



A REVIEW ON BENZOTHAIAZOLE – A VERSATILE SCAFFOLD IN THE FIELD OF PHARMACEUTICAL CHEMISTRY

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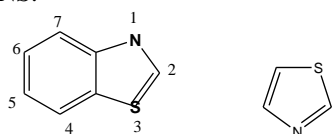
ABSTRACT

Heterocyclic chemistry is an integral part of synthetic chemistry which finds its use as one of the major parts in pharmaceutical chemistry as useful biological entities and improved pharmacological properties. Benzothiazoles are versatile bicyclic compounds with diversified pharmacological activities and their analogues are known for their incredible structural diversity. There is a wide scope for research in areas of synthetic, pharmaceutical chemistry and medical field. The objectives of the study mainly have a hawk eye over different common routes of synthesis and cyclization procedures followed and to have a light on diversified pharmacological importance of this potent moiety. Benzothiazoles have clinical effectiveness as potential anticancer, antiinflammatory, antibacterial, antifungal, analgesic, anti-HIV, antioxidant, anticonvulsant, antitubercular, antidiabetic, and other medicinal agents.

KEY WORDS: Benzothiazole, thiazoles, pharmacological activity, synthesis.

INTRODUCTION

Benzthiazoles are a group of organic compounds with a Thiazole group. It is fused with six membered and a five membered heterocyclic ring with the molecular formula C_7H_5NS .



1,3- Benzothiazole

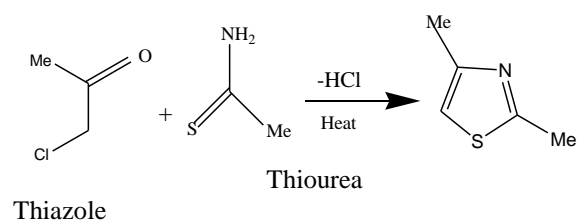
Thiazole

Thiazole was first described by Hantzsch and Waber in 1887. Popp confirmed its structure in 1889. Benzothiazole is a colourless, slightly viscous liquid with a melting point of $2^{\circ}C$ and a boiling point of $227-228^{\circ}C$. The density of benzothiazole is $1.24g/mL$, and its molecular mass is $135.19g\text{mol}^{-1}$. By the substitution of benzothiazole on various positions it shows many activities like antimicrobial, antifungal, antioxidant, anticancer etc., activities. By

substitution in the 2nd position with an imine group, it gives 2-imino benzothiazole which has anticonvulsant activity. Some newly synthesized benzothiazoles have antibacterial activity against gram positive and negative bacteria. The novel synthetic 2-(4-aminophenyl) benzothiazoles have antitumor activity. Thiazole moiety is present in natural compounds like Thiamine.

Synthesis of Thiazole:

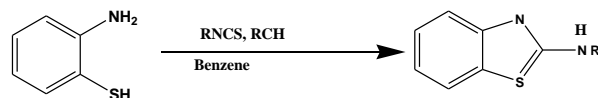
Hantzsch synthesis can be applied to synthesize the thiazole system from thioamides. The reaction involves initial nucleophilic attack by sulphur followed by a cyclocondensation.



Thiazole

Synthesis of Benzothiazole:

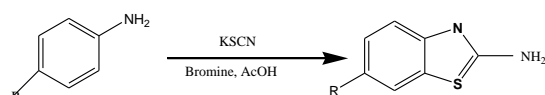
Tweit et al., in 1970, reported the synthesis of 2-aminobenzothiazole from isothiocyanates using benzene as a catalyst. [1]



Synthesis of 2- aminobenzothiazole

From substituted aniline

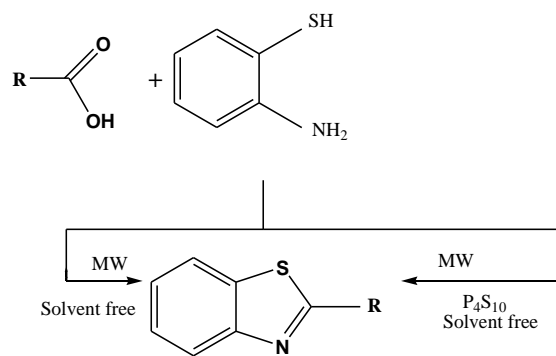
Dogreuer et al., in 1998, was successfully synthesized various 6-substituted-2-aminobenzothiazoles by the reaction of 4-substituted anilines with potassium thiocyanate in presence of bromine. [2]



Synthesis of 6- substituted 2- aminobenzothiazole.

