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Review Article

Benzothiazole - Versatile heterocyclic nucleus in medicinal chemistry: A review

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Abstract

Benzothiazole, the bicyclic ring system consists of thiazole ring fused with benzene ring. Benzothiazole moiety is very small but is fascinated by scientists because of the different biological activities by benzothiazole and their derivatives. A large number of efforts were made to synthesize different benzothiazole compounds and their derivatives in the past decade and were found to numerous pharmacological activities like antitumor, anticonvulsant, antimicrobial, anthelmintic, antileishmanial, anti-tubercular, schictosomicidal, antifungal, anti-inflammatory antipsychotic and anti diabetic activities. The present review focuses on the benzothiazoles with potential activities that are now in development.

Keywords: Benzothiazole, anti Cancer, anti microbial, anti convulsant

1. Introduction

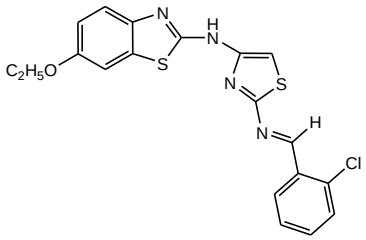
Heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways. Benzothiazole is a heterocyclic compound, weak base, is made from thiazole ring fused with benzene ring, having various biological activities and still of great scientific interest now a days.

Benzothiazole compounds and their derivatives were found to numerous pharmacological activities like antitumor[1], anticonvulsant[2], antimicrobial[3], anthelmintic[4], antileishmanial[5], anti-tubercular[6], schictosomicidal[7], antifungal[8], anti-inflammatory[9] antipsychotic[10] and anti diabetic activities[11]. The present review focuses on the benzothiazoles with potential activities that are now in development.

2. Biologically active Benzothiazoles and its derivatives

2.1 Anthelminthic activity

Amnerkar *et al*, carried out the Synthesis and biological evaluation of some 4-(6-substituted-1,3-benzothiazol-2-yl)amino-1,3-thiazole-2-amines and their Schiff bases, and were evaluated for their antibacterial, antifungal and anthelmintic activities. The results showed that several of the synthesized aminobenzothiazole derivatives exhibited significant antibacterial, antifungal and anthelmintic activities[12].



Balaji *et al*, Synthesized heterocyclic pyrazole and its derivatives from fluoro substituted hydrazino benzothiazole and. The synthesized compounds were screened for Anthelmintic and Anti-microbial activities, that the synthesized compounds showed significant activity[13].

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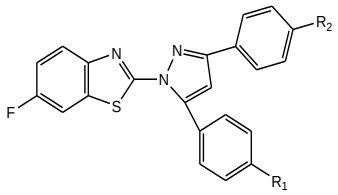
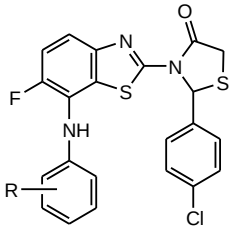


R_1= Cl, OCH_3, Furan , R_2= OH, NH_2, OCH_3, CH_3, Cl

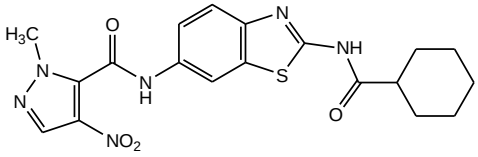
Reddy D. and Sudhakar, Synthesized Some 3-(7-Chloro-6-fluoro benzo [d] thiazol-2-yl)-2-(4-Chlorophenyl) thiazol 1,3 lidin-4-one, These were screened for anthelmintic activity at a concentration of 50, 100, 150 µg/ml using Albendnazole as a standard and DMSO to a control[14].



