Journal of Engineering, Science and Sustainability
ISSN: A/F
Volume 1, Issue 1, Jan-Jun 2025, pp. 21-25
Journal homepage: https://sprinpub.com/jess

Review article

An Introduction to the Therapeutic Potential of Boronic Acid Derivatives

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ARTICLE INFO

Keywords:
Pharmaceutical Care, healthcare, statistics analysis, patient care

Article History:
Received: 01-02-2025
Accepted: 20-04-2025
Published: 16-05-2025

ABSTRACT

Recently, boronic acid derivatives have emerged as a versatile and promising class of compounds in modern-day medicinal chemistry, owing to their ability to shape reversible covalent bonds with biological nucleophiles, together with serine and threonine residues in enzyme's binding active sites. The molecules have been verified to have extensive therapeutic potential, including oncology, infectious illnesses, and inflammatory issues. This work explores the structural functions, mechanisms, and therapeutic applications of boronic acid derivatives, highlighting their growing role in drug development and their capability in medically significant drug discovery.

Cite this article:
Yusuf M, Jayant V, Sharma D. An: Introduction to the Therapeutic Potential of Boronic Acid Derivatives. J. Eng. Sci. Sustain. [Internet]. 2025 May 17 [cited 2025 May 17];1(1):21-5. Available from: https://sprinpub.com/jess/article/view/457

1. Introduction

Boron performs a vital and multifaceted role throughout organic kingdoms. In plants, it's essential for maintaining structural integrity, particularly through its involvement in cell wall stabilization and membrane function, as well as various metabolic processes necessary for growth and reproduction. Boron derivatives, mainly borax (sodium borate) and boric acid, have been utilized in traditional medicinal drug structures consisting of Ayurveda, Traditional Chinese Medicine (TCM), and Islamic remedy [1-4]. In Ayurveda, borax (referred to as "Suhaga") changed into used in small doses to deal with digestive problems, fever, and irritation, and changed into believed to beautify sexual fitness. In TCM, borax (Peng Sha) was implemented externally for mouth ulcers, throat infections, and pores and skin conditions. Similarly, Islamic medicine used boron compounds as antiseptics for eyes and skin. These uses have typically been topical or carefully dosed because of the potential toxicity of boron at higher doses. Additionally, superior remedies like boron neutron seize therapy (BNCT) for cancer treatment illustrate the increasing medical relevance of boron. Despite its therapeutic promise, secure use remains crucial, as traditional systems additionally suggested in opposition to overdosing and emphasized proper instruction. Modern technology has supported many of those traditional programs. Boron is now known for its antibacterial, antifungal, and anti-inflammatory properties [5-7]. Boric acid remains used clinically, especially in treating vaginal yeast infections, and boron supplements are being researched for his or her position in bone health, hormonal law, and cognitive feature.

In mammals, boron significantly contributes to physiological regulation, including the modulation of vitamin D metabolism, calcium utilisation, and the maintenance of healthy bone structure.

- Boron chemistry, an often overlooked and underappreciated field in the realm of medicinal chemistry, holds a significant place in contemporary drug development. The unique properties and reactivity of boron-containing compounds make them valuable tools for medicinal chemists striving to design novel, effective pharmaceutical agents.
- *Chemical Diversity:* Boron's position on the periodic table allows it to form a wide array of compounds with varying chemical structures. Its tendency to form covalent bonds with carbon and other elements facilitates the creation of diverse molecular structures, enabling researchers to fine-tune the properties of potential drug candidates. This diversity is particularly advantageous in the quest for compounds with specific biological activities.
- *Bioisosteres:* Boron can act as a bioisostere, replacing other elements such as carbon, nitrogen, or oxygen in drug molecules. This substitution can have a profound impact on a compound's pharmacokinetics and pharmacodynamics, influencing its solubility, stability, and receptor binding properties. This ability is especially beneficial when aiming to optimize drug properties.
- *Stereochemistry and Chirality:* Boron centers can introduce chirality into drug molecules, allowing for the development of enantiopure drugs. This is crucial for designing drugs with improved selectivity and reduced side effects. The unique stereoelectronic properties of boron atoms are exploited to control stereochemistry in pharmaceutical compounds.
- *Drug Delivery and Targeting:* Boron-based compounds have been utilized in drug delivery systems. For instance, boronic acids can serve as drug-targeting moieties, specifically binding to glycoproteins on the cell surface. This facilitates targeted drug delivery and reduces off-target effects, making boron chemistry indispensable in precision medicine.

