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Benzothiazole analogues and their biological aspects: A Review

Jyoti V Popli[a]*, Manoj R Kumbhare[a], Ajay R Surana[b], Mrunal R Bhalerao[a] & Pranay A Agrawal[a]

[a] Department of Pharmaceutical Chemistry, S.M.B.T College of Pharmacy, Dhamangaon, Taluka: Igatpuri, District Nashik 422 403, India

[b] Department of Pharmacognosy, S.M.B.T College of Pharmacy, Dhamangaon, Taluka: Igatpuri, District Nashik 422 403, India

E-mail: jyotipopli97@gmail.com

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Heterocyclic compounds analogues have attracted strong interest in medicinal chemistry due to their pharmacological properties. Benzothiazole belongs to the heterocyclic class of bicyclic compounds. It is a combination of two rings six membered and five membered and both the rings are responsible for the therapeutic activity. Different methods are used to synthesize benzothiazole compounds and have been found to have numerous biological activities like – anticancer, antimicrobial, anti-inflammatory, anti-leishmanial, antidiabetic activity. This review is mainly an attempt to present the work reported in literature on pharmacological activity of benzothiazole compounds.

Keywords: Heterocyclic, antimicrobial, anticancer, anti-inflammatory

The chemistry and biological study of heterocyclic compounds has been a thought-provoking field for a long time in medicinal chemistry. A heterocyclic compound is one which contains cyclic ring made up of more than one kind of atom. In some cyclic compounds like benzene, naphthalene, cyclohexanol, etc. The ring made up of only carbon atom is called homocyclic rings. If ring contains other kind of atom in addition to carbon atom like N, S, O, etc in ring system are referred to as heterocyclic compounds[1]. In several compounds, benzene is fused with 5-membered heterocyclic system such as indole, benzothiazole, benzimidazole, benzoxazole which have been synthesized and extensively because of their pharmacological activity[2] (Figure 1).

Overview

Hantzsch and Waber in 1887 first described thiazolein and later on its structure was confirmed by Popp in 1889[3]. Benzothiazole are important class of heterocycles which functions as an exclusive and adaptable scaffold for experimental drug design[4]. The ring system in which benzene ring is fused to 4, 5 position of thiazole ring is titled as benzothiazole and is completely planar. The various positions on benzothiazole ring are numbered in manner indicated with Sulphur having the priority over other family members. Benzothiazole rarely occur in various marine or terrestrial natural compounds which have useful biological activities[5].

Benzothiazole derivatives have attracted continuing interest due to their biological activities viz. anticancer[6], antimicrobial[7], anticonvulsant[8], antiviral[9], antitubercular[10], antimalarial[11]. Recently benzothiazole have been appraised as potential amyloid binding diagnostic agent in neurodegenerative disease[12,13], inhibitors of coenzyme A-9 desatorose[14], plant protectants[15] and photographic sensitizers[16]. Being a heterocyclic, benzothiazole finds use in research as a starting material for the synthesis of large, usually bioactive structure. Its aromaticity makes it relatively stable, as a heterocycle, it has reactive sites, which allows for functionalization. Benzothiazole is a colourless, slightly viscous liquid with m.p.2ºC and b.p.237-238ºC. The density of benzothiazole is 1.24 g/ml and molecular mass is 135.19 g/mol. It is used in industry and research[17].

Chemistry

In 1887, 2- substituted benzothiazole was synthesized by A.W Hoffmann because of diversified activity as well as simple cyclization mechanism[18]. Traditional methods for preparation of the benzothiazole framework

