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Review Article

RECENT ADVANCES IN PHARMACOLOGICAL ACTIVITY OF BENZOTHIAZOLE DERIVATIVES

PRIYANKA CHAUDHARY*, PRAMOD KUMAR SHARMA, ANJANA SHARMA, JONISH VARSHNEY

Department of Pharmaceutical Technology, Meerut Institute of Engineering & Technology, Baghpat Bypass Crossing, Delhi- Haridwar Highway, NH-58, Meerut-250005 (UP) India. Email: priyankampharm123@gmail.com

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ABSTRACT

Different heterocyclic compounds are made to synthesize by large number of efforts and their derivatives were found to posses anti-tumor, anti-diabetic, anti-microbial, anti-convulsant and anthelmintic activities. Benzothiazole moiety is very small but it posses different biological activities by not only benzothiazole but its different substituted derivatives also give different biological activities. This review was focused on the benzothiazole and its different derivatives that posses different biological activities.

Keywords: Benzothiazole, Anti-Tumor, Anthelminthic, Antimicrobial.

INTRODUCTION

Benzothiazoles are bicyclic ring system. A number of 2-aminobenzothiazoles have been studied as central muscle relaxants and found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments [1]. Benzothiazole derivatives have been studied and found to have various chemical reactivity and biological activity. Benzothiazole ring made from thiazole ring fused with benzene ring. Thiazole ring is a five-member ring consists of one nitrogen and one sulfur atom in the ring.

Benzothiazole ring found to be possessing pharmacological activities such as anti- viral [2], anti- bacterial [3], anti- microbial [4] and fungicidal activities [5].They are also useful as anti-allergic [6], anti-diabetic [7], anti-tumor [8], anti- inflammatory [9], anthelmintic [10], and anti- HIV agents. Benzothiazoles show antitumor activity, the phenyl-substituted Benzothiazoles [11-13] while condensed pyrimido benzothiazoles and benzothiazolo quinazolines show anti-viral activity. Substituted 6-nitro-and 6-aminobenzothiazoles show antimicrobial activity [14].

Given below is a brief account of various biological activities of benzothiazole ring and their derivatives.

PHARMACOLOGIACL ACTIVITIES OF BENZOTHIAZOLE AND THEIR DERIVATIVES

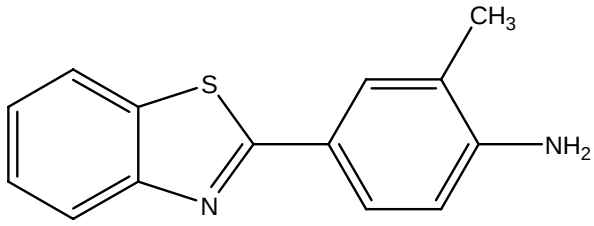
Anti-tumor activity

The benzothiazole moiety with various substitutions shows antitumor activity. Its aminomethylphenyl (fig.1) and carbonitrile (fig.2) derivatives shows selective growth inhibitory properties against human cancer cell lines[15] and proliferation of cells [16] respectively. Chlorinated and fluorinated derivatives of this moiety exhibit good *in vitro* as well as *in vivo* antitumor activity. A series of potent and selective anti-tumor agents were developed. Substituted 2-(4-aminophenyl) benzothiazoles examined, *in vitro* , shows anti-tumor activity in ovarian, breast, lung, renal and colon carnicoma human cell line [17][18] 2-(4-Aminophenyl) benzothiazoles [19][20] consists of a novel mechanistic class of antitumor agents. Pyrimido benzothiazole and benzothiazolo quinoline derivatives[21] , imidazo benzothiazoles [14][15] and polymerized benzothiazoles[22] have posses anti-tumor activity. All benzothiazole new compounds were tested on cytostatic activities against malignant cell lines. The compounds posses a different inhibitory effect, depended on concentration and type of the cells.

