SCIENCE CHINA
Chemistry

• REVIEWS •
• SPECIAL TOPIC • Chemistry for Life Sciences

October 2013 Vol.56 No.10: 1372–1381
doi: 10.1007/s11426-013-4981-y

The synthesis of benzoxaboroles and their applications in medicinal chemistry

ZHANG Jiong, ZHU MingYan, LIN YiNan & ZHOU HuChen*

School of Pharmacy, Shanghai Jiao Tong University, Shanghai 200240, China

Received August 6, 2013; accepted August 19, 2013; published online August 30, 2013

Benzoxaborole, as a versatile scaffold, plays important roles in organic synthesis, molecular recognition and supramolecular chemistry. It is also a privileged structure in medicinal chemistry due to its desirable physicochemical and drug-like properties. Recently, benzoxaboroles were widely applied as antifungal, antibacterial, antiviral, anti-parasite, and anti-inflammatory agents. This review covers the properties, synthetic methods and applications of benzoxaboroles in medicinal chemistry.

benzoxaboroles, synthetic methods, medicinal chemistry

1 Introduction

In nature, boron generally exists as boric acid, which is an essential nutrient for plant. However, only few boron-containing organic natural compounds were found, such as boromycin and autoinducer-2 [1]. But the synthetic boron-containing compounds cover a variety of structures, including boronic acids, diazaborines, oxazaborines and benzoxaboroles.

Benzoxaboroles were first synthesized and characterized in 1957 by Torssell [2]. Unsubstituted benzoxaborole (**1**) (Figure 1(a)) is generally named as 1,3-dihydro-1-hydroxy-2,1-benzoxaborole. In the past fifty five years, the applications of benzoxaboroles covered various fields, exemplified by organic synthesis, glycopeptides recognition and supramolecular chemistry [3]. But the applications in medicinal chemistry have only begun since 2006, when 5-flurobenzoxaborole (AN2690, **2**, Figure 1(b)) was found to have antifungal activity [4]. AN2690 inhibits fungal protein synthesis by targeting leucyl tRNA synthetase (LeuRS) [5]. It is now under Phase III clinical trials for the treatment of topical onychomycosis. With further research, benzoxaboroles show a variety of bioactivities, such as antibacterial [6], antiviral [7], anti-parasite [8] and anti-inflammatory [9].

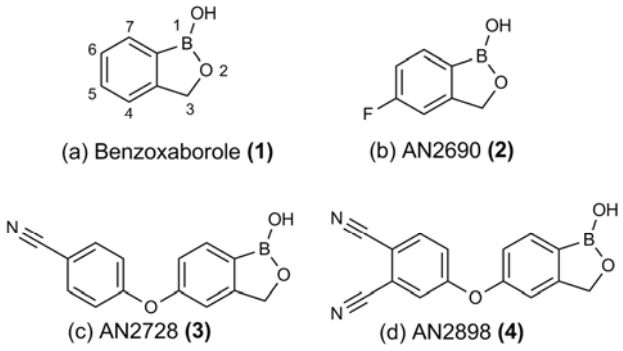


Figure 1 (a) Benzoxaborole (**1**); (b) AN2690 (**2**), Phase III trials for topical treatment of onychomycosis; (c) AN2728 (**3**), Phase II trials for topical treatment of atopic dermatitis; (d) AN2898 (**4**), Phase II trials for topical treatment of psoriasis and atopic dermatitis.

Because of the rare existence of boron-containing compounds in nature and lack of experience in drug development historically, there are concerns over benzoxaboroles' toxicology and pharmacology [1]. Fortunately, a large number of clinical trials dispelled these concerns, and literatures demonstrated that benzoxaboroles showed no genetic toxicology liability [10]. There are several benzoxaboroles

*Corresponding author (email: hczhou@sjtu.edu.cn)

in clinical trials such as AN2690 (**2**), AN2728 (**3**) and AN2898 (**4**) (Figure 1). Both of AN2728 and AN2898 are anti-inflammatory agents that are currently under Phase II clinical trials for the topical treatment of psoriasis and atopic dermatitis.

Considering the important potential applications in drug development, we provide an overview of the relevant literatures to introduce benzoxaboroles' properties, synthetic methods and applications in medicinal chemistry.

2 The properties of benoxaboroles

Compared with corresponding arylboronic acids or other compounds, benzoxaboroles show exceptional properties.

The parent structure of a benzoxaborole consists of a phenyl ring and a five-membered oxaborole ring. Single-crystal X-ray diffraction showed that the structures of benzoxaboroles in solid state were centrosymmetric dimers with two intermolecular hydrogen bonds (Figure 2) [11]. Benzoxaboroles can be treated as internal esters from corresponding *orth*-hydroxymethylphenylboronic acids. The length of exocyclic B–O bond is shorter than the endocyclic one, and the exocyclic C–B–O angle is bigger than the endocyclic one, which is the source of ring strain of the five-membered oxaborole [3]. Both experimental data and theoretical calculations indentified that the benzoxaboroles were more stable than the corresponding arylboronic acids [12], with the fact that *orth*-hydroxymethylphenylboronic acids could dehydrate spontaneously in water to generate benzoxaboroles [3]. The B–O bond of benzoxaboroles is difficult to be hydrolyzed and meanwhile the B–C bond of benzoxaboroles is also more stable than arylboronic acids. For instance, benzoxaborole could be recovered unchanged after refluxing with 10% HCl for 3 h; it could be recovered almost quantitatively after refluxing with 15% NaOH for 3 h; and it could be recovered after refluxing with thionyl chloride. By contrast, 90% *p*-tolueneboronic acid was hydrolyzed to toluene and boric acid after refluxing with 10% HCl for 1.5 h [13].

Boron contains three valence electrons and an empty p-orbital, so benzoxaboroles are electrophiles that could form dative bonds with nucleophiles. The formation of dative bonds transforms the sp^2 hybridization of boron to sp^3 hybridization, and the structure of boron is converted from uncharged, trigonal-planar structure to anionic, tetrahedral structure. This transformation releases the ring strain of the cyclic ester of benzoxaborole [1]. For example, benzoxaboroles tend to exist in charged (hydroxylated) forms under

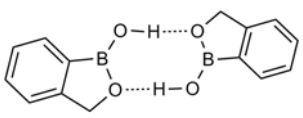


Figure 2 The dimer formed by benzoxaborole.

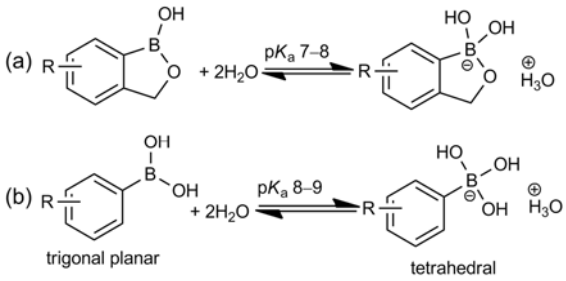


Figure 3 pK_a of benzoxaboroles (a) compared to that of phenylboronic acids (b).

