A Review: Therapeutic & Biological Activity of Benzothiazole Derivatives

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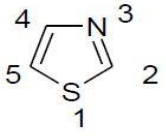
ABSTRACT

The Benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities, such as antitumor, antimicrobial, anthelmintic, antileishmanial, anticonvulsant and anti-inflammatory. The present review focuses on the benzothiazoles with potential activities that are now in development. The synthesized benzothiazole derivatives could be considered as lead molecule for the development of therapeutic agents.

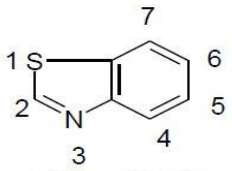
Keywords: Benzothiazole, Benzohaterocycles, anti-inflammatory.

Introduction

Benzothiazole is a privileged heterocyclic scaffold having a benzene ring fused with a five membered thiazole ring. In the 1950s, a number of 2- aminobenzothiazoles were intensively studied as central muscle relaxants. Benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity. Many polycyclic and fused ring systems containing the thiazole nucleus(I) are well known. The most important is bicyclic system wherein the second ring benzene is fused to the 4,5 position of thiazole ring i.e. Benzothiazole.(II)



(I)Thiazole



(II)Benzothiazole

In recent decades there has been constant interest in the chemistry of benzothiazole. Among compounds of this type substances with high and varied biological activity and a wide spectrum of practical qualities have been found (polymethine dyes, stabilizers of polymeric materials, antioxidants, optical sensitizers for photographic materials, etc.). Some of them were isolated from natural materials, e.g., the alkaloid luciferin [2-(2-benzothiazolyl)- 2-thiazoline-4-carboxylic acid] and a bioluminescent [2-(5-hydroxy-2-benzothiazolyl)thiazole-4-carboxylic acid].

Syntheses of Benzothiazole

Benzothiazole and its many derivatives are particularly important. The history of benzothiazole dates from 1878 when, by the action of PCl5 on phenylthiocarbamide, A.W.Hoffmann prepared a reactive chloro compound (2-chlorobenzothiazole) which was later reduced to benzothiazole (II).He also prepared 2-phenylbenzothiazole by heating benzanilide with sulphur and, supported by analogies with the known imidazoles and benzoxazoles, correctly assigned structures to the compounds on the basis of their degradation to, and synthesis from *o*-aminothiophenol.[13]
The tendency of formation of benzothiazole ring system appears to be great, and ring closure occurs readily with a large variety of compounds. Thus on treating aromatic amines or their derivative with sulfur at high temperature (180-250˚C) frequently produces benzothiazoles in satisfactory yield (up to 75%).similarly various reactants under similar condition give[14].

- **N,N'-diphenylthiourea / phenyldithiocarbamic acid / phenylisothiocyanate ⟶ 2- mercaptobenzothiazole**
- **Aniline + carbondisulphide+ sulphur ⟶ 2 mercaptobenzothiazole**
- **Dimethyl aniline ⟶ 2- mercaptobenzothiazole & benzothiazole**
- **Benzalaniline,benzylaniline /benzanilide ⟶ 2-phenyl benzothiazole**
- **Aromatic acid + Mercaptoaniline ⟶ Phenyl Benzothiazole**

Properties

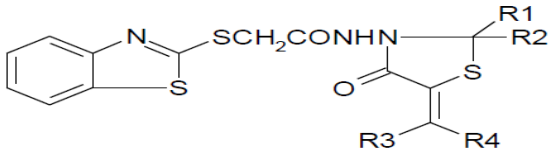
Benzothiazole is colorless mobile liquid resembling quinolin in odour and is insoluble in water but dissolves in strong aqueous acid forming salts: hydrochloride, m.p.173˚; sulphate m.p.174˚; picrate m.p.168˚. Benzothiazole methiodide and ethiodide have m.p.210˚and 139˚ respectively.[15] Benzothiazole is a feeble base, the ring system is stable but fusion of benzothiazole with alkali opens the heterocyclic ring. Benzothiazole is nitrated at position 6 and sulphonated at position 4, 6 & 7.Bromine which forms a perbromide in chloroform reacts at 450˚ to form 2-bromo- benzothiazole.[16] Substitution in 2-position takes place with PCl5 and with sodamide to give the 2-chloro and 2-amino compound respectively, and at this position halogen substituents are mobile, methyl group is reactive and amino-group is diazotisable. On the other hand there is marked tendency in 2-amino-,2-hydroxy- and 2-mercapto-benzothiazoles to assume the tautomeric forms derived from 2,3-dihydrobenzothiazole. Benzothiazole-S-dioxide, m.p. 105˚-107˚, is said to be produced from *o*-formamidophenyl methyl sulphone and phosphorus oxychloride.

