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Review Article

Boron important element in the synthesis of the new drug: A review study

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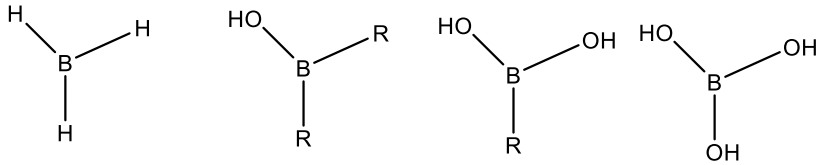
ABSTRACT

Aim to evaluate the role of the Boron atom in modern drug synthesis. Different types of boron-containing compounds (BCCs) were prepared, antimicrobials, antivirals, and anticancer. Recent developments and prospects of boronic acid in medicinal chemistry and chemical biology. The extraordinary potential of boron-containing compounds relevant molecules in antimicrobial or antiviral agents, medicinal chemistry, or pharmacology, and drug discovery as well as drug design, and thus the new wave of boron chemistry has been rapidly expanding its biomedical frontiers. This review is on how to list boron agents (Antimicrobial agents, anticancer agents, Antiviral agents, and study the physicochemical properties of boron drugs.

Keywords: Boron-containing compounds (BCCs), Antimicrobial, Antiviral, Boronic acid.

INTRODUCTION

There are many organoboron compounds, but the most active agent is boronic acid Figure 1[1]. Boron-containing compounds represent a new class for medicinal chemists to use in their drug design, antimicrobial agents (antibacterial, antifungal, antiviral)[2,3], anticancer [4], and antioxidant agents[5] .Boron compounds are found in nature in high concentrations, mainly in vegetables, fruits, and special nuts.



Borane Borinic acid Boronic acid Boric acid

Figure 1: Chemical structures of some boron-containing compounds

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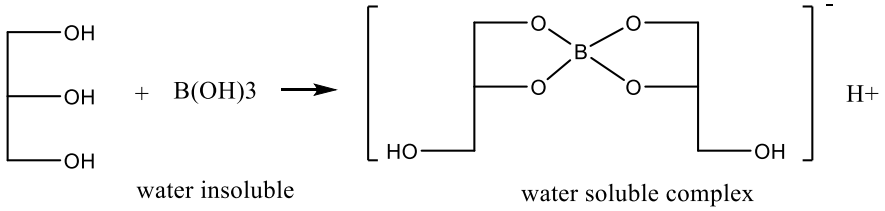
A common form of the inorganic element boron (B) is boric acid $B(OH)_3$, which is a white solid that is insoluble in water. According to the equation, boron can chemically combine with two moles of glycerin to generate a water-soluble compound called tetraboroglcerate.[6]:



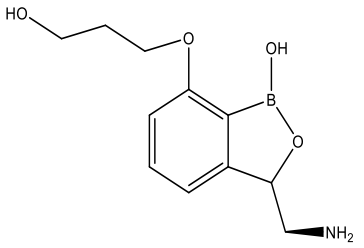
This complex can be used as an antiseptic solution and an eyewash. Also, boron can be used as an antiseptic agent for minor burns and cuts with not more than 3% solution[7] . Dewars work provided the first evidence of antimicrobial activities for a compound containing boron.

According to its general characteristics, boron is a dark, semiconductor that can appear in a variety of chemical forms as inorganic compounds (e.g. borax, sodium borate). The most prevalent form of the new image form is boronic acid, which can be coupled with various organic molecules to produce useful pharmacological and therapeutic goods[8].

In addition to being a naturally occurring mineral in our food supply, individuals also employ boron medicines as boron supplements for medical purposes. Boron is also utilized in eye drops, bone growth, osteoarthritis treatment, muscle growth, testosterone augmentation, cognitive enhancement, and strength enhancement. Boric acid, which is used in eye drops, by women to supplement their vaginal yeast, and on the skin to treat yeast infections, is the most prevalent type of boron in pharmaceuticals[9].

Boron antimicrobial agents.

We demonstrate how the aminomethylbenzoxaboroles, a new class of boron-based antibiotics that inhibits bacterial leucyl-tRNA synthetase and has activity against Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* [10] . While largely avoiding the main efflux mechanisms, were developed by modifying the oxaborole tRNA trapping (OBORT) mechanism using a structure-guided strategy.



3-(aminomethyl)-7-(3-hydroxypropoxy)benzo[*c*][1,2]oxaborol-1(3*H*)-ol

The antibacterial properties of a thousand boron-containing compounds were studied. The efficacy of new boron cluster chemical compounds against conventional and multi-drug resistant disease strains is equivalent[10].