These biological functions underscore its reputation as a micronutrient of increasing interest in both plant and animal sciences. In the sector of medicinal chemistry, boron-containing compounds—especially boronic acids and boronate esters have gathered attention for their pharmacological potential. Boron-containing compounds are characterized by their interesting structural functions and reactivities, which can be imperative to

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their roles in medicinal chemistry. Further, it exhibited biologically energetic alertness of boron derivatives in drug development, multifaceted and essential in the creation of novel pharmaceutical drugs (Fig. 1) []. These compounds are generally perceived as biocompatible and safe for therapeutic applications, and are actively being explored in the design and development of novel pharmaceuticals, including enzyme inhibitors, anticancer agents, and antimicrobial drugs. This work encompasses the overview of boronic acid derivatives for becoming more important in developing new medicines and finding new treatments for serious health conditions.

Figure 1: Salient features of boron derivatives.

2. Some FDA-approved boronic acid derivatives

Several boronic acid derivatives (Fig. 2) have received FDA approval, reflecting the growing popularity of boron's precise chemical properties and healing capacity. In May 2003, the U.S. Food and Drug Administration (FDA) permitted bortezomib, marketed as Velcade from Millennium Pharmaceuticals Inc., for the remedy of relapsed and refractory myeloma, based on positive effects from the SUMMIT Phase II scientific trial. This marked the primary FDA approval of a proteasome inhibitor for most cancers [8-10]. In 2005, the FDA extended its approval to include patients with multiple myeloma who had acquired at least one prior treatment. Later, in 2008, bortezomib received approval for use as a first-line treatment in newly recognized more than one myeloma patients. These innovative approvals replicate the developing proof of bortezomib's effectiveness throughout distinctive stages of the disease. It acts as a reversible inhibitor of the 26S proteasome by forming a covalent bond with the catalytic threonine residue on the proteasome's active site, leading to apoptosis in malignant cells. Another proteasome inhibitor, Ixazomib (Ninlaro), approved in 2015, is notable for being the first orally available drug in this class. Like Bortezomib, it targets the proteasome through its boronic acid moiety, providing a more convenient administration route for patients with multiple myeloma.

In spite of oncology, boronic acid derivatives have also shown promise in treating infectious and inflammatory diseases. Tavaborole (Kerydin), approved in 2014, is a topical antifungal agent used for onychomycosis. It inhibits fungal leucyl-tRNA synthetase, thereby disrupting protein synthesis. The boron atom plays an essential role by forming a stable adduct with the enzyme's active site, selectively targeting fungal cells. In the field of dermatology, Crisaborole (Eucrisa) was approved in 2016 for the treatment of mild to moderate atopic dermatitis. This non-steroidal topical medication works by inhibiting phosphodiesterase 4 (PDE4), an enzyme involved in inflammatory signalling. Its boron moiety is critical for high-affinity binding to the PDE4 active site, reducing inflammation and related symptoms.

In addition, Vaborbactam (Vabomere), is a combination antibiotic approved by the U.S. FDA and Health Canada in 2017 for the treatment of bacterial infections. It contains Vaborbactam, a boronic acid-based β-lactamase inhibitor, and Meropenem, a carbapenem antibiotic that inhibits bacterial cell wall synthesis. Vaborbactam protects meropenem from enzymatic degradation, enhancing its effectiveness against resistant bacterial strains.