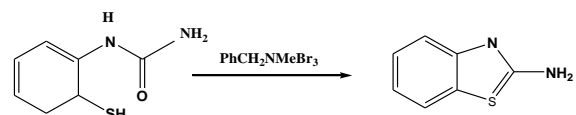
Solvent free synthesis

2-Substituted by the condensation of 2-aminophenol with various saturated aliphatic fatty acids under solvent free microwaves (path -A) and by using P_4S_{10} in (path -B), the reaction will be completed in 3-4 min. [3]

**One-pot synthesis of 2-aminobenzothiazoles**

Jordan et al., in 2003, directly synthesized 2-aminobenzothiazoles from substituted arylthioureas using Benzyltrimethylammonium tribromide as a catalyst, which is an electrophilic bromine source for the conversion of tetrabutylammonium thiocyanate, isothiocyanates and anilines into 2-aminobenzothiazoles under mild conditions in a variety of solvents with good yields and also the key benefits for $PhCH_2NMe_3Br_3$ when compared with

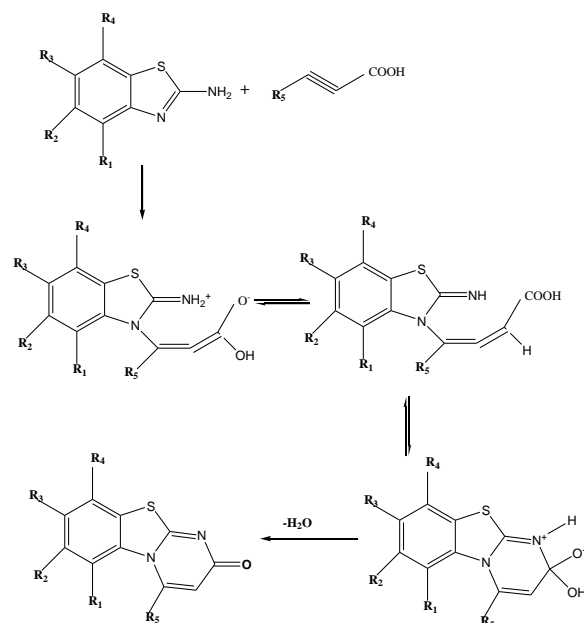
molecular bromine in ease of addition and handling, which minimizes the risk of forming brominated side products. [4]



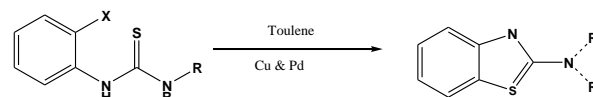
Synthesis of 2-aminobenzothiazole

Synthesis of pyrimido[2,1-b] benzothiazoles

The simple development procedure to prepare a series of imino nitrogen of 2-aminobenzothiazoles to alkyne β -carbon atom of acetylinic acid followed by closure of ring. [5]

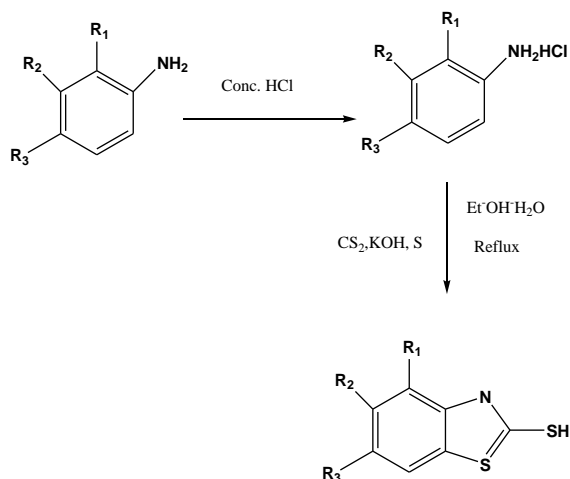
**Synthesis of intramolecular C-S bond by using Cu & Pd catalyst**

Evindar et al., in 2003 reported the synthesis of 2-aminobenzothiazoles through intramolecular C-S bond formation by cross-coupling between aryl halide and thiourea in presence of copper and palladium catalyzed medium. [6]

