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Progress in the medicinal chemistry of organoboron compounds

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The review aims to draw attention to the latest advances in the organoboron chemistry and therapeutic use of organoboron compounds. The synthetic strategies towards boron-containing compounds with proven *in vitro* and/or *in vivo* biological activities, including derivatives of boronic acids, benzoxaboroles, benzoxaborines and benzodiazaborines, are summarized. Approaches to the synthesis of hybrid structures containing an organoboron moiety as one of the pharmacophores are considered, and the effect of this modification on the pharmacological activity of the initial molecules is analyzed. On the basis of analysis of the published data, the most promising areas of research in the field of organoboron compounds are identified, including the latest methods of synthesis, modification and design of effective therapeutic agents.
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1. Introduction

The boron atom possesses specific properties, owing to its unique electronic structure. Some of its properties can be useful for the development of new diagnostic and therapeutic agents. High Lewis acidity of the boron atom, the presence of the vacant p orbital and neutron induced nuclear fission form the basis for the development of boron-based hydrolytic enzyme inhibitors, chemosensors and agents for boron neutron capture therapy.[1,2] Boron compounds considered as pharmaceutical agents can be divided into three classes: inorganic boric acid derivatives with antimicrobial activity, polyhedral boron compounds and organoboron compounds — boronic acid esters and boron-containing heterocycles.

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The interest in the pharmacologically active boron compounds markedly increased after the U.S. Food and Drug Administration (FDA) approved bortezomib (Velcade®, PS-341) as a drug for the treatment of multiple myeloma in 2003. After a short period of time, the FDA approved two benzoxaborole-based therapeutic agents developed by the Anacor company, namely, tavaborole (Kerydin®) for the treatment of onychomycosis (2014) and crisaborole (Eucrisa®) for the treatment of mild and moderate atopic dermatitis (2016). In 2017, the drug Vabomere®, a combination of the meropenem antibiotic and vaborbactam, a β-lactamase inhibitor based on a 1,2-oxaborine derivative, was approved by the FDA for the treatment of complicated urinary tract infections and pyelonephritis. Several more boron-containing compounds are under various phases of clinical trials. Among them are drugs with commercial codes AN2728 and AN2898, meant for the treatment of psoriasis, and compound AN5568 (SCYX-7158), meant for the treatment of human African trypanosomiasis (sleeping sickness).

The introduction of the boron atom into a drug molecule may give rise to activity towards biological targets that seem to be unaffected by organic compounds containing no boron. A benefit of using boron atoms in molecular design is the possibility of obtaining less complex molecules than their carbon analogues, which makes it possible to reduce the commercial cost of research and production of such pharmaceutical agents.

Thus, organoboron compounds possess a unique molecular structure, and, together with low toxicity and high specificity, this makes these compounds potentially attractive therapeutic agents.

Currently, there are published reviews covering particular aspects of studying organoboron derivatives: main types of biological activity of boron compounds,[3] synthetic approaches to key classes of organoboron compounds,[4] success in the development of boronate-based β-lactamase inhibitors,[5] the use of boron compounds in neutron capture therapy [6, 7] and the use of benzoxaboroles in various fields of medicinal chemistry.[8] However, there are no analytical reviews that would cover both the chemistry and pharmacological applications of boron compounds. In addition, with intensive research carried out in this area, some works remained beyond the scope of published reviews. Also, mention should be made of recent works dealing with the development of hybrid therapeutic agents based on organoboron systems (mainly benzoxaboroles) and other classes of biologically active molecules, in particular, antibiotics, which in some cases improves the pharmacological properties of the initial agents.

The present review describes the structure and physicochemical properties of boronic acid derivatives, benzoxaboroles, benzoxaborines, benzodiazaborines and other organoboron compounds. Approaches to the synthesis of hybrid structures containing an organoboron moiety as a pharmacophore are considered and the effect of this modification on the pharmacological activity is analyzed.

2. Structure and physicochemical properties of organoboron compounds

The biological activity of boron compounds is caused by the vacant p orbital of the boron atom, which allows the formation of coordination bonds with nucleophiles, including nucleophilic sites of biomolecules: hydroxy and amino groups of proteins, carbohydrates and nucleic acids. Boron acts as a metallomimetic, exhibiting specific ability to bind to and activate small molecules.[9] In pharmacologically active compounds, the boron atom is incorporated in a molecule [aryl(or alkyl)boronic acids and esters, including cyclic ones, and boron-containing heterocycles] or exists as boron or boron–carbon clusters (Fig. 1).

Owing to the presence of the vacant p orbital, boron-containing acids are Lewis acids with a trigonal planar geometry in the neutral state. Binding of water accompanied by the loss of a proton accounts for the acid-base properties of boronic acids, while the conjugate base has a tetrahedral structure with a negative charge formally located on the boron atom.

From the standpoint of the chemical structure, benzoxaboroles combine features of arylboronic acids and cyclic boric acid esters; their unique features are due to the presence of a free hydroxy group and high Lewis acidity of the boron atom. In the oxaborole ring, the boron atom retains a planar trigonal geometry; this brings about deformation of the five-membered ring, which, however, decreases upon binding of a water molecule. This results in a decrease in pK_a for 1-hydroxy-1,3-dihydro-2,1-benzoxaborole **1** (pK_a = 7.3) in comparison with boronic acids (*e.g.*, for phenylboronic acid, pK_a = 8.7) (Scheme 1).[10]

The structural change of benzoxaboroles in water influences their biological properties and is of interest regarding the possibility of selective interaction with biomolecules. A study of the dynamic hydrolytic equilibrium of the oxaborole ring carried out by NMR spectroscopy in a

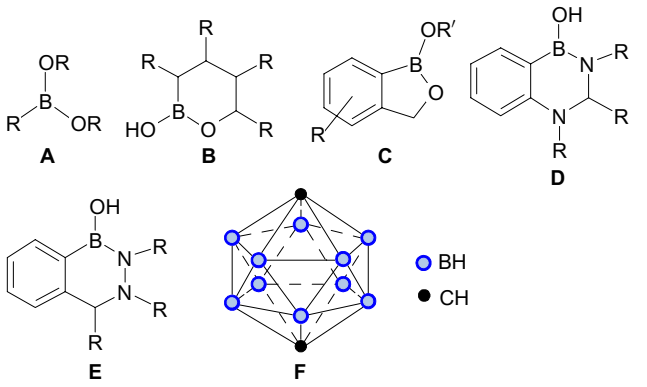
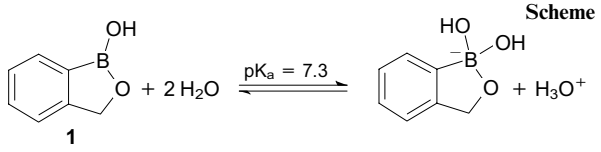


Figure 1. General structural formulae of boron compounds: **A** are boronic acids and their ester derivatives, **B** are oxaborines, **C** are benzoxaboroles, **D** are 2,4,1-diazaborines, **E** are 2,3,1-diazaborines, **F** are boron clusters and carboranes (example).

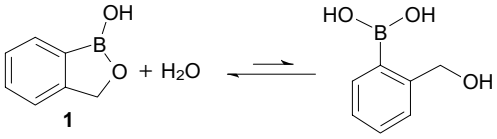
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Current research interests: chemistry of nucleosides; antiviral, anticancer and antimicrobial agents.

Translation: Z.P.Svitanko

Scheme 1



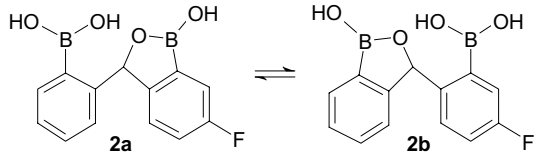
Scheme 2



water – organic medium [11] confirmed that the molecule of benzoxaborole **1** mainly exists in the closed-ring form (Scheme 2).

It was shown by NMR experiments that the structure of benzoxaborole (**1**) remains invariable in the temperature range from 203 to 303 K. For the model compound, [2-(1-hydroxy-6-fluoro-1,3-dihydro-2,1-benzoxaborol-3-yl)-phenyl]boronic acid (**2**), the exchange between isomeric closed-ring forms **2a** and **2b** was found to proceed at a noticeable frequency even at low temperature (Scheme 3).[11] Since the dynamic equilibrium between the isomers of **2** exactly reflects the molecular dynamics of benzoxaborole **1**, the authors concluded that reversible hydrolysis of the oxaborole ring occurs rather rapidly under physiological conditions (frequency > 100 Hz).

Scheme 3



Similar properties of various boron-containing heterocyclic structures (azaborines, azaboroles and oxazaboroles) were determined by *ab initio* calculations and confirmed by X-ray diffraction data.[12] The most stable isomers contain an XBHNH moiety where X, which is N, NH or O, is the main heteroatom of the ring. The planar conformations are characterized by stable energy minima for all structures except for five-membered rings.

Boron-containing therapeutic agents used in neutron capture therapy are either boronic acids and their derivatives or stable polyhedral boron hydrides and carboranes, which can be modified by organic ligands. The properties of these molecular clusters were described in detail in several reviews.[6, 13, 14] The efficiency of neutron capture therapy is related, most of all, to pharmacokinetic properties of the agent such as the capability of selective accumulation in a tumour and low toxicity, and these characteristics are determined by the structure of the modifying group.

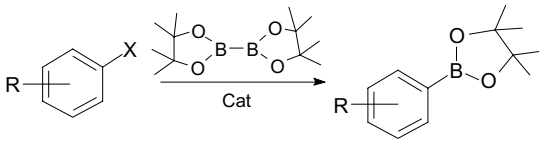
3. Boronic acids and their esters

Boronic acids and their esters form the best studied and most abundant group of pharmacologically active organoboron compounds. Since boronic acids are in high demand as reagents of synthetic organic chemistry, methods for their synthesis have been actively developed for more than 50 years. If one considers only pharmacologically significant molecules, any synthesis of such structures inevitably includes two stages: the proper introduction of a boron atom and subsequent modifications, which often require the use of specific protecting groups. The biological activities that are most often encountered for boronic acid derivatives are antitumour activity, mainly associated with their ability to inhibit the ubiquitin–proteasome complex,[15] and antimicrobial activity associated with the inhibitory activity against β-lactamases.

3.1. Current trends in the synthesis of boronic acids and their ester derivatives

A traditional method for the preparation of arylboronic acids is the Miyaura borylation, which consists in the reaction of aryl halides with bis(pinacolato)diboron (B_2Pin_2) catalyzed by palladium [16] or other metals (Scheme 4).

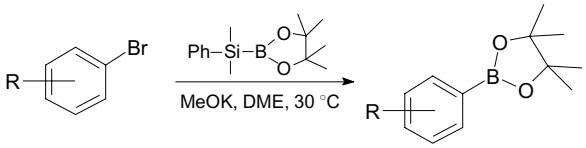
Scheme 4



X = Cl, Br, I, F, OMe, H, *etc.*; R = Alk, Ar, Het, *etc.*;
Cat = Pd, Fe, Ni, Cu, Ir, Rh, *etc.*

The considerable progress attained in recent years in the application of this reaction is associated with the use of transition metal-based catalysts. Whereas in the traditional borylation, only aryl halides act as substrates, in the presence of new catalysts, the reaction can be carried out for fluoroarenes,[17–20] methoxyarenes,[21–23] sulfonates [24] and even unsubstituted aromatic compounds,[25–28] which were previously considered inactive. The use of silylborane reagents allows for conducting the reaction without a catalyst under very mild conditions (Scheme 5).[29]

Scheme 5

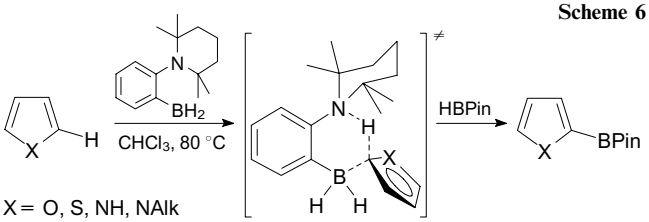


R = Alk, Ar, Het, *etc.*; DME is dimethoxyethane

The use of new catalytic systems combining Lewis acid and base in the same molecule [9, 30] makes it possible to introduce a boronic acid residue into the α-position of various five-membered π-electron rich heterocycles (Scheme 6).

Arene- and heteroarenecarboxylic acid fluorides prepared *in situ* from the corresponding acids can be converted

Scheme 6



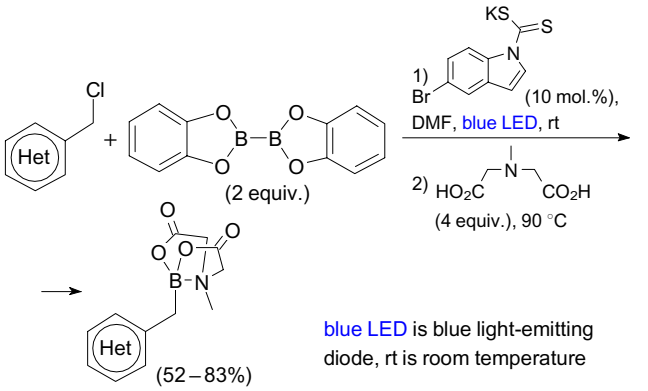
to boronates in moderate to high yields (60–70%) by reactions with diboronates in the presence of an organonickel catalyst.[31]

A variety of approaches to borylated heterocycles are considered in a review,[32] which also presents modern synthetic routes to alkylboronates.

Alkyl halides are also converted to boronic esters *via* the reactions with B_2Pin_2 type reagents. The reaction is catalyzed by palladium,[33] transition metals [34, 35] or copper [36] and can also proceed without a catalyst.[37]

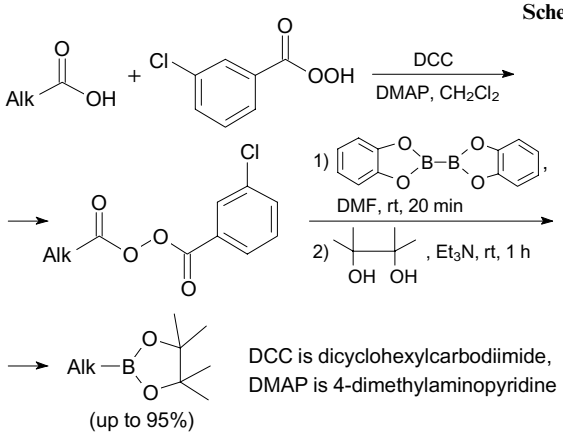
Chlorine and bromine atoms or the sulfonate group located in the allylic or benzylic position can be replaced by boronic acid moieties by a free radical mechanism involving an organic catalyst under visible light irradiation (Scheme 7).[38]

Scheme 7



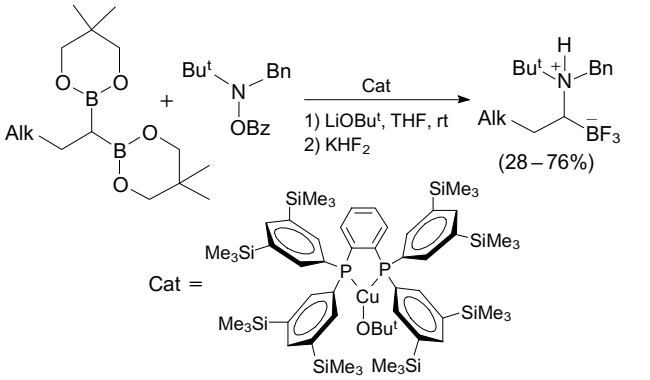
The free-radical mechanism is also typical of the decarboxylation–borylation reaction of aliphatic carboxylic acids activated by *m*-chloroperoxybenzoic acid (*m*-CPBA) (Scheme 8).[39]

Scheme 8



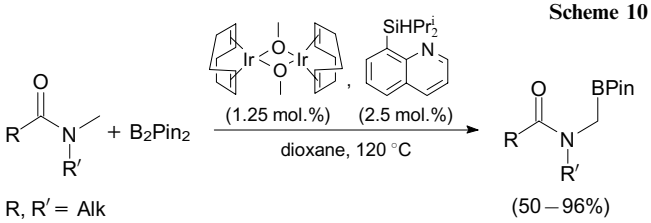
In the synthesis of many pharmacologically active derivatives, α- and β-aminoboronic acids are key compounds. The main preparation methods of these compounds are described in recent reviews.[4, 40] The present review covers only the most interesting latest publications devoted to these methods or the studies not included in the earlier reviews. For example, copper-catalyzed electrophilic amination of *gem*-diborylalkanes with hydroxylamines affords α-aminoboronic acids in moderate to quantitative yields.[41] The use of the silylated 1,2-bis(diphenylphosphino)benzene ligand in these reactions proved successful (Scheme 9).

Scheme 9



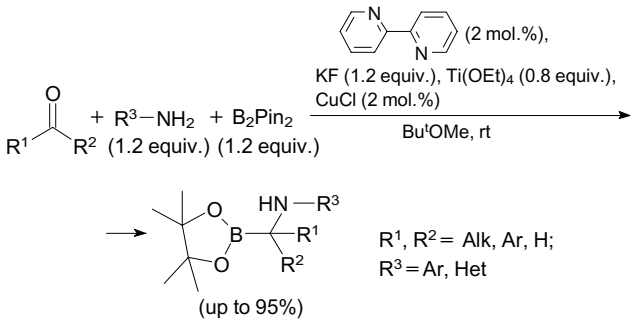
Rhodium- or iridium-catalyzed direct CH-α(β)-borylation of amides, ureas and alkylpyridines, proposed for the synthesis of amino(amido)boronates in 2012,[42, 43] is now being actively improved. For example, the synthesis of α-amidoboronates (Scheme 10) described recently by Hyland *et al.*[44] makes use of a much more readily available ligand than that employed according to the original procedure and gives products in higher yields (50–96% *versus* 35–85%).

Scheme 10



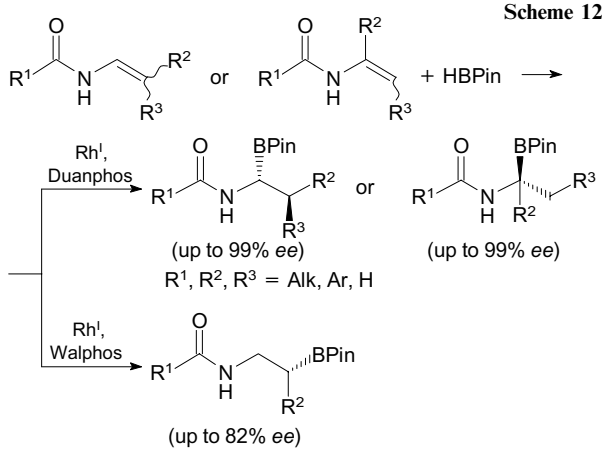
Ming *et al.*[45] proposed a synthesis of α-aminoboronates by the Borono–Strecker synthesis, a multicomponent reaction involving carbonyl compounds, amines and B_2Pin_2 (Scheme 11). By adjustment of the synthesis conditions to minimize the side reactions of the carbonyl and amine components with B_2Pin_2, this method was extended to a broad range of substrates, including aromatic and aliphatic aldehydes, ketones and amines.

Scheme 11



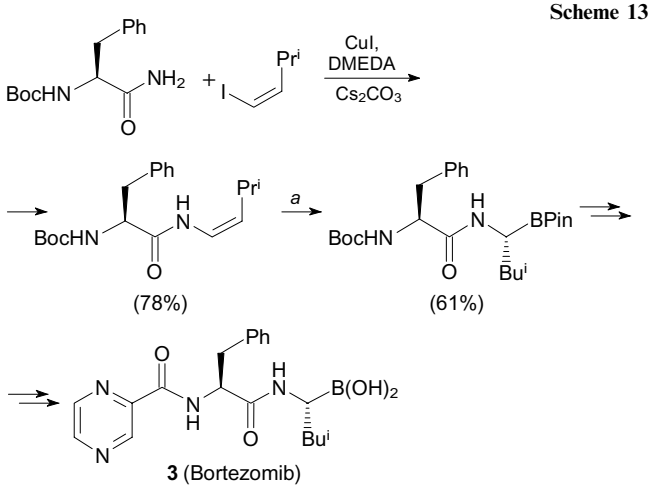
In this research area, much attention is given to asymmetric synthesis. Bai *et al.*[46] reported a new synthetic strategy, which comprises the preparation of α- and β-aminoboronic acids from enamides with high regiodivergence and stereoselectivity (Scheme 12). The structure of the starting enamide and the applied catalyst determine the

Scheme 12



Duanphos is (1*R*,1′*R*,2*S*,2′*S*)-2,2′-di-*tert*-butyl-2,3,2′,3′-tetrahydro-1*H*,1′*H*-(1,1′) biisophosphindolyl, Walphos is (1*S*)-1-{(1*R*)-1-[bis-[3,5-bis(trifluoromethyl)phenyl]phosphino]ethyl}-2-[2-(diphenylphosphino)phenyl]ferrocene

Scheme 13



(*a*) Rh^I (5 mol.%), Duanphos (6 mol.%), HBPin (2.5 equiv.);
Boc is *tert*-butoxycarbonyl, DMEDA is *N*,*N*′-dimethylethylenediamine

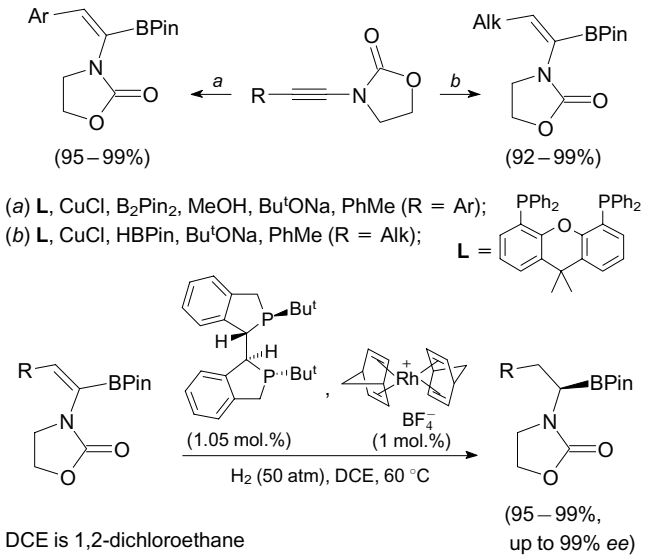
reaction pathway: *Z*-isomers of enamides are converted to α-aminoboronates, while *E*-isomers are converted to β-aminoboronates.

Scheme 13 shows the synthesis of bortezomib (**3**) by the described method.

A number of studies are devoted to rhodium-catalyzed asymmetric hydrogenation. The reaction with chiral 1,2-bis(*tert*-butylmethylphosphino)benzene catalyzed by a Rh^I complex gives 95 – 99% yields of products and 95 – 99% enantiomeric purity (*ee*) for all of the studied substrates.[47] Lou *et al.*[48] described the synthesis of α-boryl-(*Z*)-enamides and their rhodium-catalyzed asymmetric hydrogenation (Scheme 14).

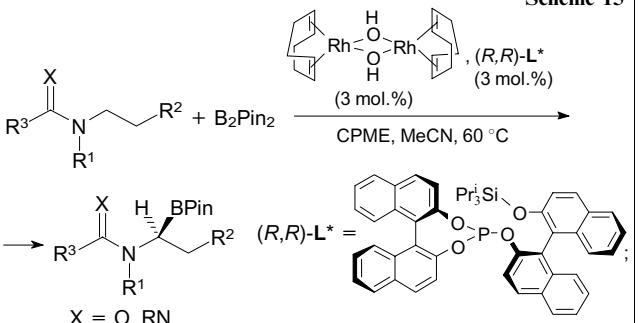
Another method for asymmetric synthesis of α-aminoboronates, also based on rhodium catalysis, was proposed by Reyes *et al.*[49] (Scheme 15). The Rh–monophosphite chiral catalytic system provides highly efficient enantioselective borylation of the C – H bond in the α-position to nitrogen for a group of substrates, including 2-(*N*-alkylamino)hetaryls, secondary and tertiary *N*-alkyl(aryl)amides and many other. The synthesis of bortezomib (**3**) by this method

Scheme 14

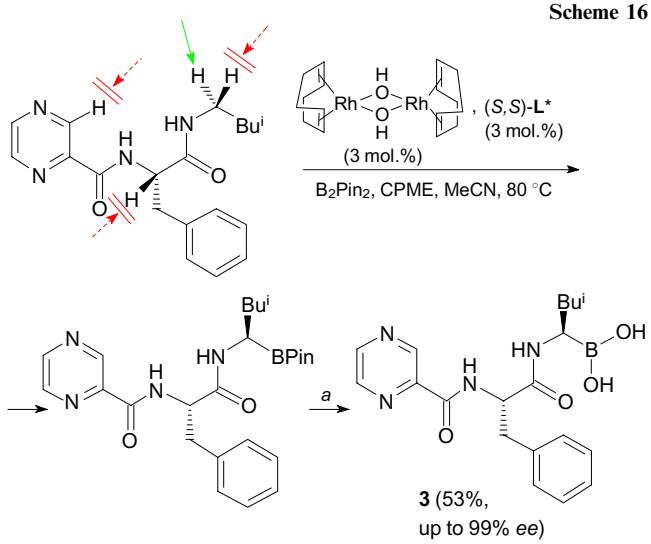


DCE is 1,2-dichloroethane

Scheme 15



Scheme 16

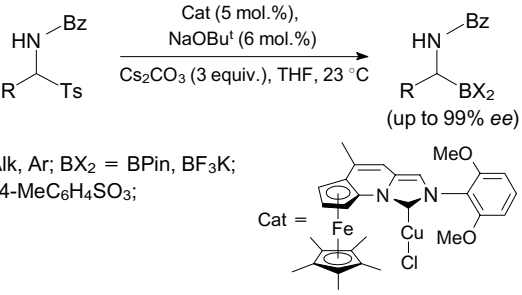


(*a*) 1) $PhB(OH)_2$, pentane, 2) MeOH, 1 M HCl (aq.), rt

is depicted in Scheme 16 (green arrow points to the H atom that is displaced and red arrows point to the H atoms that are retained).

In the presence of a copper catalyst with a *N*-heterocyclic chiral planar carbene ligand (Scheme 17), commer-

Scheme 17



cially available starting racemic α-tosyl-*N*-benzoylamines are converted to α-aminoboronates in moderate to high yields and enantiomeric purity of up to 99%.[50] This synthetic route does not include a chromatographic purification and, therefore, the process can be scaled up for industrial use. The reaction mechanism includes the stereoselective hydroboration of *N*-benzoylaldimines formed *in situ*.

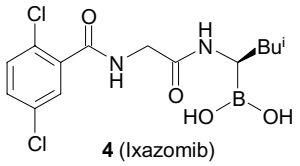
3.2. Pharmacological activity of boronic acids and their ester derivatives

Various aspects of the pharmacological activity of boronic acids and their derivatives are addressed in a number of publications.[5, 51 – 54] In the present review, we consider only the key applications of boronates as therapeutic agents and describe the latest achievements in this field.

3.2.1. Antitumour activity of boronic acid derivatives

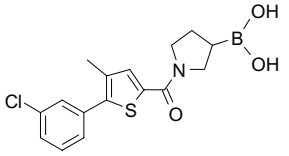
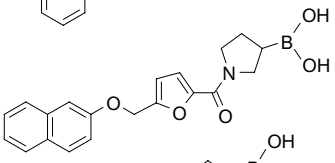
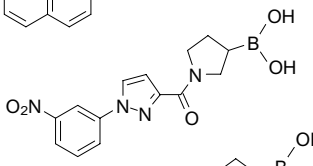
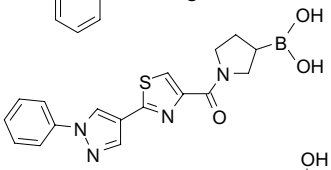
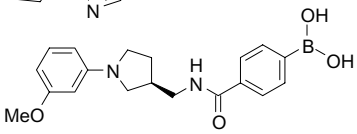
As noted above, the anticancer activity of boronic acids and their derivatives is mainly associated with inhibition of proteasomes, which are intricate enzyme complexes responsible for the intracellular degradation of proteins in eukaryotic cells. Polyubiquitinated protein molecules serve as targets for proteasome complexes,[55] and their proteolysis — an important part of the cell life cycle — is a prospective target for anticancer therapy.[53] Bortezomib (Velcade, **3**), the above-mentioned dipeptide inhibitor of the proteasome complex, was the first organoboron product approved by the FDA for the treatment of multiple myeloma [56] (see Scheme 13), while in 2015, this status was gained by ixazomib (Ninlaro, MLN2238, **4**).[57, 58] Compounds **3** and **4** are covalently bound to the 20S proteasome subunit β5 and induce apoptosis of the tumour cell. Structural analogues of these drugs, peptidomimetics containing boronic acid residues, are widely described in original papers, patents and reviews published in recent years.[3, 59] Below we consider the most important and interesting studies that are not included in the mentioned reviews for some reason.

Structure 4



Scarpino *et al.*[60] used a new procedure of virtual screening of more than 104 000 boronic acid derivatives to search for inhibitors of the chymotrypsin-like 20Suuu immunoproteasome subunit (β5i). The screening revealed 32 virtual potential hits, five of which (compounds **5a** – **e** in Table 1) demonstrated an inhibitory activity in assays. In the authors' opinion, 1-[5-(3-chlorophenyl)-4-methylthiophene-2-carbonyl]pyrrolidin-3-ylboronic acid (**5a**) — a non-peptide covalent immunoproteasome inhibitor — could be used as the initial scaffold for further chemical optimization of the structures of compounds of this series.

