CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.22055421

Available online at: http://www.iajps.com Research Article

BENZOTHIAZOLE A PRIVILEGED HETEROCYCLIC SCAFFOLD IN MEDICINAL CHEMISTRY

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Abstract:

Benzothiazole is a privileged sulphur and nitrogen containing heterocyclic scaffold that has attracted considerable attention in medicinal chemistry owing to its structural diversity, ease of functionalization, and broad spectrum of biological activities. The unique physicochemical properties of the benzothiazole nucleus enable the development of structurally diverse derivatives with significant therapeutic potential. This review provides a comprehensive overview of the chemistry of benzothiazole, including its structural features, aromatic characteristics, and commonly employed synthetic strategies for the preparation of biologically active derivatives. Particular emphasis is placed on the recent advances in the pharmacological applications of benzothiazole derivatives, highlighting their antitubercular, anticancer, antifungal, anti-inflammatory, antidiabetic, anticonvulsant, antioxidant, antimalarial, and antidepressant activities, together with representative lead compounds and their biological significance. In addition, clinically approved drugs containing the benzothiazole scaffold are discussed to demonstrate the successful translation of this pharmacophore into therapeutic agents. Overall, this review highlights the versatility of the benzothiazole nucleus as a valuable platform for rational drug design and underscores its continuing importance in the discovery and development of next-generation pharmaceuticals.

Keywords: *Benzothiazole, Medicinal Chemistry, Heterocyclic Scaffold, Pharmacological Activities, Drug Discovery.*

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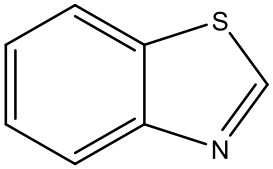
Please cite this article in press Tabasum Killedar et al., Benzothiazole A Privileged Heterocyclic Scaffold In Medicinal Chemistry. Indo Am. J. P. Sci, 2026; 13(08).

INTRODUCTION:

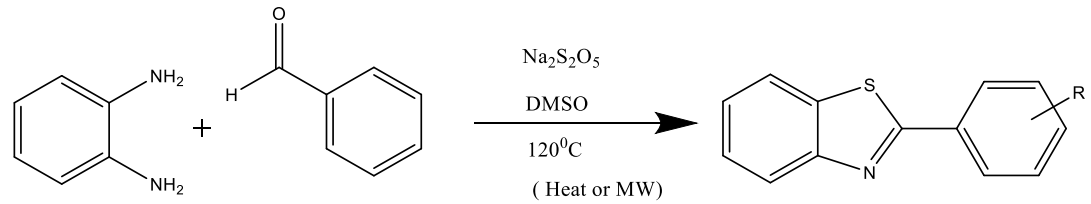
Heterocyclic compounds constitute the largest and most varied family of organic compounds. Today there are a lot of heterocyclic compounds are known, day by day the number is increasing rapidly due to the enormous synthetic research and also their synthetic utility. Heterocyclic compounds have a role in most fields of sciences such as medicinal chemistry, biochemistry also another area of sciences.[1] Benzothiazole derivatives have emerged as privileged scaffolds for the design and development of novel therapeutic agents. Benzothiazole can serve as unique and versatile scaffolds in research area especially in synthetic as well as in pharmaceutical chemistry because of its potent and significant pharmacological activities.[2] Benzothiazole is a representative sulfur- and nitrogen-containing bicyclic heterocycle comprising a benzene ring fused to a thiazole ring. The first 2-substituted benzothiazole derivative was synthesized by A. W. Hofmann in 1887, which stimulated extensive research into this versatile scaffold. Since then, numerous synthetic methodologies have been developed to access structurally diverse benzothiazole derivatives efficiently. [3] The benzothiazole nucleus has been identified in several marine and terrestrial natural products and has also found extensive applications in industrial and material sciences, including as vulcanization accelerators, plant growth regulators, enzyme inhibitors, fluorescent probes, imaging agents, and electroluminescent materials. More importantly, benzothiazole derivatives exhibit a wide spectrum of biological activities, including anti-inflammatory, antifungal, antidiabetic, analgesic, antimicrobial, antitumor, antileishmanial, anthelmintic, antirheumatic, and central nervous system (CNS) depressant activities. These diverse biological properties have established benzothiazole as one of the most promising privileged scaffolds for the discovery and development of new therapeutic agents. [4]