**Synthesis of 2-mercaptobenzothiazole**

Synthesis of substituted 2-mercaptobenzothiazoles by varying substituents at 4,5, and 6-positions in the benzothiazole ring system. This synthesis involve

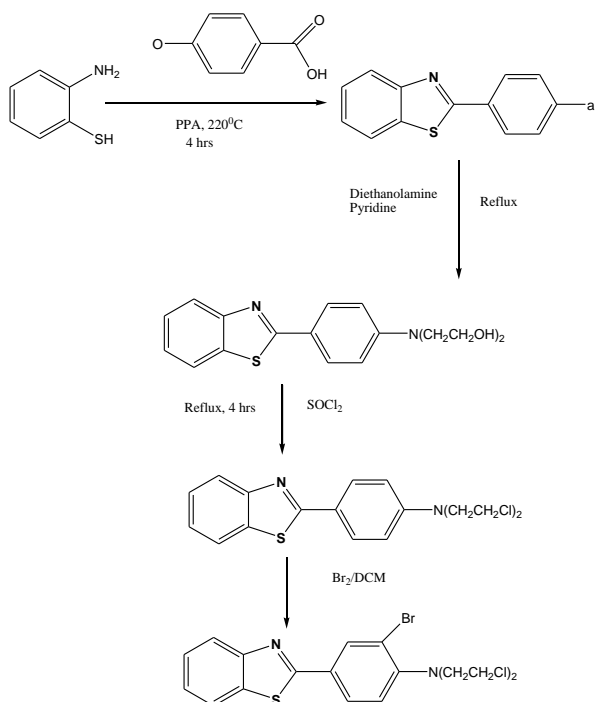
two steps. 1) Substituted anilines were converted into its hydrochloride salts. 2) This aniline hydrochloride salt was then cyclized to substituted 2-mercaptobenzothiazoles by reacting with carbon disulphide in presence of sulfur in an alkaline medium.^[7]



$R_1=CH_3$, $R_2, R_3=H$

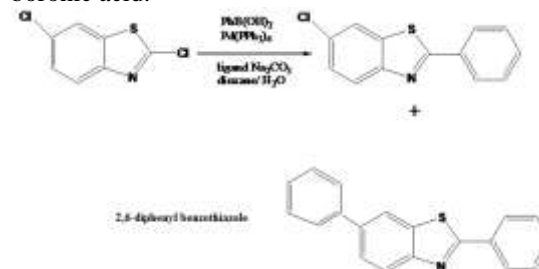
Synthesis of 2-aryl substituted benzothiazoles

Synthesis of 2-aryl substituted benzothiazole derivatives by refluxing o-aminothiophenols with substituted benzoic acids in presence of polyphosphoric acid at 220°C.^[8]



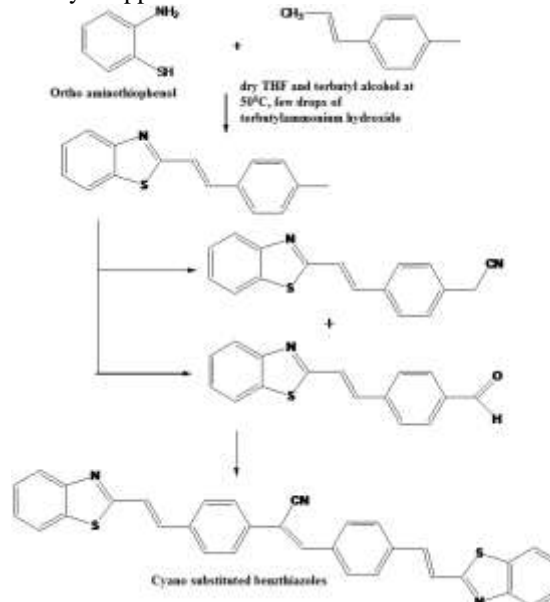
Suzuki- Miyaura coupling reaction

Development of microwave promoted Suzuki-miyaura reaction 2-chlorobenzothiazole with phenyl bromic acid was carried out using $Pb(PPh_3)_4$ as a catalyst. This reaction provides the adduct 2,6-diphenyl benzothiazole by the catalysis of 2,6-dichloro benzothiazole with excess of phenyl boronic acid.^[9]



