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Chapter - 8
Biologically Active Benzofused Bioisosters (Benzimidazole, Benzoxazole and Benzothiazole)

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Chapter - 8

Biologically Active Benzofused Bioisosters (Benzimidazole, Benzoxazole and Benzothiazole)

Dr. Lagu Surendra Babu, Dodda Suresh, V. Muralikrishna Madasu and J.L.S.S. Phanikumar

Abstract

Recently, Benzofuced bioisosters of benzimidazole, benzoxazole and benzothiazole has become an essential heterocyclic compound due to its versatile applications in the field of commercial and precursor for the synthesis of novel drug molecules by the chemist. Recently investigation implies there are numerous scientific data on the syntheses of the main scaffold and its functionalization for biological and pharmaceutical activities. So far, wide range of synthesis protocols have been reported in the literature for the construction of these scaffold with their biological significance. These bioisosters possess similar physical and chemical properties which impact on biological properties the main content of this chapter throws a light on and highlights the above-mentioned bioisosteric application and tackle the drawbacks of the syntheses and side effects on the environment. Furthermore, various selected benzofuced derivatives with potential and biological and pharmaceutical activities will be presented.

Keywords: ATDA substituents, MBT: 2-Mercapto benzimidazole; benzothiazole, CA: carbonic anhydrase: ultraviolet

Introduction

Isosteres were predominantly defined as the groups of atoms or compounds having the same number and arrangement of electrons. Irving Langmuir coined the term Isosterism in the year 1919. Bioisosteres, on the other hand, are atoms or groups of molecules that fulfil the fullest definition of isosteres and share biological features. Bioisosteres possess broadly similar physical and chemical similarities thus making comparable bio properties. In this context appropriately substituted benzofused heterocycles (heterocycles fused to benzene) exhibits bioisosterism. In this present chapter, we have chosen the three most pharmaceutically prevalent bioisosteres such as benzimidazole, benzoxazole and benzothiazole.

Benzimidazole

Benzimidazole (1) is a planar bicyclic heteroaromatic structural motif comprising of 10π electrons organized by the blending of benzene ring with 4, 5-positions of the imidazole ring (Figure 5). Among both the nitrogen atoms, nitrogen element present at position 1 (N1) behaves like pyrrole whereas at position 3 (N3) like pyridine thus exhibiting diverse nature. In nature, the NH cluster of benzimidazole is both strongly acidic and frailly basic. The hydrogen atom can be switched on any of the two nitrogen atoms, resulting in two equivalent tautomeric forms. 1a, 1b respectively as shown in Figure 6. It's also a highly polar motif, with an estimated dipole of 3.61D, and entirely water insoluble.

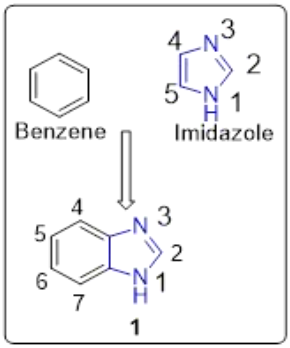


Fig 1: Structure of Benzimidazole

It was originally known as glyoxalin since it was made from glyoxal and ammonia in 1958. 1H-benzimidazole or 1,3-benzodiazole are other names for benzimidazole. 'NH' of benzimidazole forms better inter molecular hydrogen bonding interactions with the receptor and enzymes, acts as ligand for metal ions, and participate in π-π interactions and hydrophobic interactions resulting in the qualitative enhancement of biotic profiles.

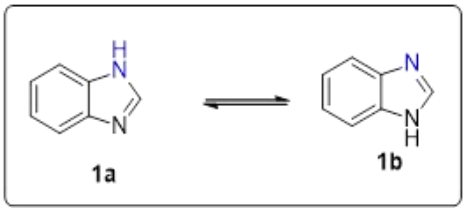


Fig 2: Tautomer's of Benzimidazole

The early 1944s was considered to be a pivotal period regarding the detection of the optimum biological responses of benzimidazole containing cores and the closely related purines (Figure 7) as delineated by woolly *et al*.

Brink *et al*. discovered the 5, 6-dimethyl-1-(D-ribofuranosyl) benzimidazole ring system as a key part of the structure of vitamin B12 five years later. (Figure 7). Benzimidazoles isolated from the Leucetta species of marine sponge have cytotoxic, antimicrobial, and anticancer properties. These primary reports sparked various research clutches to explore this privilege scaffold for further activities. Using this chemprobs, pharmaceutical, veterinary and agrochemical products were discovered. This honored stable structural motif has sparked a lot of interest over the years due to its extensive research into chemical functionality in biological active molecules and a wide range of practical applications in a variety of fields, including antivirutic against a variety of viruses, including herpes (HSV-1), influenza, HIV, and angiotensin II (AII) inhibitors,27 inhibitors of the hepatitis C virus RNA polymerase Antibacterial, antiprotozoal, antifungal, anti-inflammatory, antidepressant, antileishmanial, antitubercular, anticonvulsant, antihypertensive and anticoagulant properties are also established. Benzimidazoles have key applications in chemistry, electronics, and the polymer industry, including potential skeletal muscle fibre propagation inhibitors, antineoplastic medicines and as a therapy for viscus urinary tract infection.