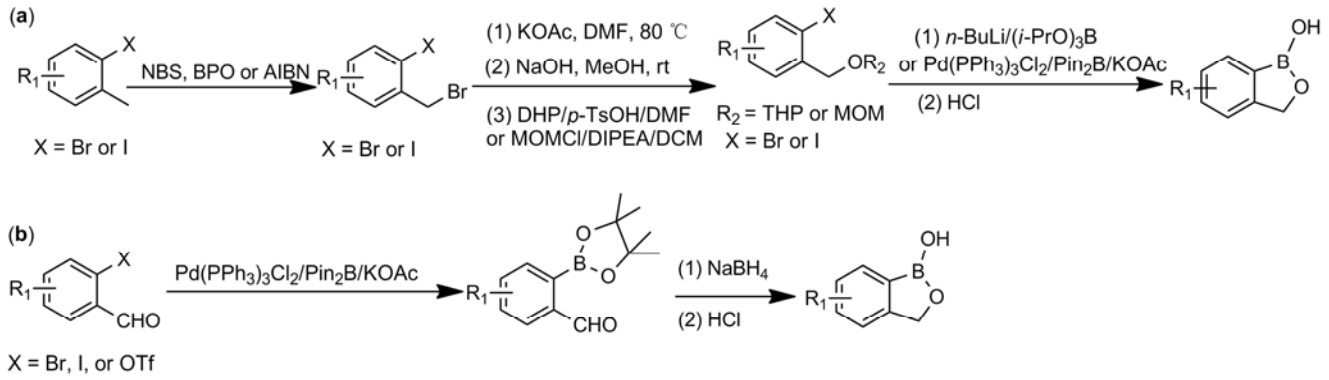
basic condition. The pK_a values of benzoxaboroles are around 7–8 [14], 1–2 units lower than the corresponding phenylboronic acids (Figure 3). Consequently, benzoxaboroles have better solubility in water at physiological pH compared with phenylboronic acids. And good solubility in physiological pH required for clinical drug candidates is one of the drug-like properties.

3 Synthesis of benzoxaboroles

3.1 Synthesis of benzoxaboroles with substitutions on the phenyl ring

The currently reported benzoxaboroles with the applications in medicinal chemistry are mainly limited to the benzoxaboroles with substitutions on the phenyl ring. For example, 5-flurobenzoxaborole (AN2690, **2**) shows broad antifungal activity [4]; 6-substituted benzoxaboroles show potent activity of anti-trypanosomiasis [8]; 7-substituted benzoxaboroles show good antimalarial activity [15].

There are various methods to synthesize these benzoxaboroles. The commonly used methods can be classified into two categories: (1) Using corresponding *ortho*-bromo or *ortho*-iodo toluene derivatives as starting materials, benzylic methyl is brominated by *N*-bromosuccinimide or bromine, followed by hydrolysis of bromide to benzyl alcohol via multistep reactions. The hydroxyl group is generally protected by 3,4-dihdropyran or MOMCl. The boronic group is installed via the reaction with butyl lithium/borate. After the protecting groups are removed under acidic condition followed by intramolecular esterification, benzoxaboroles are obtained (Scheme 1(a)) [8–9, 16–19]; (2) Starting from *ortho*-formyl-substituted aryl halides or triflates, arylboronates are obtained after reaction with bis(pinacolato) diboron with Pd catalyst ($Pd(PPh_3)_3Cl_2$ or $Pd(pddf)Cl_2$) in the presence of weak base, such as KOAc. After the formyl group is reduced to hydroxyl group, the pinacol ester is hydrolyzed to arylboronic acid followed by intramolecular esterification to form benzoxaboroles under acidic condition (Scheme 1(b)) [15, 20–23]. The latter method has the advantage of mild reaction conditions, so functional groups, such as cyano, carbonyl, remain intact. In addition, the high yields of this method [24–26] made it widely recommended



Scheme 1 The commonly used methods for the synthesis of benzoxaboroles with substituted phenyl rings.

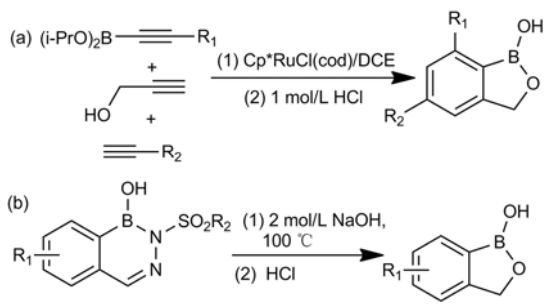
in recent literatures.

Alternative approaches have also been reported for the preparation of benzoxaboroles. For instance, Yamamoto *et al*. [27, 28] prepared benzoxaboroles via Ru catalyzed cyclotrimerization from alkynes, which can be used to prepare 5,7-disubstituted benzoxaboroles conveniently (Scheme 2(a)); Grassberger [29] hydrolyzed 1,2-dihydro-1-hydroxy-2,3,1-benzodiazaborines to corresponding benzoxaboroles (Scheme 2(b)).

The stability of the benzoxaborole core allows modifications under various reaction conditions. For instance, benzoxaborole could be nitrated with fuming nitric acid to obtain 6-nitrobenzoxaborole, which could subsequently be reduced to 6-aminobenzoxaborole under hydrogen in the presence of Raney nickel or Pd/C (Scheme 3(a)) [30]; they could be oxidized with CrO_3 without any damage of the scaffold (Scheme 3(b)) [31]; could be heated to reflux for 6 hours under 6 mol/L NaOH (Scheme 3(c)) [9]; they could tolerate concentrated hydrochloric acid or reduction with lithium aluminum hydride (Scheme 3(d)) [32].

3.2 Synthesis of 1-substituted benzoxaboroles

B–OH group in the 1-position of benzoxaboroles can react with alcohols in dry solvent to yield esters. However, simple alkyl esters are extremely sensitive to water. They absorb moisture from the air and spontaneously hydrolyze to the corresponding benzoxaboroles (Scheme 4) [33]. But some of the esters are rather stable toward hydrolysis. For example, the ethanolamine ester of benzoxaborole (**5**) (Figure 4) is stable due to the additional coordination between boron atom and amino group [3, 33]. Similarly, X-ray crystal structure [34] showed that the 10-hydroxybenzo[*h*] quinoline ester (**6**, Figure 4) also has the similar bidentate coordination, and thus showed good stability.



Scheme 2 Alternative methods for the preparation of benzoxaboroles with substitute phenyl rings.

