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A COMPREHENSIVE REVIEW: BENZOTHIAZOLES AS EMERGING NUCLEUS OF BIOLOGICAL ACTIVITIES

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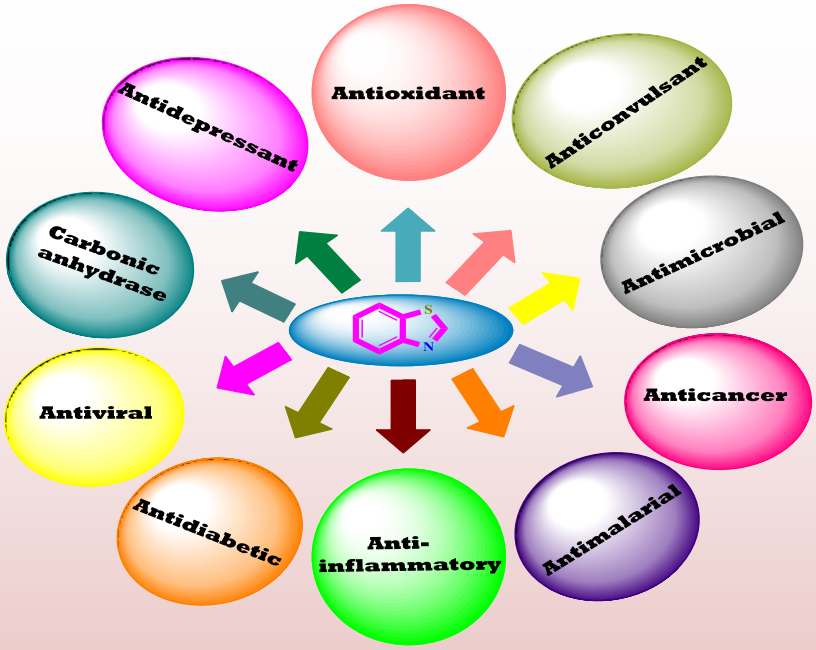
GRAPHICAL ABSTRACT



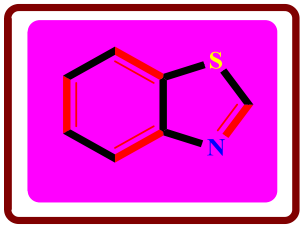
ABSTRACT

Imbibed of endocyclic sulphur and nitrogen atoms in their heterocyclic nucleus, benzothiazoles are promising candidates for the design of novel compounds of medical importance. This moiety has gained considerable attention in the field of medicinal chemistry in last few years for the development of newer molecules in near future. Modifications of benzothiazole nucleus could potentially affect the interaction of molecules with biological targets to develop more potent therapeutic agents. The present review provides a detailed periodic account of the therapeutic potential of benzothiazole derivatives.

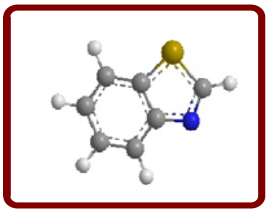
KEYWORDS: Benzothiazole, antimicrobial, anticancer, anticonvulsant, anti-oxidant, anti-inflammatory, antidiabetic, antiviral, antimalarial, carbonic anhydrase inhibitor, antidepressant.

INTRODUCTION

The chemistry and biology of fused heterocyclic compounds have been of great interest since long in the field of medicinal chemistry. A vast number of heterocyclic derivatives possessing nitrogen and sulphur atom in their structures has been proved as promising scaffolds for drug design and discovery. Benzothiazole is one of these types of bicyclic compounds, having benzene ring fused with a five-membered ring along with nitrogen and a sulphur atom in its core structure.



2D Structure of Benzothiazole

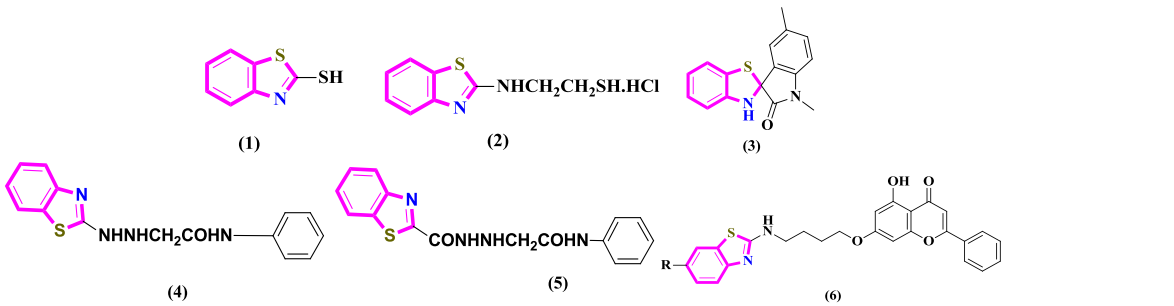


3D Structure of Benzothiazole

The chemistry and pharmacology of this core structure have attracted a great scientific interest nowadays, owing to their broad range of biological activities.

Antioxidant activity

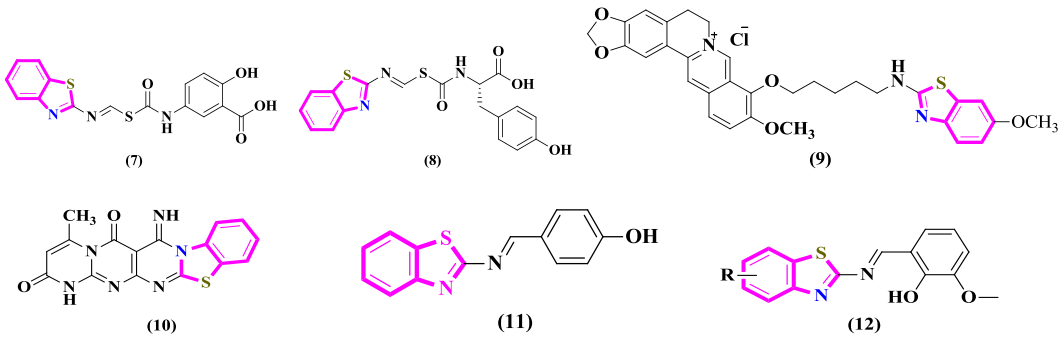
Cressine *et al.*,[1] (2009) synthesized some new molecules derived from benzothiazoles and evaluated them for antioxidant activity. Among all, the compounds **(1)** and **(2)** showed a good radioprotective effect at $LD_{99.9/30days-IRR}$. Encouraging radioprotection results showed that these compounds could act as future antioxidants. **Karali *et al.*,**[2] (2010) performed the synthesis of 1'-dimethyl-3*H*-spiro[1,3-benzothiazole-2,3-indol]2'(1'*H*)-2-one **(3).** This compound showed the highest degree of potency in inhibiting lipid peroxidation and also demonstrated strong scavenging activity against the DPPH and ABTB radicals. **Suresh *et al.*,**[3] (2011) developed new 2-hydrazino-benzothiazoles(substituted)-2-amino-(4-substituted)acetanilide derivatives. From all, compounds **(4)** and **(5)** showed good antioxidant activity with IC_{50} value in the range of 12.89 to 12.93 µM. which can be considered as a moderate range of free radical scavenging activity. **Mistry *et al.*,**[4] (2015) synthesized a series of chrysin-benzothiazole conjugates **(6)** as antioxidants. Compound **(6a, 6b, 6c, 6d and 6e)** showed good activity as DPPH and ABTS scavengers. IC_{50} values of these compounds were found to be beneficial and comparable with standard drug ascorbic acid. **Cabrera-Perz *et al.*,**[5] (2016) designed and synthesized two benzothiazole compounds named (*E*)-5-((benzo[*d*]thiazole-2-ylimino)(methylthio)methylamino)-2-hydroxybenzoic acid **(7)** and (*S*,*E*)2-(benzothiazole-2-ylimino)(methylthio)methylamino)-3-(4-hydroxyphenyl)propionic acid **(8).** These compounds exhibited potent scavenging activity, resulting to increase in the reduced glutathione content and decrease in the malondialdehyde level. Compound **(7)** were also effective in inhibiting cytochrome P450, giving a protective effect against the reactive intermediary *N*-acetyl-*p*-benzoquinoneimine. **Mistry *et al.*,**[6] (2016) discovered the antioxidant potencies of newly synthesized berberine derivatives, bearing substituted benzothiazole moiety **(9)** using DPPH and ABTS assay. The methoxy and cyano-based analogues exhibited most significant DPPH and ABTS radical scavenging activities. Compound **(9)** containing the electron donating methoxy functional group was found to be most potent with IC_{50} value of 3.03 ± 0.086 µg/ml for scavenging DPPH radicals as compared to standard drug ascorbic acid with IC_{50} value of 12.22 ± 0.106 µg/ml. **Sontakke *et al.*,**[7] (2017) synthesized 14-imino-11-methyl-9,13-dioxo-8*H*-pyrimido[1,2-*a*]pyrimido-pyrimido[2,1-*b*][1,3] benzothiazole derivatives **(10)** and evaluated its biological effects. Compound **(10)** showed good DPPH radical scavenging activity as compared to standard drug ascorbic acid. This study revealed the potential of unsubstituted benzothiazole derivatives against DPPH. **Chacko *et al.*,**[8] (2017) designed and prepared a novel series of antioxidant potential and evaluated the said compounds through DPPH method. Synthesized compound **(11)** showed good DPPH scavenging property with the IC_{50} value of 63.60 µg/ml and exhibited significant antioxidant potential as well when compared with ascorbic acid (IC_{50}=55.27 µg/ml). **Shanthalakshmi *et al.*,**[9] (2017) designed and synthesized series of benzothiazole compounds and evaluated their antioxidant activity. Compound **(12a)** VCBT (*o*-Vanilidine-2-amino-6-chloro benzothiazole) and Compound **(12b)** VBBT (*o*-vanilidine-2-amino-6-bromo benzothiazole) possessed highest antioxidant activity.



