BENZOTHIAZOLE ANALOGUES: AN IMPORTANT HETEROCYCLIC PHARMACOPHORE USED IN THE DESIGN OF VARIOUS THERAPEUTIC AREAS

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Abstract: Benzothiazole (1, 3-benzothiazole), a weak base is a crucial pharmacophore in heterocyclic compounds that displays a variety of biological properties due to its potent and significant pharmacological activities. The unique methylene centre at the C2 position present in the thiazole ring makes benzothiazole the most common and integral structure of many natural and synthetically synthesized molecules. Benzothiazole derivatives show a variety of activities, with less toxic effects, and their derivatives demonstrate proven enhanced activities. Benzothiazole ring-containing moieties possess various pharmacological activities such as anti-viral, anti-microbial, anti-allergic, anti-diabetic, anti-cancer, anti-inflammatory, anthelmintic, and anti-cancer, making benzothiazole a rapidly developing and interesting compound in the medicinal chemistry. This review briefly explores the importance, and common methods of synthesis of the benzothiazole scaffold and also enlist the popular benzothiazole molecules which have applications in various fields of chemistry. This review includes benzothiazole moieties based on various pharmacological activities and rationalized the structural variations.

Keywords: Benzothiazole, heterocyclic compounds, biological properties

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1. INTRODUCTION

Heterocyclic compounds are cyclic closed compounds with rings that contain one or more additional atoms of carbon.[1] Such non-carbon atoms are known as hetero atoms. The most common hetero atoms are nitrogen, sulphur, and oxygen. Heterocyclic compounds are widely distributed in nature and are particularly important because of the variety of physiological activities associated with this class of substances. [(2)] Important medicinal compounds that include heterocyclic rings such as vitamin B complex, alkaloids, antibiotics, chlorophyll, other plants pigments, amino acids, dyes, drugs, enzymes, genetic material, DNA, etc.[2]

1-1 Benzothiazole

Benzothiazole is an aromatic heterocyclic compound containing a five-membered 1,3 thiazole ring fused to benzene (Figure 1). The core structure of thiazole and its pharmacologically and biologically active compounds are due to the presence of sulphur and nitrogen atoms present in the ring .[1] Thiazolein was first described by Hantzsch and Waber in 1887 and its structure was confirmed by Popp in 1889. The thiazole ring is a five-member ring consisting of one nitrogen and one sulphur atom in the ring. In thiazole, moiety numbering starts from the sulphur atom. The design of active derivatives of thiazole, which have distinct pharmacological actions and aid in the treatment of various therapeutic areas, depends heavily on thiazole and its analogs, such as benzothiazole.[2]

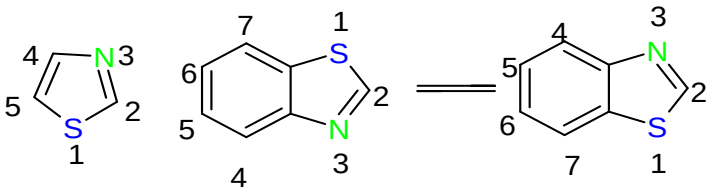


Figure 1: Structure of Benzothiazole and Thiazole

Benzothiazole is the combination of a benzene ring fused at 4, and 5 positions with thiazole (Figure 1). The presence of benzothiazole moiety in various aquatic or terrestrial natural compounds is responsible for its useful biological activities. Benzothiazole is utilized for business and research goals, both of which are highly helpful for the creation of diverse medicinal compounds. These basic benzothiazole nuclei can be found in compounds used in studies assessing novel products with diverse significant biological activity. Benzothiazole is a privileged bicyclic ring system. It has enormous medicinal value due to its powerful and substantial biological actions, hence the synthesis of these molecules is of major interest. Benzothiazole is a colourless and slightly viscous liquid with a melting point of 2 ºC and a boiling point of 227-228 °C. The density of benzothiazole is 1.238 g/ml at 25 ºC.[2]

The substitutions at the 2-position of benzothiazole have emerged in its usage as a core structure in diversified therapeutic applications. The studies of the structure-activity relationship interestingly reveal that change in the structure of the substituent group at the C-2 position commonly results in a change in its bioactivity. One of the rare derivatives of 2-substituted benzothiazoles contains fluorine. Due to their potential bioactivities, modified substances have already generated a lot of attention. [3-5] Medical chemists have not aggressively investigated the analogues of benzothiazoles even though it has been known for centuries, and active physiologically with a variety of therapeutic purposes.[3] However, since the discovery of riluzole or chemically known as (6-trifluoro-2-benzothiazolamine), benzothiazole derivatives have been the subject of extensive research, and it has been discovered that they have a wide range of chemical reactivity and biological activities in several therapeutic areas including anti-tumour, anti-tubercular, anti-malarial, anti-convulsant, anthelmintic, analgesic, anti-inflammatory, anti-fungal, diuretic, anti-hypoxic, anti-nematode, anti-coagulant and anti-psychotic activities.[2]

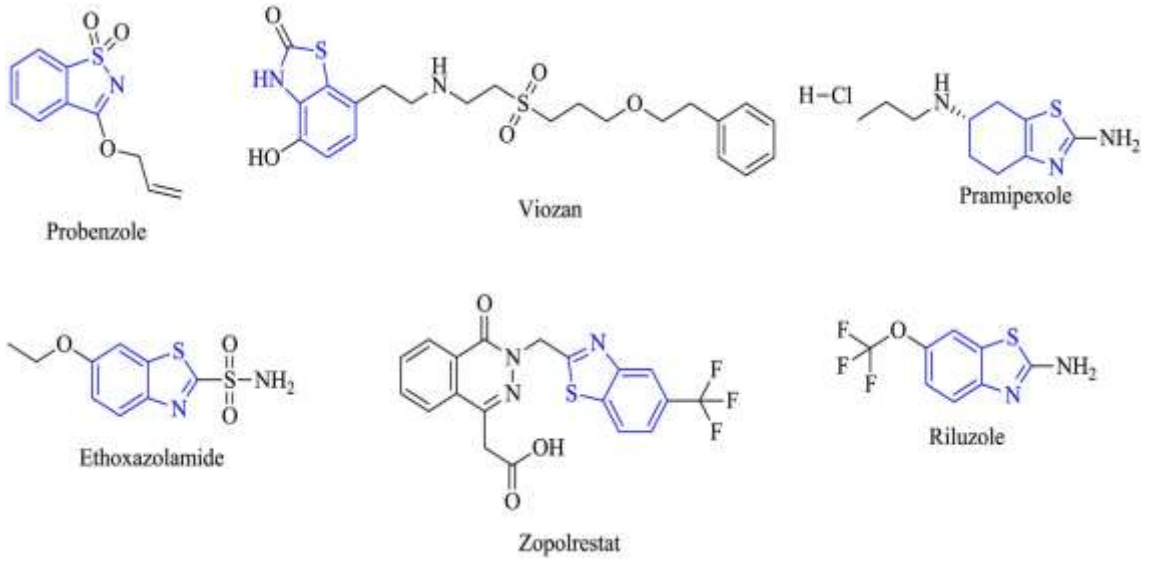


Figure 2: Marketed drugs that contain benzothiazole moiety.

