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Boron chemicals in diagnosis and therapeutics

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Abstract

Advances in the field of boron chemistry have expanded the application of boron from material use to medicine. Boron-based drugs represent a new class of molecules that possess several biomedical applications including use as imaging agents for both optical and nuclear imaging as well as therapeutic agents with anticancer, antiviral, antibacterial, antifungal and other disease-specific activities. For example, bortezomib (Velcade[®]), the only drug in clinical use with boron as an active element, was approved in 2003 as a proteasome inhibitor for the treatment of multiple myeloma and non-Hodgkin's lymphoma. Several other boron-based compounds are in various phases of clinical trials, which illustrates the promise of this approach for medicinal chemists working in the area of boron chemistry. It is expected that in the near future, several boron-containing drugs should become available in the market with better efficacy and potency than existing drugs. This article discusses the current status of the development of boron-based compounds as diagnostic and therapeutic agents in humans.

Boron has atomic number 5 and is classified as a metalloid. It is an essential trace element for plants that occurs naturally in the environment. There is increasing evidence that boron may be important for animals and humans, as it is in plants. Although an absolute requirement for boron has not been demonstrated in animals and humans, the usual dietary intake of boron in human is from 1–2 mg/day. Plant products such as fruits, vegetables, tubers and legumes are a richer dietary source of boron than animal products [1,2]. With the recognition that boron has biological activity the development of boron containing compounds has generated significant interest among medicinal chemists. Boron-based drugs have been demonstrated to possess several biomedical applications [3–5].

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Because of the unique electronic structure of boron and its ability to form covalent bonds with carbon, boron is widely used in synthetic chemistry [6,7]. Most trivalent boron reagents are electrophiles; however, when a trigonal boron atom accepts a pair of electrons from a nucleophile, it adopts a tetrahedral configuration (sp^3), and the octet rule is satisfied (Figure 1). The process of enzyme inhibition requires the conversion of sp^2 carbonyl carbon to a tetrahedral sp^3 carbon. Therefore, the substitution of carbon with boron would make a good transition state analog for the inhibition of hydrolytic enzymes (Figure 2). The use of boronic acid compounds as enzyme inhibitors is mostly based on this easy conversion of trigonal to the tetrahedral form. **Organoborane** compounds are very important in biological systems and they result from the interaction with hydroxyl and amine groups. Boron has a high affinity for oxygen forming borates that are involved in enzyme inhibition. Boron most often occurs in the form of borates, mainly as borate minerals and borosilicates. The isoelectronic nature of C=C and B-N bonding increases the use of boron in organic synthesis [7,8].

Boron has a wide range of applications in chemistry, material science, energy research, and electronics, as well as in life science. Boric acid is used as an insecticide [9] and boron is widely used in the production of glass (borosilicate glass) and ceramics [10], household laundry and cleaning products [11]. Boronic materials being metalloids are usually semiconductors and are, therefore, useful in computer and electronic industries [12]. Boron has been demonstrated to be useful as imaging (optical and nuclear probe) agents. The drug bortezomib (Velcade[®]), the only drug in clinical use with boron as an active element, was approved in 2003 as a proteasome inhibitor for the treatment of multiple myeloma (MM) and non-Hodgkins lymphoma [13]. This discovery has motivated several researchers to further explore the boron chemistry. Several drugs are in various phases of clinical trials and many compounds containing boron are being synthesized targeting various diseases, which will be discussed further in this review.

To develop a new therapeutic agent for a particular disease, one typically follows four steps: target identification (biomarker identification associated with causing disease); target validation (validate the target using imaging tools); develop target therapeutics (develop new therapeutic agents); and finally drug delivery (deliver the therapeutic agent to target site). In this review, the use of boron in each step in drug discovery (target identification, target validation, target therapeutics and target delivery) will be briefly described, giving more emphasis to developing targeted therapeutic agents, as the application of boron in other areas are in the initial phases with limited available reports. The rapid growth of the **chemical genetics** field will further exploit the use of boron chemicals in the future for target identification and validation steps of drug discovery.

Target identification & validation

The identification of molecular targets for various small molecules is an important aspect of drug discovery. This complex process uses various tools, approaches and information in order to identify the molecular target and can be categorized into direct and indirect approaches. In a direct approach, proteins that bind with the compound are purified and identified using TOF/MS. In the indirect approach, the targets are identified by profiling the biological data induced by a compound: for example, when the compound alters a cellular event whose regulatory signaling pathway is known (from the previous reported literature) the step responsible for the effect is determined and the protein (enzyme) target involved in that step is identified [14].

Activity-based protein profiling proteomics uses small molecules to tag and monitor a specific class of proteins within a complex proteome where the probe binds to the target

enzyme in its active form. Among the tagging methodologies, the use of small-molecule fluorophores is where the greatest advances. Fluorescently labeled activity-based protein profiling can be used for direct imaging of labeled targets by fluorescence microscopy. The boron-based fluorophore, dipyrromethene boron difluoride (BODIPY) (**1**; Figure 3) is one of the most common fluorophores used for this purpose.

BODIPY derivative **2** has been used as a fluorescent probe to detect the neurofibrillary tangles of hyperphosphorylated tau proteins responsible for Alzheimer's disease. It has been observed that this compound binds strongly with hyperphosphorylated tau protein but weakly to the nonphosphorylated tau protein. This enables it to differentiate between the neurofibrillary tangles and senile plaques [15]. BODIPY-labeled arachidonic acid **3** and BODIPY-labeled iodoacetamide **4** have been used as fluorescent probes for the quantification and identification of subcellular proteomes and biological processes regulated by lipid peroxidation products [16].

Similarly, various molecular probes that bear BODIPY as a fluorophore (**5–8**) have been successfully employed for *in vivo* labeling of cysteine cathepsins in whole animals (Figure 4). These probes were developed based on the cysteine protease inhibitor *trans*-epoxysuccinyl-L-leucylamido (4-guanidino) butane [17,18].

BODIPY-2'-deoxyguanosine (BODIPY-dG) derivative **9** has been studied for the detection of DNA damage due to oxidation and alkylating agents. The compound was synthesized by conjugation of 4,4-difluoro-5,7-dimethyl-4-bora-3 α , 4 α -diazia, *S*-indacene-3-propionic acid (BODIPY-FL) **10** to the 5'-position of dG. When alkylating agents, such as methanesulfonate and epichlorohydrin, were added to a solution of BODIPY-dG derivative, the solutions demonstrated strong green fluorescence after 12 h due to the release of BODIPY-FL (Figure 5) [19].

Chemical reactions that can occur in biological solutions and physiological conditions that are not affected by the complex mixture of small molecules and proteins of biological solutions, are called bioorthogonal. Recently, synthesis of a highly stable boronate ester **12** has been demonstrated providing for the possibility of bioorthogonality (Figure 6).

Bioorthogonal chemistry can be used to label biomolecules *in vivo* with reporter groups where bioorthogonal functional groups are incorporated within biological molecules and simultaneously reporter probes are covalently coupled to these functional groups [20].

Boronate affinity chromatography works on the basis of interaction of the boronic acid group (ligand) with two *cis*-hydroxyl groups that are present at the adjacent carbon atoms in coplanar configuration of biomolecules, such as carbohydrates, glycoproteins, nucleotides, nucleoside.

In basic conditions, trigonal boronate is converted to a tetrahedral anion that can further form a cyclic ester with the *cis*-diol moiety of biomolecules. This can then be hydrolyzed in acidic conditions to recover these biomolecules [21]. Phenylboronic acid has been used as a ligand in bioaffinity chromatography where phenylboronic acid is bonded to the surface of the column support. On passing the protein solution, only the glycosylated component is retained in the column due to interaction of diol groups with the boronate. By using appropriate reagents, after complete elution of non-glycosylated biomolecules, the boronate group can be removed from the diol-boronate complex to provide purified glycosylated biomolecules (Figure 7).

The boronate affinity technique has been used for the separation of sugars and nucleic acid [22]. Further exploration of these techniques facilitates the separation of a wide variety of *cis*-diol compounds such as lectins [23], thymine glycol DNA and nucleosides [24] and

serine proteinases [25]. One of the earliest reported clinical uses of the boronate affinity chromatography was for the determination of glycohemoglobin in the assessment of long-term diabetes management [26].

Optical probes for reactive oxygen species

Reactive oxygen species (ROS) are highly reactive molecules and free radicals derived from molecular oxygen. They originate mainly from the mitochondrial electron transport chain [27–29]. Almost all cells and tissues continuously convert a small proportion of molecular oxygen into superoxide anion by the univalent reduction of molecular oxygen in the electron transport chain. Other pathways, such as the respiratory burst in activated phagocytes (neutrophils, eosinophils and mononuclear phagocytes) [30] and cellular enzymes including Nox, XO and cytochrome P450 [31,32], are also responsible for the production of ROS. The balance between ROS generation and elimination is critical as excess ROS can damage cellular lipids, proteins or DNA, inhibiting their normal functions [33]. This harmful effect due to increased intracellular ROS levels, as a result of imbalance between production of ROS and antioxidant defense, is termed as 'oxidative stress'. Increased oxidative stress has been associated with various pathologic conditions such as cancer, [34–37] Alzheimer's disease and related neurodegenerative diseases [38,39], cardiovascular disorders [40–42] and aging [43,44].

Hydrogen peroxide (H_2O_2), a major ROS in living organisms, has received increased attention due to its contributions as a marker for oxidative stress [45,46] and role as messenger in normal cellular signal transduction [47]. Its production, accumulation and trafficking within cells is poorly understood. For the purpose of tracking H_2O_2 , various H_2O_2 selective optical probes are being developed. Chang *et al.* have developed various boron-based probes for the detection of H_2O_2 in living cells and *in vivo* (Figures 8 & 9) [48–52]. Peroxyfluor-1 (PF1) **13**, in its lactone form is found to be colorless and non-fluorescent. In the presence of H_2O_2 , it undergoes the hydrolytic deprotection of boronates to give the colored and fluorescent product (Figure 8) [48]. PF1 has demonstrated higher selectivity for H_2O_2 over other ROS such as *tert*-butyl hydroperoxide, O_2^- , NO, hypochlorite (^-OCl), $^-\text{O}^-\text{Bu}$ and ^-OH . **14** (peroxyresorufin-1), **15** (peroxyxanthone-1) [49], **16** (peroxy crimson-1) and **17** (peroxy green-1) [50] are other boronate dyes that belong to the peroxysensor family and work on a similar principle of emitting fluorescence after deprotection of boronates. These boronate dyes are cell permeable and can detect micromolar changes in H_2O_2 concentration in living cells.

Diboronate compounds PF1, peroxyxanthone-1 and peroxyresorufin-1 were capable of detecting only exogenously added H_2O_2 . Due to its relatively low H_2O_2 sensitivity, it was difficult to detect endogenously produced H_2O_2 . This problem was solved with the discovery of monoboronate compound peroxy green-1 and peroxy crimson-1, which can detect H_2O_2 in living cells that has been endogenously produced by EGF/Nox signaling. This led to the development of additional monoboronate dyes such as **18** (peroxyfluor-3), **19** (peroxy yellow-1) and **20** (peroxy orange-1) [51]. Furthermore, development of boronate-caged luciferin (PCL-1) **21** allows the bioluminescent imaging of H_2O_2 *in vivo* by release of free Luciferin [52]. These studying H_2O_2 boronate-based probes provide excellent tools for in biological systems.

Other applications

Molecular imaging techniques have become indispensable for disease screening programs, staging, diagnosis, early response measurement, and surveillance during follow-up. Imaging modalities like positron emission tomography (PET), single photon emission computed

tomography, and magnetic resonance spectroscopy rely on functional and metabolic changes and are valuable for cancer imaging [53].

PET is one of the most powerful imaging technologies, producing high-resolution, 3D images that provide unique information about the molecular and metabolic changes associated with disease. PET requires the use of molecules (radiopharmaceuticals) that are labeled with radioactive nuclides. [^{18}F]-2-deoxy-D-glucose is the most widely used radiopharmaceutical in PET for the diagnosis of cancer despite a relative lack of target specificity. Since ^{18}F is the optimal PET radioisotope because of its short half-life (110 min), cancer-specific small-molecule ^{18}F -labeled radiotracers are necessary to overcome the limitations of [^{18}F]-2-deoxy-D-glucose. For the use of a short-lived isotope, the radiopharmaceutical synthesis must be kinetically and thermodynamically favorable at the time of preparation, and the product must be at least kinetically stable following injection. Ting *et al.* reported the use of organoboron to capture aqueous [^{18}F] fluoride in the form of an aryltrifluoroborate (**22**; Figure 10) for ^{18}F -labeling in a rapid, onestep synthesis under acidic aqueous conditions at room temperature. Their use eliminates multistep synthetic transformations that normally follow radioisotope incorporation. The aryltrifluoroborate is considerably more stable and should be useful in developing stable biomolecule precursors for imaging [54]. In another study, a biotinylated boronic ester **23** was synthesized that is converted to the corresponding trifluoroborate salt in the presence of aqueous [^{18}F]-fluoride. The trifluoroborate appears to clear *in vivo* quite rapidly to the bladder as the stable trifluoroborate salt, further confirming that boronic esters are potentially useful as readily labeled precursors to [^{18}F]-PET reagents [55]. Marimastat, a matrix metalloproteinase inhibitor, was ^{18}F labeled, as in compound **24**, using a shelf-stable arylboronic ester conjugate as a captor for aqueous [^{18}F] fluoride in a novel, rapid one-step reaction at ambient temperature. The labeled drug cleared primarily via the hepatobiliary and GI tract, confirming the ease of this new labeling strategy [56].