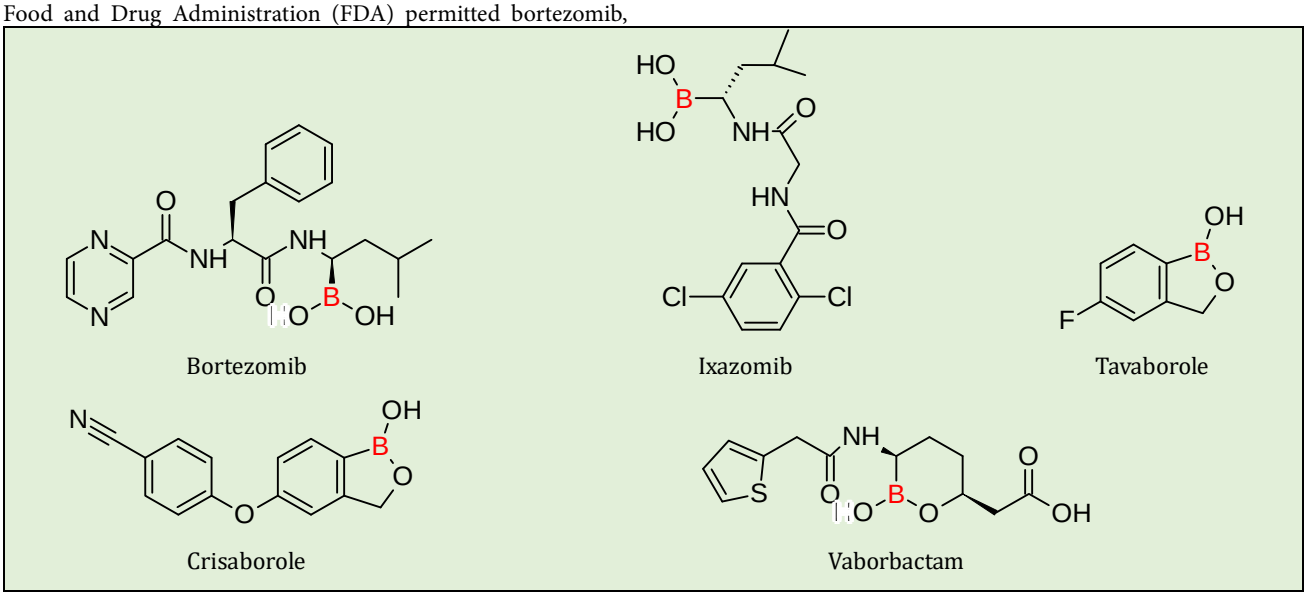

Figure 2: Chemical structures of some FDA-approved boronic acid derivatives as drugs.

3. Emerging boronic acid derivatives under Clinical Trial Stage

Several boronic acid drug candidates are in clinical trials, though not yet approved (Fig. 3) [2,3]. Acoziborole is a promising, orally available, single-dose candidate for Human African Trypanosomiasis (HAT), currently in Phase III, with an unknown

mechanism. Existing HAT treatments are toxic and much less effective. Dutogliptin, a DPP4 inhibitor, failed in Phase II for diabetes but is now in Phase II trials with G-CSF for myocardial infarction, aiming to reinforce cardiac stem restoration. GSK3036656, a benzoxaborole and leucyl-tRNA synthetase inhibitor for tuberculosis, is in Phase II. It's a resistant-optimized model of GSK2251052, showing bacterial selectivity and favorable pharmacokinetics. Similar to approved Crisaborole, AN2898 is another PDE4 inhibitor in development for atopic dermatitis. Ongoing clinical trials show it was safe and effective in a Phase II study [2,10].