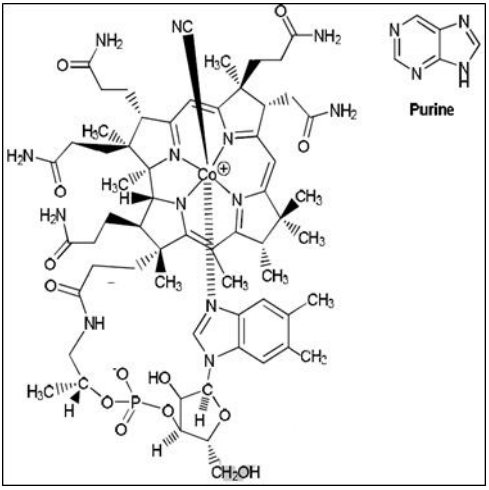


Fig 3: Structures of Vitamin B12, Purine

Benzimidazole substituted at 2nd positions is important heterocyclic pharmacophore in drug discovery. A vast number of benzimidazole and their offshoots are endowed with multiplicity of usage in therapeutics, pharmaceutical and veterinary drugs. Some of them are presented in.

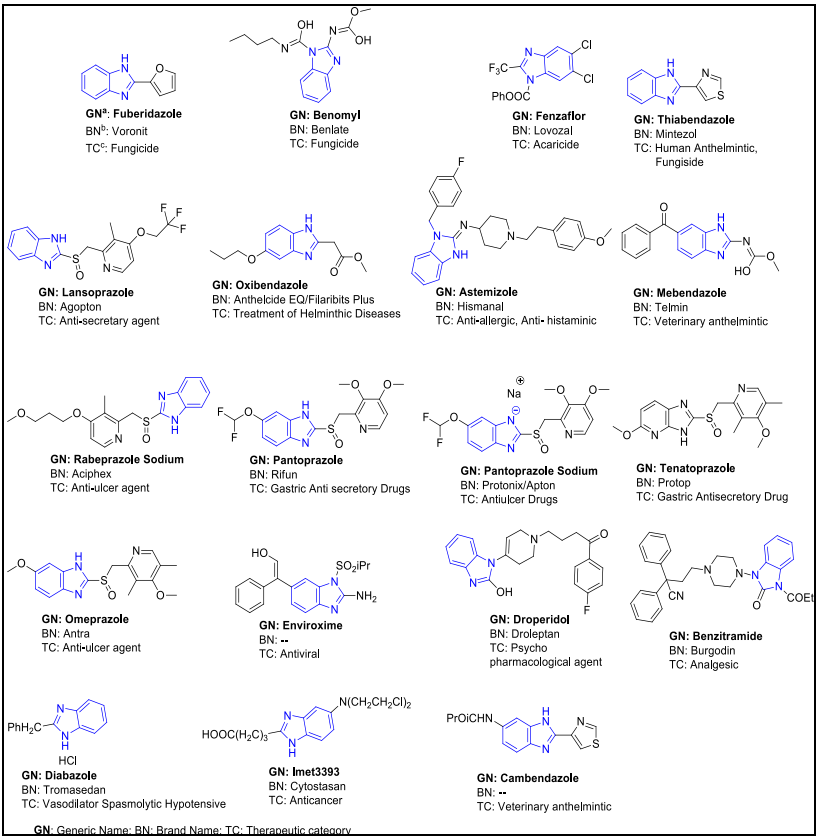
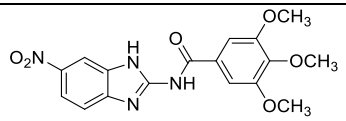
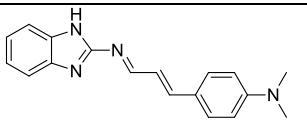