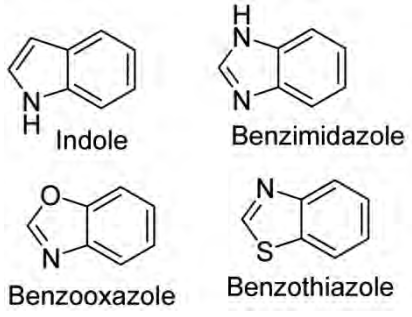


Figure 1 — Fused heterocyclic compound

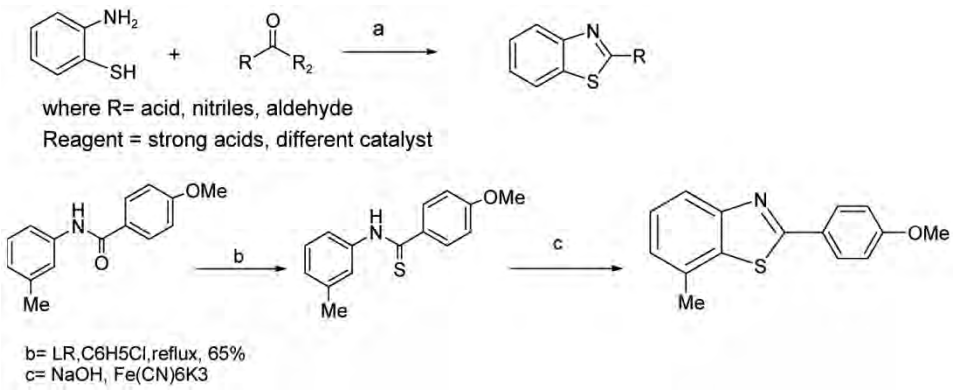


Figure 2 — General scheme for synthesis of benzothiazole

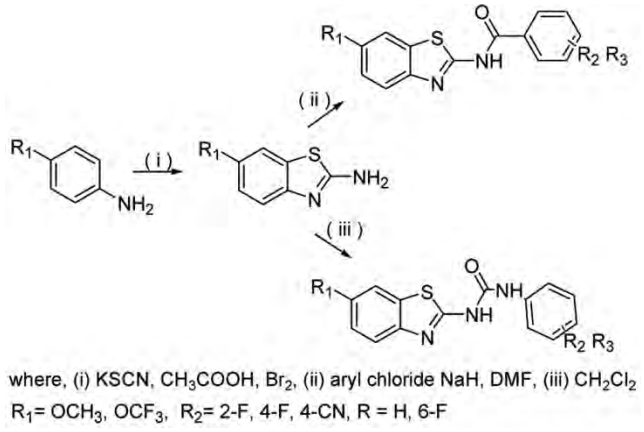


Figure 3 — Synthesis of benzothiazole aryl amide and aryl urea derivative

include condensation of 2-aminothiophenol with substituted nitriles, aldehyde, carboxylic acid or esters[19]. Another route for preparation of benzothiazole moiety is employing the Jacobson's cyclization of thiabenzanilides[20]. A number of catalyst are use for the reaction namely Br, I_2, $ZrOCl_2.8\ H_2O$, copper oxide, etc. and many more can be efficiently used to prepare benzothiazole derivative[21] (Figure 2).

Cuputo *et al.* (2011) synthesized two sets of benzothiazole derivatives having aryl amide substitution on C-2 carbon atom or an aryl urea substitution. In synthesized compounds some of them showed there in vitro anticancer activity[22] (Figure 3).

Venkatesh and Tiwari (2011) synthesized benzothiazole guanidine propanoic acid derivatives and evaluated for their cytotoxic activity against the HeLa cell lines and antimicrobial activity[23] (Figure 4).

Pharmacological Activities

Benzothiazole core is highly important scaffold for drug development because has demonstrated wide spectrum of activities. Important medicinal activities associated with the class of compounds are:

Antimicrobial activity

Microbes are the causative agent for various types of disease such as pneumonia, amoebiasis, typhoid, malaria, cough, TB, influenza, AIDS[24]. Infectious disease caused by bacteria affects millions of people and are leading cause of death[25]. BTA is one the most versatile class of compound against microbes. Verma *et al.* carried out the synthesis, characterization and antimicrobial activity of benzothiazole derivatives and the synthesized compounds showed moral antibacterial activity[26] (3). Sahu *et al.* synthesized 4H pyrimidobenzothiazole derivative and evaluated their activity against gram positive and gram negative bacteria: Staphylococcus aureus, Pseudomonas aeruginosa, S. typhi, E.coli[27] (4). Nitendra K.S *et al.* synthesized hydrazine BTA derivative against four pathogenic bacterial strain Bacillus Subtilis, E.coli, Klebsiella pneumonia and pseudomonas alkaligenes and fungal strains include Aspergillus Niger, Rhizopusoryzae and Candida Albicans[28] (5) (Figure 5).

Haroun (2018) and coworkers synthesized iminobenzothiazole derivative and evaluated for their antimicrobial activity and all synthesized compounds exhibited better activity compared to the standard drug ampicillin[29] (6). Benzothiazole sulphonamide conjugate were synthesized and screened for antimicrobial activity. The compound exhibited favorable activity against different fungal and bacterial strains with MIC values ranging from 15.5-31.25 µ/mL (7a). The presence of electron withdrawing group like F, Cl, and NO_2 at 6- position on 2- amino benzothiazole showed significant antibacterial, antifungal activity[30] (7b) (Figure 6).