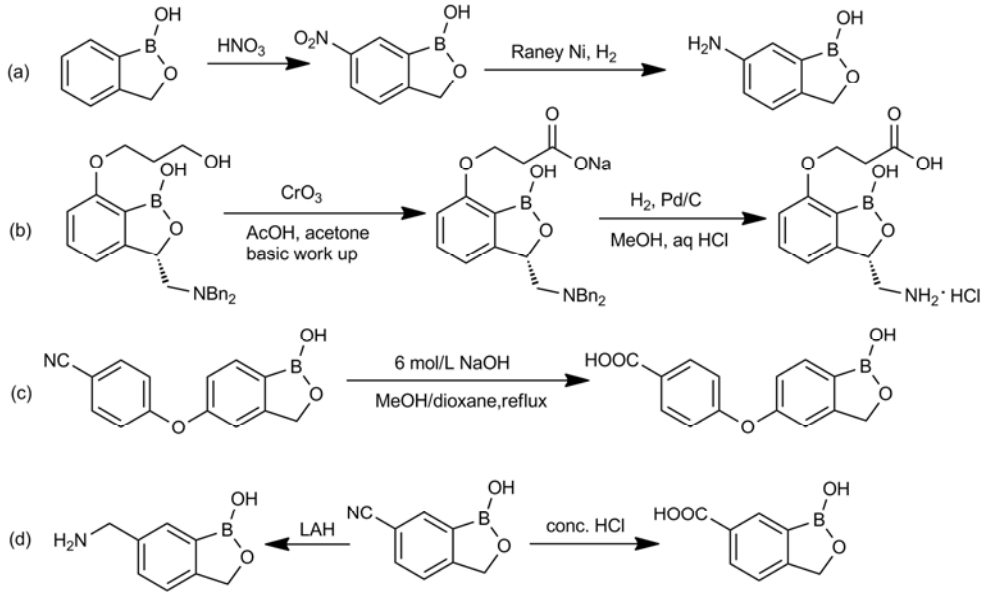
Bezoxaboroles bearing aryl or heteroaryl groups directly on the boron atom can be prepared as shown in Scheme 5 [4]. Protected 2-bromobenzyl alcohols are first treated with butyl lithium and then reacted with the corresponding boronic acid esters to give borinic acid. Subsequently, the protecting group is removed under acidic condition to form the corresponding benzoxaboroles.

3.3 Synthesis of 3-substituted benzoxaboroles

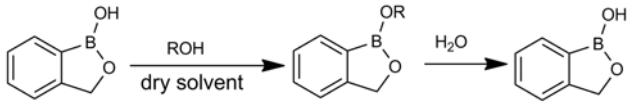
Bezoxaboroles with substituents at the C(3) position can be obtained with methods similar to those described in Section 3.1. The starting materials are brominated by *N*-bromosuccinimide, and then hydrolyzed to the alcohol intermediates, which are subsequently cyclized to form lactone under acidic conditions (Scheme 6(a)) [35, 36].

Starting from *o*-formyl arylboronic acids, followed by the treatment with nucleophiles, 3-substituted benzoxaboroles can be conveniently synthesized as shown in Scheme 6(b) [35]. Snyder and coworkers synthesized 3-substituted derivatives by the reactions of *o*-formylarylboronic acids with nucleophiles, such as sodium cyanide, isopropylidene malonate and nitromethane [37]. Sporzyński *et al*. [35, 38] used *o*-formyl arylboronic acids and secondary amines to prepare the corresponding 3-substituted derivatives.

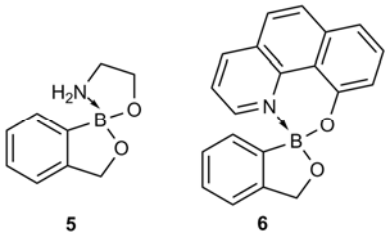
In addition, 3-substituted benzoxaboroles can be synthesized through reaction of protected arylboronic acids with butyl lithium, followed by the treatment with aldehydes (Scheme 6(c)) [3, 39].



Scheme 3 Benzoxaboroles can tolerate various reaction conditions.

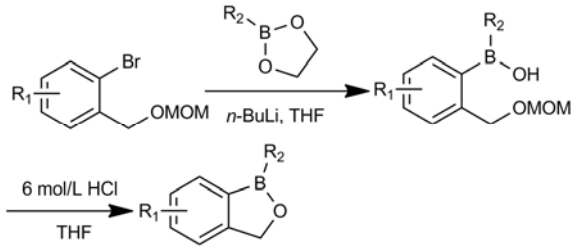


Scheme 4 The esterfication of benzoxaboroles at 1-position.



5 **6**

Figure 4 Bidentate coordination between boron atom and nitrogen-containing ligands.



Scheme 5 Synthesis of 1-substituted benzoxaboroles.

4 Applications in medicinal chemistry

4.1 Applications in organic synthesis

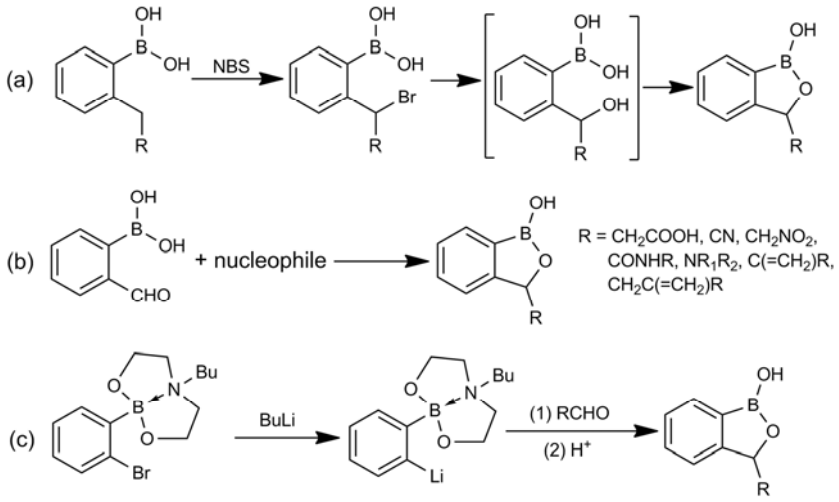
Benzoxaboroles are important organic synthetic intermediates playing a critical role in organic chemistry, especially in Suzuki-Miyaura cross coupling reaction. Benzoxaboroles can be used to prepare *ortho*-substituted benzyl alcohols through Suzuki-Miyaura cross coupling reaction. For instance, a benzoxaborole derivative was applied in the total synthesis of vancomycin by Nicolaou *et al*. [40], wherein a benzoxaborole was cross coupled with an aryl iodide to obtain the benzyl alcohol intermediate for the total synthesis of vancomycin (Scheme 7).

Yamamoto *et al.* [28] reported that benzoxaboroles could be converted to various compounds with the assistance of Ru or Pd catalysts as shown in Scheme 8.