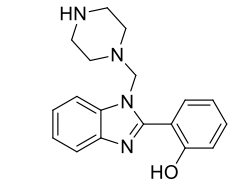
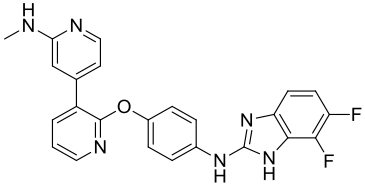
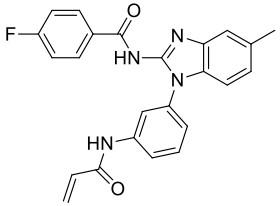
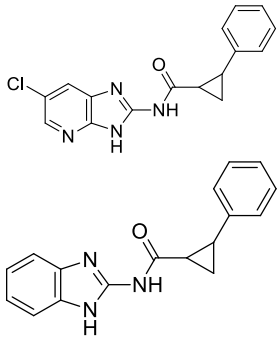
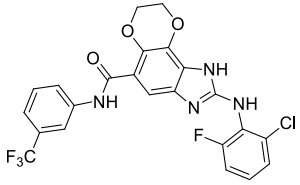
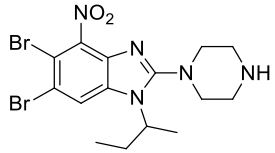
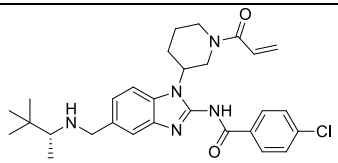
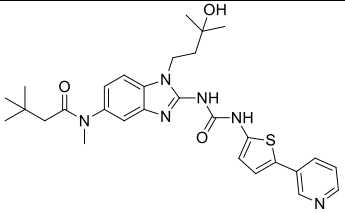
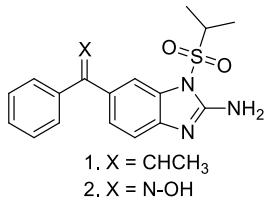
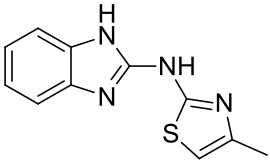
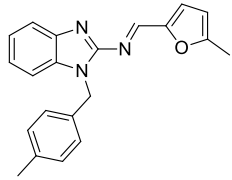
Fig 4: Some of the marketed Benzimidazole Derivatives

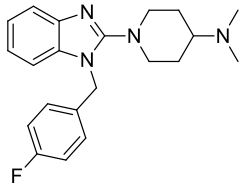
Biological activity of 2-Aminosubstituted benzimidazole substituents

According to a literature review, 2-substituted benzimidazole derivatives are pharmacologically more potent analogues. As a result, the design, planning, and synthesis of these derivatives are of interest and the Pierron methodology is one of the most important protocols for the synthesis of these compounds. Table 1 lists some of the bioactive amino substituted benzimidazoles compounds that have been identified in the literature.

Table 1: Bio-active 2-aminosubstitutedbenzimidazole

 **Anticancer agent**	 **Antibacterial agent**

 **Analgesic activity**	 **PDE10A Inhibitor**
 **EGFR activity modulator**	 **Lysophosphatidic acid antagonists**
 **mPGES-1 inhibitor**	
 **kinase inhibitor**	 **ITK inhibitor**
 **TEC kinase inhibitor**	 1. X = $CHCH_3$ 2. X = N-OH **Antiviral agents**
 **Gastroprotective agent**	 **Angiogenesis inhibitor**

 **Used for treatment of insomnia**	

Benzoxazole

Oxazole was known to the man kind since 1876 with the union of 2-methyloxazole, the information that parent oxazole (Figure 9) was combined in 1947 and 1962. The chemical structure of "oxazole" was produced during the world war when penicillin was considered to contain the oxazole skeletal ring system.

The aromatic organic compound benzoxazole is generated by the union of the benzene ring with the heterocyclic molecule oxazole in the 4,5-positions of the benzene ring, as shown in Figure 9. It has the molecular formula C7H5NO and has the odor of pyridine. It has a molar mass of 119.12 g/mol and the IUPAC name 1-Oxa-3-aza. -1H-indene. It is relatively stable due to its aromaticity. Benzoxazoles are structural isosteres of naturally occurring nucleic bases like adenine and guanine, allowing them to interact easily with polymers in living systems and demonstrating workout squat toxicity in warm-blooded mammals.

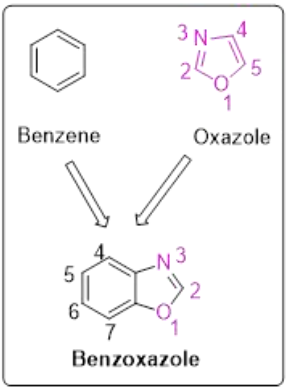


Fig 5: Benzoxazole

Naturally occurring benzoxazoles and their therapeutic solicitations

The nature has immensely distributed this small core nucleus in an array of natural products thus highlighting the prominence of this scaffold. Some of them provided by nature have been demonstrated in Figure 10.

Calcimycin, a carboxylic polyether derived from Streptomyces charteris (NRRL 3882), has been proven to be highly effective against Gram-positive bacteria, including Bacillus and Micrococcus strains. Routiennocin and cezomycin, two of its derivatives, are effective against Bacillus cereus, *Bacillus megaterium*, Micrococcus luteus and *Streptomyces rimosus*. *Pseudopterogorgia elisabethae*, a Caribbean Sea whip, is known to be rich in a subclass of marine benzoxazoles that have antitubercular activity and are so referred to as antimycobacterials. The antitubercular agents pseudopteroxazole and seco-pseudopteroxazole were isolated from the West Indian gorgonian coral *Pseudopterogorgia elisabethae*. In addition, Rodriguez *et al*. found homopseudopteroxazole, a hexane extract from the marine plume *Pseudopterogorgia elisabethae*, to be a durable growth inhibitor of Mycobacterium tuberculosis H37RV.Ileabethoxazole was also discovered from the Caribbean Sea whip *Pseudopterogorgia elisabethae*, which inhibited Mycobacterium tuberculosis H37RV by 92 percent at concentrations ranging from 128 to 64 g/mL. Taniguchi *et al*. isolated the natural product UK-1 (bis(benzoxazole)) from the mycelia cake of the actinomycete strain 517-02 and discovered that it has cytotoxic effect against B16, HeLa, and P338 cells. Tsuji *et al*. isolated AJI9561 from Streptomyces species mycelium extract, which exhibited strong cytotoxic activity against Jurkat and P388 cells. Nonetheless, the methyl and dimethyl derivatives of MUK-1 and DMUK-1 have antibacterial action against Gram-positive and Gram-negative bacteria.