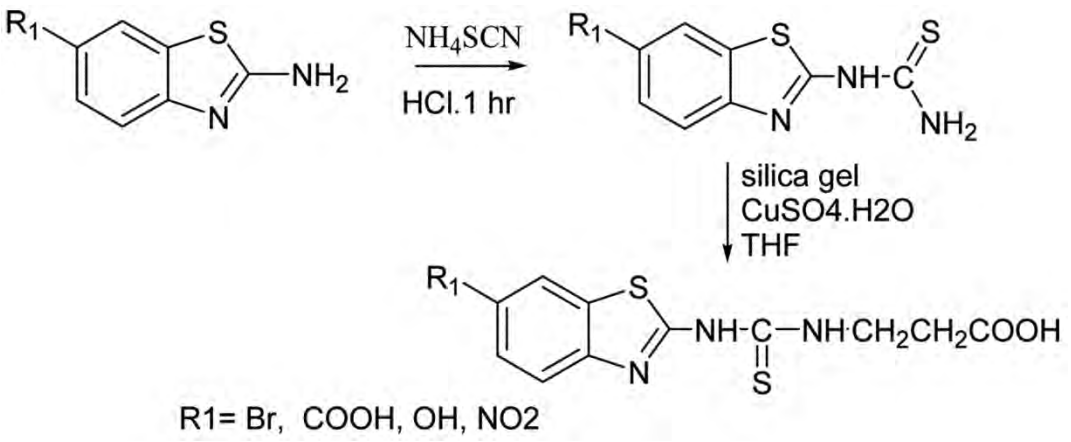


Figure 4 — Synthesis of benzothiazole guanidine derivatives

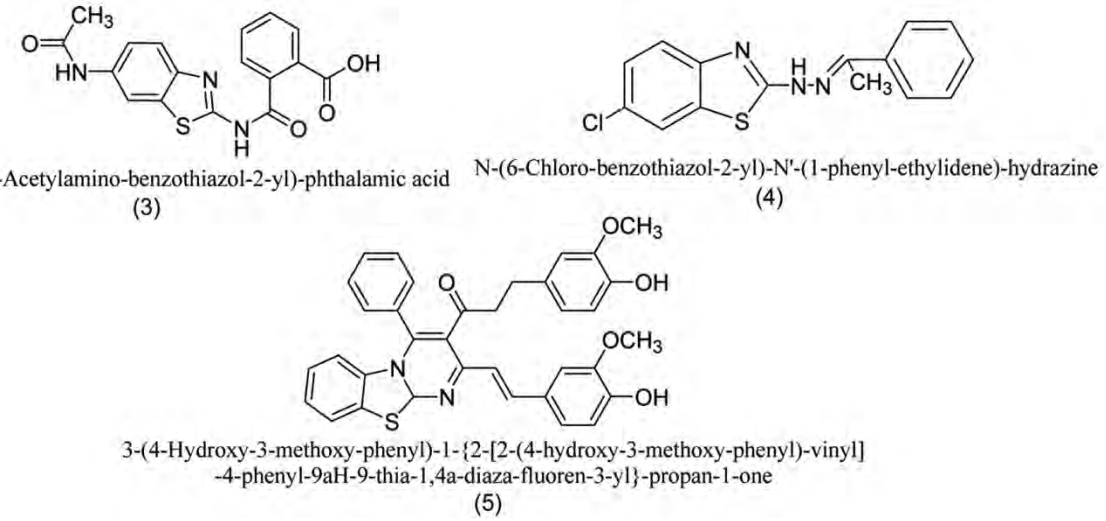


Figure 5 — Analogues of BTA as antimicrobial agent

Anticancer activity

Cancer is one of the most life threatening disease striking all over the world today. Due to the serious threat it has drawn all over attention of world today. Research has devoted to the development of effective anticancer therapy including surgical techniques, radiation therapy and chemotherapy. In efforts to develop suitable drugs with such capabilities scientist have focused upon many different aspects and among them is benzothiazole molecule derivative[31]. Anticancer drugs are more commonly developed by targeting various enzymes or receptors like topoisomerase, microtubule, cytochrome P450 enzyme, etc. 2-substituted i.e. substituted phenyl, benzyl benzothiazole derivative are synthesized and screened for DNA topoisomerase I[32] (8).

Zhuang *et al.* (2017) synthesized non sulfonamide NAE (NEDD8 activating enzyme) inhibitor and the compound showed good antitumor activity and anticancer activity against colon ulcer[33] (9a, 9b). Junjie *et al.* synthesized semicarbazone BTA derivative using substituted amines and evaluated their anticancer activity against four different cell lines- human colon cancer cell, human lung cancer cell, non-small cell lung cancer, human breast cancer[34] (10) (Figure 7).

Xuejiao *et al.* reported synthesis of substituted pyridine based acetamide BTA derivative screened for their in vitro and in vivo anticancerous activity[35] (11). Kumbhare *et al.* synthesized benzothiazolethiocarbamides using catalytic amount of 4-diMethyl amino pyridine (DMAP) by oxidation and cyclisation with 1,3- di- n-butyl Imidazolium tribromideto afford N- bis BTA analog and evaluated their cytotoxic activity against cancerous monocytic cell[36] (12) (Figure 8).

