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Review Article

# BENZOTHIAZOLE: THE MOLECULE OF DIVERSE BIOLOGICAL ACTIVITIES

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**ABSTRACT**

A large number of efforts were made to synthesize different heterocyclic compounds and their derivatives in the past decade and were found to posses promising antitumor, anticonvulsant, antimicrobial, anti-tubercular and anti diabetic activities. Although benzothiazole moiety is very small but is fascinated by scientists because of the diverse biological activities by not only benzothiazole but its various substituted derivatives as well. This review was focused on the benzothiazole and its derivatives that are now in development.

## INTRODUCTION

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease. The process establishing a new drug is exceeding complex and involves talent of people from variety of disciplines[1]. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and pharmacological activity [2].

It has been established that half of the therapeutic agents consists of heterocyclic compounds. The heterocyclic ring comprises of very core of the active moiety or the pharmacophore[3].

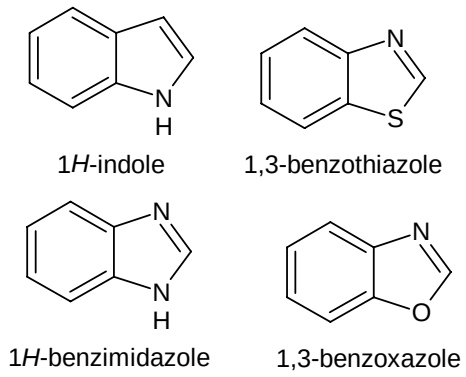



**Fig. 1**

Several Benz-fused heterocyclic systems as Indole, Benzothiazole, Benzimidazole, Benzoxazole(fig.1) have been studied and found to be possessing interesting pharmacological activities such as antiviral[4], antibacterial[5], antimicrobial[6], and fungicidal activities[7]. They are also useful as antiallergic[8], antidiabetic[9], antitumor[10], anti-inflammatory[11], anthelmintic[12], and anti HIV agents[13].

Benzothiazole ring system consists of thiazole ring fused with benzene ring. Thiazole ring is a five-member ring containing one nitrogen and one sulfur atom in the ring system.

Benzothiazoles are bicyclic ring system with multiple applications. In the 1950s, a number of 2-aminobenzothiazoles were intensively studied as central muscle relaxants. Since then medicinal chemists have not taken active interest in this chemical family. Biologist's attention was drawn to this series when the pharmacological profile of Riluzole[14](fig.2) was discovered.

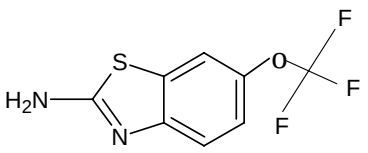


**Fig. 2**

Riluzole (6-trifluoromethoxy-2-benzothiazolamine), PK-26124, RP-25279, (Rilutek) was found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioural experiments. After that, benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity.

Although they have been known from long ago to be biologically active, their varied biological features are still of great scientific interest.

In addition, benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological properties. In last few years it was reported that benzothiazole, its bioisosters and derivatives had antimicrobial activity against Gram-negative, Gram-positive bacteria and the yeast *Candida albicans* and antimicrobial activity especially against *Enterobacter, Pseudomonas aeruginosa, E.coli,* and *Staphylococcus epidermidis*. Other activities involves are antidiabetic[15], and bradykinin $B_2$ receptor antagonist activity[16]. Given below is a brief account of various alterations conducted on benzothiazole ring and their associated biological activities.

### 1. ANTITUMOR ACTIVITY

The benzothiazole moiety with some substitution shows promising antitumor activity. Its aminomethylphenyl (1a), carbonitrile (1b) and bis-amidino-substituted 2-styryl (1c) derivatives shows selective growth inhibitory properties against human cancer cell lines[17], proliferation of cells[18], cytostatisis[19] respectively. Several chlorinated and fluorinated derivatives of this moiety exhibit excellent *in vitro* as well as *in vivo* antitumor activity.

Fluorinated analogues of 2-(4-aminophenyl) benzothiazoles have been synthesized which successfully block C-oxidation[20]. Fluorinated benzothiazole analogue 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F203, NSC 703786) (1d), exhibit selective and potent anticancer activity. It is the favoured analogue for clinical consideration possessing enhanced efficacy *in vitro* and superior potencies against human breast and ovarian tumor xenografts implanted in nude mice Its lysylamide prodrug, (Phortress, NSC 710305), (1e) is under phase I clinical trials at the United Kingdom.