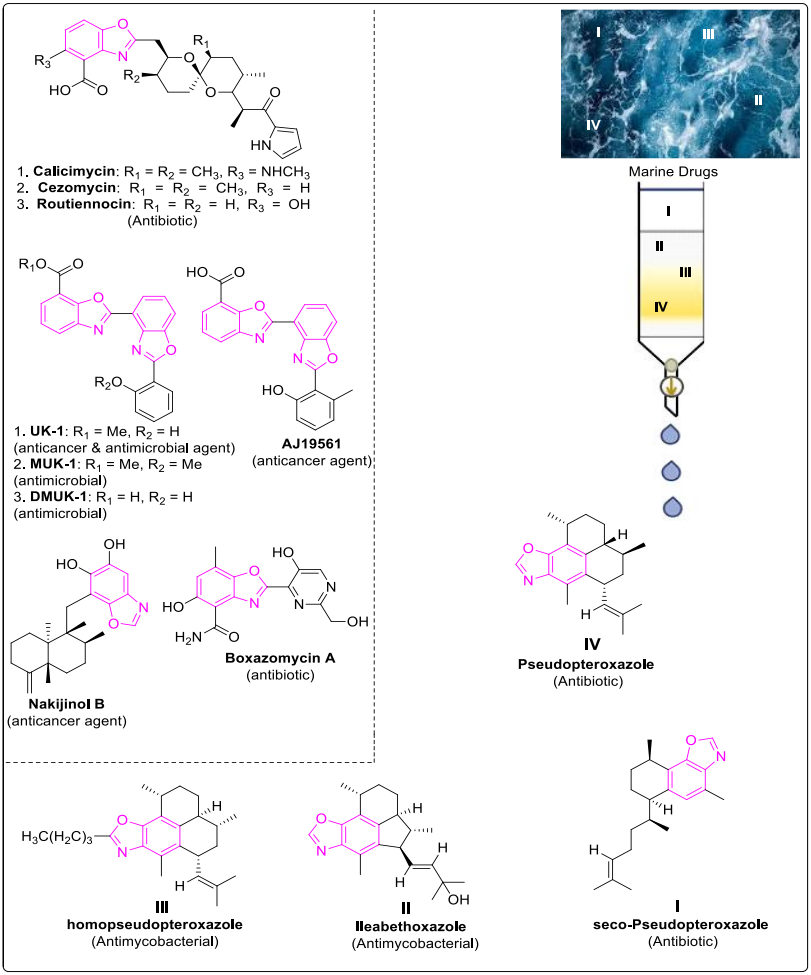


Fig 6: Benzoxazole Natural extracts and their therapeutical presentation

Commercially/Marketed benzoxazole drugs

This privileged benzoxazole core serves as an integral part of an array of promoted drugs as depicted in Figure 11.