Synthesis of cyano substituted conjugated benzothiazoles

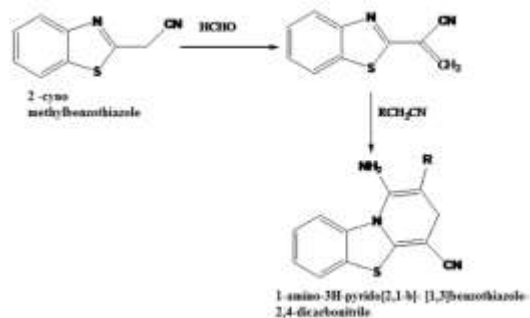
This synthesis of benzothiazoles is based on organic nano particles. The elaboration of conjugated system was performed by reacting equimolar quantities of 4 and 5 in dry THF and tertbutyl alcohol at 50°C while a small amount of tertbutylammonium hydroxide was slowly dropped in mixture.^[10]



Synthesis of fused benzothiazoles

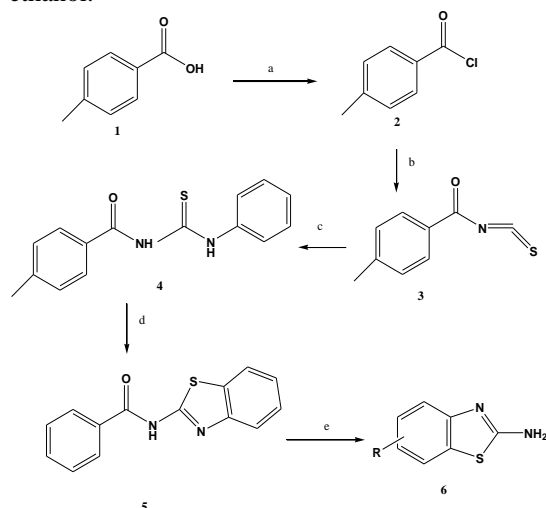
Zaki et al., in 2003, successfully synthesized 1-amino-3H-pyrido[2,1-b]-[1,3]benzothiazole-2,4-dicarbonitrile, 1-amino-4-cyano-3Hpyrido[2,1-b][1,3] benzothiazole-2-carboxamide, and 1-amino-4-cyano-3Hpyrido[2,1-b][1,3] benzothiazole-2-carbothioamide. These are synthesized by treating the equimolar amounts of formaldehyde, active methylene reagents and 2-cyano methylbenzothiazole

in presence of strong base like triethylamine in ethanol. [11]

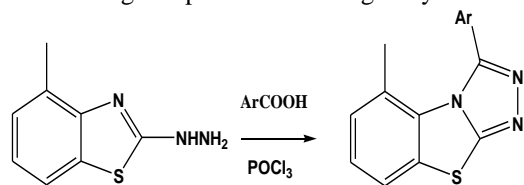


Solid phase synthesis

Conversion of resin bound isothiocyanate was to N-acyl, N-phenyl thioureas in general structure 4, X=H of 4 is cyclized to 2-acyl aminobenzothiazole 5 by treatment with 6 equivalent of bromine in acetic acid. Finally the desired compound 6 were obtained by treatment of 5 with 4% hydrazine monohydrate in ethanol. [12]



Dong et al., in 2002 reported the synthesis of 5-methyl-3-substituted-1,2,4-triazolo[3,4-b]benzothiazoles. For this he treated 2-hydrazino-4-methylbenzothiazole with various aromatic carbonic acids in presence of POCl₃ under reflux for half day. The reaction mixture was poured into crushed ice and the solution was basified with NaOH solution, the formed solids were filtered and recrystallized with ethanol to get expected one with good yield. [13]



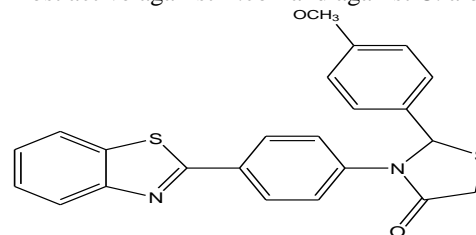
Synthesis of 5-methyl-3-substituted-1,2,4-triazolo[3,4-b] benzothiazoles

PHARMACOLOGICAL ACTIVITIES OF BENZOTHAZOLES:

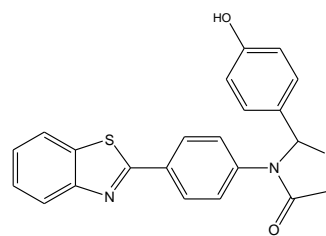
1) Antimicrobial activity:

Microbes are the organisms which cause many diseases like typhoid, malaria, jaundice, and some severe diseases like HIV -AIDS, syphilis, tuberculosis, etc. The scientists have made many approaches to check the activity of benzothiazoles on microbes.