Benzothiazole

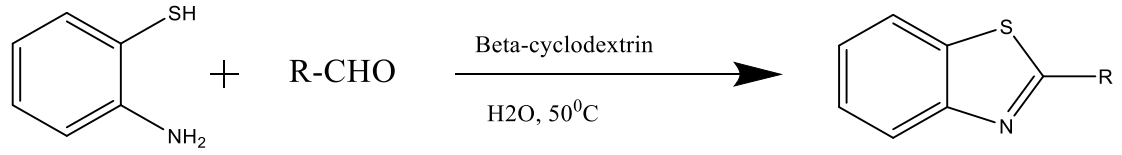
Synthesis of benzothiazoles

1. The synthesis of 2-phenylbenzothiazoles using sodium metabisulfite as an oxidant by condensation of 2-aminothiophenol and substituted benzaldehyde.[5]



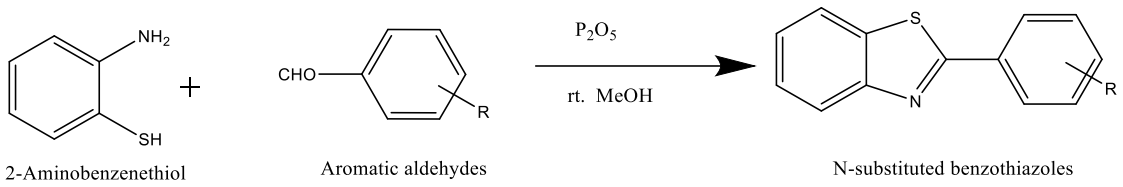
Benzene-1,2-diamine Benzaldehyde derivatives 2-Phenylbenzo[*d*]thiazole derivatives

2. The synthesis of 2-arylbenzothizole by the condensation of 2-aminothiaophenol and aryl/heteryl aldehyde using biomimetic catalyst β-cyclodextrin in water.[6]



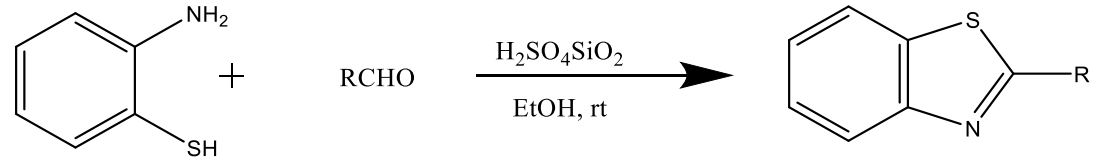
2-Aminobenzenethiol Aldehydes N-Substituted benzothiazoles

3. The synthesis of 2-arylbenzothiazole by the condensation of 2-aminothiophenol with aromatic aldehyde using P_2O_5 catalyst in methanol as solvent at ambient temperature.[7]



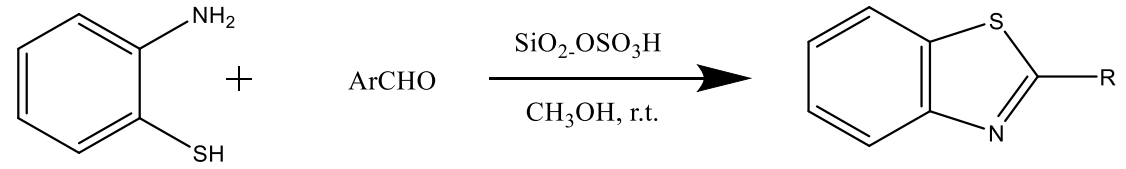
2-Aminobenzenethiol Aromatic aldehydes N-substituted benzothiazoles

4. 2-arylbenzothiazole obtained from the condensation reaction of aldehyde with 2-aminothiophenol using sulphuric acid immobilized on silica as reusable catalyst under heterogeneous and mild condition in ethanol at room temperature gives high yield.[8]