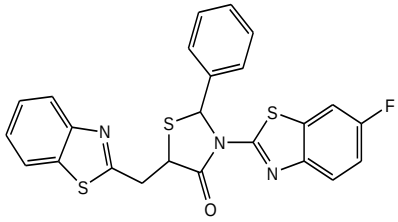
R = PABA, Diphenylamine, Dimethylamine; Diethylamine, Morpholine,M-Toulidine, Napthylamine, Phenylethylamine, Pyrrolidine, *o*-Anisidine, M-Anisidine, Tyrosine

2.2 Antitumor activity

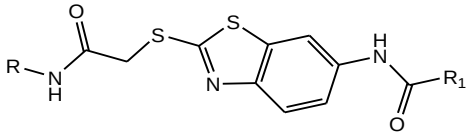
Chen *et al* carried out the QSAR study and molecular design of benzothiazole derivatives and were found to be potent anticancer agents[15].



Sekar *et al*, Synthesized some of the novel bis-benzothiazole derivatives, All the compounds synthesized were screened for *in-vitro* anticancer activity against HeLa (Human Epithelial cervix cancer cell line) cell lines by MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrasolium bromide] assay method along with control. All the newly synthesized compounds were screened for anticancer activity at a concentration of 100, 10, 1, and 0.1µM. All compounds showed good anticancer activity against HeLa cell lines[16].

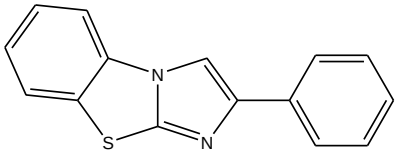


Luo-Ting Yu *et al.* synthesized a series of novel benzothiazole-2-thiol derivatives, and they were evaluated for anticancer activity. Among them, pyridinyl-2-amine linked benzothiazole-2-thiol compounds 7d, 7e, 7f and 7i exhibited potent and broad-spectrum inhibitory activities. Compound 7e displayed the most potent anticancer activity on SKRB-3 (IC50 = 1.2 nM), SW620 (IC50 = 4.3 nM), A549 (IC50 = 44 nM) and HepG2 (IC50 = 48 nM) and was found to induce apoptosis in HepG2 cancer cells[17].

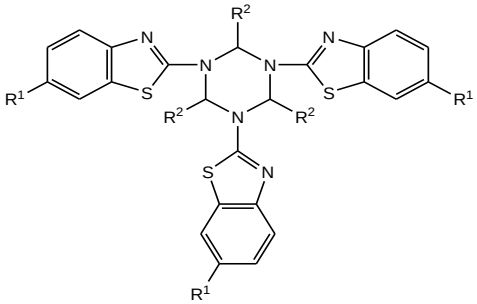


R	R1
7a. benzyl	chloroethyl
7b. benzyl	bromoethyl
7c. 2-pyridinyl	chloromethyl
7d. 5-chloro-2-pyridinyl	chloromethyl
7e. 5-bromo-2-pyridinyl	chloromethyl
7f. 5-methyl-2-pyridinyl	chloromethyl
7g. 3-pyridinyl	chloromethyl
7h. 2-chloro-4-pyridinyl	chloromethyl
7i. 2-chloro-4-methyl-3-pyridinyl	chloromethyl
7j. 2-pyrimidinyl	chloromethyl
7k .2-thiazolyl	chloromethyl

Flavio *et al*, carried out the Combined Drug Action of 2-Phenylimidazo[2,1-b]Benzothiazole Derivatives on Cancer Cells According to Their Oncogenic Molecular Signatures[18].

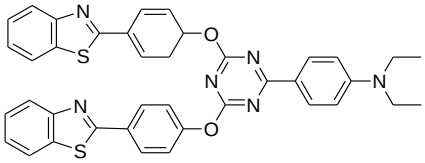


Ojha *et al*, carried out the Rapid synthesis of some medicinally important hexahydrostriazine derivatives incorporating benzothiazole and Antiproliferative activity was carried out by MTT assay method against Human hepatoma cell line (hepatic cancer) and Human breast adinocarcinoma cell line (breast cancer) and observed the marked Antiproliferative activity[19].