Sushil K ssingh et al in 2014 synthesised 4-thiazolidiones with benzothiazole moiety and reported that 3-(4-(benzo[d]thiazol-2-yl) phenyl)-2-(4-methoxyphenyl)thiazolidine-4-one and 3-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-hydroxyphenyl)thiazolidine-4-one were found to be most active against E.coli and against C. albicans. [14]

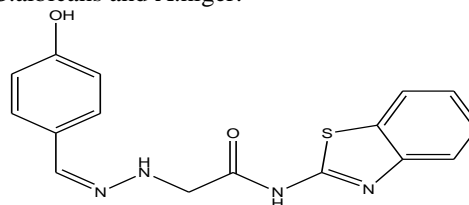


3-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-methoxyphenyl)thiazolidine-4-one

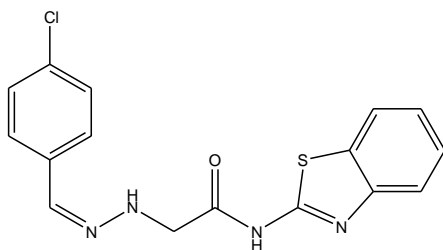


3-(4-(benzo[d]thiazol-2-yl)phenyl)-2-(4-hydroxyphenyl)thiazolidine-4-one

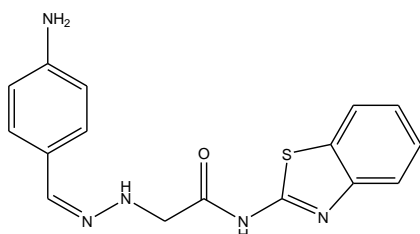
Balram soni et al in 2011 synthesized 2-substituted benzothiazoles containing azomethine linkage and reported that N-(1,3-benzothiazol-2-yl)-2-[(2Z)-2-(4-hydroxybenzylidene)hydrazinyl]acetamide, N-(1,3-benzothiazol-2-yl)-2-[(2Z)-2-(4-chlorobenzylidene)hydrazinyl]acetamide, and N-(1,3-benzothiazol-2-yl)-2-[(2Z)-2-[4-(dimethylamino)benzylidene]hydrazinyl]acetamide were found to be most active against C.albicans and A.niger. [15]



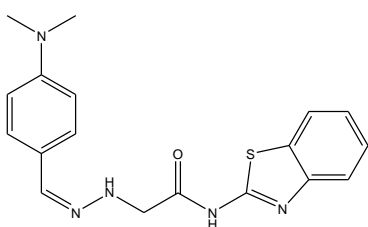
N-(1,3-benzothiazol-2-yl)-2-[(2Z)-2-(4-hydroxybenzylidene)hydrazinyl]acetamide



N-(1,3-benzothiazol-2-yl)-2-[(2Z)-2-(4-chlorobenzylidene)hydrazinyl]acetamide

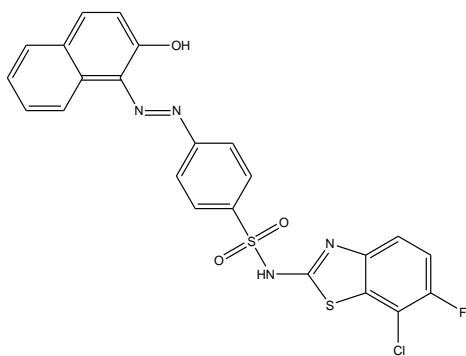


N-(1,3-benzothiazol-2-yl)-2-[(2Z)-2-(4-aminobenzylidene)hydrazinyl]acetamide



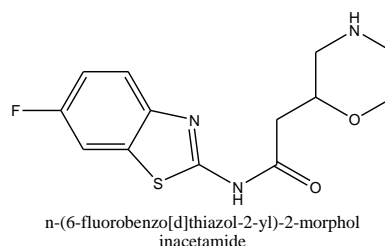
N-(1,3-benzothiazol-2-yl)-2-[(2Z)-2-[4-(dimethylamino)benzylidene]hydrazinyl]acetamide