2-Aminobenzenethiol Aldehydes N-substituted benzothiazoles

5. A one-pot synthetic approach for the preparation of 2-substituted benzothiazoles has been reported using aromatic aldehydes and *o*-aminothiophenol in the presence of silica sulfuric acid as a catalyst. The reaction was carried out in absolute methanol at room temperature, providing the desired products efficiently under mild conditions.[9]

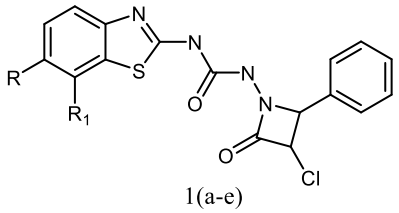


2-Aminobenzenethiol Aromatic aldehydes N-substituted benzothiazoles

Different biological activity of benzothiazole

Antitubercular activity

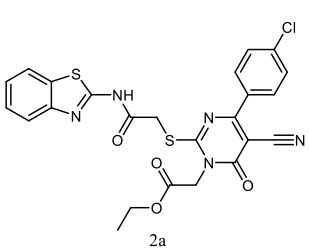
Sibaji Sarkar *et al.,* have reported design, synthesis, and evaluation of antitubercular activity of a novel benzothiazole-containing an azetidinone ring, among synthesised compounds, (1a-e) exhibited the ability to inhibit the growth of M. tuberculosis in terms of MIC.[10]



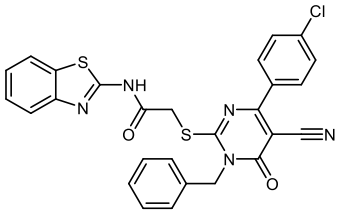
1(a-e)

Com.	R	R1	R2
1a	F	H	4-OCH3
1b	F	H	H
1c	F	H	3-CH3
1d	F	H	2-CH3
1e	F	H	2-OCH3

Loah R. Hemeda *et al.,* have reported the discovery of pyrimidine-tethered benzothiazole derivatives as novel anti-tubercular agents towards multi- and extensively drug resistant *Mycobacterium tuberculosis*, among the synthesised compounds 2a, 2b are highly active against the first-line drug-sensitive strain of *Mycobacterium tuberculosis*.[11]

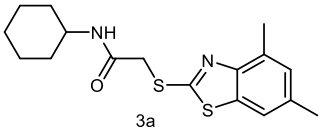


2a

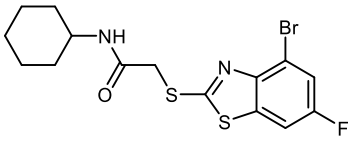


3b

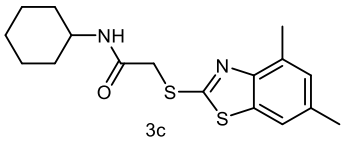
Pallavi Saha *et al.,* have reported antitubercular activity of 2-mercaptobenzothiazole derivatives targeting *Mycobacterium tuberculosis* type II NADH dehydrogenase, among synthesised compounds, Compounds 3a, 3b, and 3c were found to be the active molecules in the series and were further evaluated for their MIC90 against Mtb-resistant strains and for their bactericidal potential against Mtb H37Rv mc26230.[12]



3a



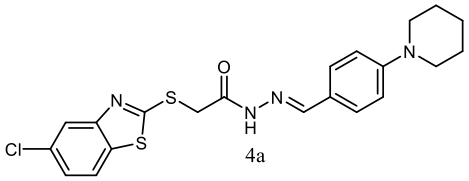
3b



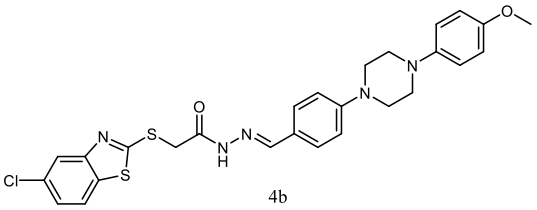
3c

ANTICANCER ACTIVITY

Osmaniye D *et al.,* have reported synthesis of new benzothiazole acylhydrazones as anticancer agents, among synthesised compounds, compounds **4a, 4b** exhibited the highest cytotoxic activity against C6 glioma cancer cell lines and showed selective inhibition of cancer cells with minimal toxicity toward healthy NIH3T3 cells.[13]