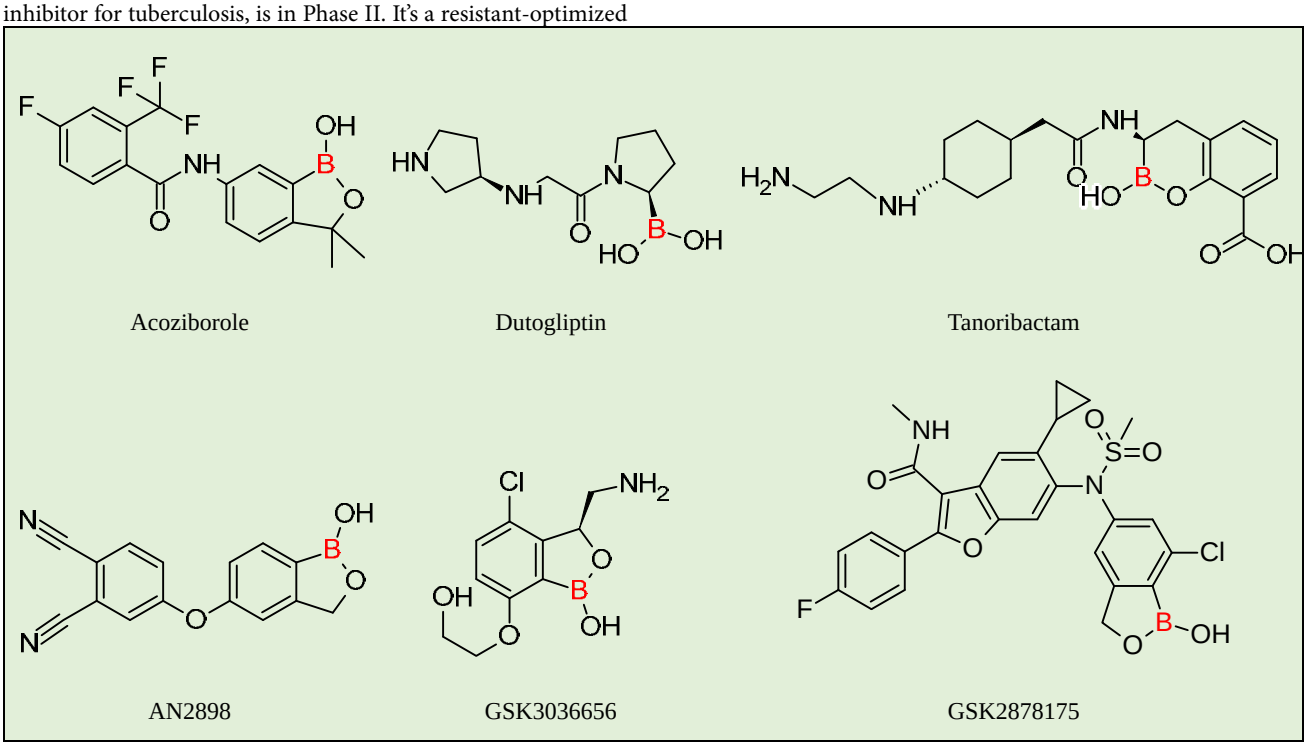

Figure 3: Chemical structures of boronic acid derivatives under Clinical trial stage.

4. Boronic acid derivatives with high potential therapeutics

While no drugs containing boron have been developed from these initiatives, various drug discovery projects have examined the use of boron in target molecules for diverse therapeutic applications. The unique chemical properties of boron—along with its ability to form reversible covalent bonds and engage with organic nucleophiles—render it a valuable scaffold in medicinal chemistry. Researchers have studied boronic acid derivatives across multiple therapeutic fields, such as oncology, infectious diseases, and metabolic disorders. Figure 4 shows the representation of chemical structures of boronic acid derivatives that possess potential for drug delivery, chiefly anticancer property [11-13]. Furthermore, the representation of chemical structures of boronic acid derivatives possesses potential for Antiviral drug delivery is depicted in Fig. 5. Viral proteases, particularly the NS3 protease from the hepatitis C virus (HCV), are prime targets for boron-based inhibitors [2]. Although several HCV NS3 serine protease inhibitors have been approved, researchers are focusing on creating analogues that replace the conventional α-ketoamide structure with boronic acid groups. This modification leverages the catalytic serine within the enzyme's active site, allowing for reversible covalent binding and potentially enhancing potency and selectivity.