Pritesh Patel et al in 2012 synthesised molecules comprising benzothiazole and sulphonamide linked to substituted aryl group via azo link and reported N-(7-chloro-6-fluorobenzothiazol-2-yl)-4-((2-hydroxynaphthalen-1-yl) diazenyl) benzenesulphonamide show most activity *S. aureus*, *B. subtilis*, *E. coli* and for *P. aeruginosa*.^[16]



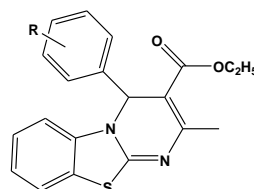
N-(7-chloro-6-fluorobenzothiazol-2-yl)-4-((2-hydroxynaphthalen-1-yl) diazenyl) benzenesulphonamide

S. Baluja et al in 2013 synthesised fluoro substituted benzothiazole and reported that N-(6-fluorobenzothiazol-2-yl)-2-morpholinoacetamide show more activity *E. coli*.^[17]



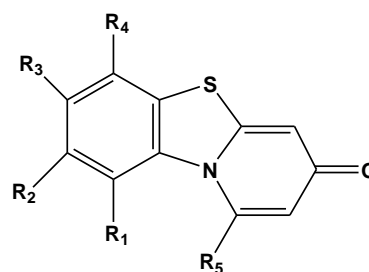
N-(6-fluorobenzothiazol-2-yl)-2-morpholinoacetamide

Sahu et al., in 2012, the 4H-pyrimido [2,1-b][1,3]benzothiazole derivatives prepared and screened for their antibacterial activities against gram-positive and gram-negative bacteria, viz., *P. aeruginosa*, *B. cereus*, *S. typhi*, *S. aureus*, *P. rettgeri* and *E. coli*.^[18]



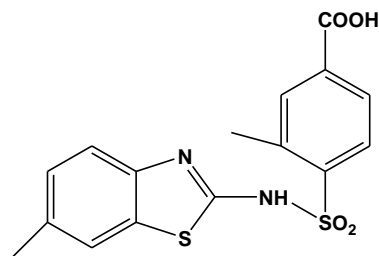
R= phenyl, 4-hydroxyphenyl, 4-methoxyphenyl

Gupta S et al reported synthesis of series of pyrimido [2,1-b] benzothiazoles by conjugation addition to imino nitrogen of 2-aminobenzothiazoles to alkyne β -carbon atom of acetylenic acid followed by ring closure and synthesized compounds are studied for antimicrobial activity against *E. coli* and *Enterobacter*.^[19]



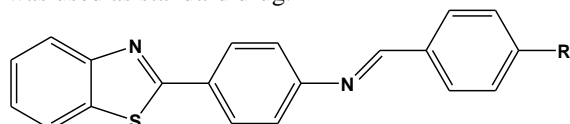
R1= H, R2=Cl, R3=H, R4=H, R5=Ph.

Hutchinson I et al., in 2001, successfully made an attempt to prepare 2-(substituted phenylsulfonamido)-6-substituted benzothiazoles and screened them for their anti bacterial activity and found to possess good antibacterial activity against *B. subtilis*, *S. dysentery* and *S. typhi*.^[20]



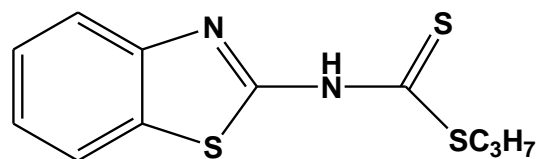
R=Cl,Br,CH₃, OCH₃
R₁= I, CH₃, NH₂

Nagarjuna A et al synthesized benzothiazole substituted thiazolidinone. Compounds were tested against pathogenic bacteria *P. mirabilis*, *S. Aureus* and *S. typhi* by disc diffusion method. Streptomycin was used as standard drug. [21]