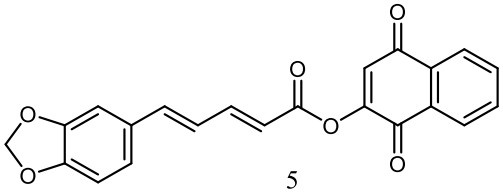


4a



4b

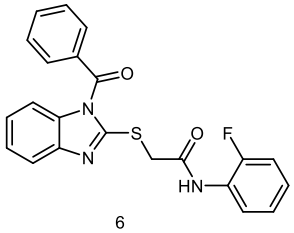
Paengsri W *et al.,* have reprted synthesis and evaluation of anti-tuberculosis and anticancer activities of hydroxynaphthoquinone derivatives among synthesised compounds, compound 5 is non-cytotoxic and showed potent activity against MCF7 breast cancer and NCI-H187-small cell lung cancer cell lines with the IC50 values of 3.84 and 2.24 µg/mL.[14]



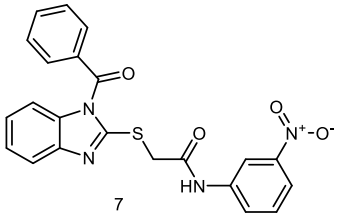
5

Yadav S *et al.,* have reported synthesis and evaluation of antimicrobial, antitubercular and anticancer activities of 2-(1-benzoyl-1 H-benzo [d] imidazol-2-ylthio)-N-substituted acetamides, among the synthesised compounds, compound 6 showed the highest cytotoxic activity against MCF-7 breast cancer cells with an IC_{50} value of 0.0047

µM/mL, while compound 7 exhibited the strongest activity against HCT116 colon cancer cells with an IC_{50} value of 0.0058 µM/mL. [15]



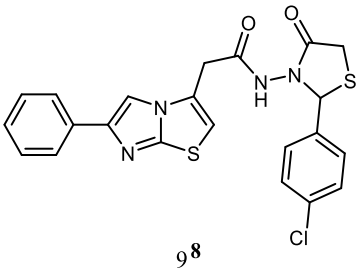
6



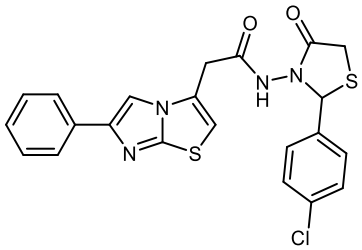
7

ANTIFUNGAL ACTIVITY

Çapan G *et al.,* have reported new 6-phenylimidazo [2, 1-b] thiazole derivatives: synthesis and antifungal activity, among synthesis compounds 2-(4-methylphenyl)-3-((6-phenylimidazo[2,1-b]thiazol-3-yl)-acetamido)-4-thiazolidinone (8) and 2-(4-chlorophenyl)-3-((6-phenylimidazo[2,1-b]thiazol-3-yl)-acetamido)-4-thiazolidinone (9) exhibited the highest antifungal activity against trichophyton mentagrophytes var. erinacei (MIC = 3 µg/mL).[16]

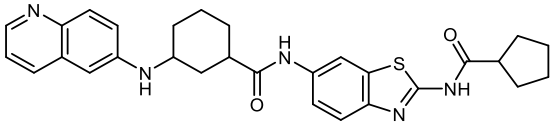


9**8**



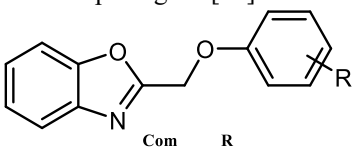
9

Liu Y *et al.,* have reported novel benzothiazole derivatives with a broad antifungal spectrum: design, synthesis and structure–activity relationships, among synthesised compounds. The 6-quinoline derivative 10 showed good antifungal activity with a broad spectrum and exhibited significant in vivo antifungal activity in the C. Elegans–Candida infection model, which represents a promising lead structure for the development of novel antifungal agents. [17]