Some Fluorinated analogues of 2-(4-aminophenyl) benzothiazoles were synthesized which block C-oxidation [23]. The 2-cyano derivatives of benzothiazole exhibit interesting *in vitro* anti-tumor activity.

Anti-microbial activity

Microbes are the causative agents for various types of diseases like pneumonia, ameobiasis, typhoid, malaria, common cough, cold and various infections and cause some severe diseases like tuberculosis, influenza, syphilis, and AIDS etc. To check the role of benzothiazole moiety as anti-microbial agent Various approaches have been made. Benzothiazoles show a chemotherapeutic activity and a considerable amount of work has been done on the synthesis of new potent antibacterial and antifungal benzothiazoles. 2-(substituted phenylsulfonamido)-6-substituted Benzothiazoles [24] (fig.3) were prepared and screened them for their anti-bacterial activity against *Bacillus subtilis*, *Salmonella typhi* and *S. dysentery*. Several benzothiazolotriazole derivatives (fig.4) were prepared [25] and found to possess good anti-bacterial activity against *S. aureus, E. coli* and *C. ablicans*.



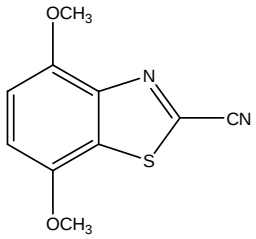
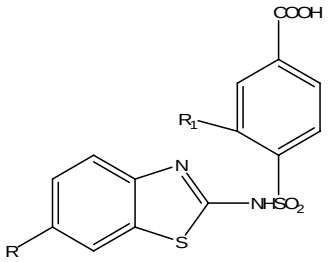


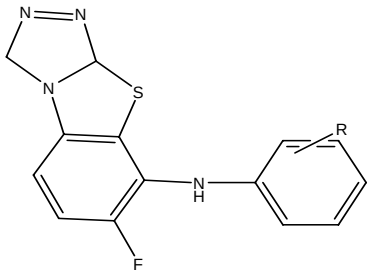
Fig. 1 and 2

Some 6-fluoro-7-(substituted)-(2- *N* -p-anilinosulfonamido) benzothiazoles (fig.5) were synthesized and studied for their anti-bacterial and anti-fungal activities and all compounds showed moderate activity against *S. aureus, S. albus* and *C.ablicans* [26]. Various benzothiazolyl carboxamido pyrazoline derivatives [27] (fig.6) were prepared and studied their anti-microbial activity. They found when R=CH_3 and R_1 =o-OCH_3 C_6H_4 , compound showed no activity and when R = Cl and R_1 = p-OCH_3 C_6H_4 , the compound was active against *S. aureus* and the compounds which are left has showed activity against, *S. aureus, E. coli, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Proteus mirabilis* have been found to possess good activity against *E. coli* [28]. In other words it can be stated that benzothiazole moiety serves as a royal warrior against almost all types of microbes.



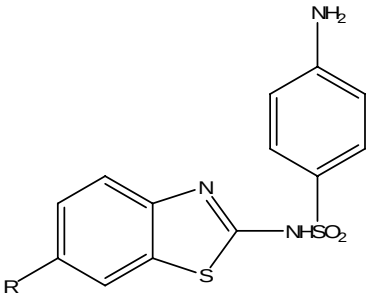
R= Cl, Br , CH_3, OCH_3

R_1= I ,CH_3, NH_2

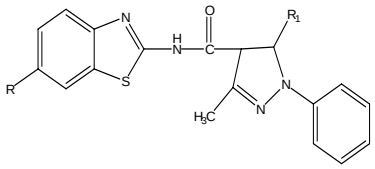


R= O-NO_2, M-NO_2 ,P-NO_2,H,O-Cl ,M- Cl

Fig. 3 and 4



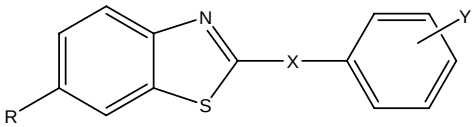
(R =o-nitroanilino, m-nitroanilino, p-nitroanilino, o-chloroanilino, m-chloroanilino, p-chloroanilino, anilino, morpholino, piperazino, dimethylamino)