(1) (2) (3) (4) (5) (6)

R= 6-Cl, 6-Br, 6-F, 4,6-di F, 6-CF_3

(6a) (6b) (6c) (6d) (6e)



(7) (8) (9)

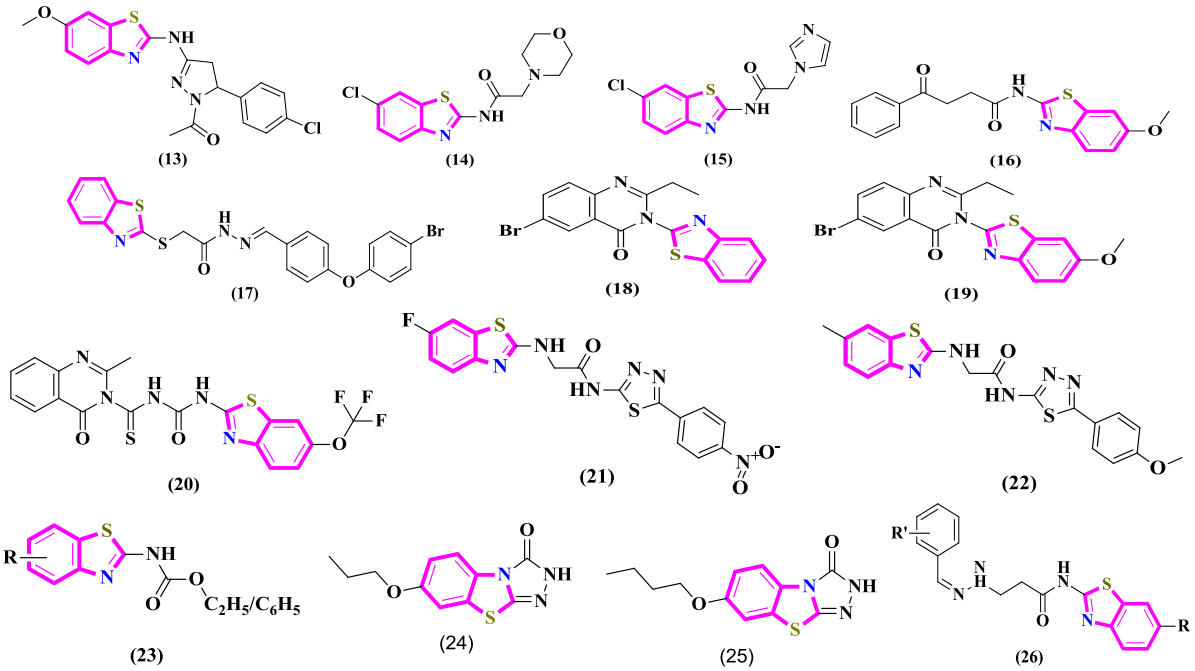
(10) (11) (12)