Boron as Beta-lactamase inhibitors

Boronic acids and boronate esters, especially cyclic ones, can inhibit both serine -β-lactamases (SBLs) and metal-β -lactamases (MBLs). A monocyclic boronate with limited -lactamase coverage called vaborbactam is approved for use in clinical setting Figure 2[11].

Chemically, the hybridization of the boronic acids between SP^2 (trigonal planar) & SP^3 (tetrahydralhybridization states), may make it easier to achieve effective inhibition[12].

Recently, the stability study of boric acid at four different temperatures, comparison of some physical and chemical properties, and screening tests for their antimicrobial activities in vitro against Gram-positive and Gram-negative bacteria using gatifloxacin and glycerin as references were conducted[13,14].

Boron as an anti-fungal agent

Researchers have found that the creation of an antifungal medicine for treating infections of the fingernails and toenails depends on the presence of a boron atom. The antifungal medication works by preventing an enzyme involved in translating fungal DNA into protein products, hence suppressing protein synthesis. The compound known as AN2690, also known as 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, is composed of a six-membered benzo ring coupled to a five-membered oxaborole ring with a single boron atom[15].

Because of their discovery in nature, the number of known boron-containing compounds (BCCs) is growing, particularly in their action against pathogen species, and some were recently approved for use in humans e.g. 5-fluorobenzo[c][1,2]oxaborol-1(*3H*)-ol (Tavaborole)[15,16].

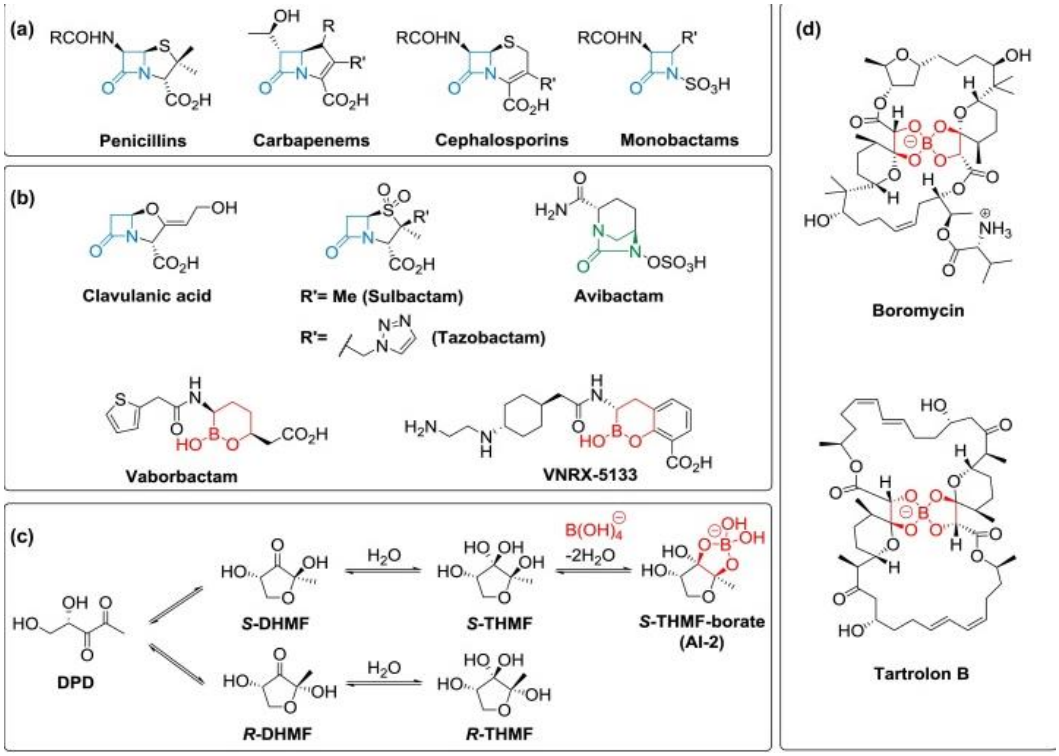
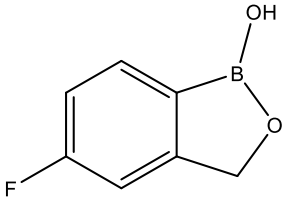


Figure 2: Chemical structures of some boronic acids as β-lactamase inhibitors[11].



5-fluorobenzo[*c*][1,2]oxaborol-1(3*H*)-ol

One specific subset of systemic fungal disorders that the boron compounds are helpful against is yeast infections. The boron-based antifungal drug tavaborole is the first to be approved for the treatment of mild to moderate onychomycosis, offering patients a new topical therapy option. Leucyl-tRNA synthetase, or LeuRS, a crucial fungal enzyme involved in protein synthesis and the ATP-dependent ligation of L-leucine to tRNA, is the mechanism through which tavaborole functions (Leu)[16] .