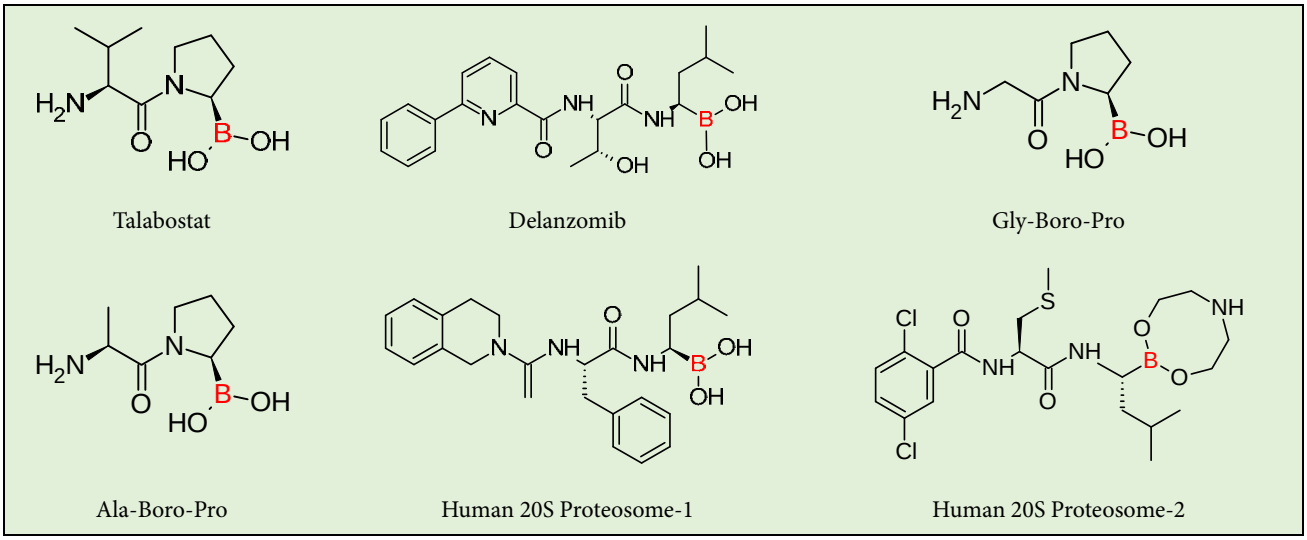

Figure 4: Chemical structures of boronic acid derivatives possess potential for drug delivery- Anticancer.