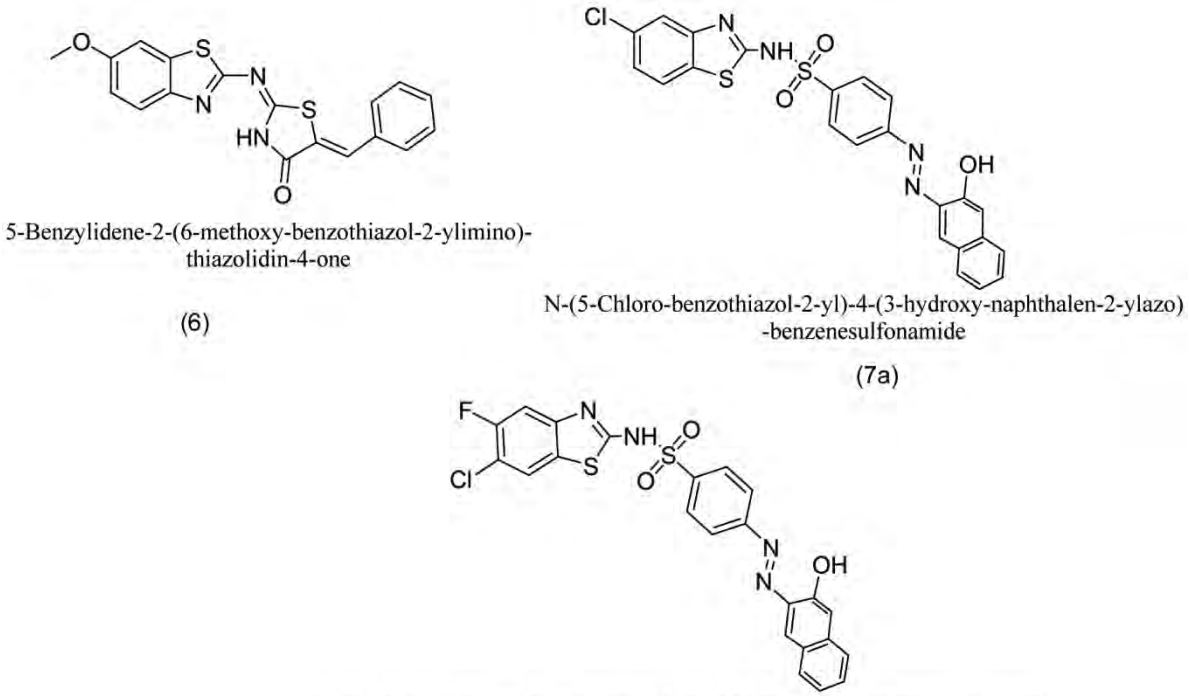


Figure 6 — Analogues of BTA as antimicrobial agent

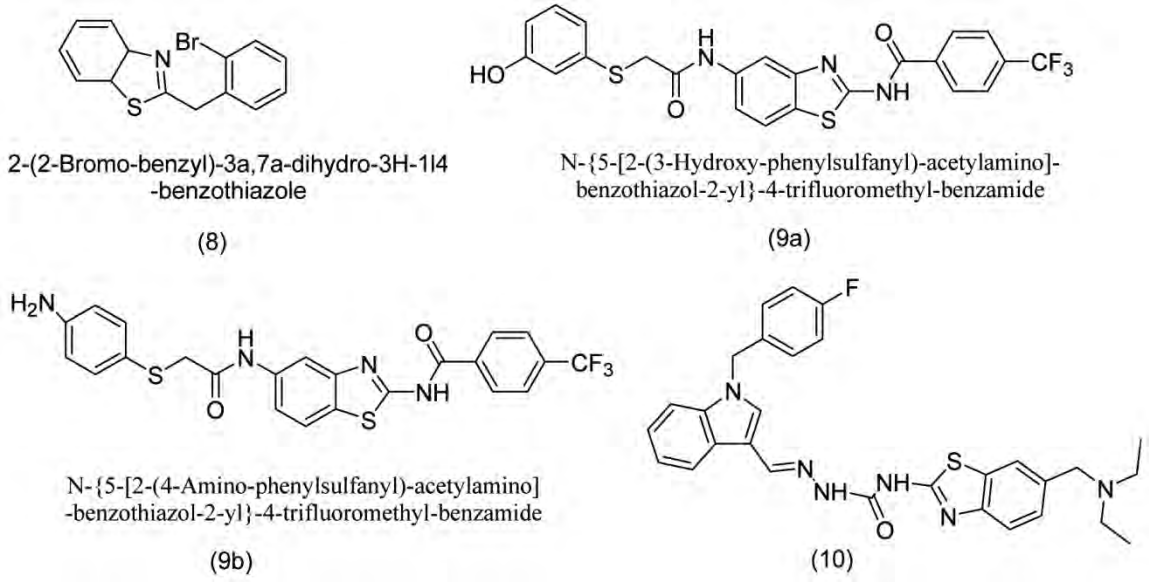
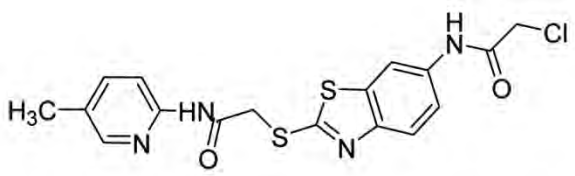


Figure 7 — Analogues of BTA as anticancerous agent

Antiviral activity

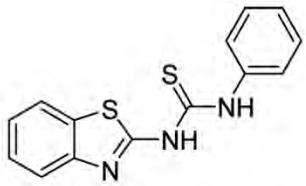
Viruses are the obligate intracellular parasites. Their replication depends totally on synthetic processes of the host cell. Effective antiviral agents inhibit virus-specific replicate events or preferentially inhibit virus-directed rather than host cell directed nucleic acid or protein synthesis.

Verma *et al.* synthesized 5-azobenzothiazole pyrimidine conjugated compounds and evaluated for hepatitis C virus and showed their high, good potency



2-Chloro-N-{2-[(5-methyl-pyridin-2-ylcarbamoyl) -methylsulfanyl]-benzothiazol-6-yl}-acetamide

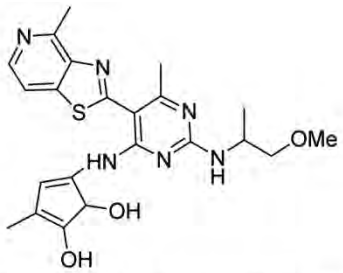
(11)



1-Benzothiazol-2-yl-3-phenyl-thiourea

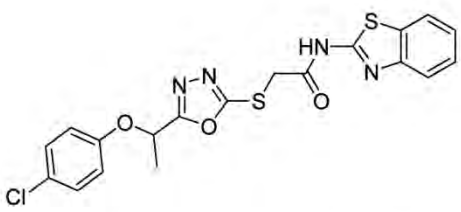
(12)

Figure 8 — Analogues of BTA as anticancerous agent



5-[2-(2-Methoxy-1-methyl-ethylamino)-6-methyl-5-(4-methyl-thiazolo[4,5-c]pyridin-2-yl)-pyrimidin-4-ylamino]-3-methyl-cyclopenta-2,4-diene-1,2-diol

(13)



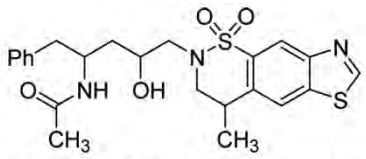
N-Benzothiazol-2-yl-2-{5-[1-(4-chloro-phenoxy)-ethyl]-[1,3,4] oxadiazol-2-ylsulfanyl}-acetamide

(14)

Figure 9 — Analogues of BTA as antiviral agent

and excellent plasma exposure and bioavailability[37] (13). Akhtar *et al.* investigated a series of new benzothiazole analogues and showed their effect on leukemia cells[38] (14) (Figure 9).