10

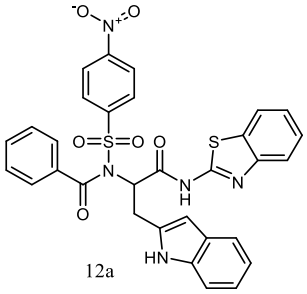
Luo B *et al.,* have reported the synthesis of antifungal activities and molecular docking studies of benzoxazole and benzothiazole derivatives, among synthesised compounds, compounds 11a, 11b, 11c, and 11d exhibited significant antifungal activities against most of the pathogens.[18]



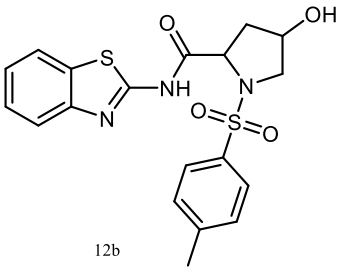
Com	R
11a	H
11b	4-F
11c	2-COCH3
11d	3-COCH3

Anti-inflammatory activity

Ugwu DI *et al.,* have reported novel anti-inflammatory and analgesic agents: synthesis, molecular docking and *in vivo* studies. Compounds were evaluated for their anti-inflammatory and analgesic activities. Two of the derivatives 12a and 12b were found to possess very good anti-inflammatory activities. [19]

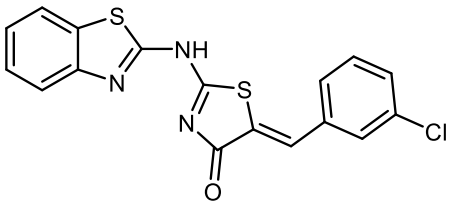


12a

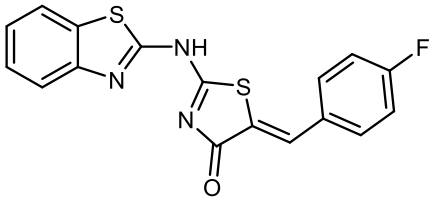


12b

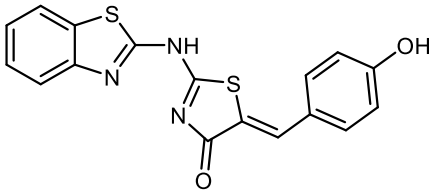
Khan A *et al.,* have reported synthesis of new benzothiazole derivatives with in-depth *in-vitro*, *in-vivo* anti-oxidant, anti-inflammatory and anti-ulcer activities. Among the synthesised compounds, 13a, 13b and 13c exhibited potent anti-inflammatory as well as anti-ulcer activity. They can be used as lead compounds for further drug discovery.[20]



13a

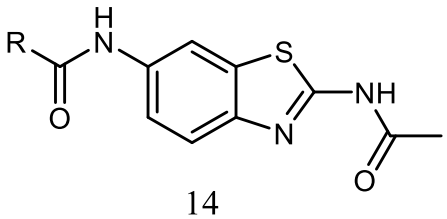


13b

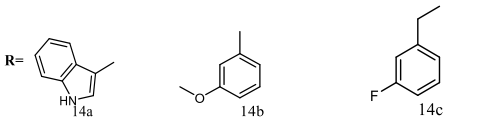


13c

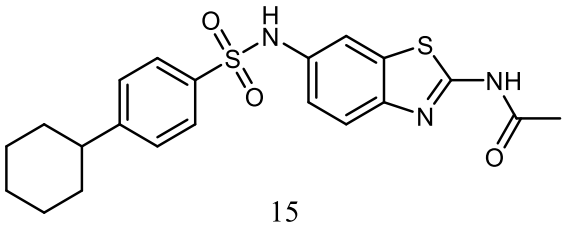
Sadhasivam g *et al.,* have reported synthesis, characterization, and evaluation of anti-inflammatory and anti-diabetic activity of new benzothiazole derivatives. Among the synthesised compounds 14a, 14b, 14c and 15, 16 also showed good anti-inflammatory activity.[21]