Table 1. Non-peptide inhibitors of 20S immunoproteasome subunit β5i detected by virtual screening.[60]

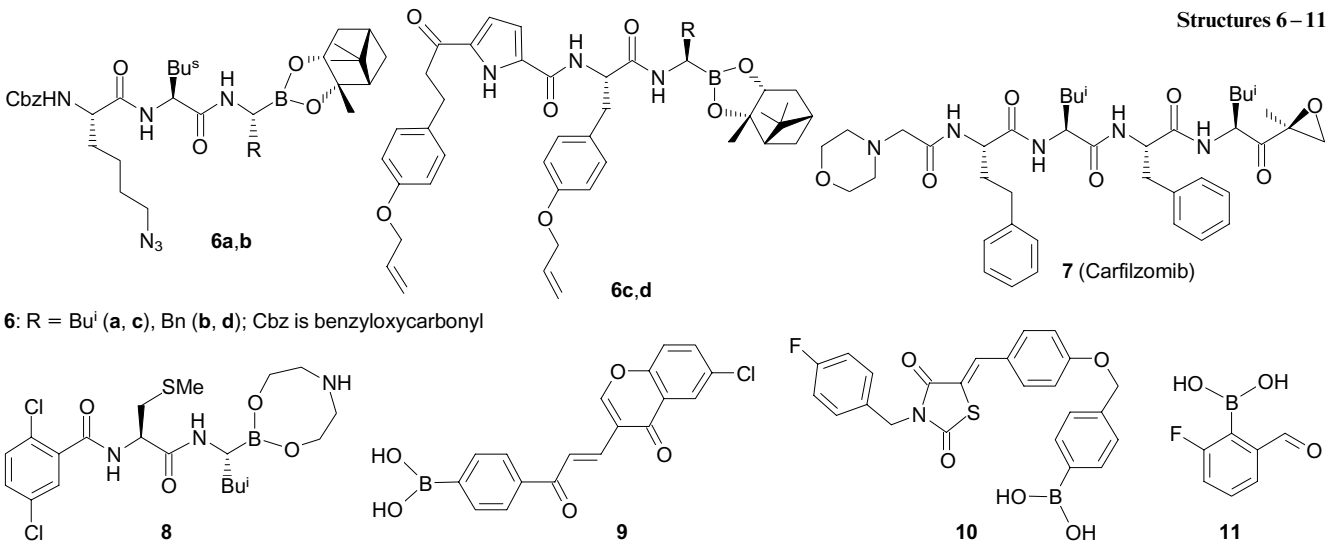
Compound	Structure	Residual activity of β5i subunit (%) at 100 μmol L^{-1}
5a		2 ± 4
5b		1 ± 4
5c		55 ± 9
5d		62 ± 2
5e		77 ± 15

Zhang *et al.*[61] investigated the inhibition of chymotrypsin-like activity of 26S proteasome by a number of new boron-containing peptidomimetics **6a** – **d**. The results were compared with the effects of bortezomib and carfilzomib (**7**), a peptide proteasome inhibitor containing no boron atoms. All compounds **6**, which contained the same cyclic boronate moiety, exhibited the target activity. In *in vitro* experiments, derivative **6a** showed a higher cytotoxicity against several tumour cell lines than the reference drugs.

Studying the structure – biological activity relationships for a series of twenty bortezomib (**3**) and ixazomib (**4**) analogues revealed a number of derivatives characterized by half-maximal inhibitory concentrations (IC_{50}) not higher than 10 nmol L^{-1} (nM) against MDA-MB-231 drug-resistant breast cancer cells and multiple myeloma cells.[62] The most promising compound of this group, 2,5-dichloro-*N*-{(*R*)-1-[((*R*)-1-(1,3,6,2-dioxazaborocan-2-yl)-3-methylbutyl)-amino]-3-(methylthio)-1-oxopropan-2-yl}benzamide (**8**), exhibited a high antiproliferative activity against the MDA-MB-231 cell line (IC_{50} = 8.4 nM, which is close to the value IC_{50} = 7.5 nM for bortezomib) and also demonstrated a high antitumour activity in *in vivo* experiments.

Apart from proteasome inhibition, other possible mechanisms of anticancer activity of boronates are known. For example, antiproliferative activity against four cancer cell lines, HCT116, MCF-7, THP-1 and NCIH322, was detected for a series of 4-[3-(4-oxo-4*H*-chromen-3-yl)acryloyl]phenylboronic acids with substituents in positions 6, 7 and

Structures 6 – 11



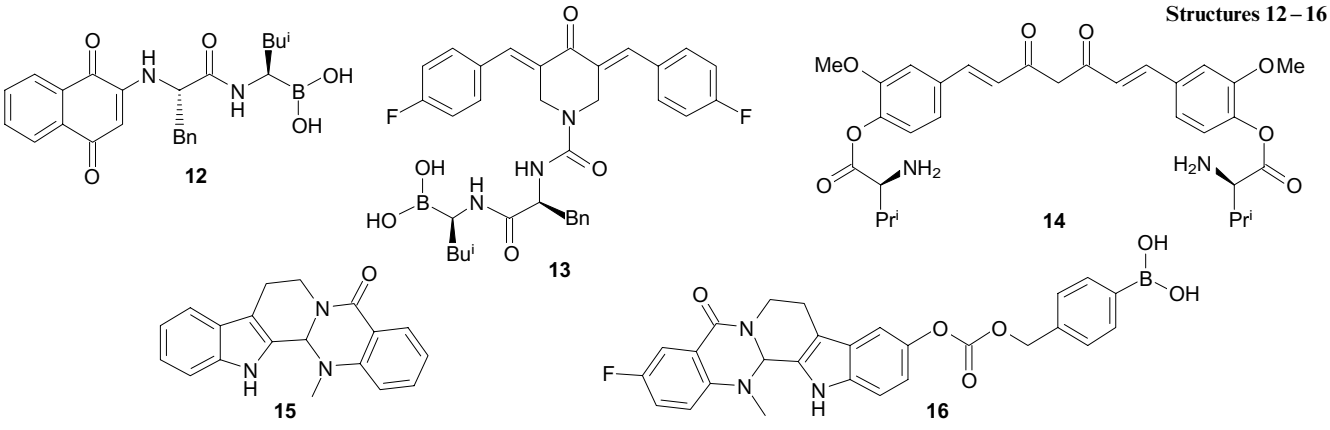
8.[63] (*E*)-4-[3-(6-Chloro-4-oxo-4*H*-chromen-3-yl)acryloyl]-phenylboronic acid (**9**) showed selective antiproliferative activity with IC_{50} = 2.35 μM against colon cancer cells (HCT-116). The authors attributed this activity to the inhibition of the MDM2 protein, which is an endogenous inhibitor of the p53 protein. The disruption of binding of these proteins leads to release of p53, inducing the synthesis of the p21 protein, which is a cell cycle inhibitor, and thus triggering the apoptotic death of tumour cells.

Katsamakas *et al.*[64] described a computing model for binding of a lipid metabolism enzyme (autotaxin) to the HA-155 inhibitor (**10**). The authors demonstrated that the interaction of the target protein with the boronic acid moiety in the inhibitor molecule gives rise to a polar covalent bond between the serine and threonine residues in the polypeptide chain, on the one hand, and the boron atom, on the other hand. Apparently, this molecular mechanism of inhibition is inherent in all pharmacologically active boronates, so that the range of biotargets for these compounds is almost infinite. For example, ixazomib (**4**) is active against various types of tumours apart from the myeloma disease, and, furthermore, it is often synergistic with other drugs.[65, 66] In the case of colorectal cancer, its mode of action is not related to proteasome inhibition, but consists in the induction of CHOP-dependent gene transcription [CHOP is the stress-induced nuclear protein (transcriptional regulator) belonging to the tumour necrosis factor (TNF) receptor family, which triggers cell apoptosis (DR5)].[67] The CHOP (or GADD153) protein is a stress-induced nuclear protein, which is dimerized with members of the transcription factor family and participates in the regulation of transcription of many genes.[68] The DR5 gene encodes the the so-called death receptor DR5, a TNF receptor family member,[69] which triggers cell apoptosis, taking place irrespective of the state of the p53 protein.

Among a series of 18 phenylboronic acids with simple substituents in the benzene ring, 2-fluoro-6-formylphenylboronic acid (**11**) demonstrated clear-cut inhibition of the growth of A2780 ovarian cancer cells (IC_{50} = 11.2 ± 0.7 μM) with the arrest in the G2/M cell cycle phase and activation of apoptosis or caspase-3.[70] A similar effect was found for some benzoxaboroles studied in the same work, which are mentioned in the relevant Section.

A promising line of research is the use of the boronate warhead for obtaining hybrid structures or for extending the range of action of known drugs. An example is provided by the design of a series of 15 compounds based on a combination of a bortezomib structural moiety and a 1,4-naphthoquinone scaffold.[71] A hybrid structure — *N*-(1,4-naphthoquinon-2-yl)-L-phenylalanine-L-boronoleucine (**12**) — possessed an inhibitory activity comparable with that of bortezomib against the chymotrypsin-like 20S proteasome subunit (IC_{50} = 11.4 nM *versus* IC_{50} = 4.7 nM) and antiproliferative activity against breast adenocarcinoma cells (MDA-MB-231) with IC_{50} = 38.3 ± 4.6 nM.

Structures 12 – 16



Out of a series of proteasome inhibitors based on modified curcumin and various α-aminoboronic acids, the highest activity against the chymotrypsin-like 20S proteasome subunit was found for derivative **13** (IC_{50} = 0.835 μM).[72] The inhibitory activity of another curcumin derivative, compound **14** (CV), against the same model was approximately an order of magnitude lower.[73]

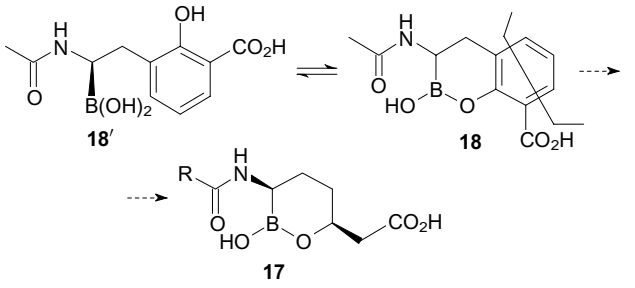
Recently, Li *et al.*[74] described modification of the molecule of the anticancer agent evodiamine (**15**) with a borate trigger, which was expected to enhance the efficiency of the hybrid structure. Earlier, high antitumour activity of evodiamine and its derivatives was found in *in vitro* experiments;[75] however, in animal experiments, they turned out to be of low efficiency. Hybrid compound **16** showed good pharmacokinetic properties, particularly, increased accumulation in the tumour and excellent antitumour activity in the HCT116 xenograft model in mice, inducing dose-dependent apoptosis and arrest of cell growth in the G2 phase.

3.2.2. Antimicrobial activity of boronic acids and their derivatives

Cleavage of the β-lactam ring by bacterial enzymes, β-lactamases (EC 3.5.2.6), is an important mechanism of development of bacterial resistance to β-lactam antibiotics such as penicillins, cephalosporins, *etc*. The resistance of bacterial strains to antibiotics of this class can be overcome by incorporation of β-lactamase inhibitor moieties into antimicrobial agents.[76]

Hecker *et al.*[77] carried out targeted design of cyclic boronic esters (oxaborines) **17** (Scheme 18) assuming that oxaborines may possess better selectivity to the enzymes responsible for the inactivation of β-lactam antibiotics in resistant bacteria than other serine hydrolases. Compound **18**, described earlier by Ness *et al.*,[78] which exhibited a high affinity for TEM-1 (class A β-lactamase) (see Fig. 3), was chosen as the lead compound. However, according to X-ray diffraction data, this compound interacts with the enzyme in the acyclic form **18′**. Docking of various structures into the active sites of class A, B and C β-lactamases resulted in identification of cyclic boronates **17** devoid of a benzene ring. These compounds were obtained in six steps from previously described[79] enantiomerically pure *tert*-butyl (*R*)-3-(*tert*-butyldimethylsilyloxy)pent-4-enoate (**19**) (Scheme 19). After the silyl protection of the hydroxy group, treatment with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole resulted in regioselective hydroboration of compound **19** catalyzed by

Scheme 18

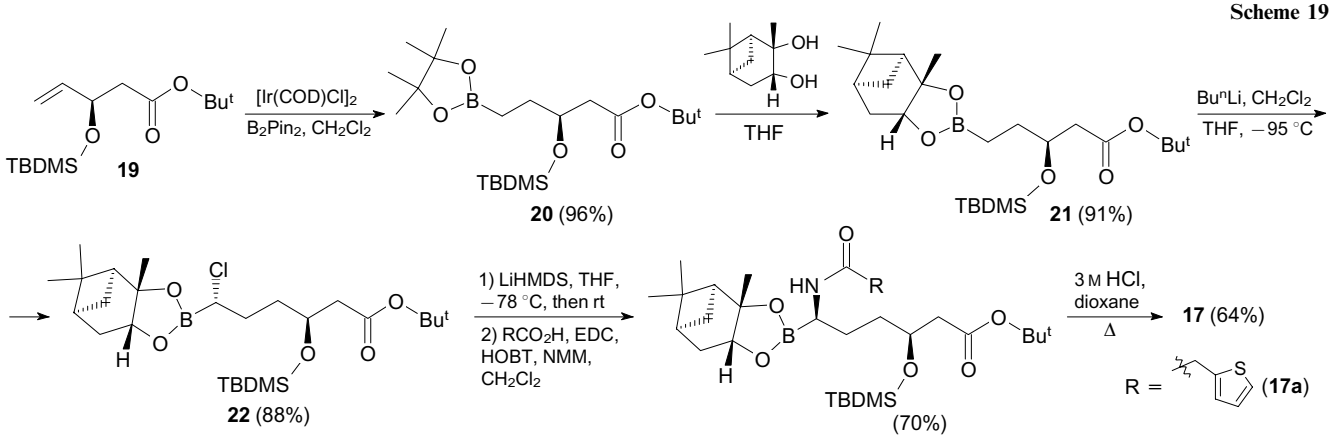


[Ir(COD)Cl]$_2$ (COD is cycloocta-1,5-diene). Pinacol boronate **20** formed in this reaction was then converted to more stable (+)-pinanediol boronate **21**. The stereoselective chloromethylation according to Matteson's method at −100 °C furnished (*S*)-chloro derivative **22** as a mixture of two diastereomers (85 : 15 ratio). The stereospecific displacement of the chlorine atom induced by lithium hexamethyldisilazide (LiHMDS) followed by acylation *in situ* yielded the corresponding acylimidoboronates, which were finally converted to target cyclic boronates **17** upon deprotection.

Studying the activity of the resulting derivatives against serine β-lactamases (SBL) and carbapenemases revealed the highest activity for compound **17a** c R = 2-ThCH_2 (Th is thienyl), which was called vaborbactam (commercial code RPX7009).[80] The replacement of thiophene by other heterocycles (aminothiazole, pyridine) or the use of an acetyl, cyclopropyl or substituted phenyl moiety did not increase the activity. It was found that the mechanism of inhibitory action of vaborbactam is based on the formation of a stable ate complex between the hydroxy group of the serine residue in the β-lactamase active site and the boron atom (Scheme 20).[81] In 2017, a combination of the meropenem antibiotic and vaborbactam called Vabomere® was approved by the FDA for the treatment of complicated urinary tract infections and pyelonephritis.[82, 83]

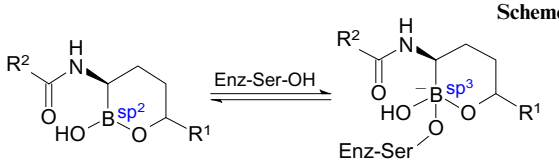
Dual action compounds inhibiting both types of bacterial β-lactamases, metallo-β-lactamases (MBL) and SBL, were found among acyl derivatives of methylaminoboronic acids.[84] (*S*)-[1-(2-Methyl-3-sulfanylpropanamido)methyl]-boronic acid (**23**) was proposed as the lead compound, inhibiting quite a few bacterial lactamases, including most abundant carbapenem-hydrolyzing metallo-β-lactamase VIM-2 and *Klebsiella pneumoniae* carbapenemase-2

Scheme 19



ECD is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, HOBT is 1-hydroxybenzotriazole, NMM is *N*-methylmorpholine

Scheme 20



Enz-Ser-OH is serine β-lactamase

(KPC-2) (EC 3.5.2.6). Compound **23** demonstrated high selectivity of inhibition of bacterial enzymes and potentiation of efficacy of meropenem towards MBL- or SBL-positive clinical isolates without obvious cytotoxicity.

The Lon enzyme (La protease) is a serine protease present in prokaryotic and eukaryotic cells; it belongs to the group of ATP-dependent proteases, which also includes proteasomes. The bacterial La protease participates in the body recovery from various types of stress; it is tolerant to fluoroquinolone antibiotics and can be considered as a potential biotarget in the therapy of bacterial infections. A study of Babin *et al.*[85] was aimed at finding selective peptide inhibitors of La protease. They reported that peptidomimetic **24**, structurally similar to bortezomib, reduces the *Escherichia coli* tolerance to ciprofloxacin, being non-toxic for mammals, as it does not inhibit eukaryotic proteasomes.

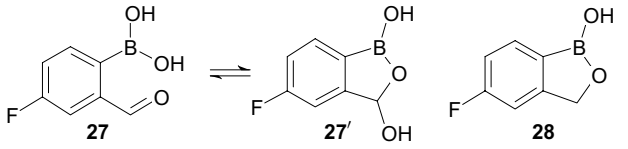
In the design of antimicrobial agents, as in the development of antitumour agents, the boronate scaffold is often used for the fabrication of hybrid structures containing different pharmacophores. This can be exemplified by branched peptides with acridine and boronic acid residues,[86] which exhibited a high antimicrobial activity against the ESKAPE panel of pathogens. For example, peptide **25** had a minimal inhibitory concentrations (MIC) of 1 μg mL^{-1} against *Staphylococcus aureus*, 8 μg mL^{-1} against *Candida albicans* yeast and 4 μg mL^{-1} against *E. coli*. Hybrid molecule **26** based on capsaicin (alkaloid of chili peppers) with a boronate moiety showed an antimicrobial activity against some gram-positive bacteria, including the vancomycin-resistant *Enterococcus faecium* strain.[87]

3.2.3. Other types of pharmacological activity of boronic acids

The diverse activities of boronates, including antiviral and anti-inflammatory activities, inhibitory activity against target enzymes[3] and immunomodulating properties,[52] have been described in detail quite recently. The problems of toxicity of boron-containing agents were discussed by Soriano-Ursua *et al.*[88] In this Section, we consider only the latest publications that are not covered by the above-mentioned papers.

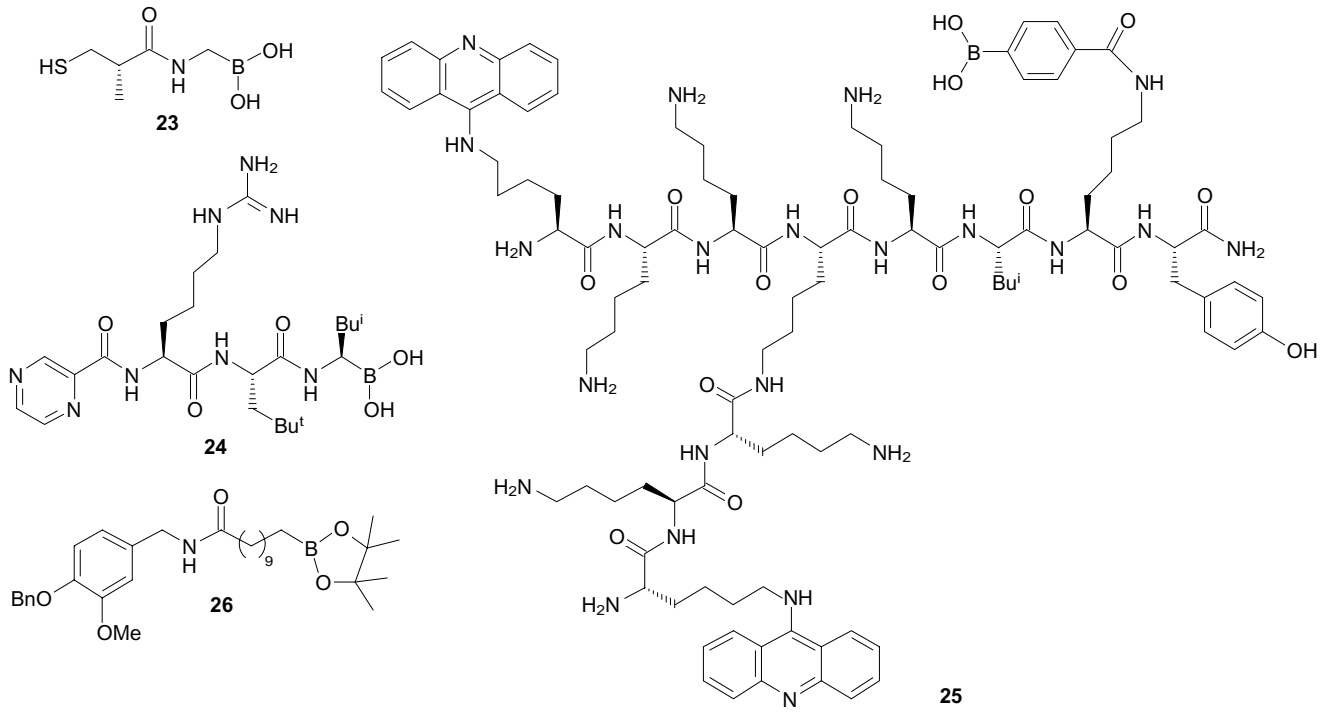
A high antifungal activity against pathogenic strains was revealed for a series of fluorine-substituted formylphenylboronic acids. The most active compound, 4-fluoro-2-formylphenylboronic acid (**27**), has MIC = 2 μg mL^{-1} for the *Aspergillus niger* mould fungus.[89] The authors attributed this activity to the tautomeric cyclization (Scheme 21), which converts this molecule to a structural analogue of the 1-hydroxy-5-fluoro-1,3-dihydro-2,1-benzoxaborole antifungal agent (tavaborole, AN2690, **28**).

Scheme 21



Currently, there are no vaccines or drugs for the treatment of recently found severe fever with thrombocytopenia syndrome, caused by the SFTS phlebovirus. A study of the antiviral activity of bortezomib (**3**) against the SFTS virus using human embryo kidney (HEK) 293T cells demonstrated that compound **3** in non-toxic concentrations sub-

Structure 23 – 26

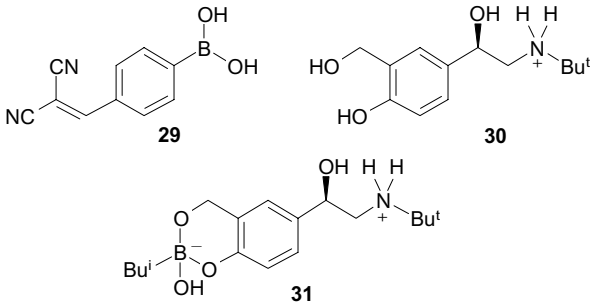


stantially decreases the viral titer in infected cells, without affecting the absorption of the virus.[90] According to dual luciferase reporter assay and western blot assay, bortezomib is able to reverse the SFTS-triggered degradation of the RIG-1 gene mediated by non-structural proteins (NS), thus preventing their inhibitory effect on interferons.

The ATP-dependent purinergic receptor 7 (P2X7R), which is an ionic channel activated by interaction with extracellular ATP molecules, is considered as a potential biotarget for anti-inflammatory drugs.[91] It was found that 4-(2,2-dicyanovinyl)phenylboronic acid (**29**) efficiently inhibits the human and mouse P2X7 receptor *in vitro*.[92] According to molecular docking, the interaction between acid **29** and the protein molecule mainly occurs *via* the formation of hydrophobic contacts with Phe residues at positions 95, 103 and 293 and hydrogen bonds with Leu97, Gln98 and Ser101.

Soriano-Ursua *et al.*[93] reported *in vitro* and *in silico* studies of the interaction of the boron-containing analogue of the drug albuterol (**30**) — politerol (**31**) — with guinea pig (gpβ2ARs) and human (hβ2ARs) adrenergic receptors. Albuterol (salbutamol) is a selective β2-adrenergic receptor agonist used to treat bronchial asthma. Experimentally, politerol (**31**) showed a higher activity towards gpβ2AR than towards hβ2AR. Molecular dynamics simulation revealed different roles of the boron atom in the politerol interactions with gpβ2ARs and hβ2ARs, affecting the movements of transmembrane domains 5 – 7, which play a key role in the activation of these receptors.

Structures 29 – 31

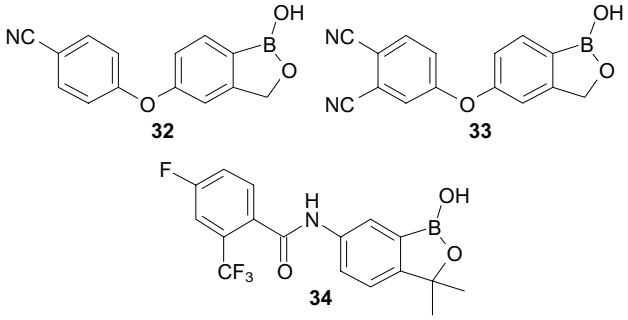


4. Benzoxaboroles

Benzoxaboroles, which were first synthesized and characterized in 1957,[94] were rarely used in organic synthesis in the subsequent decades. The interest in these compounds surged in 2006 after a publication[95] describing specific binding of the water-soluble benzoxaborole molecule to diols, in particular glucopyranoside, glucose and fructose, at physiological pH values (7.35 – 7.45). Currently, the affinity and specificity of benzoxaboroles for diols are widely used for the quantitative determination of sugars and isolation of glycosylated proteins and in the therapy of some diseases.

Studies of the pharmacological activity of benzoxaboroles also started actually only in 2006, when the antifungal activity of 5-fluorobenzoxaborole **28** was discovered.[96] Quite a number of new pharmacologically active benzoxaboroles have been synthesized in the last decade. Compounds of this class were found to exhibit various types of biological activity, including antibacterial, antiviral, antiparasitic and anti-inflammatory activities. In 2014, 5-fluorobenzoxaborole **29**, advanced by the Anacor

Structures 32 – 34



Pharmaceuticals company (which was taken over by the pharmaceutical giant Pfizer in 2016) under the name Kerydin, was approved by the FDA for the treatment of onychomycosis. Subsequently, in December of 2016, the FDA permitted the use of another drug developed by the same company, 4-(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-5-yloxy)benzonitrile (Eucrisa, AN2728, crisaborole, **32**), meant for the topical treatment of mild and moderate atopic dermatitis in patients above two years of age. At present, two benzoxaborole derivatives, compound **32** and 4-(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-5-yloxy)phthalonitrile (AN2898, **33**), are under clinical trials for the treatment of psoriasis, while 4-fluoro-*N*-(1-hydroxy-3,3-dimethyl-1,3-dihydro-2,1-benzoxaborol-6-yl)-2-(trifluoromethyl)benzamide (SCYX-7158, AN5568, **34**)[97] is under a final stage of clinical trials as a drug against human African trypanosomiasis.[98]

The Lewis acidity and the diol-binding ability of benzoxaboroles are the key factors responsible for their interaction with enzyme active sites. The introduction of additional substituents into the molecule or incorporation of the benzoxaborole moiety into various molecules enables multicentre (multipoint) intermolecular interactions, which provide better selectivity and ligand binding. The unique physicochemical properties of these boron compounds in combination with their high stability and water solubility account for the increasing interest in this scaffold, convenient for medicinal chemistry applications.

Among enzyme biotargets for benzoxaboroles, mention should be made of leucyl-t-RNA-synthetase (LeuRS). These compounds were also shown to exhibit selective activity against β-lactamase, hepatitis C virus (HCV) serine protease NS3/4A, nucleotide phosphodiesterase, DD-carboxypeptidase and carbonic anhydrases.[99 – 101]

Exhaustive reviews considering key methods for the synthesis, properties and applications of benzoxaboroles were published by Adamczyk-Wozniak *et al.*[99, 100] in 2009 and 2015; similar issues were addressed by Liu *et al.*[101] An extensive study of Mereddy *et al.*[102] is devoted to the preparation methods of benzoxaboroles and their applications in medicinal chemistry. Yang *et al.*[4] described a number of synthetic strategies for the development of new benzoxaborole derivatives possessing antibacterial, antifungal, antiparasitic, antiviral, antitumour and anti-inflammatory activities. The applications of benzoxaboroles in various fields of medicinal chemistry are also mentioned in reviews of Fernandes *et al.*[3] and Zhang *et al.*[103] The survey paper by Nocentini *et al.*[8] covers only patents related to the medicinal use of benzoxaboroles. Over the last five years, there appeared quite a number of publications that develop

the existing trends and describe new therapeutic applications of benzoxaboroles.

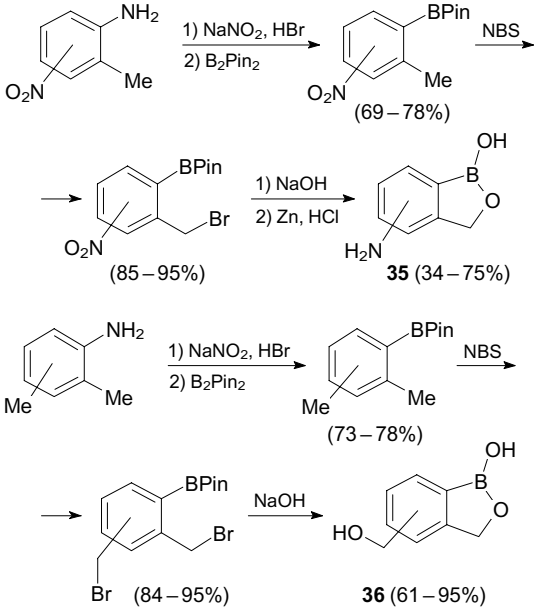
4.1. Modern approaches to the synthesis of benzoxaboroles

The key synthetic strategies towards benzoxaboroles were described in detail;[4, 99 – 102] therefore, in this review, we consider only some recent publications that are most important or overlooked by other reviews. Most of the described methods consist of numerous steps, include the use of protective groups and chromatographic purification of intermediates. The key steps are borylation, that is, introduction of a boronic acid moiety, and cyclization of this moiety with a hydroxymethyl substituent located in the *ortho* position. Fuscaldo *et al.*[104] developed an efficient synthesis of benzoxaboroles **35** and **36** containing amino and hydroxymethyl groups in positions 4, 5 and 6. The advantages of this approach over other methods include a small number of steps, the absence of complex manipulations of functional groups and low cost (Scheme 22).

One more, not less efficient synthetic route to 3-substituted benzoxaboroles **37**, including compounds with a spirocyclic substituent in position 3, also does not require protection of the hydroxy group. The method is based on the one-pot cascade reaction of unprotected *o*-bromobenzyl alcohols with B_2Pin_2 (Miyaura reaction) (Scheme 23).[105]

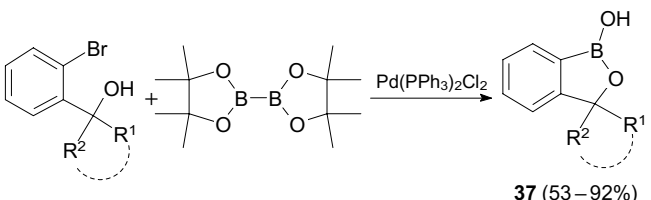
The target *N*-isobutyl-*N*-(4-ethylphenyl)-1-hydroxy-3-[(tetrahydro-2*H*-pyran-4-yl)methyl]benzoxaborole-6-sulfonamide (**37a**) was prepared [106] in a similar way directly from

Scheme 22



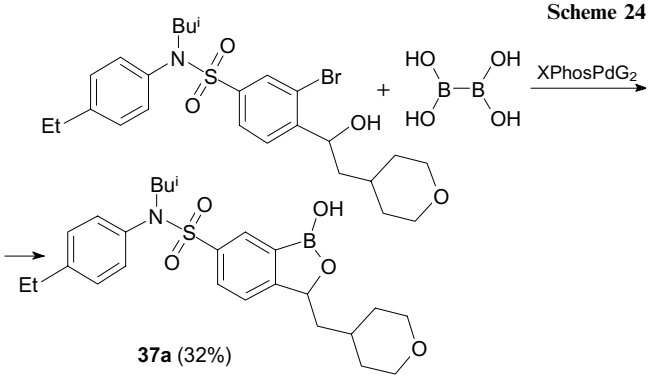
NBS is *N*-bromosuccinimide

Scheme 23



R^1, R^2 = H, Alk, Ar, *etc.*

Scheme 24



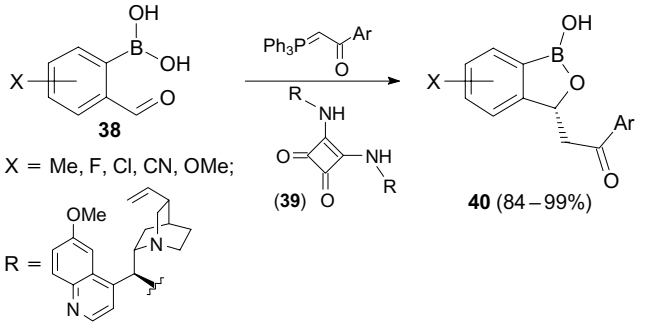
XPhosPdG2 is (2,4,6-triisopropyl-2′-dicyclohexylphosphino-1,1′-biphenyl)-[2-(2-amino-1,1′-biphenyl)]palladium(II) chloride

diboronic acid, which made it possible to avoid a pinacol impurity in the product (Scheme 24). This method was used to prepare a series of nine benzoxaboroles substituted in the aromatic ring and in position 3. It was shown that both aryl bromides and aryl iodides are good starting compounds for this synthetic route.