Nagaranjan *et al.* synthesized benzothiazole sulphonamide analog which shows good antiviral activity with good bioavailability[39] (15) (Figure 10).



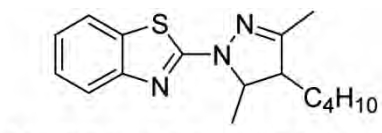
N-[1-Benzyl-3-hydroxy-4-(8-methyl-5,5-dioxo-7,8-dihydro-5H-1, 5λ6-dithia-3,6-diaza-cyclopenta[b]naphthalen-6-yl)-butyl]-acetamide

(15)

Figure 10 — Analogues of BTA as antiviral agent

Anti-inflammatory activity

Inflammatory diseases are widely prevalent throughout the world and inflammation remains a common as well as often poorly controlled disease, which can be life threatening in extreme form of allergy, autoimmune diseases and rejection of transplanted organs, and similar chronic inflammation has been found to mediate a wide variety of disease includes cardiovascular diseases, cancer, diabetes, arthritis, AD, pulmonary diseases[40]. NSAIDs have been used for the treatment of ailments such as pain, fever, inflammation. They act by two different mechanisms: a direct contact mechanism on the gastro intestinal mucosa and systemic action appearing after intravenous dosing[41]. Viegas and Junior *et al.* in 2007 synthesized, characterized and evaluated their antiinflammatory activity of pyrazolones and pyrazolinones for their excellent activity[42] (16) (Figure 11).

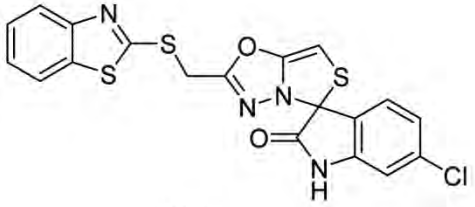


2-(4-Butyl-3,5-dimethyl-4,5-dihydro-pyrazol-1-yl)-benzothiazole

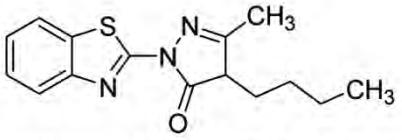
(16)

Figure 11 — BTA as anti-inflammatory

Kumar *et al.* synthesized benzothiazole conjugated with spiroimdoline i.e. chloroindolybenzothiazoleanalog that exhibited most potent anti-inflammatory activity [72% oedema inhibition[43] (17). Singh *et al.* (1986) synthesized pyrazole derivative and screened their anti-inflammatory activity[44] (18) (Figure 12).



(17)



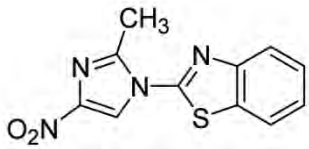
2-Benzothiazol-2-yl-4-butyl-5-methyl-2,4-dihydro-pyrazol-3-one

(18)

Figure 12 — Analogues of BTA as anti-inflammatory agent

Anti- HIV activity

Acquired HIV (Human Immunodeficiency virus) is the most fatal disorder for which no complete successful chemotheraphy has been developed. The current theraphy against AIDS is based on six categories of drugs: nucleoside/ nucleotide reverse transcriptase inhibitor (NRTI's), non-nucleotide reverse transcriptase (NNRTI's), protease inhibitors (PI's), cell entry inhibitors and co-receptor inhibitors (CRI's) and integrase inhibitor (INI's)[45]. Saud et. al (2006) synthesized benzothiazole conjugated with 4-nitro imidazole and screened for their in vitro anti-HIV-1 and HIV-2 in human lymphocyte (MT-4) cells[46] (19) (Figure 13).



2-(2-Methyl-4-nitro-imidazol-1-yl)-benzothiazole

(19)

Figure 13 — BTA as anti-HIV

Antitubercular activity

Mycobacterium tuberculosis causes the TB disease and is spread through the air. TB is caused by pathogens and mainly affects lungs. The TB is more common for people suffering from HIV/AIDS[47]. Landge *et al.* (2015) synthesized 2- substituted benzothiazole to exhibit potent anti-mycobacterium activity through specific inhibition of decaprenyl phosphoryl-beta-D-ribose-2'- oxidase (DprE1)[48] (20). Sangamesh A. Patel *et al.* synthesized Co(I), Ni(II), Mn(III) metal complexes that showed their activity against mycobacterium tuberculosis strain H_37Rv[49]. Huang *et al.* synthesized 2- methyl BTA analogs depicting anti-TB properties[50]. Palmer *et al.* synthesized BTA derivative having potent greatest activity against M.tuberculosis along with antimicrobial activity against gram positive and gram negative bacteria[51] (22) (Figure 14).