In addition, it has been reported that *bis*-boronic acid rhodamine dye (RhoBo) (**25**; Figure 11), was able to bind to peptides having tetraserine sequence. This study reported that there is an intense change in fluorescence upon binding with tetraserine sequence as compared with a range of monosaccharides. Cells treated with RhoBo demonstrated fluorescence throughout the interior of the cell but not on the cell surface. Therefore, RhoBo has a potential to be used as a selective cell-permeable small-molecule tag for proteins containing tetraserine motifs [57]. The above reports clearly indicate the growing use of boron chemicals in target identification and target validation. In the future, there will likely be much more use of boron chemistry to identify new biomarkers related to oxidative stress signaling pathways and glycobiology, in addition to phenotypic drug discovery.

Therapeutic applications

Considerably less attention has been given to boron as compared with other elements such as oxygen, nitrogen, carbon and hydrogen. Yet, the use of boron atoms in pharmaceutical drug design has a high potential for discovery of new biological activities. The physical properties of boronic acids appear to make this group applicable to drug discovery. The pK_a of boronic acid is approximately 9–10, so it remains largely protonated under physiological pH conditions. It has been suggested that hydrogen bonds, as well as boron-nitrogen bonds, can be formed, and thus, boronic acid could potentially provide a functional group that enhances the interactions between a ligand and its protein receptor. The boron atom has a vacant orbital and inter-converts with ease between the neutral sp^2 and the anionic sp^3 hybridization states, which generates a new stable interaction between the boron atom and a donor molecule through an ionic bond.

Therefore, it is anticipated that boron atoms introduced into biologically active molecular frameworks could interact with a target protein through strong hydrogen bonds and very minor covalent bonds, and this interaction might produce potent biological activity (i.e., antifungal, antiparasitic, protease inhibitors and so forth), a concept that is well supported by the literature. Boron-containing compounds are usually air-stable and no special handling is needed when testing them. Moreover, there has been no reported toxicity especially associated with boronic acid isosteres, and recently Velcade has been US FDA approved for use in MM [58]. Proof of this concept is provided by boron-containing compounds for antifungal and antibacterial therapy (AN2690, AN2728, GSK221052) developed by Anacor Pharmaceutical that are now in Phase II clinical trials [201].

Based on these described properties, boron has significant potential in the design of therapeutic agents. This section will review the importance of boron-based compounds in various therapeutic areas as illustrated in Figure 12.

Anticancer activity

Chemical & pro-drug therapy—Bortezomib (PS-341) (**26**; Figure 13), trade name Velcade, is a boron compound from Millennium Pharmaceuticals (now Takeda Pharmaceutical) and is the first proteasome inhibitor approved for the treatment of newly diagnosed MM, relapsed/refractory MM and mantle cell lymphoma [58–60]. It is a dipeptide boronic acid derivative that contains pyrazinoic acid, phenylalanine and leucine with boronic acid. Besides MM and mantle cell lymphoma, this compound alone, or in combination, has been investigated for the treatment of solid tumors such as carcinomas of the breast [61,62], lung [63,64], colon [65,66], prostate [67,68] and pancreas [69]. Bortezomib exhibits its anticancer activity by reversibly and specifically inhibiting the threonine residue of the 26S proteasome, which has a key role in regulating protein degradation in a controlled manner. Inhibition of this enzyme causes an imbalance between the inhibitory and stimulatory proteins involved in the cell cycle, thereby causing cell death [70,71]. Bortezomib has been reported to inhibit nuclear factor- κ B, and to induce cell cycle blockade and apoptosis *in vitro*, as well as tumor growth inhibition *in vivo* [72]. Moreover, intracellular calcium metabolism dys-regulation, which causes caspase activation and apoptosis, is also responsible for the anticancer activity of bortezomib [73].

Talabostat (PT100) **27**, a methanesulfonate salt of L-valinyl-L-boroproline, is a specific inhibitor of DPP4 including tumor associated FAP. In addition, it enhances the tumor-specific T-cell immunity by increasing the production of cytokines and chemokines, as well as stimulating the T-cell-independent antitumor activity of macrophages, neutrophils and natural killer cells [74]. It has entered clinical trials for the treatment of non-small-cell lung cancer as a drug combination with docetaxel [75].

Limitations of bortezomib, including limited activity in solid tumors [76], side effects such as the emergence of reversible peripheral neuropathy [77] and the invasive intravenous route of administration, have prompted researchers to develop various second generation proteasome inhibitors for anti-cancer activity [78]. Peptide boronic acid derivatives **28** (MLN9708) is easily hydrolyzed to the active form **29** (MLN2238) in plasma (Figure 14). MLN2238 is an N-capped dipeptidyl leucine boronic acid. It is an orally bioavailable compound that reversibly inhibits the chymotrypsin-like subunit of 26S proteasome. This compound can avoid the invasive intravenous delivery that is one of the drawbacks of bortezomib. It is in Phase I clinical studies for patients with lymphoma and hematologic malignancies [79].

Similarly, CEP-18770 is a P2 threonine boronic acid that reversibly inhibits the chymotrypsin-like activity of the proteasome (**30**; Figure 14). It has demonstrated complete

tumor regression in MM xenografts and at the same time it has demonstrated diminished cytotoxicity against a variety of normal human cells [80]. It is in phase I clinical study for patients with advanced solid tumors or non-Hodgkin's lymphoma.

Study of the tripeptide boronic acid derivative **31** (where P, P² and P³ refers to various substituents) led to the discovery of *N*-(2-pyrazinecarbonyl)-L-leucine-L-(2-naphthyl)-alanine-L-leucine boronic acid **32**, a potent proteasome inhibitor (Figure 15). It has an IC₅₀ value of 0.079 nM and is twofold more active than bortezomib with an IC₅₀ value of 0.161 nM. Hydrophobic substituents rather than hydrophilic substituents at P² or P³ are found to be beneficial for the cytotoxic activity of the compounds [81].

Similarly, boronic acid derivatives **33–36** have demonstrated promising proteasome inhibitory activity. These compounds were developed on the basis of **33** (TP-110) as a lead compound (Figure 15). Compounds **33–36** have demonstrated good chymotryptic inhibitory activity, with the Leuboronate **36** being the most potent, having an IC₅₀ value even lower than that of bortezomib [82].

Boronic acid derivatives of chalcones were observed to exhibit anticancer activity through the inhibition of the cellular proteasome. Among the tested boronic acid chalcone derivatives, 3,5-*bis*-(4-boronic acid-benzylidene)-1-methyl-piperidin-4-one (AM114) (**37**; Figure 16) demonstrated the most potent growth inhibition activity. AM114 induces a significant cytotoxic effect through inhibition of the cellular proteasome [83].

Recently, various boron-based derivatives of 4-hydroxytamoxifen **38–40** were studied for the treatment of tamoxifen-resistant breast cancer (Figure 17). These three prodrugs share common boron-aryl carbon bonds and are converted into the active form 4-hydroxytamoxifen under favorable oxidative conditions in breast cancer. These bioisosteres were found to inhibit the growth of two breast cancer cell lines, MCF-7 and T47D, to a comparable or greater extent than that achieved by 4-hydroxytamoxifen [84].

Boronic acid-based compounds bearing an α -amino acid moiety have been developed for the study of HDAC inhibition. Inhibition of HDACs causes histone hyperacetylation and leads to transcriptional activation of various genes that are associated with growth arrest and apoptosis in tumor cells [85,86]. Compounds **41–43** containing boronic acid (Figure 18) were found to be potent HDAC inhibitors. Immunoblotting data suggest that inhibition of HDACs was responsible for the cancer cell growth inhibitory activity of these compounds. Molecular modeling revealed that the hydrated boronic acid moiety of these compounds interacts with the zinc ion, Tyr residue, and His residue in the active site of the HDACs [87].

Chemical library screening led to the discovery of thiazolidinediones as selective inhibitors of autotaxin (ATX) mediated lipid mediator lysophosphatidic acid (LPA) production both *in vitro* and *in vivo*. ATX is responsible for the production of LPA, which has a role in stimulation of migration, proliferation and survival of cells. ATX is associated with vascular development and is over-expressed in various cancers [88–90] and for these reasons, it is an attractive target for cancer therapy. Thiazolidinediones were optimized to obtain the boronic-acid based compound HA130 (**44**; Figure 19) that demonstrated a 100-fold increase in inhibitory activity. Administration of this compound to mice rapidly decreased the LPA level in plasma [91].

Boronic acid derivatives **45** and **46** of combretastatins A-4 (Figure 20) have demonstrated significant cell growth inhibition. The hydroxy group on the aromatic ring B of combretastatin A-4 was replaced with the boronic acid to produce compounds **45** and **46**. These compounds significantly inhibit tubulin polymerization [92].

Our research group has also reported the synthesis of boron-containing 1,2,4-oxadiazoles **47** and **48** as analogs of combretastatins (Figure 20) [93]. The biological studies evaluating these compounds as anti-angiogenic agents and as hypoxia-inducible factor (HIF) inhibitors are currently in progress.

Phenoxyacetanilide boronic-derivative GN26361 (**49**; Figure 21) demonstrated potent inhibitory activity against HIF-1 α accumulation under hypoxic conditions. It also inhibited hypoxia-induced HIF-1 α transcriptional activity in HeLa cells, as well as VEGF mRNA expression without interfering with HIF-1 α mRNA [94]. It contains not only boronic acid, but also a carborane ring on the aromatic rings.

Several boron-based ROS activated prodrugs are under investigation to target cancer cells. The design of ROS-activated prodrugs requires three components; a trigger, a linker and an effector. Trigger moieties are designed to accept ROS, which can forward the reaction to release the effector. Various prodrugs with a boronic acid moiety as a trigger have been reported. As the tumor cell consists of higher concentration of H₂O₂ and boronic acid is selective to H₂O₂, the use of boron-based prodrugs has provided promising hope for the development of anti-cancer drugs [95]. This is a frontier area for cancer drug discovery and also diseases modulated by overproducing ROS. The nitrogen mustard prodrugs **50** and **51** [96], and quinone methide prodrug **52** [97] (Figure 22) are some of examples that are reported to possess ROS activated anticancer activity.

Boron-based compounds **53** [98] and **54** (BE360) [99] have been reported for their potent estrogen receptor agonistic activity (Figure 23). Compound **54** (BE360) acts as a selective estrogen receptor modulator for bone, indicating the possibility of a new therapy option for osteoporosis.

Peptidyl boronic acid derivatives were reported to inhibit serine protease prostate-specific antigen. These inhibitors are intended for the development of prostate cancer-targeted therapies and imaging agents [100].

Moreover, boron-based compounds have been used in boron neutron capture therapy (BNCT) for anticancer purposes. There are many excellent review articles available in this field [101–104], and this is beyond the scope of this review article. However, here the BNCT field is briefly introduced to readers.

BNCT—BNCT attempts to exploit nuclear capture and fission reactions that occur when a non-radioactive constituent of natural elemental boron (¹⁰B) is irradiated with low energy (0.025 eV) thermal neutrons, resulting in the production of high linear energy transfer alpha particles (⁴He) and recoiling ⁷Li nuclei. High linear energy transfer particles can travel limited distances in tissue (5–9 μ m), so that the destructive effects of these high-energy particles is limited to boron-containing cells, providing a way to selectively destroy malignant cells and spare adjacent normal cells. Clinical interest in BNCT has focused mainly on the treatment of high-grade gliomas, recurrent tumors of head and neck, melanoma and hepatic metastasis. Two boron drugs have been used clinically (Figure 24), a dihydroxyboryl derivative of phenylalanine, boronophenylalanine **55**, and sodium borocaptate (Na₂B₁₂H₁₁SH) **56** [101–104].

Intensive investigation is ongoing to improve the selectivity of boron delivery agents and has led to the discovery of various low- or high-molecular-weight agents with stable boron groups or clusters attached via a hydrolytically stable linkage to a tumor-targeting moiety. Compounds **57** (GB-10), N5 (**58**), N5-2OH (**59**), and boron-containing porphyrins **60**

(H₂DGP) and dequalinium derivatives **61** are some of examples of low-molecular-weight boron-based compounds studied for BNCT (Figure 25) [105–108].