Kunihiro *et al.*[107] reported the development of a new one-pot synthesis of benzoxaborole using the SiliaCat DPP-Pd catalyst and diboronic acid as the source of boron. The heterogeneous SiliaCat DPP-Pd catalyst is based on Pd^{II} and diphenylphosphine, incorporated in the functionalized organosilicon matrix. The authors were able to implement a flow process, which may enable the design of a large-scale and cheap continuous flow synthesis of benzoxaboroles.

The Wittig olefination of *o*-formylphenylboronic acids **38** followed by the spontaneous stereoselective intramolecular Michael reaction of the chalcone-containing orthoboric acid in the presence of chiral bifunctional catalyst **39** resulted in a series of 3-substituted benzoboroxoles **40** (Scheme 25).[108] This reaction sequence is a promising approach to the synthesis of benzoxaboroles with excellent enantioselectivity and a broad range of synthetic applications.

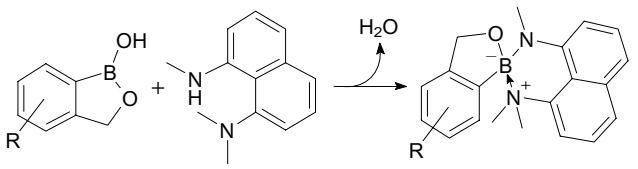
Scheme 25



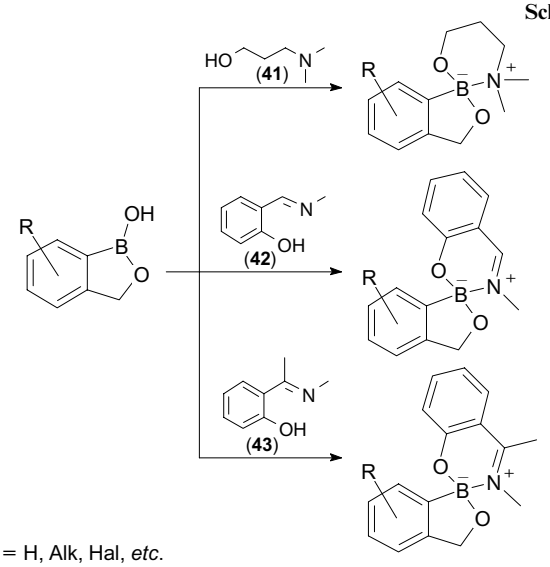
If it is necessary to protect the benzoxaborole moiety or increase the solubility of some benzoxaboroles in organic solvents, the use of divalent protective groups was shown to be preferable.[109] An example of such protective group is the fluorescent 1-dimethylamino-8-methylaminonaphthyl group, which is stable in basic media, but is easily eliminated in weak acids (Scheme 26).

However, benzoxaboroles protected by this group are insoluble in common organic solvents such as DMF or

Scheme 26



Scheme 27



R = H, Alk, Hal, *etc.*

DMSO. In addition, this protection proved to be incompatible with oxidizing reagents. For increasing the diversity of chemical transformations possible for molecules containing a benzoxaborole moiety, Gamrat *et al.*[110] proposed three new protective reagents for the benzoxaborole OH group: 3-(*N*,*N*-dimethylamino)propanol (**41**) and salicylaldehyde (**42**) and *o*-hydroxyacetophenone (**43**) methylimines (Scheme 27). In the authors' opinion, protection of the hydroxy group of benzoxaboroles with reagent **41** can be useful in one-step reactions in which it is installed *in situ* and removed on treatment with water, while reagents **42** and **43** can be used in multistep synthetic sequences.

4.2. Pharmacological applications of benzoxaboroles

Historically, antifungal activity was the first type of pharmacological activity to be identified for benzoxaboroles.[96] Infections caused by parasitic fungi (mycoses) are very widespread, and their therapy is complicated by high drug resistance of the pathogens. Numerous research groups are permanently looking for antifungal agents.

4.2.1. Antifungal activity of benzoxaboroles

Tevyashova *et al.*[111] described a series of hybrid antibiotics **44** – **53**, benzoxaborole derivatives with amphotericin B (AmB), in which the benzoxaborole moiety is attached to the antibiotic *via* an amide, *N*-acyl, *N*-sulfonamide or *N*-alkyl bond.

The antifungal activity of compounds **44** – **53** containing 3-, 5-, 6- or 7-substituted benzoxaborole was tested in relation to *Candida albicans* and *Cryptococcus humicolus* yeast strains and *Aspergillus niger* and *Fusarium oxysporum* fungi. The activity of hybrid derivatives against the studied strains was similar to the activity of AmB, whereas the toxicity against human cells varied. The introduction of the benzoxaborole moiety into compounds **52** and **53** resulted in increasing antifungal activity of the products, which was, however, accompanied by increasing cytotoxicity of the compound against the HCT116 cell line in comparison with that of AmB. It is noteworthy that conjugate **51** showed the best combination of a high antifungal effect with a low cytotoxicity and haemolytic activity.

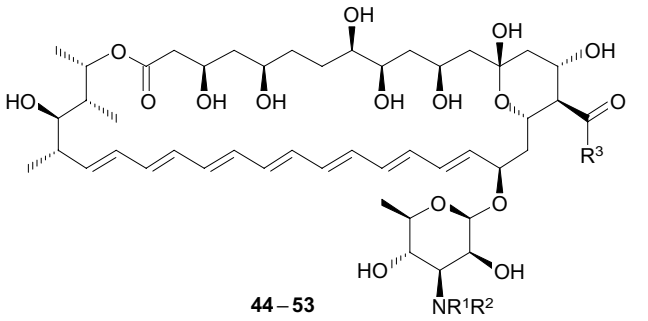
Since the *N*-(fluorophenyl)piperazine moiety is a 'privileged' group in the design of antimicrobial agents, Borys *et al.*[112] synthesized *N*-(fluorophenyl)piperazine benzoxaborole derivatives **54a**,**b** and studied them for fungicidal activity. Estimation of the antifungal activity of the compounds against the *Aspergillus niger*, *A. terreus*, *Penicillium-ochrochloron*, *Candida tenuis* and *Fusarium dimerum* strains confirmed the moderate antifungal activity of benzoxaboroles **54** (MIC for *A. niger* was 62.5 μg mL^{-1}).[112]

Adamczyk-Wozniak *et al.*[113] investigated the structure – activity relationships for 6-, 4- and 7-fluoro-substituted benzoxaboroles **55a** – **c** and tavaborole (**28**) and six fungal strains: *A. niger*, *A. terreus*, *F. oxysporum*, *F. solani*, *P. ochrochloron* and *C. tenuis*. The presence of the fluorine atom in the molecule and its position in the benzene ring were found to substantially affect the antifungal action; 5-fluoro-substituted benzoxaborole **28** showed the highest activity against filamentous fungi.[113]

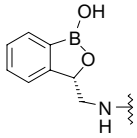
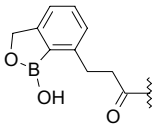
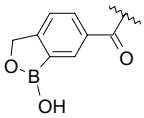
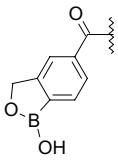
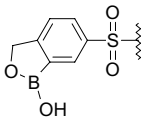
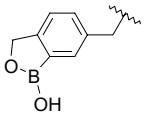
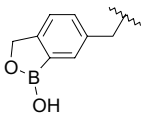
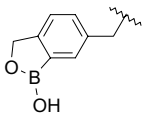
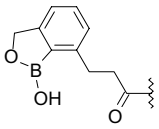
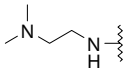
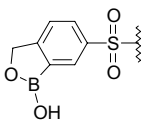
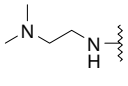
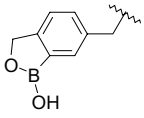
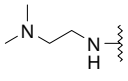
Nocentini *et al.*[114] reported the inhibitory activity of (thio)urea derivatives of 6-aminobenzoxaboroles **56** at nanomolar concentrations against β-carbonic anhydrases (β-CA) of three pathogenic fungal species: *C. neoformans* (Can2), *Malassezia globosa* (MgCA) and *C. glabrata* (CgNce103). The cited paper reported the inhibitory effect of benzoxaborole on not only carbonic anhydrases from (CA) from pathogenic fungi, but also off-target human carbonic anhydrases (hCA I and hCA II). The structure – activity relationships for inhibitors **56** show that varying the substituent at the (thio)urea moiety gives rise to different inhibitory activities and selectivities of the compound to hCA I and hCA II. Meanwhile, the replacement of the oxygen atom by sulfur does not have a pronounced influence on the activity. The same group of authors[115] demonstrated, using a moderate range of (thio)urea benzoxaborole derivatives, that these compounds can be efficiently employed as a new class of inhibitors of hCA, a new promising biotarget for the treatment of cancer. The results of these studies indicate that even a slight variation in the structure causes noticeable changes of the inhibitory properties against all human carbonic anhydrase isoforms, with some compounds exhibiting nanomolar inhibition constants (K_i). However, these benzoxaborole derivatives do not show a higher activity against Can2 and CgNce compared with the clinically used sulfonamide drug acetazolamide. Meanwhile, their inhibitory activity against MgCA is comparable with that for acetazolamide. Exceptions are compounds **56a** – **c**, which are approximately 10 times as active ($K_i \approx 5-9\times10^3$ nM) as acetazolamide ($K_i = 76\times10^3$ nM).[115] According to molecular modelling data, the key factor for the inhibitory activity is the pattern of binding of benzoxaborole derivatives in the Can2 or MgCA active site.[115]

Biochemical and structural studies demonstrated that tavaborole (**28**) inhibits yeast cytoplasmic leucyl-t-RNA-synthetase (LeuRS), with the inhibition mechanism being based on unique properties of the boron atom.[116] In the tavaborole molecule, the boron atom forms covalent bonds with *cis*-2′,3′-hydroxy groups of the ribose ring of the

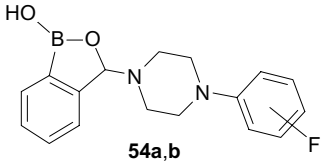
Structures 44 – 53



44 – 53

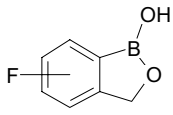
Compound	R^1	R^2	R^3
44	H	H	
45		H	OH
46		H	OH
47		H	OH
48		H	OH
49		H	OH
50			OH
51		H	
52		H	
53		H	

Structures 54 – 56



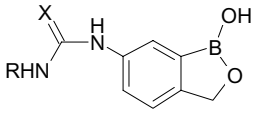
54a,**b**

Isomers: 2 (**a**), 4 (**b**)



55a – c, **28**

Isomers: 6 (**56a**), 4 (**55b**), 7 (**55c**), 5 (**28**)



56

X = O, S;
X = S: R = 4-$O_2NC_6H_4$ (**a**), Bn (**b**); 2-$FuCH_2$ (**c**); Fu is furyl

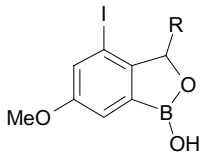
adenosine terminal residue (A76) to give a stable tRNA adduct with tavaborole in the LeuRS editing domain, which blocks tRNA translocation and interrupts the enzyme cycle.[116, 117] The tavaborole inhibition of the LeuRS domain suppresses the synthesis of proteins and blocks the fungal growth.

4.2.2. Antibacterial activity of benzoxaboroles

The expression process of bacterial genes is an important biological target for many antibacterial drugs. Aminoacyl-tRNA synthetases are involved in the first stage of protein synthesis and are important components of this process. The search for inhibitors of these enzymes is a promising trend in the development of antimicrobial therapeutic agents.[118]

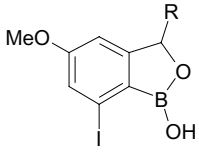
In a study of the antibacterial activity of 3-substituted 4-iodo-6-methoxybenzoxaboroles (**57a – d**) and 7-iodo-5-methoxybenzoxaboroles (**58a – c**) against *Micrococcus luteus* (ATCC 9341) and *Bacillus cereus* (ATCC 11778), compound **57c** was most active. It showed a somewhat higher activity against *B. cereus*. 7-Iodo-3-methyl-5-methoxybenzoxaborole (**58c**) was ten times less active against both strains than **57c**.[119] Considering their results, the authors concluded that the substituent in position 3 of iodinated benzoxaboroles has a significant effect on the antibacterial action.

Structures 57, 58



57a – d

R = 4-BrC_6H_4 (**a**), Bu^n (**b**), H (**c**), Me (**d**)



58a – c

R = 4-BrC_6H_4 (**a**), Bu^n (**b**), Me (**c**)

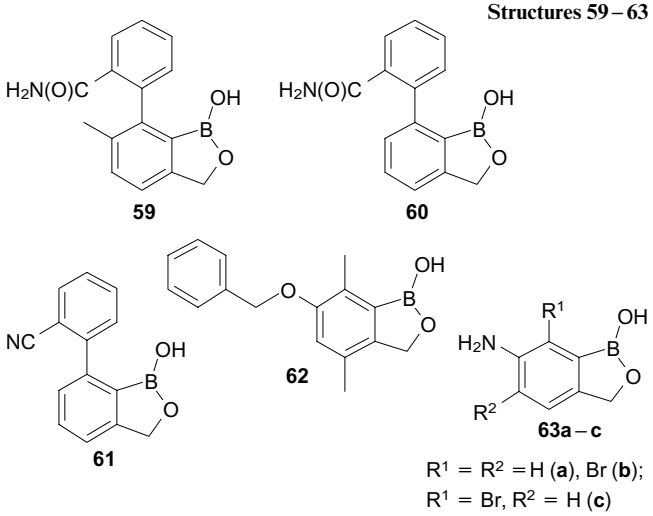
Parish and co-workers[120] described a series of 7-aryl-benzoxaborole derivatives **59 – 61** possessing *in vitro* activity against *Mycobacterium tuberculosis*. The highest activity was found for 2-(1-hydroxy-6-methyl-1,3-dihydro-2,1-benzoxaborol-7-yl)benzamide (AN11987, **59**), which had 90% inhibitory concentration (IC_{90}) of 1.8 μM, whereas 2-(1-hydroxybenzoxa-1,3-dihydro-2,1-borol-7-yl)benzonitrile (AN6288, **61**) was the least active (IC_{90} = 30 μM). A possible target for 7-arylbenzoxaboroles is NADH dehydrogenase (Ndh) rather than LeuRS. This assumption is based on the fact that mutations in the Ndh-encoding gene are responsible for resistance to all three compounds and result

in the loss of binding. The deletion of the mce3R gene results in upregulation of regulon members and, hence, the Mce3R regulatory protein influences the activity of genes involved in the development of resistance.

Screening of a library of boron compounds developed by Anacor Pharmaceuticals revealed a series of 6-benzyl benzoxaborole ethers possessing antitubercular activity. In particular, 6-(benzyloxy)-1-hydroxy-4,7-dimethyl-1,3-dihydro-2,1-benzoxaborole (**62**) exhibited high *in vitro* activity against *M. tuberculosis* in solid and liquid media and activity against intracellular bacteria, but possessed no cytotoxicity.[121] Patel *et al.*[121] defined two ways of development of resistance to this compound associated with Rv1683, Rv0047c and Rv3068c genes. The Rv1638 gene encodes the possible bifunctional protein involved in the catabolism and anabolism of triglycerides. Mutations in Rv0047c give rise to premature stop codon, whereas mutations in Rv3068c account for the replacement of threonine by alanine. The Rv0047c gene is located upstream of ino1, which is involved in the phosphatidylinositol metabolism and is needed for the growth of mycobacteria on inositol, while Rv3068c encodes a non-essential enzyme, PgmA, a putative phosphoglucomutase, which is involved in the glucose metabolism.

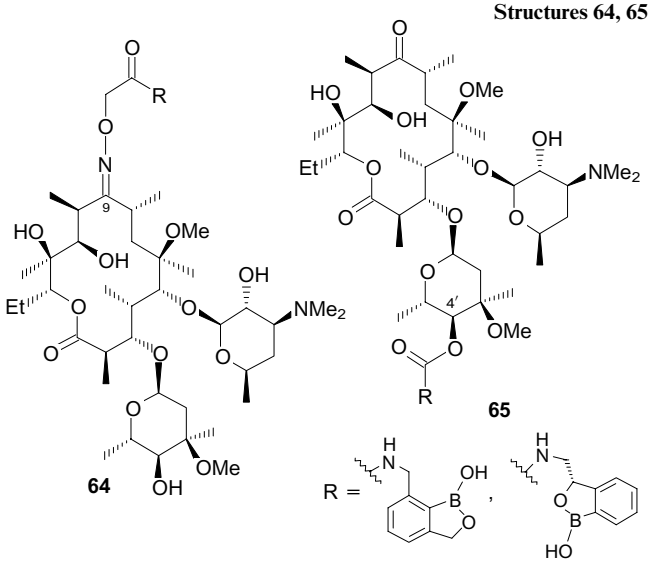
Most of 6-aminobenzoxaborole derivatives proved to be inactive or had little activity against *Mycobacterium smegmatis*. Derivatives **63a**,**b** were several times more effective than benzoxaborole against the *M. tuberculosis* H37Rv strain in 7H9 and GAST media. Relying on these data, the authors chose 6-amino-7-bromobenzoxaborole **63b** with 99% minimal inhibitory concentrations (MIC_{99}) of 7.8 (7H9) and 1.9 μM (GAST) as the lead compound.[122]

Structures 59 – 63



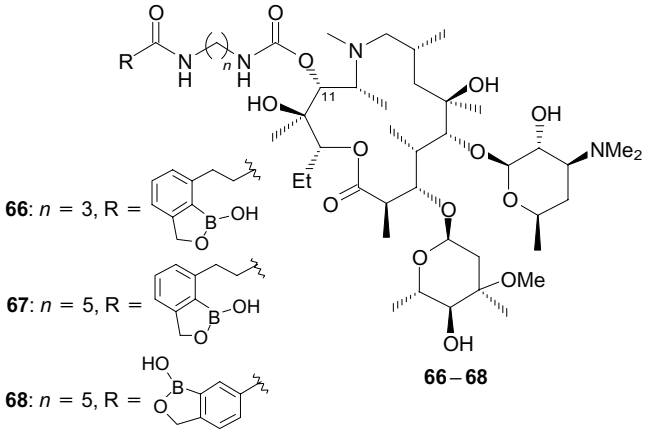
A combination of known antibiotics and active groups of small molecules targeting the same or different sites of a pathogenic microbe is one of the ways to develop new antibacterial drugs and overcome antibiotic resistance.[123] Lapa *et al.*[124] described the synthesis of various benzoxaborole conjugates **64** and **65** by functionalization of the C(9) and O(4″) atoms of clarithromycin. These semisynthetic antibiotics demonstrated activity against gram-positive bacteria, but had low activity against gram-negative bacteria. The introduction of the benzoxaborole moiety into position 4″ of cladinose affords compounds **65**, more active against gram-positive bacteria than those formed upon the replacement of the carbonyl group at C(9). Conversely, the presence of a substituent in position 9 of clarithromycin (compounds **64**) proved to be more beneficial for the activity against sensitive gram-negative bacterial strains, *E. coli* tolC and tolC/pUC/erm42, although the activity of new derivatives did not exceed the activity of the initial antibiotic.

Structures 64, 65



Two series of hybrid antibiotics were prepared from azithromycin and benzoxaborole. In the first series (compounds **66** – **68**), benzoxaborole was linked to the 11-hydroxy group of azithromycin *via* an aminoalkylcarbamoyl spacer. The antibacterial action was studied using a panel of gram-positive and gram-negative bacteria. Compound **66** was the best regarding the breadth of the range of antibacterial activity, but all compounds **66** – **68** had a high activity against *Streptococcus pneumoniae*.[125]

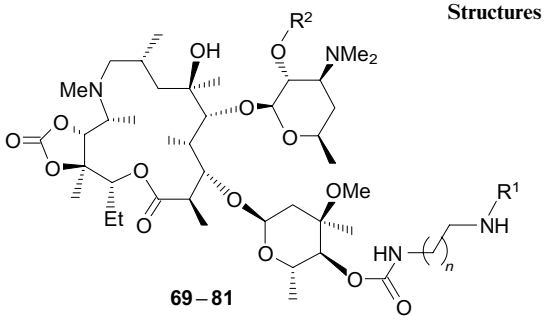
Structures 66 – 68



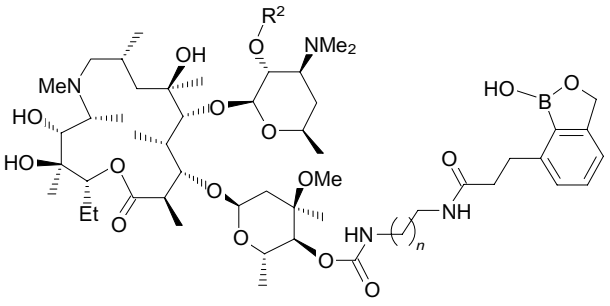
The second series represented benzoxaborole conjugates with azithromycin (**69** – **83**) in which the benzoxaborole moiety was attached to the 4″-hydroxy group of the antibiotic.[126]

All of the studied azithromycin derivatives exhibited a wide range of antibacterial activity against a panel of gram-positive and gram-negative bacteria; the conjugates were generally less active against gram-negative bacteria than

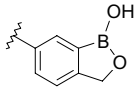
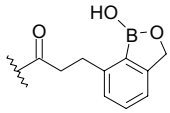
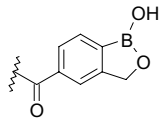
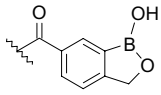
Structures 69 – 83



69 – 81



n = 1 (**82**), 2 (**83**) **82**, **83**

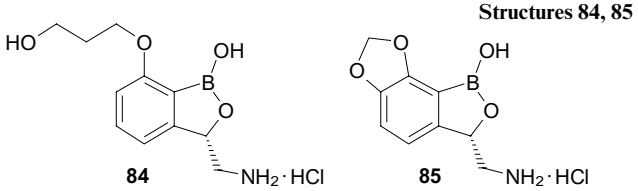
Compound	R^1	R^2	*n*
69		Ac	1
70		Ac	1
73		Ac	2
76		H	1
79		H	2
71		Ac	1
74		Ac	2
77		H	1
80		H	2
72		Ac	1
75		Ac	2
78		H	1
81		H	2

azithromycin. Apparently, the presence of the 2′-*O*-acetyl or 11,12-cyclocarbonate group did not considerably influence the antibacterial activity, whereas the use of a longer spacer between the benzoxaborole and azithromycin moieties (compounds **76**, **79**, **82** and **83**) was more beneficial for the activity against gram-negative bacteria. It is also noteworthy that the cyclic carbonate moiety present in the molecule (**69**, **71**, **76**, **77**, **79** and **81**) increased the activity against *S. pneumoniae* and *E. faecium* in comparison with that of compounds **82** and **83**.

Development of agents active against gram-negative bacteria is usually complicated by the efflux mechanism characteristic of these infections and their ability to acquire multidrug resistance.[127, 128] The therapeutic protocols for infections caused by gram-negative bacteria are scanty, which is due to the appearance of numerous multidrug resistant (MDR) strains and isolates resistant to drugs under nosocomial conditions.

(*S*)-3-(Aminomethyl)-1-hydroxy-(3-hydroxypropoxy)-1,3-dihydro-2,1-benzoxaborole (epetraborole, GSK2251052, AN3365, **84**) was the first benzoxaborole derivative shown to be active against drug resistant strains of gram-negative bacteria.[129] However, the clinical trials of this drug, meant for the treatment of complex urinary tract infections, were terminated in phase II due to fast development of resistant mutant strains.[130] Another promising benzoxaborole derivative, (*S*)-3-(aminomethyl)-1-hydroxy[1,3]dioxolo[4′,5′:5,6]benzoxaborole **85** (DS86760016), showed high activity against gram-negative pathogenic bacteria and excellent pharmacokinetics (longer plasma elimination half-life and higher renal excretion) compared to GSK2251052 in experiments in mice, rats, monkeys and dogs. It was shown that benzoxaborole **85** inhibits recombinant *E. coli*, *P. aeruginosa* and *A. baumannii* LeuRS and shows selectivity to aerobic gram-negative bacteria except for *A. baumannii*.[131] Probably, this is related to the absence of the hydroxypropyl group in position 7 of the benzoxaborole moiety, which is associated with the inhibitory activity.[129] Compound **85** showed a considerably lower risk of drug resistance in mouse models of urinary tract infections compared with compound **84**.[131] High antibacterial activity of the former against MDR strains of the blue pus bacillus (*P. aeruginosa*) was demonstrated by Kumar *et al.*[132] In addition, the authors ascertained that the activity of compound **85** against *P. aeruginosa* was retained in biofilms *in vitro*; also, this compound was shown to be effective against these bacteria in the mouse model of catheter-associated urinary tract infection (CAUTI) with a decreased risk of resistance.

Structures 84, 85

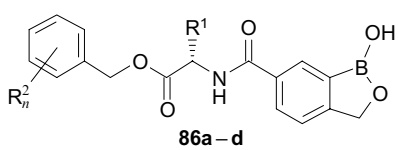


84 **85**

4.2.3. Application of benzoxaboroles for the treatment of protozoal and parasitic infections

Screening of a library of benzoxaboroles produced by Anacor Pharmaceuticals demonstrated that benzyl (*S*)-2-(benzoxaborole-6-carboxamido)propanoate **86a** has a pronounced activity against *Trypanosoma congolense* (IC_{50} = 5 nM) and *T. vivax* (IC_{50} = 69 nM), which are the main causative agents of the animal African trypanosomiasis (AAT). Seventy benzoxaborole derivatives were synthesized with the goal to enhance the antiprotozoal activity.[133] The design of new molecules included, in particular, a change of substituents in positions 3 and 7 of benzoxaborole and in the benzyl group, modification of amino acid residues and heteroaromatic methyl esters and introduction of hydrophilic or aliphatic ester groups into the benzyl moiety. For example, benzyl (*S*)-2-(benzoxaborole-6-carboxamido)-4-methylpentanoate (**86b**) exhibited activity against *T. congolense* and *T. vivax* with IC_{50} = 2 nM. Two compounds, 4-fluorobenzyl (**86c**) and 3,4-difluorobenzyl

Structure 86



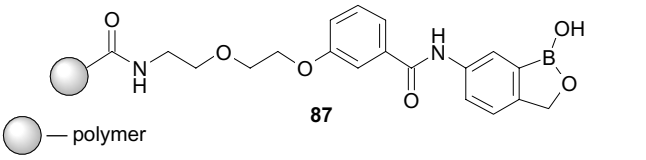
86a – d

R^1 = Me, R^2_n = H (**a**);
R^1 = Pr^i: R^2_n = H (**b**), 4-F (**c**), 3,4-F_2 (**d**)

(**86d**) esters of (*S*)-2-(benzoxaborole-6-carboxamido)-4-methylpentanoic acid, showed 100% therapeutic efficacy upon intramuscular administration of a single dose of 10 mg kg^{-1} to mice infected with *T. congolense* or *T. vivax*. Compound **86c** (AN11736), which had IC_{50} values against *T. congolense* and *T. vivax* of down to 0.15 and 1.3 nM, respectively, also showed 100% therapeutic efficacy upon intramuscular administration of a single dose of 10 mg kg^{-1} to bovine cattle infected with these microorganisms.

Understanding of the currently unknown mechanism of action of benzoxaboroles against *T. brucei* may prove to be the key for selection of appropriate agents active against resistant microbial strains and for the search for new drugs. Therefore, attempts were made to locate the intracellular target for the action of benzoxaboroles. The genomic and proteomic approaches using benzoxaborole **87** immobilized on a resin for affinity chromatography made it possible to identify 14 genes involved in the antitrypanosomal action of benzoxaboroles.[134]

Structure 87



87

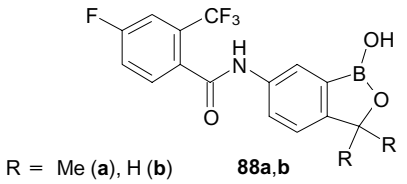
A promising therapeutic agent, *N*-(3,3-dimethylbenzoxaborol-6-yl)-4-fluoro-2-(trifluoromethyl)benzamide **88a** (acoziborole, AN5568, SCYX-7158), has been under phase 2/3 clinical trials since the end of 2016 as a drug for treatment of human African trypanosomiasis both in the early and late stages of the disease.[135] Analysis of metabolic disorders that are induced by acoziborole (**88a**) in the *T. brucei* Lister427 laboratory strain showed 50 considerable metabolic disorders in trypanosomes, most of which were identified as components of amino acid metabolism. In particular, the number of metabolic products of L-methionine and (*S*)-adenosylmethionine was found to increase, which suggests methyltransferases as possible targets.[136] However, these effects have not yet been directly attributed to particular enzyme or to transfer of the methyl group to a particular atom of the target protein.