Antihelminthic activity

Helminth parasitism remains an under appreciated scourge of humans in most of the developing world. As individuals are infected with filariae, hookworms, whipworm, large roundworm, or schistosomes which results in chronic, are debilitating morbidity[52]. Reddy D and Sudhakar synthesized thiazolidindione substituted BTA and were screened for their antihelminthic activity at a conc. of 50,100,150 µ/mL using DMSO as a standard[53] (23). Nadkarni *et al.* synthesized substituted phenyl imidazole BTA and showed antihelminthic activity[54] (24) (Figure 15).

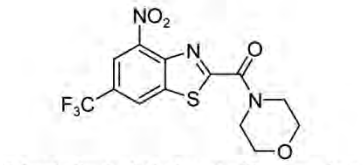
Antioxidant activity

Antioxidant compounds in food plays an important role as health protecting factors. The main characteristics of antioxidant are its ability to trap free radicals. These free radicals are able to oxidize nucleic acid, proteins, and lipids and initiate degenerative disease. Anion compounds inhibit oxidative mechanism that lead to degenerative diseases[55]. J.Joseph and G. Boomadevi Janaki studied structural characterization of 2-amino BTA which showed their antioxidant activity before forming complex with free ligands[56] (25) (Figure 16).

Hazra *et al.* (2011) synthesized fluoro benzo pyrazoline derivative and showed their antioxidant activity at 0.01 mm concentration with DPPH method substitution with electron donating group at 4 th position increases the potency[57] (26) (Figure 17).

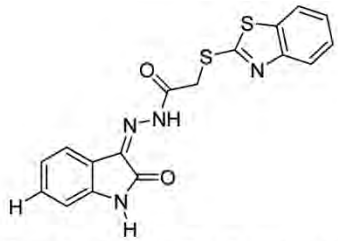
Anticonvulsant activity

Epilepsy is a syndrome of different cerebral disorders of the central nervous system and is characterized by paraoxysmal, excessive and hyper synchronous discharge of large number of neurons. Data show that only 28-30 % of patients are poorly treated with currently available antiepileptic drugs and these drugs may also cause serious side effects



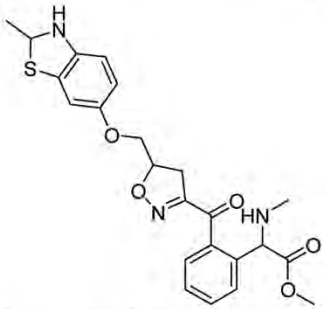
Morpholin-4-yl-(4-nitro-6-trifluoromethyl-benzothiazol-2-yl)-methanone

(20)



(Benzothiazol-2-ylsulfanyl)-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide

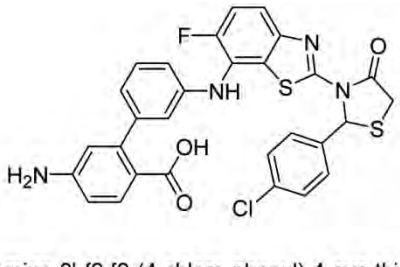
(21)



Methylamino-{2-[5-(2-methyl-2,3-dihydro-benzothiazol-6-yloxymethyl)-4,5-dihydro-isoxazole-3-carbonyl]-phenyl}-acetic acid methyl ester

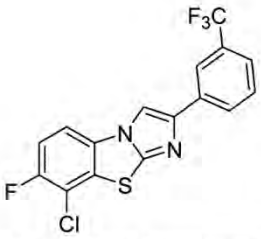
(22)

Figure 14 — Analogues of BTA as antitubercular agent



5-Amino-3'-{2-[2-(4-chloro-phenyl)-4-oxo-thiazolidin-3-yl]-6-fluoro-benzothiazol -7-ylamino}-biphenyl-2-carboxylic acid

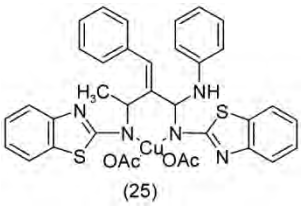
(23)



8-Chloro-7-fluoro-2-(3-trifluoromethyl-phenyl)-benzo[*d*]imidazo[2,1-*b*]thiazole

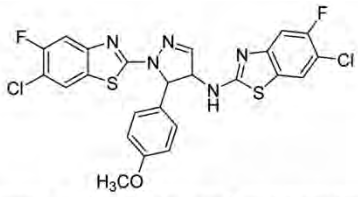
(24)

Figure 15 — Analogues of BTA as antihelminthic agent



(25)

Figure 16 — BTA as antioxidant



(6-Chloro-5-fluoro-benzothiazol-2-yl)-[1-(6-chloro-5-fluoro-benzothiazol-2-yl)-5-(4-methoxy-phenyl)-4,5-dihydro-1H-pyrazol-4-yl]-amine

(26)

Figure 17 — Analogues of BTA as antioxidant agent

including ataxia, nausea, mental dulling and hepatotoxicity[58]. Siddique *et al.* synthesized a series of benzothiazoleisothiourea derivative as anticonvulsant agent. The compounds emerged as more active compounds in comparison to phenytoin carbamazepine[59] (27) (Figure 18).