2,6-dichloro-N-[2-(cyclopropanecarbonylamino)benzothiazole-6-yl]benzamide (1f) have been synthesized[21] and is biologically stable derivative, containing no nitro group. This is a highly potent derivative and exhibit excellent *in vivo* inhibitory effect on tumor growth.

The oxidation reactions of 2-(4-hydroxy-3-methoxyphenyl) benzothiazole (1g) have been studied and the synthesized compounds were found to possess the *in vitro* growth inhibition of human breast cancer cell lines[22].

### 2. ANTI CONVULSIVE ACTIVITY

Role of benzothiazoles as anticonvulsive agents were first observed in 1978 against phenyltetrazolone induced convulsions on 2-(-4-

arylthiosemicarbazidocarbonylthio) benzothiazoles[23] (2a) and since then several benzothiazoles containing sulphonamide derivatives[24] (2b), benzothiazolyl guinidines[25] (2c), benzothiazolamines[26] (2d) were synthesized and evaluated for their activity against electroshock and phenyltetrazolone induced seizures. The review of these literatures revealed the benzothiazole moiety as a dynamic agent against convulsive seizures.

A series of 2(3H)-benzoxazolone and 2(3H)-benzothiazolone derivatives have been synthesized and evaluated for their anticonvulsant activity[27]. The compounds were assayed intraperitoneally in mice against seizures induced by maximal electroshock and pentylenetetrazole. Compound 2e and 2f was the most active compound against Maximal Electroshock Seizures.

New sulphonamide derivatives having benzothiazole nucleus is synthesized by treating 2-(4-aminophenylsulphonamido)-6-halo/alkyl benzothiazoles with alkyl isothiocyanate[24]. The synthesized compounds were evaluated for their anticonvulsant activity.

**3. ANTIMICROBIAL ACTIVITY**

Microbes are causative agents for various types of disease like pneumonia, ameobiasis, typhoid, malaria, common cough and cold various infections and some severe diseases like tuberculosis, influenza, syphilis, and AIDS as well. Various approaches were made to check the role of benzothiazole moiety as antimicrobial agent from the discovery of molecule to the present scenario. Various diaminophenyl sulfonyl[28] (3a). Aryl-1,3,4-oxadiazol-5-yl)-mercapto methyl[29] (3b), amino (substituted) acetanildes[30] (3c), arylidene sulphonamide[31] (3d) were synthesized in past decade and checked for their activity against various microbial stains like *E. coli, S. aureus, S. typhi, P. aeruginosa, Bacillus subtilis, Candida albicans and Pneumococci*, and found to posses promising antiviral, antiprotozoal, antifungal, and antibacterial activities.

A series of multi substituted benzoxazoles, benzimidazoles, and benzothiazoles had been synthesized (3e-3g), as non-nucleoside fused isosteric heterocyclic compounds and tested for their antibacterial activities against *Staphylococcus aureus* , *Streptococcus faecalis* , *Bacillus subtilis* as gram positive and *E. coli* , *Klebsiella pneumoniae* , *Pseudomonas aeruginosa* as gram negative bacteria and yeast *Candida albicans* using twofold serial dilution technique. The synthesized compounds possessed a broad spectrum of activity against the tested microorganisms at MIC values between 100 and 3.12 µg/ml. Benzothiazole ring system enhanced the antimicrobial activity against *Staphylococcus aureus*[32].

Various 8-Fluoro-9-substitued (1,3)benzothiazolo(5,1-*b*)-1,2,4-trizoles (3h-3i) were synthesisized and evaluated for antimicrobial activity against S.aureus, E.coli and C. Albicans [33]. All the compounds showed good antimicrobial activity. Some 6-fluoro-7-(substituted)-(2- *N* -p-anilinosulfonamido) benzothiazoles (R =o-nitroanilino, m-nitroanilino, p-nitroanilino, o-chloroanilino, m-chloroanilino, p-chloroanilino, anilino, morpholino, piperazino, dimethylamino) were synthesized and studied for their antibacterial and antifungal activities. All compounds showed moderate activity against *S. aureus, S. albus* and *C.ablicans*[34].