Currently, a number of drugs containing benzothiazoles as the core nucleus are available in the market (Figure.2). These drugs perform different biological activities. For example, violin as a dual D2 dopamine receptor and β2-adrenoceptor agonist; probenazole is used as herbicide; riluzole is used as an anti-depressant and anxiolytic; zopolrestat acts as a aldose reductase inhibitor for the treatment of late-stage diabetic complications including neuropathy, nephropathy; ethoxazolamide is used as a carbonic anhydrase inhibitor. [5–7]

2. General Methods for Preparation of Benzothiazoles

Benzothiazole has been synthesized successfully through various methods such as condensation of 2-aminophenol with various groups to synthesize various compounds. Some of the methods of synthesis are discussed below:

Maradolla et al.(2008) reported One-pot synthesis of 2-aryl benzimidazoles, benzoxazoles and benzothiazole's in excellent yields promoted by imidazolium based ionic liquid [(bmim)BF4] under ambient conditions at higher temperature (Figure 3a).[8]

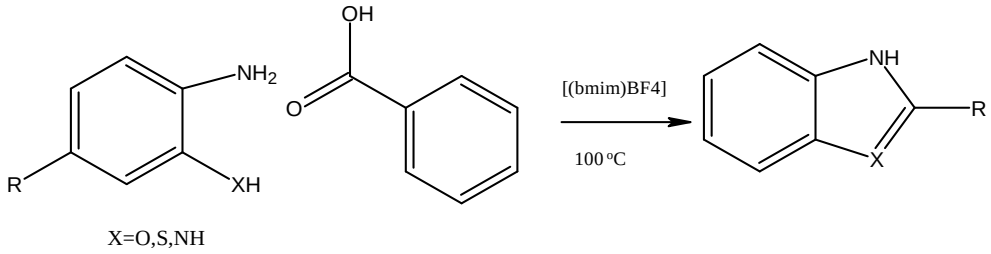


Figure 3a: One-pot synthesis of 2-aryl benzimidazoles, benzoxazoles and benzothiazoles using imidazolium based ionic liquid [(bmim)BF4]

Mali et al. (2010) synthesized 2-aryl substituted benzothiazoles with high yields by cyclocondensing 2-aminothiophenol with a variety of aryl/heteryl aldehydes in polyethylene glycol-400 as a catalyst and reaction medium at room temperature (Figur3b).[9]

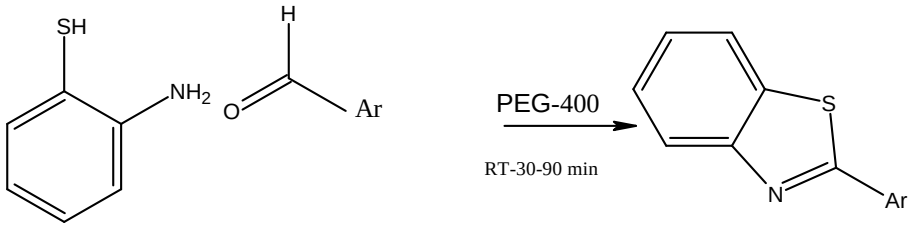


Figure 3b: Cyclocondensing 2-aminothiophenol with a variety of aryl/heteryl aldehydes in polyethylene glycol-400 as a catalyst

Inamoto et al. (2008) using a palladium catalyst, C-H functionalization and C-S bond formation were used to catalyse the synthesis of 2-substituted benzothiazoles from thiobenzanilides. This approach makes use

of a brand-new catalytic system that contains 10 mol% Pd(II), 50 mol% Cu(I), and 2 equivalent of Bu4NBr to create a variety of substituted benzothiazoles in high yields with strong functional group tolerance(Figure3c) [10]

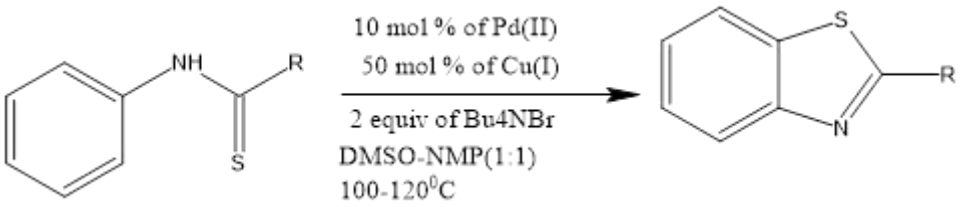


Figure 3c: Synthesis of 2-substituted benzothiazoles from thiobenzanilides using palladium catalyst

Zhu et al. (2010) used a one-pot tandem approach for the synthesis of benzothiazoles from benzyl halides and o-aminobenzenethiol were obtained in high chemical yields under mild conditions in Dimethyl sulfoxide in the absence of an additional oxidant. Both benzyl chlorides and bromides bearing a range of substituents proved to be suitable substrates. (Figure 3d). [11]

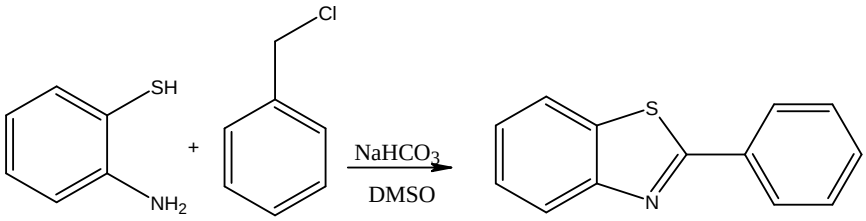


Figure 3d: One-pot tandem approach for the synthesis of benzothiazoles from benzyl halides and o-aminobenzenethiol using DMSO

Muhammad Shareef et al. (2014) used Brønsted acid catalyzed cyclization reactions of 2-amino thiophenols/anilines with β-diketones (Figure 3e). [12]

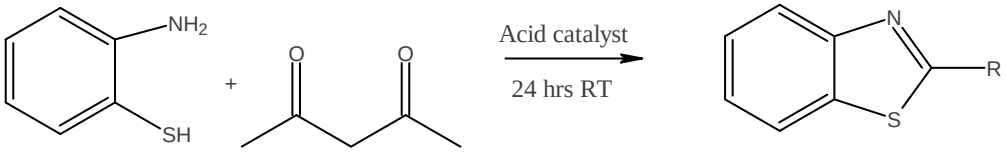
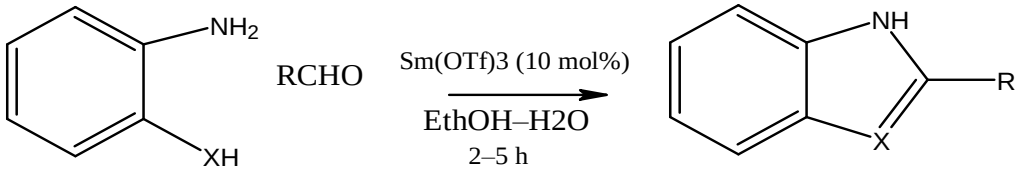


Figure 3e: Brønsted acid catalyzed cyclization reactions of 2-amino thiophenols/anilines with β-diketones

