Organoboron Compounds

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The unique electron deficiency and coordination property of boron led to a wide range of applications in chemistry, energy research, materials science and the life sciences. The use of boron-containing compounds as pharmaceutical agents has a long history, and recent developments have produced encouraging strides. Boron agents have been used for both radiotherapy and chemotherapy. In radiotherapy, boron neutron capture therapy (BNCT) has been investigated to treat various types of tumors, such as glioblastoma multiforme (GBM) of brain, head and neck tumors, etc. Boron agents playing essential roles in such treatments and other well-established areas have been discussed elsewhere. Organoboron compounds used to treat various diseases besides tumor treatments through BNCT technology have also marked an important milestone. Following the clinical introduction of bortezomib as an anti-cancer agent, benzoxaborole drugs, tavaborole and crisaborole, have been approved for clinical use in the treatments of onychomycosis and atopic dermatitis. Some heterocyclic organoboron compounds represent potentially promising candidates for anti-infective drugs.

Keywords: organoboron compound ; anti-cancer drug ; anti-tuberculosis ; anti-malaria drug ; neglected tropical disease ; crypto and toxoplasmosis treatment

1. Introduction

Four types of such frequently occurring diseases, in which organoboron compounds have already shown high potential as acceptable drug agents, have been selected to survey in this review. The four common diseases are tuberculosis, malaria, neglected tropical diseases, and the parasitic diseases of cryptosporidiosis and toxoplasmosis, and they are briefly introduced as follows. (2) Malaria is a disease caused by the Plasmodium parasite and accounts for one of the leading causes of death worldwide despite decades of strategic interventions aimed at reducing incidence and mortality [1]. are other dangerous diseases caused by important protozoan pathogens of humans, while Cryptosporidium is a common cause of moderate-to-severe diarrhea in children under five years of age [2].

For example, boron compounds, 4-borono-L-phenylalanine (BPA) and sodium borocaptate (BSH), have been used as boron carriers in boron neutron capture therapy (BNCT) for decades to treat various tumors, such as malignant brain tumor and melanoma [3]. Cluster-based boron compounds are in the latest class that takes advantage of the properties of many boron atoms in the cage [4][5], including their unique electronic properties and ability to form covalent bonds in organoboron compounds, which make them a suitable agent for drug discovery. In addition, several organoboron compounds also demonstrate strong antibacterial activity, specifically against the enteric group of Gram-negative bacteria. Earlier observations of anti-fungal, anti-bacterial, and anti-inflammatory activities of benzoxaboroles and other organoboron compounds represented the key result that led to the discovery of their potential for the treatment of various infectious diseases [6].

2. Tuberculosis and Antifungal Activity

The Mtb is transmitted by aerosol and infection occurs when a person inhales droplet nuclei containing tubercle bacilli that reach the alveoli of the lungs. If the bacilli remain alive, they may spread by way of lymphatic channels or the bloodstream to other tissues and organs (brain, larynx, lymph node, lung, spine, bone, or kidney). Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. In this regard, many efforts have been dedicated to the discovery and development of new anti-TB agents with new mechanisms of action to control drug-resistant disease [7].

1,3-Dihydro-1-hydroxyl-2,1-benzoxaboroles (or dihydrobenzoxaborole or benzoboroxoles) were first synthesized and characterized in 1957 by Torssell [8]. After the discovery that ortho-hydroxyalkyl arylboronic acids can form a complex with glycosides under physiologically relevant conditions, they have been investigated as molecular receptors for sugars and glycoconjugates, in supramolecular chemistry and as building blocks and protecting groups in organic synthesis [9]. Reviews describing these applications of benzoxaboroles were recently published [10][11].

The dihydrobenzoxaboroles bearing aryl, heteroaryl, or vinyl substituents at the 1-position (6a–i), as shown in Figure 2, were reported [10][11][12][13][14]. These substitutions showed equal or decreased activity against fungi. The first lead compound was 1-phenyldihydrobenzoxaborole, 6a, which showed weak activity on a broad spectrum of fungi with minimum inhibitory concentration (MIC) values of 4–8 µg/mL. Starting from compound 6a to determine the effect of hydrophobicity, many derivatives with various substitutions of R′ in the phenyl ring in position 1 (1-phenyldihydrobenzoxaborole 7a-h)

To enhance hydrophilicity, the 1-phenyl group was replaced with a 1-hydroxy group to prepare 1-hydroxydihydrobenzoxaboroles (8a), as per the published report. Compound 8a showed an 8-fold increase in activity against C. neoformans, and 2 (AN2690) showed an 8-fold increase in activity against A. fumigatus, respectively [10][11][12][13][14]. To determine the structure–activity relationship of this scaffold, the 5-F group was substituted with other groups (8b–m). The 5-chloro-substituted benzoxaborole 8b (AN2718) is being developed now by Anacor pharmaceutical, a company pioneering the field of boron compounds, for the topical treatment of tinea pedis, dermatophyte fungal infection of the soles of the feet and the interdigital spaces [10][11][12][13][14].

