungal activity against dermatophytes and several other fungi.

The versatility of several boron-based compounds to modifications that optimize physiochemical and pharmacological characteristics that conform to specific therapeutic needs has been central to the successful screening of many diverse compounds. Due to the variety of compounds and their versatility, different boron-based compounds have been found to interact with and inhibit specific functional proteins involved in different disease states and/or microbial pathogens. In dermatology, several preclinical and clinical studies have been completed with boron-based compounds, including tavaborole for topical treatment of onychomycosis and phosphodiesterase-4 inhibitors for atopic dermatitis and psoriasis. Additional research including clinical studies will further define the best indications and the efficacy and safety profiles of individual boron-based compounds. Importantly, this research approach provides a diverse platform of many interesting and promising medicinal compounds with potential uses in many areas of medicine, including dermatology.

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