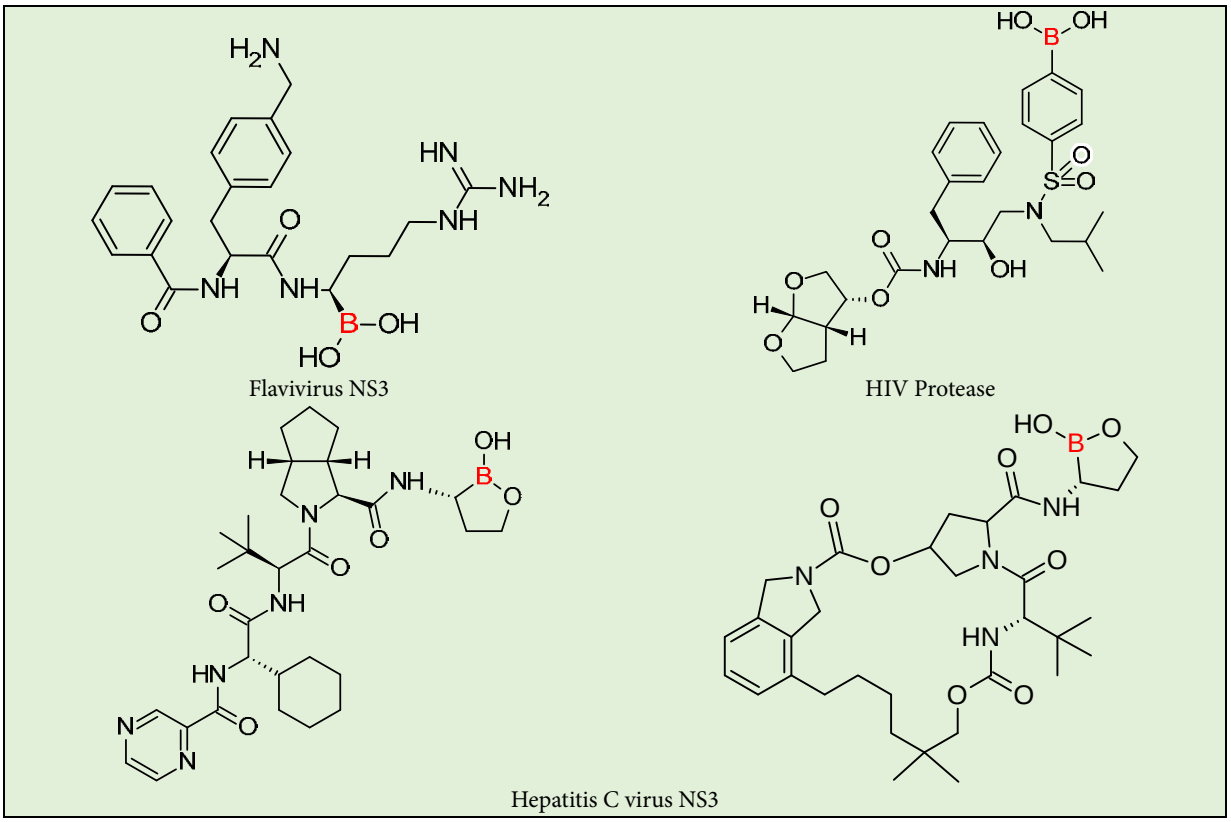

Figure 5: Chemical structures of boronic acid derivatives possess potential for drug delivery- Antiviral.