Gorepatil et al, (2013) employed a simple, green, and efficient method for the synthesis of benzoxazoles

and benzothiazoles from reaction of o-aminophenols, o-aminothiophenols, and aliphatic or aromatic aldehydes using samarium triflate as a reusable acid catalyst under mild reaction conditions in aqueous medium (Figure 3f).[13]



X = O, S
R = aliphatic, aromatic, heteroaromatic

Figure 3f: Synthesis of benzoxazoles and benzothiazoles from reaction of o-aminophenols, o-aminothiophenols, and aliphatic or aromatic aldehydes using samarium triflate

Yadong.et al. (2013) developed an efficient method using Copper acetate catalyzed formation of 2-substituted benzothiazoles via condensation of 2-aminobenzenethiols with wide range of nitriles containing different functional groups, Optimization of the reaction conditions explored that the optimal catalytic conditions consist of Cu(OAc)2 (10 mol %) and triethylamine (1.0 equiv.) in ethanol) at 70 °C for 6 hrs. gives best results in terms of yield (Figure 3g) [14]

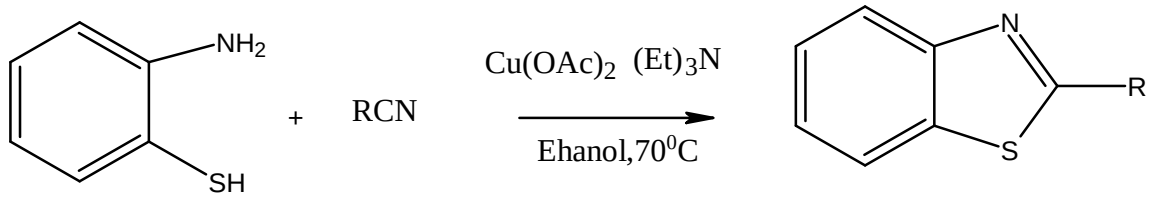


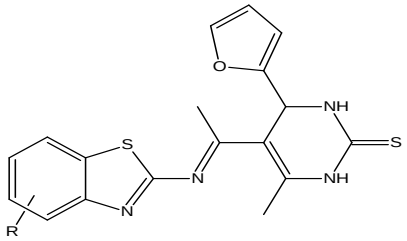
Figure 3g: Formation of 2-substituted benzothiazoles via a copper acetate catalyzed condensation of 2-aminobenzenethiols with nitriles

3 Benzothiazoles of Therapeutic Interest

Benzothiazoles are also used in industry as vulcanization accelerators. 2-aryl benzothiazoles are unique structures and their uses as agents for imaging radioactive amyloid. Benzothiazole ring is present in various marine or terrestrial natural substances with beneficial biological characteristics. Benzothiazole isosteres and derivatives have antibacterial effects on both gram-negative and gram-positive bacteria (such as *Escherichia. coli*, *Pseudomonas aeruginosa*, Enterobacter, *Staphylococcus epidermis*, etc) and the yeast (*Candida albicans*).

3-1 Anti-microbial Activity

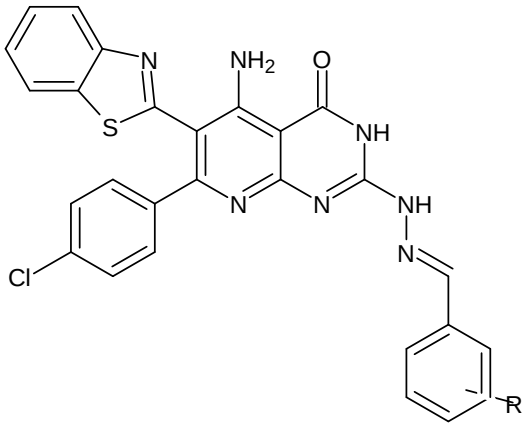
Waghamode KT, et al. (2017) synthesized several benzothiazole derivatives (Figure 4a) and tested them against good activity against Gram +ve (*Staphylococcus aureus*) and Gram –ve bacteria (*E. coli*), they discovered that all of the generated compounds have strong antibacterial activity.[15]



Where R=H, -Cl. CH_3, -Cl, $-NO_2$, $-OC_2H_5$

Figure. 4a: Substituted derivative of 5-[(1E)-N-(1,3-benzothiazol-2-yl)ethanimidoyl]-4-(furan-2-yl)-3,4-dihydropyrimidine-2(1H)-thiones

Lavanya P. et al. (2013) synthesized benzothiazole pyrimidine derivatives (Figure 4b) and tested their antibacterial activity against *S. aureus*, *E. coli*, *Klebsiella pneumonia*, *P. aeruginosa*, and *Streptococcus pyogenes* as well as their antifungal activity against *Aspergillus flavus* and *Aspergillus fumigatus*.[16]



R=H, -F, CH_3, -Cl, $-NO_2$, $-OC_2H_5$, OCH_3 .C_2H_5

Figure 4b: 5-amino-6-(benzo[d]thiazol-2-yl)-2-(2-(substituted benzylidene) hydrazi-nyl)-7-(4-chlorophenyl)pyrido[2,3-d]pyrimidin-4(3H)-one derivatives

Sekar N. et al. (2016) synthesized a small number of substituted benzothiazole compounds. Using the serial dilution approach, Figure. 4c assessed their antibacterial activity against *E. coli* and *S. aureus* and antifungal

activity against *Candida albicans* and *Aspergillus niger*. They discovered in their research that the substance 2-(1, 3-Benzothiazole-2-yl)-5-(N, N-diethylamino)phenol has effective antifungal properties.[17]

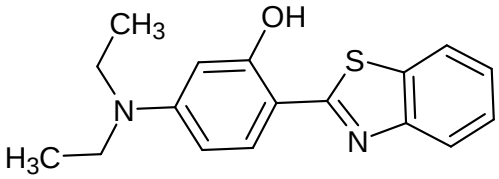


Figure 4c :2-(1,3-benzothiazol- 2-yl)-5-(diethylamino)phenol

Amir M, et al. (2011) synthesized 1, 3, 4-thiadiazole and imidazoline derivatives including benzothiazole, (Figure 4d) and used the cup-plate agar diffusion technique to screen them for both antibacterial and antifungal activities. Reference standards for antibacterial and antifungal activities were ofloxacin (50 g/ml) and ketoconazole (50 g/ml), respectively. *E. coli*, *S. aureus*, *C albicans*, and *A. flavus* were tested for antimicrobial activity as well as *A. flavus* and *C. albicans* for antifungal activity.[18]

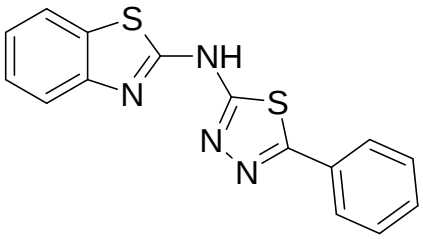


Figure 4d: 2-Aryl-5-(6′-chloro-1′,3′-benzothiazole-2-yl-amino)-1,3,4-thiadiazoles

3-2 Anticancer Activity

Nearly 7 million individuals die from cancer each year, making it a huge threat to global health and a major obstacle for medical science. The development of new effective anticancer drugs (ligands) and the identification of new molecular receptors (target proteins) are the main focuses of worldwide research projects on this subject.