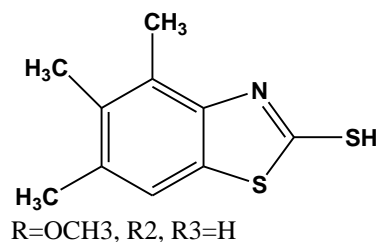


R=Cl,Br,F

Maharan M, et al synthesized series of benzothiazole-2-yl-dithiocarbamates along with copper complexes via reaction of suitable alkyl or heteroaryl halide with sodium salt of benzothiazole-2-yl-dithiocarbamic acid followed by complexation with copper sulphate and selected derivatives checked for their schistosomicidal activity against *Schistosoma mansoni*. [22]

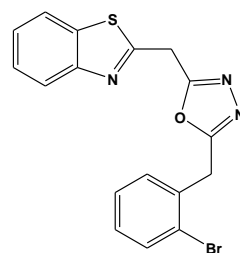


Murthi Y, et al synthesized some new 2-mercaptobenzothiazoles and correlated the effect on antimicrobial potency by varying the substituents in benzene part of the benzothiazole ring system. Antimicrobial screening was performed against *E. coli*, *S. aureus*, *C. albicans* and antifungal activity against *Aspergillus flavus* and *Candida albicans* at conc. 100µg/ml using agar plate Kirby-Bauer disc diffusion method in DMF as solvent. Ofloxacin (100µg/ml) and gricofulvin (100µg/ml) were used as standard drug for antibacterial and antifungal activity respectively. [23]



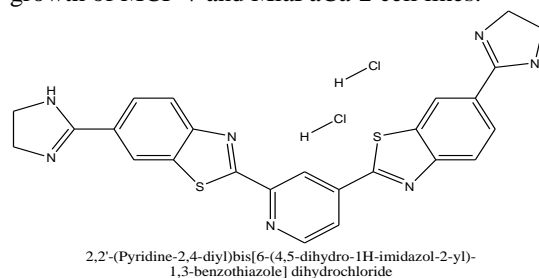
R=OCH₃, R₂, R₃=H

Rajeeva B, et al synthesized some new 2-substituted benzothiazole derivatives by refluxing benzothiazolylcarboxyhydrazide with different aryl acids in phosphoryl chloride and screened the derivative for antimicrobial activity against *B. subtilis*, *E. coli* and *P. aeruginosa*. [24]

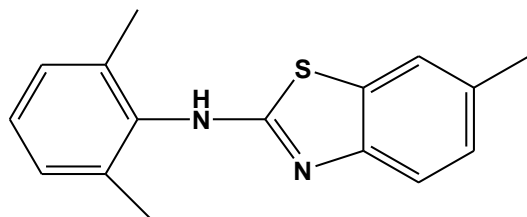


ANTICANCER ACTIVITY

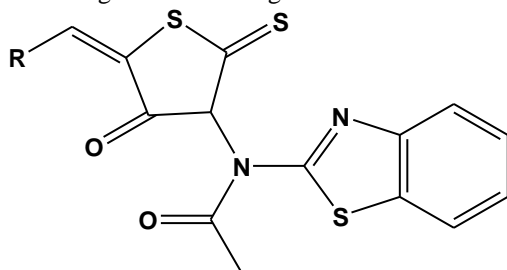
Sandra Kraljević Pavelić et al synthesized amidino-substituted bis-benzothiazolyl-pyridines and pyrazine and reported that 2,2'-(Pyridine-2,4-diyl)bis[6-(4,5-dihydro-1H-imidazol-2-yl)-1,3-benzothiazole] dihydrochloride has antiproliferative effect on the growth of MCF-7 and MiaPaCa-2 cell lines. [25]



Havrylyuk et al., in 2010, prepared several novel 4-thiazolidinones using benzothiazole nucleus and performed the in vitro anticancer activity for all synthesized compounds by the help of National Center Institute. In his studies he noticed that two of the synthesized compounds having activity against the lung, ovarian, melanoma, Central nervous system, leukemia, prostate, breast and Colon cancers cell lines. [26]

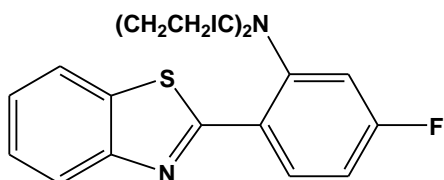


Mallesappa et al., 2012, has performed anticancer screening for 7-chloro-N-(2,6-dichlorophenyl)benzothiazol-2-amine it reveals that compound shows good results against Non-Small Cell Lung Cancer causing cell lines.^[27]