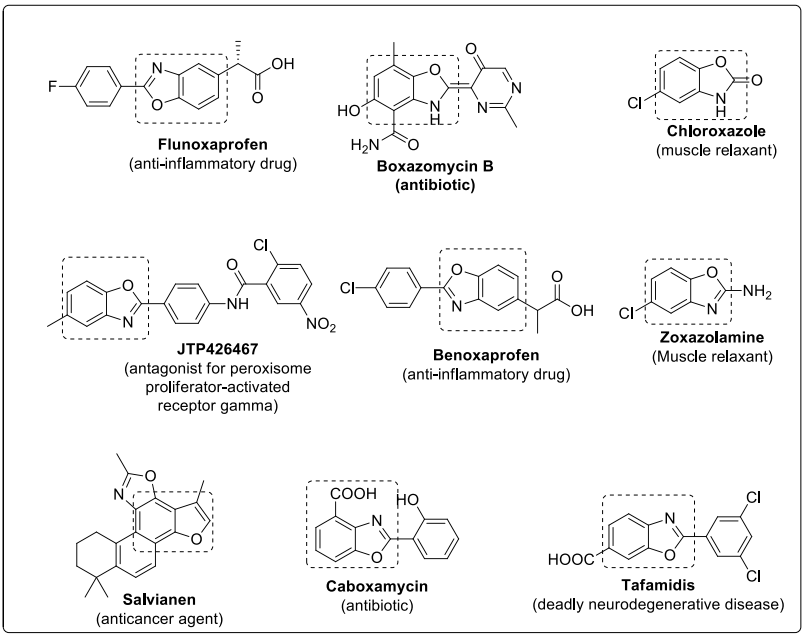


Fig 7: Some of the marketed drugs comprising benzoxazole nucleus

Biological activity of ATDA substituent's

Benzoxazole and its derivatives are privileged organic compounds of medicinal significance and have captured immense attention and are of paramount interest with respect to their medicinal significance payable to their renowned biological and therapeutic solicitations due to the peculiar features possessed by this privileged nucleus (Figure 12). Benzoxazole is predominantly jumble-sale in research and industry-for the creation of larger bioactive structures. This heterocyclic gibbet has combative sites which allow for functionalization. An appreciable high number of combinations found by laboratory production have ended up being potential chemotherapeutic and pharmacotherapeutic agents. Different artificial equivalents with enhanced remedial properties achieved from single component of lead by auxiliary adjustment. From the published collected works it is obvious that 2-substituted benzoxazoles are decisive for qualitative fluctuations and 5-substituted benzoxazole products enhance the intensity of biological effects respectively. Some of the pharmacological applications of benzoxazoles are tabulated in Table 2. Recent medicinal chemistry applications include organic brightening agents, laser dyes, organic plastic scintillators, whitening agents, and crown-ether cyanine dyes, which are photostable, extremely effective UV dyes. Organic brightening

agents, laser dyes, organic plastic scintillators, whitening agents, and crown-ether cyanine dyes, which are photostable, exceptionally powerful UV dyes, are only a few of the recent medicinal chemistry uses. They're also employed as fluorescent probes like metal cation and non-metal anion sensors, which have a strong Stokes shift and are thermally and photophysically stable thanks to an excited state intramolecular proton transfer mechanism. It inhibits the enzyme phytoene desaturase, which is being researched as a possible bleaching herbicide, interfering with the formation of coloured carotenoids.

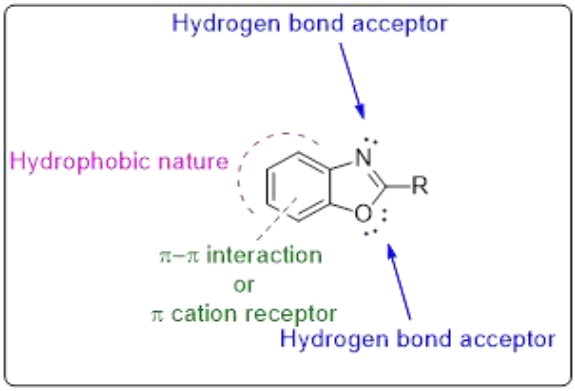
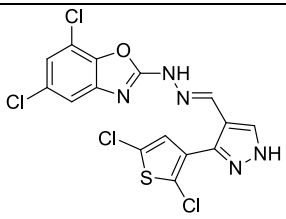
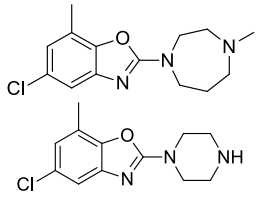
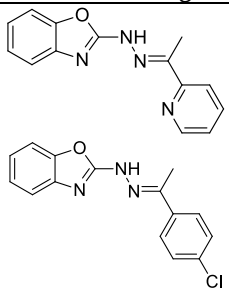
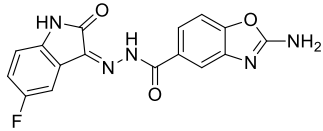
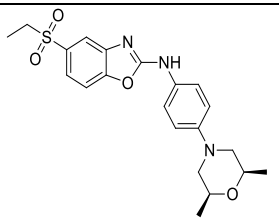
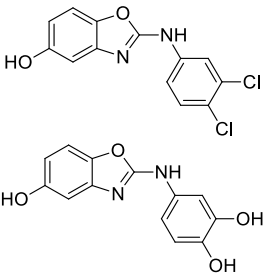
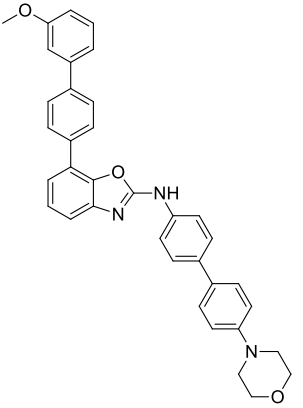
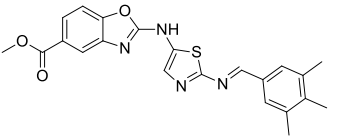
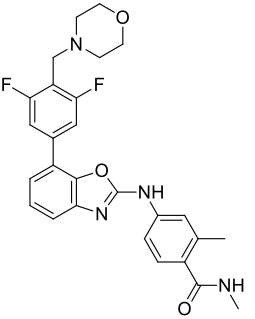
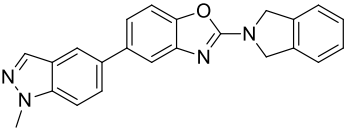
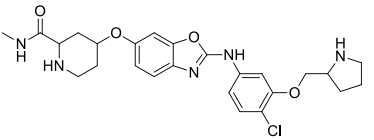
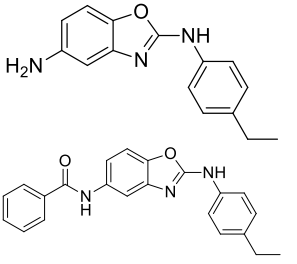
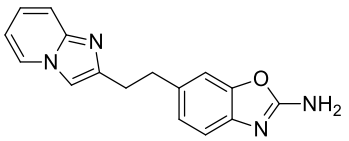
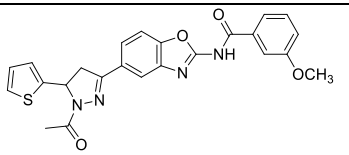
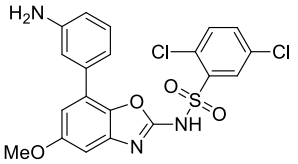
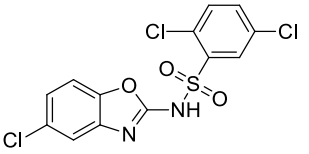
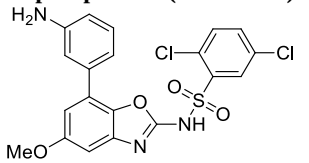
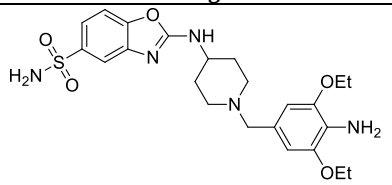
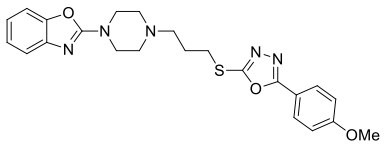