Wall *et al.*[137] successfully used the determination of overexpression to identify the target gene for benzoxaboroles. The cleavage and polyadenylation specificity factor 3 (CPSF3/CPSF73/Ysh1) was found to be the target for the trypanocidal action of five benzoxaborole derivatives — acoziborole (**88a**), *N*-(benzoxaborol-6-yl)-4-fluoro-2-(trifluoromethyl)benzamide **88b** (SCYX-6759), 5-[4-(aminomethyl)phenoxy]benzoxaborole **89** (AN3057), *N*-(benzoxaborol-6-yl)benzenesulfonamide **90** (oxaborole-1) and 4-fluorobenzyl (*S*)-2-(7-methylbenzoxaborole-6-carboxamido)-3-isovalerate **91** (AN11736). The molecular docking and experiments with the Asn232His mutant protein demonstrated that acoziborole (**88a**) binds to the active site of the *T. brucei* the cleavage and polyadenylation specificity factor 3 (CPSF3), thus blocking pre-mRNA endonuclease activity. In the model enzyme, the benzoxaborole moiety occupies the same active site as the RNA phosphate group where two zinc atoms are located. The boron atom reacts with an activated water molecule located at the bimetallic site, giving rise to tetrahedral negatively charged intermediates, which mimic the transition state of the phosphate of the RNA substrate. The bulky Tyr side chain present in the human CPSF3 implies a steric clash with acoziborole (**88a**), which accounts for its selective activity and safety profile. Thus, the CPSF3 subunit can be considered as a genetically and chemically validated target for the search for new therapeutic agents with antitrypanosomal activity.

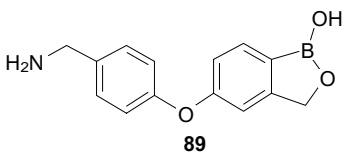
For determining the mechanism of action of benzoxaboroles in the treatment of African trypanosomiasis, Zhang *et al.*[138] attempted to determine the metabolic pathway needed to attain a trypanocidal activity of 4-(aminomethyl)-phenoxy- (**89**) and 6-[4-(aminomethyl)phenoxy]-1-hydroxy-1,3-dihydro-2,1-benzoxaboroles (**92**). It was shown that this pathway consists of two oxidation reactions, which successively take place in the host and parasite bodies, namely, enzymatic oxidative cascade comprising the host semicarbazide-sensitive monoamine oxidase and trypanosomal aldehyde dehydrogenase (TbALDH3).[138] Thus, methylamide-derived prodrugs are converted, first, to aldehydes and then to carboxylate metabolites, which are the active molecules. Comparative biochemical assay and crystallographic analysis revealed the catalytic specificity of TbALDH3 to benzaldehyde metabolites of benzoxaboroles as xenogenic substrates.

Clayton and co-workers[139] used a large range of methods for determining the mechanism of suppression of *T. brucei* growth on treatment with 2-chloro-*N*-(3,3-dimethyl-1-hydroxy-1,3-dihydro-2,1-benzoxaborol-6-yl)-4-(1*H*-pyrazol-1-yl)benzamide (AN7973, **93**) in comparison with other benzoxaboroles. Benzamide **93** and other compounds of this series were found to affect the *T. brucei* metabolism. The inhibition of mRNA processing, resulting in decreasing amount of mRNA and suppression of protein synthesis, was the earliest detectable effect of compound **93**. In view of the obtained results, the authors suggested that benzamide **93** and other benzoxaboroles block the gene expression.

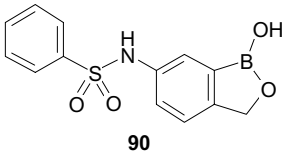
Structures 88 – 93



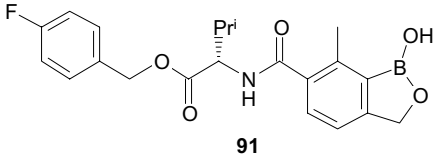
R = Me (**a**), H (**b**) **88a**,**b**



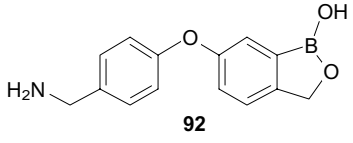
89



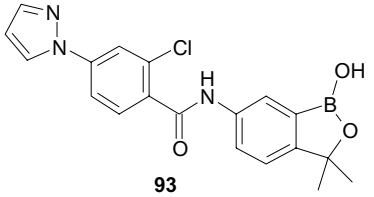
90



91



92



93

According to the results of additional experiments, the CPSF3 protein was identified as the target for molecule **93**.

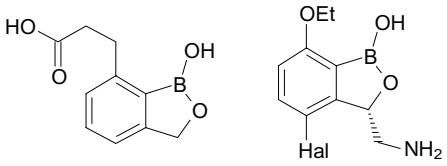
Trypanosoma cruzi and *Leishmania donovani chagasi*, which belong to the family *Trypanosomatidae*, are of considerable interest for studying the mechanisms of action of antitrypanosomal agents. These microorganisms cause transmissible diseases such as the Chagas disease (American trypanosomiasis) and leishmaniosis, included in the World Health Organization (WHO) list of neglected tropical diseases, which mainly affect the poorest, vulnerable social groups and which are still relevant for African countries. Owing to accessibility of the full-genome sequences of both protozoa, their wide-scale analysis can be carried out to identify the targets of therapeutic agents. Recently, protozoan carbonic anhydrases (EC 4.2.1.1) were identified as potential targets of these parasitic microorganisms.[140 – 142]

Nocentini *et al.*[143] investigated the inhibitory activity of some 6-substituted (thio)urea benzoxaboroles similar to compound **56** against the carbonic anhydrases from two parasitic protozoa — *Trypanosoma cruzi* (TcCA) and *Leishmania donovani chagasi* (LdcCA). The authors also estimated the selectivity index of these agents against LdcCA over human CA isoform II. Like in the case of antifungal action, the replacement of the oxygen atom by sulfur did not affect significantly the inhibitory activity.[114] The inhibitory activity of most such derivatives against LdcCA was comparable with the activity against hCA I and hCA II. Compound **56a** with the *p*-nitrophenylthiourea substituent was the most potent inhibitor: its selectivity index for the pathogenic LdcCA isoform over hCA II was approximately 110.

A promising drug candidate for the treatment of protozoal infections is 3-(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-7-yl)propanoic acid (AN3661, **94**). Sonoiki *et al.*[144] ascertained that acid **94** is active against *Plasmodium falciparum*, which causes malaria in humans. However, elucidation of the mechanisms of action and identification of particular targets for the antiprotozoal agents should include studies using resistant mutants. For example, *P. falciparum* protozoa species, which demonstrated resistance to compound **94** *in vitro*, had point mutations in the pfcpsf3 site encoding a homologue of mammalian cleavage and polyadenylation specificity factor subunit 3. All *Toxoplasma gondii* strains causing toxoplasmosis and *P. falciparum* strains resistant to compound **94** also carried mutations within the CPSF3 active site.[145] It is noteworthy that the insertion of these mutations by CRISPR/Cas9 gene editing *in vitro* generated AN3661 resistance in *T. gondii* and *P. falciparum*. In addition, mice infected with the resistant $TgCPSF3^{E545K}$ strain and then treated with compound **94** did not survive, whereas mice infected with the wild type strain and treated in a similar way completely recovered. This fact is evidence of the selection of CPSF3 as the *in vivo* target for acid **94** in the case of *Plasmodium falciparum* and *Toxoplasma gondii*. In combination, both studies support the conclusion that this compound acts by inhibiting CPSF3 in apicomplexan parasites. Docking of molecule **94** showed that the boron atom occupies the position of the phosphate group of the mRNA substrate and that the benzoxaborole oxygen atom can interact with two zinc ions in the active site.[144]

Screening of the library of benzoxaborole derivatives against the cultured multidrug-resistant *P. falciparum* W2 strain revealed two benzoxaboroles — (*S*)-3-(aminomethyl)-4-chloro-7-ethoxybenzoxaborole **95a** (AN6426) and (*S*)-3-(aminomethyl)-4-bromo-7-ethoxybenzoxaborole **95b** (AN8432) — with a nanomolar activity (IC_{50} = 310 and 490 nM, respectively), which also demonstrated activity in the mouse model of malaria.[146] By genetic and biochemical experiments, it was shown that the activity of compounds **95a**,**b** against *P. falciparum* is due to inhibition of leucyl-tRNA synthetase. The structure determination of the LeuRS editing domain from *P. falciparum* demonstrated the key role of mutations for LeuRS editing. Thus incubation with benzoxaboroles **95a**,**b** induced dose-dependent inhibition of inclusion of [^{14}C]-leucine by only wild type strains, but not resistant strains. Considering their results, the authors suggested that benzoxaboroles **95a**,**b** act, at least partly, *via* blocking of the *P. falciparum* LeuRS editing domain.[146]

Structures 94, 95

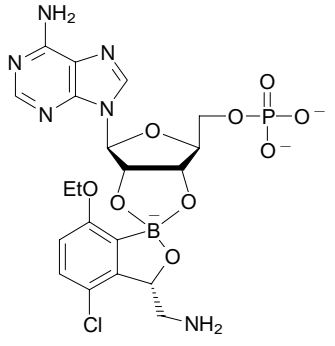


94 **95a**,**b**

The same group of researchers[147] found that 3-(aminomethyl)benzoxaboroles **95a**,**b** noticeably inhibit the development of *Cryptosporidium parvum* microorganisms in the Madin – Darby canine kidney (MDCK) cells with a 50% effective concentration (EC_{50}) of 2.2 and 6.9 μM, respectively. It was shown that benzoxaborole **95a** is also active against *Toxoplasma* parasitic microorganisms: when present in micromolar concentrations, this compound suppresses proliferation of the parasite in human fibroblasts. The activity of the agent increases in the presence of norvaline, which is consistent with the assumption that the inhibitor blocks the LeuRS editing site and then disrupts the editing activity of the LeuRS enzyme.[147] A study of the crystal structure of the CmLeuRS-AN6426-AMP complex demonstrated that the inhibitor and the adenosine monophosphate (AMP), mimicking the Ade76 purine base, form covalent adduct **96**, which is strongly bound in the editing active site and occupies the same position as the editing substrate. Thus, it was assumed that benzoxaborole **95a** inhibits the synthesis of proteins in both *Cryptosporidium* and *Toxoplasma* by forming a covalent adduct with tRNALeu in the editing site of LeuRS.[147]

Zhang *et al.*[148] synthesized and characterized a series of 6-hetaryloxybenzoxaboroles, out of which 6-[2-(methoxycarbonyl)pyrazinyl-5-oxy]benzoxaborole **97** demonstrated a

Structure 96

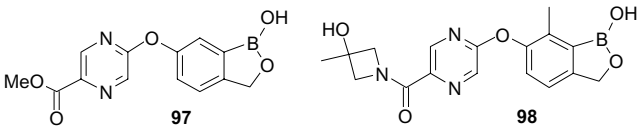


96

high *in vitro* activity against the *P. falciparum* W2 and 3D7 strains (IC_{50} = 1.4 and 1.9 nM, respectively) and also a high *in vivo* activity against *P. berghei* in infected mice [the 90% effective dose (ED_{90}) was 7.0 mg kg^{-1}].

However, this compound showed an unsatisfactory pharmacokinetic profile. In particular, it had a short half-life ($t_{1/2}$ = 1 h) and low bioavailability (F = 23%) in mice, which is attributable to fast hydrolysis of the methyl ester to the corresponding carboxylic acid. Further structural optimization of the lead compound, which implied the replacement of the easily hydrolyzable ester group, furnished a new antimalarial agent — 6-{2-[(3-hydroxy-3-methylazetidin-1-yl)-carbonyl]pyrazinyl-5-oxy}-1-hydroxy-7-methyl-1,3-dihydro-2,1-benzoxaborole (AN13762, **98**). This benzoxaborole derivative exhibited a high *in vitro* activity against *P. falciparum* W2 and 3D7 strains (IC_{50} = 33 and 43 nM, respectively), enhanced the pharmacokinetic properties in comparison with those of compound **97** (high plasma concentration, longer elimination half-life and high bioavailability) and also demonstrated high *in vivo* efficacy for the treatment of mice infected with *P. falciparum* (ED_{90} = 0.85 mg kg^{-1}) or *P. berghei* (ED_{90} = 1.92 mg kg^{-1}).[149]

Structures 97, 98



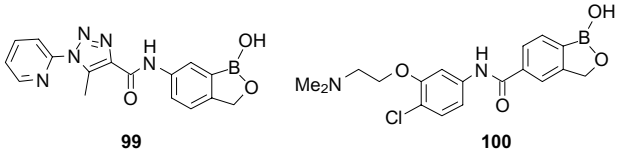
97 **98**

The mechanism of action of compound **98** was studied using *P. falciparum* strains with reduced sensitivity to the product. Resistant strains had single nucleotide polymorphism (SNP) in the genes encoding microtubules and actin-binding protein (PFC0960c), lysophospholipase (PF07_0040), ubiquitin-like modifier activating enzyme 2 (PFL1790w) and unknown function protein (PF14_059).[150] Thus, the plasmodium resistance to product **98** develops, apparently, by a combined mechanism.

Van Bocxlaer *et al.*[151] described an approach to rational preclinical selection of drug candidates for the treatment of cutaneous leishmaniasis. A series of benzoxaborole-6- and benzoxaborole-5-carboxamides, active against several types of parasitic protists of the genus *Leishmania*, were screened for physicochemical properties and studied for the ability to penetrate and be retained in the skin using various models. The assay revealed two promising candidates, *N*-(benzoxaborol-6-yl)-5-methyl-1-(pyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxamide **99** (LSH001, DNDI-6148) and *N*-{3-[2-(dimethylamino)ethoxy]-4-chlorophenyl}benzoxaborole-5-carboxamide **100**, which showed a high antileishmanial activity. Compound **99** also possessed considerable capability of penetrating the mouse skin to reach leishmania amastigotes in *in vitro* experiments.[151]

Compound **99** was active against some *Leishmania* parasite species (*L. major*, *L. aethiopica*, *L. amazonensis*, *L. panamensis*, *L. mexicana* and *L. tropica*) and effective in a dose of 50 mg kg^{-1} day^{-1} for the treatment of murine cutaneous leishmaniasis.[152] Thus, benzoxaborole derivative **99** is considered to be a promising candidate for the treatment of both visceral and cutaneous leishmaniasis, and in October 2018, an application was submitted for phase I clinical trials of this product.[153]

Structures 99, 100



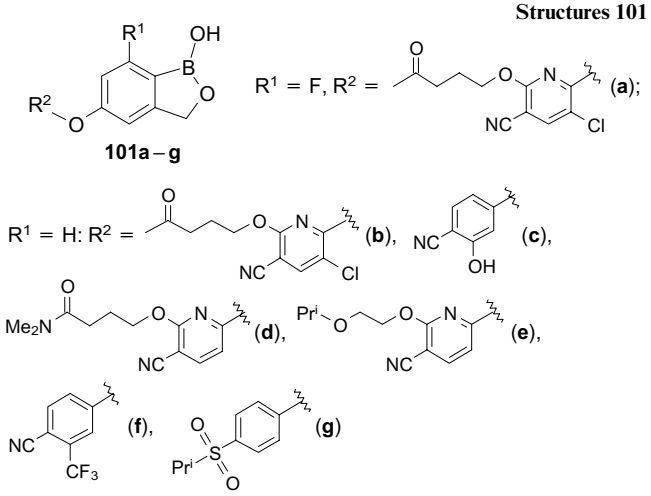
99 **100**

Leucyl-tRNA synthetase is the validated target for tavaborole (**28**), used as an antifungal agent against filamentous fungi. It is known that tavaborole inhibits the fungal cytoplasmic LeuRS enzyme by covalent binding tRNA-Leu, thus interrupting the catalytic cycle and blocking the protein synthesis.[117] It is reasonable to suggest that tavaborole can also act on *Leishmania donovani* leucyl-tRNA synthetase (LdLeuRS). Madhubala and co-workers[154] studied the interaction of tavaborole (**28**) with LdLeuRS. They showed that the binding ability of this compound is sufficient for inhibiting the aminoacylation potential of the recombinant LdLeuRS enzyme, with IC_{50} being down to 0.83 ± 0.2 μM.[117] Tavaborole inhibited the growth of *L. donovani* in *in vitro* and *in vivo* experiments and proved to be effective against the wild type *L. donovani* in various cellular forms, promastigote and amastigote ones, with EC_{50} = 2.67 and 2.38 μM, respectively. The parasite load in the spleen of mice administered with tavaborole decreased threefold compared to that in the control group.

Pandey *et al.*[155] selected potential antileishmanial therapeutic agents by screening a series of benzoxaborole analogues using molecular docking into trypanothione reductase (TR) from the *Leishmania* parasitic protist.

Caffrey and co-workers[156] utilized a library of 5-aryloxybenzoxaboroles of Anacor Pharmaceuticals to develop drugs against schistosomiasis, also known as bilharziasis, which is caused by *Schistosoma* trematodes. The phenotypic screening of benzoxaborole derivatives **101a** – **g** with *S. mansoni* revealed a certain phenotype – chemotype relationship, which allowed the authors to propose phosphodiesterase 4 (PDE4) as the main molecular target. Using *C. elegans* as the transgene expression system, they confirmed the role of the catalytic domain of schistosome phosphodiesterase (SmPDE4A) as the molecular target for compounds **101**.

Structures 101



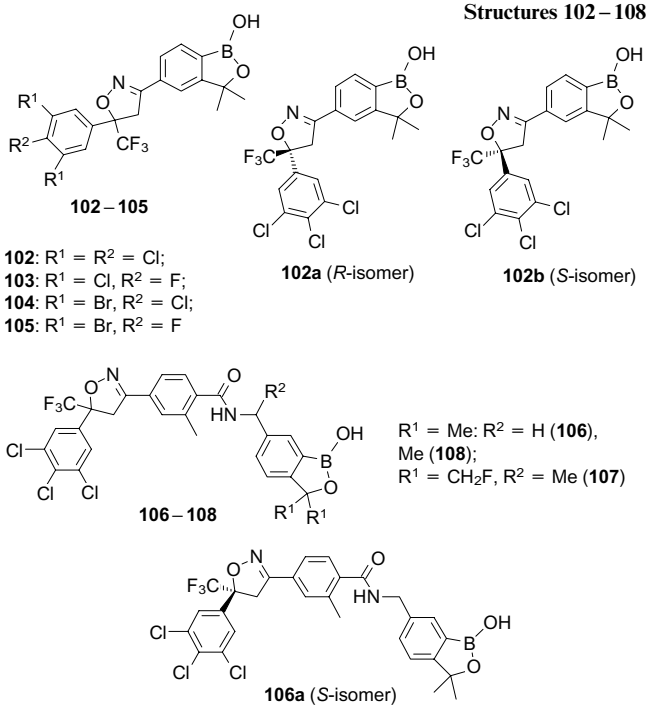
101a – **g**

Benzoxaboroles are also active against ectoparasites. Zhang *et al.*[157] identified four effective molecules — 3,3-dimethyl-5-(5-aryl-5-trifluoromethyl-4,5-dihydroisoxazol-3-yl)benzoxaboroles **102** – **105**. These compounds

showed high activity against larval-stage *Amblyomma americanum* lone star tick in *in vitro* larval immersion microassay and 95 – 100% efficacy in 5 mg kg^{-1} dose for the treatmentt of rats infected with American dog ticks. Since 3,3-dimethyl-1-hydroxy-5-[5-(trifluoromethyl)-5-(3,4,5-trichlorophenyl)-4,5-dihydroisoxazol-3-yl]-1,3-dihydro-2,1-benzoxaborole (**102**) showed high stability when tested in the microsomal fraction of rat and dog liver, the subsequent studies were carried out using stereoisomers of this compound. *R*-Enantiomer **102a** did not show acaricidal activity, while *S*-enantiomer **102b** (AN8030) taken in a dose of 2.5 mg kg^{-1} was effective in *in vivo* models.[157]

Lead compound **102b** was used to prepare a series of derivatives. The effect of the nature of substituents was studied by introducing various groups into oxaborole position 3, in the benzyl position and to the amide nitrogen atom; by introducing of halogen atom into position 5 of the aryl ring; by varying the position and length of the linker between the benzoxaborole and isoxazoline rings; and by using different configurations of the asymmetric carbon atom in the five-membered ring. It was found that three close analogues, compounds **106** – **108**, possess 90 – 100% efficacy when used in a dose of 5 mg kg^{-1} for the treatment of rats infected with the *Dermacentor variabilis* American dog ticks. The *S*-enantiomer of *N*-[(1-hydroxy-3,3-dimethyl-1,3-dihydro-2,1-benzoxaborol-6-yl)methyl]-2-methyl-4-[5-(trifluoromethyl)-5-(3,4,5-trichlorophenyl)-4,5-dihydroisoxazol-3-yl]benzamide (**106a**) exhibited a 97% efficacy in the treatment of American dog tick-infected dogs and 98% efficacy upon oral administration in a single dose of 25 mg kg^{-1} for the treatment of dogs infected by *Ctenocephalides felis* cat flea.[158]

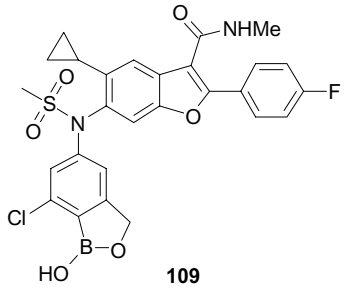
Structures 102 – 108



4.2.4. Antiviral activity of benzoxaborole derivatives

The molecular mechanism of inhibition of the hepatitis C virus (HCV) serine protease by compounds with a benzoxaborole moiety was described rather long ago.[159,160] The GlaxoSmithKline company[161] explored the second generation inhibitors of another viral target, RNA-dependent RNA polymerase (NS5B proteins) of hepatitis C virus. Among these compounds, *N*-methyl-6-[*N*-(7-chloro-1-hydroxy-1,3-dihydro-2,1-benzoxaborol-5-yl)methylsulfonylamino]-2-(4-fluorophenyl)-5-cyclopropylbenzofuran-3-carboxamide (GSK8175, **109**) showed a low excretion rate *in vivo* and high activity against HCV replicons. Benzoxaborole derivative **109** exhibited a high degree of inhibition of GT1a316Y replicon. Analysis of the crystal structure of compound **109** with the NS5B GT1a316Y protein revealed an extensive network of interactions mediated by highly ordered water molecules. Compound **109** has finished phase 2 clinical trials for the treatment of AIDS; the results of the trials are to be reported in the near future. Arrington *et al.*[162] described an optimized method for the synthesis of compound **109**, which included eight steps and gave the product in 20% overall yield.

Structure 109

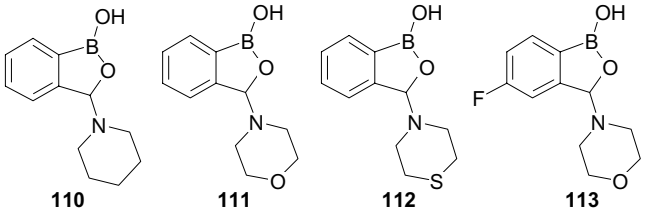


4.2.5. Anticancer activity of benzoxaboroles

The above-mentioned study of Psurski *et al.*,[70] dealing with the structure – activity relationships of boronic acids and benzoxaboroles with simple substituents, reports benzoxaboroles to be promising anticancer and proapoptotic compounds functioning by a cell cycle-specific mechanism. Several benzoxaborole derivatives — tavaborole (**28**), 4-, 6- and 7-fluorobenzoxaboroles **55a** – **c**, 3-piperidinobenzoxaborole **110**, 3-morpholinobenzoxaborole **111**, 3-thiomorpholinobenzoxaborole **112** and 3-morpholino-5-fluorobenzoxaborole **113** — were shown to obey an accurate structure –activity relationship, and some compounds had a high antiproliferative activity characterized by micromolar IC_{50} values. The tested compounds had the highest selectivity to ovarian cancer cells (A2780) and leukemia cells (MV-4-11) over breast cancer cells (MCF7), which were generally resistant to benzoxaboroles. Tavaborole (**28**) had the highest activity against MCF7, 5637 (bladder cancer) and A549 (human lung cancer) cells. Substituents in position 3 of benzoxaborole (compounds **110** – **113**) had virtually no effect on the antiproliferative activity against A2780, A549, MCF7 and 5637 cell lines. The only cell line that benefited from this modification of the benzoxaborole structure was MV-4-11. 3-Morpholino-5-fluorobenzoxaborole **113** induced cell cycle arrest in the G2/M phase associated with caspase-3 activation in A2780 cancer cells. The inhibitory effect was accompanied by changes in the morphology of cell nuclei, organelles and cytoplasmic membrane and increasing percentages of aneuploid and tetraploid cells, although the mechanism of this process remained unknown.

Jonnalagadd and co-workers[163] synthesized a series of substituted *N*-benzylaminobenzoxaboroles using 6-aminobenzoxaborole for reductive amination of aromatic

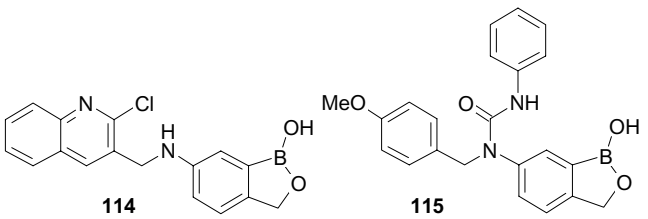
Structures 110 – 113



110 **111** **112** **113**

aldehydes. Then 6-[(2-chloroquinolin-3-yl)methylamino]-benzoxaborole **114** was converted to the corresponding *N*-nitrosoaminobenzoxaborole, while other 6-benzylamino-substituted benzoxaboroles were reacted with phenyl, cyclohexyl and 2-chloroethyl isocyanates to give *N*-benzoxaborolylureas [for example, 1-(benzoxaborol-6-yl)-1-(4-methoxybenzyl)-3-phenylurea **115**]. The antiproliferative activity of these functionalized aminobenzoxaboroles was evaluated in relation to human breast cancer (MDA-MB-231) and human pancreatic cancer (MIAPaCa-2) cell lines. Although most of the tested compounds did not show noticeable cytotoxicity below a concentration of 50 μM; compounds **114** and **115** were active against MIAPaCa-2 cells at a concentration of 12.5 μM. The IC_{50} values for these most active compounds were 11.5 and 11.9 μM for MDA-MB-231 cells and 8.3 and 2.7 μM for MIAPaCa-2 cells.

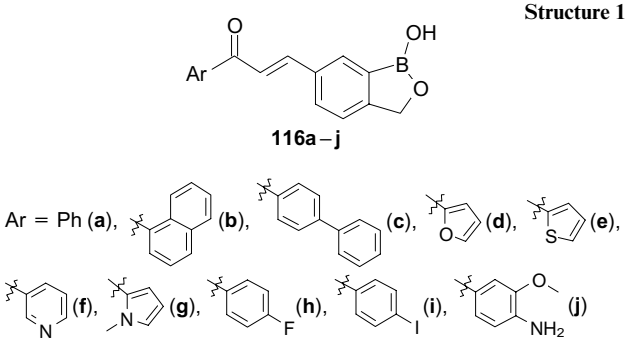
Structures 114, 115



114 **115**

Zhou and co-workers[164] screened a series of hybrid (benzoxaborol-6-yl)chalcones **116a – j** for the activity against three human cancer cell lines [SKOV3 (ovarian carcinoma), MDA-MB231 (breast cancer) and HCT116 (colorectal carcinoma)] and two human normal cell lines [MCF-10A (breast epithelial cells) and WI-38 (lung fibroblasts)]. The lead compound, 3-(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-6-yl)-1-phenylprop-2-en-1-one (**116a**), exhibited antiproliferative activity against SKOV3, MDAMB231 and HCT116 cells characterized by IC_{50} = 3.4, 2.3 and 6.1 μM, respectively. Derivative **116a** demonstrated an eight-fold selectivity to the breast cancer cell culture (MDA-MB231) over normal lung fibroblasts (WI-38). To establish the structure – activity relationship, the authors investigated the effect of various aromatic groups and the nature and positions of substituents in the chalcone benzene ring on the antitumour activity. 3-(Benzoxaborol-6-yl)-1-(4-fluorophenyl)prop-2-en-1-one **116h** showed a high activity against tumour cells (IC_{50} = 1.4 μM) and high toxicity to normal cells, whereas 1-(4-iodophenyl)- (**116i**) and 1-(4-amino-3-methoxyphenyl)-3-(1-hydroxy-1,3-dihydro-2,1-benzoxaborol-6-yl)prop-2-en-1-ones (**116j**) possessed activity against the cancer cells (IC_{50} = 4.2 and 1.7 μM, respectively) and a higher selectivity. It is noteworthy that usual 2′- and 4′-aminochalcones with hydrophobic substituents in the

Structure 116



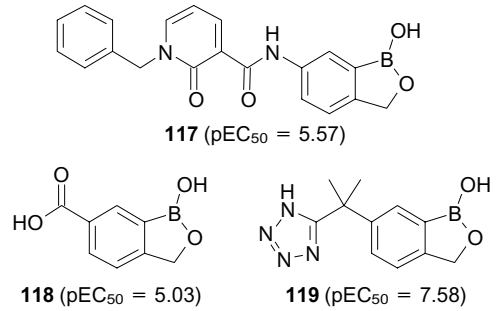
styrene moiety also proved to be effective antiproliferative agents causing the death of DH82 canine histiocytic cells.[165]

4.2.6. Other types of biological activity of benzoxaboroles

Benzoxaborole-based phosphodiesterase PDE4 inhibitors such as crisaborole (**32**) can be used as topical therapeutic agents for the treatment of inflammatory skin diseases, including atopic dermatitis and psoriasis.[166 – 168] Benzoxaboroles **101b**,**e** were shown to be potent phosphodiesterase (PDE4) inhibitors with a similar affinity for other isoenzymes (PDE1 – PDE3, PDE5 – PDE11) and equivalent inhibition of the catalytic domain and the full-size enzyme, 1 – 2 orders of magnitude higher than the action of crisaborole.[169] It was noted that benzoxaboroles **101b**,**e** predominantly inhibit PDE4 and are less active against other PDE isoforms. In relation to compound **101b**, it was shown that benzoxaborole PDE4 inhibitors directly interact with the bimetallic active site of the enzyme, with the boron atom functioning as a phosphomimetic, and compound **101b** gains additional affinity for the PDE4 adenine pocket.[169] In human white blood cells, benzoxaborole PDE4 inhibitors suppress the release of tumour necrosis factor (α-TNF), γ-interferon and interleukins IL-4, IL-5, IL-13, IL-17, IL-22 and IL-23. These cytokines induce pathological changes in the structure and barrier function of skin and are involved in the hyperimmune response inherent in atopic dermatitis and psoriasis. For example, it was demonstrated that compound **101e** penetrates mouse skin and thus mitigates the inflammatory response and decreases the phorbol myristate acetate-induced IL-13, IL-22, IL-17F and IL-23 transcription and calcipotriol-induced thymic stromal lymphopoietin expression by mouse skin epithelial cells.