Similarly, various boronated unnatural cyclic amino acids have been studied as delivery agents for neutron capture therapy. In one study, *cis* and *trans* isomers of a boronated unnatural amino acid 1-amino-3-boronocyclopentane-carboxylic acid were tested in a mouse model. It was found that the racemic mixtures of the 1-amino-3-boronocyclopentanecarboxylic acid were able to deliver boron to B16 melanoma cells both *in vitro* and *in vivo* as comparable to boronophenylalanine [109].

The possible use of boron nitride nanotubes (BNNT) as boron carrier agents for BNCT is also being tested. BNNTs are structurally similar to carbon nanotubes with carbon atoms entirely substituted with boron and nitrogen. Boron nitrides contain boron and nitrogen atoms in equal numbers and are able to exist in various crystalline forms [110]. The folate-functionalized BNNTs can be selectively uptaken by glioblastoma multiforme cells but not by normal human fibroblasts. This indicates that folate-functionalized BNNTs have potential to be used as boron delivery agents to malignant glioblastoma cells [111]. There remains a considerable opportunity to explore the functionalized BNNTs as boron-target agents in BNCT. The presence of BNNTs in an irreversible lethal electroporation assay was found to increase tumor cell death, which indicates potential use of BNNTs as therapeutics. Irreversible lethal electroporation is a promising clinical method for cancer treatment where the short pulses of high amplitude static electric fields are used to create irreversible pores in the cell membrane. It is believed that BNNTs locally increase the electric field of cells exposed to a static electrical field, resulting in cell death [112].

Antiviral activity

Anacor Pharmaceuticals has studied various boron-based compounds for the development of antiviral agents against hepatitis C virus (HCV). This is a disease that affects more than 170 million people worldwide and is the major cause of chronic liver disease, which can lead to cirrhosis, carcinoma and liver failure [113–115]. As HCV NS3/4A protease is vital for replication of the HCV virus, it has emerged as a good therapeutic target for the development of anti-HCV agents [116,117]. A novel series of P2–P4 macrocyclic HCV NS3/4A protease inhibitors with α -amino cyclic boronates at the P1 site were designed and synthesized. Compounds with cyclic structures have demonstrated better potency in cell-based replicon activity assays compared with linear analogs. Compounds **62** and **63** (Figure 26) are the most promising agents in the series. x-ray crystallography of compound **62** with NS3 protease reveals that Ser-139 in the enzyme active site traps boron in the P1 region of **62**, which confirms the importance of the boron moiety for activity [118].

Further work on macrocyclic HCV NS3/4A protease inhibitors has led to the development of several boron-based compounds **64–68** (Figure 27). These were developed by the optimization of danoprevir ITMN-191, which is in advanced clinical trials [119,120]. The cyclopropyl acylsulfonamide of danoprevir was replaced with acylsulfamoyl benzoxaborole moiety to obtain the boron-containing derivatives. The unoptimized P1–P3 and P2–P4 macrocyclic inhibitors were equipotent in an enzyme assay and somewhat less potent in replicon assays, compared with danoprevir [121].

Similarly, various boron-based derivatives **69–72** were developed by incorporating an α -amino oxaborole moiety at the P1 position of several NS3 protease inhibitor templates along with VX-950 (telaprevir) and SCH-503034 (boceprevir) templates (Figure 28). Compound **71** was found to be the most potent [122]. In addition, exploration of the boceprevir template has resulted in the discovery of boronic acid derivative **73**, which demonstrated improved activity in the picomolar range ($K_i = 200$ pM) [123].

For the development of an anti-HIV drug, substituted analogs of 3-acetyl-4-hydroxy-2-pyranones and their difluoridoborate complexes were developed as HIV-1 integrase inhibitors (Figure 29). Some of the difluoridoborate complexes of the pyranones were found to be more potent than uncomplexed pyranones, with compound **74** being the most potent [124].

Antifungal activity

Anacor Pharmaceuticals developed several derivatives of dihydrobenzoxaborole bearing aryl, heteroaryl or vinyl substituents [201]. Screening of the library revealed these dihydrobenzoxaboroles had good antifungal activity against *Candida albicans*. Further screening against yeast, filamentous fungi and dermatophytes demonstrated that these compounds had broad-spectrum activity against all these fungal pathogens including the major dermatophytes that cause onychomycosis, *Trichophyton rubrum* and *Trichophyton mentagrophytes*. An investigation for efficacious therapy to treat onychomycosis, a fungal infection of the toe and fingernails, led to the discovery of 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole **75** (AN2690 or tavorole), which is currently in Phase III clinical trials for onychomycosis topical treatment (Figure 30). It was demonstrated that the compound forms a covalent adduct with the 3' adenosine of tRNA^{leu} and inhibits leucyl-tRNA synthetase. Another candidate, **76** (AN2718), has recently completed a Phase I clinical trial for the treatment of skin and nail fungal infections [125–127].

In another study, boron-containing thiosemicarbazones (Figure 31) were investigated for their potential antifungal activity against four fungi: *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans*, and *Saccharomyces cerevisiae*, using Amphotericin B as a control. Among the reported compounds, **77–79** demonstrated appreciable activity [128].

Antibacterial activity

β -lactam antibiotics are among the most frequently prescribed antibiotics used in the treatment of bacterial infections. Hydrolysis of β -lactam antibiotics by β -lactamases is the most common mechanism of resistance for this class of antibacterial agents in clinically important Gram-negative bacteria. The use of the three classical β -lactamase inhibitors (clavulanic acid, tazobactam and sulbactam) in combination with β -lactam antibacterials is currently the most successful strategy to combat β -lactamase-mediated resistance. The molecular classification of β -lactamase is based on the amino acid sequence and divides β -lactamases into class A, C and D enzymes that utilize serine for β -lactam hydrolysis, and class B metalloenzymes that require divalent zinc ions for substrate hydrolysis. Since the clinically relevant inhibitors are especially active on class A enzymes, there is a need for broad-spectrum inhibitors [129–131].

Boronic acids have proven to be effective inhibitors of β -lactamases (Figure 32). New AmpC β -lactamase inhibitors **80–82** were designed to gain interactions with highly conserved residues, such as Asn343, and to bind more tightly to the enzyme [132]. A new group of class A extended-spectrum β -lactamases, called CTX-M enzymes, has emerged worldwide and is now the most frequently observed extended-spectrum β -lactamases in several areas. CTX-M enzymes hydrolyze not only the penicillins but also the first-, second- and third-generation cephalosporins, yet there are few effective inhibitors. Compound **83**, a ceftazidime-like boronic acid compound, binds to CTX-M-16 with a K_i value of 4 nM [133].

Both β -lactamase inhibitors and the β -lactamase-resistant antibiotics currently in use are themselves β -lactams. Bacteria respond to these compounds by expressing variant enzymes that are resistant to inhibition or that inactivate β -lactamase-resistant antibiotics. In an effort to identify non- β -lactam-based β -lactamase inhibitors, several boronic acid-based inhibitors

were modeled and were ultimately tested for β -lactamase inhibition. Benzo[b] thiophene-2-boronic acid **84** was found to be a potent non- β -lactam-based class C β -lactamase inhibitor, with an affinity for *Escherichia coli* AmpC of 27 nM [134].

A number of boron-containing compounds possess strong antibacterial activity specifically against the enteric group of Gram-negative bacteria. These compounds comprise two distinct chemical groups, with disubstituted boronic acids or a diazaborine ring (Figure 32). The most active compounds were **85** (ICI 75,188) and **86** (ICI 78,911), which inhibited the growth of *E. coli* 198 by 50% at 0.28 μ M and 3.1 μ M respectively [135].

The Biomedical Advanced Research and Development Authority, a US government preparedness organization, awarded GlaxoSmith-Kline US\$38.5 million over 2 years towards development of GSK2251052, a molecule co-developed with Anacor Pharma several years previously, as a counter-bioterrorism agent. The full funding amount may rise to \$94 million, which is dependent on the Biomedical Advanced Research and Development Authority's budget. The goal here is to develop GSK '052, a new antibiotic active against especially vicious and virulent Gram-negative bacteria, such as the classic foes plague (*Yersinia pestis*) or anthrax (*Bacillus anthracis*) [202].

Boronic acids have also been developed as inhibitors of the mechanistically related serine β -lactamases and serine proteases. However, they have not been explored extensively as PBP inhibitors. 3-(dihydroxyboryl)benzoic acid analogue **87** containing an amide substituent in the *meta*, but not *ortho* position, were up to 17-fold more potent inhibitors of the R39 PBP and displayed some activity against other PBPs. These compounds may be useful for the development of even more potent boronic acid based PBP inhibitors with a broad spectrum of antibacterial activity [136]. In another study, a number of acylaminomethylboronic acids as inhibitors of PBPs from different classes were synthesized and the (2-nitrobenzamido) methylboronic acid **88** (Figure 32) was identified as a good inhibitor of PBPs of class A, B and C [137]. Further optimization of these compounds may be worthwhile for the development of more potent boronic acid based inhibitors with a broad spectrum of antibacterial activity.

Miscellaneous

The boron-based compound PHX1149 (dutogliptin) (**89**; Figure 33), a low-molecular-weight and orally bioavailable selective DPP4 inhibitor, has been investigated as an antidiabetic agent [138,139]. It is currently in clinical trials for the treatment of Type 2 diabetes mellitus.

Thrombin is a trypsin-like serine protease that plays a central role in hemostasis and induces platelet aggregation and secretion. Compounds that inhibit thrombin are effective inhibitors of blood clotting. Compound **90** (TRI50c) (Figure 33) proved to be a highly potent ($K_i = 22$ nM) and selective competitive inhibitor of thrombin with high efficacy in animal models of venous and arterial thrombosis and minimal effect on bleeding. Two salts/esters of TRI50c, compounds TGN-255 (parenteral formulation) and TGN-167 (oral formulation), from Trigen pharmaceutical are in Phase III clinical trials as anticoagulants [140,141].

A boron-based compound **91** (SCYX-7158), (Figure 33) has demonstrated potent activity against strains of *Trypanosoma brucei*, including *T.b. rhodesiense* and *T.b. gambiense*. In animal models of human African trypanosomiasis, SCYX-7158 demonstrated significant activity, including cure of a CNS *T. brucei* infection following 7 days of administration at a dose of 25 mg/kg perorally. The *in vivo* study reveals that this compound is able to cross the blood-brain barrier to obtain a therapeutically relevant concentration in the brain and cerebrospinal fluid of rodents [142]. It is in a clinical trial for the treatment of human African trypanosomiasis.

In one study, organotrifluoroborate salt **92** (Figure 34) was studied for analgesic activity. The compound, when administered orally to mice, was observed to reduce the peritoneovisceral pain induced by acetic acid [143]. Moreover, compounds **93–95**, organotrifluoroborate salts (Figure 34), were reported to inhibit the sodium/iodide symporter glycoprotein. The sodium/iodide symporter facilitates the accumulation of iodide into thyroid follicular cells responsible for the biosynthesis of iodinated hormones T4 and T3. Among them, **95** was the most potent compound [144]. This is an emerging area of research as this type of compound (organotrifluoroborate salts) could increase water solubility and cross cell membranes for potential use as novel therapeutic agents. However, there are currently limited reports available in this literature.

Cancer and neurodisorder diseases are heterogeneous in nature, as a variety of factors contribute to progression of the disease. Therefore, multitarget therapies may prove to be more effective than single-target therapies. For multi-target therapy, rather than developing multiple drugs each having a different target, we are developing single drugs with multiple targets. For this drug development process (single drug, multitarget), we are focused on diseases modulated by retinoic acid signaling pathways. For proof of concept, we have developed novel receptor specific boron-containing retinoid agonists and antagonists considering these compounds as novel therapeutic agents for different diseases areas [145–148].

Boron in drug delivery

BNNTs, structural analogues of carbon nanotubes in nature, because of their unique 1D hollow nanostructure (Figure 35), are being investigated for the possibility of developing a new class of nanodevices for cell therapy or other medical applications [149]. It has been demonstrated that BNNTs can deliver DNA oligomers to the interior of cells with no cytotoxicity, supporting the idea that BNNTs can be used as biological probes and in biomaterials [150].

Future perspective

Since the approval of bortezomib in 2003, as a proteasome inhibitor for the treatment of MM myeloma and non-Hodgkin's lymphoma, medicinal chemists are rapidly adapting the idea of boron-containing compounds as therapeutics. Numerous compounds have been synthesized with boron demonstrating a wide range of biological activities (including anticancer activity). Boron is a versatile element in chemical synthesis, and has found a range of applications from a material in organic synthesis to an approved drug component in medicine. Several boron-containing compounds are in the pipeline, such as AN2690 and AN2718 as antifungal agents, Januvia, Talabostat (PT100) and PHX1149 as DPP4 inhibitors, AN2728 for the treatment of psoriasis, AN0128 for the treatment of periodontal disease and acne, and TRI50c as an anticoagulant. The growing interest in boron chemistry is expected to aid in further expanding this field and lead to optimization of the pathways for synthesis and new paradigms for the development of potent therapeutic agents. The free p-orbital of the boron atom displays unique characteristics in enzyme inhibition and many pharmaceutical companies are exploiting this phenomenon to discover new therapeutic agents. In addition to the role that boron-containing organic compounds and potassium trifluoroborate salts will play in drug discovery, these compounds also have a role as new tools for molecular imaging, biomarker discovery, stem cell biology and chemical biology. Typically, in biomedical research steps towards curing a disease comprise target identification, target validation, development of targeted therapeutics and drug delivery. This article clearly demonstrates that boron-containing compounds have been used in all these four processes of drug discovery to cure disease. In the future, it is anticipated that

boron chemistry and compounds will be fully exploited in the field of biomedical research to cure many deadly diseases. Boron-based compounds will be more useful for the treatment of brain cancer as these compounds are able to cross the blood–brain barrier. Perhaps, in the future, biologists will discover boron channels in neurons. There is a new horizon waiting for boron chemists to develop new imaging and therapeutic agents for different neurodegenerative diseases.