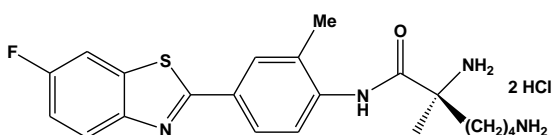


R= 4-Chlorophenyl, 4-dimethylaminophenyl

Kini S, et al refluxed o-aminophenols with substituted benzoic acid in presence of polyphosphoric acid at higher temperature to get aryl substituted benzothiazoles and evaluated them against Human Cervical Cancer cell lines as anticancer drugs.^[28]

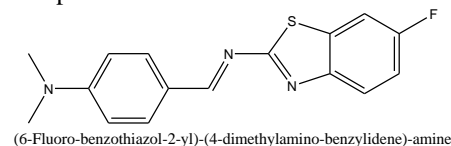


Hutchinson I et al have been synthesized Fluorinated analogues of 2-(4-aminophenyl) benzothiazoles which successfully block C-oxidation. Fluorinated benzothiazole analogue 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole, exhibit selective and potent anticancer activity. in vitro and superior potencies against human breast and ovarian tumor xenografts implanted in nude mice Its lysylamide prodrug, is under phase I clinical trials at the United Kingdom.^[29]



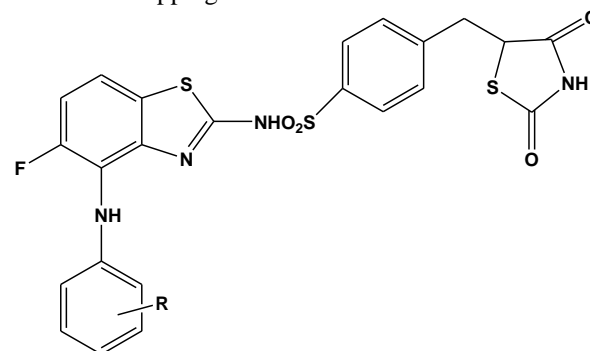
ANTICONVULSANT ACTIVITY

Ranjana Singh, et al in 2014 synthesized 2-amino-6-substituted benzothiazoles and reported that (6-Fluoro-benzothiazol-2-yl)-(4-dimethylamino-benzylidene)-amine has more activity where Phenytoin was used as the standard for the comparison.^[30]



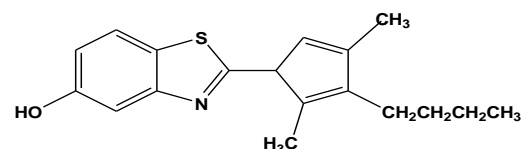
ANTIDIABETIC ACTIVITY

Pattan S et al synthesized 2-amino[5-(4-sulphonylbenzylidene)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole series and screened for their antidiabetic activity on albino rat by alloxan induced tail tipping method.^[31]



ANTI INFLAMMATORY ACTIVITY

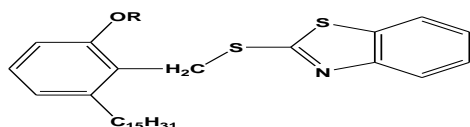
Sawhney et al., have prepared some novel 2-(2-benzothiazolyl)-6-aryl-4, 5-dihydro-3(2 H)-pyridazinone and found that they possessed low to moderate anti-inflammatory activity.^[32]



R=H, Cl, F, CH₃, OCH₃

2-(2-benzothiazolyl)-6-aryl-4, 5-dihydro-3(2 H)-pyridazinone

Paramashivappa R. et al., Design, synthesis and biological evaluation of a series of 2-[[2-alkoxy-6-pentadecylphenyl) methyl] thio]-1H-benzimidazoles/benzothiazoles and benzoxazoles from anacardic acid and investigated their ability to inhibit human cyclooxygenase-2 enzyme (COX-2). The active compounds were screened for cyclooxygenase-1 (COX-1) inhibition.^[33]



R= -CH₃, -CH₂CH₃

2-[[2-alkoxy-6-pentadecylphenyl) methyl] thio]-1H-benzothiazoles

CONCLUSION

From this review the synthesis of benzothiazoles and their activity were studied. In this most of the benzothiazoles show antimicrobial properties. Hereby

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we conclude that, this class of drugs have a diversified pharmacological activities which can studied further to increase the research to screen for more pharmacological activities.

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