Boron as antiviral agent

Viral infections pose a serious risk to human health, as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic illustrated. In antiviral research, boronic acids are expected to be successful in facilitating medicine binding to the target protein even in the presence of resistance mutations by producing many hydrogen bonds or a covalent adduct. The glycan-binding characteristics of boronic acid derivatives can also be employed to block viral entry into the cell and attachment to the cell membrane.

Different chemical reaction pathways from the prodrug were identified. Although the boronic acid moiety significantly aids in target binding, the antiviral activity in cells is very mild. The boronic acid moiety's and the basic side chain's high polarity, which forbids passage through the cell membrane, are to blame. Prodrugs were developed as a solution by esterifying boronic acid with diols:

$$Drug + HO\text{-}B\text{-}(OR)_2 = Drug\text{-}B\text{-}(OR)_2$$

The product is known as a prodrug of boronic acid usually as a covalent bond, the boron atom can form hydrogen atoms with metals (Zn^{+2}, Fe^{+2}, Mg^{+2}, Co^{+2}) in either open or a cyclic form as shown in Figure 3:

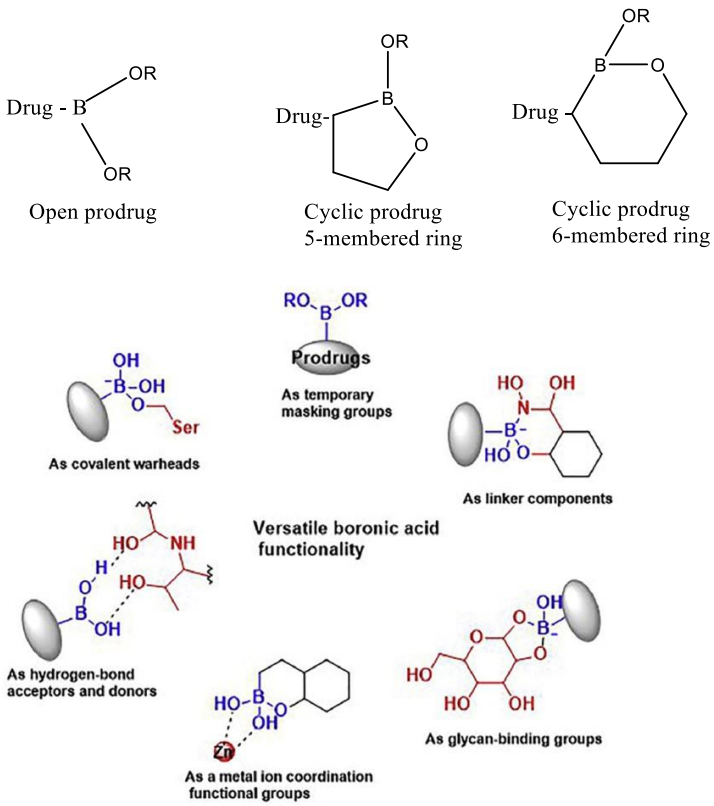


Figure 3: Chemical structures of some boron-prodrugs

Boronic acid-based prodrugs have also been used to enhance the pharmacokinetic properties of anti-estrogens because of their ability to attach to glycans. BNCT is also utilized to treat cancer because of boron's ability to capture thermal neutrons. We'll examine the targets of boron-based anticancer medications in this section. Probably, there are other receptors, still undiscovered, which might have a major significance in the fight against coronavirus disease 2019 (COVID-19). Recent studies report that the neuropilin-1 receptor and the humanized transferrin receptor (an omnipresent expressed host receptor on cell membranes) represent host factors for COVID-19 infection[17,18,19] .

Boron as an anti-cancer agent

The first-line therapy for multiple myeloma is bortezomib. However, the majority of individuals develop drug resistance, which causes the disease to return. Overexpression of class I histone deacetylase (HDAC1) in MM cells confers resistance to bortezomib (proteasome inhibitor, Bortezomib ,1), yet HDAC1 medicines may be able to alleviate this resistance Figure 4[20,21].