6-Cl, 6-Br = **(12a) (12b)**

Anticonvulsant activity

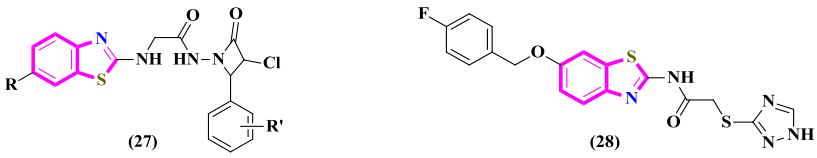
Amnerker *et al.*,[10] (2010) reported the synthesis of some 1-acetyl-pyrazolin and prop-2-eneamido derivatives of aminobenzothiazole which were evaluated for anticonvulsant activity by MES test. Compound **(13)** exhibited an ED_{50} value of 25.49 µmol/kg and TD_{50} of 123.87 µmol/kg and high protective index (PI) of 4.86 when compared with standard drug phenytoin. **Amir *et al.*,**[11] (2011) synthesized a chain of benzothiazole compounds containing acetamido and carbothioamide pharmacophores and evaluated *in-vivo* as anticonvulsant agents**.** *N*-(6-chlorobenzothiazol-2-yl)-2-morpholinoacetamide **(14)**, *N*-(6-chlorobenzothiazol-2-yl)-2-(1*H*-imidazol-1-yl)acetamide **(15)** showed excellent anti-seizures activity. These new aspects of benzothiazole derivatives may be useful in development of potential anticonvulsant agents. **Hassan *et al.*,**[12] (2012) reported the synthesis of *N*-(substituted benzothiazol-2-yl)amides derivatives as anticonvulsant and neuroprotective agents. *N*-(6-methoxybenzothiazol-2-yl)-4-oxo-4-phenylbutanamide **(16)** displayed promising anticonvulsant activity by increasing the level of GABA, reducing the progression of ACR-induced neurotoxicity and decreasing MDA and LDH enzyme activity. **Kumar *et al.*,**[13] (2012) designed and synthesized some novel 1,3-benzothiazol-2-yl hydrazones and acetohydrazones for anticonvulsants activity and neurotoxicity. Compound **(17)** was evaluated by using the 6 Hz psychomotor seizure test. Computational studies were done for prediction of pharmacokinetic parameter and pharmacophore patterns. All the compounds possessed good pharmacokinetic profile. These observations indicated that benzothiazol-2-yl-acetohydrazones can be called more promising anticonvulsants as compared to 1,3-benzothiazole hydrazides. **Ugale *et al.*,**[14] (2012) synthesized a new series of quinazolino-benzothiazole derivatives and evaluated their anticonvulsant activity through MES and scPTZ induced seizure models screening test. Among the tested compound, 3-(benzo[*d*]thiazol-2-yl)-6-bromo-2-ethylquinazolin-4(3*H*)-one **(18)** and 6-bromo-2-ethyl-3-(6-methoxybenzo[*d*]thiazol-2-yl)quinazoline-4(3*H*)-one **(19)** were found to be most active against both type of seizure such as tonic seizure by the MES model and clonic seizure by scPTZ-induced seizure model. **Malik *et al.*,**[15] (2013) designed, synthesized and new evaluated new *N*-(benzo[*d*]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4*H*)carbothioamide derivatives to get the anticonvulsant effects against MES and scPTZ induced seizures. The quantitative assessment showed that the most active compound 2-methyl-4-oxo-*N*-(6-(trifluoromethoxy)benzo[*d*]-2-ylcarbamoyl)quinazoline-3(4*H*)-carbothioamide **(20)** had ED_{50} value of 82.5 µmol/kg in MES & 510.5 µmol/kg in scPTZ. The potency of said compound was more than the reference drug phenytoin and ethosuximide. **Siddiqui *et al.*,**[16] (2013) designed, synthesised some benzothiazole derivatives and evaluated them for *in vivo* anticonvulsant activity against maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ) and minimal neurotoxicity test. This preliminary screening results showed that two most potent substituent 2-[(6-Fluoro-1,3-benzothiazol-2-yl)amino]-*N*-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]acetamide **(21)** and *N*-[5-(4-Methoxyphenyl)-1,3,4-thiadiazol-2-yl]-2-[(6-methyl-1,3-benzothiazol-2-yl)amino]acetamide **(22)** as lead compound**.** The quantitative study of the active compound showed nearly 2-10 and 7-67 folds increase in the protective index for the MES test and the scPTZ test, respectively. **Naval *et al.*,**[17] (2010) synthesized newly substituted benzo[*d*]thiazole-2-ylcarbamates **(23)** and investigated them for anticonvulsant activity using scPTZ induced and maximal electroshock models. Among all synthesized analogues (**23a, 23b, 23c, 23d, 23e)** exhibited maximum protection against scPTZ induced and maximal electroshock induced seizures as compared to control. **Liu *et al.*,**[18] (2014) reported the synthesis and anticonvulsant action of a new series of 7-alkoxy[1,2,4]triazolo[3,4-*b*]benzothiazol-3(2*H*)-ones. Among all two derivatives 7-propoxy[1,2,4]triazolo[3,4-*b*]benzothiazol-3(2*H*)-one **(24),** 7-butoxy[1,2,4]triazolo[3,4-*b*]benzothiazol 3(2*H*)-one **(25)** showed the maximum activity against maximal electroshock (MES)-induced toxic extensions with effective dose (ED_{50}) of 11.4 and 13.6 mg/kg, respectively. **Ali *et al.*,**[19] (2014) synthesized a new series of 3-(2-(substituted benzylidene)hydrazinyl)-*N*-(substituted benzo[*d*]thiazol-2-yl)-propanamide having structural requirements necessary for anticonvulsant activity **(26).** Preliminary *in vivo* anticonvulsant screening was performed by two most adopted seizures models like MES and scPTZ. In anticonvulsant

screening, compounds **(26a** and **26b)** were found to be most active as compared to standard drugs-phenytoin and carbamazepine. **Ali *et al.*,**[20] (2015) reported the synthesis of some new benzo[*d*]thiazole-2-yl-aminoacetamides **(27)** having potential anticonvulsant activity based on pharmacophoric features. In MES and scPTZ test, compounds **(27a** and **27b)** demonstrated effective median dose (ED_{50}) of 20.7 mg/kg and 34.9 mg/kg and protective indices of 15.4 and 18.6 when compared to standard drug phenytoin and carbamazepine. **Liu *et al.*,**[21] (2016) synthesized novel benzothiazole derivatives as potential anticonvulsant agents. Among the tested compounds, **(28)** was found to be the most potent with an ED_{50} value of 54.8 mg/kg in MES test 52.8 mg/kg in scPTZ tests, respectively. A compound, 2-((1*H*-1,2,4-triazol-3-yl)thio)-*N*-(6-((4-fluorobenzyl)oxy)benzo[*d*]thiazol-2-yl)acetamido **(28)** exhibited a lower level of neurotoxicity with higher protective index (P1) and was found to be more effective than standard drugs (carbamazepine/valproic acid). **Siddiqui *et al.*,**[22] (2017) designed and synthesized 2-[(6-substituted benzo[*d*]thiazol-2-ylcarbamoyl]-1-(4-substituted phenyl)isothioureas derivatives**.** Majority of the compounds were found active when tested via MES and scPTZ models. The most potent compound **(29)** was found active at a lower dose of 30 mg/kg and also displayed a good docking score and higher binding energy for GABA-A receptor.

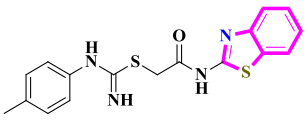


R= 6-CH_3, 6-OCH_3, H, 6-CH_3, 6-NO_2
(23a) (23b) (23c) (23d) (23e)

R= OCH_3, 2-OH
R'= OCH_3, 4-CH_3
(26a) (26b)



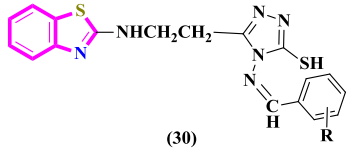
R= F, F
R'= H, 2-Cl
(27a), (27b)



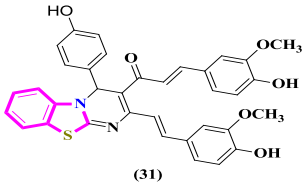
Antimicrobial activity

Soni *et al.*,[23] (2010) synthesized and evaluated new benzothiazole derivatives **(30)** as potential antimicrobial agents. Condensation of 5-[2-(1,3-benzothiazole-2-yl-amino)ethyl]-4-amino-3-mercapto-(4*H*)-1,2,4-triazoles with appropriate aromatic aldehydes afforded the title compounds. The results of antibacterial activity showed that compounds 4-hydroxy, 4-dimethylamino and the 3,4-dimethoxy substituent on the aromatic ring showed good antibacterial activity. Among these synthesized compounds, 4-hydroxy and 4-*N*-dimethyl groups were the most active antibacterial agents with MIC=100 µg/ml. Thus they could be assigned as promising antimicrobial candidates. **Sahu *et al.*,**[24] (2012)