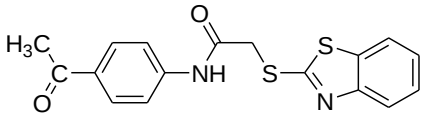


2.3 Antimicrobial activity

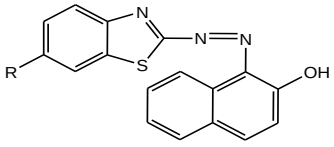
Sekar *et al*, studied the novel dipodal-benzimidazole, benzoxazole and benzothiazole from cyanuric chloride: Structural, photophysical and antimicrobial studies, compounds exhibited good antimicrobial activity, good thermal stability and photophysical properties with improved quantum yield[20].



Maru *et al*, Synthesized and studied of some novel benzothiazole derivatives, The new compounds examined for antibacterial effects again different strain of bacteria and antifungal were high to lowest minimum inhibition concentration (MIC) values, *N*-(4-Acetylphenyl)-2-(benzothiazole-2-ylsulfanyl)-acetamide with different substituted of anilines were observed as good antimicrobial agents[21].

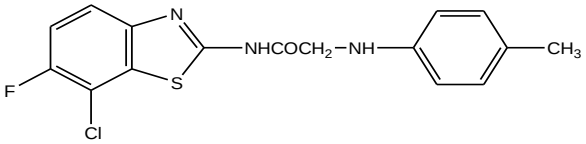


Bele *et al*, carried out the Synthesis and antimicrobial activity of some Benzothiazole derivatives. All the derivatives were screened for antimicrobial activity against *S. aureus*, *S. pyrogens*, *E. coli*, *P. mirabilis*, *C. albicans* and *A. fumigates* using Ciprofloxacin and Amphotericin B as standard drugs for evaluation of antibacterial and antifungal activity respectively. Some derivatives exhibit mild to moderate activity[22].

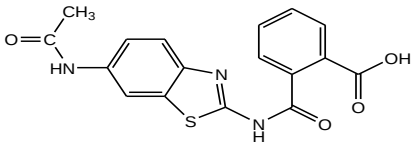


R = H, CH_3,OCH_3, Cl, NO_2

Yadav *et al*, carried out Microwave Assisted Synthesis of Fluoro, Chloro-2-(α-Substituted aryl amino acetamido) Benzothiazole and evaluated for antimicrobial activities[23].

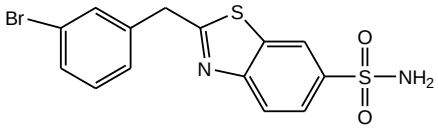


Verma *et al*, carried out the Synthesis, characterization and antibacterial activity of benzothiazole derivatives. The synthesized derivatives showed very good antibacterial activities against previously reported derivatives of benzothiazole[24].

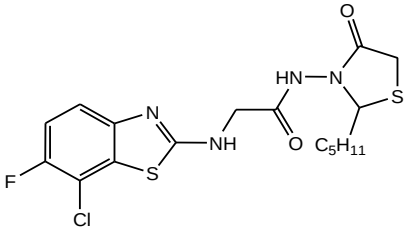


2.4 Ant-inflammatory activities

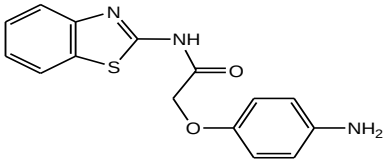
Mahtab *et al*, Synthesized the novel 2-benzylbenzo[d] thiazole-6-sulfonamide derivatives. These compounds were screened for anti-inflammatory activity by carrageenan induced paw oedema method in rats at a dose of 100 mg/kg body weight. All the newly synthesized benzothiazole derivatives have shown considerable anti-inflammatory activity[25].



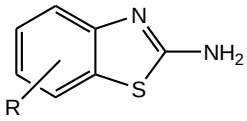
Ashok Kumar and Gopalakrishna, carried out the Synthesis and Biological, Pharmacolgical Activites of Bioactive Benzothiazole Derivatives and they have been screened for their antifungal and anti-inflammatory activities[26].