R=Cl ,CH_3

R_1=C_6H_5 ,o-$CH_3C_6H_4$,p-$OCH_3C_6H_4$

Fig. 5 and 6



X=S ,SO_2

Y=4-NH_2 ,2,4 diNH_2 ,2,4 diNHA_C

Fig. 7: A 2-(4-amino/2, 4-diaminophenyl) sulfonyl derivatives of benzothiazoles

Anthelmintic activity

Benzimidazoles recent reports of resistance have been forced the researchers to develop new drugs with anthelmintic activity, to fight against helminthiasis, which is causing untold misery to the infected individuals. Benzothiazole derivatives have been synthesised , which is sulfur isostere of benzimidazole, in the hope of achieving better anthelmintic activity. A 8-fluoro-9-substituted benzothiazolo (5, 1-b)-1, 3, 4-triazoles[29] (fig.8), compounds were prepared and were studied for their anthelmintic activity against earthworm, *Perituma*

*posthuma.*A compound with R= *o* -nitro anilino substituent was found to possess excellent anthelmintic activity, than the other compounds ,were as all the other compounds are found to possess low level of activity. A 8-bromo-9-substituted (fig.9,10) benzothiazolo (5, 1-b) -1, 3, 4-triazoles (fig.8)compounds were synthesized and examined for their anthelmintic activity against earthworm, *Perituma posthuma* . Some substituted imidazobenzothiazoles were examined *in vivo* anthelmintic activity against *H. nana* infection and were found to show good to moderate activity [30].

The antiprotozal properties depended on the chemical structure of the position 2 substitution-bearing group.

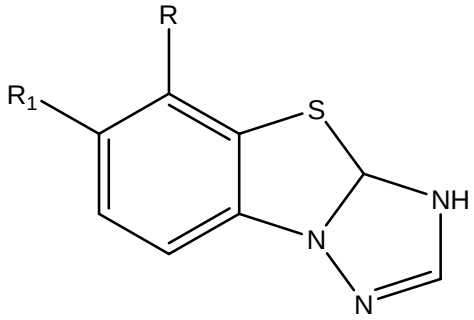
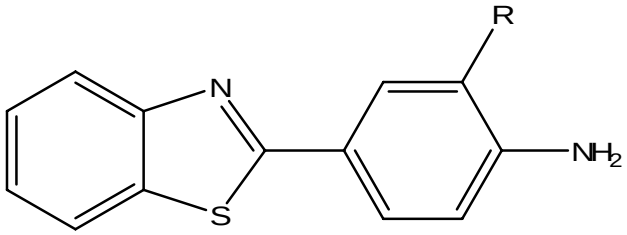


Fig. 8

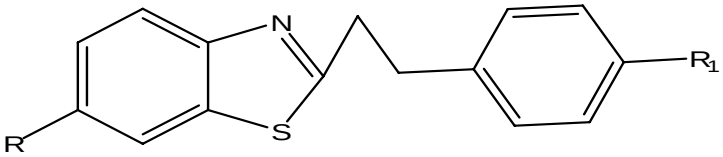
R=aniline ,o-nitroanilino ,m-nitroanilino ,p-nitroanilino ,o-methylanilino guanidine ,hydrazine ,p-methylanilino ,diphenylamino ,2-cacboxyanilino ,4-carboxyanilino ,morpholino ,piperzino.