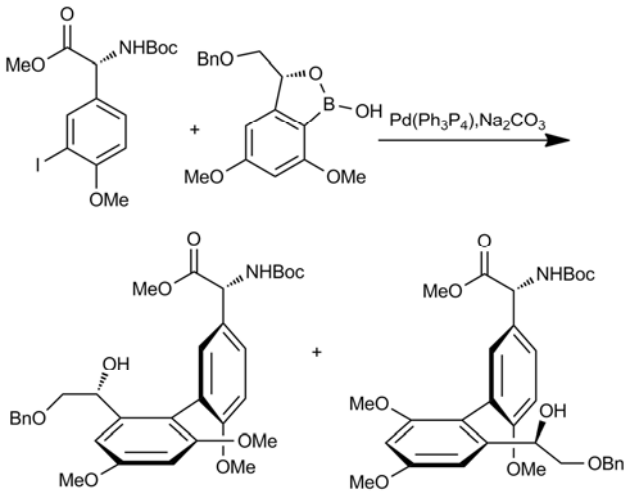
4.2 Application as antifungal agents

AN2690 (**2**, Figure 1(b)) is the first well studied benzoxaborole antifungal agent [4]. It effectively penetrates the nail plate and nail bed [41], and is currently in Phase III clinical trials for the topical treatment of onychomycosis [42]. AN2690 is a broad spectrum antifungal agent targeting various pathogens including *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Cryptococcus neoformans* and *aspergillus* [1, 4]. Structure-activity relationship (SAR) studies [4, 5] demonstrated that the five-membered oxaborole ring was indispensable for its antifungal activity. Its 5-chloro analog (AN2718) showed greater potency in the inhibition of *Trichophyton rubrum* and *Trichophyton mentagrophytes*, and had completed Phase I clinical trials [42].

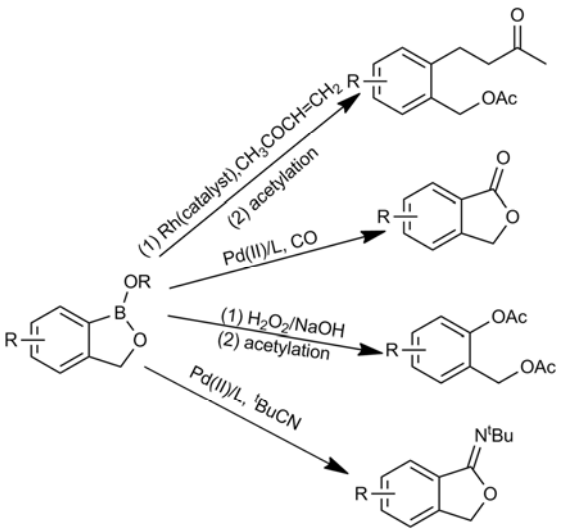
Benzoxaboroles block protein synthesis by targeting fungal leucyl-tRNA synthetase (LeuRS) [5]. Aminoacyl-tRNA synthetases catalyze the attachment of amino acids to their corresponding cognate tRNAs, which precedes the transportation of the resultant aminoacyl-tRNA to ribosome



Scheme 6 Synthesis of of 3-substituted benzoxaboroles.



Scheme 7 A benzoxaborole derivative was applied in the total synthesis of vancomycin.



Scheme 8 Application of benzoxaboroles in organic synthesis.

for protein synthesis. Seven out of the twenty aminoacyl-tRNA synthetases have both an editing domain and a synthetic domain. The synthetic domain charges the correct amino to the terminus of corresponding tRNA, while the editing domain is responsible for the proof-reading of aminoacyl-tRNA, and hydrolyzes mis-charged tRNA. The boron atom of the benzoxaborole inhibitors forms a covalent tetrahedral adduct with the 2′- and 3′-hydroxy groups of tRNA's 3′-terminal adenosine in the editing pocket [1, 5] (Figure 5), thus trapping the tRNA in the editing site and blocking protein synthesis as the consequence.

4.3 Application as antibacterial agents

Benzoxboroles also inhibit bacterial aminoacyl tRNA synthetases. GSK2251052 (**7**, Figure 6) [31] was proved to target bacterial LeuRS. Its antibacterial activity was not affected by general resistance mechanisms including efflux pumps and β-lactamases. Unfortunately, although GSK2251052 showed good inhibitory activity against Gram-negative bacterial infections, it was discontinued in the Phase II clinical trials due to the findings of resistance in a small number of patients undergoing treatment of complicated urinary tract infections.

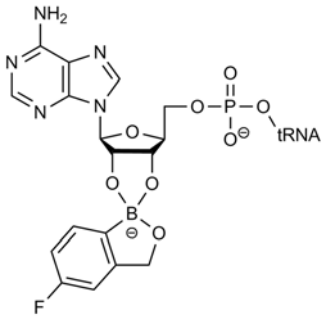


Figure 5 The complex of tRNA-AN2690.

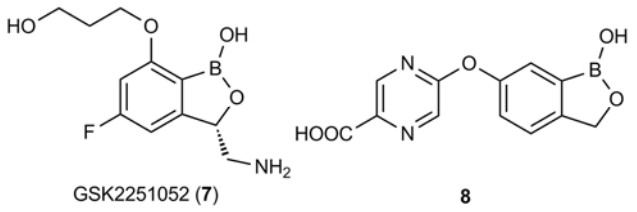


Figure 6 The structures of benzoxaboroles as antibacterial agents.

Benzoxaboroles have been reported to inhibit β-lactamases. The β-lactam antibiotics is one of the most widely used antibacterial agents. Resistance to β-lactam antibiotics occurs when bacteria acquire the β-lactamases which catalyze the hydrolysis of β-lactam ring [43]. Xia *et al*. [6] reported 6-aryloxy benzoxaboroles as a new class of β-lactamase inhibitors. As an example, compound **8** (Figure 6) inhibits CMY-2 and AmpC P99, which are class C β-lactamases, with K_i values in low nanomolar range. With the presence of compound **8** at the concentration of 8 μg/mL, the minimum inhibitory concentration (MIC) of ceftazidime, which is a third-generation cephalosporin antibiotic, was restored from > 128 μg/mL to 1 μg/mL against *E. cloacac* expressing AmpC P99 and 0.5 μg/mL against *E. coli* expressing CMY-2.

4.4 Application as antiviral agents

Hepatitis C virus (HCV) is one of the main causes of chronic liver diseases, such as cirrhosis, liver cancer and hepatic failure [44]. There are approximately 200 million people worldwide infected by HCV. The general treatment for HCV is the combination therapy of ribavirin and injectable pegylated interferon-α. But this treatment is restricted by the limited efficacy and side effects, so it is urgent to develop new drugs against HCV [45]. Since HCV NS3 serine protease plays an important role in the replication of the virus, HCV NS3 became a promising target for the treatment of HCV infection [46]. Extensive efforts have been made to develop novel benzoxaborole-containing macrocylic (Figure 7(a, b)) and acyclic (Figure 7(c)) HCV NS3 protease inhibitors [7, 32, 47]. Some of these compounds showed excellent inhibitory activity against HCV NS3 protease and viral replication.

4.5 Application as antiparasitic agents

Benzoxaboroles represent a novel class of anti-parasitic agents. A number of studies demonstrated their applications in the treatment of African trypanosomiasis and malaria, which has been reviewed in detail [48–50]. Here, we summarize the status of discovery and the latest developments in this field.

African trypanosomiasis, also named sleeping sickness, is prevalent in sub-Saharan Africa. More than one million people were infected by the causative pathogen *Trypanosome brucei*, including *T. b. gambiense* and *T. b. rhodesiense*. Over 95% of the cases are caused by *T. b. gambiense*, while less than 5% attribute to *T. b. rhodesiense* [49, 50].