Fig 8: Peculiar features of benzoxazole

Table 2: 2,5-disubstituted-1,3,4-oxadiazoles are bioactive 2,5-disubstituted-1,3,4-oxadiazoles

 **Antimicrobial and analgesic agent**	 **5-HT3 antagonist**
 **Anticancer and Antimicrobial agents**	 **Antioxidant and Antifungal**

 **NPY Y5 Antagonist**	 **Anti-inflammatory agent**
 **Anticancer agent**	 **Anti-inflammatory agent**
 **JAK2 inhibitor**	 **FAAH inhibitor**
 **VEGFR-2 inhibitor**	 **IL-6 Inhibitor**

 **Histamine H_2-receptor Antagonist**	 1. R_1 = 2-pyridyl, R_2 = H 2. R_1 = 2-thiazolyl, R_2 = H 3. R_1 = 2-pyridyl, R_2 = NO_2 4. R_1 = 2-thiazolyl, R_2 = NO_2 **Anti-tubercular agent**
 **5-HT6 ligands**	 **Inhibitor of human fructose-1,6-bisphosphatase (hFBPase-1)**  **inhibitor of fructose-1,6-bisphosphatase (FBPase-1)**
 **somatostatin receptor subtype 5 antagonists**	 **Active against HepG2 cell line**

Benzothiazole

Hantzsch and Waber first defined ‘Thiazole’ in 1887. In addition, Popp validated its structure in 1889. The numbering of the thiazole moiety begins with the element sulphur. The skeletal structure of benzothiazole (BTA), a six-membered bicyclic heteroaromatic molecule, is created by the fusion of the thiazole ring's 4,5 position with the benzene ring's ring. (Figure 13). BTA is a colourless, slightly viscous liquid with a melting point of 2 degrees Celsius and a boiling temperature of 227-228 degrees Celsius. BTA has a density of 1.238 g/mL at 25 degrees Celsius. The occurrence of the BTA

core edifice is responsible for the various therapeutic applications of a variety of marine or terrestrial natural substances. BTAs are fragrance ingredients of tea leaves and cranberries generated by fungi *Aspergillus clavatus* and *Polyporus frondosus*. They are found in the structure of firefly luciferin.