Davis IW et al. (2007) synthesized new benzothiazole-2-thiol derivatives and examined how well they inhibited cancer cell proliferation.[19] Several chemicals were learned to be more effective than cisplatin at preventing cellular development. Havrylyuk et al. (2010) assessed the anticancer efficacy of several novel 4-thiazolidinones with benzothiazole moiety. The *in vitro* anticancer properties of synthesized substances

were evaluated by the National Cancer Institute. [20] In the treatment of anemia, carcinoma, lung illness, prostate, renal, ovarian, central nervous system, colon, as well as breast cancer cellular collections, some of them have proven to be effective. [20]

New benzothiazole acyl hydrazone compounds were synthesized by Ozkay Y et al. in 2008, and their anticancer efficacy was assessed. [21] They discovered that the substance 2-((5-Chlorobenzothiazol-2-yl) thio)-N-(4-(3 methyl piperidine-1-yl) benzylidene) acetohydrazide had good anticancer activity in their investigation.[21] Kini SG et al. produced 2 amino benzothiazoles and assessed their antitumor efficacy in a different investigation. In their research, they discovered the good action of the chemical (E)-N-(6-chloro-1, 3-benzothiazole-2-yl)-1-(2, 5 dimethoxyphenyl) methanimine (Figure 5a). [22]

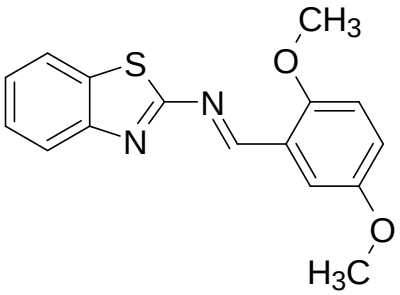


Figure 5a: (E)-N-(6-chloro-1,3-benzothiazole-2-yl)-1-(2, 5 dimethoxyphenyl) methanimine

Leal KZ et al. (2016) synthesized several derivatives of the chemical (E)-2-benzothiazole hydrazone and assessed their anticancer efficacy. They discovered in their research that the chemical (E)-2-((2-(benzo[d]thiazol-2-yl) hydrazone) methyl) benzene-1,4-diol had high anticancer action (Figure 5b).[23] In 2010, Saeed et al. synthesized five series of benzothiazole-modified thiourea compounds and tested them for their anticancer potential. The thiourea derivatives a, b, and c with substitution indicated in were shown to be the most powerful in preliminary MTT [3-(4, 5- dimethyl thiazol-2-yl) -2, 5- diphenyltetrazolium bromide] cytotoxicity assays. [24]

	R1	R
A	Br	2-thiophene
B	NH 2	4-morpholine
C	Br	4-morpholine

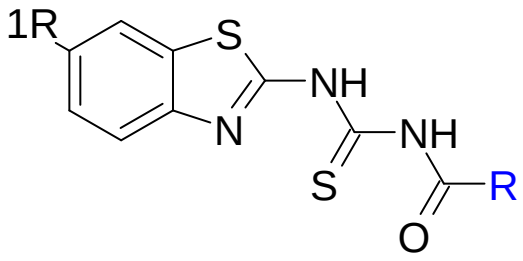


Figure 5b: (E)-2-benzothiazole hydrazone derivatives

Ashraf et al. (2016) modified the combretastatin A-4 (CA4) pharmacophore using benzothiazole scaffolds, and then developed and produced a series of colchicine site-binding tubulin inhibitors. [25] On a few different cancer cell lines, these substances were tested for their ability to inhibit cancer cell proliferation. The most effective compounds, showed an antiproliferative activity that was both equivalent to and superior to that of CA4 (GI50 = 0.06 0.001 M and 0.04 0.001 M, respectively, against HeLa cells and human cervical cancer cell line. According to molecular docking experiments, these drugs attach to the tubulin's colchicine site similarly to combretastatin A-4. The methoxy group on the benzothiazole moiety's C-6 position was shown to be crucial for antiproliferative action (Figure 5c).[25]

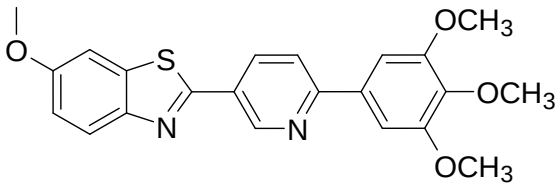


Figure 5c: 6-methoxy-2-(6-phenylpyridin-3-yl)benzo[d]thiazole derivatives

Prabhu et al (2012) synthesized several 2-(34-oxo-2-substituted phenyl thiazolidine-3-yl)phenyl) benzo [d] thiazole-6-carboxylic acid derivatives. Various benzothiazole Schiff's bases were combined with thioglycolic acid to synthesize the compounds shown in Figure. 5d. In contrast to compounds b, c, and d, compound a had the most notable action.[26]

	R1
a	p-Cl
b	p-OCH_3
c	p-CH_3
d	p-OH

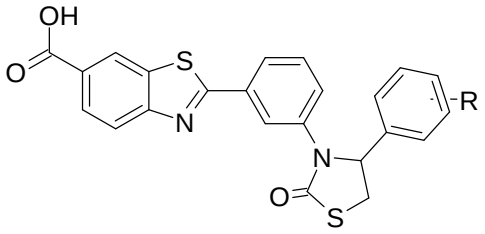


Figure 5d: 2-(3-(4-oxo-2-substituted phenyl thiazolidine-3-yl)phenyl) benzo [d] thiazole-6-carboxylic acid derivatives

Xiang et al. (2012) synthesized twenty benzothiazole derivatives bearing a 1,3,4-oxadiazole moiety and evaluated them for both antioxidants as well as anti-inflammatory activities. [27] These were more potent than the reference drug (indomethacin) Figure 5e. Molecular modeling studies showed the binding interaction of the representative compounds with the cyclooxygenase (COX)-2 enzyme. *In vitro* enzyme study implied that compound exerted its anti-inflammatory activity through COX-2 inhibition.[27]

	R
a	o-Cl
b	p-F
c	p-Br

d	p-NO_2

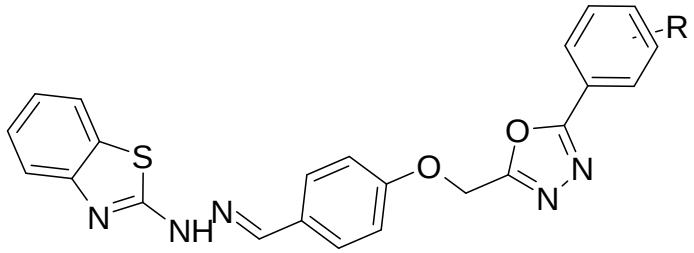


Figure 5e: Substituted 1,3,4-oxadiazole moiety of benzothiazole

Abhay K V et al., (2014) synthesized benzothiazole nucleus and then treated it with various substituted aromatic aldehydes to get the corresponding Schiff's bases followed by treatment with phthalic anhydride to form 2-(6- acetamidobenzo[d]thiazol-2-ylcarbamoyl) benzoic acid Figure 5f. The products' analgesic and anti-inflammatory properties were assessed. When compared to the standard (acetaminophen), few substances showed strong activity. [28]