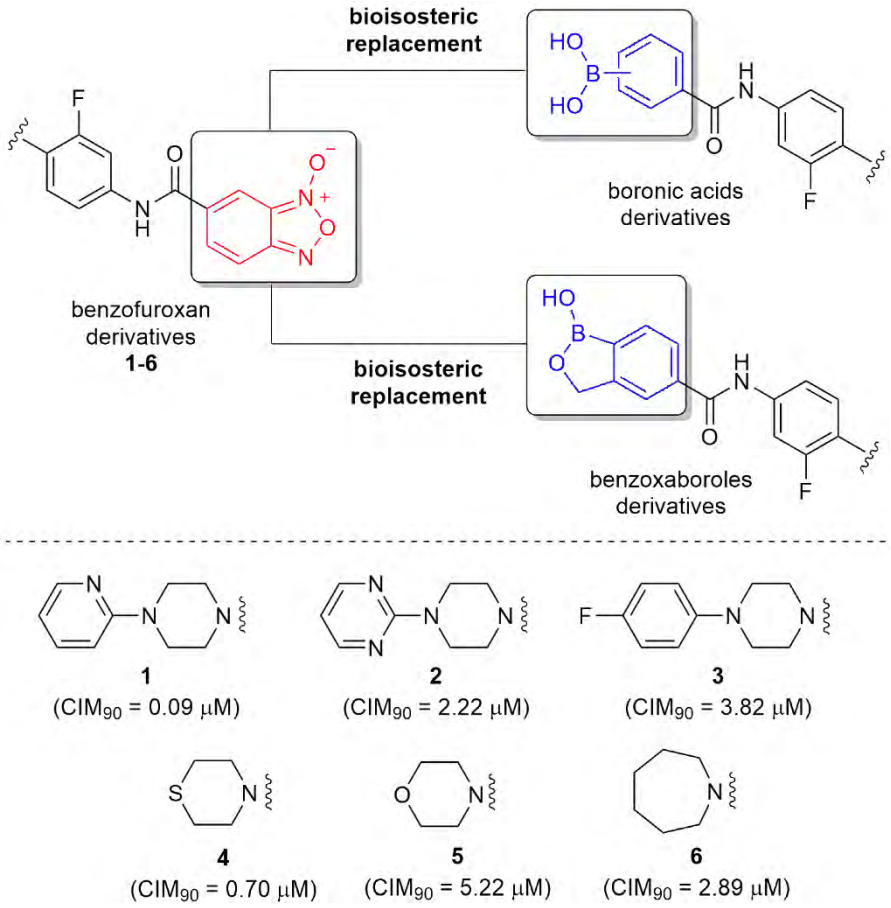

Figure 6: Schematic representation of boronic acid and benzoxaborole derivatives (Reproduced from ref. [14] under CCBY, MDPI, Basel, Switzerland 2025)

Prates et al., [14] recently studied organoboron compounds with boronic acid and benzoxaborole moieties (Fig. 6), which have probably important scaffolds in medicinal chemistry. Their prominence increased after FDA approval of bortezomib for

multiple myeloma and tavaborole for onychomycosis, both highlighting the therapeutic potential of boron-based drugs. These compounds are particularly valuable for their ability to form reversible covalent bonds with biological targets, offering high specificity and potency. Their known antimicrobial and anticancer properties have encouraged further development of novel derivatives for broader therapeutic use. In this study, fourteen new boron-containing derivatives were synthesized and fully characterized using various analytical methods. Additionally, their antimicrobial activity was tested against Mycobacterium tuberculosis H37Rv and fungal pathogens, including Candida albicans (ATCC 90028), Trichophyton rubrum (ATCC 28189), and Trichophyton mentagrophytes (ATCC 11481). Anticancer activity was also evaluated against oral squamous cell carcinoma (SCC) cell lines. Several compounds showed promising biological activity, making them strong candidates for further structure–activity relationship studies and optimization in the development of new antimicrobial and anticancer agents.

5. Conclusion and Future Outlook

Boron's natural abundance and protection make it an attractive element in drug discovery. Its unique chemical features enable selective, reversible interactions with organic molecules. Since the approval of bortezomib, massive medicinal chemistry efforts have focused on developing boronic acid-primarily based drugs for most cancers, infections, and other therapeutic areas. Advancements in drug design have been carefully followed with the aid of development in the synthesis of boronic acids. Following the approval of bortezomib, enormous interest has been shown in the improvement of aliphatic boronic esters and acids, especially α-amino boronic derivatives. These synthetic breakthroughs have paved the way for several research corporations to incorporate boronic acid frameworks into their drug discovery pipelines, capitalising on their particular chemical and biological properties.

The growing interest in research on boronic acid derivatives highlights their great potential as significant drug candidates. As extra synthetic techniques and organic applications emerge, boron-based compounds are in all likelihood to play an increasingly crucial role in addressing unmet scientific needs. These explorations into boron-primarily based drug discovery are anticipated to further remove light from the precise benefits of boron incorporation consisting reversible covalent binding, tunable reactivity, and organic compatibility. Moving ahead, it seems that medicinal and pharmaceutical chemists will more and more comprehend boronic acids and esters as precious equipment and viable scaffolds in modern-day drug discovery programs for novel treatments across an extensive range of diseases.

Acknowledgements

The authors are thankful to Glocal University, Saharanpur, Uttar Pradesh, India, for providing technical support and facilities to carry out this work.

Declarations

Author contribution

Mohd Yusuf: Concept, data analysis, visualisation, drafting, manuscript submission.

Deepa Sharma: Concept, data analysis, data interpretation, drafting.

Funding Source: None.

Ethics approval and consent to participate: Not applicable.

Conflict of Interest: The authors declare no competing interests.

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