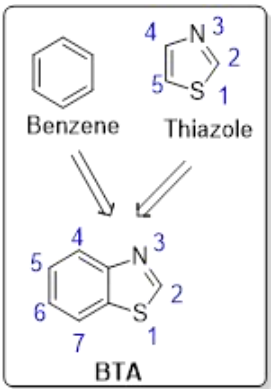


Fig 9: BTA

BTA is a top-tier bicyclic ring structure that also happens to be a popular heterocyclic class with intriguing therapeutic properties. BTA is one of the most prominent privileged bicyclic ring skeletons, having a spectrum of biotic accomplishments with application in drug discovery programme and thence is in the eyes of most scientists prompting them towards the construction of this privileged small skeletal core aiming at the generation of newer products that possess interesting pharmacy deeds. The largest amount of benzothiazoles are used as vulcanization accelerators, such as 2-morpholinothiobenzothiazole in rubber production, antioxidants. The creation of sulphide links (reticulation) between unsaturated elastomeric polymers is catalysed by BTA derivatives, resulting in a flexible and elastic cross-linked material. 2-Mercaptobenzothiazole (MBT) is the most commonly utilised rubber accelerator in a variety of speciality products, including tyre manufacturing. The BTA scaffolds were found to be essential in inhibiting the metalloenzyme carbonic anhydrase (CA). BTA derivatives' reluctance to tumor-connected CAs is better understood, and such drugs could be employed to treat hypoxic tumours. It is to be noted that benzothiazole has no domiciliary use. Figures 14 and 15 show examples of naturally occurring and commercially available pharmaceuticals that include the benzothiazole structural skeleton core.

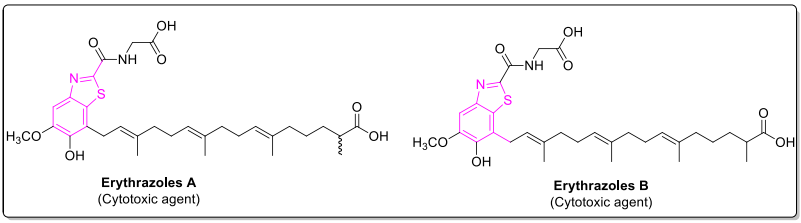


Fig 10: Naturally occurring BTA

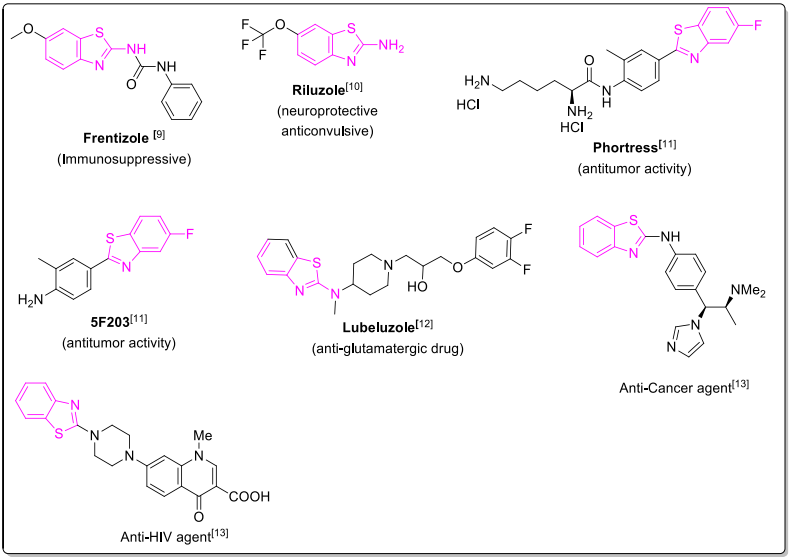


Fig 11: Marketed BTA

The nature and locations of different substituents have diverse effects on the considerable and powerful activity of the benzothiazole nucleus. Substitutions at the 2nd, 4th, 5th, and 6th positions are particularly important for achieving various activities, according to a survey of various publications. In this regard, it's worth noting that combining 2-aminobenzothiazoles with other heterocyclic designs is a well-known method for developing novel drug-like compounds, since it allows for improved pharmacological efficacy while reducing toxicity. As illustrated in Figure 16, 2-substituted BTA derivatives are a broad range of xenobiotics that are generated worldwide for a variety of purposes. A number of 2-aminobenzothiazoles were intensively studied and reported to possess central muscle relaxant whereas biologist's attention was grabbed by the discovery of pharmacological profiles of Riluzole. Due to their unusual structure and potential applications as radioactive amyloid imaging agents and anticancer

agents, 2-aryl benzothiazoles have gained a lot of attention among the many benzothiazoles.