synthesized 4*H*-pyrimido[2,1-*b*] benzothiazole derivatives and evaluated their antibacterial activities against Gram± bacteria, viz, *Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhii, Escherichia coli, Bacillus cereus* and *Providencia rettgeri.* The compound **(31)** showed good activity against all strains of microorganisms when compared with standard drug ciprofloxacin. **Padalkar *et al.*,**[25] (2012) in search of a new class of antimicrobial agents synthesized some benzothiazole deivatives and evaluated them*in-vitro* antibacterial activities against *Escherichia Coli* and *Staphylococcus aureus* strains and *in-vitro* antifungal activity against *Aspergillus niger* and *Candida albicans* strains using serial dilution method. Compound 2-(1,3-benzothiazol-2-yl)-5-(*N,N*-diethylamino)phenol **(32)** displayed excellent inhibitory growth against tested bacterial strains. **Singh *et al.*,**[26] (2013) reported the synthesis of benzothiazole analogues and screened these compounds for their antibacterial activity against Gram +ve bacteria (*Enterococcus faecalis* and *Staphylococcus aureus*) and Gram -ve bacteria (*Escherichia coli, Klebsiella pneumonia, Salmonella typhi, shigella boydii, Pseudomonas aeruginosa)* and antifungal activity against *Candida albicans, Candidatropicalis, Cryptococcus neoformans.* Compound **(33a)** with 2,4-difluoro substituent showed maximum potency against all Gram ± ve bacterial strains with MIC value 3.12 µg/ml, which was found to be two-fold more active when compared with standard drug ciprofloxacin (MIC = 6.25 µg/ml) whereas 4-bromo substituted **(33b)** was found to be most active against all fungal strains exhibiting MIC value 1.56 - 12.5mg/ml. **Zhao *et al.*,**[27] (2014) designed and prepared a series of benzothiazole and amide-imidazole scaffolds to combat the increasing rate of drug-resistant fungal infection. The antifungal activity of these compounds was evaluated *in-vitro*, and their structure-activity relationship (SARs) was assessed. Majority of these compound exhibited inhibitory activity against *Candida albicans* and *Cryptococcus neoformans*. Among all, compounds **(34a, 34b and 34c)** revealed minimum inhibitory concentration (MIC) values in the range of 0.125-2 µg/ml. Preliminary mechanism studies exhibited that the compound **(34b)** significantly act by inhibiting the CYP51 of *Candida albicans*. This could act as SARs and binding mode set in this study are useful for further lead optimization. **Bhatt *et al.*,** [28] (2017) reported the synthesis of 2-(5-chlorobenzo[*d*]thiazol-2-ylimino)-5-((3-(*p*-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) thiazolidin-4-ones **(35)** as antifungal agents. Compound **(35)** showed very good activity for all bacterial strains *S. pyogenes, S. aureus, C.albicans, A. niger, A. clavatus, P. aeruginosa* when compared with standard drug ampicillin. **Sharma *et al.*,**[29] (2017) reported the synthesis, characterization, and evaluation of a new series of *N*-(6-methoxybenzo[*d*]thiazol-2-yl)-2-substituted phenyl-1*H*-benz[*d*]imidazole-1-carbothioamide derivatives **(36)** for their antibacterial effects. Compounds **(36a)** and **(36b)** were found to be most potent against bacterial strains, *P. aeruginosa, S. aureus, E. coli* when compared with standard drug ampicillin. Also compound **(36c)** was more active against *C. albicans* as compared to standard drug griseofulvin.



(30)



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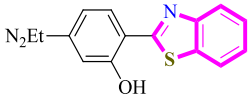

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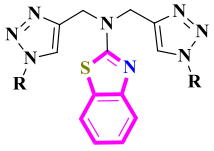
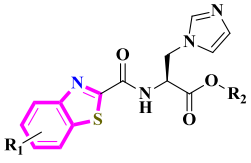


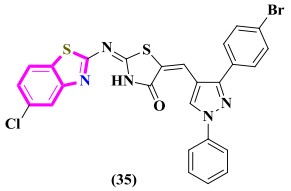
(33)

R= 4-OH, 4-N$(CH_3)_2$, 3,4-OCH_3

R= 2,4-diF, 4-Br
(33a) (33b)



(34)



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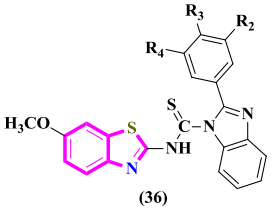


(36)

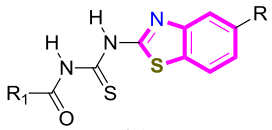
R_1= 6-Br, 6-Br, 6-CF_3

R_2= $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH_2CH(CH_3)_2$
(34a) (34b) (34c)

R_2= OCH_3, H
R_3= OCH_3, NH_2
R_4= OCH_3, H
(36a) (36b)

Anticancer activity

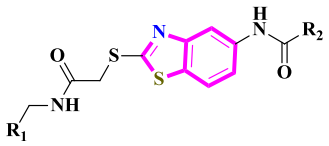
Saeed *et al.*,[30] (2010) reported the synthesis, characterization and evaluation of new benzothiazole derivatives as potential anticancer agents. Among all the synthesized compounds, the results of preliminary MIT cytotoxicity studies showed that compounds **(37a, 37b and 37c)** were most potent in MCF-7 and Hela cell lines when compared to the reference compound, doxorubicin, the IC_{50} values were observed in the range of 18-26 µM and 38-46 µM, respectively. **Wang *et al.*,[31]** (2011) reported the antitumor activity of benzothiazole-2-thiol derivatives on HepG2 and MCF-7 cells, the compound were found to have good inhibitory effects on cell growth and some of them were found to be even more effective than standard drug cisplatin. Among them, the two most active compounds **(38a** and **38b)** showed good inhibitory activity against human cancer cell lines. Substituent chloromethyl emerged as having a crucial role in this series of benzothiazole-2-thiol derivatives. **Kumbhare *et al.*,[32]** (2012) synthesized and evaluated novel 2-phenyl benzothiazole derived compounds for their anticancer activity. Isoxazoles and triazoles linked 2-phenyl benzothiazole exhibited good cytotoxicity against colo-205 and A549 cells. Among the tested compounds, (**39**) was found to have good cytotoxic activity. **Waghmare *et al.*,[33]** (2013) reported novel heterocyclic 3-cyano-6,9-dimethyl-4-imino 2-methylthio-4*H*-pyrimido[2,1-*b*][1,3]benzothiazoles and their 2-substituted analogs and evaluated their activity against a different type of cancer cell lines. The synthesized compound 4-imino-6,9-dimethyl-2-(methylthio)-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carbonitrile **(40),** exhibited maximum *in-vitro* anticancer activity against a different cancer cell lines. **Xie *et al.*,[34]** (2014) constructed a class of antitumor activity oriented benzothiazole sub-library, the antitumor activity of compounds was screened against 60 human cancer cell lines. Compound (**41), (42)** and **(43)** were found to be most effective and showed GI_{50} at 0.38 µM concentration. **Prabhu *et al.*,[35]** (2015) prepared a novel series of eight 2-(3-(4-oxo-2-substituted phenylthiazolidine-3-yl)phenyl)benzo[*d*]thiazole-6-carboxylic acid derivatives. Synthesized compounds were evaluated for their *in vitro* anticancer activity by 3-(4,5-dimethylthiazole-2yl)-2,5-diphenyltetrazoliumbromide (MTT) assay on human cervical (Hela) cancer cell lines. Compound with 4-chloro substituent **(44)** exhibited most significant activity as compared to other synthesized compound. **Al Ghorbani *et al.*,[36]** (2016) synthesized a novel series of benzoic acid benzoic acid *N'*-[2-(4-benzothiazol-2-yl-piperazin-1-yl)-acetyl]-hydrazides. The compounds were evaluated against Dalton's lymphoma ascites (DLA) cells and compound **(45)** showed promising antiproliferative efficacy with bromo group on the phenyl ring emerged as the potent cytotoxicity agents. This compound also exhibited antiangiogenic activity in *in vitro* treatment models. **El-Damasy *et al.*,[37]** (2016) designed and synthesized a new series of benzothiazole amide and urea derivatives tethered with the privileged pyridylamide moiety **(46)** as a potent anticancer agent. Among all compound 4-((2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)benzo [*d*]thiazol-6-yl)oxy)-*N*-methylpicolinamide **(46)** exhibited promising growth inhibition and was the most potent and efficacious derivative and RAF inhibitor, with IC_{50} values of 1.23 µM. This result can act as promising candidates for further development of potent anticancer agents. **P. Lad, *et al.*,[38]** (2017) synthesized a novel series of 4 and 5-substituted methylsulfonyl benzothiazoles and evaluated them for anticancer activity. The compounds 5-ethoxy-2-(methylsulfonyl)-*N*-(4-nitrophenyl)benzo[d]thiazole-4-sulfonamide **(47),** and N-(tert-butyl)-5-ethoxy-2-(methylsulfonyl)benzo[d]thiazol-4-sulfonamide **(48)**, significantly reduced the cell growth and showed higher efficiency and produced 50% cell growth inhibition at <0.1 µM concentration. These compounds can be explored further and could act as potential candidates for cervical cancer treatment.