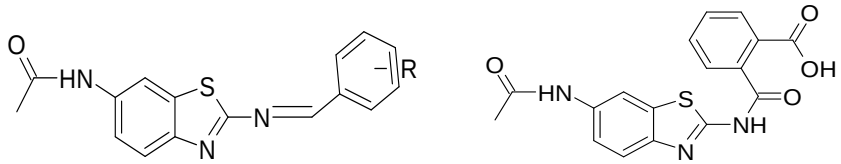


Figure 5f: 2-(6- acetamidobenzo[d]thiazol-2-ylcarbamoyl) benzoic acid

Shafi et al. (2014) synthesized a series of 2-mercaptobenzothiazole and 1,2,3-triazoles (Figure 5g). These synthesized compounds were evaluated for their anti-inflammatory activity by using biochemical COX activity assays and carrageenan-induced hind paw edema. The compound 13d demonstrated a potent, selective COX-2 inhibition with a COX- 2/COX-1 ratio of 0.44. Compounds showed potent anti-inflammatory activity as compared to the standard drug Ibuprofen. [29]

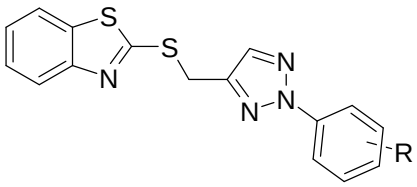


Figure 5g: 2- mercaptobenzothiazole and 1, 2, 3-triazoles derivatives

Venkatesh P et al. (2009) synthesized a series of substituted 1, 3-benzothiazole-2-amine Figure. 5h in which three compounds (5-chloro-1, 3- benzothiazole-2-amine), (6-methoxy-1, 3-benzothiazole-2-amine) and (4-methoxy-1, 3- benzothiazole-2-amine) [Figure 5h] were found the most active compounds for anti-

inflammatory activity. [30]

	R
a	5-Cl
b	6-OCH_3
c	4-OCH_3

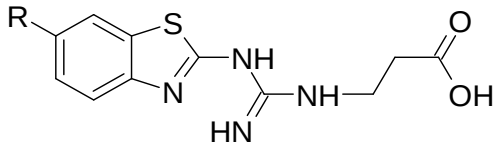


Figure 5h: (1,3-benzothiazole-2-amine),(6-methoxy-1,3-benzothiazole-2-amine derivatives

Paramashivappa R et al. (2003) synthesized some of 2-[(2- alkoxy-6-pentadecylphenyl) methyl] thio- 1-Hbenzimidazoles/benzothiazole from anacardic acid (pentadactyl salicylic acid) [Figure 5i] and studied for their ability to inhibit human COX enzyme-230. [31]

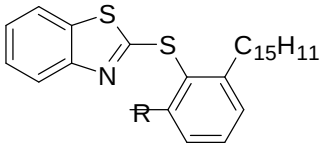


Figure 5i: 2- [(2- alkoxy-6-pentadecylphenyl) methyl] thio- 1-Hbenzimidazoles/benzothiazole derivatives

Abbas et al. synthesized a novel class of compounds with the benzothiazole-2-one or benzothiazole ring system coupled to several additional heterocycles.[32] The synthetic compounds' anti-inflammatory and antinociceptive effects were assessed using rat paw edema models caused by carrageenan and the hot-plate test, respectively. In comparison to standard medication indomethacin (78.04%) and standard tramadol (reaction time after 2 h: 20.33 0.08 s), the compound in Figure. 5j with the 1,3-diphenyl-1H-pyrazole-4-ylmethylene group demonstrated the strongest anti-inflammatory activity (82.16%). According to structure-activity relationship (SAR) investigations, diphenyl pyrazole nucleus attachment to Schiff's base of benzothiazole was crucial for the compound's dual anti-inflammatory and antinociceptive action. [32]

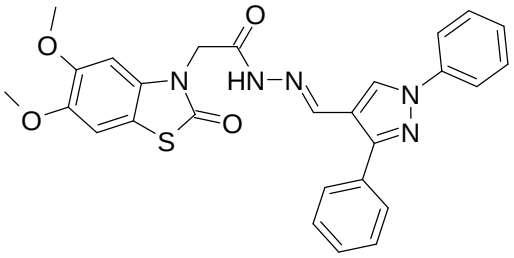


Figure 5j: 2-(5,6-dimethoxy-2-oxobenzo[d]thiazol-3(2H)-yl)-N'-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)acetohydrazide.

Ali et al. (2016) assessed the anti-inflammatory activity of 2-(3-(4-chlorophenyl)-5-phenyl substituted 4,5-dihydro-1H-pyrazol-1-yl)benzo[d]thiazole-6-sulfonamide derivatives (Figure 5k). Inflammation was reduced more than that of celecoxib, the conventional medication. They also reduced TNF-alpha production and COX-2 enzyme activity without being cytotoxic or ulcerogenic. According to SAR investigations, adding a halogen to the aryl group boosted *in vivo* anti-inflammatory activity and the ability to inhibit mediators like COX-2 and TNF-alpha. To evaluate their interactions with the target protein 2AZ5, all the produced compounds were docked on the chosen protein target. It was observed that most of the compounds exhibited strong hydrogen bonding or π–π stacking with amino acid residues present in the active site. [33]

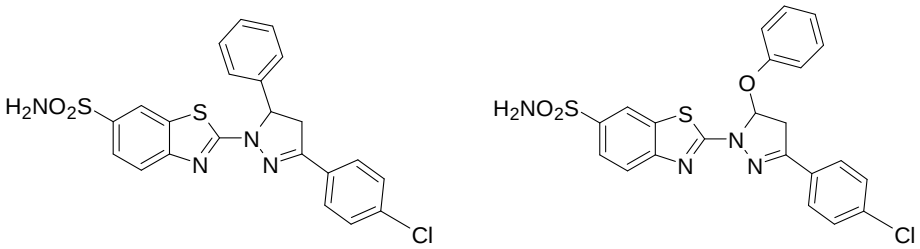


Figure 5k: 2-(3-(4-chlorophenyl)-5-phenyl substituted -4,5-dihydro-1H-pyrazol-1-yl)benzo[d]thiazole-6-sulfonamide

3-3 Anticonvulsant Activity

Siddiqui et al. (2017) conceived and synthesized 2-[(6- substituted-benzo[d]thiazol-2-ylcarbamoyl)methyl]-1-(4-substituted phenyl)isothiourea derivatives as anticonvulsant drugs (Figure. 6a). Comparing all of the compounds to phenytoin and carbamazepine the conventional compounds, were most effective compounds for the maximal electroshock seizure model (MES), pentylenetetrazole (PTZ) models. Additionally, the synthesized compounds showed larger binding free energies (dG bind) for GABA-A in molecular docking tests, suggesting that they may be more selective for GABA. [34]