The only FDA-approved drug for the treatment of sickle cell anemia is hydroxyurea, which elevates the level of embryonic haemoglobin (HbF) in red blood cells and decreases the frequency of vaso-occlusive (pain) crises (sludging of red blood cells with vascular occlusion). Despite the importance of hydroxyurea for the treatment of sickle cell anemia patients, there are serious limitations on its use. Screening of a library comprising ~8000 compounds showed that *N*-(benzoxaborol-6-yl)-1-benzyl-2-oxo-1,2-dihydropyridine-3-carboxamide **117** induces the synthesis of HbF in human erythroid precursor cells, with the negative logarithm of 50% effective concentration (pEC_{50}) reaching 5.57.[170] The target and the mechanism by which compound **117** induces the synthesis of HbF are yet unknown. Nevertheless, the authors made an attempt to establish the relationship between the HbF-inducing capacity of benzoxaborole derivatives and the nature of substituents in their molecules. Using modifications of **117**,

Structures 117 – 119



117 (pEC_{50} = 5.57)

118 (pEC_{50} = 5.03) **119** (pEC_{50} = 7.58)

it was shown that, like in the case of benzoxaborole-6-carboxylic acid (**118**), the carboxy group is an important structural unit for the desired activity to be manifested. The structure of **118** was further optimized to obtain 1-hydroxy-6-[2-(1*H*-tetrazol-5-yl)propan-2-yl]-1,3-dihydro-2,1-benzoxaborole (**119**), which was ~100 times more active than the starting compound **117**.

5. Benzoxaborines. Synthesis and applications

Although synthetic approaches to benzoxaborines resemble those to benzoxaboroles, the former are much less studied.

The design of β-lactamase inhibitors with a broad range of action based on benzoxaborines implies the introduction of a hydrophobic substituent into the molecule in order to enhance the van der Waals interactions of the ligand with the enzyme active site. The carboxy group in the benzene ring, the hydroxy group at the boron atom and the oxygen atom in the boronate ring should presumably ensure the interaction with the Zn^{2+} ion of metallo-β-lactamases [171] (Fig. 2).

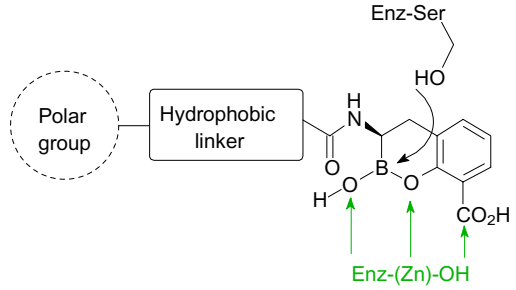


Figure 2. Design of serine and metallo-β-lactamase inhibitors based on benzoxaborines. The Figure was drawn by the authors of the review using data of Ref. 171. Enz is enzyme.

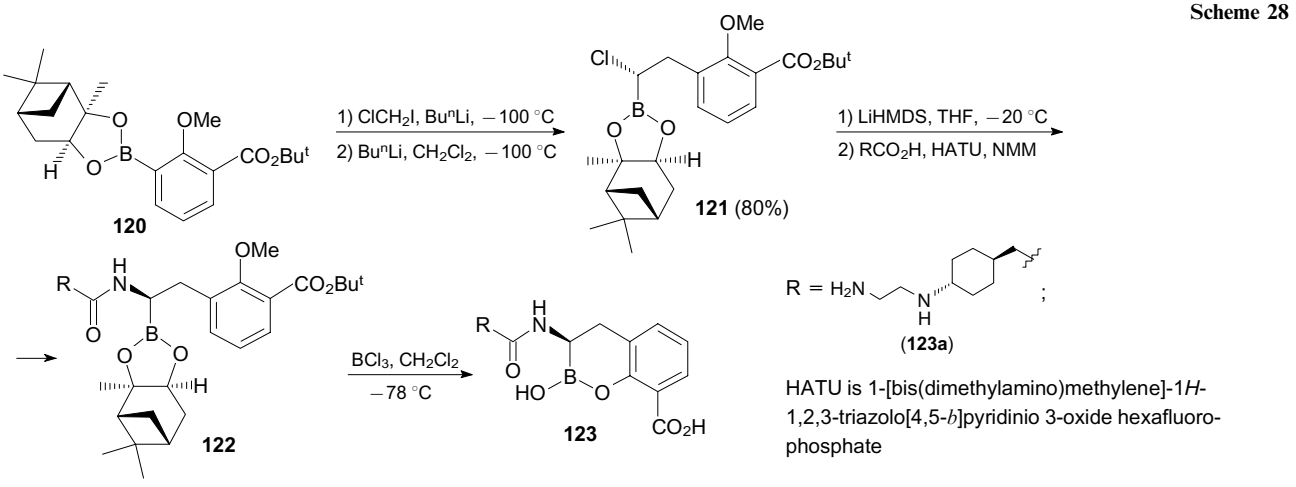
Liu *et al.*[171] carried out two Matteson homologation reactions of 3-(*tert*-butoxycarbonyl)-2-methoxyphenylboronic acid (+)-pinanediol ester (**120**), first with chloromethyllithium and then with dichchloromethane. This gave (*S*)-2-[3-(*tert*-butoxycarbonyl)-2-methoxyphenyl]-1-chloroethylboronate (**121**) (Scheme 28). Stereoselective replacement of the chlorine atom by an amino group followed by acylation with various acids in the presence of 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinio 3-oxide hexafluorophosphate and *N*-methylmorpholine resulted in the formation of (*R*)-1-acylamido-2-[3-(*tert*-butoxycarbonyl)-2-methoxyphenyl]ethylboronates **122**, which were cyclized, after deprotection, by treatment with BCl_3 at −78 °C to give the target (*R*)-3-acylaminobenzoxaborine-8-carboxylic acids **123**. Unfortunately, the authors [171] did not report the yields of intermediate compounds in the key synthetic steps.

Among the studied compounds with different substituents (phenyl, cycloalkyl, guanidine, amino, hydroxy, carboxy and other groups), taniborbactam (VNRX-5133, **123a**) exhibited the highest activity against serine and metallo-β-lactamases and efficient penetration of the cell wall of gram-negative bacteria.[172] Currently, this compound in combination with cefepime is under phase 3 clinical trials for the treatment of complicated urinary tract infections and pyelonephritis.[173]

The replacement of the α-amide group in molecule **123** by a thioester group was considered [174] in the quest for β-lactamase inhibitors with a broad range of action. Akama *et al.*[175] described a method for the synthesis of *N*-substituted 7-aminobenzoxaborines **124** containing an amide or sulfonamide substituent in the aromatic ring and possessing an antiprotozoal activity. The key step of the synthesis of these compounds is nitration of benzoxaborine **125**, which is obtained in two steps from protected (2-bromophenyl)-ethanol **126** (Scheme 29). After Pd/C-catalyzed reduction of the nitro group of 7-nitrobenzoxaborine **127**, modification of the amino group with acyl and sulfonyl chlorides in the presence of triethylamine was carried out.

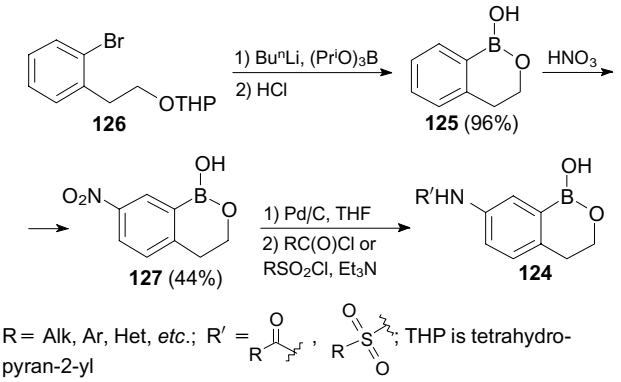
Lu *et al.*[176] described the synthesis of a series of 3-aryl-2*H*-naphtho[2,3-*e*][1,2]oxaborines **128** (Scheme 30) exhibiting a pronounced antioxidant activity and inhibitory activity against β-amyloid aggregation, a pathological process

Scheme 28

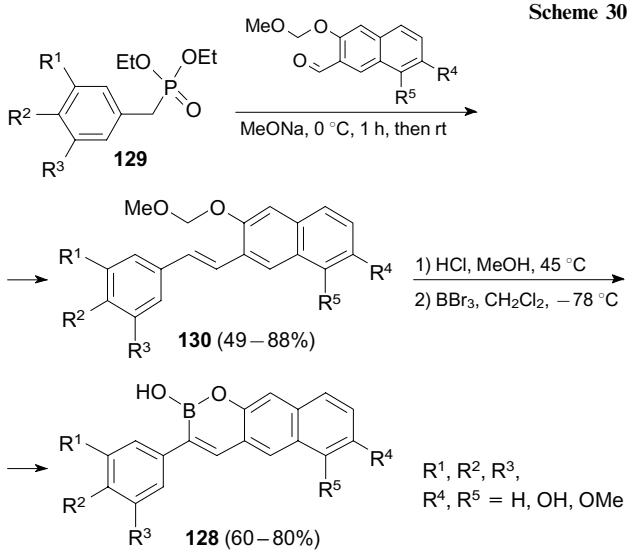


HATU is 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinio 3-oxide hexafluorophosphate

Scheme 29



Scheme 30

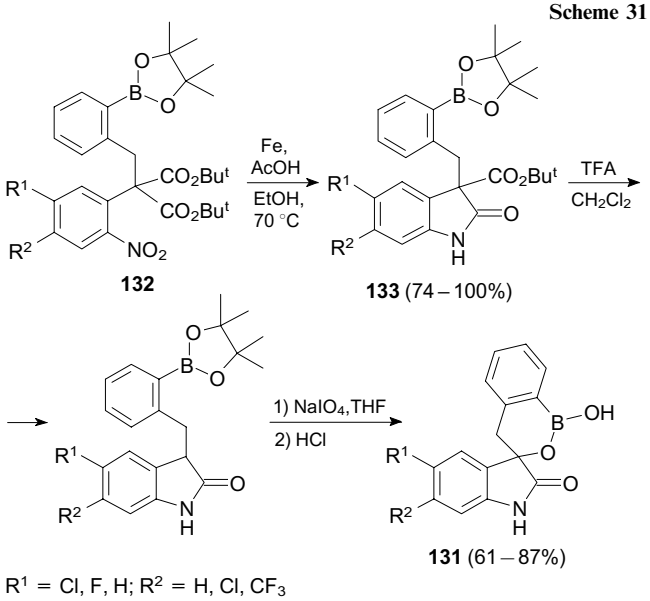


involved in the pathogenesis of Alzheimer's disease.[177] Horner reagents, diethyl benzylphosphonates (**129**), prepared in three steps from the appropriate substituted benzaldehydes, are the key intermediates in the synthesis. The authors subjected these compounds to Horner olefination in the presence of protected 2-methoxymethyloxy-1-naphthaldehydes, followed by deprotection on treatment with HCl and demethylation. The target naphthoxaborines **128**, substituted with various combinations of hydroxy, methoxy and dimethylamino groups, were obtained by cyclization of 3-styrylnaphthalen-2-ols (**130**) in the presence of BBr_3 in dichloromethane.

Compounds with two hydroxy groups in the benzene or naphthalene ring had the most pronounced biological action.

Natsutani *et al.*[178] prepared 3-spirooxindole benzoxaborine derivatives **131** and described them as promising scaffolds for the design of a new class of therapeutic agents (Scheme 31). The key intermediate **132** was obtained from readily accessible *o*-fluoronitrobenzenes. The tandem reduction and cyclization reactions in the presence of the Fe/AcOH catalyst afforded 3,3′-disubstituted oxindoles **133**; the *tert*-butylcarbonyl protection was removed by treatment with trifluoroacetic acid (TFA). The optimized conditions enabled the tandem oxidation of position 3 of the oxindole ring and elimination of pinacol ester in the presence of $NaIO_4$ and HCl. Finally, this furnished the desired products **131**, which were stable in human liver microsomes and

Scheme 31



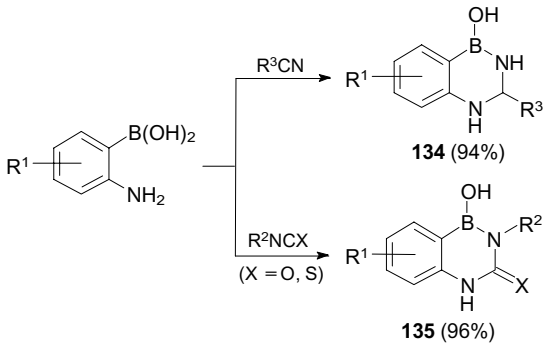
exhibited high permeability in the parallel artificial membrane permeability assay (PAMPA).

6. Diazaborines. Synthesis and application

6.1. 2,4,1-Diazaborines

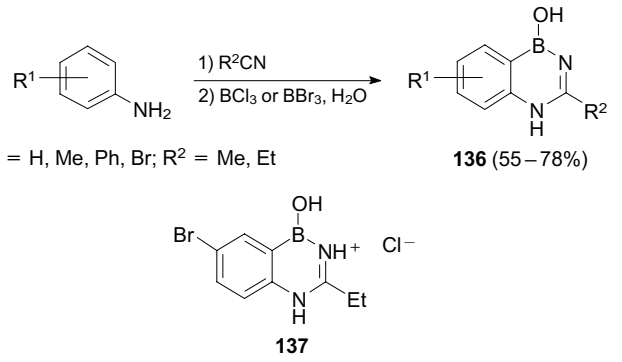
Examples of the synthesis of 2,4,1-diazaborines are relatively scarce and are mainly reduced to the preparation of benzodiazaborines. A key approach includes the condensation of *o*-aminophenylboronic acids with isocyanates, isothiocyanates or carbonitriles (Scheme 32). Among the substituted benzodiazaborines **134** and **135** obtained by Davis *et al.*,[179] the highest activity against *M. tuberculosis* bacteria was found for two compounds without substituents in the benzene ring — 1-hydroxy-3-(pyrazin-2-yl)-3,4-dihydro-2,4,1-benzodiazaborine (**134a**) and 1-hydroxy-2-(pyridin-3-yl)-1,4-dihydro-2,4,1-benzodiazaborine-3-thione (**135a**).

Scheme 32



Lee *et al.*[180] developed a general approach to the synthesis of 2,4,1-diazaborines, which included the condensation of anilines with carbonitriles followed by introduction of a boron atom by the reaction with a boron halide and condensation on heating (Scheme 33). Diazaborines **136** were isolated as hydrochlorides. The structure of one derivative, 7-bromo-1-hydroxy-3-ethyl-2,4,1-benzodiaza-

Scheme 33



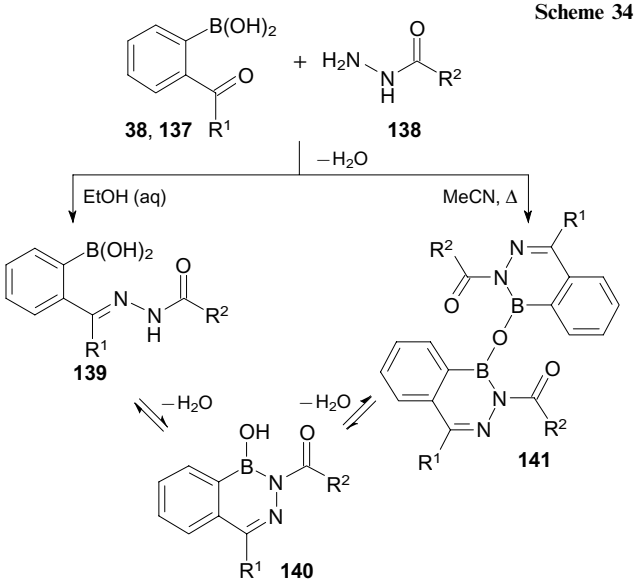
borinium hydrochloride (**137**), was confirmed by X-ray diffraction; however, the biological activity of this series of compounds was not studied.

6.2. 2,3,1-Diazaborines

2,3,1-Diazaborines synthesized to date are much more structurally diverse than known 2,4,1-diazaborines and include 2,3,1-benzo-, furano-, thieno- and pyrrolodiazaborines, which demonstrate various types of biological activity.[181]

Kanichar *et al.*[182] described the synthesis of 2,3,1-diazaborines by the condensation of *o*-acyl-substituted aromatic (or heteroaromatic) boronic acids **38** (R^1 = H) and **137** (R^1 = Me) with acylhydrazines **138** (Scheme 34).

Scheme 34

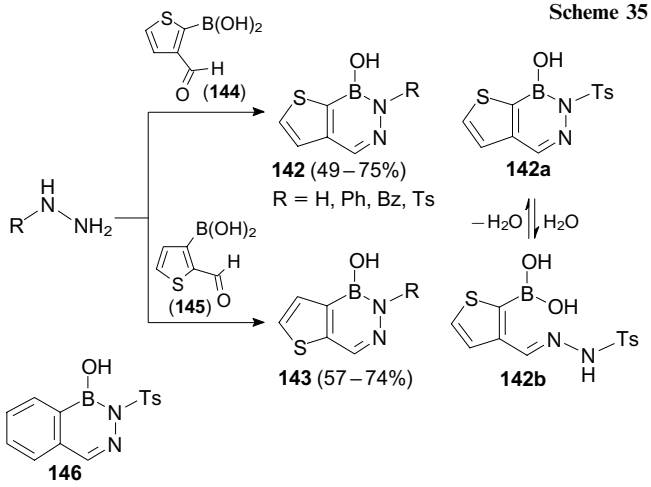


R^1 = H (**38**), Me (**137**); R^2 = H, Alk, Ar, Het, NH_2, N_2H_3

It is noteworthy that, depending on the reaction conditions and the structure of substituents, the final products were isolated in the open (**139**), monomeric (**140**) or dimeric form (**141**). When (2-acylthienyl)boronic acids were used as the starting compounds, the target products were formed only in the open form. Irrespective of the form, some of the obtained products exhibited antibacterial activity against *E. coli* and *M. smegmatis*.

The synthesis of thieno[2,3-*d*]- (**142**) or thieno[3,2-*d*][1,2,3]diazaborines (**143**) by the condensation of

Scheme 35



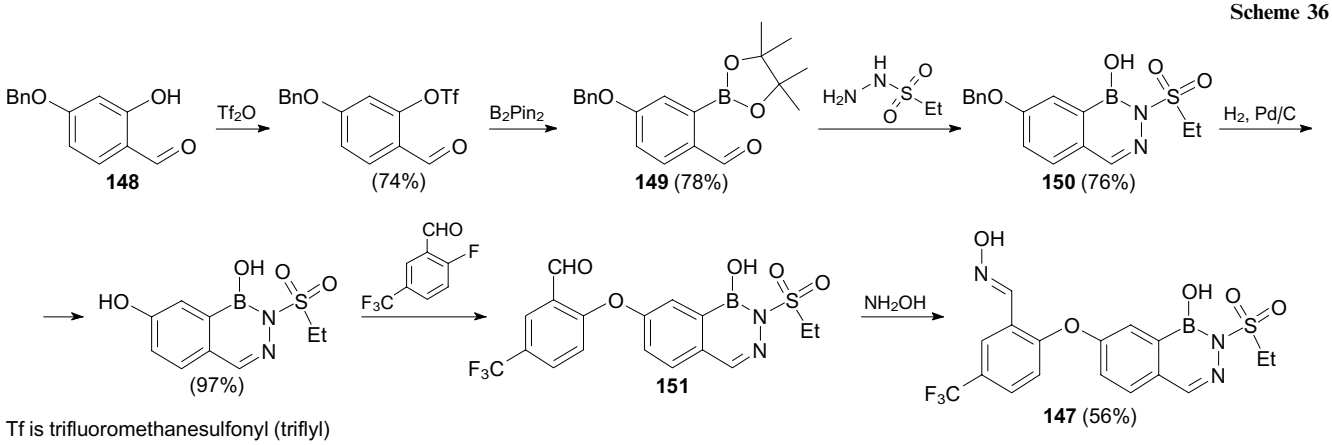
3-formyl-2-thienylboronic acid (**144**) or 2-formyl-3-thienylboronic acid (**145**) with hydrazines (Scheme 35) was reported by Antonio *et al.*[183] A similar synthetic route was used to convert *o*-formylphenylboronic acids to a series of benzannulated 2,3,1-diazaborines.

Thiophene derivatives proved to be more active and selective inhibitors of not only human neutrophil elastase, but also serine protease, which is produced by neutrophils upon their activation and plays an important role in inflammation. The mechanism of action of 2,3,1-diazaborines is based on the covalent binding between the boron atom and the oxygen atom of the serine residue in the enzyme active site. In addition, the thiophene ring, unlike the benzene ring, provides additional stabilization of the complex *via* interaction of the thiophene sulfur atom with the Ser195 nitrogen atom. The most active compound, 2-tosylthieno[2,3-*d*][1,2,3]diazaborine (**142a**), and acyclic 3-formyl-2-thienylboronic acid tosylhydrazone (**142b**) had similar IC_{50} values for neutrophil elastase: 3.4 ± 0.1 and 12.0 ± 1.4 μM.

Moderate selectivity of benzo-2,3,1-diazaborines was also confirmed by other research groups. In particular, 2-tosyl-2,3,1-benzodiazaborine (**146**) (see Scheme 35) exhibited antimicrobial activity[184] and the ability to block the biogenesis of eukaryotic cell ribosomes[185, 186] and biosynthesis of fatty acids of gram-negative bacteria *via* the inhibition of enoyl-ACP reductase (ACP is acyl-carrier protein).[187]

The studies of Anacor Pharmaceuticals dealing with the development of therapeutic agents based on boron compounds resulted in the synthesis of benzoxaboroles and benzo-2,3,1-diazaborines substituted in the benzene ring, which exhibited antitubercular activity.[188] The most active compound of this series, 2-[2-ethylsulfonyl-2,3,1-benzodiazaborin-7-yl]oxy-5-(trifluoromethyl)benzaldehyde oxime (AN12855, **147**), was obtained from 4-(benzyloxy)-2-hydroxybenzaldehyde (**148**) after phenol group activation, borylation to give [5-(benzyloxy)-2-formylphenyl]boronic acid pinacol ester (**149**) and cyclization with ethanesulfonic hydrazine (Scheme 36). The intermediate 7-benzyloxy-2-ethylsulfonylbenzo-2,3,1-diazaborine (**150**) was subjected to benzyl deprotection, then the phenolic hydroxy group was alkylated with 2-fluoro-5-(trifluoromethyl)benzaldehyde, and finally the reaction of intermediate **151** with hydroxylamine afforded oxime **147**.

Scheme 36

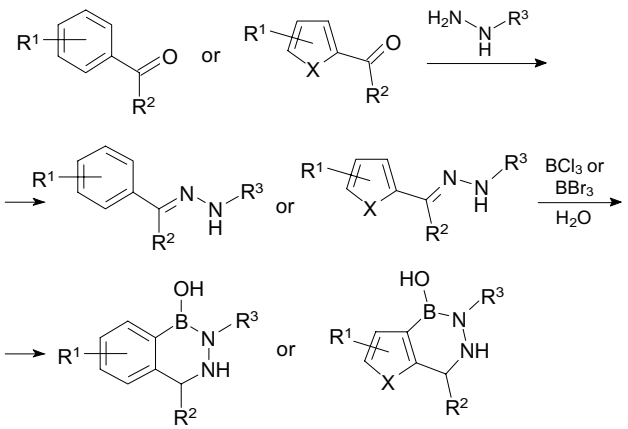


Tf is trifluoromethanesulfonyl (triflyl)

Structural studies demonstrated that AN12855 binds to and inhibits the substrate-binding site of 2-*trans*-enoyl-ACP reductase from *M. tuberculosis* mycobacteria (InhA) in a cofactor-independent manner. Compound AN12855 has a good bioavailability upon intravenous and oral administration and is effective *in vivo* in acute and chronic murine models of tuberculosis infection, with its activity being comparable with that of isoniazid. Thus, compound **147** is a promising candidate for the development of new antituberculosis drugs.

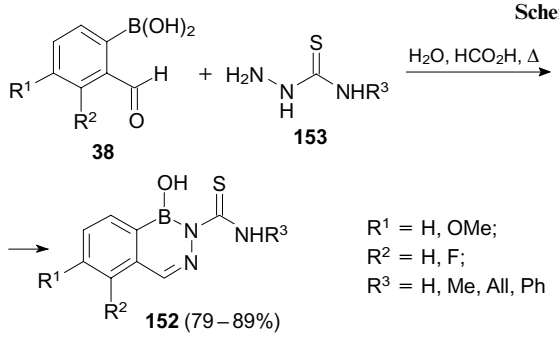
An alternative pathway to 2,3,1-diazaborines possessing antimicrobial activity is the condensation of (hetero)aromatic aldehydes or ketones with hydrazine or its derivatives, introduction of a boron atom by the reaction with boron halide and cyclization [189] (Scheme 37).

Scheme 37

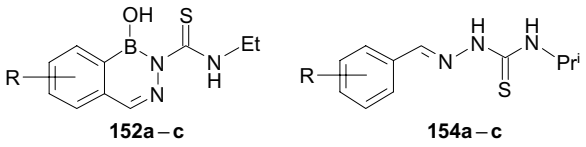


X = O, S, NH, NAlk; R^1, R^2, R^3 = H, Alk, Ar, Het, *etc.*

Scheme 38



Structures 152, 154



R = H (**a**), 3-F (**b**), 4-OMe (**c**)

R = H (**a**), 3-B(OH)$_2$ (**b**), 4-B(OH)$_2$ (**c**)

Yang *et al.*[190] described the synthesis (Scheme 38) of a series of 2,3,1-benzodiazaborine-2-carbothioamides **152**, containing a fluorine atom and/or a methoxy group in the benzene ring, by the condensation of 3,4-substituted *o*-formylphenylboronic acids **38** with thiosemicarbazides **153**. Whereas substitution in the benzene ring was, in some cases, beneficial for the antifungal activity, substitution in the thioamide moiety resulted in a substantial decrease in the biological action.

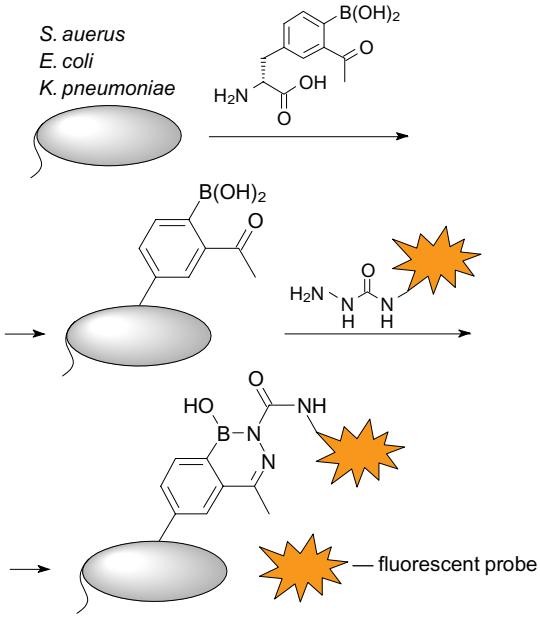


Figure 3. Detection of bacterial cells by fluorescent-labelled diazaborines. The Figure was drawn by the authors of the review using data of Ref. 192.

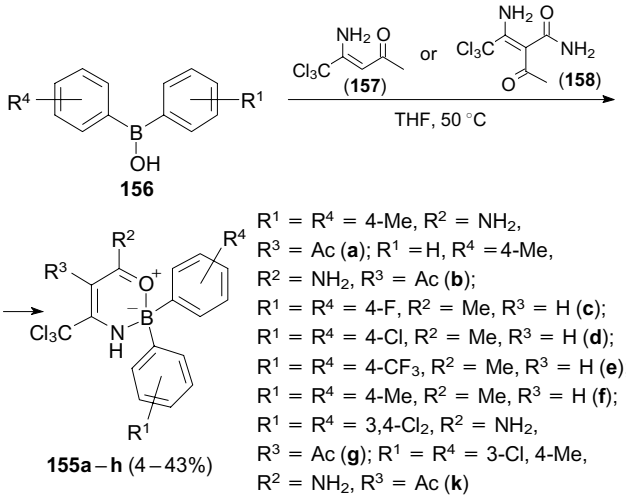
It is noteworthy that Scott *et al.*[191] investigated the antifungal activity against *Saccharomyces cerevisiae* for compounds **152a** – **c** and **154a** – **c**. The highest activity was observed for two *N*-propylthiosemicarbazones derived from unsubstituted benzaldehyde (**154a**) and 3-formylphenylboronic acid (**154b**) and for one substituted benzodiazaborine, *N*-ethyl-2,3,1-benzodiazaborine-2-carbothioamide **152a**.

Bandyopadhyay *et al.*[192] reported the possible use of conjugation of semicarbazide and *o*-carbonylarylboronic acids to give diazaborines for the detection of bacteria in blood serum or cell lysates (Fig. 3). This method proved to be most sensitive to *E. coli*; a fluorescent probe present in semicarbazide makes it possible to detect microbial cells by spectrophotometry.

6.3. Oxazaborines and triazaborines

Currently, there are relatively few publications dealing with the synthesis and biological activity assays of oxaza- and triazaborines. Baldwin *et al.*[193, 194] described a series of 2,2-diaryl-1,3,2-oxaborinium derivatives **155a** – **h** by the condensation of substituted diphenylboronic acids (**156**) with (*Z*)-4-amino-5,5,5-trichloropent-3-en-2-one (**157**) or with (*Z*)-3-amino-2-acetyl-4,4,4-trichlorobut-2-enamide (**158**) in THF (Scheme 39).

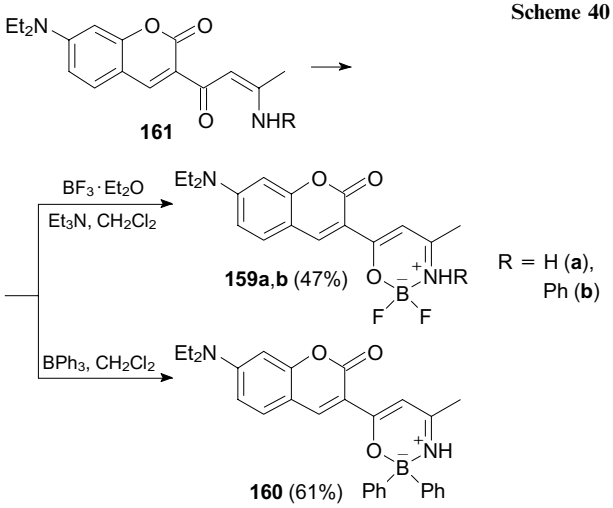
Scheme 39



The products showed inhibitory activity against a NOD-like receptor containing a pyrin domain (NLRP3), the activation of which is involved in the development of chronic inflammation in gout, atherosclerosis, type 2 diabetes mellitus and Alzheimer's disease.[195] The presence of a CCl_3 group was found to be the key factor for the activity to be manifested. The nature of substituents in the benzene rings does not affect the anti-inflammatory activity, while the replacement of CCl_3 by CF_3 leads to complete loss of the inhibitory activity against NLRP3.

Mikysek *et al.*[196] obtained oxazaborines **159** and **160** from 3-[3-(alkylamino)but-2-enoyl]-7-diethylamino-2*H*-chromen-2-ones **161** (Scheme 40). According to photo- and electrophysical experiments, these products represent a new, promising class of luminophores. The key step of the synthesis is chelation of the boron atom by the O,N-ligand using boron trifluoride etherate or triphenylborane. The target oxazaborines **159a**,**b** and **160** were isolated in moderate yields (40 – 60%).