(37)

R= Br, Br, NH_2
(37a) (37b) (37c)

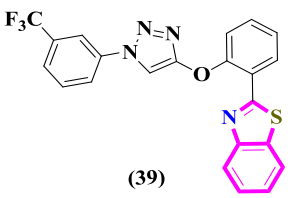
R_1= 2-thiophene, 4-morpholine, 4-morpholine
(37a) (37b) (37c)



(38)

R_1= 4-chloromethyl, 2-methoxyphenyl

R_2= Phenyl, chloromethyl
(38a) (38b)



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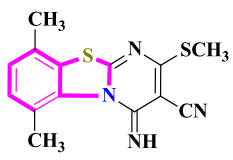

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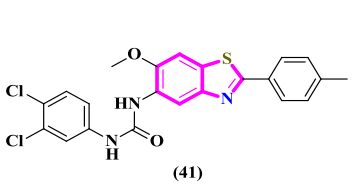
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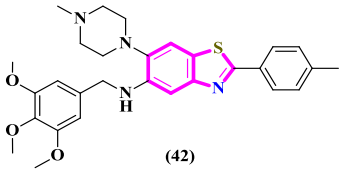
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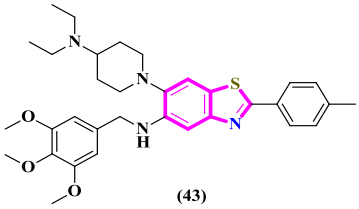
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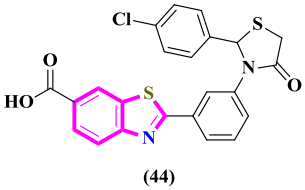
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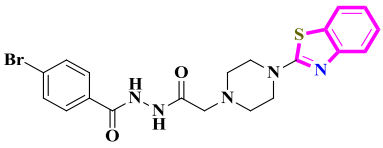
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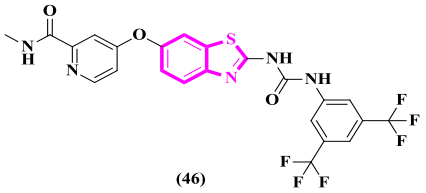
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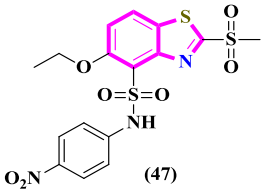
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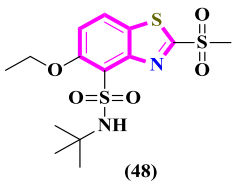
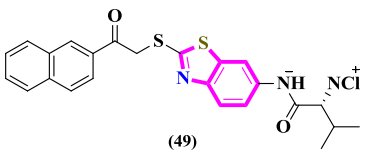

(48)

Antimalarial activity

Shah *et al.*,[39] (2011) designed**,** synthesized some novel benzothiazole analogs as inhibitors of *Plasmodium falciparum* as antimalarial agents. Fifteen structural analogues of both series showed moderate inhibition of falcipain-2. In benzothiazole series, compound **(49)** and **(50)** with protonated amines inhibited both homoglobinases but both compounds were found inactive against cathepsin B. **Ongarora *et al.*,**[40] (2012) synthesized a new class of benzothiazole analogues and evaluated their antiplasmodial activity and cytotoxicity. Compounds possess excellent ability to inhibit W2 and K1 chloroquine-resistant strains of *Plasmodium falciparum*. Further, these derivatives of 2,6-substituted and 2,4-substituted benzo[*d*]thiazoles were screened for mosquito repellent activity against *anopheles arabeensis*. Among them, compound **(51)** displayed good repellent activity against standard drug chloroquine. **Vanugapala *et al.*,**[41] (2013) developed and synthesized a novel efficient route for one pot synthesis of 2,6-substituted benzothiazoles analogs and 2,4-substituted-benzothiazole analogs. Among these analogous, compounds 1-[(6-chloro-benzo[*d*]thiazol-2-ylamino)-phenyl methyl]naphthalen-2-ol **(52),** 1-((6-chlorobenzo[*d*]thiazol-2-ylamino)-(4-nitrophenyl)-methyl)-naphthalen-2-ol **(53),** 1-((4-methoxyphenyl)-(4-methylbenzo[*d*]thiazol-2-ylamino)-methyl)-naphthalen-2-ol **(54)**, exhibited highest repellent activity when compared to the positive control DEET. **Sadhasivam *et al.*,**[42] (2016) synthesized and characterized six compounds of benzothiazole derivatives and reported their antiplasmodial activity against *Plasmodium falciparum* by Giemsa stain. Compound 1-(2-furoyl)-*N*-(6-nitro-1,3-benzothiazol-2-yl)piperidine-4-carboxamide **(55)** exhibited good antiplasmodial activity. **Sharma, *et al.*,**[43] (2017) synthesized a new series of *N*-(6-methoxy benzo[*d*]thiazole-2-yl)-2-substituted phenyl-1*H*-benz[*d*]imidazole-1-carbothioamide derivatives**.** The compounds **(56)** substituted with (3,4,5-trimethoxy) and **(57)** with (3,4-dinitro) groups showed maximum inhibition against *P.falciparum* (IC_{50} values 0.18 µg/ml and 0.11 µg/ml, respectively) when compared to reference drug chloroquine (0.020 µg/ml) and quinine (0.268 µg/ml).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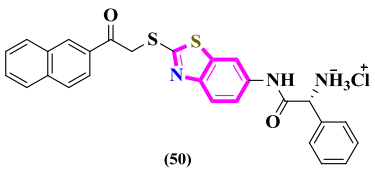
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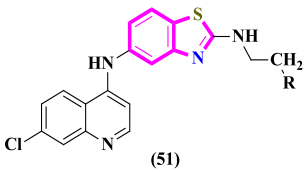
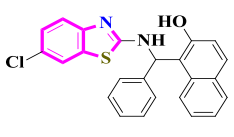

(51)