LeuRS belongs to aminoacyl-tRNA synthetases (aaRS), a class of enzymes which are crucial for gene translation. Thus, LeuRS is a proofreading aaRS, which possesses distinct synthetic aminoacylation and editing active sites separated by more than 30Å. The aminoacylation reaction occurs in two steps: the formation of an enzyme-bound aminoacyl-adenylate (I), followed by the transfer of this activated amino acid to either the 2′- or 3′-hydroxy group on the 3′-terminal adenosine of tRNA (II) [13]. The inhibition of either one of these enzymatic stages (I, II) leads to the accumulation of uncharged tRNA molecules, which bind to ribosomes, causing the interruption of polypeptide chain elongation [13]. These enzymes have been a focus of antimicrobial research as potential targets for more than a decade [15].

The derivatives of 11 and 12 with primary amino groups showed good antimycobacterial activity against Mtb H37Rv (11, MIC 1.9 µM, 12 MIC 15.6 µM) The incorporation of 3-aminomethyl and 7-ethoxy moieties into one molecular structure to form compound 15 showed an increase in activity (15, MIC 0.13 µg/mL Crystallization with different editing domain constructs of Mtb LeuRS was attempted in the presence of compound 15 with AMP. These compounds showed an increase in activity against Mtb H37RV (MIC 0.02–0.05 µM), an increase in potency towards Mtb LeuRS (IC50 0.06–0.08 µM) and, therefore, they were selected for in vivo murine pharmacokinetic analysis.

First, lipophilicity optimization of the sidechain was investigated by incorporating aromatic moieties to the 7-alkoxyl group, but these derivatives showed a reduction or loss of antitubercular activity and a decrease in Mtb LeuRS potency. The introduction of one or two fluorine in the sidechain resulted in a slight decrease or similar antitubercular activity [16]. In addition, the ring-fused compounds of 23 and 24 exhibited enhanced anti-tubercular activity against Mtb H37Rv with the MIC of 0.08 µM and The typical Mtb LeuRS inhibitor shows low molecular weight, low polar surface area (PSA), and clogD7.4 value similar to frontline Mtb drugs of isoniazid, pyrazinamide, and ethambutol [16].

To evaluate the ability of these Mtb LeuRS inhibitors for tuberculosis, treatment tests were conducted in vivo using an animal model. Compound 19 showed the best efficacy with an ED99 (efficacious dose that gives a two log colony-forming units (CFU) reduction compared to the untreated control) of 0.4 mg/kg among the evaluated compounds. For the best profile, with excellent in vivo efficacy at low doses in acute and chronic mouse TB infection models, compound 19 has been progressed to clinical development for the treatment of tuberculosis, the first time in Human (FTIH) safety and pharmacokinetics (PK) study of GSK3036656 in Healthy Subjects [17].

with no cytotoxicity; thus, the profile of this compound is also encouraging for future development [18]. Meanwhile, a series of novel 7-phenyl benzoxaboroles were also investigated, where compounds 26–29 showed reasonable activity against Mtb in vitro This series of compounds shows potential for further development and to target validation work. In addition, dimeric benzoboroxoles were reported recently, and they were found to possess excellent selectivity and activity for mycobacteria, including the Mtb pathogen, and were capable of complexing to Mtb glycans without resistance [19].

Boronates may interact with a target protein through covalent bonding with nucleophilic entities (such as hydroxyl and amine groups of enzymes, Figure 1B) to form a stable bond with the enzymes, thereby leading to their reversible inhibition. (1, Figure 1C), trade name Velcade, is a dipeptide boronic acid and is the first human proteasome (H. proteasoma) inhibitor approved by the U.S. FDA for the treatment of multiple myeloma [20]. The X-ray crystal structure of the proteasome in a complex with bortezomib displayed a covalent bond formation between the boronic acid moiety of 1 and the hydroxyl group of Thr1 at the chymotrypsin-like active site of the 20S proteasome, leading to enzyme dysfunction and apoptosis in cancer cells [21][22] (H. proteasome IC50 0.005 µM). However, bortezomib presented major drawbacks, such as high costs and poor pharmacokinetics with significant side effects (peripheral neuropathy, neutropenia, and cytopenia) despite its use to treat many cancers successfully [23].