Liu *et al.* synthesized a series of triazole substituted BTA derivative and showed maximum activity against maximal electric shock (MES) – induced toxic extension[60] (28). Navale *et al.* synthesized a series of

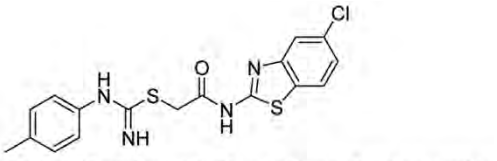
BTA carbamide and were screened for activity using psychometer seizure test[61] (29). Ajeet, Arvind Kumar synthesized hybrid form of BTA quinazoline derivative and found that they have higher affinity values than gamma aminobutyric acid and is better GABA-A inhibition for anticonvulsant activity[62] (30) (Figure 19).

Analgesic activity

Ashok Kumar et. al worked on various BTA analog and screened for their analgesic and antibacterial activity[63] (31) (Figure 20).

Antimalarial activity

Malaria is one of the most serious global health problems in subtropical and tropical zones of the world. The disease is caused by four species of the plasmodium of which Plasmodium Falciparum is the most virulent and potentially deadly. Most serious issue is that malaria parasites develop resistance to clinically used chemotherapeutic agents such as chloroquine, mefloquine and pyrimethamine[64]. Bowyer *et al.* synthesized BTA containing compounds by use of scintillation proximity assay and identified activity against both recombinant – N - myristoyl transferase and asexual stages of P. falciparum[65] (32). Hout .S *et al.* reported antimalarial activity of 2-substituted-6-nitro and 6-amino benzothiazole and their anthranilic acid were carried out on W2 and3D7 strains of Plasmodium falciparum[66] (33) (Figure 21).



N-(5-Chloro-benzothiazol-2-yl)-2-p-tolylcarbamimidoylsulfanyl-acetamide

(27)

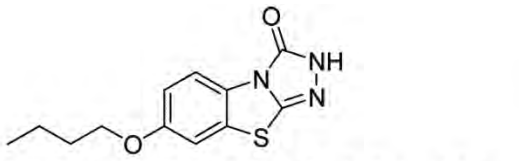
Figure 18 — Analogues of BTA as anticonvulsant agent

Antidiabetic activity

Diabetes mellitus is characterized by chronic hyperglycemia and it belongs to a group of metabolic disorder. According to estimation there are 171 million people in world with diabetes. There is thus a growing need for effective therapies to realize optimal glycemic control within the management of diabetes. Navarrete Vazquez *et al.* prepared ethyl benzothiazoleoxo acetate derivative using one step reaction. The in vitro inhibitory activity of compounds against protein tyrosine phosphatase was evaluated. The compounds are also evaluated for in vivo hypoglycemic activity, shows significant lowering of plasma glucose concentration in acute normal glycemic model and oral glucose tolerance similar to drug glibenzclamide[67] (34). Jeon *et al.* (2006) synthesized BTA thiazolidinedione's conjugated with the alkyl groups on exocyclic nitrogen and found the activity against peroxisome activator-γ (PPAR-γ). Compounds containing methyl group on exocyclic nitrogen for PPAR-γ agonist[68] (35) (Figure 22).

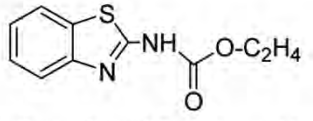
MTP inhibition activity

Chi.B.*et al.* synthesized triamide BTA derivative. These compounds shown potent entero cyclic specific microsomal triglyceride transfer protein (MTP).Inhabitation of MTP by small molecules lead to a reduction in plasma triglyceride and cholesterol level[69] (36) (Figure 23).



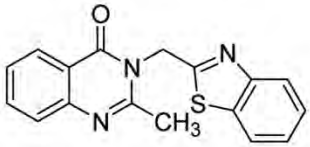
7-Butoxy-2H-benzo[4,5]thiazolo[2,3-c][1,2,4]triazol-3-one

(28)



N-Benzothiazol-2-yl-acetamide

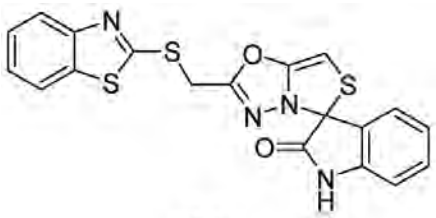
(29)



3-Benzothiazol-2-ylmethyl-2-methyl-3H-quinazolin-4-one

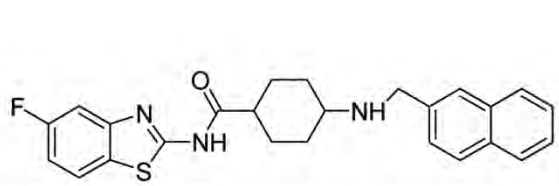
(30)

Figure 19 — Analogues of BTA as anticonvulsant agent



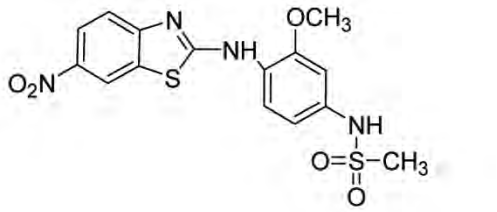
(31)

Figure 20 — BTA as analgesic



4-[(Naphthalen-2-ylmethyl)-amino]-cyclohexanecarboxylic acid (5-fluoro-benzothiazol-2-yl)-amide

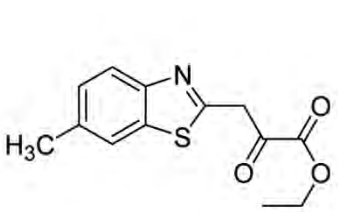
(32)