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BC Das and S Das dedicate this review article to their mentor George W Kabalka, University of Tennessee, TN, USA.

Key Terms

Organoborane	Derivative of a borane (boron hydride) in which one or more hydrogen atoms have been replaced by functional groups
Chemical genetics	Phenotype-driven screening process to identify chemicals that produce a desired effect in living cells or animals
Activity-based protein profiling	Functional proteomic technology that utilizes active site-directed probes to profile the functional state of enzymes in whole proteomes
Bioorthogonal chemistry	Chemical reactions that can occur in biological solutions and under physiological conditions, which are not affected by the complex mixture of small molecules and proteins of biological solutions

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Executive summary

Target identification & validation

- The boron-based fluorophore, dipyrromethene boron difluoride is one of the most common fluorophores used for fluorescently labeled activity-based probe profiling proteomics to identify new targets.
- Boronate affinity chromatography is used to identify biomolecules, such as carbohydrates, glycoproteins, nucleotides and nucleosides, by interaction of a boronic acid group (ligand) with two *cis*-hydroxyl groups that are present at the adjacent carbon atoms in coplanar configuration.
- The balance between the reactive oxygen species (ROS) generation and elimination is critical as excess ROS can damage cellular lipids, proteins, or DNA inhibiting their normal functions.
- Molecular imaging techniques have become indispensable for disease-screening programs, staging, diagnosis, early-response measurement and surveillance during follow-up.
- The use of organoboron to capture aqueous [¹⁸F] fluoride in the form of an aryltrifluoroborate for ¹⁸F-labeling in a rapid, one-step synthesis under acidic aqueous conditions is a novel technology to develop PET based radiopharmaceuticals.

Therapeutic applications

- Bortezomib (PS-341) trade name Velcade[®], a boron compound from Millenium Pharmaceuticals, is the first proteasome inhibitor approved for the treatment of newly diagnosed multiple myeloma and relapsed/refractory multiple myeloma and mantle cell lymphoma.
- Boronic acid derivatives of chalcones were found to exhibit anticancer activity through the inhibition of cellular proteasome.
- Boron-based derivatives of 4-hydroxytamoxifen were studied for the treatment of tamoxifen-resistant breast cancer.
- Boronic acid-based compounds bearing an α -amino acid moiety have been developed for the study of HDAC inhibition.
- Boronic acid-based thiazolidinediones compounds are novel autotaxin inhibitors.
- Boronic acid derivatives of combretastatins A-4 have demonstrated significant cell growth inhibition.
- Synthesis of boron-containing 1,2,4-oxadiazoles analogs of combretastatins has been reported. Evaluating biological activity of these compounds as anti-angiogenic agents and as HIF inhibitors is in progress.
- As tumor cells contain higher concentration of H₂O₂ and boronic acid is selective to H₂O₂, so several boron-based ROS activated prodrugs are under investigation to target cancer cells.
- Boron neutron capture therapy is a binary therapy approach for the treatment of cancer.

- Clinical interest in boron neutron capture therapy has focused mainly on the treatment of high-grade gliomas, recurrent tumors of head and neck, melanoma and hepatic metastasis.
- Anacor Pharmaceutical has studied various boron-based compounds for the development of antiviral agents against hepatitis C virus.
- 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690 or tavaborole), is currently in Phase III clinical trials for onychomycosis topical treatment.
- Boronic acids have proven to be the effective inhibitors of β -lactamases.
- A number of boron-containing compounds possess strong antibacterial activity specifically against the enteric group of Gram-negative bacteria.
- The boron-based compound PHX1149 (dutogliptin), a low-molecular-weight and orally bioavailable selective DPP4 inhibitor, has been investigated as an antidiabetic agent, and is currently in clinical trials for the treatment of Type 2 diabetes mellitus.
- Organotrifluoroborate was studied for analgesic activity and also inhibits the sodium/iodide symporter glycoprotein.

Boron in drug delivery

- Boron nitride nanotubes have promise as new nanotechnology drug-delivery systems.

Future perspective

- In the future, boron-containing organic compounds and potassium trifluoroborate salts will play a significant role in drug discovery, drug delivery and in the development of new organic reactions for their synthesis. In addition, these compounds have a role as new tools for molecular imaging, biomarker discovery, drug discovery, stem cell biology and chemical biology.

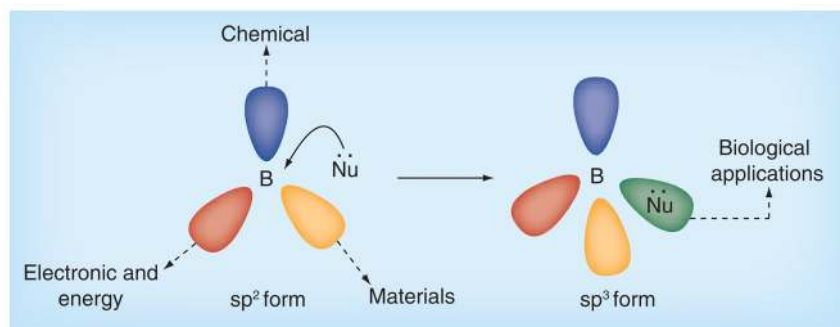


Figure 1.
Configurational modifications of boron.

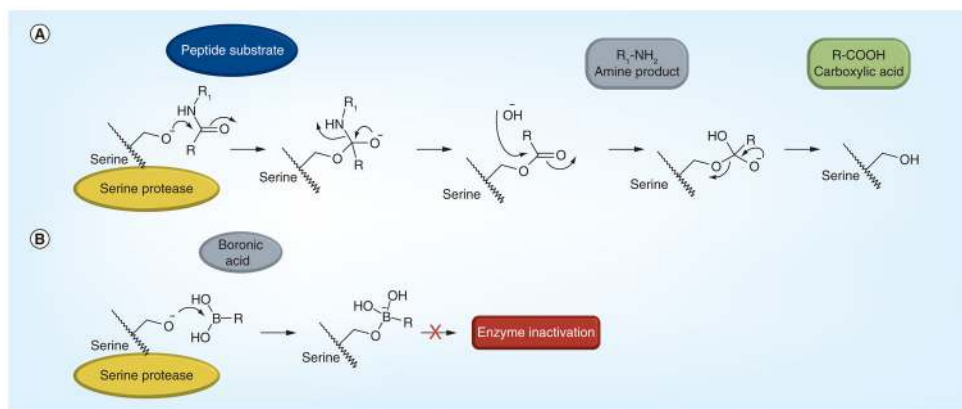


Figure 2. Possible mechanism of action of boron-based compounds for enzyme inhibition
(A) General mechanism of action of serine protease. (B) Boronic acid forms a transition state analog thereby causing inactivation of enzyme.

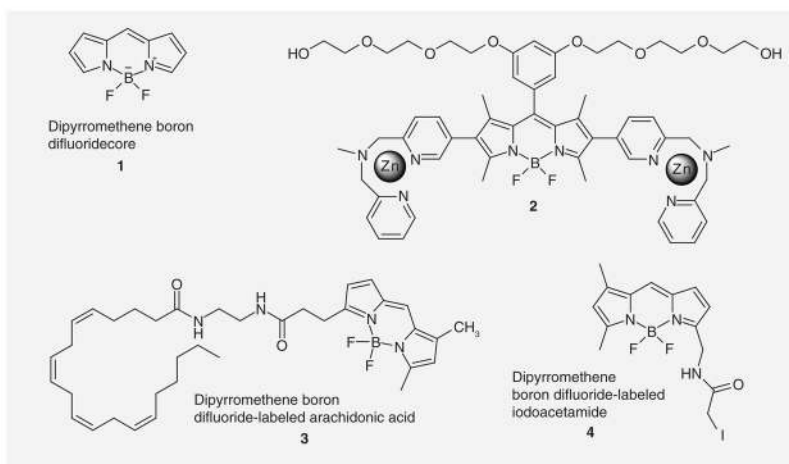


Figure 3.
Dipyrromethene boron difluoride-labeled fluorescent probes.

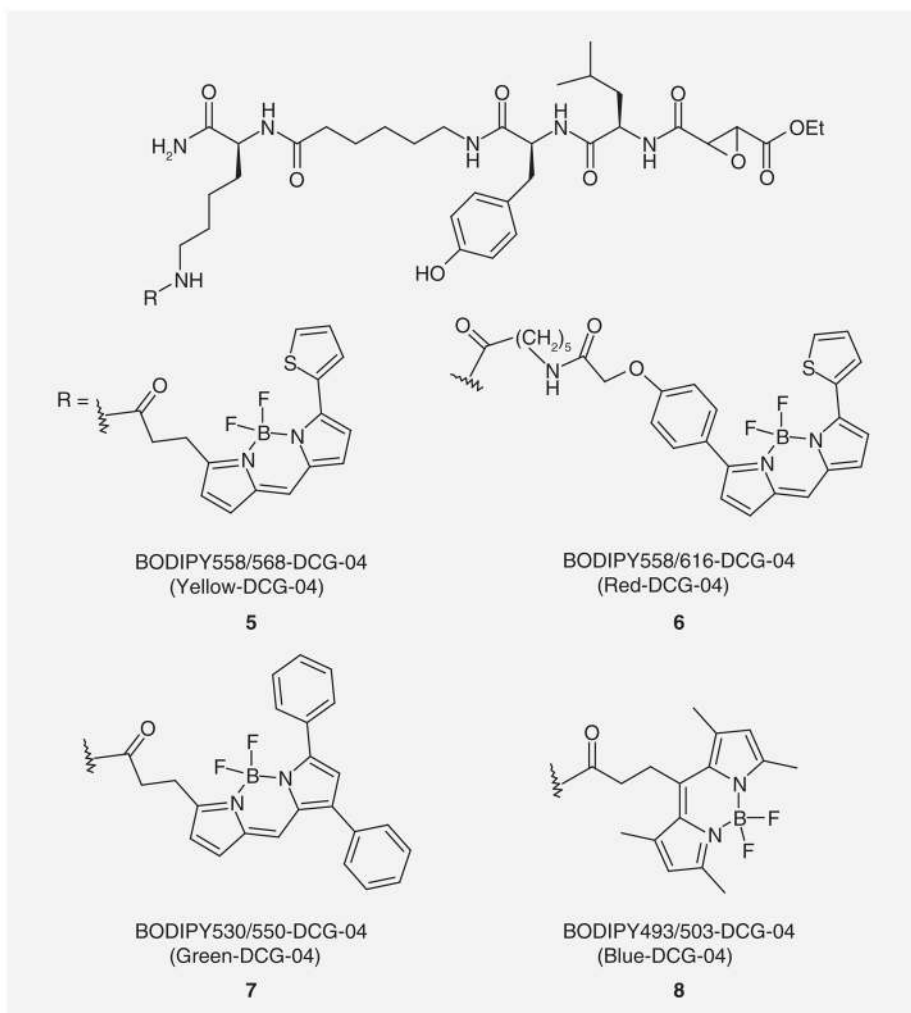


Figure 4. Probes for *in vivo* labeling of cysteine cathepsins
BODIPY: Dipyrrromethene boron difluoride.