Velingkar *et al*, worked on the Synthesis, characterization, biological evaluation and ADME studies using *in silico* techniques of novel derivatives of benzothiazolyl-amides. The effect of the synthesized compounds on inflammation, using the carageenan induced mouse paw edema model was studied. In general, the studied compounds were found to be potent as non-acidic anti-inflammatory agents. The tested compounds did not present any side effects from the gastrointestinal route because of its non-acidic in nature[27].

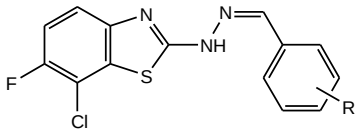


Venkatesh *et al*, Synthesized some of 2-amino benzothiazole derivatives and evaluated the anti-inflammatory activities of synthesized compounds were determined by λ-Carrageenan-induced mice paw edema method using diclofenac sodium as a standard, the phenyl ring substituted with chloro at 5 position, methoxy substitution at 4 and 6-position in benzothiazole ring system showed better anti-inflammatory activity[28].



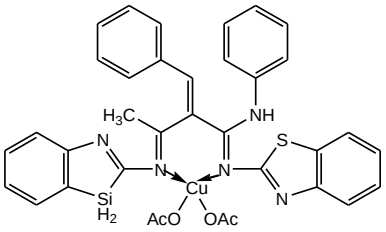
R = Bt_1. H; Bt_2= 5-C;l Bt_3= 6-Cl; Bt_4= 6-NO_2;
Bt_5= 5-NO_2; Bt_6= 6-methoxy; Bt 7= 4-methoxy;
Bt 8= 6-Br

Muttu *et al*, worked on the Microwave assisted synthesis and evaluation of flouro, chloro 2 N- (substituted Schiff bases) amino benzothiazole derivatives for their anti-inflammatory activities[29].

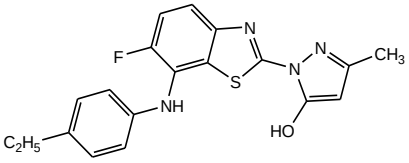


2.5 Antioxidant activities

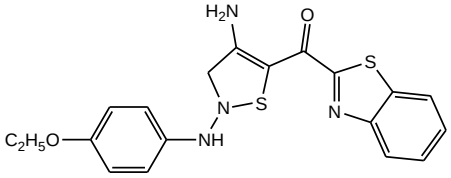
J. Joseph and G. Boomadevi Janaki carried out the Synthesis, structural characterization and biological studies of copper complexes with 2-aminobenzothiazole derivatives and observed Antibacterial screening of all the complexes show higher activities than the free ligands. Antioxidant and SOD studies also performed[30].



Reddy *et al*, worked on the antimicrobial, anti oxidant and anticonvulsant evaluation of some novel 6-fluorobenzothiazole substituted pyrazole analogues and identified the Benzothiazole substituted with anisidine, pyrrolidine, *o*-phenylene diamine on seventh position enhances the anti-microbial, anti-oxidant activities[31].

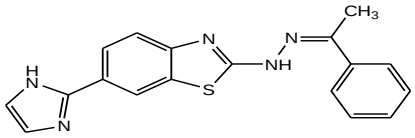


Yardily and T.F. Abbs Fen Reji, synthesized the novel 2-(4-amino-2-aryllaminothiazol-5-oyl)benzothiazole derivatives have been synthesized from amidinothioureas and 2-(2-bromoacetyl)benzothiazole with triethylamine. The antioxidant activity of the synthesized compounds was determined by DPPH free radical scavenging activity. The compounds 3c and 3e shows higher antioxidant dose than standard BHA antioxidant[32].

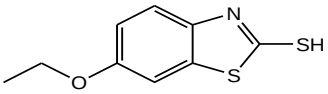


Compound R
3a C_6H_5-
3b 4-$MeOC_6H_4$-
3c 4-$EtOC_6H_4$-
3d 4-MeC_6H_4-
3e 4-ClC_6H_4-

Priyadharsini *et al*, synthesized new compounds incorporating various structurally important moieties like benzothiazole, Schiff bases and were docked against CDK2 kinases protein target when BTZ 6 ligand showed two interactions and found to give a good docking score. All the synthesized compounds were screened to study their antioxidant effect comparing to the known standard drug and found to be exhibiting promising antioxidant activity[33].