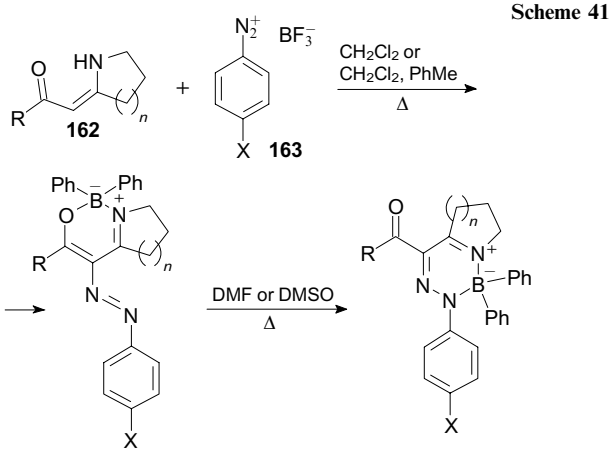
Scheme 40



Josefík *et al.*[197] described the synthesis and fluorescent properties of oxazaborines and a thermal rearrangement of oxazaborines to triazaborines (Scheme 41). First, cyclic β-enaminones **162**, containing a secondary amino group, were allowed to react with phenyldiazonium tetrafluoroborates **163** to give substituted [1,3,2]oxazaborines **164**, which irreversibly rearranged to isomeric 2*H*-[1,2,4,3]-triazaborines **165** on heating in DMF or DMSO or without a solvent.

Most of products **165** had fluorescent properties in the solid state and in frozen solutions in 2-methyltetrahydrofuran.[198, 199]

Scheme 41



n = 1 – 3; X = H, Alk, Hal, *etc.*

7. Organoboron compounds in neutron capture therapy and in medical diagnostics

The use of organoboron compounds in medicine is not reduced to the pharmaceutical drugs mentioned above. Back in 1936, boron neutron capture therapy (BNCT) based on the properties of ^{10}B was proposed for the treatment of cancer.[200] The thermal-neutron capture cross-section of ^{10}B nucleus is three orders of magnitude greater than that of other nuclei. Furthermore, the nuclear reaction induced by capture of a neutron is accompanied by a considerable release of energy, 80% of which is absorbed within the dimensions of a single cell, resulting in the cell death. Thus, the design of agents for neutron capture

therapy requires the maximum accumulation of boron atoms (as any chemical species) in tumour cells.

The most important requirements for a boron delivery agent are as follows:[200]

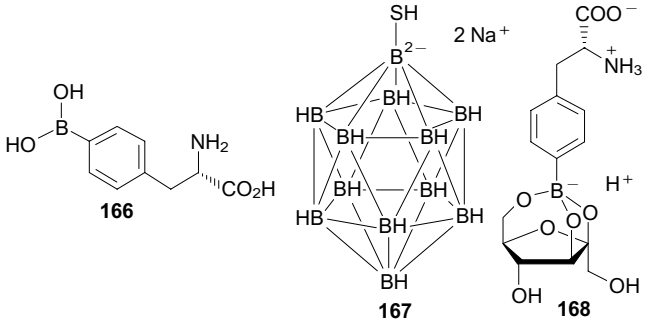
— low toxicity;

— high tumour uptake (~20 – 50 μg of ^{10}B) and low uptake in normal cells of tissues and organs (ideally, the tumour to normal tissue and tumour to blood ratio of boron concentrations should be > 3);

— relatively fast clearance from the blood and from intact tissue and organ cells and retention in tumour cells for at least several hours during irradiation with neutrons.

The real treatment of patients with severe diseases such as melanoma and brain tumours started at the end of the 1960s first in Japan and the USA and later in Finland, Sweden, Czechia, Germany, Italy, *etc*. Since then, more than 1000 patients were subjected to BNCT in 15 research centres of 10 countries, and many of the patients survived for several years after the therapy. However, currently, clinical trials for the treatment of brain tumours are conducted only for two boron compounds — 4-borylphenylalanine (BPA, **166**) and sodium sulfanylundecahydro-*closo*-dodecaborate (BSH, **167**);[6] the former is also used as a complex with fructose (**168**).

Structures 166 – 168



Despite the fact that hundreds of new agents for targeted delivery of boron have been developed and studied in cellular models and experimental animals in recent years, none of the compounds have reached the clinical trial stage as yet.[201] The causes behind this are not only high cost of BNCT, but also the limited availability of the necessary equipment (until recently, only nuclear reactors served as sources of thermal neutrons). The boron delivery systems developed to date are based on borylated amino acids, nucleosides, porphyrins and conjugates of borate clusters with peptides and antibodies. The structures of the most promising agents can be found in a number of reviews[6, 200, 202] and monographs (see Ref. 203, pp. 945 – 984, and Refs 204, 205). Boron clusters and boron – carbon clusters (carboranes) are good warheads for these agents due to relatively low toxicity and high boron content in each molecule, but their considerable drawback is high hydrophobicity. Anionic boron clusters, such as cobalt and iron bis(dicarbollides) $[(C_2B_9H_{11})_2M]^-$ (M = Co, Fe), *closo*-decaborate anions $(B_{10}H_{10})^{2-}$ and *closo*-dodecaborate anions $(B_{12}H_{12})^{2-}$, which are much more readily soluble, represent a new promising type of boron carriers for BNCT.[7]

The major synthetic challenge associated with the use of borate clusters and carboranes is the development of efficient methods for their functionalization. This issue is considered in detail in a number of publications;[202, 206 – 212] here we present only the latest and the most interesting examples. In the case of carboranes, the main approaches to functionalization are associated with differences between the boron and carbon vertices of the cluster. Upon replacement of the boron atom by carbon, the icosahedral cage becomes polarized, which results in the formation of weakly acidic C – H bonds and basic B – H bonds.

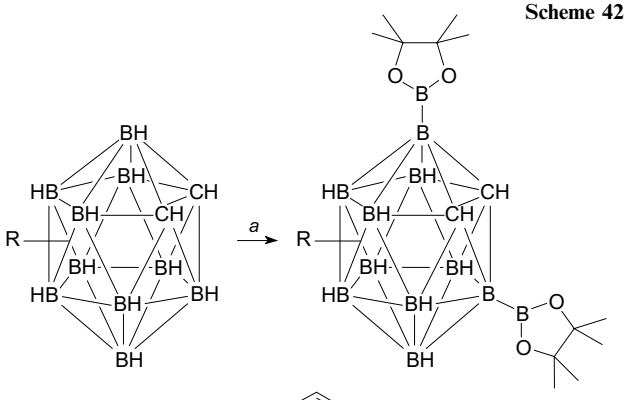
The common strategies of carborane functionalization are as follows:

— treatment with strong bases for deprotonation of the C – H bonds followed by a transition metal-catalyzed reaction with electrophiles in the case of carbon-substituted carboranes;

— electrophilic substitution at the boron vertices of the cluster.

The most complex and interesting task is regioselective functionalization, which usually requires assistance of directing groups. Bai *et al.*[213] reported the theoretical mechanisms of regioselective Ir-catalyzed direct borylation of *o*-carboranes (Scheme 42). The reaction selectively involves the B atoms in positions 3 and 6 of the molecule, and the catalytic cycle is fairly complex and includes a reversible conversion of Ir^{I} to Ir^{III}.

Scheme 42



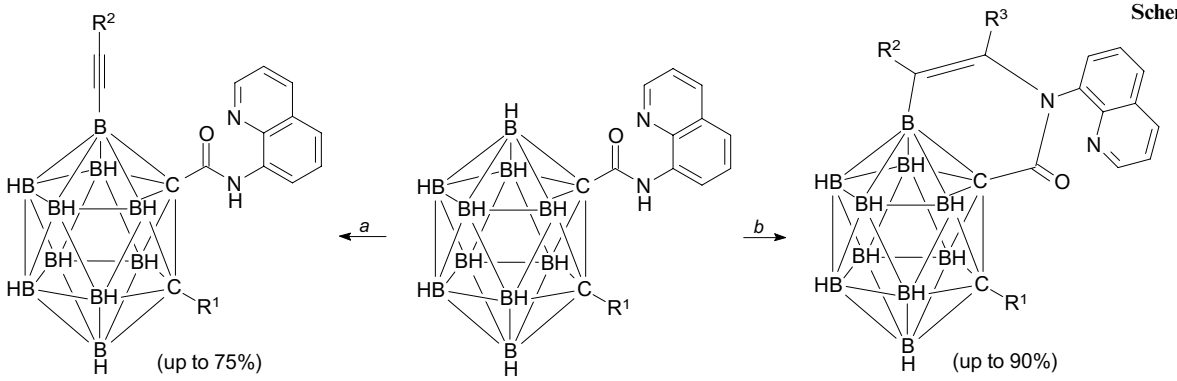
(*a*) B_2Pin_2 (4 equiv.), $[Ir(COD)Cl]_2$, , THF, 110 °C, 5 h;
R = Alk, Ar, Hal, *etc*.

Chen *et al.*[214] proposed a copper-catalyzed direct alkyne addition to carboranes mediated by bidentate directing groups (Scheme 43). The reaction of *o*-carboranylamides with internal alkynes allows for easy synthesis of a broad range of previously inaccessible C,B-derivatives of fused carboranopyridone. Meanwhile, the reaction of carboranylamides with terminal alkynes yields B(4)-alkynylated carboranes. The bidentate directing group is of crucial importance for copper-induced BH activation.

Another recent paper[215] presents the first example of catalytic regioselective B(8) – H-functionalization of *o*-carboranes. The acylamino directing group at B(3) and palladium catalysis provided the route to a series of 8-aryl-, 4,7,8-triaryl- and 4,7,8-trifluoro-*o*-carboranes. The reaction mechanism proposed by the authors includes Pd^{IV}-induced 'cage walking' from B(4) to B(8).

Selective one-pot arylation of B(3) and B(6) atoms of *o*-carborane was described by Xu *et al.*[216] The palladium-based catalytic system formed *in situ* performs selective arylation of *o*-carborane boron atoms successively in positions 3 and 6 under mild conditions (Scheme 44).

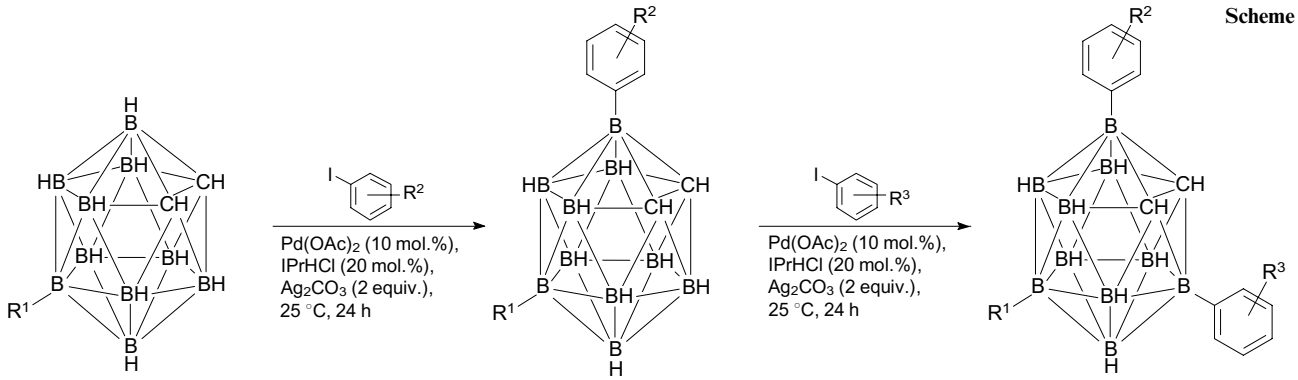
Scheme 43



(*a*) R^2—≡CH, $Cu(OTf)_2$ (2 equiv.),  (2 equiv.), Ag_2CO_3 (2 equiv.), K_2HPO_4 (2 equiv.), DCE, 130 °C, 12 h;

(*b*) R^2—≡—R^3, $Cu(OTf)_2$ (20 mol.%),  (20 mol.%), Ag_2CO_3 (2 equiv.), DCE, 130 °C, 12 h; R^1 = Alk: R^2, R^3 = Ar, Het

Scheme 44



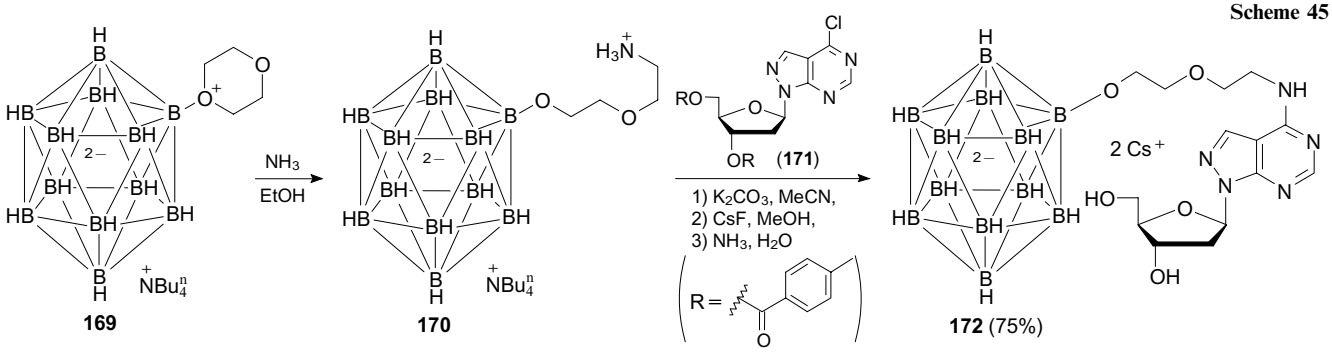
IPrHCl is 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride; R^1 = H, Alk, Ar; R^2, R^3 = H, Hal, CN, CO_2Et, CHO, *etc.* (in various positions)

The construction of systems for boron delivery to tumour cells on the basis of functionalized borate clusters and carboranes is a separate challenge. The most recent studies in this area not included by the mentioned reviews of Barth *et al.*[200] and Hu *et al.*[6] are briefly considered below.

A review of Druzina *et al.*[217] is devoted to conjugation of polyhedral boron compounds with nucleosides. The authors consider the key types of reactions that can be used to link a nucleoside scaffold to a borate cluster (most often, through a linker group). In most cases, the attachment of the cluster to the nucleoside is accomplished by a nucleophilic substitution reaction. The nature and chemical properties of the cluster are the key factors in this case; the synthesis is often multistep and labour-consuming. The cross-coupling or [3 + 2]-dipolar cycloaddition reactions are used much more rarely. The two last-mentioned approaches are versatile, *i.e.*, they do not depend on the nature of the polyhedral borate and usually include one to three simple steps. The authors concluded that these approaches are most promising.

A typical example of the conjugation of a borate cluster with a nucleoside is depicted in Scheme 45.[218] Tetra-n-butylammonium 1,4-dioxanio-*closo*-undecahydrododecaborate (**169**) reacts with ammonia to give tetra-n-butylammonium [2-(2-ammonioethoxy)ethoxy]undecahydro-*closo*-dodecaborate (**170**), which is in turn alkylated with

Scheme 45

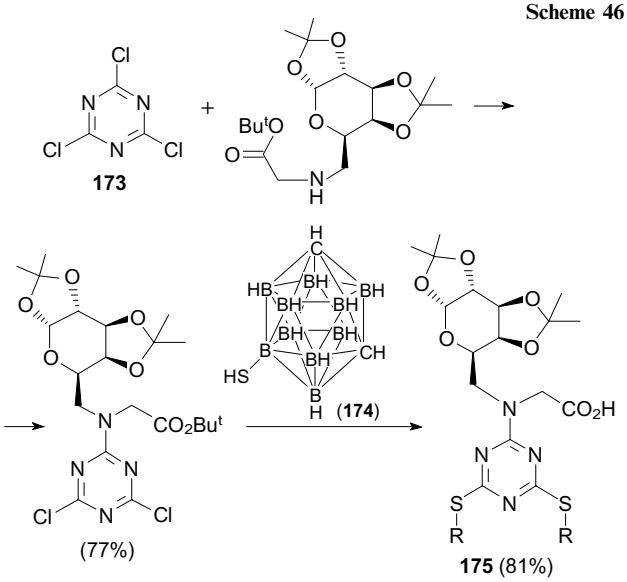


169 **170** **172** (75%)

4-chloro-1-(2-deoxy-3,5-di-*O*-(*p*-toluyl)-β-D-*erythro*-pentafuranosyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**171**). The protected 8-aza-7-deaza-2′-deoxyadenosine derivative was reprecipitated as a caesium salt and deprotected by treatment with aqueous ammonia. The yield of target caesium (2-{2-[1-(2-deoxy-β-D-*erythro*-pentafuranosyl)-1*H*-pyrasolo-[3,4-*d*]pyrimidin-4-ylamino]ethoxy}ethoxy)undecahydro-*closo*-dodecaborate (**172**) was 75%.

A German research team headed by Professor Hey-Hawkins [219] proposed a modular approach to the design of boron delivery agents (Scheme 46). Cyanuric chloride (**173**) acted as the central linking unit, to which a diisopropylidene-α-D-galactopyranose residue was attached through a glycine linker and then borate warheads made of 9-sulfanyl-1,7-dicarba-*closo*-dodecaborane (**174**) were added. This gave *N*-[4,6-bis(1,7-dicarba-*closo*-dodecaboran-9-ylthio)-1,3,5-triazin-2-yl]-*N*-(1′,2′:3′,4′-di(*O*-isopropylidene)-6′-deoxy-α-D-galactopyranos-6′-yl)glycine (**175**), a molecule with a high boron content and high hydrophilicity that can be inserted into peptide chains. Then compound **175** was used to a prepare a derivative with a recently developed [220] selective gastrin-releasing peptide receptor (GRPR) agonist. The GRP receptor is often used as a delivery system since it is commonly overexpressed in breast or prostate cancer and can be internalized together with the peptide drug conjugate, which results in cellular uptake of the drug.[221] A study of receptor binding and transfer to the cell carried out using isotope-labelled conjugates demonstrated that a galactopyranosyl moiety considerably enhances the transport properties of molecules.

Scheme 46



R is 1,7-dicarba-*closo*-dodecaboran-9-yl

Another system for the delivery of boron atoms to tumour cells based on a GRPR agonist, L-galactopyranose and cluster **174** (Fig. 4) was developed by the same research team.[222] Using this method, it is possible to introduce up to 80 boron atoms per molecule without any cytotoxicity. This system was shown to activate the GRP receptor and to be taken up by PC3 tumour cells; the L-galactose moiety efficiently suppressed the conjugate uptake by normal liver cells. Owing to the high content of boron and excellent selectivity to the GRP receptor, this conjugate can be regarded as a promising boron delivery agent for BNCT.

The same research group [223] proposed a similar system based on the neuropeptide receptor Y1 (hY1R) agonist. The basic principles of the design of such delivery systems, the possible protein carriers and methods of conjugation of not only borate clusters, but also other drug types are integrated in a review by Worm *et al.*[224]

A system presumably suitable for not only drug delivery, but also diagnosis of a neoplastic process by means of contrast enhanced magnetic resonance imaging (MRI) was proposed by Matveev *et al.*[225] Potassium 2-{5-[2-(bis(carboxymethyl)amino)ethyl]-1-carboxy-2-carboxymethyl-7-oxo-8,11-dioxa-2,5-diazatridecan-13-yloxy}nonahydro-*closo*-decaborate (**176**) contains a *closo*-decaborate anion and a diethylenetriaminepentaacetic acid (DTPA) pendant group attached to the boron cluster through an alkoxyl spacer chain. Compound **176** is a polydentate ligand capable of coordination to a metal both *via* the donor atoms of the DTPA moiety and *via* the formation of a three-centre two-electron bonds. It reacts with gadolinium(III) carbonate to form a stable complex. Such complexes can be useful for two purposes, therapeutic (BNCT) and diagnostic (MRI) ones.[226]

Li *et al.*[227] synthesized a series of non-toxic boron carriers containing two target groups and capable of being

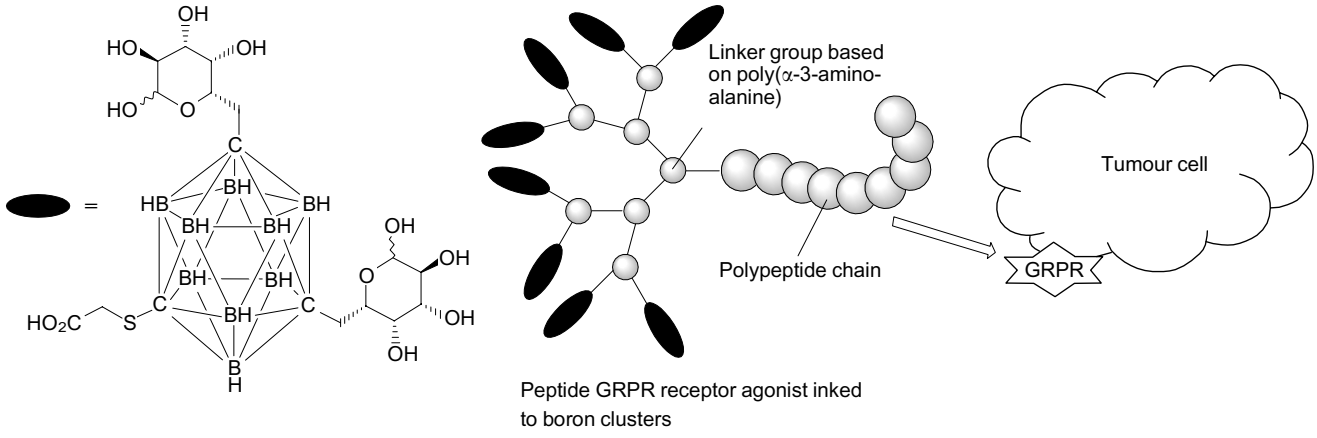
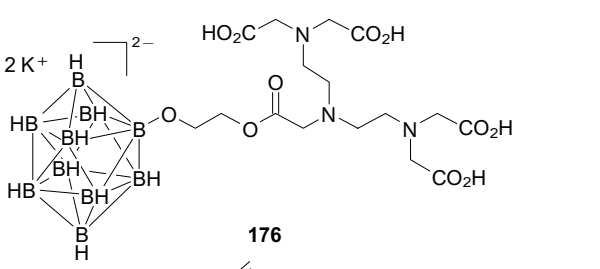
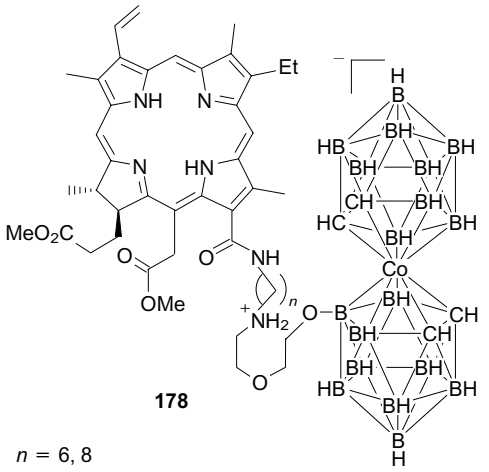


Figure 4. Delivery system based on a GRPR agonist — L-galactopyranose conjugate with 9-sulfanyl-1,7-dicarba-*closo*-dodecaboane **174**. The Figure was drawn by the authors of the review using data of Ref. 222.

Structures 176 – 179

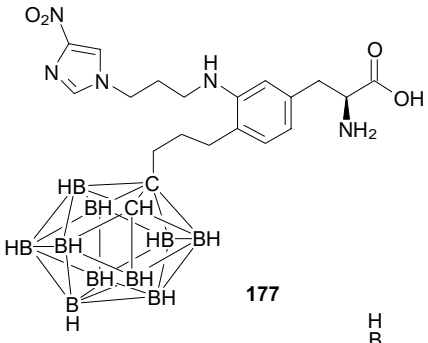


176

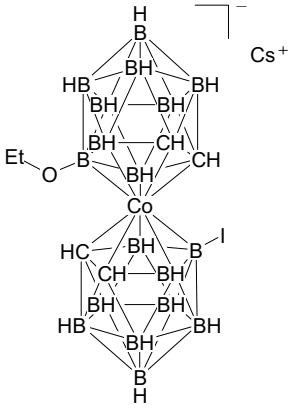


178

n = 6, 8



177



179

specifically accumulated in tumour cells. The tumour cell uptake of *O*-[3-(*o*-carboran-1-yl)propyl]-3-{[3-(4-nitro-1*H*-imidazol-1-yl)propyl]amino}-D-tyrosine (**177**) was high, and the boron content was 70 times as high as that for BPA. In addition, according to *in vivo* studies, compound **177** can be retained in tumour cells for long periods of time, with effective therapeutic concentration of up to 50.7 μg g^{-1} being maintained and the ratio of boron concentrations in the tumour cells and normal tissue or organ cells being > 3, which thus provides perfect conditions for BNCT. Toxicity assays in mice additionally confirmed the safety of compound **177**, which, in the authors' opinion, has a high potential as a safe and effective boron delivery agent for BNCT.

Volovetskiy *et al.*[228] undertook a study with the goal to determine the biodistribution of the conjugates of anionic cobalt bis(dicarbollide) with aminoamide chlorin *e*6 derivative (**178**). The experiments were carried out in Balb/c inbred mice with transplanted murine CT26 colon carcinoma. The accumulation of compound **178** in the tumour and in the organs was studied by laser scanning microscopy, with the amount of the boron-containing conjugate being determined from the fluorescence intensity of the samples. Three hours after injection, intense fluorescence was observed in the liver, spleen and lungs. The ratio of fluorescent conjugate amounts accumulated in tumour and muscle cells was ~3.

Another type of actively developed delivery systems is based on various sorts of nanomaterials — nanoparticles, liposomes, polymerosomes, *etc*. Examples of these systems were presented in reviews.[6, 200] Among the most interesting trends, mention should be made of immobilization of boron clusters on magnetic nanoparticles for targeted delivery,[229 – 231] the use of BNCT-combined immunotherapy† (Ref. 232) and the use of 2D nanomaterials based on boron nitride (so-called white graphene).[233, 234]

Wang *et al.*[235] used conjugates of self-assembling fluorescent gold nanoparticles with an aminocarborane derivative for precise bioimaging of transformed cells and the targeted delivery of the carborane derivative to tumours. The authors proposed a new strategy for determining the exact tumour cell site using the fluorescent carborane derivative; this reduces the damage of normal tissue or organ cells and allows visual control over the delivery of the source of boron to the tumour. The authors reported that the conjugates were efficiently accumulated in tumour cells due to the so-called enhanced permeability and retention (EPR) effect inherent in many types of nanoparticles. However, the EPR effect that was proved in mice, was not observed by Danhier[236] in human tissue or organ cells.

It should be noted that borate clusters and carboranes can not only act as a passive boron load in drug design. These groups can themselves serve as pharmacophores. For example, the caesium salt of cobalt 8-iodo-8′-ethoxy bis(1,2-dicarbollide) (**179**) showed a high activity against the methicillin-resistant *S. aureus* strain (MIC = 8 mg mL^{-1}).[237] The introduction of a *closo*-carborane cluster into the organic molecule of an agonist, antagonist or inhibitor completely changed the drug activity profile and modulated the effect of the drug on the viability of various tumour cells. This role of carborane is the subject of a review by Stockmann *et al.*[238]

8. Organoboron compounds as a tool for biomedical research and technologies

Due to increasing number of therapeutic agents based on organoboron compounds being under clinical trials, it is important to understand how these compounds can be incorporated into and released from biodegradable and biocompatible materials. Sene *et al.*[239] described the inclu-

† An immunotherapeutic agent, haemagglutinating virus of Japan envelope (HVJ-E), was modified by the boron-containing polymer.

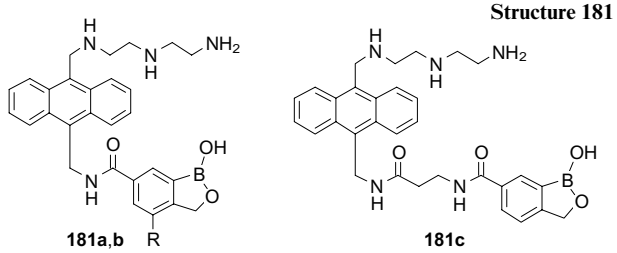
sion of benzoxaborole **1** and tavaborole (**28**) into a biocompatible and biodegradable inorganic matrix — Mg/Al layered double hydroxide (LDH). This material was studied by physicochemical methods (solid-phase NMR spectroscopy, small-angle X-ray scattering, *etc.*), which, in particular, determined the environment of organoboron molecules. In addition, according to *in vitro* studies, therapeutic compounds were rapidly released from the matrix because of their lower affinity to LDH layers and owing to easy ion exchange, including phosphate exchange. The cited study also revealed unusual reactivity of the benzoxaborole moiety on contact with inorganic LDH, particularly, benzoxaboroles can decompose on long-term storage at room temperature.

The same researchers [240] found that benzoxaboroles can be easily inserted into biopolymeric poly(L-lactic acid) (PLLA), with the degree of homogeneous inclusion reaching 10 mass %. It was shown that the molecular structure of benzoxaboroles remains invariable, but their Lewis acidity affects the PLLA matrix, because it promotes degradation of PLLA films when they are placed into a phosphate buffer. Benzoxaboroles had a high affinity for this matrix, and there were several ways of tuning their release in physiological media. In a phosphate buffer, two-stage release (a surge followed by retarded release) takes place. By changing the composition of the matrix (addition of polyethylene oxide) or fabrication of composites of benzoxaborole-intercalated layered double hydroxide (LDH), it is possible to adjust the desired release parameters. A favourable circumstance is that the drugs released from the matrix retain their biological activity. Finally, experiments were carried out to study migration of MDA-MB-231 breast tumour cells (metastasis model), which showed for the first time that benzoxaboroles are able to inhibit the migration of these cells.

Raines and co-workers [241] reported the development of a targeted delivery system for the transport of exogenous proteins into the cell, which uses the affinity of benzoxaborole for the carbohydrates present on the surface of cytoplasmic membrane of mammalian cells (Fig. 5). Passive protein transport through the cell membrane is almost impossible; therefore, the use of exogenous proteins and peptides as therapeutic agents or probes functioning within the cell has scarcely been studied until now. In the carrier proposed by the cited authors,[241] benzoxaborole is linked to amino groups of the exogenous protein *via* the *o*-hydroxydihydrocinnamic acid derivative, known as the trimethyl lock (TML). Thus, the carrier, 2-[1,1-dimethyl-3-oxo-3-(*N*-succinimidoyloxy)propyl]-3,5-dimethylphenyl ester of *N*-[(benzoxaborol-6-ylamino)carbonyl]-β-alanine (**180**), consists of three modules: benzoxaborole, TML linker (activating esterase) and *N*-hydroxysuccinimide (NHS) ester. It is noteworthy that this delivery system leaves no trace contaminants, since the intracellular esterase activity promotes the restoration of proteins to their original state.[241]

Since a benzoxaborole molecule can be used for the recognition of the *cis*-1,2-diol moiety, Kusano *et al.*[242] synthesized three series of water-soluble anthracene-containing benzoxaboroles **181a – c** and studied their binding to *cis*-1,2-diols. These compounds can act as selective fluorescent probes.