R= 1-methylpiperidine, 1-methylpyrrolidine, methylethanamine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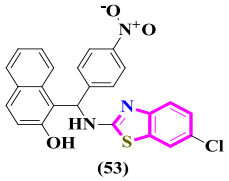
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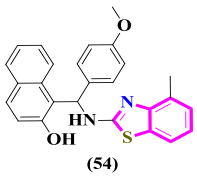
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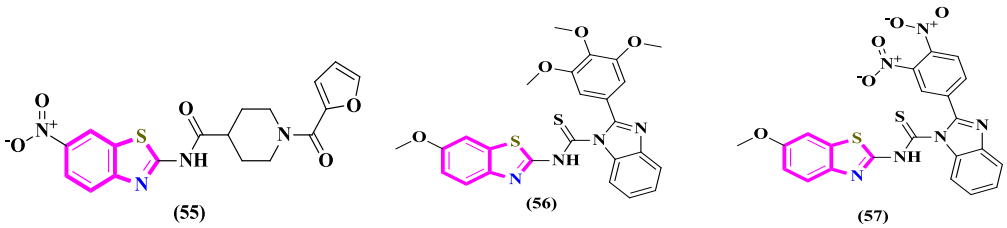
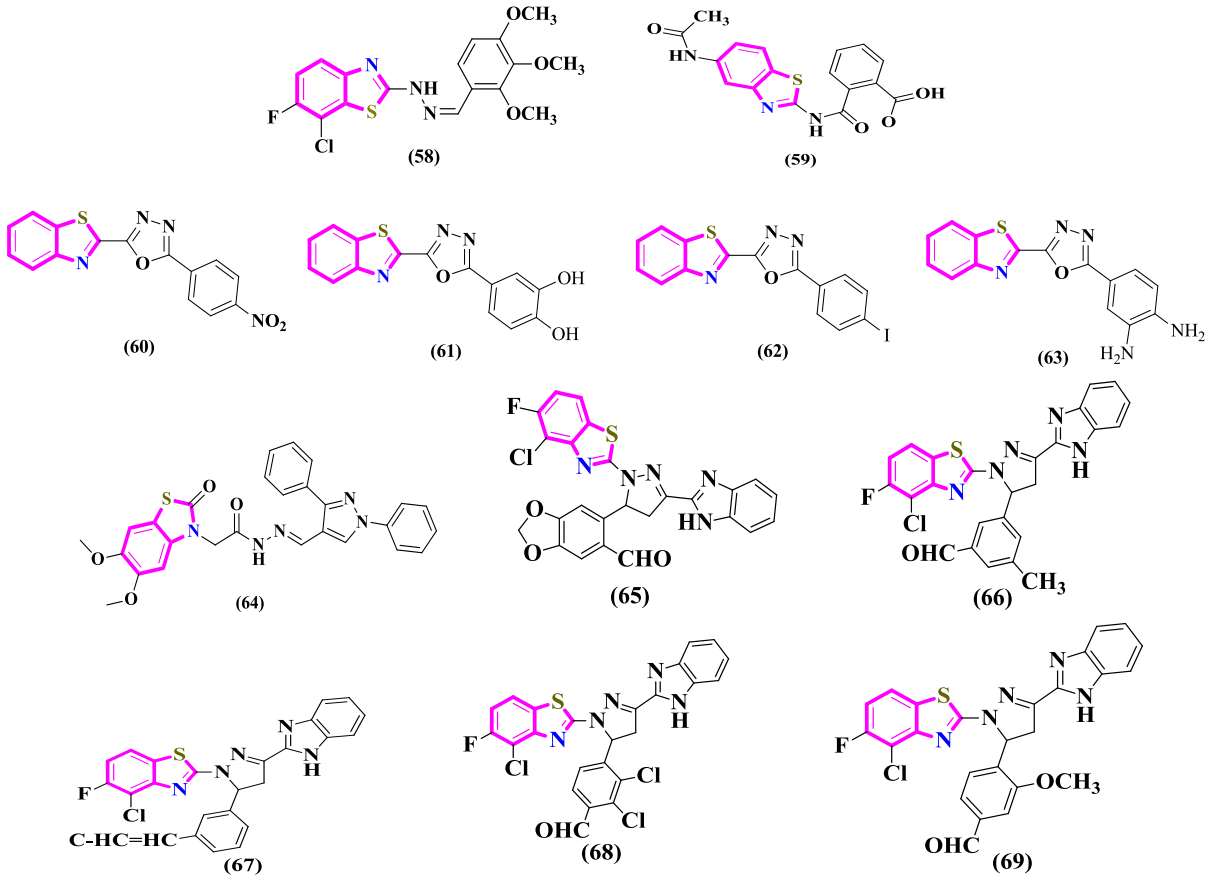


(55) (56) (57)

Anti-inflammatory activity

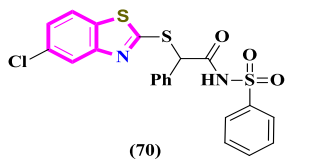
Muttu *et al.*,[44] (2010) synthesized and reported a series of various substituted benzothiazole derivatives containing 7-(chloro-6-floro-*N*-substituted hydrazones). Most of the compound were evaluated for anti-inflammatory acting using carragenan injected by paw edema. Compound **(58)** showed good anti-inflammatory activity as compared to the standard drug diclofenac sodium. **Verma *et al.*,**[45] (2014) worked on a compound 2-(6-acetamidobenzo[*d*]thiazole-2-ylcarbamoyl) benzoic acid **(59).** The newly synthesized compound was characterized by analytical and spectral methods. Compound **(59)** exhibited significant anti-inflammatory activity as compared to the reference drugs. **Kumar *et al.*,**[46] (2015) synthesized and evaluated the anti-inflammatory and analgesic activity of 2-(5-substituted-1,3,4-oxadiazole-2-yl-1,3-benzothiazole derivatives **(60).** Their *in-vivo* anti-inflammatory and analgesic evaluation was performed 50 mg/kg and 10 mg/kg dose levels. Compounds **(60), (61), (62)** and **(63)** exhibited most significant anti-inflammatory activity in comparison to the reference drug pentazocine. **Abbas *et al.*,**[47] (2015) reported a new series of benzothiazole-2-one or benzothiazole ring system and evaluated them for an anti-inflammatory agent by using 5,6-dimethoxy-3-benzothiazole-2-(3*H*)-one. The result of screening carragennan rat paw edema was used to evaluate the anti-inflammatory properties. The newly synthesized compounds were characterized by analytical and spectral methods. Results obtained revealed that tested derivatives exhibited significant anti-inflammatory activity. Compound **(64)** was most potent derivative as compared to standard drug indomethacin. **Sharmila, *et al.*,**[48] (2016) synthesized and evaluated a new series of 7-chloro-2-[3-(1*H*-benzimidazol-2-yl)-5-aryl-4,5-dihydro-1*H*-pyrazol-1-yl]-6-fluoro-1,3-benzothiazol compound. They observed that among all the compounds **(65), (66), (67), (68) and (69)** were the found to be most potent analgesic and anti-inflammatory agents.



(58) (59) (60) (61) (62) (63) (64) (65) (66) (67) (68) (69)

Anti-diabetic activity

Ammazzalarso *et al.*,[49] (2011) synthesized a novel class of potent PPARα antagonists, *N*-(phenylsulfonyl)amides containing the benzothiazole derivatives as antidiabetic agents. Compound **(70)** evaluated *in-vitro* against the agonistic effects of GW7647 in a dose-dependent way; they showed an inhibitory effect on PPARα activation. **Mariappan *et al.*,**[50] (2012) reported a novel series of benzothiazole derivatives and assayed *in vivo* study of their hypoglycemic agent which exhibited considerable biological efficacy when compared to glibenclamide. Among them, compound **(71)** exhibit more potent activity at 100 mg /kg p.o. Experimental result of these compound statistically significant at $p<0.01$ and $p<0.05$ level. The antioxidant screening results revealed that *N*-(6-chlorobenzo[*d*]thiazol-2-yl)-2-morpholino acetamide was more potent due to the presence of the heterocyclic amine. **Patil *et al.*,** [51] (2013) synthesized a novel series of substituted (*E*)-3-benzo[*d*]thiazol-2-ylamino)phenylprop-2-en-l-one derivatives**.** Some of the compounds **(72a, 72b, 72c, 72d, 72e** and **72f)** showed promising glycosidase inhibitors activity. Antidiabetic screening results indicate that importance of these novel compounds as potential lead candidates. **Kharbanda *et al.*,**[52] (2016) reported a nine of twenty novel piperine analogs exhibiting significantly high antidiabetic activity in comparison with rosiglitazone (standard) drugs. These active derivatives **(73)** were evaluated for their action as PPAR-γ agonist demonstrating their mechanism of action. The results of antidiabetic activity showed that compound **(73a)** with 6-Cl and **(73b)** with 6-Br substituent on the aromatic ring can act as promising antidiabetic agents. These compounds exhibited their effect by enhancing PPAR-γ gene expression. **Puranik *et al.*,**[53] (2016) synthesized new benzothiazole derivatives and assessed their antidiabetic potential using α-glucosidase, α-amylase, non-enzymatic glycosylation of hemoglobin and advanced end product inhibition assays: tested benzothiazole derivatives. The compound 2-(4-(*N*, *N*-dimethylamino)phenyl)-1,3-benzothiazole **(74)** were found to be most active in various stages. This compound showed low IC_{50} value of 0.31, 0.98, 0.59 and 0.19 µM in α-amylase, α-glucosidase, non-bonded interaction with α-amylase (3 OLD) < α-glycosidase (2 ZEO) showed that it binds to the inactive site pocket and is surrounded by residues ASP197, Glu233, Asp300 in 3OLD and Asp199, Glu256, Asp326 in 2ZEO. **Kumar, *et al.*,**[54] (2017) performed synthesis and evaluation of a novel series of benzothiazole derivatives**.** These derivatives showed remarkable biological efficacy, compound **(75)** was found to be most potent antidiabetic activity at 350 mg/kg exerted maximum glucose lowering effects as compared with standard drug Glibenclamide.