Zhou *et al*. [17] reported benzoxaborole-based *T. brucei* LeuRS inhibitors as antitrypanosomal agents (Figure 8(a)). More antitrypanosomal benzoxaboroles have been discovered by phenotypic screening approaches (Figure 8(b–d)) [8, 19, 51, 52]. Their mechanisms of action remain unclear and are currently under investigation.

All currently reported benzoxaborole antitrypanosomal agents belong to 6-substituted benzoxaboroles. SCYX-7158 (**9**, Figure 8(d)) is currently in Phase I clinical trials.

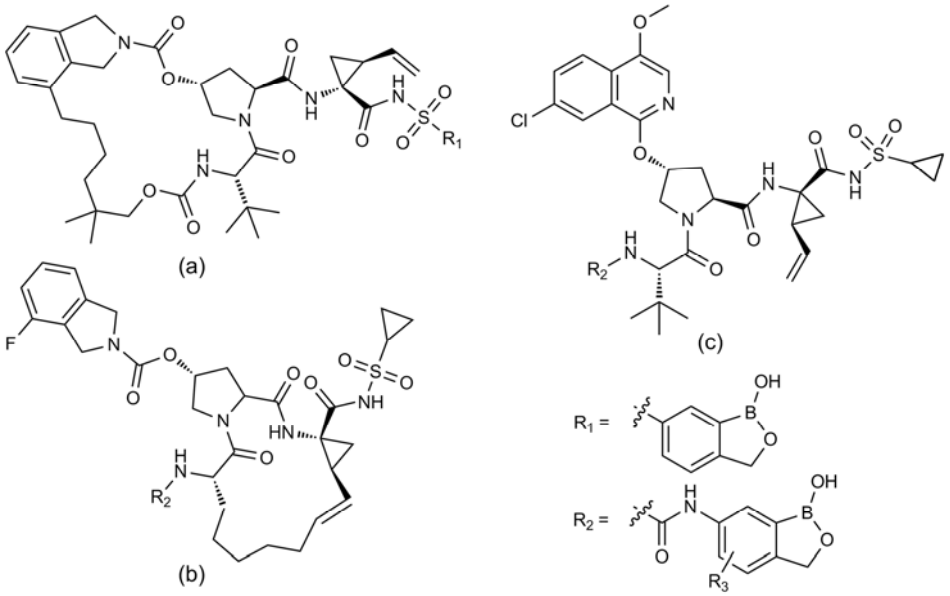


Figure 7 Benzoxaborole-containing macrocylic (a, b) and acyclic (c) HCV NS3 protease inhibitors.

Malaria is caused by the infection of *Plasmodium falciparum* via mosquitoe as the vector. It strikes an estimated 250 million population and leads to 1 million deaths worldwide annually. Compound **10** (Figure 9) was discovered to be a potent antimalarial agent with inhibitory IC_{50} of 26 nmol/L against *Plasmodium falciparum*. It also showed desirable drug-like properties, including low molecular weight (206), low Clog*P* (0.86) and high water solubility (750 μg/mL at pH 7.0) [15]. Structure-activity relationship studies revealed that the 4-fluoro derivative **11** (Figure 9) showed 1.7 fold increase of activity against *Plasmodium falciparum* when compared to compound **10** [22].

4.6 Application as anti-inflammatory agents

Benzoxaboroles also display anti-inflammatory activity. Akama and coworkers [9, 16] reported studies about 5/6-substituted benzoxaboroles as anti-inflammatory agents. The 5-substituted AN2728 (**3**) and AN2898 (**4**) (Figure 1(c)), and 6-substituted AN3485 (**12**, Figure 10) were found to be potent anti-inflammatory agents. AN2728 shows inhibitory activity against phosphodiesterase 4 (PDE4), which is a known anti-inflammatory target, with an IC_{50} of 0.49 μmol/L, and simultaneously blocks the release of cytokines such as TNF-α (IC_{50} = 0.54 μmol/L) and IFN-γ (IC_{50} = 2.4 μmol/L) [9]. Currently AN2728 is in Phase II clinical trials for the topical treatment of psoriasis and atopic dermatitis. AN2898, which is an analog of AN2728, is also a PDE4 inhibitor and is currently in Phase II clinical trials for topical treatment of psoriasis and atopic dermatitis. AN3485 shows excellent inhibitory activity against cytokines, including TNF-α, IL-6, and IL-1β, with IC_{50} values in the range of 33 nmol/L to 83 nmol/L [16]. It suppresses the production of TNF-α and IL-6 with an ED_{50} of 30 mg/kg in a murine model. Furthermore, it can be administered orally. The 5-substituted benzoxaborole **13** (Figure 10) also shows good inhibitory activity against PDE4 (IC_{50} = 47 nmol/L) with low systemic side effects [23].

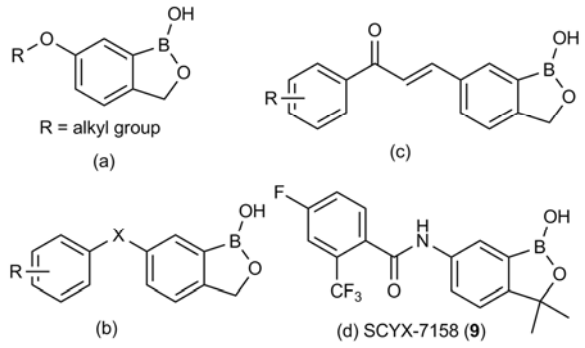


Figure 8 The structures of benzoxaboroles as antitrypanosomal agents.

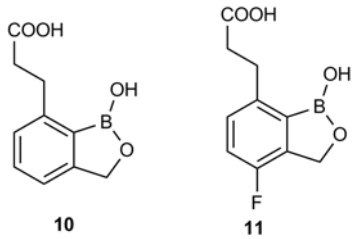


Figure 9 The structures of benzoxaboroles as antimalarial agents.

4.7 Application as anticancer agents

There are very limited literatures on the application of benzoxaboroles in the field of antitumor research. Kumar *et al.* [53] tested benzoxaboroles against cancer cell lines including breast cancer cells MCF-7 and multiple myeloma cells RPMI-8226, but none of the compounds showed any inhibitory activity.

It is worth mentioning the boron neutron capture therapy (BNCT) [21, 54] in this context. After the absorption of thermal neutrons, ^{10}B self-destructs to release lithium ion (^{7}Li) and high energy α-particles (^{4}He). *p*-Boronophenylalanine (BPA, **14**, Figure 11) is a boron-containing amino acid with high affinity to tumor cells, thus when, ^{10}B-containing BPA is enriched in tumor tissues it could kill cancer cells upon irradiation of thermal neutrons. But the clinical use is limited due to its poor water solubility at physiological pH. With pK_a values in the range of 7–8, benzoxaboroles have the advantage of improved water solubility at the physiological pH of 7.4. Li *et al.* [21] synthesized benzoxaborole-containing phenylalanine analogs **15** and **16** (Figure 11) which showed 2–3 folds of increased water solubility as compared with BPA. These analogs may be of use in BNCT, but subsequent study was not reported.