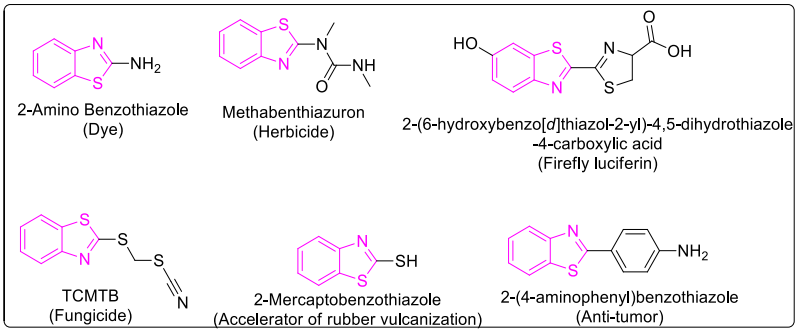
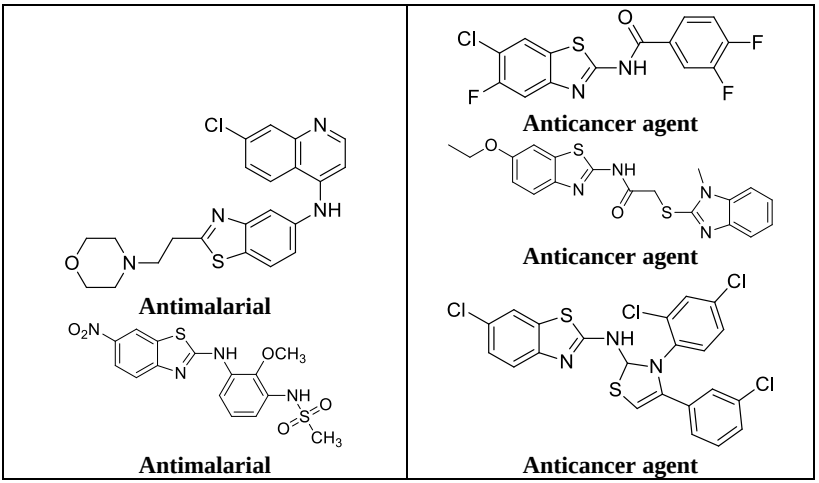


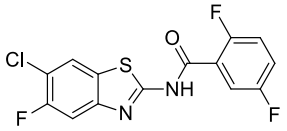
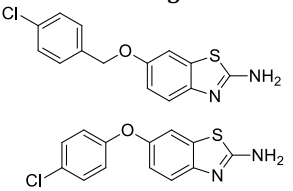
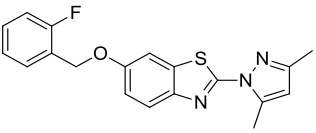
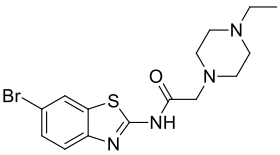
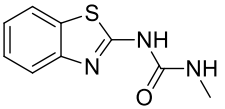
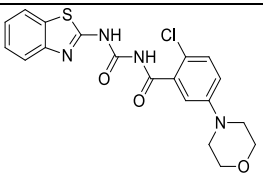
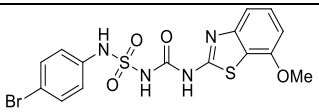
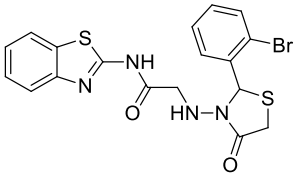
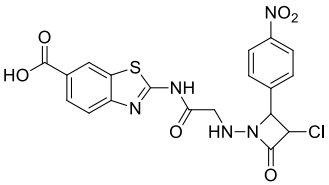
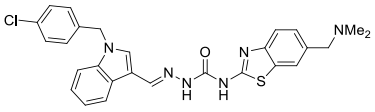
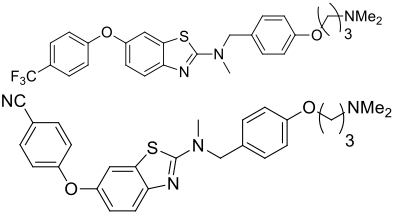
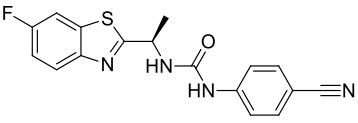
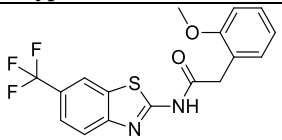
Fig 12: Chemical structures of BTA xenobiotics

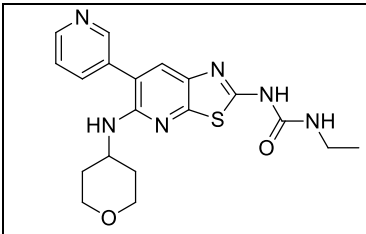
Biological activity of BTA substituents

With its innate kinfolk for numerous biological receptors, BTAs are the archetypal structures that epitomise an appropriate source of core scaffolds and capping fragments for the design and manufacture of targeted smidgens on a reasonable time scale. The use of these molecules allows medicinal chemists to quickly find physiologically active compounds in a variety of therapeutic domains over a long period of time. Some of the biological perspective application of 2-aminobenzothiazoles is tabulated in Table 3.

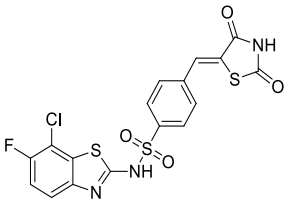
Table 3: Bio-active BTAs



 **Antifungal**  **Antifungal**	 **Anticonvulsant**  **Anticonvulsant**
 **Herbicide**	 **Topoisomerase inhibitor**
 **Anti-bacterial**  **Anti-bacterial**  **Anti-bacterial**	 **Anti-tumor agent**  **N- & T-type calcium channel blockers**
 **Acetylcholinesterase Inhibitor**	 **Amyotrophic Lateral Sclerosis drug**



Anti-tubercular agent



Antidiabetic

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