Structure 181



R = H (**a**), F (**b**)

Binding of benzoxaborole to biomolecules containing a *cis*-1,2-diol moiety was also studied by Ishihara and coworkers [243] in relation to the reaction of benzoxaborole with D-fructose; the publication presents the mechanism of reaction in an alkaline solution and kinetic data for this reaction. Kurogochi *et al.*[244] proposed tandem mass spectrometric analysis of benzoxaborole-based borate complexes with monosaccharide for the development of probes that allow one to identify differences in the conformations of monosaccharides by reversible complex formation methods.

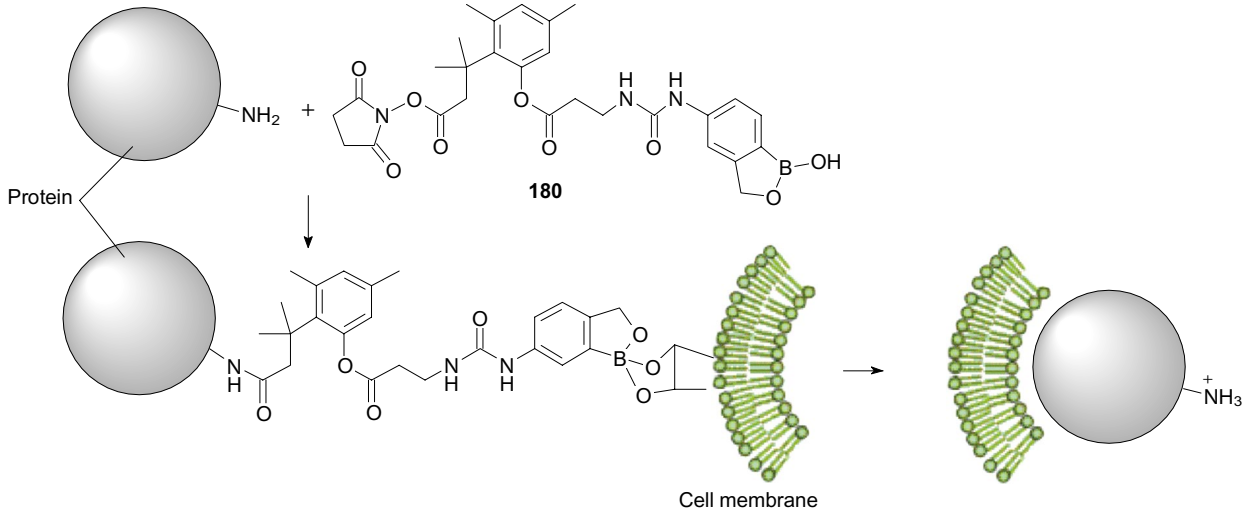


Figure 5. Molecular delivery system for exogenous proteins. The Figure was drawn by the authors of the review using data of Ref. 241.

9. Conclusion

There are only few naturally occurring boron compounds known to date, and the studies of the ways of introducing boron atoms into therapeutic agents were started only recently. Generally, two trends can be distinguished in the development of the medicinal chemistry of boron compounds. The first trend is concerned with compounds containing one boron atom and makes use of the easy conversion of the planar sp^2 state of boron to the anionic tetrahedral sp^3 state under physiological conditions. This enables the formation of coordination bonds with nucleophiles, including those incorporated in biomolecules: hydroxy and amino groups of proteins, carbohydrates and nucleic acids. The formation of complexes with *cis*-diol systems is one more example of manifestation of biological activity of boron compounds. Currently, the medicinal chemistry of systems containing one boron atom has actually become an independent field of research, which has already resulted in the development of a number of therapeutic agents for clinical use.

The second key trend of development of boron products for medicine is concerned with the use of boron clusters, the biological action of which is based on specific properties of these species capable of unique interactions with protein and cell targets. Studies of borate clusters, which differ from organic clusters in the electronic properties, by the presence of six-coordinate carbon and boron atoms and by specific ionic forms require specific tools and synthetic strategies. Despite certain lacunes in this fields, successful development of drugs based on borate clusters seems very likely.

The skeptical view on the application of boron in medicinal chemistry caused by the presumed toxicity of boron compounds has been largely overcome because of the promising results attained in the development of therapeutic agents based on boronic acids and benzoxaboroles by Millennium Pharmaceuticals, Point Therapeutics and Anacor Pharmaceuticals. Recently, quite a few boron-containing drug candidates have been under clinical trials, and the pharmaceutical industry begins to pay close attention to this promising class of compounds. However, there are no available dedicated studies addressing specific toxic properties caused by the presence of a boron atom in a molecule of a pharmacologically active compound in comparison with similar properties of compounds containing no boron. Furthermore, examples of in-depth studies of the metabolism of boron compounds in the human body are sparse. For example, it was shown that bortezomib is mainly metabolized under the action of cytochromes CYP3A4, CYP2C19 and CYP1A2,[245] while vaborbactam is not biotransformed in the human body.[83] Tavaborole metabolism is described only relying on the results of mouse experiments, but not all of the metabolites were detected in humans.[246] The currently available data suggest that the metabolism of boron-containing molecules generally follows the same patterns as the metabolism of other drugs and is determined by the structure of the whole molecule rather than some its part such as, for example, the boron atom.

The unique physical, chemical and biological properties of boron compounds offer the opportunity for studies and discovery of new effective therapeutic agents. The introduction of a boron atom may give rise to activity towards new biological targets. One more advantage of using the boron atom in the molecular drug design is that the obtained molecules are structurally less complex than their carbon analogues, which reduces the costs associated with research and production of these compounds. Cyclic boronates and benzoxaboroles are among the most promising classes of organoboron compounds, which is apparently attributable to enhancement of Lewis acidity of the boron atom due to the presence of six- and five-membered heterocycles.

Certainly, the use of boron compounds is not a silver bullet, but there is a good chance that in the near future, organoboron compounds would become a common trend in the development of new-generation drugs. The wide diversity of biological activities of both the molecules containing one boron atom and boron clusters indicates that the medicinal chemistry of these compounds has enormous potential for further research.

10. List of acronyms

The following acronyms are used in the review:

ACP — acyl-carrier protein,
AmB — amphotericin B,
B_2Pin_2 — bis(pinacolato)diboron,
BNCT — boron neutron capture therapy,
BPA — 4-borylphenylalanine,
BSH — sodium sulfanylundecahydro-*closo*-dodecaborate,
CA — carbonic anhydrase,
Can2 — *Cryptococcus neoformans* carbonic anhydrase,
CAUTI — catheter-associated urinary tract infection,
CgNce103 — *Candida glabrata* carbonic anhydrase,
CHOP — stress-induced nuclear protein (transcription regulator),
CPME — cyclopentyl methyl ether,
CPSF3 — homologue of cleavage and polyadenylation specificity factor subunit 3,
DMEDA — *N*,*N*′-dimethylethylenediamine,
DR5 — a member of TNF receptor family triggering tumour cell apoptosis,
DTPA — diethylenetriaminopentaacetic acid,
Duanphos — (1*R*,1′*R*,2*S*,2′*S*)-2,2′-di-*tert*-butyl-2,3,2′,3′-tetrahydro-1*H*,1′*H*-(1,1′) biisophosphindolyl,
EC_{50} — 50% effective concentration,
EDC — 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide,
EPR — enhanced permeability and retention,
FDA — U.S. Food and Drug Administration,
gpβ2AR — guinea pig β2-adrenergic receptor,
GRPR — gastrin-releasing peptide receptor,
HATU is 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinio 3-oxide hexafluorophosphate (hexafluorophosphate azabenzotriazole tetramethyl uronium)
HbF — embryonic haemoglobin,
hCA I and hCA II — human carbonic anhydrases 1 and 2,
HCV — hepatitis C virus,
HOBT — 1-hydroxybenzotriazole,
HVJ-E — haemagglutinating virus of Japan envelope,
hβ2AR — human β2-adrenergic receptor,
IC_{90} — 90% inhibitory concentration,
IL — interleukin,
IPrHCl — 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride,
$[Ir(COD)Cl]_2$ — bis(cycloocta-1,5-dienyl)diiridium(I) dichloride,
K_i — inhibition constant,
KPC-2 — *Klebsiella pneumoniae* carbapenemase-2,

LdcCA — *Leishmania donovani chagasi* carbonic anhydrase,
LDH — Mg/Al layered double hydroxide,
LdLeuRS — *Leishmania donovani* leucyl-tRNA synthetase,
LeuRS — leucyl-tRNA synthetase,
LiHMDS — lithium bis(trimethylsilylamide),
MBL — metallo-β-lactamases,
m-CPBA — *m*-chloroperoxybenzoic acid,
MDR — multiple drug resistance,
MgCA — *Malassezia globosa* carbonic anhydrase,
MIC — minimal inhibitory concentration,
Ndh — NADH dehydrogenase,
NHS — *N*-hydroxysuccinimide,
NMM — *N*-methylmorpholine,
NS — non-structural viral protein,
NS5B — RNA-dependent RNA polymerase of hepatitis C virus,
P2X7R — ATP-dependent purinergic receptor 7,
PDE4 — phosphodiesterase 4,
pEC_{50} — negative logarithm of 50% effective concentration,
PLLA — poly(L-lactide),
RIG-1 — retinoic acid inducible gene-1,
SBL — serine β-lactamases,
SFTS — severe fever with thrombocytopenia syndrome,
SNP — single nucleotide polymorphism of a gene,
TbALDH3 — trypanosomal aldehyde dehydrogenase,
TBDMSCl — *tert*-butyldimethylsilyl chloride,
TcCA — *Trypanosoma cruzi* carbonic anhydrase,
TML — trimethyl lock,
TNF — tumour necrosis factor,
TR — trypanothione reductase,
VIM-2 — carbapenem-hydrolyzing metallo-β-lactamase,
Walphos — (1*S*)-1-{(1*R*)-1-[bis[3,5-bis(trifluoromethyl)-phenyl]phosphino]ethyl}-2-[2-(diphenylphosphino)phenyl]-ferrocene,
XPhosPdG2 — (2,4,6-triisopropyl-2′-dicyclohexylphosphino-1,1′-biphenyl)-[2-(2-amino-1,1′-biphenyl)]palladium(II) chloride.

References

1. L.M.Rendina. *Aust. J. Chem.*, **72**, 652 (2019)
2. F.Ali, N.S.Hosmane, Y.Zhu. *Molecules*, **25**, 828 (2020)
3. G.F.S.Fernandes, W.A.Denny, J.L.Dos Santos. *Eur. J. Med. Chem.*, **179**, 791 (2019)
4. F.Yang, M.Zhu, J.Zhang, H.Zhou. *MedChemComm*, **9**, 201 (2018)
5. A.Krajnc, P.A.Lang, T.D.Panduwawala, J.Brem, C.J.Schofield. *Curr. Opin. Chem. Biol.*, **50**, 101 (2019)
6. K.Hu, Z.Yang, L.Zhang, L.Xie, L.Wang, H.Xu, L.Josephson, S.H.Liang, M.-R.Zhang. *Coord. Chem. Rev.*, **405**, 213139 (2020)
7. I.B.Sivaev, V.V.Bregadze. *Eur. J. Inorg. Chem.*, 1433 (2009)
8. A.Nocentini, C.T.Supuran, J.Y.Winum. *Expert Opin. Ther. Pat.*, **28**, 493 (2018)
9. M.A.Legare, C.Pranckevicius, H.Braunschweig. *Chem. Rev.*, **119**, 8231 (2019)
10. J.W.Tomsho, A.Pal, D.G.Hall, S.J.Benkovic. *ACS Med. Chem. Lett.*, **3**, 48 (2012)
11. S.Vshyvenko, M.L.Clapson, I.Suzuki, D.G.Hall. *ACS Med. Chem. Lett.*, **7**, 1097 (2016)
12. R.J.Doerksen, A.J.Thakkar. *J. Phys. Chem. A*, **103**, 2141 (1999)
13. I.B.Sivaev, V.I.Bregadze. *Ros. Khim. Zh.*, **48** (4), 109 (2004)
14. Z.J.Lesnikowski. *J. Med. Chem.*, **59**, 7738 (2016)
15. L.D.Fricker. *Annu. Rev. Pharmacol. Toxicol.*, **60**, 457 (2020)
16. T.Ishiyama, M.Murata, N.Miyaura. *J. Org. Chem.*, **60**, 7508 (1995)
17. T.Niwa, H.Ochiai, Y.Watanabe, T.Hosoya. *J. Am. Chem. Soc.*, **137**, 14313 (2015)
18. P.J.Xia, Z.P.Ye, Y.Z.Hu, J.A.Xiao, K.Chen, H.Y.Xiang, X.Q.Chen, H.Yang. *Org. Lett.*, **22**, 1742 (2020)
19. Y.M.Tian, X.N.Guo, M.W.Kuntze-Fechner, I.Krummenacher, H.Braunschweig, U.Radius, A.Steffen, T.B.Marder. *J. Am. Chem. Soc.*, **140**, 17612 (2018)
20. X.Zhao, M.Wu, Y.Liu, S.Cao. *Org. Lett.*, **20**, 5564 (2018)
21. C. Zarate, R. Manzano, R. Martin. *J. Am. Chem. Soc.*, **137**, 6754 (2015)
22. S.Jin, H.T.Dang, G.C.Haug, R.He, V.D.Nguyen, V.T.Nguyen, H.D.Arman, K.S.Schanze, O.V.Larionov. *J. Am. Chem. Soc.*, **142**, 1603 (2020)
23. M.C.Schwarzer, R.Konno, T.Hojo, A.Ohtsuki, K.Nakamura, A.Yasutome, H.Takahashi, T.Shimasaki, M.Tobisu, N.Chatani, S.Mori. *J. Am. Chem. Soc.*, **139**, 10347 (2017)
24. H.Minami, S.Otsuka, K.Nogi, H.Yorimitsu. *ACS Catal.*, **8**, 579 (2018)
25. M.A.Larsen, J.F.Hartwig. *J. Am. Chem. Soc.*, **136**, 4287 (2014)
26. M.A.Larsen, R.J.Oeschger, J.F.Hartwig. *ACS Catal.*, **10**, 3415 (2020)
27. W.C.Shih, O.V.Ozerov. *J. Am. Chem. Soc.*, **139**, 17297 (2017)
28. R.J.Oeschger, M.A.Larsen, A.Bismuto, J.F.Hartwig. *J. Am. Chem. Soc.*, **141**, 16479 (2019)
29. E.Yamamoto, K.Izumi, Y.Horita, H.Ito. *J. Am. Chem. Soc.*, **134**, 19997 (2012)
30. M.A.Legare, M.A.Courtemanche, E.Rochette, F.G.Fontaine. *Science*, **349**, 513 (2015)
31. C.A.Malapit, J.R.Bour, S.R.Laursen, M.S.Sanford. *J. Am. Chem. Soc.*, **141**, 17322 (2019)
32. J.W.B.Fyfe, A.J.B.Watson. *Chemistry*, **3**, 31 (2017)
33. A.Joshi-Pangu, X.Ma, M.Diane, S.Iqbal, R.J.Kribs, R.Huang, C.Y.Wang, M.R.Biscoe. *J. Org. Chem.*, **77**, 6629 (2012)
34. P.K.Verma, K.S.Prasad, D.Varghese, K.Geetharani. *Org. Lett.*, **22**, 1431 (2020)
35. T.C.Atack, S.P.Cook. *J. Am. Chem. Soc.*, **138**, 6139 (2016)
36. S.K.Bose, S.Brand, H.O.Omoregie, M.Haehnel, J.Maier, G.Bringmann, T.B.Marder. *ACS Catal.*, **6**, 8332 (2016)
37. Q.Liu, J.Hong, B.Sun, G.Bai, F.Li, G.Liu, Y.Yang, F.Mo. *Org. Lett.*, **21**, 6597 (2019)
38. D.Mazzarella, G.Magagnano, B.Schweitzer-Chaput, P.Melchiorre. *ACS Catal.*, **9**, 5876 (2019)
39. D.Wei, T.M.Liu, B.Zhou, B.Han. *Org. Lett.*, **22**, 234 (2020)
40. A.Šterman, I.Sosič, S.Gobec, Z.Časar. *Org. Chem. Front.*, **6**, 2991 (2019)
41. S.Nishino, K.Hirano, M.Miura. *Org. Lett.*, **21**, 4759 (2019)

42. T.Iwai, R.Murakami, T.Harada, S.Kawamorita, M.Sawamura. *Adv. Synth. Catal.*, **356**, 1563 (2014)
43. S.Kawamorita, T.Miyazaki, T.Iwai, H.Ohmiya, M.Sawamura. *J. Am. Chem. Soc.*, **134**, 12924 (2012)
44. S.N.Hyland, E.A.Meck, M.Tortosa, T.B.Clark. *Tetrahedron Lett.*, **60**, 1096 (2019)
45. W.Ming, X.Liu, A.Friedrich, J.Krebs, T.B.Marder. *Org. Lett.*, **22**, 365 (2020)
46. X.Y.Bai, W.Zhao, X.Sun, B.J.Li. *J. Am. Chem. Soc.*, **141**, 19870 (2019)
47. D.Fan, J.Zhang, Y.Hu, Z.Zhang, I.D.Gridnev, W.Zhang. *ACS Catal.*, **10**, 3232 (2020)
48. Y.Lou, J.Wang, G.Gong, F.Guan, J.Lu, J.Wen, X.Zhang. *Chem. Sci.*, **11**, 851 (2020)
49. R.L.Reyes, M.Sato, T.Iwai, M.Sawamura. *J. Am. Chem. Soc.*, **142**, 589 (2020)
50. C.B.Schwamb, K.P.Fitzpatrick, A.C.Brueckner, H.C.Richardson, P.H.Cheong, K.A.Scheidt. *J. Am. Chem. Soc.*, **140**, 10644 (2018)
51. A.A.Garcia, A.Rayevski, E.Andrade-Jorge, J.G.Trujillo-Ferrara. *Curr. Med. Chem.*, **26**, 5077 (2018)
52. K.S.Romero-Aguilar, I.M.Arciniega-Martinez, E.D.Farfan-Garcia, R.Campos-Rodriguez, A.A.Resendiz-Albor, M.A.Soriano-Ursua. *Expert Opin. Ther. Pat.*, **29**, 339 (2019)
53. H.Yang, X.Chen, K.Li, H.Cheaito, Q.Yang, G.Wu, J.Liu, Q.P.Dou. *Semin. Cancer. Biol.*, **68**, 105 (2021); https://doi.org/10.1016/j.semcancer.2019.12.013
54. D.G.Jackson, L.A.Cardwell, E.Oussedik, S.R.Feldman. *J. Dermatol. Treat.*, **31**, 2 (2020)
55. M.H.Glickman, A.Ciechanover. *Physiol. Rev.*, **82**, 373 (2002)
56. P.Robak, T.Robak. *Drugs RD*, **19**, 73 (2019)
57. J.Xie, N.Wan, Z.Liang, T.Zhang, J.Jiang. *Leuk. Lymphoma*, **60**, 610 (2019)
58. N.Gupta, M.J.Hanley, C.Xia, R.Labotka, R.D.Harvey, K.Venkatakrishnan. *Clin. Pharmacokinet.*, **58**, 431 (2019)
59. J.Zhang, P.Wu, Y.Hu. *Curr. Med. Chem.*, **20**, 2537 (2013)
60. A.Scarpino, D.Bajusz, M.Proj, M.Gobec, I.Sosic, S.Gobec, G.G.Ferenczy, G.M.Keseru. *Molecules*, **24**, 2590 (2019)
61. X.Zhang, A.Adwal, A.G.Turner, D.F.Callen, A.D.Abell. *ACS Med. Chem. Lett.*, **7**, 1039 (2016)
62. M.Lei, H.Feng, E.Bai, H.Zhou, J.Wang, Y.Qin, H.Zhang, X.Wang, Z.Liu, O.Hai, J.Liu, Y.Zhu. *Org. Biomol. Chem.*, **17**, 683 (2019)
63. R.K.Bhatia, L.Singh, R.Garg, M.Kaur, M.Yadav, J.Madan, S.Kancherla, R.R.S.Pissurlenkar, E.C.Coutinho. *Med. Chem.*, **16**, 212 (2020)
64. S.Katsamakas, A.G.Papadopoulos, D.Hadjipavlou-Litina. *Molecules*, **21**, 1185 (2016)
65. O.C.Cohen, F.Sharpley, J.D.Gillmore, H.J.Lachmann, S.Sachchithanantham, S.Mahmood, M.Fontana, C.J.Whelan, A.Martinez-Naharro, C.Kyriakou, N.Rabin, R.Popat, K.Yong, S.Cheesman, R.Shah, P.N.Hawkins, A.D.Wechalekar. *Br. J. Haematol.*, **189**, 643 (2020); https://doi.org/10.1111/bjh.16401
66. F.C Passero Jr., D.Ravi, J.T.McDonald, A.Beheshti, K.A.David, A.M.Evens. *Br. J. Haematol.*, **188**, 295 (2020)
67. D.Yue, X.Sun. *Cancer Biol. Ther.*, **20**, 284 (2019)
68. Y.Li, Y.Guo, J.Tang, J.Jiang, Z.Chen. *Acta Biochim. Biophys. Sin. (Shanghai)*, **46**, 629 (2014)
69. P.M.Chaudhary, M.Eby, A.Jasmin, A.Bookwalter, J.Murray, L.Hood. *Immunity*, **7**, 821 (1997)
70. M.Psurski, A.Lupicka-Slowik, A.Adamczyk-Wozniak, J.Wietrzyk, A.Sporzynski. *Invest. New Drugs*, **37**, 35 (2019)
71. Y.Ge, A.Li, J.Wu, H.Feng, L.Wang, H.Liu, Y.Xu, Q.Xu, L.Zhao, Y.Li. *Eur. J. Med. Chem.*, **128**, 180 (2017)
72. W.Zhang, H.Bai, L.Han, H.Zhang, B.Xu, J.Cui, X.Wang, Z.Ge, R.Li. *Bioorg. Med. Chem. Let.t*, **28**, 2459 (2018)
73. S.B.Wan, H.Yang, Z.Zhou, Q.C.Cui, D.Chen, J.Kanwar, I.Mohammad, Q.P.Dou, T.H.Chan. *Int. J. Mol. Med.*, **26**, 447 (2010)
74. X.Li, S.Wu, G.Dong, S.Chen, Z.Ma, D.Liu, C.Sheng. *ACS Med. Chem. Lett.*, **11**, 439 (2020)
75. S.Wang, K.Fang, G.Dong, S.Chen, N.Liu, Z.Miao, J.Yao, J.Li, W.Zhang, C.Sheng. *J. Med. Chem.*, **58**, 6678 (2015)
76. C.González-Bello, D.Rodríguez, M.Pernas, Á.Rodríguez, E.Colchón. *J. Med. Chem.*, **63**, 1859 (2020)
77. S.J.Hecker, K.R.Reddy, M.Totrov, G.C.Hirst, O.Lomovskaya, D.C.Griffith, P.King, R.Tsivkovski, D.Sun, M.Sabet, Z.Tarazi, M.C.Clifton, K.Atkins, A.Raymond, K.T.Potts, J.Abendroth, S.H.Boyer, J.S.Loutit, E.E.Morgan, S.Durso, M.N.Dudley. *J. Med. Chem.*, **58**, 3682 (2015)
78. S.Ness, R.Martin, A.M.Kindler, M.Paetzel, M.Gold, S.E.Jensen, J.B.Jones, N.C.Strynadka. *Biochemistry*, **39**, 5312 (2000)
79. C.-H.Tan, T.Stork, N.Feeder, A.B.Holmes. *Tetrahedron Lett.*, **40**, 1397 (1999)
80. O.Lomovskaya, D.Sun, D.Rubio-Aparicio, K.Nelson, R.Tsivkovski, D.C.Griffith, M.N.Dudley. *Antimicrob. Agents Chemother.*, **61**, e01443-17 (2017)
81. S.T.Cahill, J.M.Tyrrell, I.H.Navratilova, K.Calvopina, S.W.Robinson, C.T.Lohans, M.A.McDonough, R.Cain, C.W.G.Fishwick, M.B.Avison, T.R.Walsh, C.J.Schofield, J.Brem. *Biochim. Biophys. Acta Gen. Sub.*, **1863**, 742 (2019)
82. L.A.Petty, O.Henig, T.S.Patel, J.M.Pogue, K.S.Kaye. *Infect. Drug Resist.*, **11**, 1461 (2018)
83. S.Dhillon. *Drugs*, **78**, 1259 (2018)
84. Y.L.Wang, S.Liu, Z.J.Yu, Y.Lei, M.Y.Huang, Y.H.Yan, Q.Ma, Y.Zheng, H.Deng, Y.Sun, C.Wu, Y.Yu, Q.Chen, Z.Wang, Y.Wu, G.B.Li. *J. Med. Chem.*, **62**, 7160 (2019)
85. B.M.Babin, P.Kasperkiewicz, T.Janiszewski, E.Yoo, G.M.Dra, M.Bogyo. *ACS Chem. Biol.*, **14**, 2453 (2019)
86. J.E.Wynn, W.Zhang, J.O.Falkinham 3rd, W.L.Santos. *ACS Med. Chem. Lett.*, **8**, 820 (2017)
87. S.Ramsaywack, A.Bos, C.M.Vogels, C.A.Gray, S.A.Westcott. *Can. J. Chem.*, **96**, 1065 (2018)
88. M.A.Soriano-Ursua, E.D.Farfan-Garcia, S.Geninatti-Crich. *Curr. Med. Chem.*, **26**, 5005 (2019)
89. K.M.Borys, D.Wieczorek, K.Pecura, J.Lipok, A.Adamczyk-Wozniak. *Bioorg. Chem.*, **91**, 103081 (2019)
90. S.Liu, H.Liu, K.Zhang, X.Li, Y.Duan, Z.Wang, T.Wang. *Virol. Sin.*, **34**, 572 (2019)
91. F.Di Virgilio, D.Dal Ben, A.C.Sarti, A.L.Giuliani, S.Falzoni. *Immunity*, **47**, 15 (2017)
92. R.X.Faria, N.de Jesus Hiller, J.P.Salles, J.A.L.C.Resende, R.T.Diogo, N.L.von Ranke, M.L.Bello, C.R.Rodrigues, H.C.Castro, D.de Luna Martins. *J. Bioenerg. Biomembr.*, **51**, 277 (2019)
93. M.A.Soriano-Ursua, M.Bello, C.F.Hernandez-Martinez, I.Santillan-Torres, R.Guerrero-Ramirez, J.Correa-Basurto, J.A.Arias-Montano, J.G.Trujillo-Ferrara. *Eur. Biophys. J.*, **48**, 83 (2019)