Caseinolytic proteases (ClpP) are serine proteases found in a wide range of bacteria, and they have the ability to remove the aborted translation products [24]. The tmRNA trans-translation system, a bacterial rescue system that frees ribosomes stuck during protein synthesis, tags partially synthesized proteins with a caseinolytic-protease-specific (SsrA) degradation peptide. The caseinolytic protease complex is composed of catalytic protease subunits (ClpP) and regulatory subunits (ATPases).

instead of the boronic acid, was synthesized and its potencies against the bacteria and human enzymes were determined [25]. (IC50: 25 μM), against bactericidal Mtb (IC50: 25 μM) and was active against the mycobacterial proteasome (MIC50: 25 ± 1.3 μM), but was found to be devoid of activity against the mammalian human proteasome (IC50: >500 μM Subsequent studies showed that a bulky group (benzyl and phenyl) in position X could increase the ClpP1P2 inhibitory activity without a reduction in proteasome activity. This series of changes of X offers options for subsequent P1–P2–X combinations for the future phase of SAR exploration.

Pro125 interact with P1 (phenethyl group). Physicochemical properties such as molecular weight, numbers of hydrogen bond donors and acceptors and lipophilicity (LogP) were examined according to Lipinski's rule of five [26]. plasma protein binding and human liver microsome stability was moderate, clearance in mouse microsomes was high (8min), and the inhibition of cytochrome P450 enzymes was not detected at the highest concentration tested. The Oral/i.v. pharmacokinetics of 37a indicated moderate clearance and low bioavailability [27][28].

Diazaborines are a family of boron-containing compounds, in which the boron atom is stabilized in the form of an aromatic boron-based heterocycle. It has been proposed that the mechanism of action of diazaborines in E. coli is by the complexation of nicotinamide adenine dinucleotide (NAD+) and the inhibition of enoyl-reductase (ENR) [29]. Similar to the benzoxaboroles such as 37b (AN2918) and 37c (AN3418), diazaborine inhibitors of ENR were found to form a covalent B–O bond with the OH group at C (2′) of the NAD cofactors ribose unit (Enoyl-[acyl-carrier-protein] reductase [NADH]), which is required for mycolic acid biosynthesis [30].

c (R1= -pyrazinyl/R2 -H, -nBu, -pyridyl), showing potent inhibitory activity against M. tuberculosis (Figure 5D) [31]. Subsequently, a set of 2-acylated 2,3,1-benzodiazaborines 39a–d was synthesized, characterized, and tested with Mycobacterium smegmatis (Figure 5D) [32]. In addition, 2-formylphenyl boronic acids 40 (R= H, allyl, Ph) and their derivatives of 41 were also reported as potential antifungal agents, and their activity was examined against four fungi (Aspergillus niger, Aspergillus flavus, Candida albicans, and Saccharomyces cerevisiae) using Amphotericin B as a control and showed appreciable activity [33][34]. (MIC50: 80 nM) with strong bactericidal activity and low cytotoxicity vs. HepG2.

3. Malaria

and P. vivax being the most virulent [35]. These sporozoites migrate to the liver where they undergo further development into schizonts, which produce "merozoites" that enter into the systemic circulation where they infect red blood cells and cause the typical symptoms of malaria. The successful exploitation of semisynthetic ART derivatives was a major breakthrough in malaria chemotherapy because of their profound and rapid therapeutic response against malaria parasites. However, reports of decreased efficacy, reduced parasite clearance time in the case of ACT treatment and widespread resistance by Plasmodium parasites [36][37] suggest the need for a new search for novel pharmaceutical interventions for malaria [38].

Early observation of antifungal, antibacterial and anti-inflammatory activities of benzoxaboroles led to the discovery of their potential for therapy of protozoan disease such as malaria, human African trypanosomiasis (HAT) and Chagas disease [38]. A series of analogs of 43 were designed to assess the structural features required for potent antimalarial activity, including the length of the sidechain on the oxaborole nucleus (44, 45), the sidechain functional groups (46–56), the attaching positions of the sidechain (57–59), and modifications to the benzoxaborole scaffold (60–62) [39][40]. Further structural modification, such as the introduction of fluoro, phosphonic and hydroxamic groups, was found to decrease the activity potency dramatically; it was also that the removal of the boron atom from the five-membered oxaborole ring reduced the antimalarial activity [41].