Pharmacological Activities

Benzothiazoles are bicyclic ring system with multiple applications. In the 1950s,. After that benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity.

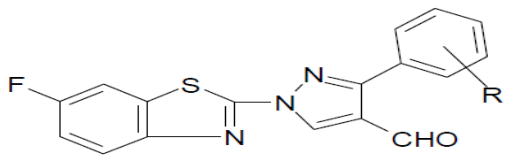
Antimicrobial

- A series of 5-arylidene-2-aryl-3-[(2-benzothiazolylthio)-acetamidyl]-1,3-thiazol-idin-4-ones have been synthesized and screened for their antimicrobial activity against *Bacillus subtilis , Salmonella typhimurium and Escherchia coli*[17].



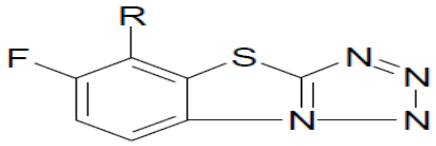
R_1=H,CH_3
R_2=2,4-$(NO_2)_2C_6H_3$,3-ClC_6H_4,2-BrC_6H_4,2-$OCH_3C_6H_4$,2-OHC_6H_4
R_3= H,CH_3
R_4=2,4-$(NO_3)_2C_6H_4$,3-ClC_6H_4,2-BrC6H4,2-$OCH_3C_6H_4$,2-OHC_6H_4

- 6-Fluoro-2-[4-formyl-3-(substituted phenyl) pyrazo-1-yl] benzothiazoles have been synthesized and screened for their antibacterial activity[18].



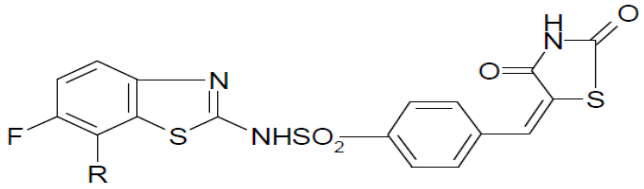
R=H,4-OH,2-OH,4-OH,4-Br
4-NO_2 ,4-OCH_3,4-Cl

- A series of 6-fluoro-7-substituted-1,2,3,4-tetrazolo(5,1-b) benzothiazoles were synthesized and screened for their antibacterial activities[19].

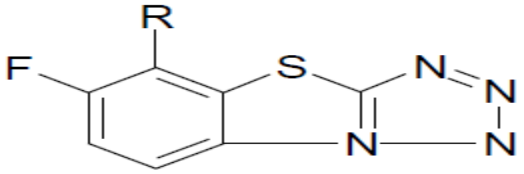


R=amines

- A new series of various 2-amino [5'-(4-sulphonyl benzylidene)-2,4-tiazolidine dione]-7-(substituted)-6-fluoro benzothiazoles containing different substitution at seventh position have been synthesized and found to possess promising antibacterial activity[20].