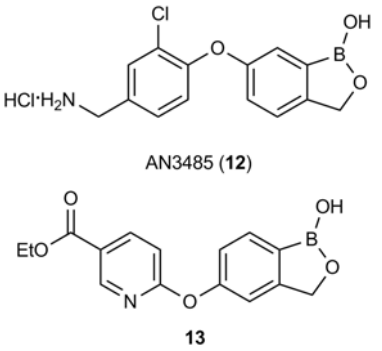


Figure 10 The structures of benzoxaboroles as anti-inflammatory agents.

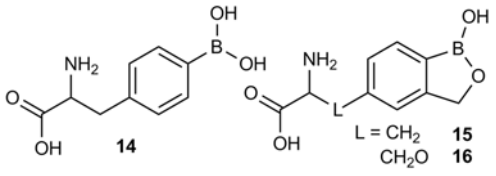


Figure 11 The structure of *p*-boronophenylanine (**14**) and benzoxaborole-containing phenylalanine analogs (**15**, **16**).

4.8 Application of natural products conjugated with benzoxaboroles

Privileged scaffolds from natural products possess a variety of bioactivities. These scaffolds were used as chemoyl or a combination of chemoyls [55] in conjugation with benzoxaboroles to acquire new properties. Zhou *et al.* conjugated chalcone structure with benzoxaboroles to obtain chalcone-benzoxaborole hybrids (Figure 12(a)), which showed excellent antitrypanosomal activity. For example, compound **17** (Figure 12(b)) showed an IC_{50} value of 0.01 μg/mL against the blood stream form of the parasites and was effective in a murine infection model [8].

Glycopeptide antibiotics, such as vancomycin, exert their antibacterial activity by inhibiting the synthesis of bacterial cell wall. When the D-alanine at the C-terminal of peptidoglycan is replaced by D-lactate the bacterium renders resistance to glycopeptide antibiotics. Preobrazhenskaya and coworkers [56] conjugated benzoxaboroles with glycopeptide antibiotics, such as vancomycin, eremomycin, and teicoplanin, to obtain teicoplanin aglycone-benzoxaborole derivatives (Figure 13) which overcame resistance of gram-positive bacteria to vancomycin.

5 Conclusion and prospect

Benzoxaboroles were largely neglected in the past and have begun to draw interests from researchers in recent years. They have been applied in organic synthesis, molecular recognition, supramolecular chemistry, and medicinal chemistry. Benzoxaboroles display desirable physicochemical properties and low toxicity. Their successful applications in antifungal, antibacterial, antiviral, and antiparasitic fields demonstrate that benzoxaboroles have become a new class of anti-infective agents. We believe that more benzoxaboroles with promising efficacy and low toxicity would emerge in the future.

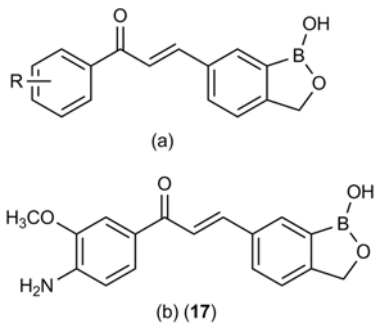


Figure 12 Chalcone-benzoxaborole hybrids.

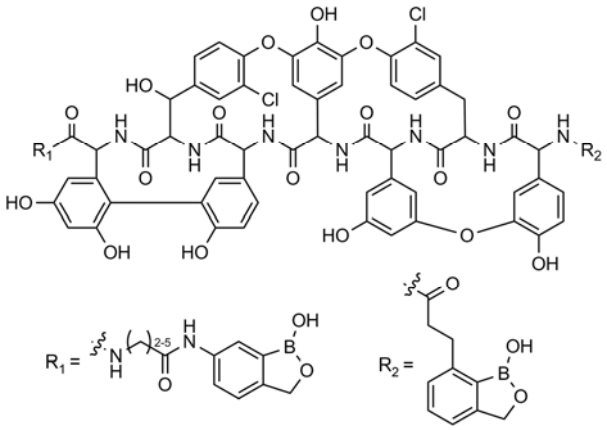


Figure 13 Teicoplanin aglycone-benzoxaborole derivatives.

This work was financially supported by National Natural Science Foundatoin of China (81222042) and National Basic Research Program of China (2009CB918404, 2012CB518001).

1 Baker SJ, Tomsho JW, Benkovic SJ. Boron-containing inhibitors of synthetases. *Chem Soc Rev*, 2011, 40: 4279–4285
2 Torssell K. Arylboronic acids. III. Bromination of tolylboronic acids according to Wohl-Ziegler. *Ark Kemi*, 1957, 10: 507–511
3 Adamczyk-Woźniak A, Cyrański MK, Żubrowska A, Sporzyński A. Benzoxaboroles—Old compounds with new applications. *J Organomet Chem*, 2009, 694: 3533–3541
4 Baker SJ, Zhang YK, Akama T, Lau A, Zhou HC, Hernandez V, Mao WM, Alley MRK, Sanders V, Plattner JJ. Discovery of a new boron-containing antifungal agent, 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690), for the potential treatment of Onychomycosis. *J Med Chem*, 2006, 49: 4447–4450
5 Rock FL, Mao WM, Yaremchuk A, Tukalo M, Crepin T, Zhou HC, Zhang YK, Hernandez V, Akama T, Baker SJ. An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site. *Science*, 2007, 316: 1759–1761
6 Xia Y, Cao K, Zhou Y, Alley MRK, Rock F, Mohan M, Meewana M, Baker SJ, Lux S, Ding CZ, Jia GF, Kullyb M, Plattner JJ. Synthesis and SAR of novel benzoxaboroles as a new class of β-lactamase inhibitors. *Bioorg Med Chem Lett*, 2011, 21: 2533–2536
7 Li XF, Zhang SM, Zhang YK, Liu YD, Charles Z, Zhou Y, Plattner JJ, Baker SJ, Bu W, Liu L, Kazmierski WM, Duan MS, Grimes RM, Wright LL, Smith GK, Jarvest RL, Ji JJ, Cooper JP, Tallant MD, Crosby RM, Creech K, Ni ZJ, Zou WX, Wright J. Synthesis and SAR of acyclic HCV NS3 protease inhibitors with novel P4-benzoxaborole moieties. *Bioorg Med Chem Lett*, 2011, 21: 2048–2054
8 Qiao ZT, Wang Q, Zhang FL, Wang ZL, Bowling T, Nare B, Jacobs RT, Zhang J, Ding DZ, Liu YG, Zhou HC. Chalcone-benzoxaborole hybrid molecules as potent antitrypanosomal agents. *J Med Chem*, 2012, 55: 3553–3557
9 Akama T, Baker SJ, Zhang YK, Hernandez V, Zhou HC, Sanders V, Freund Y, Kimura R, Maples KR, Plattner JJ. Discovery and structure-activity study of a novel benzoxaborole anti-inflammatory agent (AN2728) for the potential topical treatment of psoriasis and atopic dermatitis. *Bioorg Med Chem Lett*, 2009, 19: 2129–2132
10 Ciaravino V, Plattner J, Chanda S. An assessment of the genetic toxicology of novel boron-containing therapeutic agents. *Environ Mol Mutagen*, 2013, 54: 338–346
11 Adamczyk-Woźniak A, Cyrański MK, Jakubczyk M, Klimentowska P, Koll A, Kołodziejczak J, Pojmaj G, Żubrowska A, Żukowska GZ, Sporzyński A. Influence of the substituents on the structure and properties of benzoxaboroles. *J Phys Chem*, 2010, 114: 324–2330
12 Jezierska A, Panek JJ, Zukowska GZ, Sporzynski AA. A combined experimental and theoretical study of benzoxaborole derivatives by Raman and IR spectroscopy, static DFT, and first-principle molecular dynamics. *J Phys Org Chem*, 2010, 3: 451–460
13 Snyder HR, Reedy AJ, Lennarz WJ. Synthesis of aromatic boronic acids. Aldehydo boronic acids and a boronic acid analog of tyrosine. *J Am Chem Soc*, 1958, 80: 835–838