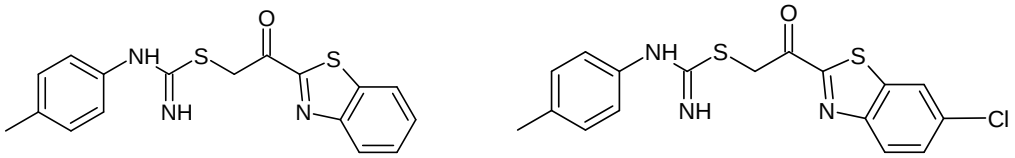


Figure 6a: 2-[(6-substituted-benzo[d]thiazol-2-ylcarbamoyl)methyl]-1-(4-substitutedphenyl) isothiourea derivatives

Ali et al. (2015) synthesized brand-new derivatives of N-(substituted-2-oxo-4-phenylazetidin-1-yl)-2-((6-substitutedbenzo[d]thiazol-2-yl) amino) acetamide Figure 6b. MES and scPTZ tests on albino mice were used to check the activity of these synthesized substances. The compounds, shown in Figure 6b were found to exhibit promising activity in these tests, with effective dose (ED 50) values of 15.4 and 18.6 mg/kg and protective indices of 20.7 and 34.9 in the MES test, respectively. These values were significantly higher than those of the common medications, phenytoin (6.9) and carbamazepine (8.1). Additionally, the compounds lacked neurotoxicity.[34]

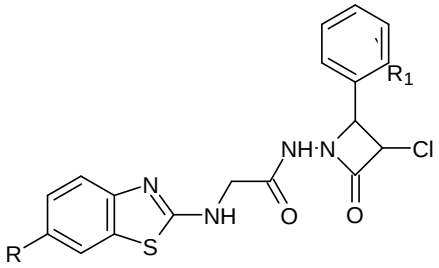


Figure 6b: N-(substituted-2-oxo-4-phenylazetidin-1-yl)-2-((6-substitutedbenzo[d]thiazol-2-yl) amino) acetamide

Liu et al. (2016) synthesized a novel series7-alkoxy[1,2,4]triazolo[3,4-b]benzothiazol-3(2H)- ones and their anticonvulsant activity was reported (Figure 6c). [35]Two derivatives were produced from all the synthetic chemicals. In comparison to carbamazepine (ED50 = 11.8 mg/kg, 49.94 mmol/kg), 7-propoxy[1,2,4]triazolo[3,4-b]benzothiazol-3(2H)-one and 7-butoxy[1,2,4]triazolo[3,4-b]benzothiazol-3(2H)-one (Figure 6c) shown the greatest action against maximal electroshock (MES)-induced. [35]

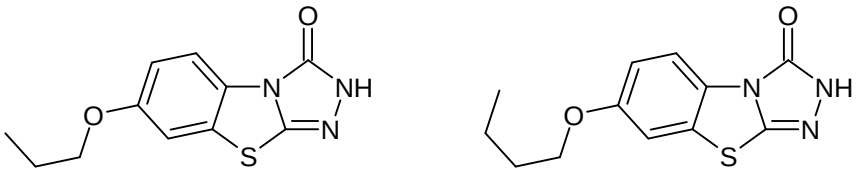


Figure 6c: 7-alkoxy substituted [1,2,4]triazolo[3,4-b]benzothiazol-3(2H)-one

A unique series of N-(benzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide derivatives were synthesized by Malik et al. 2016 (Figure. 6d). Their anticonvulsant activity was assessed

using the MES, scPTZ, and 6 Hz models of seizures. In the anticonvulsant experiment, it was discovered that the compounds [2-methyl-4-oxoquinazoline- 3(4H)-carbothio-N-(6-chlorobenzo[d]thiazol-2-ylcarbamoyl)amide (Figure 6d) and [2-methyl-4-oxoquinazoline-3(4H)-carbothio-N-(6-trifluoromethoxybenzothiazole (Figure 6e) . According to SAR investigations, the sixth-position electron-withdrawing group of a benzothiazole, such as Cl, favored the anticonvulsant action.[36]

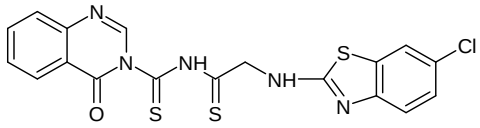


Figure 6d: [2-methyl-4-oxoquinazoline-3(4H)-carbothio-N-(6-chlorobenzo[d]thiazol-2-ylcarbamoyl)amide

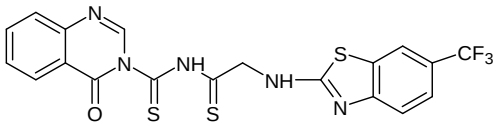


Figure 6e :2-methyl-4-oxoquinazoline-3(4H)-carbothio-N-(6-trifluoromethoxybenzothiazole

Saeed et al. (2017) produced several N-(substituted benzo-thiazol-2-yl)amide compounds and assessed their anticonvulsant and neuroprotective effects.[37] With median dosages of 40.96 mg/kg (MES ED50), 85.16 mg/kg (scPTZ ED50), and 347.6 mg/kg, the compound in (Figure.6f) N-(6-methoxybenzo[d]thiazol-2-yl)-4-oxo-4-phenylbutanamide showed the most effective anticonvulsant (TD50. A molecular docking investigation was conducted on the GABA-AT enzyme to learn more about the GABAnergic impact of compounds. This compound's overall SAR revealed that the derivatives with electron-releasing groups were more active than the derivatives with electron-withdrawing groups. [37]

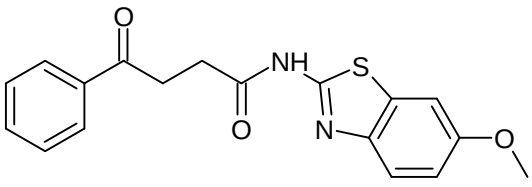


Figure 6f: N-(6-methoxybenzo[d]thiazol-2-yl)-4-oxo-4-phenylbutanamide

3-4 Antimalarial activity

Thakkar et al. (2017) synthesized a brand-new series of benzothiazole analogs. The compounds' *in vitro* cytotoxicity and genotoxicity toward Schizosaccharomyces pombe cells and *in vitro* antimalarial activity were investigated. The most potent compounds were(E)-N-(3-nitrobenzylidene)benzo[d]thiazol-2-amine (Figure. 7a) and (E)-N-(4-chlorobenzylidene)benzo[d]thiazol-2-amine (Figure 7b). The active substances were docked to the dihydrofolate reductase from Plasmodium falciparum (PDB ID: 4DPD). [38]

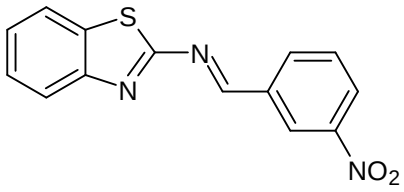


Figure 7a: (E)-N-(3-nitrobenzylidene)benzo[d]thiazol-2-amine

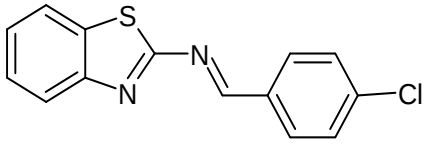


Figure 7b: (E)-N-(4-chlorobenzylidene)benzo[d]thiazol-2-amine

Sharma et al. (2017) developed a brand-new class of N-(6-methoxy-benz[d]thiazole-2-yl)-2-substituted phenyl-1H-benz[d]imidazole-1-carbothioamide derivatives (Figure 7c). When compared to the reference drugs quinine (IC50: 0.268 g/mL) and chloroquine (IC50: 0.020 g/mL), the molecule substituted with (3,4,5-trimethoxy) and with (3,4-dinitro) groups demonstrated the greatest inhibition against *Plasmodium falciparum* (IC50: 0.18 and 0.11 g/mL, respectively). **[39]**