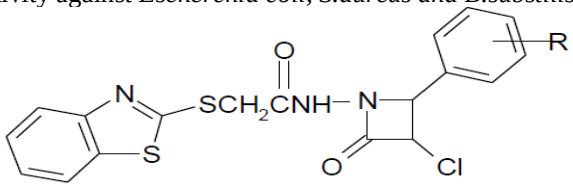


R=anilino,*m*-nitroanilino,*p*-carboxy anilino,Morpholino,Benzylamino



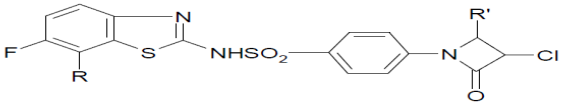
R=amines

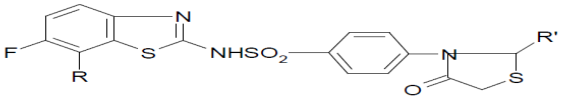
- An efficient and extremely fast procedure for the synthesis of 4-aryl-3-chloro-1-[(2-benzothiazolylthio) acetamidyl]-2-azetidinone under microwave irradiation is described and these compounds were screened for their antibacterial activity against *Escherchia coli, S.aureus and B.substilis*[21].



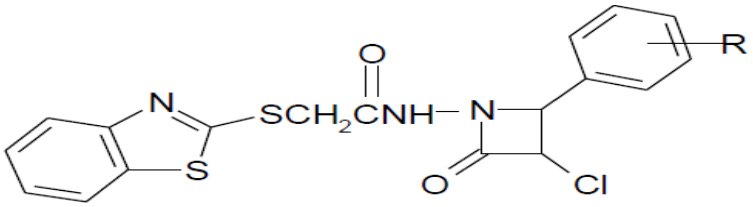
R=4-NO_2, 3,4,5-$(OCH3)_3$, 2-OH, 3-OH, 4-OH
2-OCH_3, 4-OCH_3, 2-Cl, 3-Cl, 4-Cl

- Various 6-fluoro-7-(substituted)-2-[p-(3'-chloro-2'-oxo-4'substituted aryl-1'-aze-tidinyl)benzene sulphonamido] benzothiazoles and 6-fluoro-7-(substituted)-2-[p-(2'-substituted phenyl-4'-thiazolidinon-3'-yl) benzene sulphonamido]benzothiazoles containing different functional groups have been synthesized and screened for their antimicrobial activities[22].

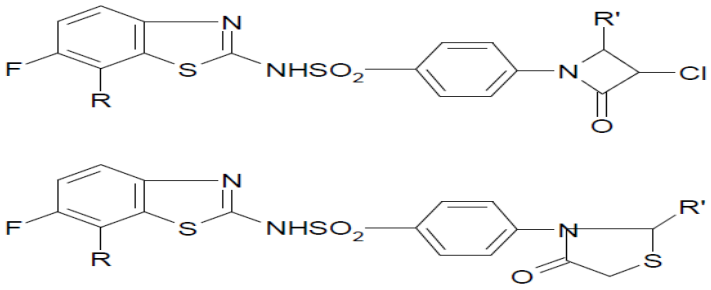




R=Anilino, *m,p*-Nitro anilino
R'=N,N-Dimethylamino phenyl,
m-Nitro phenyl, *p*-chloro phenyl



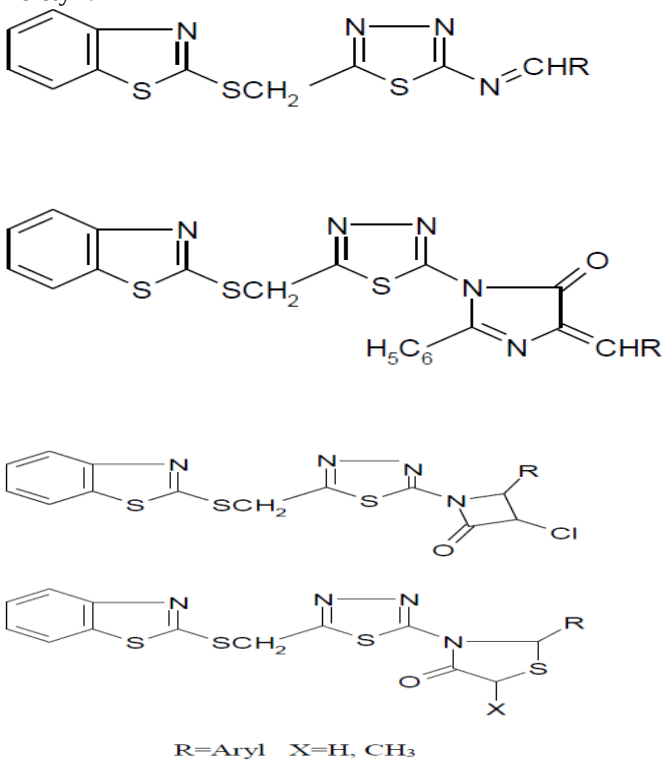
R=4-NO_2, 3,4,5-$(OCH3)_3$, 2-OH, 3-OH, 4-OH
2-OCH_3, 4-OCH_3, 2-Cl, 3-Cl, 4-Cl