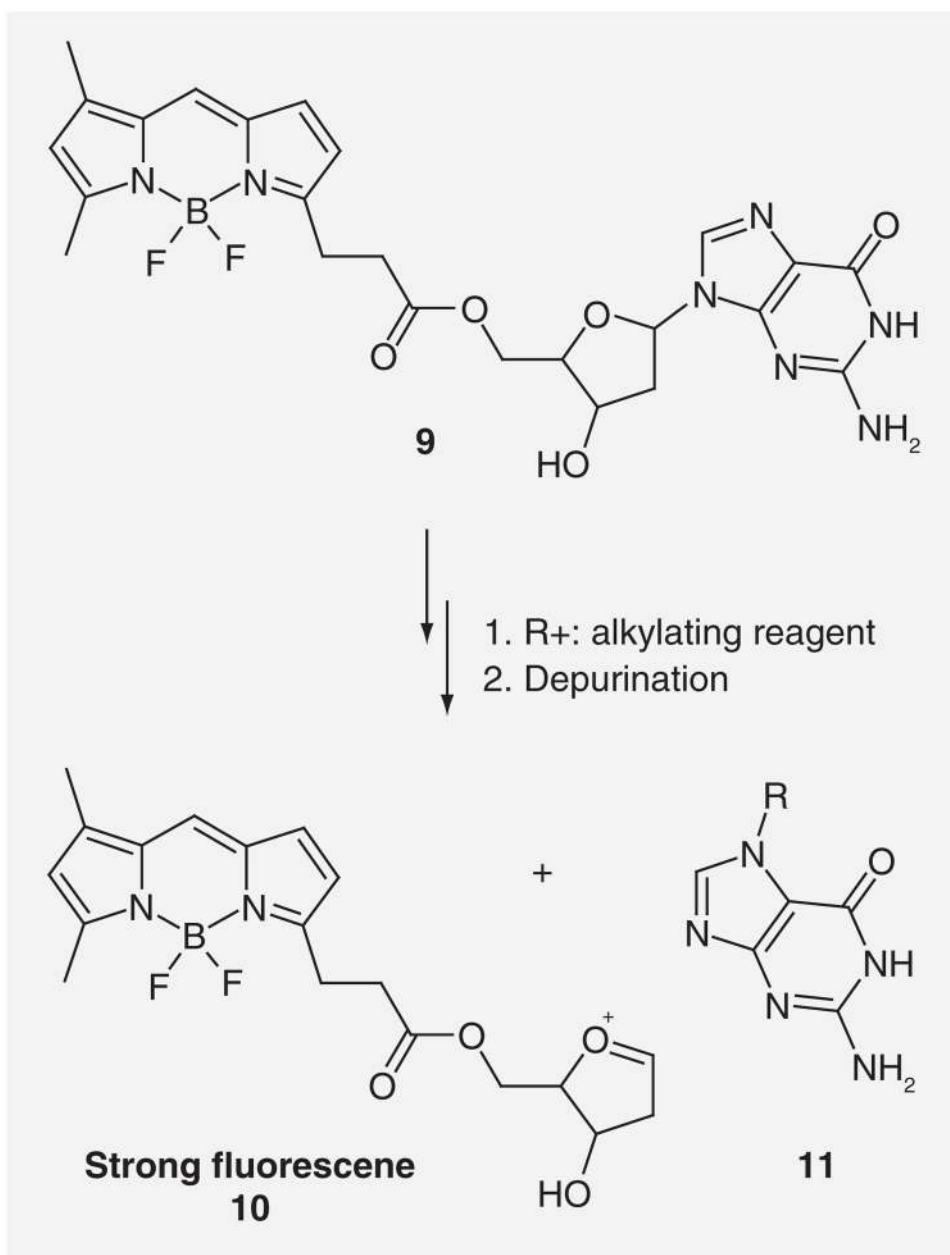


Figure 5. Conversion of the dipyrromethene boron difluoride-2'-deoxyguanosine derivative to give strong fluorescence.

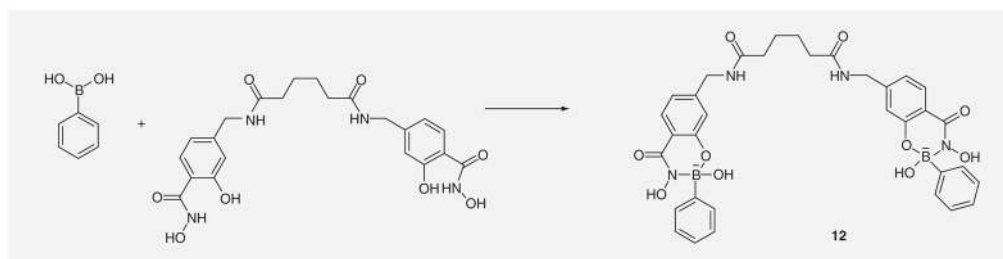


Figure 6.
Synthesis of a highly stable boronate ester.

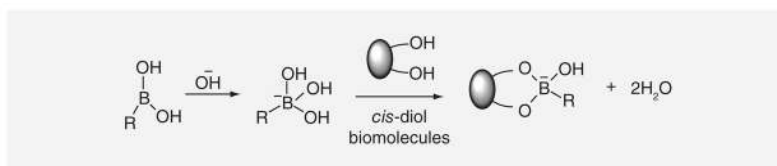


Figure 7.
Process of diol–boronate complex formation.

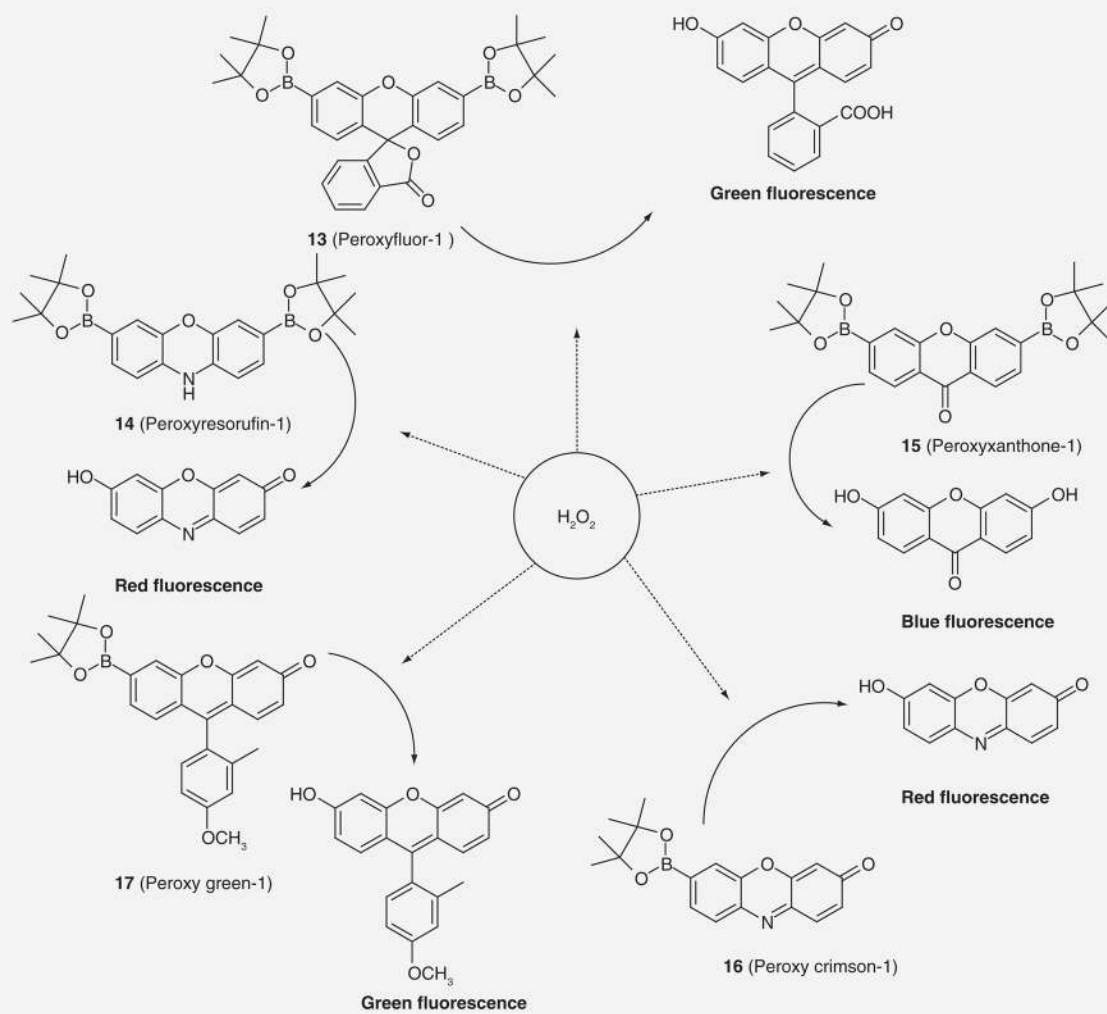


Figure 8. Boronate-based probes give colored and fluorescent product in the presence of H_2O_2 .

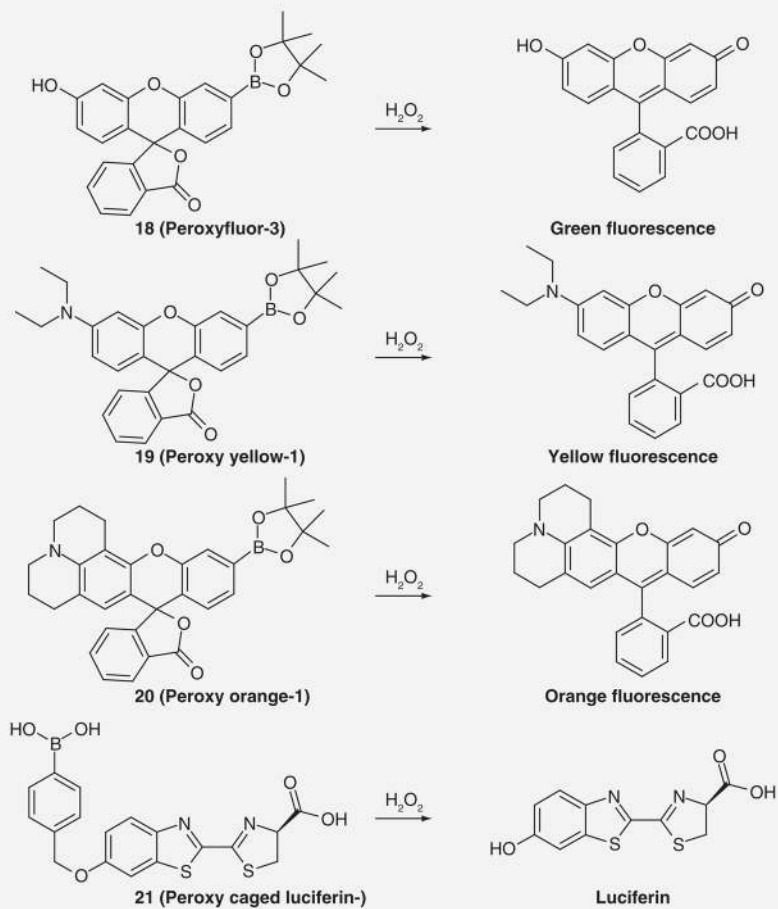


Figure 9. Monoboronate probes give colored and fluorescent product in the presence of H_2O_2 .

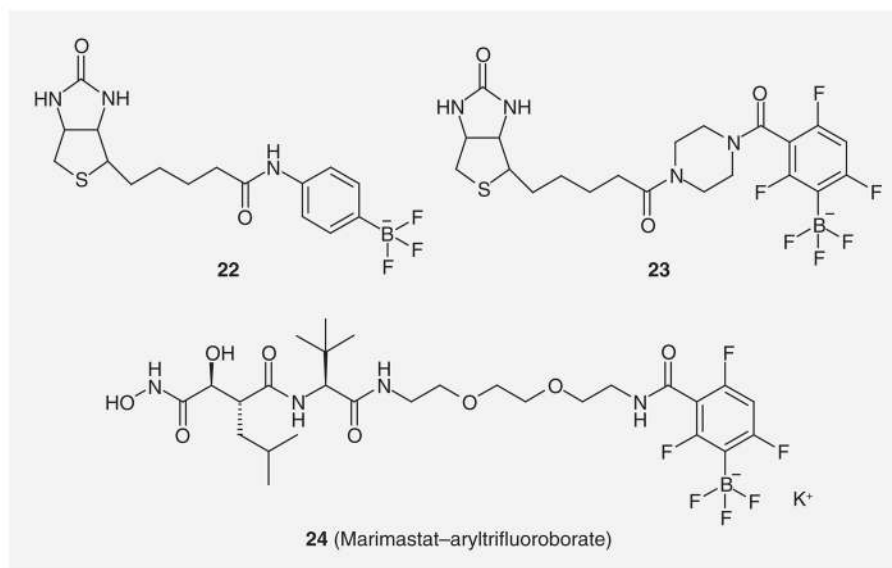


Figure 10.
Aryltrifluoroborates for ^{18}F labeling.

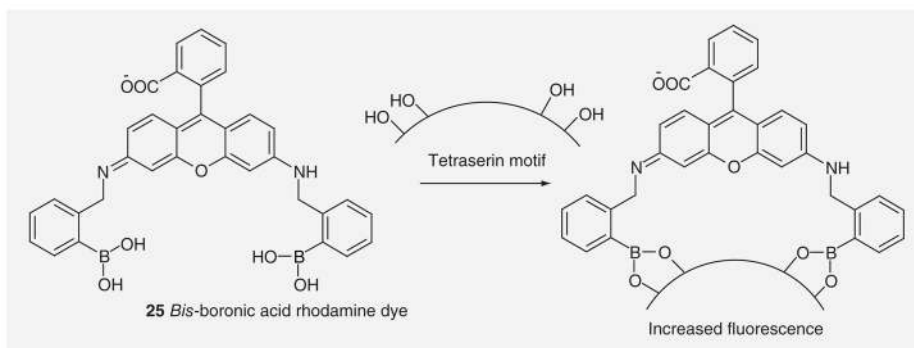


Figure 11.
Binding of *bis*-boronic acid rhodamine dye with tetraserin motifs.