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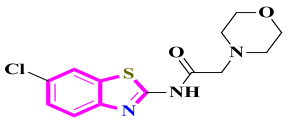

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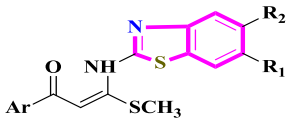

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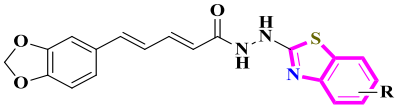


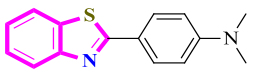
(73)

R= 6-Cl, 6-Br
(73a) (73b)

Ar= 4-$CH_3C_6H_4$,4-BrC_6H_4,4-BrC_6H_4,4-BrC_6H_4, 4ClC_6H_4, 4ClC_6H_4
(72a) (72b) (72c) (72d) (72e) (72f)

R_1= 6-OC_2H_5, 6-OC_2H_5, H, 6-CH_3, H, 6-OC_2H_5
(72a) (72b) (72c) (72d) (72e) (72f)

R_2= H, H, H, 5-CH_3, H, H
(72a) (72b) (72c) (72d) (72e) (72f)



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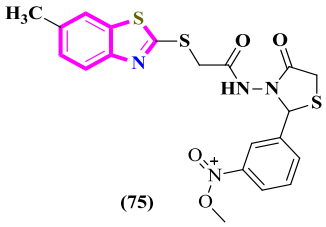
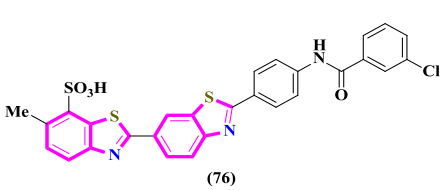
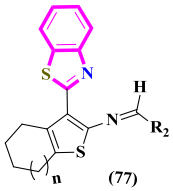


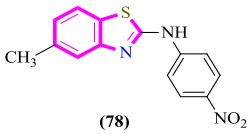
(75)

Antiviral activity

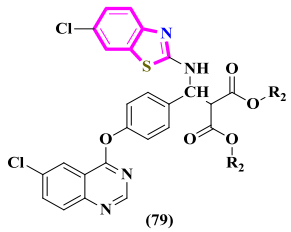
Li *et al.*,[55] (2012) screened NS3 helicase inhibitors for the optimization of potent hepatitis C virus. The results revealed that the commercial dye thioflavin S was the most potent inhibitor of NS3-catalysed. Compound **(76)** was the most potent helicase inhibitor of the replicon and inhibited 50% at 2.6 ± 1 µM. **Ke *et al.*,**[56] (2013) reported the synthesis, characterization, and evaluation of a series of novel cycloalkylthiophene-imine derivatives for potential antiviral agents. This bio-evaluation indicated that some of the newly synthesized compounds exhibited moderate to good antiviral activities. Compound **(77)** was most potent and showed higher antiviral activities in comparison with reference drug ribavirin. **Peng *et al.*,** [57] (2013) rationally designed and synthesized a series of novel anilinobenzothiazole derivatives and evaluated their effect on HCV RdRp and replication of the viral genome. 2-(4-nitroaniline)-6-methylbenzothiazole **(78)** inhibited HCV RNA-dependent polymerase activity and replication (EC_{50} = 8 ± 0.5µM). This compound acted synergistically with IFN-α, telaprevir, PSI7977, or BMS790052 in reducing HCV RNA levels. **Xiao *et al.*,**[58] (2014) synthesized benzothiazoles and evaluated them for anti-tobacco mosaic virus (TMV) activity**.** Compounds **(79)** was found to have strong protective and curative effect against TMV, with –Cl and H derivatives and was found comparable to the ningnanmycin standard drug. **Sweeney *et al.*,**[59] (2015) prepared a benzothiazole and pyrrolone flavivirus inhibitors targeting the viral helicase. ML283 analogs were better inhibitors of DENV helicase than the HCV helicase. The most potent, compounds **(80)** and **(81)** were >10 times more active against the DENV protein and reduce the replication of a subgenomic DENV replicon in cells. **Zhang *et al.*,**[60] (2017) reported a series of enantiomeric α-aminophosphonate derivatives with high anti-TMV activities. Synthesized compound of **(82)** (*R*)-diphenyl-1-(4-methylbenzothiazole-2-amino)-1-(thiophene-2-yl)-methylphosphonate were found to be superior to (*S*)-diphenyl-1-(4-methylbenzothiazole-2-amino)-1-(thiophene-2-yl)-methyl phosphonate, **Q-R** evaluated higher antiviral activity and was observed at 500 µg/ml (curative activity 61%, protective activity 58%, inactivation activity 98%) which was found to be more active than **Q-S.**

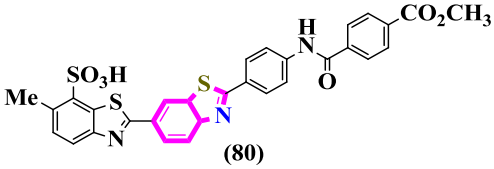


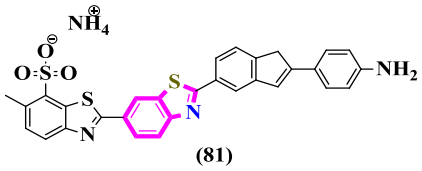




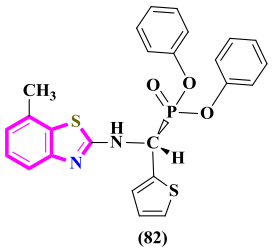
R_2=2-F-Ph, 4-Cl-Ph







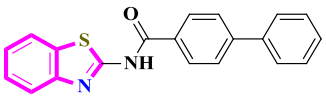
R_2= CH_3, C_2H_5, n-C_3H_7, $CH_2C_6H_5$



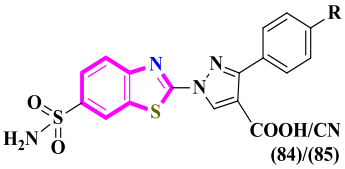
Carbonic-anhydrase inhibitors

Yar *et al.*,[61] (2009) reported the *in-vivo* diuretic activity of biphenylbenzothiazole-2-carboxamide derivatives. Among the series, compound *N*-(1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide **(83)** was highly significant 16.08 ± 0.650 ($p<0.01$), showed a potent diuretic action which is more potent than a standard drug acetazolamide (AZA). **Sitaram *et al.*,**[62] (2014) synthesized a series of a new compound in which **(84a, 85a, 85b, 85c and 85d)** exhibit potent carbonic anhydrase inhibition compared to standard drug acetazolamide. Sitaram *et al*, illustrated inhibitory potency data for those compound against isozymes like hCA I, hCA II, hCA IX, hCA XII in which all compound exhibited excellent inhibitory activity against three isozymes such as hCA I, hCA IX, hCA XII except hCA II. **Ibrahim *et al.*,**[63] (2015) designed, synthesized and investigated a series of novel 2-aminobenzothiazole derivatives bearing sulphonamide at position 6 as inhibitors of four isoforms of the metalloenzymes carbonic anhydrase**.** Most of the novel compounds were acting as highly potent inhibitors of the tumor. The compound, 2-[(4-amino-1*H*-pyrazol[3,4-*d*]pyrimidin-6-yl)thio]-*N*-[6-(aminosulfonyl)-1,3-benzothiazol-2-yl]acetamide **(86)** showed good