Latrofa *et al*[35] prepared a series of *N* -cycloalkylidene, *N* -cycloalkyl-2-acylalkylidene-2,3-dihyro-1,3-benzothiazoles, and *N* -alkyl-2-acylalkylidene-2,3-dihydro-1,3-benzothiazole and tested for *in vitro* antibacterial and antifungal activities against four gram positive and five gram negative bacteria. The findings obtained showed that some of the tested compounds were effective against bacterial strains, whereas, only few compounds exhibited a moderate antifungal activity against the yeast strains evaluated

The series of 2-benzylsulfanyl derivatives of benzoxazole and benzothiazoles were synthesized by Koci *et al*[36] and evaluated for their *in vitro* antimycobaterial activity against *Mycobaterium tuberculosis* and non tuberculous mycobateria, and the activity was expressed as the minimum inhibitory concentration (MIC) in µMl/l. The substances bearing two nitro groups or a thioamide group exhibited appreciable activity particularly against non-tuberculous strains.

In other words it can be stated that benzothiazole moiety serves as a royal warrior against almost all types of microbes.

**4. ANTIINFLAMMATORY ACTIVITY**

Pyrazolones and pyrazolinones rank among the more venerable non-steroidal antiinflammatory agents. Phenylbutazone and its congeners incorporating a pyrazoline-3,5-dione structure are more potent antiinflammatory agents. In the recent years a number of Benzothiazole derivatives have been synthesized and found to display antiinflammatory activity.

Oketani *et al.*[37] studied the *in vitro* pharmacological profiles of 6-hydroxy-5,7-dimethyl-2-(methylamino)-4-(3-pyridylmethyl)benzothiazoles (4a), against the 5-lipooxygenase activity of rat basophilic leukemia cells. This result indicate that the compound potently inhibited 5-lipooxygenase and thromboxane $A_2$ synthetase and blocked thromboxane $B_2$ production in rat peritoneal and human blood cells

In the year 2003 a series of 2-[(2-alkoxy-6-pentadecylphenyl)methylthio]-1H-benimidazole/benzothiazole has been reported (4b-4c) and investigated for their ability to inhibit human cyclooxygenase-2 enzyme (COX-2)[38]. Compounds were found to possess moderate anti inflammatory activity.

Dogruer *et al*[39] synthesized sixteen (2-benzothiazolone-3-yl and 2-benzoxazolone-3yl) acetic acid derivatives and tested them for antinociceptive and antiinflammatory activity. 4-[2-(6-Benzoyl-2-benzoxazolone-3-yl) acetyl] morpholino, 4-{2-[6-(2-chloro-benzoyl)-2-benzoxazolone-3-yl] acetyl} morpholino, 4-{2-[6-(2-chloro-benzoyl)-2-benzoxazolone-3yl] acetyl} morpholine, 1-[2-(5-chloro-2-benzoxazolone-3-yl) acetyl] pyrrolidine, methyl ((6-methyl-2-benzoxazolone-3-yl) acetate and *N, N* -diethyl-2- (2-benzothiazolone-3-yl) acetamide have shown more potent antinonciceptive activity than others.

2-(4'-butyl-3'-5'-dimethylpyrazol-1'-yl)-6-substituted-benzothiazoles (4d) and 4-Butyl-1-(6'-substituted-2'-benzothiazolyl)-3-methylpyrazol-5-ols (4e) have been synthesized by the condensation of 6-substitued-2-hydrazinobenzothiazoles with 3-butylpentane-2,4-dione and ethyl α-(n-butyl)acetoacetate respectively[40]. Selected compounds of the series were subjected to preliminary testing for their anti-inflammatory activity. All the compounds belonging to series display significant antiinflammatory activity.

**5. MISCELLANEOUS ACTIVITIES**

Srinivasan *et al*[41] have shown that the replacement of the urea moiety by benzothiazolesulfonamide provided inhibitors of HIV-1 protease with improved potency and antiviral activities. Certain members of the class showed good oral bioavailability in rats.