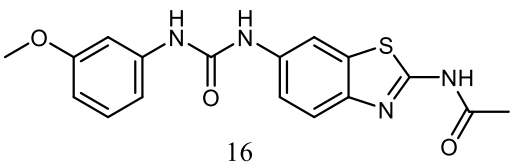
14



14a 14b 14c



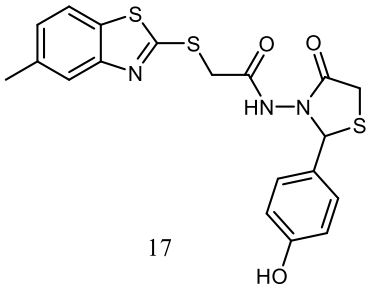
15



16

Anti diabetic activity

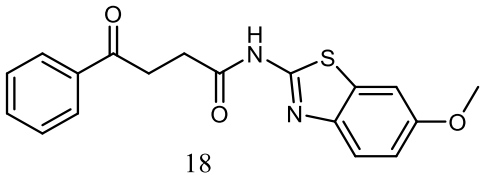
Kumar SU *et al.,* have reported synthesis and evaluation of some benzothiazole derivatives as antidiabetic agents. Among the synthesised compounds, compound 17 demonstrated potent anti-diabetic activity and would be of better use in drug development to combat the metabolic disorder in future.[22]



17

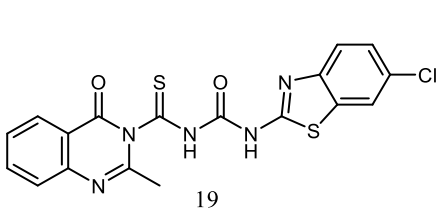
Anticonvulsant activity

Hassan MZ *et al.,* have reported the synthesis and evaluation of N-[substituted benzothiazol-2-yl) amides as anticonvulsant and neuroprotective. Among the synthesised compound 18 emerged as the most effective anticonvul sant with median doses of 40.96 mg/kg (MES ED50).[23]

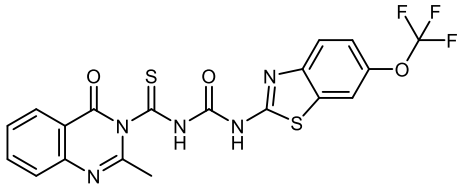


18

Malik S *et al.,* have reported synthesis and anticonvulsant evaluation of N-(benzo [d] thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3 (4H)-carbothioamide derivatives: A hybrid pharmacophore approach. Among the synthesized benzothiazole–quinazoline derivatives showed promising anticonvulsant activity, with compounds 19 and 20 exhibiting potency comparable to or greater than standard drugs in multiple seizure models.[24]

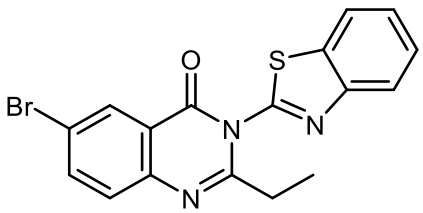


19

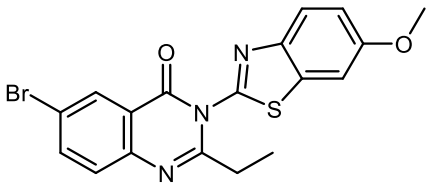


20

Ugale VG *et al.,* have reported quinazolino–benzothiazoles: fused pharmacophores as anticonvulsant agents. Among the synthesized benzothiazole–quinazolinone derivatives demonstrated notable anticonvulsant activity, with compound 21 showing significant protection in the MES model and compound 22 exhibiting strong activity in the PTZ-induced.[25]



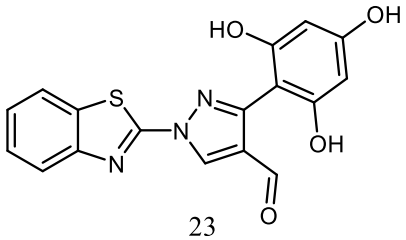
21



22

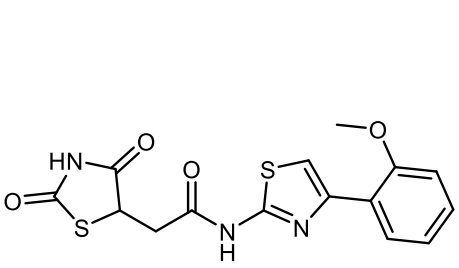
Antioxidant activity

Yadav AG *et al.,* have reported anti-oxidant and anti-microbial activities of pyrazolyl-benzothiazole derivatives using Vilsmeier-Haack reaction, among synthesised compounds 23 shows good antioxidant activity.[26]