selectivity and potent activity towards CA II and CA XII. **Kucukbay *et al.*,**[64] (2015) reacted *N*-protected amino acids substituted benzothiazoles produce corresponding *N*-protected amino acids benzothiazole conjugates**.** These conjugates were investigated for carbonic anhydrase inhibitory activity against (hCA I, hCA II, hCA IV, and hCA XII) CA isoforms in which find out that compound 1-3 possess more potent CA inhibitory activity and showed inhibitory power (45.4-67.5mm) in relation to standard drug acetazolamide but reported compounds **(87)** had affinity towards hCA I as compared to another isoform. **Husain *et al.*,**[65] (2016) reported the synthesis of some new sulfonamides containing quinoxaline ring as a new class of diuretic agents and revealed its diuretic action showed CAII in the cytosol and additionally CAIV, XII, and XIV isozymes. This compound,2-[3-[2-(4-methoxyphenyl)-ethenyl]-1*H*-quinoxalin-2-ylideneamino]-1,3-benzothiazole-6-sulfonic acid amide **(88)** showed a good *in-vivo* diuretic activity of 1.13 to be more intense than acetazolamide. It gave off an impression of being the most encouraging lead compound as the diuretic among all the recently integrated sulphonamide mixes. **Petrou *et al.*,**[66] (2016) synthesized a series of benzothiazole based sulfonamides **(89)** and tested their CA inhibitors. Several derivatives on investigation showed interesting inhibitory activity and selectivity for inhibiting hCA IX and hCA XII over the off-target ones hCA I and hCA II.



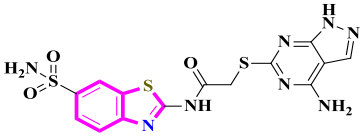
(83)



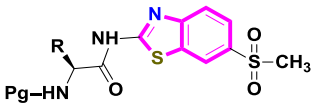
(84)/(85)

R= H, H, CH_3, OCH_3

(84a) (85a) (85b) (85c)



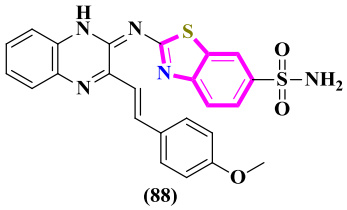
(86)



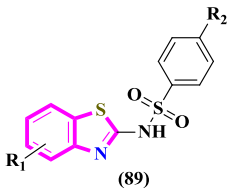
(87)

R= H, H, CH_2Ph
(**87a) (87b) (87c)**

Pg= Z, Boc, Boc
(87a) (87b) (87c)



(88)

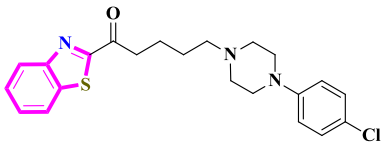


(89)

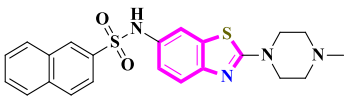
R_1= 4-Cl, 5,6-diMe, 6-Cl, 6-F, 4-Me
R_2= 4-Cl, 4-NO_2, H, 4-OMe, 4-F, 4-Me

Antidepressant activity

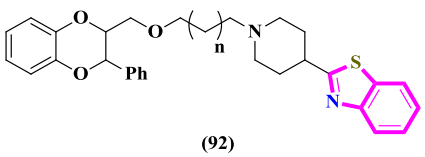
Zhu *et al.*,[67] (2012) performed the synthesis and evaluation of several benzothiazoles as new potential antidepressants agents probes the $5HT1_A$ receptor and serotonin transporter (SERT). It has been shown that antidepressants activity resides in the majority of the synthesized compounds showed modest binding affinity at the $5HT1_A$ receptor and the SERT site and thus, have the potential to be further explored as dual acting agents. The compound, 1-(benzo[*d*]thiazol-2-yl)-5-(4-(4-chlorophenyl) piperazin-1-yl)pentan-1-one hydrochloride **(90)** bind with low affinity to the dopamine transporter, norepinephrine transporter and $5HT2_c$ receptor. **Hayat *et al.*,**[68] (2013) synthesized novel benzothiazole derivatives as a new series of aryl sulfonyl piperazine derivatives as 5-HT6 ligands was evaluated by measuring the 5-HT induced Ca^{2+} increases using Hela cell line. Compound 2-(4-methylpiperazin-1-yl)-6-(1-naphthalenyl) sulfonamidebenzo[*d*]thiazol **(91)** is a potent 5-HT6 receptor antagonist with higher selectivity over 5-HT4 and 5-HT7 receptors. **Wang *et al.*,**[69] (2014) synthesized and reported a series of benzoxazole/benzothiazole-2,3-dihydrobenzo[*b*][1,4]dioxine derivatives. Compound **(92)** exhibited high affinities for the $5-HT1_A$ receptor (ki = 31nM) with potent affinity for the $5HT2_A$ receptor (ki = 24nM) receptors. These results concluded that it cans antidepressant-like activity.



(90)



(91)



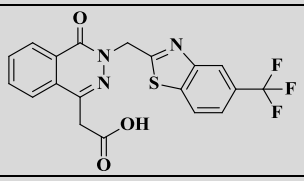
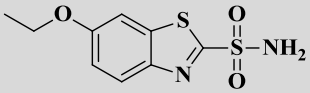
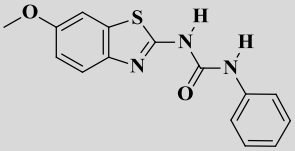
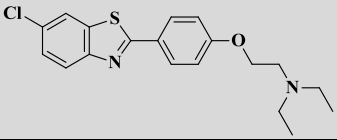
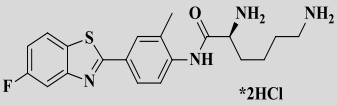
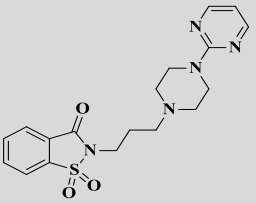
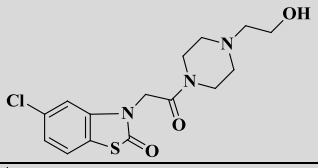
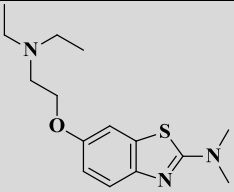
(92)

n= 2

CONCLUSION

From the review of literature on the biologically active benzothiazole, it is concluded that variations on benzothiazoles moiety can be done to develop potent therapeutic agents. A new generation of benzothiazoles thus obtained, serve as a therapeutic lead in the field of medicinal chemistry as benzothiazoles have gained huge scientific interest and are still getting the same extent of attention of researchers worldwide.

MARKETED PREPARATIONS HAVING BENZOTHIAZOLE CORE NUCLEUS

S.No.	Marketed drug	Brand Name/Manufacturer	structure	Use
1.	Zopolrestat	Alond, Xedia (Pfizer)		Diabetic- cardomyopathy, Diabetic- neuropathies
2.	Ethoxzolamide	6-Ethoxayzolamide (Sigma Aldrich)		Carbonic anhydrase inhibitor, Diuretic
3.	Frentizole	Frenazole (Shanghai Haoyuan Chem. Express Co., Ltd.) China		Antiviral
4.	Halethazole	Septomixine forte		Antiseptic and Antifungal
5.	Phortress	(Tocrisa biotechne) Bristol, UK.		Antitumor
6.	Revospirone	_		Anxiety and Anxiolytic agent.
7.	Tiaramide Hydrochloride	Slantal (Asteuas Pharma) Japan		Anti-inflammatory agent.
8.	Dimazole	Danogen (100/50 mg) (Cipla)		Antifungal

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