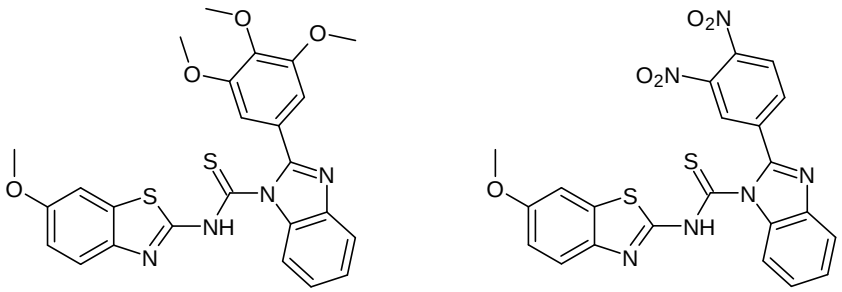


Figure 7c: N-(6-methoxy-benz[d]thiazole-2-yl)-2-substitutedphenyl-1H-benz[d]imidazole-1-carbothioamide derivatives

3-5 Anti-diabetic Activity

Kumar S et al. (2016) synthesized few 2- ((benzothiazole-2-ylthio) methyl)-5-phenyl-1, 3, 4 oxadiazoles and their anti-diabetic efficacy was assessed. They discovered in their research that the substances 2-(6-nitrobenzo [d]thiazol-2-yl) thio) methyl)-5-(4-nitrophenyl)-1, 3, 4-oxadiazole (Figure 8a) show outstanding anti-diabetic action.**[40]**

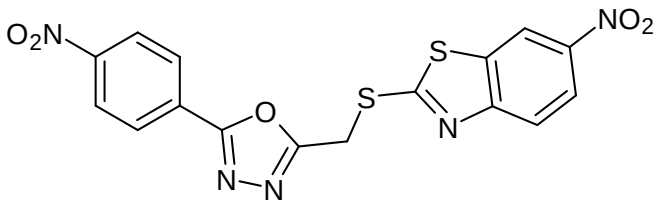


Figure 8a :2-(((6-nitrobenzo [d]thiazol-2-yl) thio) methyl)-5-(4-nitrophenyl)-1, 3, 4-oxadiazole

A few benzothiazole derivatives were synthesized by Sasson S et al. (2013) and their anti-diabetic efficacy was assessed. They discovered in their research that the substance 2- (benzo[d] thiazol-2-ylmethyl thio)-6-ethoxybenzo[d] thiazole (Figure 8b) had a good antidiabetic effect. These substances increased the rate of glucose absorption up to 2.5 times more than vehicle-treated cells and up to 1.1 times more than prothrombin time (PT) . It also increased the amount of glucose transporter protein type-4 (GLUT4). present in the myotubes' plasma membrane and turned on AMP-activated protein kinase (AMPK) concurrently.[41]

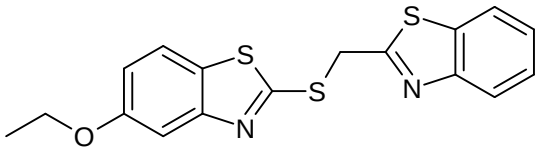


Figure 8b: 2- (benzo[d] thiazol-2-ylmethyl thio)-6-ethoxybenzo[d] thiazole

Mariappan G et al. (2012) synthesized N-(6-chlorobenzoate [d] thiazol-2-yl)-2-morpholinoacetamide (Figure 8c). They synthesized various benzothiazole derivatives and evaluated the antidiabetic activity in their study. They discovered that all synthesized compounds possessed prominent antidiabetic activity. [42]

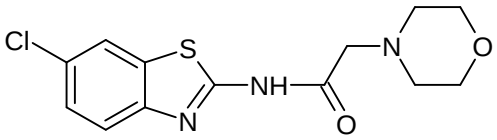


Figure 8c: N-(6-chlorobenzoate [d] thiazol-2-yl)-2-morpholinoacetamide

3-6 Miscellaneous Activity

Taha et al. (2019) developed numerous fresh benzothiazole analogues and their urease-inhibiting potential was examined. All of these compounds displayed exceptional urease inhibitory potential, ranging from 11.4 ± 0.10 to 34.43 ± 2.10 µM when compared with standard thiourea (IC50 19.46 ± 1.20 µM). Below mentioned Compound 2-(4-(benzo[d]thiazol-2-yl)benzoyl)-N-(4-nitrophenyl)hydrazinecarbothioamide (Figure 9a) emerged as the strongest in the series (IC50 1.4 ± 0.10 µM.[43]

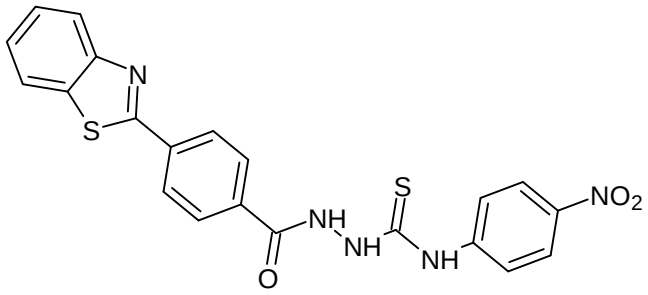


Figure 9a :2-(4-(benzo[d]thiazol-2-yl)benzoyl)-N-(4-nitrophenyl)hydrazinecarbothioamide

Setyan et al. (2010) designed and synthesized a number of novel benzothiazole-piperazine compounds in order to discover potential acetylcholine esterase (AChE) inhibitors,. The compound's ability to inhibit AChE enzyme was investigated. The AChE enzyme was extremely responsive to the chemicals N-(5,6--dimethoxybenzo[d]thiazol-2-yl)-3-(4-(2-(dimethylamino)ethyl)piperazin-1-yl)propenamide (Figure 9b) and N-(5,6-dimethoxybenzo[d]thiazol-2-yl)-3-(4-(3-(dimethylamino)propyl)piperazin-1-yl)propenamide (Figure 9c). There were other investigations on cytotoxicity and genotoxicity.[44]

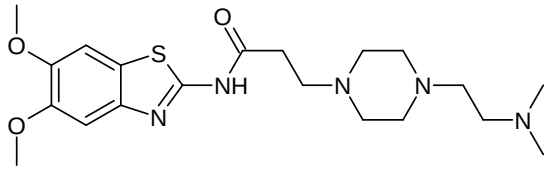


Figure 9b: N-(5,6--dimethoxybenzo[d]thiazol-2-yl)-3-(4-(2-(dimethylamino)ethyl)piperazin-1-yl)propenamide

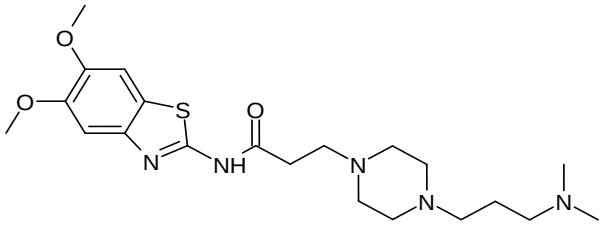


Figure 9c: N-(5,6-dimethoxybenzo[d]thiazol-2-yl)-3-(4-(3-(dimethylamino)propyl)piperazin-1-yl)propenamide

4 Benzothiazole in Clinical Trials and Patents

Apart from the various derivatives of benzothiazole which have been mentioned above some of the derivatives are currently studied and are in different stages of clinical trials. Some of the important compounds in the clinical trial are listed in Table 1. Similarly, some important compounds of Benzothiazole derivatives investigated have been granted patents, which highlight its importance. Some of which are given in Table 2.