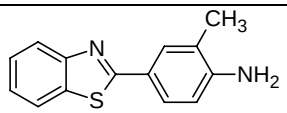
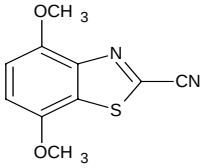
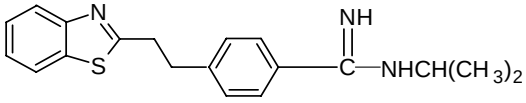
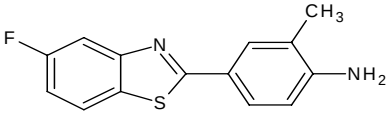
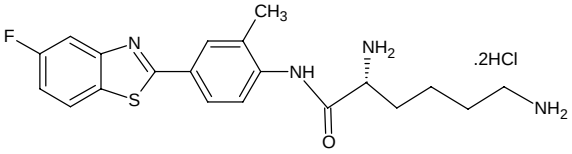
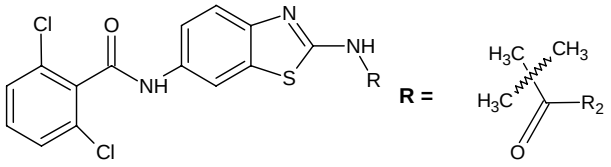
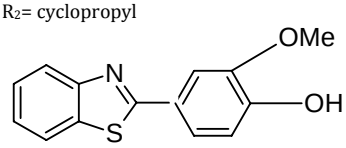
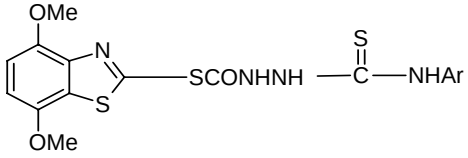
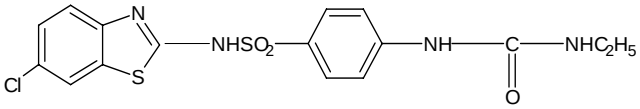
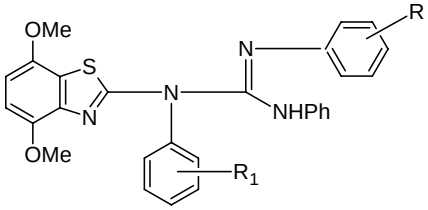
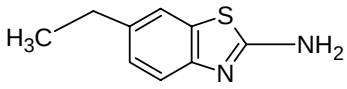
Original derivatives of 2-piperazinyl benzothiazoles (5a) were synthesized and studied as mixed ligand for serotoninergic 5-$HT_{1A}$ and 5-$HT_3$ receptors[42]. The studied compounds exhibited significant affinities for these two serotoninergic receptor subtypes. Compounds with such a pharmacological profile are of clinical relevance in the treatment of psychotropic diseases e.g. anxiety, depression and schizophrenia.

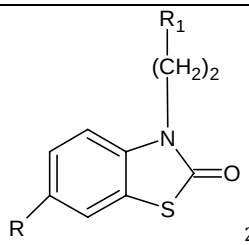
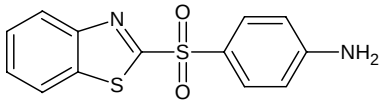
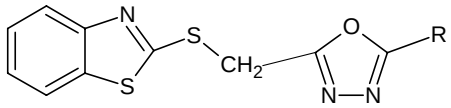
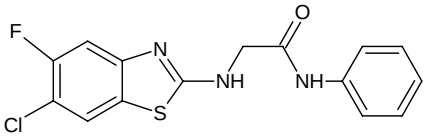
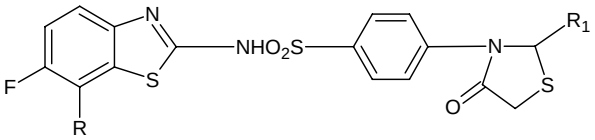
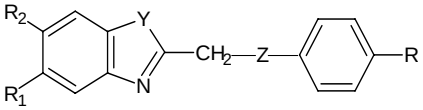
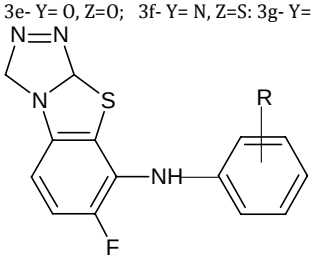
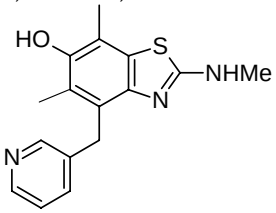
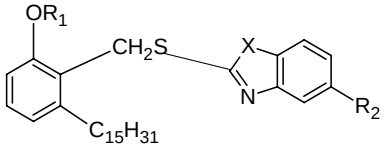
Das *et al.*[43] prepared a series of structurally novel benzothiazoles based small molecule inhibitors of $p56^{lck}$(a member of the Src family of non receptor protein tyrosine kinase). BMS-243117 (5b) is identified as a potent and selective Lck inhibitor with good cellular activity, whereas BMS-350751 (5c) and BMS-358233 (5d) are identified as potent Lck inhibitors with excellent cellular activities against T-cell proliferation.