N-[3-Methoxy-4-(6-nitro-benzothiazol-2-ylamino)-phenyl]-methanesulfonamide

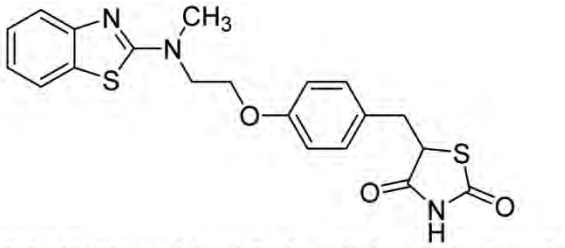
(33)

Figure 21 — Analogues of BTA as antimalarial agent



3-(6-Methyl-benzothiazol-2-yl) -2-oxo-propionic acid ethyl ester

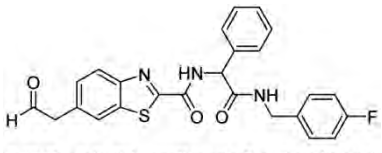
(34)



5-{4-[2-(Benzothiazol-2-yl-methyl-amino)-ethoxy]-benzyl}-thiazolidine-2,4-dione

(35)

Figure 22 — Analogues of BTA as antidiabetic agent



6-(2-Oxo-ethyl)-benzothiazole-2-carboxylic acid [(4-fluoro-benzylcarbamoyl)-phenyl-methyl]-amide

(36)

Figure 23 — BTA as MTP inhibitor

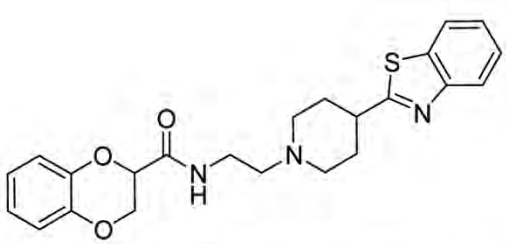
Antidepressant activity

Depression is a serious life threatening illness and is characterized by loss of interest in activities, loss of energy, hypersomnia and thinking for suicide. Wang *et al.* (2014) synthesized BTA containing dihydro-dioxane derivative and evaluated for their binding affinity to serotonin receptor[70] (37). Several 2-substituted BTA compounds exhibit dual acting 5HT receptor and serotonin transfer inhibitor antidepressant[71] (38) (Figure 24).

Antialzhiemer activity

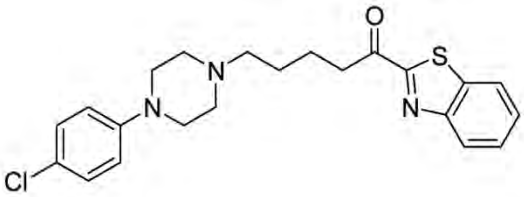
Alzheimer disease is a progressive neuro-degenerative disease characterized by the memory loss, loss of ability to carry out conversation and respond. Amyloid aggregates play an important role in the development of Alzheimer disease, quantification of this amyloidal plaque can be detected by Positron Emission Tomography (PET). Ono *et al.* (2009) synthesized the benzothiazole 2- substituted derivative exhibited the beta amyloid imaging probes. Synthesized compounds showed the fluorescence properties and were visualized in human brain[72] (39) (Figure 25).

Tacrine linked with phenyl BTA three carbon spacers are potent compound for AchE inhibitor at



2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid [2-(4-benzothiazol-2-yl-piperidin-1-yl)-ethyl]-amide

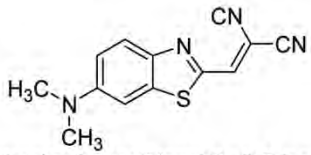
(37)



1-Benzothiazol-2-yl-5-[4-(4-chloro-phenyl)-piperazin-1-yl] -pentan-1-one

(38)

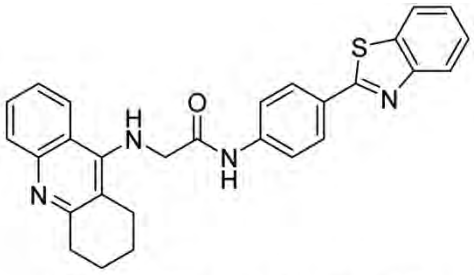
Figure 24 — Analogues of BTA as antidepressant agent



3-(6-Dimethylamino-benzothiazol-2-yl)-2-isocyano-acrylonitrile

(39)

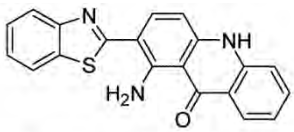
Figure 25 — Analogues of BTA as antidepressant agent



N-(4-Benzothiazol-2-yl-phenyl)-2-(1,2,3,4-tetrahydro-acridin-9-ylamino)-acetamide

(40)

Figure 26 — Analogues of BTA as antialzheimer agent



1-Amino-2-benzothiazol-2-yl-10H-acridin-9-one

(41)

Figure 27 — Analogues of BTA as antileishmanial agent

IC50 value 0.017 microMconc and also showed the AB aggregation activity 51.8% at 20 microM conc[73] (40) (Figure 26).

Anti-leishmanial activity

Delmas *et al.* synthesized BTA – acridindione derivative using Ullman reaction and screened their in vitro ant leishmanial activity[74] (41) (Figure 27).

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Conflict of Interest

The author declares no conflict of interest.

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