Further studies of structure–activity relationship (SARs) were performed by varying the 6-aryloxy group (64–71), substituent modification on the pyrazine ring (72–88) and exploring the effect of side-chain ester group (89–97) To examine the effect of the left-side aromatic moiety on antimalarial activity, compounds 64–71 were designed. None of the compounds showed antimalarial activity better that 71, and that would indicate the presence of the carboxylic ester as a crucial functionality. Other ester compounds (89–97) were designed and synthesized to further explore the effects of different esters.

To optimize the potency, stability and PK profile of such benzoxaborole derivatives, various carboxamide functional groups were incorporated. The result of the P. falciparum-infected mouse model experiment demonstrated that the in vivo parasite clearance profile of 98 was rapid and similar to that of artesunate (water-soluble injectable derivative of ART) and chloroquine, two well-known fast parasite-killing antimalarial medicines [42]. Compound 98 (AN13762) was subjected to potency evaluation against other resistant P. falciparum strains, in vivo parasite reduction rate evaluation (or number of parasites the compound could kill in a parasite life cycle, PRR), and for preliminary genotoxicity studies. Therefore, 98 was further investigated for the development of preclinical studies in humans beginning in 2019 (MMV-Supported Projects.

The highly electrophilic nature of the boron component of these compounds could lead to interactions with a variety of protein targets via reversible covalent bonds (Figure 1B). In the course of searching for new antimalarial drugs, a benzoxaborole library of LeuRS inhibitors was screened for potency against cultured multidrug-resistant W2 P. falciparum strains and the antimalarial activity was investigated [43]. Subsequently, 99 and CQ were investigated in different stages of parasites, and inhibition of parasite development was observed across the life cycle of plasmodium, particularly against trophozoites (Figure 9B) [43]. Biochemical studies showed that 99 and 100 caused a dose-dependent inhibition with the incorporation of [14C] leucine, indicative of a block in wild-type protein synthesis (using artemisinin as a negative control and, as a positive control, cycloheximide, protein synthesis inhibitor)

During the screening process, 3-(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-7-yl)-propanoic acid was identified as a potent antimalarial agent against P. falciparum asexual blood stage parasites known to be resistant to standard antimalarial drugs [44]. (ED90: 0.57 mg/kg) infections in mice, with minimal cytotoxicity to mammalian cell lines. The PfCPSF3 is a Plasmodium homologue of mammalian CPSF-73. In these models, the identified PfCPSF3 resistance mutations (T406I, Y408S, T409A and D470N) were found on the PfCPSF3 active site of amino acids interacting with AN3661 [44].

4. Neglected Tropical Diseases (NTD)

Human African trypanosomiasis (also known as African sleeping sickness or HAT), a Neglected Tropical Disease (NTD) that occurs in sub-Saharan Africa, is transmitted to humans through the bite of different species of tsetse fly (Glossina spp.). The parasites enter the lymphatic system, pass into the bloodstream (stage I, hemolymphatic system) and then transform into bloodstream trypomastigotes, which are carried to other sites (stage II, CNS, central nervous system, spinal fluid). The currently available drugs for the treatments for early-stage infection (stage I) are pentamidine and suramin, while melarsoprol and eflornithine are for late-stage infection (stage II or CNS). Thus, there is an urgent need to develop bioavailable oral treatment with improved efficacy and low toxicity at an affordable cost for the treatment of HAT [45][46].

In 2010, the UCSF Sandler Centre of Drug Discovery, in collaboration with Anacor Pharmaceuticals, identified several compounds through an antitrypanosomal screening of 400 compounds, leading to the discovery of drugs with high potency to inhibit T. b. brucei, as shown in Figure 10. Thus, the oxaborole functionality was crucial for the observed antitrypanosomal activity, as demonstrated by low activity (IC50 > 10 µg/mL) or loss of activity upon removal of the oxaborole ring or substitution with carbon (101–109) The length between the hydrogen bond acceptor O and the benzoxaborole C(6) of the linkage group “L” had a significant effect on the antitrypanosomal activity (i.e., in sulfonamide, O-C(6) distance 3.52 Å, IC50 0.02 µg/mL vs. sulfoxide, O-C(6) distance 2.38 Å, IC50 0.17 µg/mL). Compounds with amide linkers showed high potency.