14 John W. Tomsho JW, Pal A, Hall DG, Benkovic SJ. Ring structure and aromatic substituent effects on the pK_a of the benzoxaborole pharmacophore. *ACS Med Chem Lett*, 2012, 3: 48–52

15 Zhang YK, Plattner JJ, Yvonne R. Freund, Easom EE, Zhou Y, Gut J, Rosenthal PJ, Waterson D, Gamo F, Angulo-Barturen I, Ge M, Li ZY, Li LC, Jian Y, Cui H, Wang HL, Yang J. Synthesis and structure-activity relationships of novel benzoxaboroles as a new class of anti-malarial agents. *Bioorg Med Chem Lett*, 2011, 21: 644–651

16 Akama T, Virtucio C, Dong C, Kimura R, Zhang YK, Nieman JA, Sharma R, Lu XS, Sales M, Singh R. Structure-activity relationships of 6-(aminomethylphenoxy)-benzoxaborole derivatives as anti-inflammatory agent. *Bioorg Med Chem Lett*, 2013, 23: 1680–1683

17 Ding DZ, Meng QQ, Gao GW, Zhao YX, Wang Q, NareB, Jacobs R, Rock F, Alley MRK, Plattner JJ, Chen GQ, Li DW, Zhou HC. Design, synthesis, and structure-activity relationship of trypanosoma brucei leucyl-tRNA synthetase inhibitors as antitrypanosomal agents. *J Med Chem*, 2011, 54: 1276–1287

18 Baker SJ, Zhang YK, Akama T, Wheeler C, Plattner JJ, Rosser RM, Reid RP, Nixon NS. Synthesis of isotopically labelled (3-^{14}C)- and (3, 3-$^{2}H_2$)-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690), a new antifungal agent for the potential treatment of onychomycosis. *J Labelled Compd Radiopharm*, 2007, 50: 245–250

19 Ding DZ, Zhao YX, Meng QQ, Xie DS, Nare B, Chen DT, Bacchi CJ, Yarlett N, Zhang YK, Hernandez V. Discovery of novel benzoxaborole-based potent antitrypanosomal Agents. *ACS Med Chem Lett*, 2010, 1: 165–169

20 Zhang YK, Plattner JJ, Easom EE, Waterson D, Ge M, Li ZY, Li LC, Jian Y. An efficient synthesis for a new class antimalarial agent, 7-(2-carboxyethyl)-1, 3-dihydro-1-hydroxy-2, 1-benzoxaborole. *Tetrahedron Lett*, 2011, 52: 3909–3911

21 Li XF, Plattner JJ, Hernandez V, Ding CZ, Wu W, Yang Y, Xu MS. Synthesis of novel benzoxaborole-containing phenylalanine analogues. *Tetrahedron Lett*, 2011, 52: 4924–4926

22 Zhang YK, Plattner JJ, Freund YR, Easom EE, Zhou Y, Ye L, Zhou HC, Waterson D, Gamo F, Sanz LM, Ge M, Li ZY, Li LC, Wang HL, Cui H. Benzoxaborole antimalarial agents. Part 2: Discovery of fluoro-substituted 7-(2-carboxyethyl)-1,3-dihydro-1-hydroxy-2,1-benzoxaboroles. *Bioorg Med Chem Lett*, 2012, 22: 1299–1307

23 Zhang YK, Plattner JJ, Akama T, Baker SJ, Hernandez VS, Sanders V, Freund YR, Kimura R, Bu W, Hold KM, Lu XS. Design and synthesis of boron-containing PDE4 inhibitors using soft-drug strategy for potential dermatologic anti-inflammatory application. *Bioorg Med Chem Lett*, 2010, 20: 2270–2274

24 Murata M, Oyama T, Watanabe S, Masuda Y. Palladium-catalyzed borylation of aryl halides or triflates with dialkoxyborane: A novel and facile synthetic route to arylboronates. *J Org Chem*, 2000, 65: 164–168

25 Murata M, Watanabe S, Masuda Y. Novel palladium (0)-catalyzed coupling reaction of dialkoxyborane with aryl halides: Convenient synthetic route to arylboronates. *J Org Chem*, 1997, 62: 6458–6459

26 Ishiyama T, Murata M, Miyaura N. Palladium (0)-catalyzed cross-coupling reaction of alkoxydiboron with haloarenes: A direct procedure for arylboronic esters. *J Org Chem*, 1995, 60: 7508–7510

27 Yamamoto Y, Ishii J, Nishiyama H, Itoh K. One-pot sequential four-component coupling via Cp*RuCl-catalyzed cyclotrimerization and Suzuki-Miyaura coupling. *Tetrahedron*, 2005, 61: 11501–11510

28 Yamamoto Y, Ishii J, Nishiyama H, Itoh K. Cp*RuCl-catalyzed formal intermolecular cyclotrimerization of three unsymmetrical alkynes through a boron temporary tether: Regioselective four-component coupling synthesis of phthalides. *J Am Chem Soc*, 2005, 127: 9625–9631

29 Grassberger M. Zum Abbau von 1,2-dihydro-l-hydroxy-2-organosulfonyl-2,3,1-benzodiazaborinen und -thieno[3,2-d][1,2,3]diazaborinen in alkalischer wäBriger Lösung. *Liebigs Ann Chem*, 1985: 683–688

30 Lennarz WJ, Snyder HR. Arylboronic acids. IV. reactions of boronophthalide. *J Am Chem Soc*, 1960, 82: 2172–2175

31 Bowers GD, Tenero D, Patel P, Huynh P, Sigafoos J, O'Mara K, Young GC, Dumont E, Cunningham E, Kurtinecz M, Stump P, Conde JJ, Chism JP, Reese MJ, Yueh YL, Tomayko JF. Disposition and metabolism of GSK2251052 in humans: A novel boron-containing antibiotic. *Drug Metab Dispos*, 2013, 41: 1070–1081