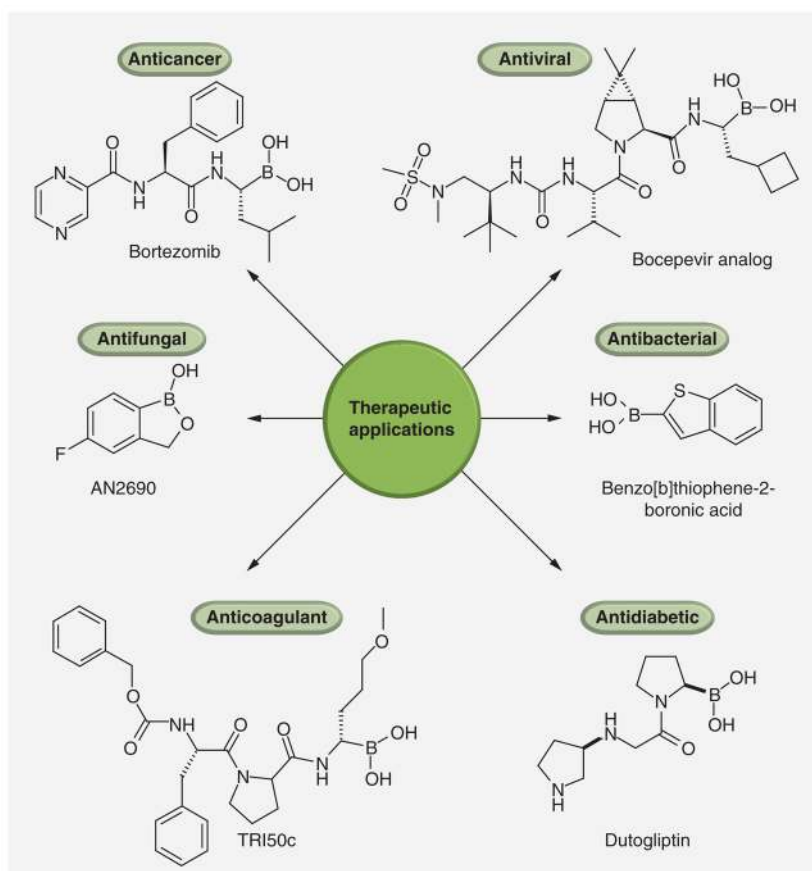


Figure 12.
Boronic acid-containing therapeutic agents.

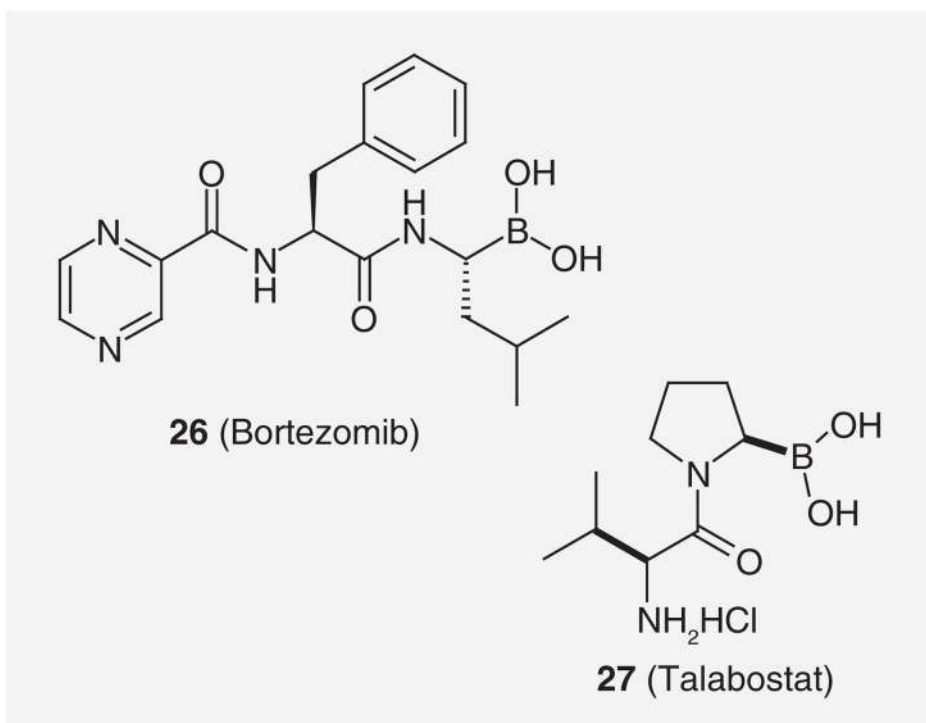


Figure 13.
Bortezomib and talabostat.

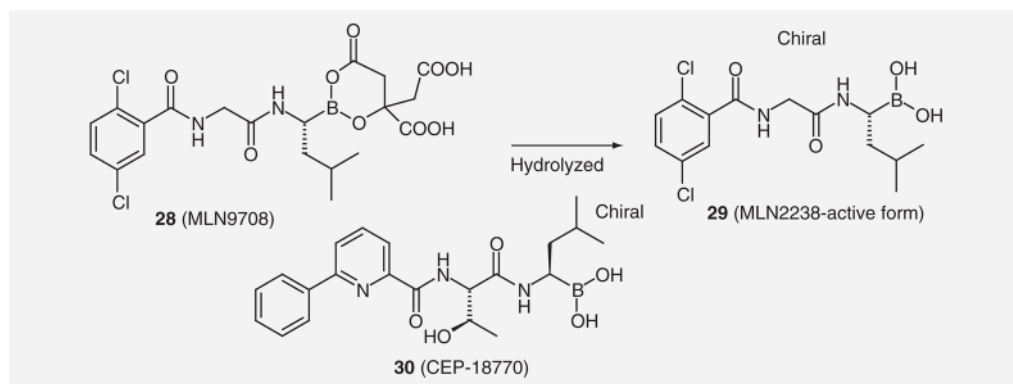


Figure 14.
Bortezomib derivatives as second-generation proteasome inhibitors.

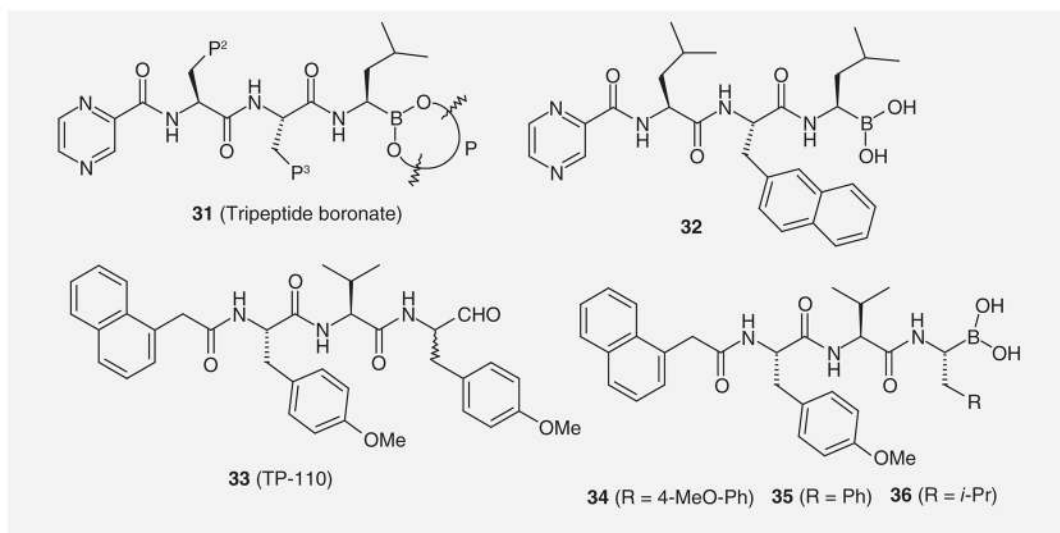


Figure 15.
Tripeptide boronic acid derivatives as promising proteasome inhibitors.

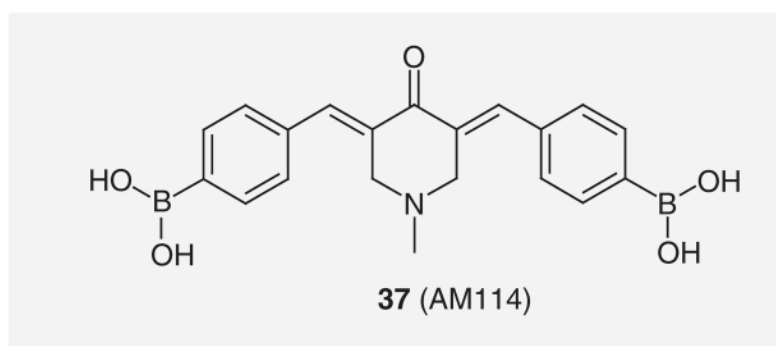


Figure 16.
Boron-based chalcone as an anticancer agent.

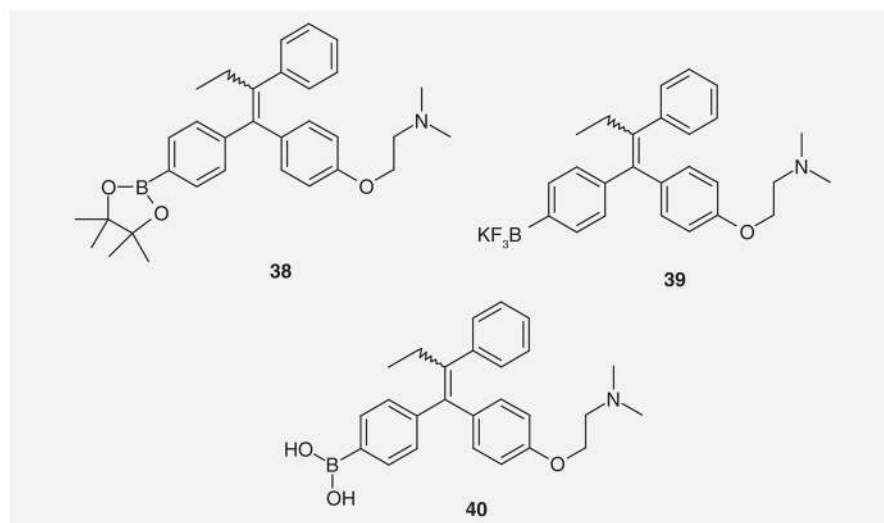


Figure 17.
4-hydroxytamoxifen derivatives with boron substituents.

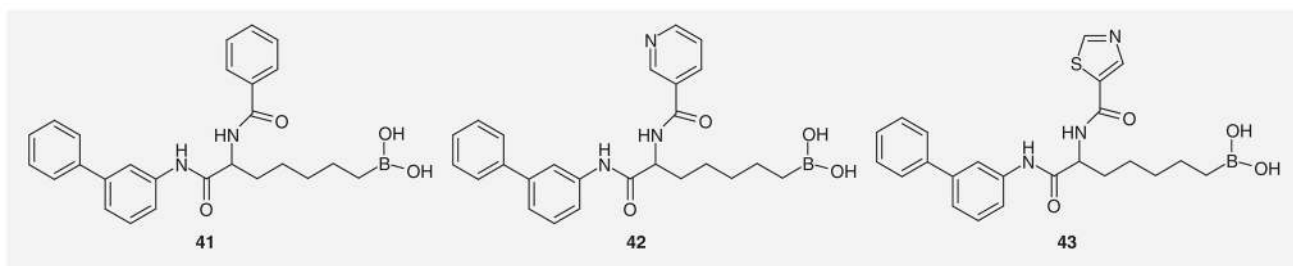


Figure 18.
Potent HDAC inhibitors.

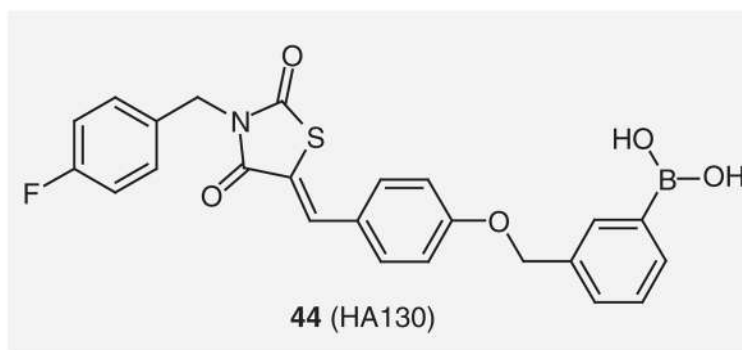


Figure 19.
Boron-based thiazolidinediones.