R=Anilino, *m,p*-Nitro anilino

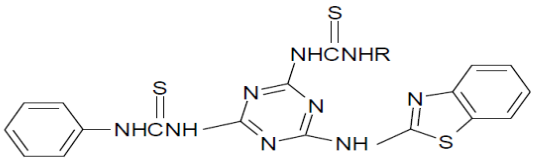
R'=N,N-Dimethylamino phenyl,
m-Nitro phenyl, *p*-chloro phenyl

- Synthesis and antibacterial activity of 2-azetidinones, 4-thiazolidinones, 5-imida-zolinones having benzothiazole moiety[23].

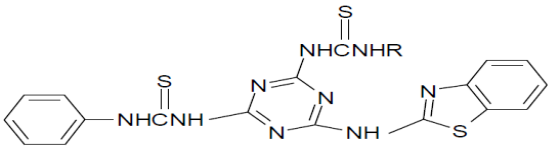


R=Aryl X=H, CH_3

- Synthesis of some Benzothiazolyl-S-triazines and their antibacterial activity against *S.subtilis, S.paratyphii ,E.coli and P.vulgaris*[24].

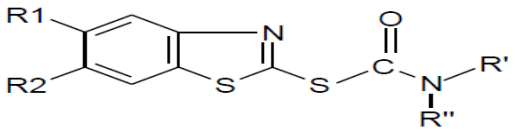


R=Ph, OCH_3-C_6H_4, *m*-CH_3- C_6H_4, *p*-CH_3- C_6H_4, *o*-Cl- C_6H_4, *m*-Cl- C_6H_4, *p*-Cl- C_6H_4, *o*-NO2- C_6H_4.



R=Ph, OCH_3-C_6H_4, *m*-CH_3- C_6H_4, *p*-CH_3- C_6H_4, *o*-Cl- C_6H_4, *m*-Cl- C_6H_4, *p*-Cl- C_6H_4, *o*-NO2- C_6H_4.

- Synthesis of 5,6-disubstituted-(2-N,N'-dialkylthiacrbamido)benzothiazoles havi-ng antibacterial,antifungal activity. The compounds were screened against *S.aureus* , *C.albicans* , *S.typhii, T.rubrum, T.mentagrophyles*[25].

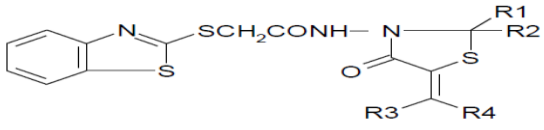


R_1=H, Cl, NO_2 R_2=H, Cl, F, OCH_3,OEt, OC_4H_9

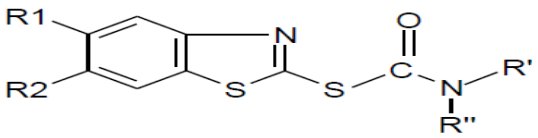
R'=R''= CH_3, Et

Antihelmintic

Benzimidazole resistance forced the researchers to urgently develop new drugs with more potency. This prompted to synthesize benzothiazole derivatives which is sulphur isoester of benzimidazole. A series of 5-arylidene-2-aryl-3-[(2-benzothiazolylthio)-acetamidyl]-1,3-thia-zolidin-4-ones have been synthesized and screened for their antihelmintic activity against the experimental infection of *Ancyclostoma ceylanicum* and *Hymenolepsis nana* in rats.