94. K.Torssell. *Ark. Kemi*, **10**, 507 (1957)
95. M.Dowlut, D.G.Hall. *J. Am. Chem. Soc.*, **128**, 4226 (2006)
96. S.J.Baker, Y.K.Zhang, T.Akama, A.Lau, H.Zhou, V.Hernandez, W.Mao, M.R.Alley, V.Sanders, J.J.Plattner. *J. Med. Chem.*, **49**, 4447 (2006)
97. R.T.Jacobs, B.Nare, S.A.Wring, M.D.Orr, D.Chen, J.M.Sligar, M.X.Jenks, R.A.Noe, T.S.Bowling, L.T.Mercer, C.Rewerts, E.Gaukel, J.Owens, R.Parham, R.Randolph, B.Beaudet, C.J.Bacchi, N.Yarlett, J.J.Plattner, Y.Freund, C.Ding, T.Akama, Y.K.Zhang, R.Brun, M.Kaiser, I.Scandale, R.Don. *PLoS Negl. Trop. Dis.*, **5**, e1151 (2011)
98. M.P.Barrett. *PLoS Negl. Trop. Dis.*, **12**, e0006925 (2018)
99. A.Adamczyk-Wozniak, M.K.Cyrański, A.Zubrowska, A.Sporzynski. *J. Organomet. Chem.*, **694**, 3533 (2009)
100. A.Adamczyk-Wozniak, K.M.Borys, A.Sporzynski. *Chem. Rev.*, **115**, 5224 (2015)
101. C.T.Liu, J.W.Tomsho, S.J.Benkovic. *Bioorg. Med. Chem.*, **22**, 4462 (2014)
102. G.R.Mereddy, A.Chakradhar, R.M.Rutkoski, S.C.Jonnalagadda. *J. Organomet. Chem.*, **865**, 12 (2018)
103. J.Zhang, M.Zhu, Y.Lin, H.Zhou. *Sci. China Chem.*, **56**, 1372 (2013)
104. R.S.Fuscaldo, P.H.V.Vontobel, E.O.Boeira, A.V.Moro, J.S.D.Costa. *Eur. J. Org. Chem.*, 2050 (2019)
105. J.Zhu, Y.Wei, D.Lin, C.Ou, L.Xie, Y.Zhao, W.Huang. *Org. Biomol. Chem.*, **13**, 11362 (2015)
106. G.Lafitte, K.Kunihiro, C.Bonneaud, B.Dréan, F.Gaigne, V.Parnet, R.Pierre, C.Raffin, R.Vatinel, J.-F.Fournier, B.Musicki, G.Ouvry, C.Bouix-Peter, L.Tomas, C.S.Harris. *Tetrahedron Lett.*, **58**, 3757 (2017)
107. K.Kunihiro, L.Dumais, G.Lafitte, E.Varvier, L.Tomas, C.S.Harris. *Adv. Synth. Catal.*, **360**, 2757 (2018)
108. G.Hazra, S.Maity, S.Bhowmick, P.Ghorai. *Chem. Sci.*, **8**, 3026 (2017)
109. B.Vanveller, M.R.Aronoff, R.T.Raines. *RSC Adv.*, **44**, 21331 (2013)
110. J.M.Gamrat, G.Mancini, S.J.Burke, R.C.Colandrea, N.R.Sadowski, B.C.Figula, J.W.Tomsho. *J. Org. Chem.*, **83**, 6193 (2018)
111. A.N.Tevyashova, A.M.Korolev, A.S.Trenin, L.G.Dezhenkova, A.A.Shtil, V.I.Polshakov, O.Y.Savelyev, E.N.Olsufyeva. *J. Antibiot.*, **69**, 549 (2016)
112. K.M.Borys, A.Matuszewska, D.Wieczorek, K.Kopczyńska, J.Lipok, I.D.Madura, A.Adamczyk-Wozniak. *J. Mol. Struct.*, **1181**, 587 (2019)
113. A.Adamczyk-Wozniak, M.K.Cabaj, P.M.Dominiak, P.Gajowiec, B.Gierczyk, J.Lipok, L.Popenda, G.Schroeder, E.Tomecka, P.Urbanski, D.Wieczorek, A.Sporzynski. *Bioorg. Chem.*, **60**, 130 (2015)
114. A.Nocentini, R.Cadoni, S.Del Prete, C.Capasso, P.Dumy, P.Gratteri, C.T.Supuran, J.Y.Winum. *ACS Med. Chem. Lett.*, **8**, 1194 (2017)
115. V.Alterio, R.Cadoni, D.Esposito, D.Vullo, A.D.Fiore, S.M.Monti, A.Caporale, M.Ruvo, M.Sechi, P.Dumy, C.T.Supuran, G.De Simone, J.Y.Winum. *Chem. Commun.*, **52**, 11983 (2016)
116. Q.H.Hu, R.J.Liu, Z.P Fang, J.Zhang, Y.Y.Ding, M.Tan, M.Wang, W.Pan, H.C.Zhou, E.D.Wang. *Sci. Rep.*, **3**, 2475 (2013)
117. F.L.Rock, W.Mao, A.Yaremchuk, M.Tukalo, T.Crepin, H.Zhou, Y.K.Zhang, V.Hernandez, T.Akama, S.J.Baker, J.J.Plattner, L.Shapiro, S.A.Martinis, S.J.Benkovic, S.Cusack, M.R.Alley. *Science*, **316**, 1759 (2007)
118. J.G.Hurdle, A.J.O'Neill, I.Chopra. *Antimicrob. Agents Chemother.*, **49**, 4821 (2005)
119. R.M.Al-Zoubi, M.S.Al-Zoubi, K.T.Jaradat, R.McDonald. *Eur. J. Org. Chem.*, 5800 (2017)
120. A.Korkegian, T.O'Malley, Y.Xia, Y.Zhou, D.S.Carter, B.Sunde, L.Flint, D.Thompson, T.R.Ioerger, J.Sacchettini, M.R.K.Alley, T.Parish. *Tuberculosis*, **108**, 96 (2018)
121. N.Patel, T.O'Malley, Y.K.Zhang, Y.Xia, B.Sunde, L.Flint, A.Korkegian, T.R.Ioerger, J.Sacchettini, M.R.K.Alley, T.Parish. *Antimicrob. Agents Chemother.*, **61**, e01205 (2017)
122. M.A.Alam, K.Arora, S.Gurrapu, S.K.Jonnalagadda, G.L.Nelson, P.Kiprof, S.C.Jonnalagadda, V.R.Mereddy. *Tetrahedron*, **72**, 3795 (2016)
123. P.Fernandes, E.Martens. *Biochem. Pharmacol.*, **133**, 152 (2017)
124. G.B.Lapa, E.P.Mirchink, E.B.Isakova, M.N.Preobrazhenskaya. *J. Enzyme Inhib. Med. Chem.*, **32**, 452 (2017)
125. S.S.Printsevskaya, A.M.Korolev, E.P.Mirchink, E.B.Isakova, A.N.Tevyashova. *Antibiot. Khimioterap.*, **63** (1 – 2), 3 (2018)
126. A.N.Tevyashova, A.M.Korolev, E.P.Mirchink, E.B.Isakova, I.A.Osterman. *J. Antibiot.*, **72**, 22 (2019)
127. A.Y.Peleg, D.C.Hooper. *New Engl. J. Med.*, **362**, 1804 (2010)
128. E.Ruppe, P.L.Woerther, F.Barbier. *Ann. Intensive Care*, **5**, 61 (2015)
129. V.Hernandez, T.Crepin, A.Palencia, S.Cusack, T.Akama, S.J.Baker, W.Bu, L.Feng, Y.R.Freund, L.Liu, M.Meewan, M.Mohan, W.Mao, F.L.Rock, H.Sexton, A.Sheoran, Y.Zhang, Y.K.Zhang, Y.Zhou, J.A.Nieman, M.R.Anugula, M.Keramane, K.Savariraj, D.S.Reddy, R.Sharma, R.Subedi, R.Singh, A.O'Leary, N.L.Simon, P.L.De Marsh, S.Mushtaq, M.Warner, D.M.Livermore, M.R.Alley, J.J.Plattner. *Antimicrob. Agents Chemother.*, **57**, 1394 (2013)
130. K.O'Dwyer, A.T.Spivak, K.Ingraham, S.Min, D.J.Holmes, C.Jakielaszek, S.Rittenhouse, A.L.Kwan, G.P.Livi, G.Sathe, E.Thomas, S.Van Horn, L.A.Miller, M.Twynholm, J.Tomayko, M.Dalessandro, M.Caltabiano, N.E.Scangarella-Oman, J.R.Brown. *Antimicrob. Agents Chemother.*, **59**, 289 (2015)
131. K.P.Purnapatre, M.Rao, M.Pandya, A.Khanna, T.Chaira, R.Bambal, D.J.Upadhyay, N.Masuda. *Antimicrob. Agents Chemother.*, **62**, e01987-17 (2018)
132. M.Kumar, M.Rao, K.P.Purnapatre, T.K.Barman, V.Joshi, A.Kashyap, T.Chaira, R.B.Bambal, M.Pandya, S.A.Khodor, D.J.Upadhyay, N.Masuda. *Antimicrob. Agents Chemother.*, **63**, e02122-18 (2019)
133. T.Akama, Y.K.Zhang, Y.R.Freund, P.Berry, J.Lee, E.E.Easom, R.T.Jacobs, J.J.Plattner, M.J.Witty, R.Peter, T.G.Rowan, K.Gillingwater, R.Brun, B.Nare, L.Mercer, M.Xu, J.Wang, H.Liang. *Bioorg. Med. Chem. Lett.*, **28**, 6 (2018)
134. D.C.Jones, B.J.Foth, M.D.Urbaniak, S.Patterson, H.B.Ong, M.Berriman, A.H.Fairlamb. *PLoS Negl. Trop. Dis.*, **9**, e0004299 (2015)
135. https://www.dndi.org/diseases-projects/portfolio/acoziborole (Last access 15.03.2021)
136. P.C.Steketee, I.M.Vincent, F.Achcar, F.Giordani, D.H.Kim, D.J.Creek, Y.Freund, R.Jacobs, K.Rattigan, D.Horn, M.C.Field, A.MacLeod, M.P.Barrett. *PLoS Negl. Trop. Dis.*, **12**, e0006450 (2018)

137. R.J.Wall, E.Rico, I.Lukac, F.Zuccotto, S.Elg, I.H.Gilbert, Y.Freund, M.R.K.Alley, M.C.Field, S.Wyllie, D.Horn. *Proc. Natl. Acad. Sci. USA*, **115**, 9616 (2018)
138. N.Zhang, M.Zoltner, K.F.Leung, P.Scullion, S.Hutchinson, R.C.Del Pino, I.M.Vincent, Y.K.Zhang, Y.R.Freund, M.R.K.Alley, R.T.Jacobs, K.D.Read, M.P.Barrett, D.Horn, M.C.Field. *PLoS Pathogens*, **14**, e1006850 (2018)
139. D.Begolo, I.M.Vincent, F.Giordani, I.Pohner, M.J.Witty, T.G.Rowan, Z.Bengaly, K.Gillingwater, Y.Freund, R.C.Wade, M.P.Barrett, C.Clayton. *PLoS Pathogens*, **14**, e1007315 (2018)
140. C.Capasso, C.T.Supuran. *Expert Opin. Ther. Targets*, **19**, 1689 (2015)
141. A.B.Vermelho, G.R.Capaci, I.A.Rodrigues, V.S.Cardoso, A.M.Mazotto, C.T.Supuran. *Bioorg. Med. Chem.*, **25**, 1543 (2017)
142. C.T.Supuran. *Future Med. Chem.*, **8**, 311 (2016)
143. A.Nocentini, R.Cadoni, P.Dumy, C.T.Supuran, J.Y.Winum. *J. Enzyme Inhib. Med. Chem.*, **33**, 286 (2018)
144. E.Sonoiki, C.L.Ng, M.C.Lee, D.Guo, Y.K.Zhang, Y.Zhou, M.R.Alley, V.Ahyong, L.M.Sanz, M.J.Lafuente-Monasterio, C.Dong, P.G.Schupp, J.Gut, J.Legac, R.A.Cooper, F.J.Gamo, J.DeRisi, Y.R.Freund, D.A.Fidock, P.J.Rosenthal. *Nat. Commun.*, **8**, 14574 (2017)
145. A.Palencia, A.Bougdour, M.P.Brenier-Pinchart, B.Touquet, R.L.Bertini, C.Sensi, G.Gay, J.Vollaire, V.Josserand, E.Easom, Y.R.Freund, H.Pelloux, P.J.Rosenthal, S.Cusack, M.A.Hakimi. *EMBO Mol. Med.*, **9**, 385 (2017)
146. E.Sonoiki, A.Palencia, D.Guo, V.Ahyong, C.Dong, X.Li, V.S.Hernandez, Y.K.Zhang, W.Choi, J.Gut, J.Legac, R.Cooper, M.R.Alley, Y.R.Freund, J.DeRisi, S.Cusack, P.J.Rosenthal. *Antimicrob. Agents Chemother.*, **60**, 4886 (2016)
147. A.Palencia, R.J.Liu, M.Lukarska, J.Gut, A.Bougdour, B.Touquet, E.D.Wang, X.Li, M.R.Alley, Y.R.Freund, P.J.Rosenthal, M.A.Hakimi, S.Cusack. *Antimicrob. Agents Chemother.*, **60**, 5817 (2016)
148. Y.K.Zhang, J.J.Plattner, E.E.Easom, R.T.Jacobs, D.Guo, V.Sanders, Y.R.Freund, B.Campo, P.J.Rosenthal, W.Bu, F.J.Gamo, L.M.Sanz, M.Ge, L.Li, J.Ding, Y.Yang. *J. Med. Chem.*, **58**, 5344 (2015)
149. Y.K.Zhang, J.J.Plattner, E.E.Easom, R.T.Jacobs, D.Guo, Y.R.Freund, P.Berry, V.Ciaravino, J.C.L.Erve, P.J.Rosenthal, B.Campo, F.J.Gamo, L.M.Sanz, J.Cao. *J. Med. Chem.*, **60**, 5889 (2017)
150. K.M.V.Sindhe, E.Sonoiki, D.H.Guo, J.Gut, J.Legac, Y.Tran, Y.K.Zhang, P.Berry, V.Ciaravino, F.J.Gamo, L.Sanz, E.E.Easom, J.L.DeRisi, J.J.Plattner, Y.R.Freund, P.J.Rosenthal. *Am. J. Trop. Med. Hyg.*, **95**, 8 (2017)
151. K.Van Bocxlaer, E.Gaukel, D.Hauser, S.H.Park, S.Schock, V.Yardley, R.Randolph, J.J.Plattner, T.Merchant, S.L.Croft, R.T.Jacobs, S.A.Wring. *Antimicrob. Agents Chemother.*, **62**, e02419-17 (2018)
152. K.Van Bocxlaer, D.Caridha, C.Black, B.Vesely, S.Leed, R.J.Sciotti, G.J.Wijnant, V.Yardley, S.Braillard, C.E.Mowbray, J.R.Ioset, S.L.Croft. *Int. J. Parasitol. Drugs Drug Resist.*, **11**, 129 (2019)
153. https://www.dndi.org/diseases-projects/portfolio/dndi-6148 (Last access 15.03.2021)
154. R.Manhas, S.Tandon, S.S.Sen, N.Tiwari, M.Munde, R.Madhubala. *Antimicrob. Agents Chemother.*, **62**, e00079-18 (2018)
155. R.K.Pandey, B.V.Kumbhar, S.Sundar, A.Kunwar, V.K.Prajapati. *J. Recept. Signal Transduct. Res.*, **37**, 60 (2017)
156. T.Long, L.Rojo-Arreola, D.Shi, N.El-Sakkary, K.Jarnagin, F.Rock, M.Meewan, A.A.Rascon Jr., L.Lin, K.A.Cunningham, G.A.Lemieux, L.Podust, R.Abagyan, K.Ashrafi, J.H.McKerrow, C.R.Caffrey. *PLoS Negl. Trop. Dis.*, **11**, e0005680 (2017)
157. Y.K.Zhang, J.J.Plattner, E.E.Easom, Y.Zhou, T.Akama, W.Bu, W.H.White, J.M.Defauw, J.R.Winkle, T.W.Balko, S.Guo, J.Xue, J.Cao, W.Zou. *Bioorg. Med. Chem. Lett.*, **25**, 5589 (2015)
158. Y.K.Zhang, J.J.Plattner, E.E.Easom, T.Akama, Y.Zhou, W.H.White, J.M.Defauw, J.R.Winkle, T.W.Balko, J.Cao, Z.Ge, J.Yang. *Bioorg. Med. Chem. Lett.*, **26**, 3182 (2016)
159. A.Wadood, M.Riaz, S.B.Jamal, M.Shah, M. A.Lodhi. *Bioinformation*, **9**, 309 (2013)
160. X.Li, Y.K.Zhang, Y.Liu, S.Zhang, C.Z.Ding, Y.Zhou, J.J.Plattner, S.J.Baker, L.Liu, W.Bu, W.M.Kazmierski, L.L.Wright, G.K.Smith, R.L.Jarvest, M.Duan, J.J.Ji, J.P.Cooper, M.D.Tallant, R.M.Crosby, K.Creech, Z.J.Ni, W.Zou, J.Wright. *Bioorg. Med. Chem. Lett.*, **20**, 7493 (2010)
161. P.Y.Chong, J.B.Shotwell, J.Miller, D.J.Price, A.Maynard, C.Voitenleitner, A.Mathis, S.Williams, J.J.Pouliot, K.Creech, F.Wang, J.Fang, H.Zhang, V.W.Tai, E.Turner, K.M.Kahler, R.Crosby, A.J.Peat. *J. Med. Chem.*, **62**, 3254 (2019)
162. K.Arrington, G.A.Barcan, N.A.Calandra, G.A.Erickson, L.Li, L.Liu, M.G.Nilson, I.I.Strambeanu, K.F.Van Gelder, J.L.Woodard, S.Xie, C.L.Allen, J.A.Kowalski, D.C.Leitch. *J. Org. Chem.*, **84**, 4680 (2019)
163. P.Suman, B.P.Patel, A.V.Kasibotla, L.N.Solano, S.C.Jonnalagadda. *J. Organomet. Chem.*, **798**, 125 (2015)
164. J.Zhang, F.Yang, Z.Qiao, M.Zhu, H.Zhou. *Bioorg. Med. Chem. Lett.*, **26**, 5797 (2016)
165. M.B.Santos, V.C.Pinhanelli, M.A.R.Garcia, G.Silva, S.J.Baek, S.C.Franca, A.L.Fachin, M.Marins, L.O.Regasini. *Eur. J. Med. Chem.*, **138**, 884 (2017)
166. L.F.Stein Gold, L.Spelman, M.C.Spellman, M.H.Hughes, L.T.Zane. *J. Drugs Dermatol.*, **14**, 1394 (2015)
167. D.F.Murrell, K.Gebauer, L.Spelman, L.T.Zane. *J. Drugs Dermatol.*, **14**, 1108 (2015)
168. K.Jarnagin, S.Chanda, D.Coronado, V.Ciaravino, L.T.Zane, E.Guttman-Yassky, M.G.Lebwohl. *J. Drugs Dermatol.*, **15**, 390 (2016)
169. C.Dong, C.Virtucio, O.Zemska, G.Baltazar, Y.Zhou, D.Baia, S.Jones-Iatauro, H.Sexton, S.Martin, J.Dee, Y.Mak, M.Meewan, F.Rock, T.Akama, K.Jarnagin. *J. Pharmacol. Exp. Ther.*, **358**, 413 (2016)
170. A.B.Benowitz, H.C.Eberl, C.L.Erickson-Miller, A.G.Gilmartin, E.R.Gore, M.N.Montoute, Z.Wu. *Bioorg. Med. Chem. Lett.*, **28**, 3676 (2018)
171. B.Liu, R.E.L.Trout, G.H.Chu, D.McGarry, R.W.Jackson, J.C.Hamrick, D.M.Daigle, S.M.Cusick, C.Pozzi, F.De Luca, M.Benvenuti, S.Mangani, J.D.Docquier, W.J.Weiss, D.C.Pevear, L.Xerri, C.J.Burns. *J. Med. Chem.*, **63**, 2789 (2020)

172. A.Krajnc, J.Brem, P.Hinchliffe, K.Calvopiña, T.D.Panduwawala, P.A.Lang, J.J.A.G.Kamps, J.M.Tyrrell, E.Widlake, B.G.Saward, T.R.Walsh, J.Spencer, C.J.Schofield. *J. Med. Chem.*, **62**, 8544 (2019)
173. K.M.Papp-Wallace. *Expert Opin. Pharmacother.*, **20**, 2169 (2019)
174. A.Parkova, A.Lucic, A.Krajnc, J.Brem, K.Calvopiña, G.W.Langley, M.A.McDonough, P.Trapencieris, C.J.Schofield. *ACS Infect. Dis.*, **6**, 1398 (2020); https://doi.org/10.1021/acsinfecdis.9b00330
175. Patent WO 2014121124A1 (2014)
176. C.J.Lu, J.Hu, Z.Wang, S.Xie, T.Pan, L.Huang, X.Li. *MedChemComm*, **9**, 1862 (2018)
177. F.Li, Y.Wang, H.Yang, Y.Xu, X.Zhou, X.Zhang, Z.Xie, J.Bi. *BMC Mol. Biol.*, **20**, 23 (2019)
178. I.Natsutani, R.Iwata, Y.S.Yamai, K.Ishida, Y.Nagaoka, T.Sumiyoshi. *Chem. Biol. Drug Des.*, **93**, 657 (2019)
179. M.C.Davis, S.G.Franzblau, A.R.Martin. *Bioorg. Med. Chem. Lett.*, **8**, 843 (1998)
180. G.T.Lee, K.Prasad, O.Repič. *Tetrahedron Lett.*, **43**, 3255 (2002)
181. J.W.Hicks, C.B.Kyle, C.M.Vogels, S.L.Wheaton, F.J.Baerlocher, A.Decken, S.A.Westcott. *Chem. Biodivers.*, **5**, 2415 (2008)
182. D.Kanichar, L.Roppiyakuda, E.Kosmowska, M.A.Faust, K.P.Tran, F.Chow, E.Buglo, M.P.Groziak, E.A.Sarina, M.M.Olmstead, I.Silva, H.H.Xu. *Chem. Biodivers.*, **11**, 1381 (2014)
183. J.P.M.Antonio, L.M.Goncalves, R.C.Guedes, R.Moreira, P.M.P.Gois. *ACS Omega*, **3**, 7418 (2018)
184. M.A.Grassberger, F.Turnowsky, J.Hildebrandt. *J. Med. Chem.*, **27**, 947 (1984)
185. B.Pertschy, G.Zisser, H.Schein, R.Koffel, G.Rauch, K.Grillitsch, C.Morgenstern, M.Durchschlag, G.Hogenauer, H.Bergler. *Mol. Cell. Biol.*, **24**, 6476 (2004)
186. M.Loibl, I.Klein, M.Prattes, C.Schmidt, L.Kappel, G.Zisser, A.Gungl, E.Krieger, B.Pertschy, H.Bergler. *J. Biol. Chem.*, **289**, 3913 (2014)
187. C.A.Jordan, B.A.Sandoval, M.V.Serobyan, D.H.Gilling, M.P.Groziak, H.H.Xu, J.L.Vey. *Acta Crystallogr., Sect. F*, **71**, 1521 (2015)
188. Y.Xia, Y.Zhou, D.S.Carter, M.B.McNeil, W.Choi, J.Halladay, P.W.Berry, W.Mao, V.Hernandez, T.O'Malley, A.Korkegian, B.Sunde, L.Flint, L.K.Woolhiser, M.S.Scherman, V.Gruppo, C.Hastings, G.T.Robertson, T.R.Ioerger, J.Sacchettini, P.J.Tonge, A.J.Lenaerts, T.Parish, M.Alley. *Life Sci. Alliance*, **1**, e201800025 (2018)
189. Patent WO 2014167133A1 (2014)
190. J.Yang, B.J.Johnson, A.A.Letourneau, C.M.Vogels, A.Decken, F.J.Baerlocher, S.A.Westcott. *Aust. J. Chem.*, **68**, 366 (2015)
191. R.S.Scott, A.J.Veinot, D.L.Stack, P.T.Gormley, B.N.Khuong, C.M.Vogels, J.D.Masuda, F.J.Baerlocher, T.J.MacCormack, S.A.Westcott. *Can. J. Chem.*, **96**, 906 (2018)
192. A.Bandyopadhyay, S.Cambray, J.Gao. *J. Am. Chem. Soc.*, **139**, 871 (2017)
193. A.G.Baldwin, J.Rivers-Auty, M.J.D.Daniels, C.S.White, C.H.Schwalbe, T.Schilling, H.Hammadi, P.Jaiyong, N.G.Spencer, H.England, N.M.Luheshi, M.Kadirvel, C.B.Lawrence, N.J.Rothwell, M.K.Harte, R.A.Bryce, S.M.Allan, C.Eder, S.Freeman, D.Brough. *Cell Chem. Biol.*, **24**, 1321 (2017)
194. A.G.Baldwin, V.S.Tapia, T.Swanton, C.S.White, J.A.Beswick, D.Brough, S.Freeman. *ChemMedChem*, **13**, 312 (2018)
195. S.L.Cassel, F.S.Sutterwala. *Eur. J. Immunol.*, **40**, 607 (2010)
196. T.Mikysek, P.Nikolaou, M.Kafexholli, P.Šimůnek, J.Váa, A.Marková, M.Vala, G.Valenti. *ChemElectroChem*, **7**, 1550 (2020)
197. F.Josefík, M.Svobodová, V.Bertolasi, P.Šimůnek, V.Macháček, N.Almonasy, E.Černošková. *J. Organomet. Chem.*, **699**, 75 (2012)
198. T.Mikysek, H.Kvapilová, F.Josefík, J.Ludvík. *Anal. Lett.*, **49**, 178 (2015)
199. F.Josefík, T.Mikysek, M.Svobodová, P.Šimůnek, H.Kvapilová, J.Ludvík. *Organometallics*, **33**, 4931 (2014)
200. R.F.Barth, P.Mi, W.Yang. *Cancer Commun.*, **38**, 35 (2018)
201. R.F.Barth, J.C.Grecula. *Appl. Radiat. Isot.*, **10**, 109029 (2020)
202. C.Vinas, R.Nunez, I.Bennour, F.Teixidor. *Curr. Med. Chem.*, **26**, 5036 (2019)
203. R.N.Grimes. *Carboranes*. (3rd Edn.). (Amsterdam: Elsevier, 2016)
204. *Boron-Based Compounds*: *Potential and Emerging Applications in Medicine*. (Eds E.Hey-Hawkins, C.V.Teixidor). (Hoboken, NJ: Wiley, 2018)
205. *Handbook of Boron Science with Application in Organometallics, Catalysis, Materials and Medicine*. Vol. 4. (Eds N.S.Hosmane, R.Eagling). (London: World Scientific Publishing, 2019)
206. W.-B.Yu, P.-F.Cui, W.-X.Gao, G.-X.Jin. *Coord. Chem. Rev.*, **350**, 300 (2017)
207. Y.Quan, Z.Qiu, Z.Xie. *Chemistry*, **24**, 2795 (2018)
208. S.P.Fisher, A.W.Tomich, S.O.Lovera, J.F.Kleinsasser, J.Guo, M.J.Asay, H.M.Nelson, V.Lavallo. *Chem. Rev.*, **119**, 8262 (2019)
209. Y.Quan, Z.Xie. *Chem. Soc. Rev.*, **48**, 3660 (2019)
210. X.Zhang, H.Yan. *Coord. Chem. Rev.*, **378**, 466 (2019)
211. K.Cao, C.Y.Zhang, T.T.Xu, J.Wu, X.Y.Wen, W.J.Jiang, M.Chen, J.Yang. *Molecules*, **25**, 391 (2020)
212. H.H.Li, H.Yan, C.S.Lu. *Chin. J. Inorg. Chem.*, **33**, 1313 (2017)
213. H.Bai, H.Xu, H.Zhang, Y.Guo, J.Shan, D.Wei, Y.Zhu, S.Zhang, W.Zhang. *Catal. Sci. Technol.*, **8**, 5165 (2018)
214. Y.Chen, Y.K.Au, Y.Quan, Z.Xie. *Sci. China Chem.*, **62**, 74 (2018)
215. H.Lyu, J.Zhang, J.Yang, Y.Quan, Z.Xie. *J. Am. Chem. Soc.*, **141**, 4219 (2019)
216. T.T.Xu, K.Cao, C.Y.Zhang, J.Wu, L.F.Ding, J.Yang. *Org. Lett.*, **21**, 9276 (2019)
217. A.A.Druzina, V.I.Bregadze, A.F.Mironov, A.A.Semioshkin. *Russ. Chem. Rev.*, **85**, 1229 (2016)
218. J.Laskova, A.Kozlova, M.Białek-Pietras, M.Studzińska, E.Paradowska, V.Bregadze, Z.J.Leśnikowski, A.Semioshkin. *J. Organomet. Chem.*, **807**, 29 (2016)
219. M.Kellert, P.Hoppenz, P.Lonnecke, D.J.Worm, B.Riedl, J.Koebberling, A.G.Beck-Sickinger, E.Hey-Hawkins. *Dalton Trans.*, **49**, 57 (2020)
220. P.Hoppenz, S.Els-Heindl, A.G.Beck-Sickinger. *J. Pept. Sci.*, **25**, e3224 (2019)
221. V.Sancho, A.Di Florio, T.W.Moody, R.T.Jensen. *Curr. Drug Deliv.*, **8**, 79 (2011)
222. P.Hoppenz, S.Els-Heindl, M.Kellert, R.Kuhnert, S.Saretz, H.G.Lerchen, J.Kobberling, B.Riedl, E.Hey-Hawkins, A.G.Beck-Sickinger. *J. Org. Chem.*, **85**, 1446 (2020)

223. D.J.Worm, P.Hoppenz, S.Els-Heindl, M.Kellert, R.Kuhnert, S.Saretz, J.Kobberling, B.Riedl, E.Hey-Hawkins, A.G.Beck-Sickinger. *J. Med. Chem.*, **63**, 2358 (2020)
224. D.J.Worm, S.Els-Heindl, A.G.Beck-Sickinger. *Pept. Sci.*, **112**, e24171 (2020)
225. E.Y.Matveev, S.S.Akimov, A.S.Kubasov, V.M.Retivov, K.Y.Zhizhin, N.T.Kuznetsov. *Fine Chem. Technol.*, **14**, 59 (2019)
226. L.N.Goswami, L.Ma, S.Chakravarty, Q.Cai, S.S.Jalisatgi, M.F.Hawthorne. *Inorg. Chem.*, **52**. 1694 (2013)
227. R.X.Li, J.J.Zhang, J.X.Guo, Y.Xu, K.Y.Duan, J.R.Zheng, H.Wan, Z.W.Yuan, H.Y.Chen. *Mol. Pharm.*, **17**, 202 (2020)
228. A.B.Volovetskiy, N.Y.Shilyagina, V.V.Dudenkova, S.O.Pasynkova, A.A.Ignatova, A.F.Mironov, M.A.Grin, V.I.Bregadze, A.V.Feofanov, I.V.Balalaeva, A.V.Maslennikova. *Biophysics*, **61**, 133 (2016)
229. I.V.Korolkov, K.Ludzik, A.L.Kozlovskiy, M.S.Fadeev, A.E.Shumskaya, Y.G.Gorin, B.Marciniak, M.Jazdzewska, D.Chudoba, R.Kontek, A.Nazarova, V.S.Rusakov, M.V.Zdorovets. *Mater. Today Commun.*, **24**, 101247 (2020)
230. D.Z.Tulebayeva, A.L.Kozlovskiy, I.V.Korolkov, Y.G.Gorin, A.V.Kazantsev, L.Abylgazina, E.E.Shumskaya, E.Y.Kaniukov, M.V.Zdorovets. *Mater. Res. Express*, **5**, 105011 (2018)
231. K.Dukenbayev, I.V.Korolkov, D.I.Tishkevich, A.L.Kozlovskiy, S.V.Trukhanov, Y.G.Gorin, E.E.Shumskaya, E.Y.Kaniukov, D.A.Vinnik, M.V.Zdorovets, M.Anisovich, A.V.Trukhanov, D.Tosi, C.Molardi. *Nanomaterials (Basel)*, **9**, 494 (2019)
232. S.Yoneoka, Y.Nakagawa, K.Uto, K.Sakura, T.Tsukahara, M.Ebara. *Sci. Technol. Adv. Mater.*, **20**, 291 (2019)
233. S.M.Sharker. *Int. J. Nanomed.*, **14**, 9983 (2019)
234. L.Cheng, X.Wang, F.Gong, T.Liu, Z.Liu. *Adv. Mater.*, **32**, e1902333 (2019)
235. J.Wang, L.Chen, J.Ye, Z.Li, H.Jiang, H.Yan, M.Y.Stogniy, I.B.Sivaev, V.I.Bregadze, X.Wang. *Biomacromolecules*, **18**, 1466 (2017)
236. F.Danhier. *J. Control. Release*, **244**, 108 (2016)
237. Y.Zheng, W.Liu, Y.Chen, H.Jiang, H.Yan, I.Kosenko, L.Chekulaeva, I.Sivaev, V.Bregadze, X.Wang. *Organometallics*, **36**, 3484 (2017)
238. P.Stockmann, M.Gozzi, R.Kuhnert, M.B.Sarosi, E.Hey-Hawkins. *Chem. Soc. Rev.*, **48**, 3497 (2019)
239. S.Sene, S.Begu, C.Gervais, G.Renaudin, A.Mesbah, M.E.Smith, P.H.Mutin, A.van der Lee, J.-M.Nedelec, C.Bonhomme, D.Laurencin. *Chem. Mater.*, **27**, 1242 (2015)
240. S.Sene, J.McLane, N.Schaub, S.Begu, P.H.Mutin, L.Ligon, R.J.Gilbert, D.Laurencin. *J. Mater. Chem. B*, **4**, 257 (2016)
241. K.A.Andersen, T.P.Smith, J.E.Lomax, R.T.Raines. *ACS Chem. Biol.*, **11**, 319 (2016)
242. S.Kusano, S.Konishi, Y.Yamada, O.Hayashida. *Org. Biomol. Chem.*, **16**, 4619 (2018)
243. Y.Suzuki, M.Shimizu, T.Okamoto, T.Sugaya, S.Iwatsuki, M.Inamo, H.D.Takagi, A.Odani, K.Ishihara. *Chemistry Select*, **1**, 5141 (2016)
244. M.Kurogochi, M.Mizuno, A.Matsuda. *Chemistry Select*, **3**, 8193 (2018)
245. T.Pekol, J.S.Daniels, J.Labutti, I.Parsons, D.Nix, E.Baronas, F.Hsieh, L.-S.Gan, G.Miwa. *Drug Metab. Dispos.*, **33**, 771 (2005)
246. S.Jinna, J.Finch. *Des. Devel. Ther.*, **9**, 6185 (2015)