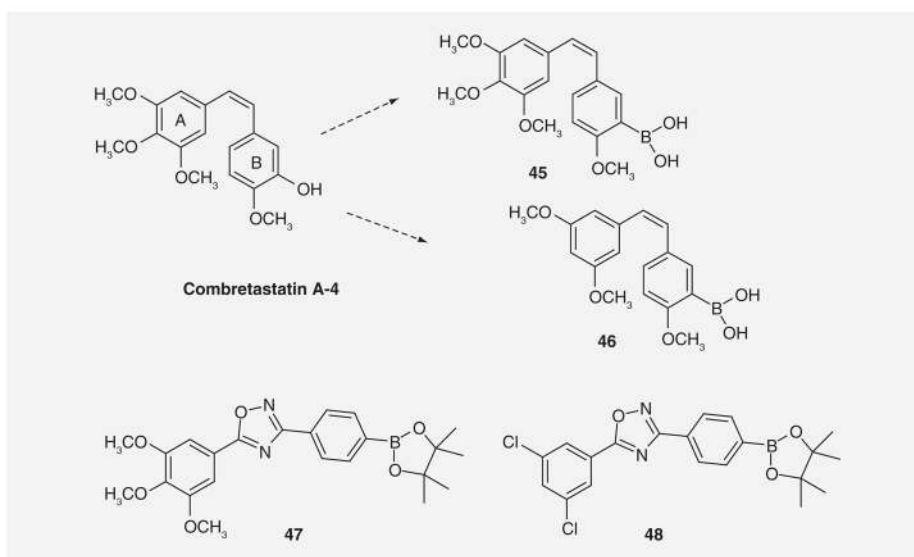


Figure 20.
Boronic acid derivatives of combretastatins.

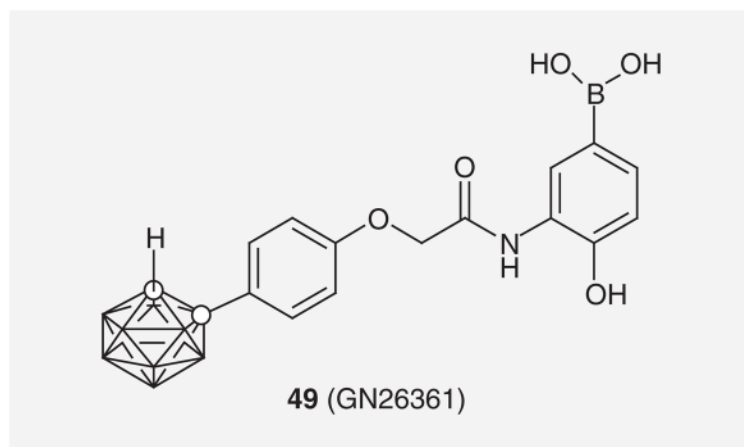


Figure 21.
Phenoxyacetanilide derivative is a HIF-1 α inhibitor.

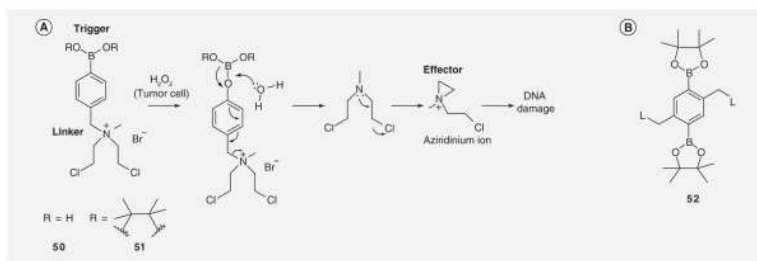


Figure 22. Boron-based reactive oxygen species activated pro-drugs
(A) Nitrogen mustard prodrugs and mechanism of activation. (B) Quinone methide prodrug.

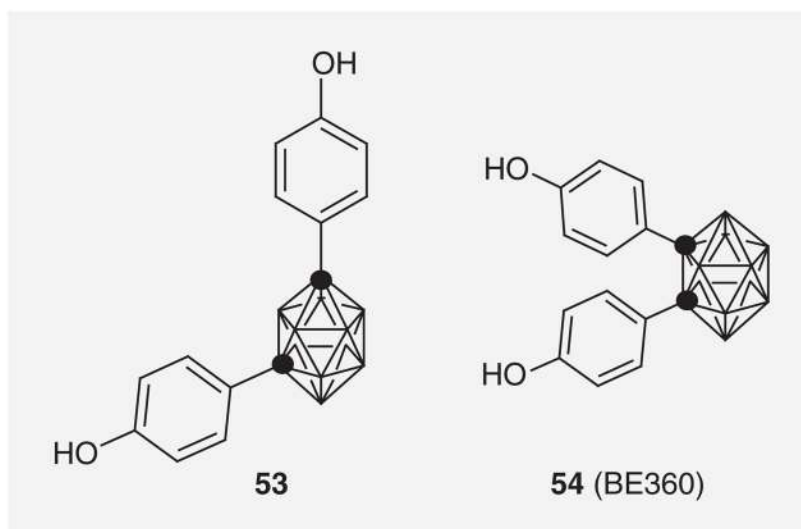


Figure 23.
Estrogen receptor modulators.

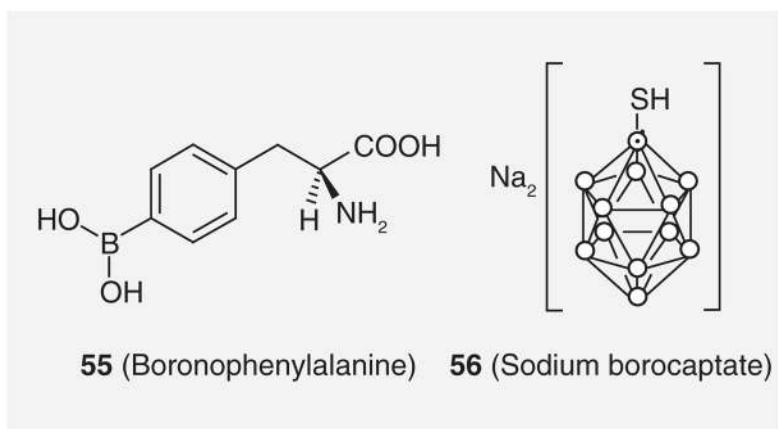


Figure 24.
Clinically used drugs boronophenylalanine and sodium borocaptate.

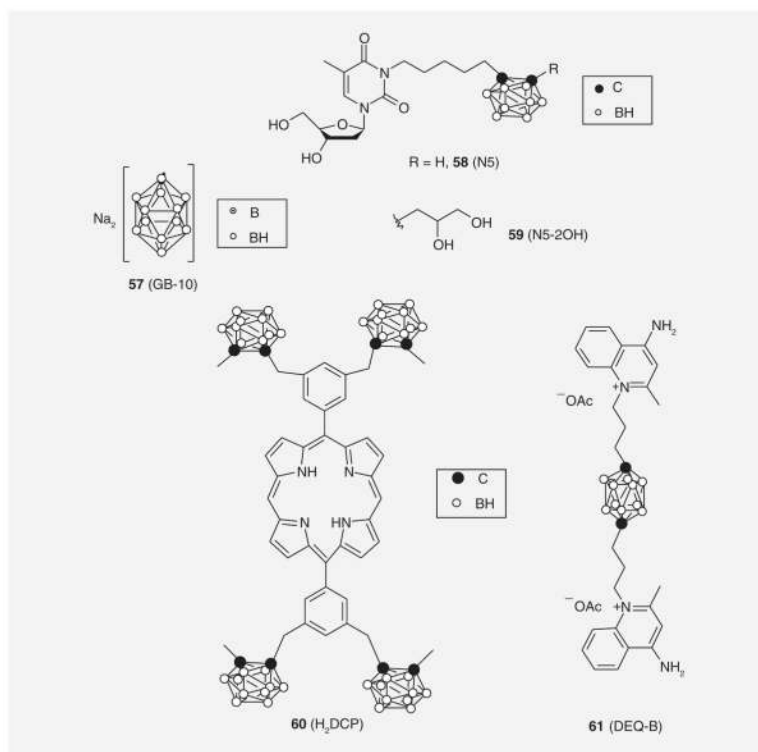


Figure 25. Low-molecular-weight compounds for boron neutron capture therapy
 DEQ-B: Dequalinium-B.

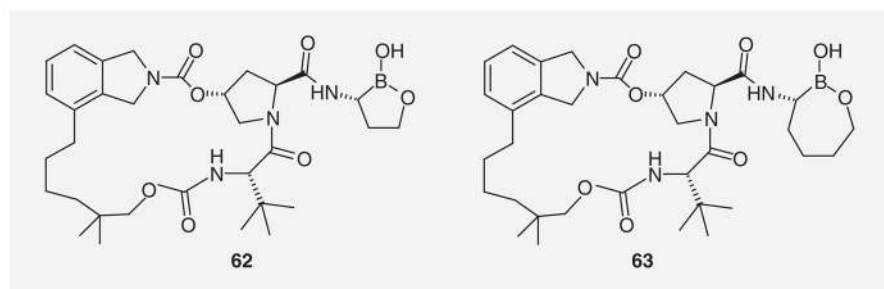


Figure 26.
P2–P4 macrocyclic hepatitis C virus NS3/4A protease inhibitors.

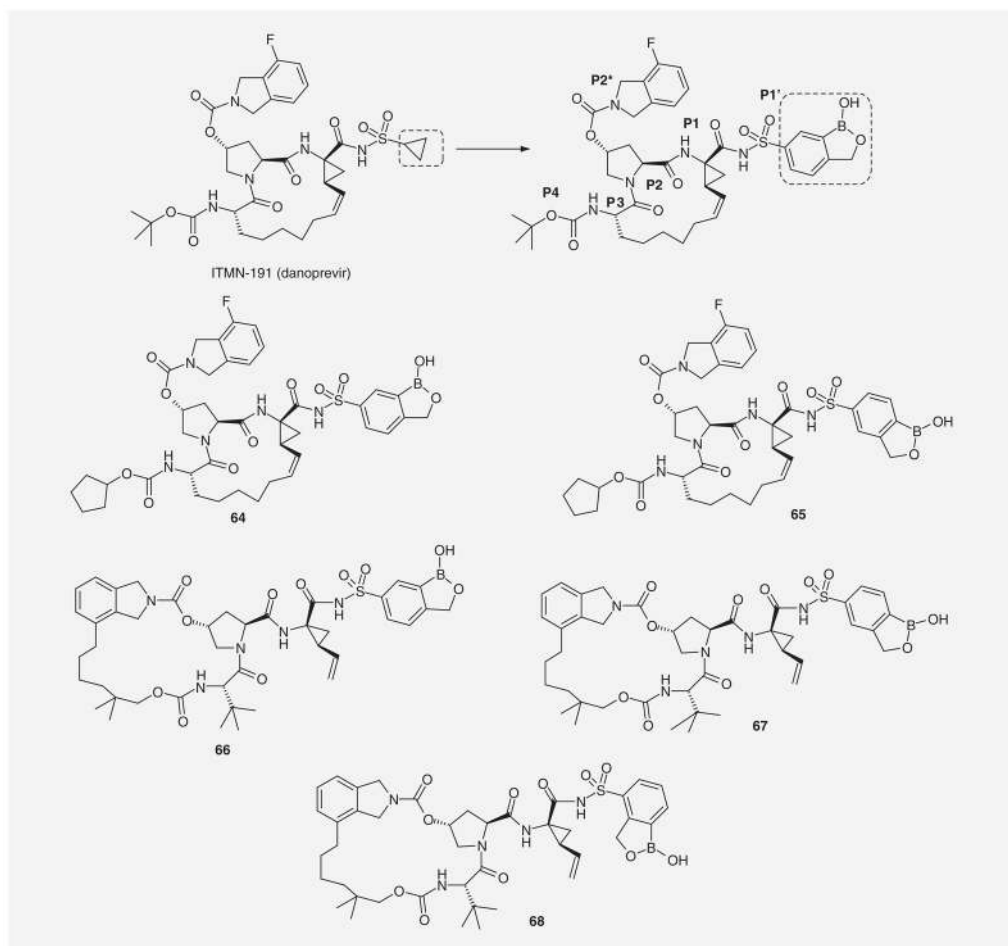


Figure 27.
Boron-based danoprevir ITMN-191 derivatives.