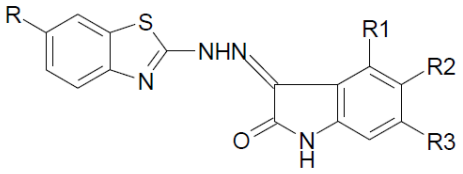
R_1=H, CH_3
R_2=2,4-$(NO_2)_2C_6H_3$, 3-ClC_6H_4, 2-BrC_6H_4, 2-$OCH_3C_6H_4$, 2-OHC_6H_4
R_3= H, CH_3
R_4=2,4-$(NO_3)_2C_6H_4$, 3-ClC_6H_4, 2-BrC6H4, 2-$OCH_3C_6H_4$, 2-OHC_6H_4



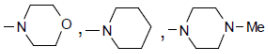
R_1=H, Cl, NO_2 R_2=H, Cl, F, OCH_3,OEt, OC_4H_9

R'=R''= CH_3, Et

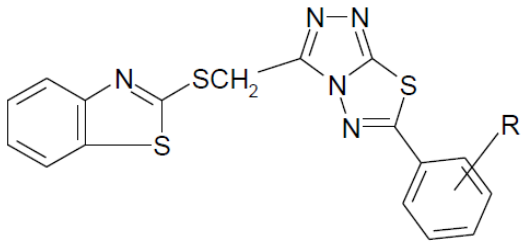
- 3-(6'-substituted-2'-hydrazonobenzothiazolyl)-4/6-bromo-5-methoxy-2-indo-linones and 3-(6'-substituted-2'-hydrazonobenzothiazolyl)-1-aminomethyl4/6-bromo-5-methoxy-2-indolinones(***Mannich bases***) have been synthesized under microwave irradiation and tested for their antileishmanial potential[26].



R=Cl,OMe,Me
R_1=H,Br,R_2=OMe
R_3=H,Br,

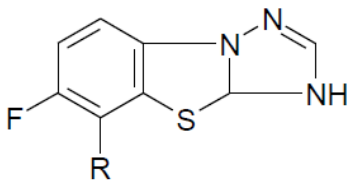
R_4= 

- A series of 3-[(2-benzothiazolyl)methyl]-1,2,4-triazolo-[3,4,b][1,3,4]thiadiazol-6-yl substituted phenyl has been synthesized and screened for antihelmintic activity against *H.nana* in mice[27].



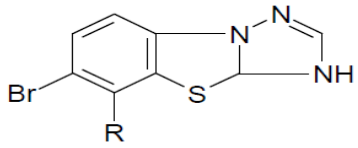
R=H,4-NO_2,3-NO_2,4-Cl,2-Cl,4-NH_2,2-NH_2,4-OH

- Synthesis of novel 8-fluoro-9-substituted (1,3) benzothiazolo(5,1-b)-1,3,4-tria-zoles, which was found active against earth worm *Perituma posthuma*[28].



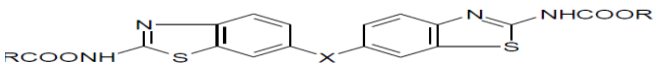
R= *o*-nitroanilino, *o*-chloroanilino, aniline, piperazino, diphenylamino

- Synthesis of novel 8-bromo-9-substituted(1,3) benzothiazolo- (5,1-b)-1,3,4 triazoles[29].

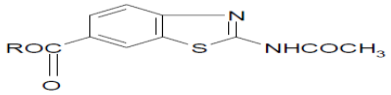


R= *p*-methyl anilino, *o*- methyl aniline, *p*-nitroanilino, *m*-nitroanilino, 4-carboxy anilino,2-carboxy anilino, morphilino, hydrazino.

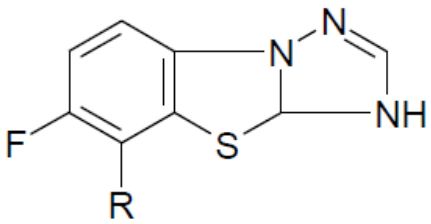
- Synthesis of 2-acylamino-6-substituted benzothiazoles which were reported to be active against *Ancyclostoma celanicum* and *H.nana*[30].