23

Koppireddi S *et al.,* have reported novel 2-(2, 4-dioxo-1, 3-thiazolidin-5-yl) acetamides as antioxidant and/or anti-inflammatory compounds. Among the synthesised compounds, compounds 24 and 25 have exhibited good antioxidant activity.[27]



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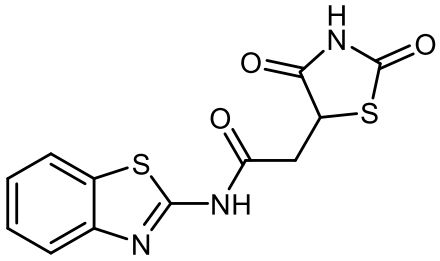
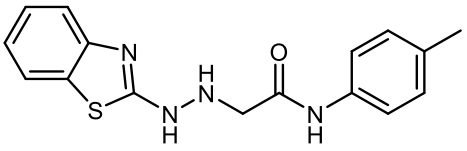


25

Suresh C *et al.,* have reported synthesis of 2-hydrazino benzothaizoles-2-amino-(4-substituted)-acetanilides for antioxidant activity among the synthesised compounds the most significant of them was found to be series of compounds 26, 27 and 28 that showed the highest percentage of free radical scavenging activity.[28]



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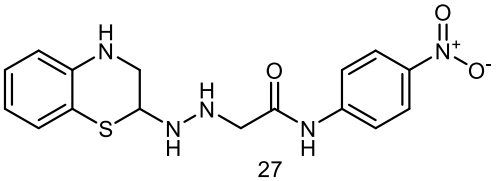

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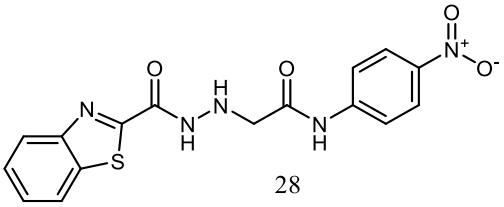
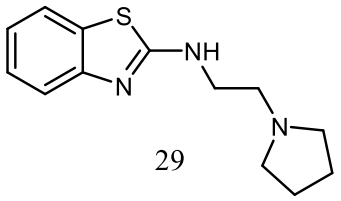


28

Antimalarial activity

Ongarora DS *et al.,* have reported benzo heterocyclic amodiaquine analogues with potent ant plasmodial activity. Among the synthesised compounds, the benzothiazole analogues 29, 30, and 31 demonstrated excellent ant plasmodial activity against chloroquine-resistant *Plasmodium falciparum* strains.[29]



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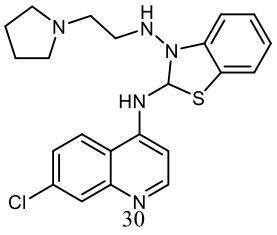

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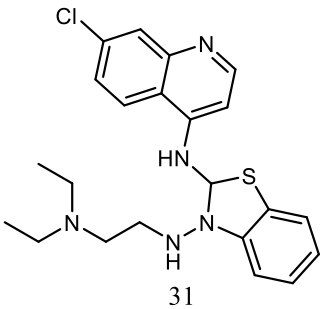
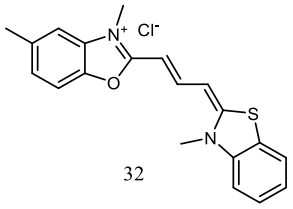


31

Ge JF *et al.,* have reported the synthesis of cyanine dyes and investigation of their in vitro antiprotozoal activities. Among the synthesised compounds nine trimethine cyanines were active against *P. falciparum*, two trimethine cyanines (32, 33) were active against T. cruzi, one pentamethine cyanine (34) exhibited strong activity against T. b. rhodesiense.[30]