R1=F ,Br



R=H ,CH_3 ,Cl ,I ,Br

Fig. 9

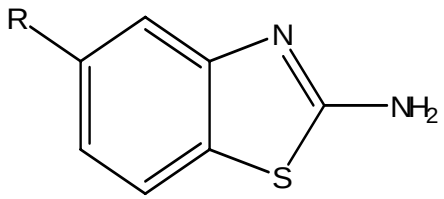


$R=R_1=H$, CN

Fig.10

Anti-convulsant activity

For anticonvulsant activity a large number of benzothiazole derivatives were evaluated and found to possess significant activity against various types of seizures. In the search of new anticonvulsant agents having benzothiazole nucleus, synthesized a lot of substituted-2-benzothiazolamines[31] (fig.11). Benzothiazoles were first observed in 1978 as anticonvulsive agents against phenyltetrazolone induced convulsions on 2-(-4-arylthiosemicarbazidocarbonylthio) benzothiazoles [32] (fig.12) and then several benzothiazoles containing sulphonamide derivatives [33] (fig.13), Benzothiazoles guanidine's [34],(fig.14).



R=CH_3, C_2H_5, n-prop, i-prop, n-but, n-pent, t-pent, $OCHF_2$, CF_3, OC_2H_5, CF_3, 4-OCF_3, 5-OCF_3, 7-OCF_3

Fig. 11

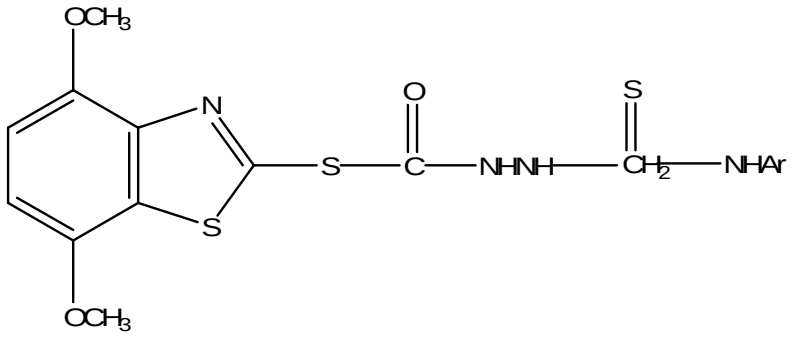


Fig. 12

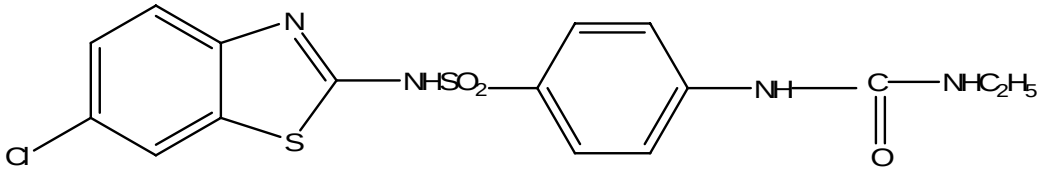


Fig. 13

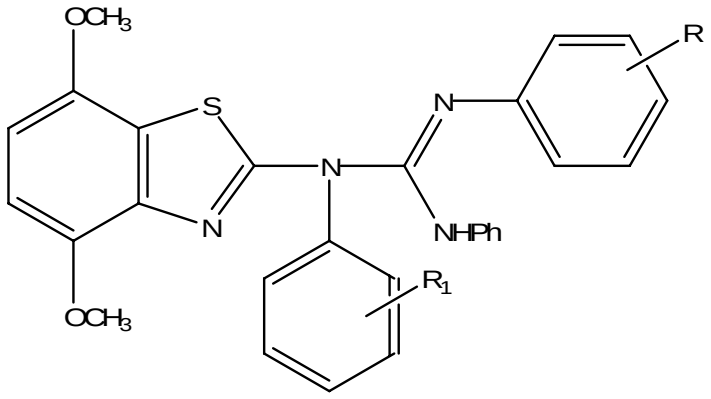


Fig. 14

Benzothiazolamines [35] (fig.15) were synthesized and evaluated for their activity against electroshock and phenyltetrazolone induced seizures.This review revealed that benzothiazole moiety as a dynamic agent against convulsive seizures.Sulphonamide derivatives having benzothiazole nucleus is synthesized by treating 2-(4-aminophenylsulphonamido)-6- halo/alkyl Benzothiazoles