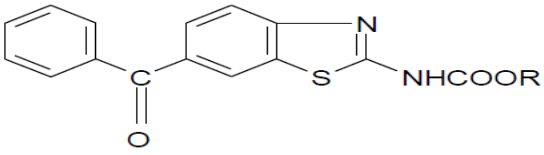
R= CH_3,Et X= O,S AND SO_2



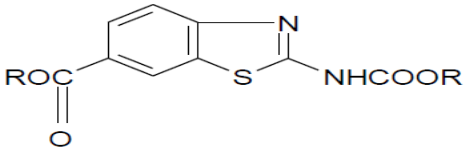
R= H, CH_3, Et, *n*-prop, *i*-prop, *n*-but



R= *o*-nitroanilino, *o*-chloroanilino, aniline, piperazino, diphenylamino



R= CH_3,Et

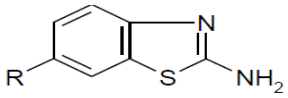


R=OH, OMe, OEt, OProp-*n* , OProp-*i*, OBut-*n*, Ph.

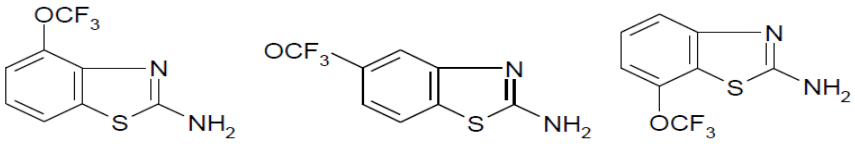
Anticonvulsant

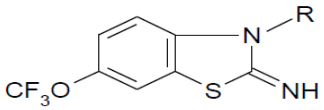
A large number of benzothiazole derivatives were evaluated for anticonvulsant activity and found to possess significant activity against various types of seizures. The most important compound of this series having anticonvulsant activity is Riluzole. (6-trifluoromethoxy-2- benzothiazolamine) which was found to interfere with Glutamate neurotransmission in biochemical electrophysiological behavior experiments. [31]

- Synthesis of substituted-2- benzothiazolamines and substituted-2-iminobenzo-thiazolamines[32].

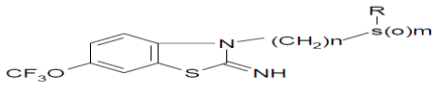


R=Me, Et, *n*-prop, *i*-prop, *n*-but, *t*-pent, $OCH_2C_2H_5$, OCH_2F_2, OC_2F_5, CF_3

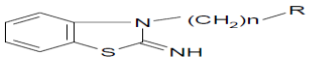




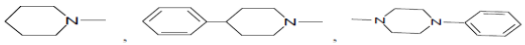
R= Me, Et, *n*-prop, *n*-but, allyl, propargyl, CH_2CN, CH_2COOMe, CH_2Ph, CH_2COOH, CH_2CONH_2, CH_2CONEt_2

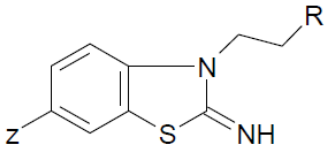


R= Me, Et, prop, Ph, m=0,1,2 n=1,2,3

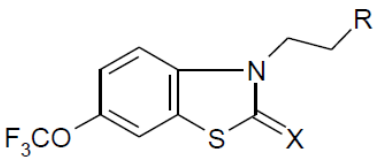


R=NHMe, -N(Me)-CH_2-Ph , -N(Me)-CH_2-CH_2-Ph,



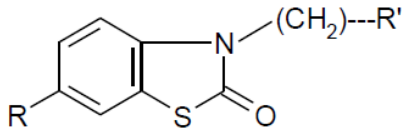


R= -NMe_2, -SOEt, SO_2Et Z=H, OC_2F_5, OCF_3, *n*-but, *t*-but



R=-SMe, -SEt X= =NH, =NMe, =NEt , =NOMe, =NOH, =NCOMe

- Synthesis of 2-(3H) benzothiazolone derivatives and their evaluation for anticonvulsant activity in mice[33].