32 Ding CZ, Zhang YK, Li XF, Liu Y, Zhang SM, Zhou YS, Plattner JJ, Baker SJ, Liu LA, Duan MS, Jarvest RL, Ji JJ, Kazmierski WM, Tallant MD, Wright LL, Smith GK, Crosby RM, Wang AA, Ni ZJ, Zou WX, Wright J. Synthesis and biological evaluations of P4-benzoxaborole-substituted macrocyclic inhibitors of HCV NS3 protease. *Bioorg Med Chem Lett*, 2010, 20: 7317–7322

33 Haynes RR, Snyder HR. Arylboronic acids. VIII. Reactions of boronophthalide. *J Org Chem*, 1964, 29: 3229–3233

34 Robin B, Buell G, Kiprof P, Nemykin VN. 3H-2,1-Benzoxaborole-1-spiro-4′-(5-oxa-3a-aza-4-borapyrene). *Acta Cryst*, 2008, 64: o314–o315

35 Adamczyk-Wozniak A, Madura I, Velders AH, Sporzynski A. Diverse reactivity of 2-formylphenylboronic acid with secondary amines: synthesis of 3-amino-substituted benzoxaboroles. *Tetrahedron Lett*, 2010, 51: 6181–6185

36 Zhdankin VV, Persichini PJ, Zhang L, Fix S, Kiprof P. Synthesis and structure of benzoboroxoles: Novel organoboron heterocycles. *Tetrahedron Lett*, 1999, 40: 6705–6708

37 Tschampel P, Snyder HR. Arylboronic acids. VII. Some reactions of o-formylbenzeneboronic acid. *J Org Chem*, 1964, 29: 2168–2172

38 Sporzynski A, Lewandowski M, Rogowska P, Cyranski MK. 1,3-Dihydro-1-hydroxy-3-morpholin-4-yl-2,1-benzoxaborole: Product of the reaction of o-formylphenylboronic acid with morpholine. *Appl Organometal Chem*, 2005, 19: 1202–1203

39 Dąbrowski M, Kurach P, Luliński S, Serwatowski J. Anortho-lithiated derivative of protected phenylboronic acid: An approach to ortho-functionalized arylboronic acids and 1,3-dihydro-1-hydroxybenzo [c][2,1]oxaboroles. *Appl Organometal Chem*, 2007, 21: 234–238

40 Nicolaou KC, Natarajan S, Li H, Jain NF, Hughes R, Solomon ME, Ramanjulu JM, Boddy CNC, Takayanagi M. Total synthesis of vancomycin aglycon-part 1: Synthesis of amino acids 4-7 and construction of the AB-COD ring skeleton. *Angew Chem Int Ed*, 1998, 37: 2708–2714

41 Hui XY, Baker SJ, Wester RC, Barbadillo S, Cashmore AK, Sanders V, Hold KM, Akama T, Zhang YK, Plattner JJ. *In vitro* penetration of a novel oxaborole antifungal (AN2690) into the human nail plate. *J Pharm Sci*, 2007, 96: 2622–2631

42 Gupta AK, Simpson FC. New therapeutic options for onychomycosis. *Expert Opin Pharmacother*, 2012, 13: 1131–1142

43 Livermore DM. β-Lactamase-mediated resistance and opportunities for its control. *J Antimicrob Chemother*, 1998, 41: 25–41

44 Zoulim F, Chevallier M, Maynard M, Trepo C. Clinical consequences of hepatitis C virus infection. *Rev Med Virol*, 2003, 13: 57–68

45 Fried MW. Side effects of terapy of Hepatitis C and their management. *Hepatology*, 2002, 36: S237

46 Reiser M, Timm J. Serine protease inhibitors as anti-hepatitis C virus agents. *Expert Rev Anti Infect Ther*, 2009, 7: 537–547

47 Li XF, Zhang YK, Liu Y, Zhang SM, Ding CZ, Zhou Y, Plattner JJ, Baker SJ, Liu L, Bu W, Kazmierski WM, Wright LL, Smith GK, Jarvest RL, Duan MS, Ji JJ, Cooper JP, Tallant MD, Crosby RM, Creech K, Ni ZJ, Zou WX, Wright J. Synthesis of new acylsulfamoyl benzoxaboroles as potent inhibitors of HCV NS3 protease. *Bioorg Med Chem Lett*, 2010, 20: 7493–7497

48 Barrett MP, Croft SL. Management of trypanosomiasis and leishmaniasis. *Brit Med Bull*, 2012, 104: 175–196

49 Jacobs RT, Plattner JJ, Keenan M. Boron-based drugs as antiprotozoals. *Curr Opin Infect Dis*, 2011, 24: 586–592

50 Brun R, Don R, Jacobs RT, Wang MZ, Barrett MP. Development of novel drugs for human African trypanosomiasis. *Future Microbiol*, 2011, 6: 677–691

51 Jacobs RT, Plattner JJ, Nare B, Wring SA, Chen DT, Freund Y, Gaukel EG, Orr MD, Perales JB, Jenks M, Noe RA, Sligar JM, Zhang YK, Bacchi CJ, Yarlett N, Don R. Benzoxaboroles: A new class of potential drugs for human African trypanosomiasis. *Future Med Chem*, 2011, 3: 1259–1278

52 Jacobs RT, Nare B, Wring SA, Orr MD, Chen DT, Sligar JM, Jenks

MX, Noe RA, Bowling TS, Mercer LT, Rewerts C, Gaukel E, Owens J, Parham R, Randolph R, Beaudet B, Bacchi CJ, Yarlett N, Plattner JJ, Freund Y, Ding C, Akama T, Zhang YK, Brun R, Kaiser M, Scandale I, Don R. SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 Human African trypanosomiasis. *PLoS Negl Trop Dis*, 2011, 5: e1151

53 Kumar JS, Alam MA, Gurrapu S, Nelson G, Williams M, Corsello MA, Johnson JL, Jonnalagadda SC, Mereddy VR. Synthesis and biological evaluation of novel benzoxaboroles as potential antimicrobial and anti-cancer agents. *J Heterocyclic Chem*, 2013. doi: 10.1002/jhet.1777

54 Kabalka GW, Yao ML. Anticancer agents. *Med Chem*, 2006, 6: 111–125

55 Xu J, Gu Q, Liu HB, Zhou JJ, Bu XZ, Huang ZS, Lu G, Li D, Wei DQ, Wang L, Gu LQ. Chemomics and drug innovation. *Sci China Chem*, 2013, 56: 71–85

56 Printsevskaya SS, Reznikova MI, Korolev AM, Lapa GB, Olsufyeva EN, Preobrazhenskaya MN, Plattner JJ, Zhang YK. Synthesis and study of antibacterial activities of antibacterial glycopeptide antibiotics conjugated with benzoxaboroles. *Future Med Chem*, 2013, 5: 641–652