Sulfonamide 106 was further modified using various linkers between the heterocyclic core and pendant aryl group to show reasonable potency in the whole-cell T. b. brucei assay with low cytotoxicity (IC50 > 10 µg/mL for mouse lung fibroblast cells (L929)) [47]. I assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of SCYX-7158 by applying a single oral ascending dose in 128 healthy human volunteers of sub-Saharan origin. As the drug has a long half-life (>300 min), the study was extended to 210 days to ensure safety monitoring of the healthy volunteers [48]. Based on the results of this study, DNDi (Drugs for Neglected Diseases Initiative) and partners proceeded to Phase II/III—efficacy and safety study of SCYX-7158 as a single dose oral treatment of patients with HAT [49].

Chalcones have attracted considerable scientific attention and continue to be a versatile scaffold in anticancer and antiprotozoal research. The 4-NH2 derivative 112a and 3-OMe derivative 112b (Figure 12A) were found to have excellent potency against T. b. brucei (112a, IC50: 0.024 µg/µM; 112b, IC50: 0.022 µg/µM) and good cytotoxicity (L929 cells, IC50 > 10 µg/mL). (IC50: 0.09 µg/mL for 113a; 0.03µg/mL for 113b; 0.07 µg/mL for 113c) and good cytotoxicity (L929 cells, Meanwhile, a set of cinnamoyl–oxaborole amides were also synthesized and screened against nagana T. b. brucei for antitrypanosomal activity.

As discussed before, compound 2 (Figure 1), which is under clinical investigation, was indicated as an antifungal agent by inactivating fungal LeuRS [13]. Encouraged by the inhibitory activity of such compounds, C(6)-ester group-functionalized 115a and 115b were synthesized, while 115b showed a 4-fold improvement in activity (TbbLeuRS IC50: 3.5 μM) i were also screened as an effort to improve the stability of the leading ester compounds in vivo while retaining their activity. The addition of methyl or ethyl substituents in the α-position to ketone resulted in a significant enhancement of activity, as demonstrated by compounds 115f–I (TbbLeuRS IC50 2.5, 2.9 and 3.8 μM, respectively)

Leishmaniasis is a vector-borne parasitic disease caused by at least twenty species of the genus Leishmania, with three main clinical forms of visceral leishmaniasis (VL), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis [50]. The absence of effective vaccines gives way to treatment by chemotherapy using drugs such as pentavalent antimonials and amphotericin B as primary control of the disease [51]. However, these drugs require parenteral administration. They are nephrotoxic and an increasing drug resistance in visceral leishmaniasis has been identified [52].

Compound 2 (Figure 1) exhibited anti-leishmanial activity against both promastigote and amastigote stages, in vitro, as well as in vivo in BALB/c mice, as shown in Figure 13A. Recently, protozoan carbonic anhydrases (CAs) were explored as new targets for drug development for bacteria, fungi and protozoa [53][54]. The ureido and thioureido benzoxaboroles (116) exhibited low micromolar inhibitory activities against protozoans, and their derivative, 116a, showed the most activity with an inhibition Compounds 117 and 118, which showed anti-parasitic activity against P. falciparum, T. brucei, T. cruzi or L. donovani, were tested with five different species of Leishmania and found to be new leading compounds for its treatment.

Onchocerciasis, also known as “river blindness”, is a parasitic disease caused by the filarial worm Onchocerca volvulus and it is transmitted to humans through exposure to repeated bites of infected blackflies of the genus Simulium. More than 99% of infected people live in African countries [55]. Lymphatic filariasis impairs the lymphatic system and can lead to the abnormal enlargement of body parts, causing pain, severe disability and social stigma. Almost 120 million people in 72 countries worldwide remain threatened by lymphatic filariasis, and they require preventive chemotherapy to stop the spread of this parasitic infection [56].

Pleuromutilin and its derivatives are antibacterial drugs through binding to the peptidyl transfer center (PTC) of the ribosomes and consequently inhibiting protein synthesis of the bacteria [57][58]. Compound 7-fluoro-6-oxybenzoxaborole, 122 (AN11251), was identified as a leading compound that showed good in vitro anti-Wolbachia activity and physicochemical and pharmacokinetic properties with high exposure in plasma. This compound was effective in reducing the Wolbachia parasites following oral administration in mice (Figure 13B). The efficacy of 122 in these models suggests more extensive evaluation of this compound, both alone and in combination with other known anti-Wolbachia drugs.

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