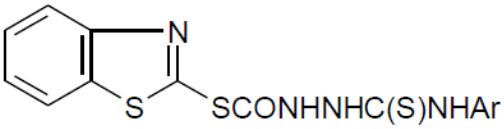


R=H, COEt , COPh ,C_3H_7, C_5H_{11}, COC_4H_9 ,

R'= H, COEt , COPh ,C_3H_7, $CH_2C_6H_5$,COC_4H_9 , COC_6H_5, NOC_4H_8,

n= 0,2,3

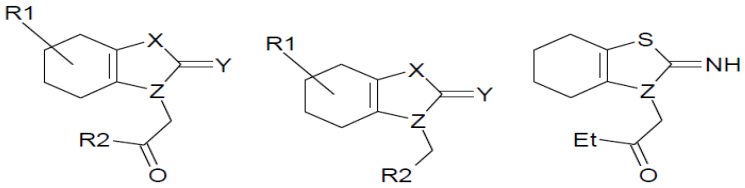
- Synthesis of 2-(4-arylthiosemicarbazidocarbamoylthio) benzothiazoles which have anticonvulsant activity in PET induced convulsant in mice[34].



Ar=Ph, *o*-$CH_3C_6H_4$, *m*- $CH_3C_6H_4$, *p*-$CH_3C_6H_4$, *p*-$OCH_3C_6H_4$, *p*-Cl C_6H_4

Neuroprotective Agents

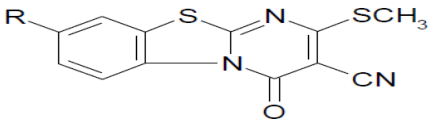
- Synthesis of tetrahydrobenzothiazole analogues as neuroprotective agents[35].



X= O,S Y=NH,O,S,NR_2 Z=N,CH,H,CN R_1= R_2=alkyl or aryl

CNS Depressant

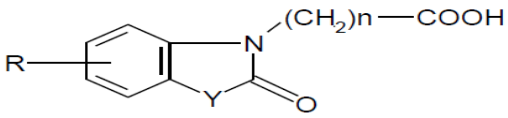
- 4-H-Pyrimido[2,1-b]benzothiazole-8-substituted-2-thiomethyl-3cyano-4-ones were prepared and evaluated for CNS depressant activity and compared with standard Diazepam[36].



R=Cl,Br,NO_2,OCH_3,OC_2H_5,COOH,SO_2NH_2

Cytoprotective Agents

- Synthesis of benzoheterocycleones as novel cytoprotectors.The compound was tested for apoptosis (programmed cell death) inhibition activity[37]

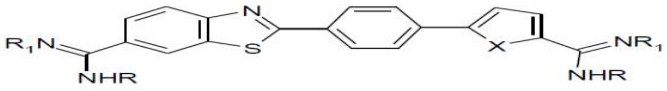


R=H, 5-OH, 5-Br, 5-F, 5-OMe

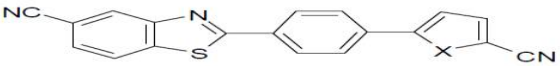
Y= S, O, NH

Antiviral Agents

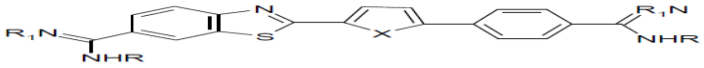
- Synthesis of bis-amidinobenzothiazoles as potential anti-HIV agents[38]



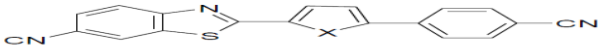
X=O,S R=Me_2CH R_1=H



X=O,S



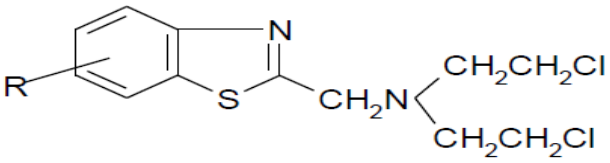
X=O,S R=Me_2CH R_1=H



X=O,S

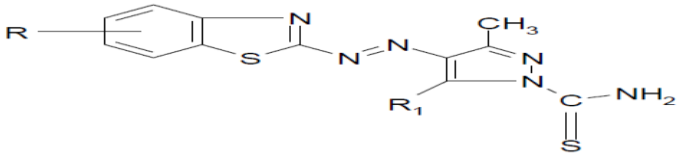
Antitumor

The compounds 2-[2-(bis-(2-chloroethyl)amino)-methyl]-benzothiazoles were synthesised by standard procedure.The biological evaluation is carried out by various methods such as short term *invitro cytotoxic* activity and *invivo anticancer* Screening[39].