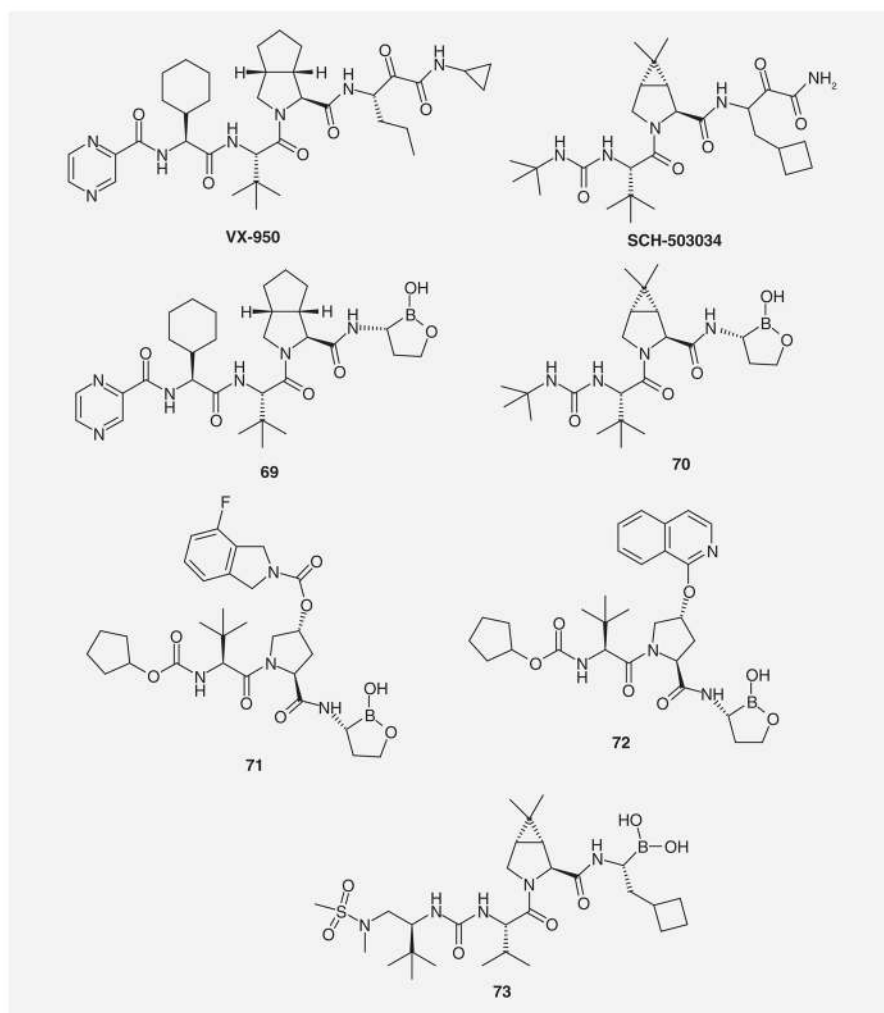


Figure 28.
NS3 protease inhibitors based on telaprevir and boceprevir templates.

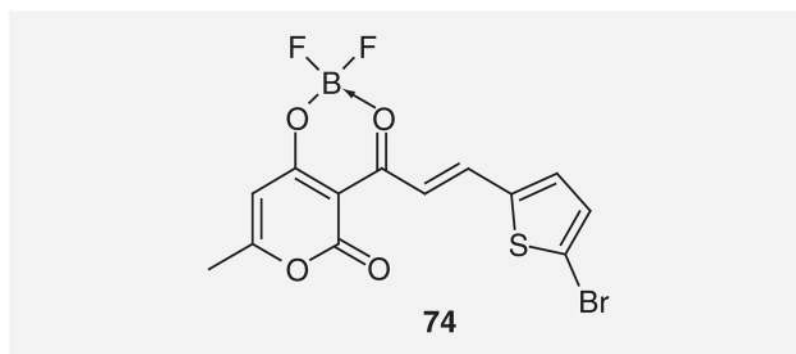


Figure 29.
Boron-based compound as HIV-1 integrase inhibitor.

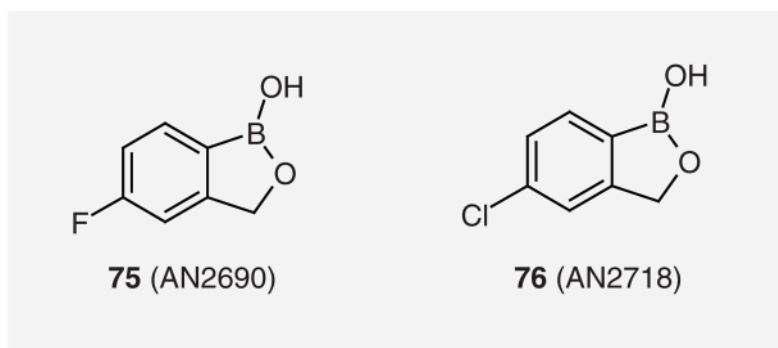


Figure 30.
Antifungal agents in clinical trials.

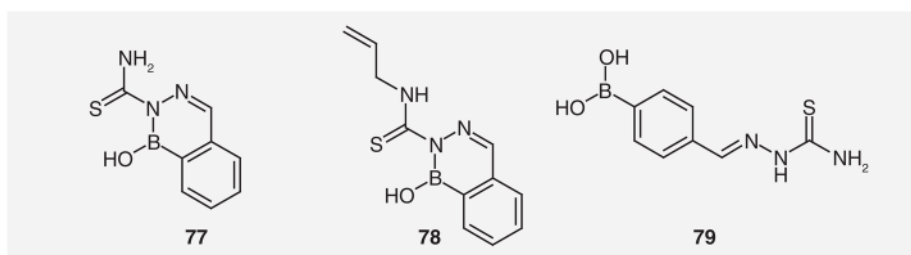


Figure 31.
Thiosemicarbazones as potential antifungal agents.

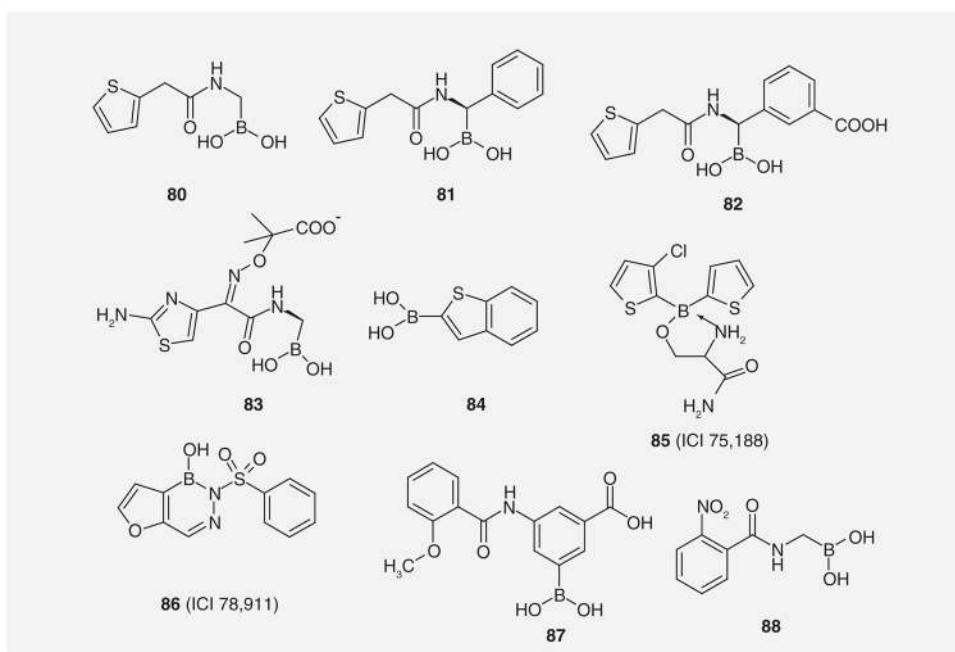


Figure 32.
Boron-based compounds as antibacterial agents.

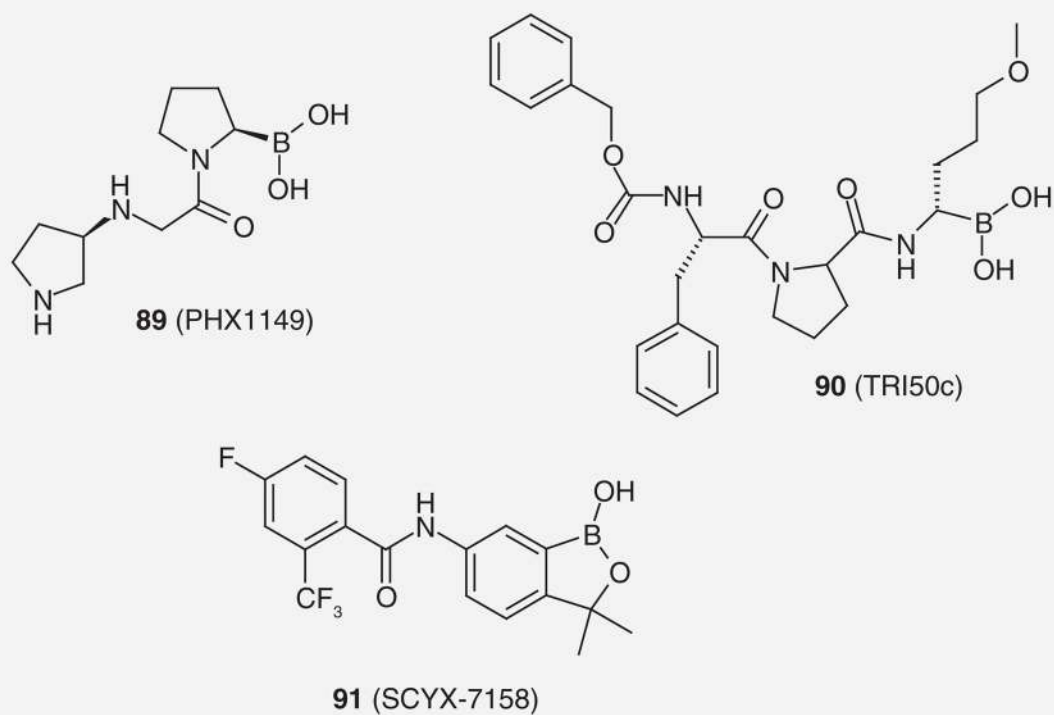


Figure 33. Clinical candidates for Type 2 diabetes (89), anticoagulation (90) and human African trypanosomiasis (91).

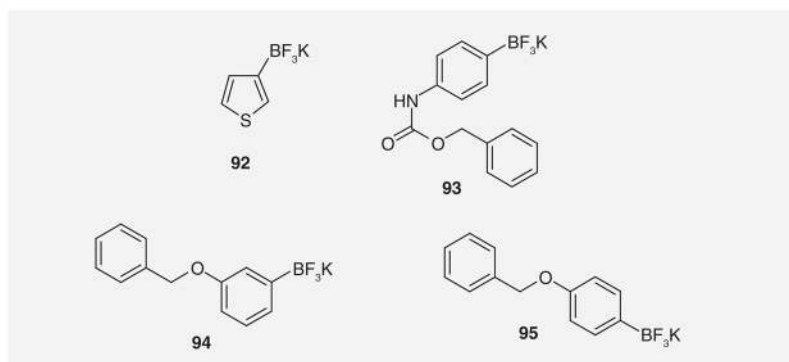


Figure 34.
Organotrifluoroborate salts.

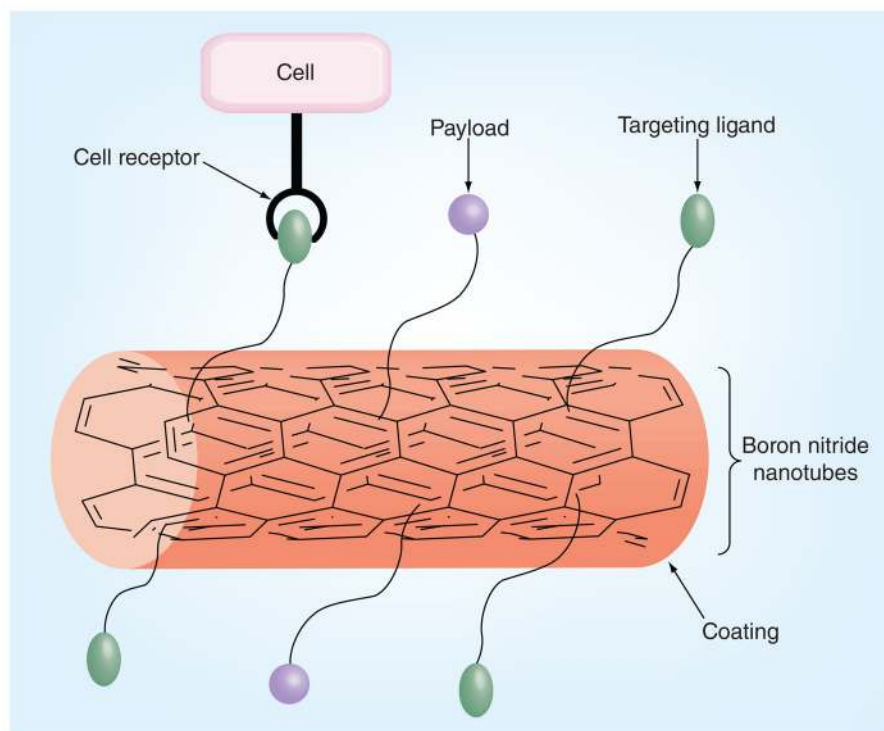


Figure 35.
Boron nitride nanotubes as a drug-delivery and targeting system.