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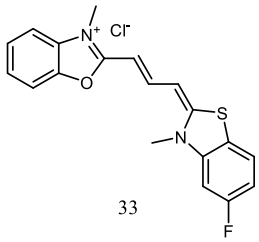

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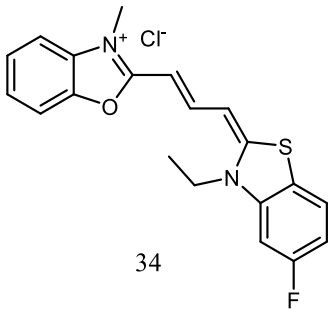
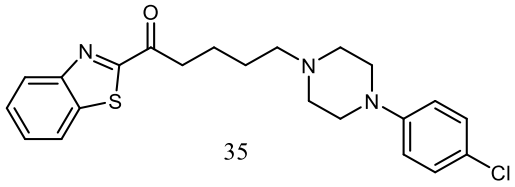


34

Anti-depressant

Zhu XY *et al.,* have reported benzothiazoles as probes for the 5HT1A receptor and the serotonin transporter (SERT). Among the synthesised compounds 35 and 36 demonstrate simultaneously relatively moderate affinity binding at both 5HT1A receptor.[3]



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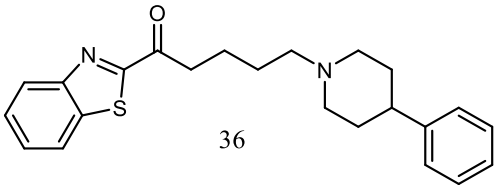
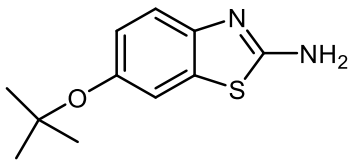


36

DRUGS CONTAINING BENZATHIAZOLE NUCLEUS

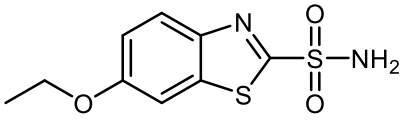
Neuroprotective agent

Riluzole

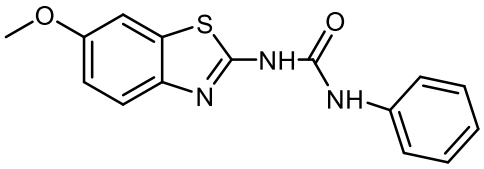


Diuretic/Antiglaucoma activity

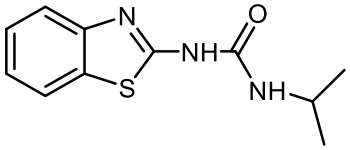
Ethoxzolamide



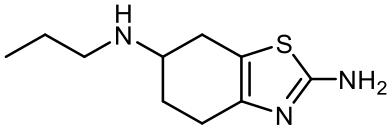
Immunosuppressant
Frentizole



Fungicidal activity
Bentaluron



Antiparkinsonian activity
Pramipexole



CONCLUSION:

Benzothiazole represents a versatile sulphur and nitrogen-containing heterocyclic scaffold with significant importance in medicinal chemistry. Its favourable structural characteristics and ease of functionalization have enabled the development of numerous biologically active derivatives. The reviewed literature demonstrates that benzothiazole derivatives possess a broad range of pharmacological activities, particularly antitubercular, anticancer, antifungal, anti-inflammatory, antidiabetic, anticonvulsant, antioxidant, antimalarial, and antidepressant activities. Several reported derivatives have shown promising potency in different biological models, highlighting the importance of structural modification of the benzothiazole nucleus. The scaffold is also present in therapeutically useful compounds, further demonstrating its pharmaceutical relevance. Overall, benzothiazole provides a valuable platform for molecular hybridization, structure–activity relationship studies, and lead optimization. Continued exploration of new substitutions and synthetic strategies may provide more potent and selective derivatives. Therefore, benzothiazole remains a promising pharmacophore for the discovery and development of novel therapeutic agents.

ACKNOWLEDGEMENT:

We thank Dr. H. V. Dambal, President and Dr. V. G Jamakandi, Dean SET's College of Pharmacy, Dharwad, Karnataka, for providing the facilities.

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