R=H,I,Br,NO_2

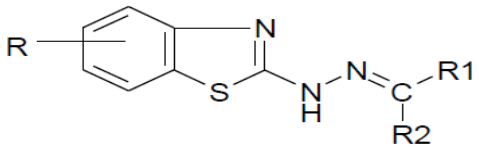
- Synthesis of substituted 4- benzothiazolylazo-N-thiocarbamoyl pyrazoles and they proved to have good antineoplastic activity[40].



R= H, CH_3, Cl ,Br, NO_2, OCH_3

R_1= CH_3, NHC_6H_5, NHC_6H_4,Cl

- Synthesis of benzothiazolyl hydrazones and these are reported as antitumor agents.

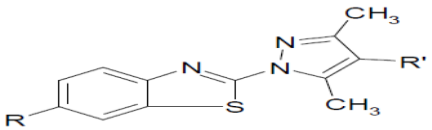


R= H, CH_3, Cl ,Br, NO_2, OCH_3 R1=$COCH_3$,$COOCH_3$

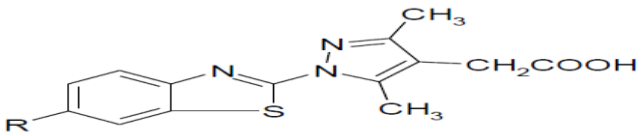
R2= $COCH_3$,$COOCH_3$,$CONHC_6H_5$,COOEt

Analgesic and Anti-inflammatory

- A number of 2-(4'-alkyl-3',5'-dimethylpyrazol-1'-yl)benzothiazoles and 2-(4'-carbethoxymethyl-3',5'-dimethylpyrazol-1'-yl)benzothiazoles have been synthesized by the condensation of 2-hydrazinobenzothiazoles with 3-substituted pentane 2,4'-diones.

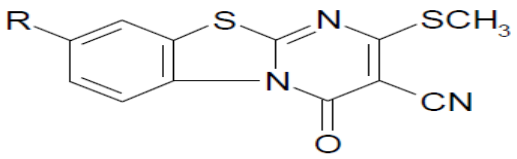


R= H, CH_3, Cl, F, OCH_3, NO_2
R'=H, CH_3, C_2H_5 ,C_2H_5, / -C $_3H_7$



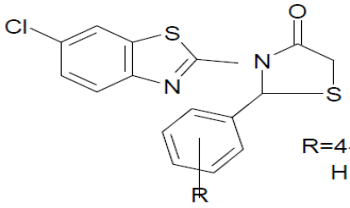
R=H,CH_3,Cl,F,OCH_3,NO_2

- 4-H-Pyrimido[2,1-b]benzothiazole-8-substituted-2-thiomethyl-3cyano-4-ones were prepared and evaluated analgesic activity.



R=Cl,Br,NO_2,OCH_3,OC_2H_5,COOH,SO_2NH_2

- Some 2-(substituted phenyl)-3-(6-chloro-2-benzothiazole-2-yl)-5H-thiazolidino-nes were prepared and screened for anti-inflammatory activity**.**



R=4-N(CH_3)$_2$,3,4,5-OCH_3,2,4-OH,3-OCH_3, H,4-Cl,2-NO_2

Conclusion

The present review highlights the use of Benzothiazole moiety as important moiety for development of newer therapeutic agents. Biological properties of the nucleus include anticancer, antidiabetic, analgesic, anti-inflammatory, and antimicrobial. With proper designing benzothiazole, prospective compounds can be designed and synthesized for a variety of biological activities.

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Source of Support: Nil
Conflict of Interest: None