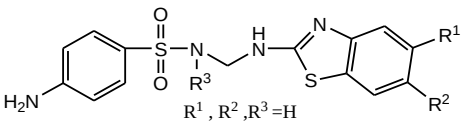


Damien *et al*, Synthesizes new benzothiazoles and thiadiazoles and observed the antioxidant properties and radio protective effects[34].



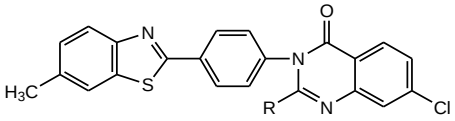
2.6 Anti-tubercular activity

Naira *et al*, Synthesized some Mannich bases from sulphonamides and benzothiazole derivatives, the synthesized compounds were screened for their anti tubercular activity using Lowenstein-Jensen (L.J) medium against *Mycobacterium tuberculosis* H37 RV strains. Compounds 6a, 6b, 6c were active against Mycobacterium tuberculosis H37 RV strains[35].

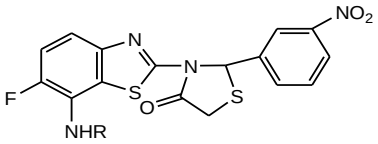


R^1 , R^2 ,R^3 =H
R^1 = Cl, R^2 ,R^3 =H
R^1 = Cl, R^2 = F, R^3 =H

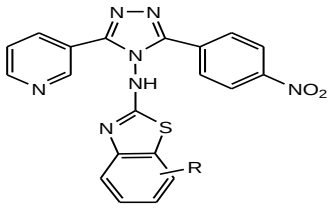
Shaik *et al*, studied the newly synthesized 3-(4-(6-methylbenzo[*d*]thiazol-2-yl) phenyl) quinazolin-4(3*H*)-ones, *In vitro* antitubercular activity was carried out against *Mycobacterium tuberculosis H37Rv* strain using Lowenstein-Jensen medium[36].



Sathe *et al*, synthesized fluoro benzothiazole comprising potent thaizolidinone derivatives, some compounds showed promising antimycobacterial activity[37].



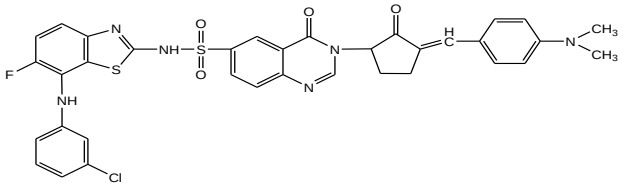
Navin B. Patel et.al, Synthesizrd the 1,2,4-triazole derivatives containing benzothiazoles and *in vitro* antimicrobial and antitubercular activity of various series of 3-(3-pyridyl)-5-(4-nitrophenyl)-4-(*N*-substituted-1,3-benzothiazol-2-amino)-4*H*-1,2,4-triazole[38].



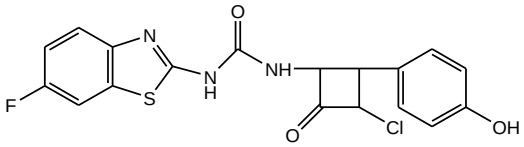
R = 6-Cl, 6-OCH_3, 6-F

2.7 Anticonvulsant activity

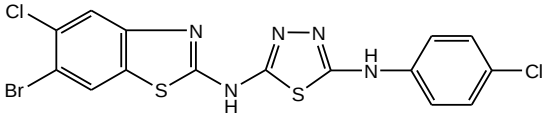
Shanmukha *et al*, carried out the comparative Study of Anticonvulsant Property among Different Fluoro Substituted Synthesized Benzothiazole Derivatives, and observed the anticonvulsant action of SSBDs is better against strychnine induced seizures than MES seizures. AP-3, AP-6 and BZ-9 were shown significant anticonvulsant activity against both MES and strychnine induced models[39].