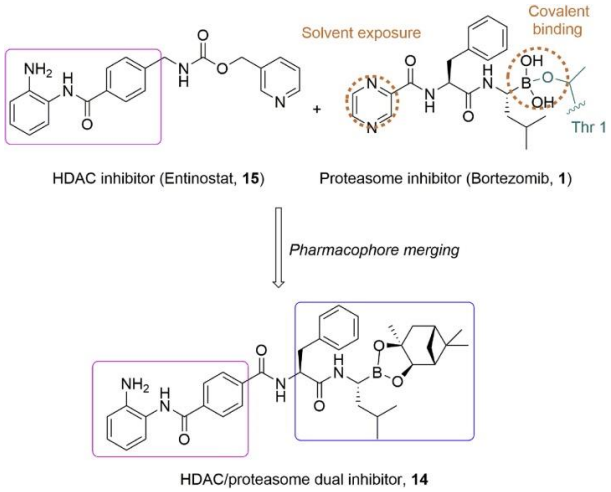
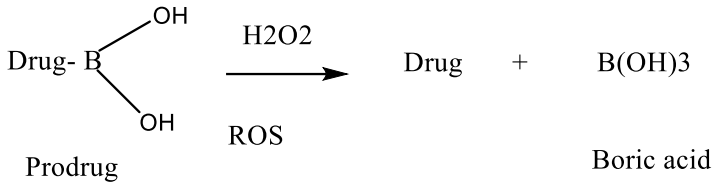


Figure 4: Some proteasome inhibitor agents.

The proteasome inhibitor bortezomib (Velcade®) was approved in 2003 for the treatment of non-Hodgkins lymphoma and multiple myeloma (MM) (NHL). The only medication with boron as an active component that is currently being used in clinical settings.

Boron as reactive oxygen species (ROS) targeting

According to the chemical equation, boric acid, which is considered non-toxic to humans, is created when boric acids and their esters (prodrugs) are broken by H_2O_2 and other ROS:



There are two pathways for hydrolysis of the prodrug Figure 5.

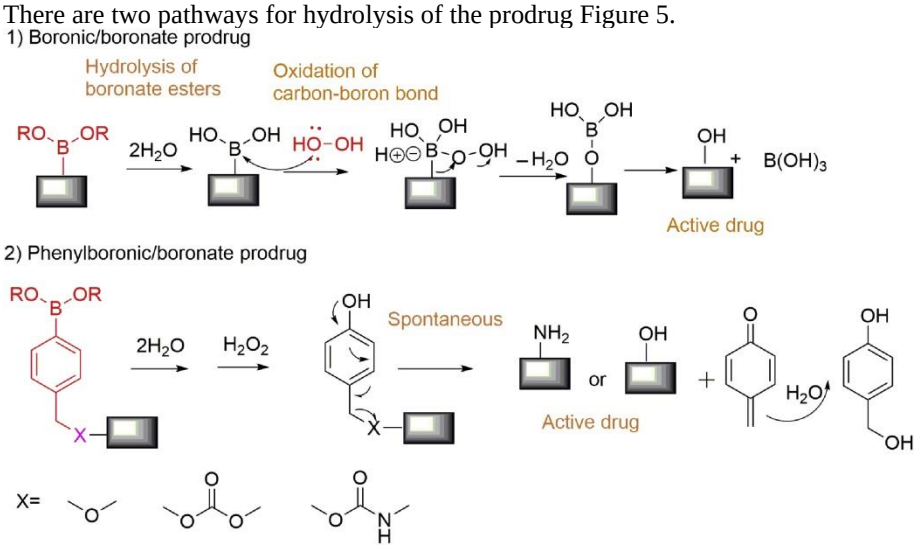


Figure 5: Mechanism of the hydrolysis boronate esters

The H_2O_2 breaks down mustard's boronic ester, a mild alkylating agent, in cancer cells to produce a highly electrophilic aziridinium ring, or "active," which causes DNA cross-linking. Due to the boronate group's ability to pull electrons, these prodrugs are not harmful to healthy cells Figure 6[22,23].

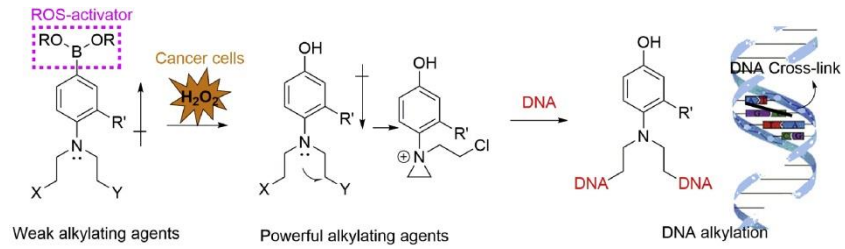


Figure 6: The role of ROS- activator in the mustard agent forming aziridinium ion[24] .

Conclusion

This review's objective is to highlight recent advancements in the study of boron-containing compounds and their potential medical applications (antibacterial, antifungal, antiviral, and anticancer). Only substances that have recently been reported to have shown in vitro and/or in vivo efficacy in the therapeutic domain and to be the most biologically active were taken into consideration.

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