Table 1: Benzothiazole derivatives investigated in clinical trials

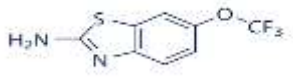
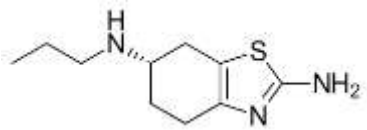
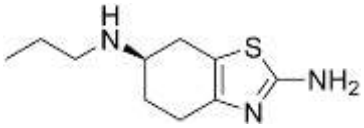
Drug	Indication	Clinical trial
Riluzole 	Post-traumatic stress disorder (PTSD)	Phase 147, Phase 2 [45]
	Depression	Phase 2[46]
	Adult solid meoplasm, recurrent melanoma	Phase 1[47]
	Obsessive-compulsive disorder (OCD)	Phase 2 [48]
Pramipexol 	Amyotrophic lateral sclerosis	Phase 2[49]
	Early Parkinson's disease	Phase 4[50]
	Bipolar disorder	Phase 4 [51]
	]	Phase 2 [52]
Dexpramipexole 	Hypereosinophilic syndrome	Phase 2 [53]
	Chronic sinusitis with nasal polyps and eosinophilia	Phase 2 [54]

Table 2: Benzothiazole derivatives list of patents[55]

S. no	Patent no.	Application/ publication no.	Patent date	Inventors	Title
1	WO2017120198 A1[65]	PCT/US2017/ 012139	Jul 13, 2017	Jerry Yang	Benzothiazole amphiphiles
2	WO2017063966 A1[66]	PCT/EP2016/ 074122	Apr 20, 2017	Kai Thede	Substituted 2-(1*H*-pyrazol-1-yl)-benzothiazole compounds
3	WO2017025980 A3[67]	PCT/IN2016/ 000207	Apr 6, 2017	Kalpana Chauhan et al.	Novel benzothiazole derivatives with enhanced biological activity
4	WO2016079688 A1[68]	PCT/IB2015/ 058919	Nov 11, 2015	Christine Schmitt et al.	Antibacterial benzothiazole derivatives
5	US8691185 B2[69]	US 13/548,014	Apr 8, 2014	Prasad Raje et al.	Benzothiazole derivative compounds, compositions, and uses
6	WO2014036242 A3[70]	PCT/US2013/ 057264	Aug 29, 2013	Russell Dahl et al.	Benzothiazole or benzoxazole compounds as SUMO activators
7	US20130004422 A1[71]	US20130004422A1	Jan 03, 2013	W. E. Klunk et al.	Benzothiazole derivative compounds, compositions, and uses
8	US20130079340 A12[72]	US 13/660,045	Mar 28, 2013	Florencio Zaragoza Dorwald et al.	Benzothiazoles having histamine H3 receptor activity
9	US8546393	US	Oct 1,	Eva Albert	6-Triazolopyridazine

	B2[73]	12/693,736	2013	et al.	sulfanyl benzothiazole derivatives as MET inhibitors
10	US20120101094 A1[74]	US8252811 B2	Aug 28, 2012	Wenge Xie et al.	Indazoles, benzothiazoles, and benzoisothiazoles, and preparation and uses thereof
11	US20120095021 A1[75]	US13232407	Sep 14, 2011	Ahmed Kamal et al.	Synthesis of new benzothiazole derivatives as potential anti-tubercular agents
12	EP2358689 A1[76]	EP20090775337	Aug 24, 2011	Masanori Okaniwa et al.	Benzothiazole derivatives as anticancer agents
13	US7928140 B2[77]	US 12/221,416	Apr 19, 2011	Shon Booker	Benzothiazole PI3 kinase modulators for cancer treatment
14	WO2011075631 A1[78]	PCT/US2010/ 060981	Jun 23, 2011	Alfonzo D. Jordan et al.	Substituted benzothiazole and benzoxazole derivatives useful as inhibitors of dpp-1
15	WO2010066357 A1[79]	PCT/EP2009/ 008499	Jun 17, 2010	Jorma Hassfeld	Benzothiazole amides for detection of amyloid beta
16	US8143258 B2[80]	US12628697	Dec 1, 2009	Masanori Okaniwa et al.	Benzothiazole compounds useful for Raf inhibition
16	US7553854 B2[81]	US 11/737,069	Jun 30, 2009	James C. Sutton	6-*O*-Substituted benzoxazole and

					benzothiazole compounds and methods of inhibiting CSF-1R signaling
17	US20090118272 A1[82]	US 12/333,425	May 7, 2009	Chunjian Liu et al.	Benzothiazole and azabenzothiazole compounds useful as kinase inhibitors
18	WO2009039553 A1[83]	PCT/AU2007/ 001442	Apr 2, 2009	Keith Geoffrey Watson	Benzothiazole compounds
19	WO2008124393 A1[84]	PCT/US2008/ 059024	Oct 16, 2008	Yun He et al.	Benzothiazole derivatives and their use as protein kinase inhibitors
20	US20080227985 A1[85]	US 12/049,235	Sep 18, 2008	Prasad Raje	Benzothiazole derivative compounds, compositions, and uses. Synthesis of chirally purified substituted benzothiazoles

5 CONCLUSIONS

The diverse family of heterocyclic chemicals known as benzothiazoles displays a wide range of biological actions. The condensation of 2-aminothiophenols with different acids, aldehydes, ketones, nitriles, and esters is one of the several methods for their synthesis that have been established. Recent years have seen the development of several benzothiazoles, many of which have significant anti-tubercular, antibacterial, antimalarial, anticonvulsant, anthelmintic, analgesic, anti-inflammatory, antidiabetic, and anticancer properties. The benzothiazole nucleus' significance is further demonstrated by the fact that it is present in a number of clinically effective medications, including the neuroprotective medicine riluzole, the diuretic drug ethoxolamide, the antiparkinsonian drug pramipexole, and medications for Alzheimer's disease (Thioflavine). Due to its many molecular targets, this advantageous scaffold has a vast application space. The knowledge presented in this study may be helpful for further investigation into this moiety's biological

potential and for the further creation of pharmacologically effective medicinal medicines.

ACKNOWLEDGEMENTS

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