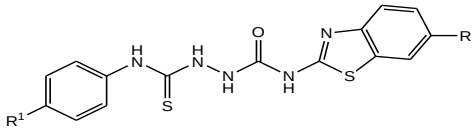
A number of new 1-[2-(3,4-disubstituted phenyl)-3-chloro-4-oxoazetidin-1-yl]-3-(6-substituted-1,3-benzothiazol-2-yl)urea compounds (**5a-t**) were synthesized by Nadeem Siddiqui *et al*, and evaluated for their anticonvulsant, hepatotoxic and neurotoxic properties[40].



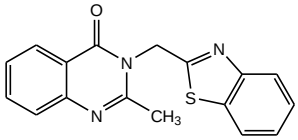
N. Siddiqui *et al.* Various *N*-(5-chloro-6-substituted-benzothiazol-2-yl)-*N*'-(substituted phenyl)-[1,3,4]thiadiazole-2,5-diamines (5a-t) were designed. All the newly synthesized compounds were screened for their anticonvulsant activity and were compared with the standard drug phenytoin sodium. Thiadiazole incorporated benzothiazole derivatives can be regarded as a new structural class of anticonvulsant agents. Some of the compounds displayed encouraging activities in the MES test with less neurotoxicity and minimal effect on the liver[41].



Nadeem Siddiqui *et al*, carried out the Computational parameters of newer benzothiazoles synthesized and screened for anticonvulsant activity. All the compounds possessed the pharmacophoric elements required for the anticonvulsant activity[42].

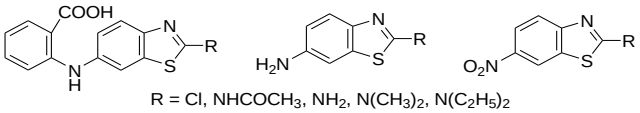


Ajeet, Arvind Kumar worked on the Designing of Hybrid form of Benzothiazole-quinazoline The hybrid form of benzothiazole-quinazoline derivatives were docked with GABA-A then all the 10 designed molecules were found with the higher affinity values (more than double affinity value) as compared to the γ-aminobutyric acid, so it could be concluded that these hybrid derivatives may be proved the better inhibitors of GABA-A for the anticonvulsant activity[43].



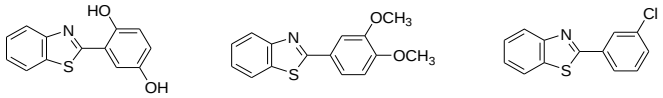
Antileishmanial activity

Carole *et al*, carried out the *In Vitro* Activities of Position 2 Substitution-Bearing 6-Nitro- and 6-Amino-Benzothiazoles and Their Corresponding Anthranilic Acid Derivatives against *Leishmania infantum* and *Trichomonas vaginalis*[44].



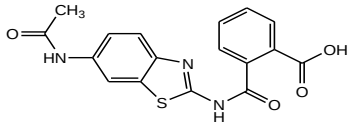
R = Cl, $NHCOCH_3$, NH_2, $N(CH_3)_2$, $N(C_2H_5)_2$

Fazal *et al*, studied Antileishmanial Activities of Benzothiazole Derivatives and all synthetic compounds were screened for *in vitro* antileishmanial activity[45].

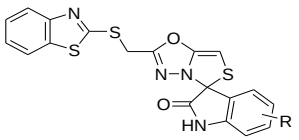


2.8 Analgesic activity

Verma *et al*, carried out the Synthesis, Characterization and evaluation of Anti-inflammatory and Analgesic activity of Benzothiazole derivatives. The synthesized derivatives showed very good anti-inflammatory and analgesic activities against previously reported derivatives of benzothiazole[46].

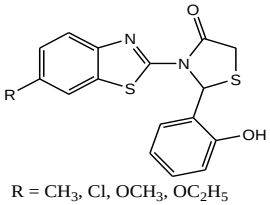


Ashok Kumar *et al*, worked on the Synthesis, characterization and biological activity of various substituted benzothiazole derivatives and screened for their anti-inflammatory, analgesic and antibacterial activities[47].