(fig.16) with alkyl isothiocyanate and were evaluated for their anticonvulsant activity. A 2-(4-arylthiosemicarbazidocarbonylthio) Benzothiazoles [36] were prepared and were screened for their anticonvulsant activity against pentylenetetrazole induced convulsions in mice and found that all the compounds possess measurable anticonvulsant activity. A large number of 2-(3 *H*)-benzothiazolone derivatives [37] (fig.17) have been synthesized and evaluated for their anticonvulsant activity in mice and were found to be significantly anticonvulsant activity.[38.]

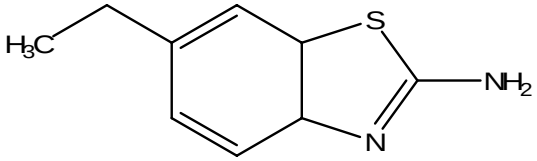
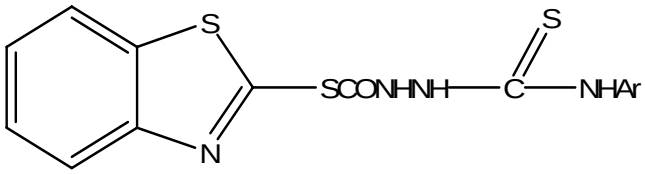
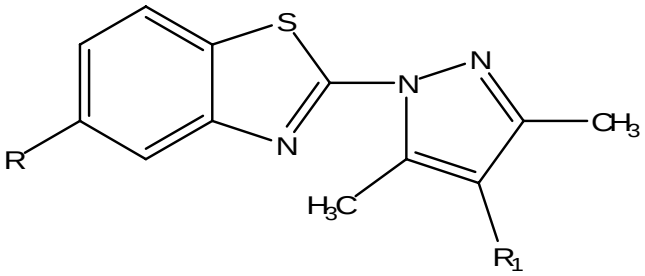


Fig. 15



$Ar=C_6H_5, o\text{-}CH_3C_6H_4, m\text{-}CH_3C_6H_4, p\text{-}CH_3C_6H_4, o\text{-}OCH_3C_6H_4, p\text{-}CH_3C_6H_4, p\text{-}ClC_6H_4, p\text{-}BrC_6H_4$

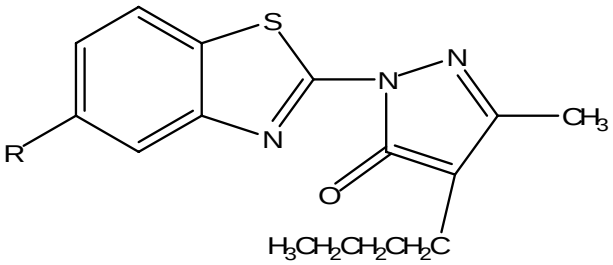
Fig. 16



$R=H, CH_3, OCH_3, Cl, F, NO_2$

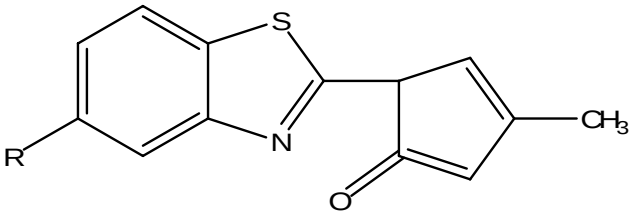
$R_1=H, CH_3, C_2H_5, i\text{-}C_3H_7, Br, CH2COOH$

Fig. 17



$R=H, CH_3, OCH_3, Cl, F$

Fig.18



R=H, CH_3, C_6H_5, p-ClC_6H_4

Fig. 19

Anti-inflammatory activity

Pyrazolones and pyrazolinones are more valuable non-steroidal anti-inflammatory agents. Phenylbutazone and its congeners incorporating a pyrazoline-3, 5-dione structure are more potent anti-inflammatory agents. In the recent years a number of Benzothiazole derivatives have been synthesized and found to posses anti-inflammatory activity. Some new 2-(4'-butyl-3', 5'-dimethylpyrazol-1'-yl)-6-substituted benzothiazoles[39] (fig.18) were prepared and 4-butyl-1-(6'-susbtituted-2'-benzothiazolyl)-3-methylpyrazol-5-ones (fig.19) were prepared and were found to posses significant anti-inflammatory activity.