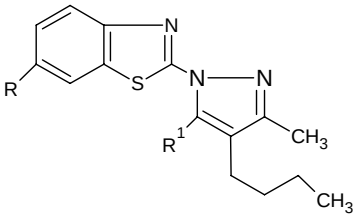
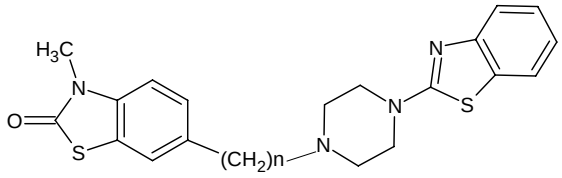
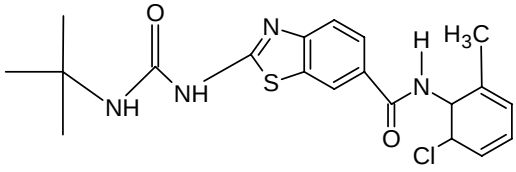
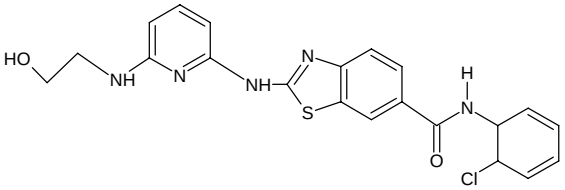
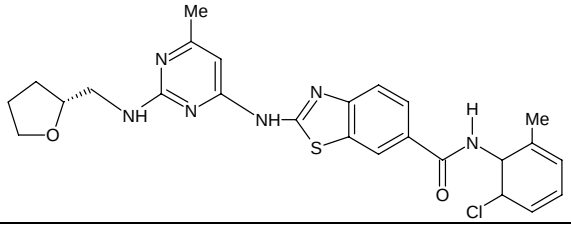
Antileishmanial activity of synthesized (1,3- Benzothiazol-2-yl )amino-9-(10H)-acridinone derivatives was tested by Florence Delmas *et al.*[44]. Two derivatives, 4-(6-nitro-benzothiazol-2-ylamino)-10H-acridin-9-one and 1-(6-amino-benzothiazol-2-ylamino)-10H-acridin-9-one (51c) showed moderate antileishmanial activity.

Nargund *et al.*[45] have been synthesized a series of 8-fluoro-9-substituted (1,3)benzothiazole(5,1-b)-1,3,4-triazoles, and all compounds were screened for their Anthelmintic activity against earthworm, *Perituma posthuma* and were found to possess markedly higher Anthelmintic activity.

**Table 1: It shows various biological activities**

| Structure no. | Structure | Activity | Workers |
|---|---|---|---|
| 1a |  | Antitumor | Kashiyama E *et al.* |
| 1b |  | Antitumor | Besson T *et al.* |
| 1c |  | Antitumor | Caleta I *et al.* |
| 1d |  | Antitumor | Hutchinson I *et al.* |
| 1e |  | Under clinical trials for antitumor activity | Hutchinson I *et al.* |
| 1f |  $R_2$= cyclopropyl | Antitumor | Yoshida M *et al.* |
| 1g |  | Antitumor | Wells G *et al* |
| 2a |  | Anti convulsant | Singh S.P *et al.* |
| 2b |  | Anti convulsant | Siddiqui N *et al.* |
| 2c |  | Anti convulsant | Pandeya S.N *et al.* |
| 2d |  | Anti convulsant | Jimonet P *et al.* |