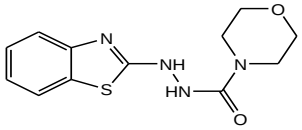
2.9 Miscellaneous

Deepak Pareek *et al*, Synthesized some bioactive 4-thiazolidinone derivatives incorporating benzothiazole moiety. These were screened for their entomological (Antifeedant activity, Acaricidal activity, Contact toxicity, Stomach toxicity) activities[48].

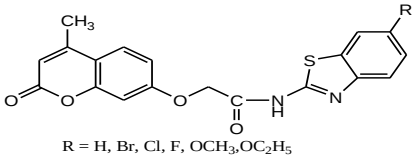


R = CH_3, Cl, OCH_3, OC_2H_5

M. A. Mahran *et al*, Synthesis of some new benzothiazole derivatives and the compounds were screened for their anti-parasitic activity. Most of them showed reasonable antinematodal or schistosomicidal activity[49].

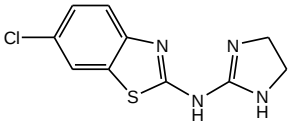


Arora *et al*, Synthesized Some of the Novel Chromene-2-one Derivatives and evaluated for antipsychotic activity. All the synthesized compounds showed antipsychotic activity with muscle relaxant property[50].

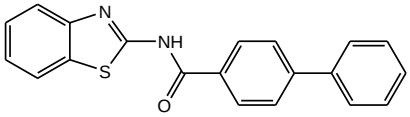


R = H, Br, Cl, F, OCH_3,OC_2H_5

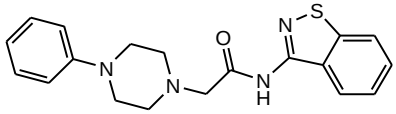
Pareek *et al*, Synthesized some of the benzothiazole derivatives and found to be antibacterial, potent antiulcer, anti-inflammatory and antitumor. Antifeedant activity, contact toxicity and stomach toxicity tested against *Spodoptera litura* and acaricidal activity tested against *Tetranychus urticae*[51].



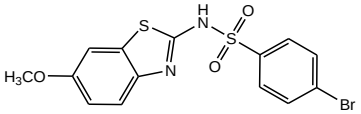
Shahar Yar *et al*, carried out the synthesized a series of biphenylbenzothiazole-2-carboxamide derivatives and evaluated their diuretic potential. Substitution at position 6 of benzothiazole ring system with electron withdrawing group (Cl, F, Br) significantly increases urinary excretion[52].



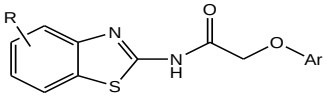
Geronikaki *et al*, performed the evaluation of the local anaesthetic activity of 3-aminobenzo[d]isothiazole derivatives using the rat sciatic nerve model with lidocaine which was used as a reference compound[53].



Verma *et al*, worked on the Design and Synthesis of some Benzothiazole Analogs and found as α_{2A} Receptor Antagonist as a potential α_{2A} therapeutic target for the treatment of conditions such as insomnia, pain, depression, drug addiction and Parkinson's disease[54].



Bendre *et al*, carried out the Synthesis, Characterization and Plant Growth Regulator Activity of Some Substituted 2-Amino Benzothiazole Derivatives were tested on the germination of wheat seeds. Almost, all the compounds showed good activity at tested concentrations. The tested derivatives characterized as biologically active substances with auxin like growth promoting activity[55].



R = H, 4-CH_3, 6-CH_3, 6-OCH_3
Ar = 2-Cl-Ph, 4-Cl-Ph, 4-Cl, 3,5-diMe-Ph

3. Conclusion

From the above literature review concluded that the benzothiazoles and their derivatives have shown a wide spectrum of biological activities. It is a versatile nucleus in the field of medicinal chemistry. Hence this unique molecule must serve as future therapeutic leads of developing various biological agents. The biological profiles of this new generation of benzothiazoles represent much progress with regard to the older compounds.

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