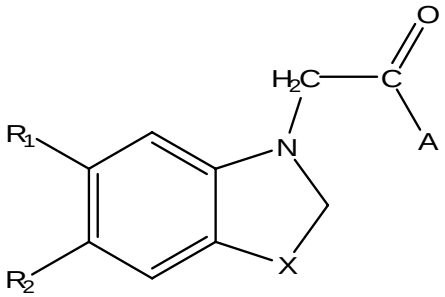
A series of 2-(2-alkoxy-6-pentadecylphenyl) methyl thio-1 *H* -benimidazoles/ benzothiazoles and benzoxazoles from an anacardic acid and investigated their ability to inhibit human cycloxygenase-2-enzyme (COX-2) [40].

Anti-oxidant activities

Antioxidants were important because of their prophylactic and therapeutic agents in many diseases. Free radicals are formed as a result of normal organ functions or excessive oxidative stress[41]. Free radicals of high levels can cause damage to biomolecules such as lipids, proteins, enzymes and DNA in cells and tissues, resulting in mutations can lead to malignancy. DNA mutation is a critical step in carcinogenesis. Role of free radicals was discovered in cancer, diabetes, cardiovascular diseases, autoimmune diseases, neurodegenerative disorders, aging and other diseases has led to new medical insight[42] and [43]. Minimizing a oxidative damage is primary prevention or treatment of these diseases, since antioxidants may stop the free-radical formation, or interrupt an oxidizing chain reaction. The antioxidant behaviour of a series of substituted indoline-2-ones and indoline-2-thiones was investigated using an oxygen radical absorbance capacity assay. The results indicated that the examined indoline derivatives had effective activities as radical scavengers [44].

Miscellaneous

The replacement of the urea moiety by benzothiazoles sulfonamide showed inhibitors of HIV-1 protease with improved potency and anti-viral activities. Certain members of the class showed good oral bioavailability in rats. Derivatives of 2-piperazinyl benzothiazoles[45] (fig.20) were prepared and studied as mixed ligands for serotoninergic 5-HT $_{1A}$ and 5-HT $_3$ receptors and this compounds exhibited significant affinities for these two serotoninergic receptor subtypes. The pharmacological profile of these ligands was agonist for 5-HT $_{1A}$ receptors and antagonist for 5-HT $_3$ receptor sub sites. Compounds with such a pharmacological profile are of clinical relevance in the treatment of psychotropic diseases e.g., anxiety, depression and schizophrenia.



X=O, S

R_1=H, Cl

R_2=H, CH_3, C_6H_5-CO, (oCl-C_6H_4-CO)

A=1-morpholinyl, 1-pyrrolidinyl diethylamino, OCH_3, OC_2H_5,

Fig. 20

CONCLUSION

This review shows that 2-substituted aminobenzothiazoles has a wide spectrum of biological activities. 6-fluoro-7 benzothiazoles were synthesized and studied for their antibacterial and antifungal activities. The substituted benzothiazolylimino dithiazolidines and the 2-(2'-aryl-1, 3, 4-oxadiazol-5-yl) mercaptomethyl benzothiazoles are having significant antibacterial activity. Significant anti inflammatory 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. In search of new anticonvulsants, riluzole and benzothiazolyl guanidines 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.

The biological profiles of these new generations of benzothiazoles represent much progress with regard to the older compounds.

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