| | | | |
|---|---|---|---|
| 2e-2f |  2e- R= $C_2H_5CO$, R1= $C_5H_{10}N$ 2f- R= $C_3H_7$, R1=$C_5H_{10}N$ | Anti convulsant | Ucar H *et al.* |
| 3a |  | Antimicrobial | Ghoneim K.M *et al.* |
| 3b |  | Antimicrobial | Trivedi B. H *et al.* |
| 3c |  | Antimicrobial | Pattan S. R *et al.* |
| 3d |  | Antimicrobial | Shastry C.S *et al.* |
| 3e-3g |  3e- Y= O, Z=O; 3f- Y= N, Z=S: 3g- Y= S, Z= O | Antimicrobial | Yilidiz-Oren I *et al.* |
| 3h-3i |  3h- R= o-$NO_2$, 3i- R= m-Cl, | Antimicrobial | Sreenivasa M.V *et al.* |
| 4a |  | Anti-inflammatory | Oketani K *et al.* |
| 4b-4c |  4b-$R_1$= H, $R_2$= $OCH_3$, X=NH 4c $R_1$= $CH_3$, $R_2$= H, X=S | Anti-inflammatory | Paramashivappa R *et al.* |

| | | | |
|---|---|---|---|
| 4d-4e |  <br>4d-R= H/$CH_3$/$OCH_3$, $R_1$= $CH_3$<br>4e- R= H/$CH_3$/$OCH_3$, $R_1$= OH | Anti-inflammatory | Singh, S.P *et al.* |
| 5a |  | Anti- psychotic | Diouf, O *et al.* |
| 5b |  | Lck inhibitor | Das, J *et al.* |
| 5c |  | Lck inhibitor | Das, J *et al.* |
| 5d |  | Lck inhibitor | Das, J *et al.* |

**SOME MARKET PREPERATIONS HAVING BENZOTHIAZOLE NUCLEUS**

**Mirapex** [46]

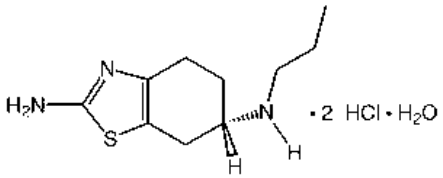


**Fig. 3**

**Riluzole** [47]

Riluzole (6- trifluoro methoxy- 2-benzothiazolamine) Patent No. -PK-26124, RP-25279 (Riluteck). Riluzole was found to interfere with neurotransmission in biochemical, electrophysiological and behavioural experiments.

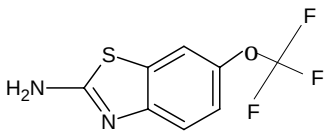


**Fig. 4**

**Tiaramide** [48]

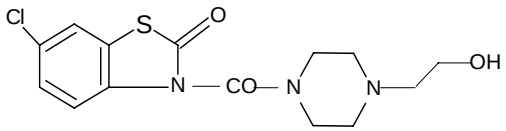


**Fig. 5**

**CONCLUSION**

The reviewed aminobenzothiazoles has shown a wide spectrum of biological activities. The substituted benzothiazolylimino dithiazolidines and the 2-(2'-aryl-1,3, 4-oxadiazol-5-yl)mercaptomethyl benzothiazoles are having significant antibacterial activity. Significant antiinflammatory activity is displayed by some new 2-(4'-butyl-3'-5'-dimethylpyrazol-1-yl)-6-substituted benzothiazoles and 4-butyl-1-(6'-substituted -2'-benzothiazolyl)-3-methylpyrazol-5-ones.

Benzothiazolylguanidines are found to have potent activity. Potent antitumor activity was demonstrated by a number of 2-(4-aminophenyl) benzothiazoles. The 2-(4-acetamido-2-bromo-5-methylphenyl sulfonamide) benzothiazole is found to be effective as antituberculor agents, whereas ethoxazolamide and o-acyl

derivatives of 6-hydroxybenzothiazole-2-sulfonamides are found to show the carbonic anhydrase inhibitory action. The biological profiles of this new generation of benzothiazoles represent much progress with regard to the older compounds.

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