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# Benzothiazole: Different Methods of Synthesis and Diverse Biological Activities

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**ABSTRACT**
Substituted 1, 3-benzothiazole derivatives are an important class of heterocyclic compounds. In recent years heterocyclic compounds analogues and derivatives have attracted strong interest due to their biological and pharmacological properties. The benzothiazole nucleus containing compounds involved in research aimed at evaluating new products that possess biological activities, such as antimicrobial, anticancer, antifungal, anthelmintic, anti-diabetic, amyloid imagining agents and anticancer agents. The present review focus on the different methods of synthesis of substituted benzothiazoles with potential activities that are now in developing phase.

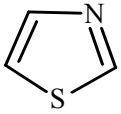
**Keywords:** Substituted benzothiazole derivatives, antibacterial activity, anticancer activity, anti-diabetic activity.

## INTRODUCTION

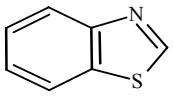
A heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring. Nitrogen, oxygen, and sulphur are the most common heteroatoms. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways. Most of the sugars and their derivatives, including vitamin C, for instance, exist in the form of five-membered (furan) or six-membered (pyran) rings containing one oxygen atom. Most member of vitamin B group possess heterocyclic ring containing nitrogen. One example is vitamin $B_6$ (pyridoxine), which is a derivative of pyridine, essential in amino acid metabolism. [1]

Benzothiazole is a heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiazole moites are part of compounds showing numerous biological activities such as antimicrobial [6-10] anticancer [11-13, 27], anthelmintic [15], anti-diabetic [16] activities. They have also found application in industry as anti-oxidants, vulkanisation accelerators. Various benzothiazoles such as 2-aryl benzothiazole received much attention due to unique structure and its uses as radioactive amyloid imagining agents [3], and anticancer agents. [4] Benzothiazoles are bicyclic ring system with multiple applications. In the 1950s, a number of 2-aminobenzothiazoles were intensively studied, as the 2-amino benzothiazole scaffold is one of privileged structure in medicinal chemistry [3, 5] and reported cytotoxic on cancer cells. [5] It must be emphasized that combination of 2-aminobenzothiazoles with other heterocyclic is a well known approach to design new drug like molecules, which allows achieving new pharmacological profile, action, toxicity lowering. The 2-(4-aminophenyl) benzothiazoles are novel class of potent and selective antitumor agents and display characteristic profile of cytotoxic response across the cell lines. 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 activities against Gram-negative, Gram-positive bacterias (e.g., *Enterobacter, Pseudomonas aeruginosa, E. coli,* and *Staphylococcus epidermidis* etc.) and the yeast (e.g., *Candida albicans*).

Benzothiazoles are fused membered rings, which contain the heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds.




[1]




[2]

Thiazole (1) is structurally related to thiophene and pyridine, but in most of its properties it resembles to the latter. Thiazole was first described by Hantzsch and Waber in 1887. Popp confirmed its structure in 1889.The numbering

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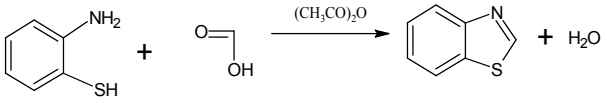
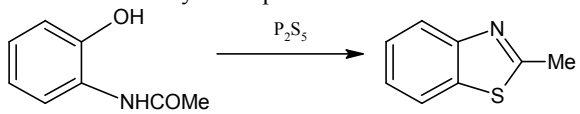
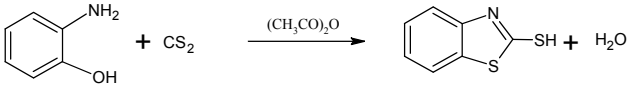
in thiazole starts from the sulphur atom. Structure (2) is benzothizole. The basic structure of benzothiazole consist of benzene ring fused with 4, 5 position of thiazole. The two rings together constitute the basic nucleus 1, 3-benzothiazle. Benzothiazole may be prepared by action of acid anhydrides (or) chlorides on o-aminophenols and formic acid in presence of acetic anhydride. [28]



Benzothiazoles are also formed by action of phosphorus pentasulfide on o-acylaminophenoles. [28]



2-mercaptobenzothiazole is vulkanisation accelerator it may be prepared as follows. [28]

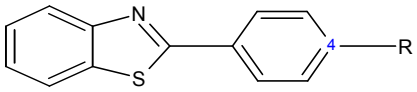


**IR SPECTROSCOPIC STUDIES**

The IR spectrum of the compound showed absorption peak at 3344cm$^{-1}$, 3025cm$^{-1}$, 1630cm$^{-1}$, 690cm$^{-1}$ due to stretching of N-H, C-H, C=N, C-S. IR spectra (KBr) were recorded on Shimadzu IR spectrophotometer. [29]

**SAR STUDY**

Presence of hydrophobic moieties in molecule is conductive for cytotoxic activity of benzothiazole derivitives against cancer cell lines. The amino, hydroxyl, and chloro group containing benzothiazole shows better anticancer activity. [13]

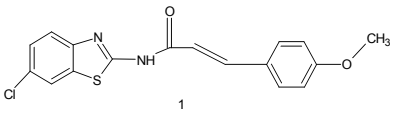


R= -$NH_3$, -OH, -Cl

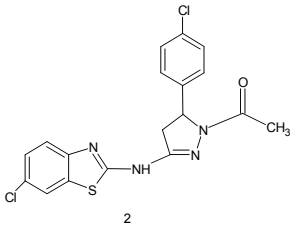
The substituents at second position of benzothiazole ring like mercapto group and hydrazine group are responsible for marked bactericidal activity and anti-inflametory activity. [22]

Introduction of methoxy group (-$OCH_3$) at position 4 of 2-mercaptobenzothiazole increase antibacterial activity and introduction of chloro group (-Cl) at same position increase antifungal activity. [8]

Anticancer activity of compounds (1,5) are due to substituent at position 2nd of aminobenzothiazole. Compound 1 with prop-2-enamido derivative and p-hydroxyphenyl substitution demonstrate most marked effect and possess significant anticancer activity. Compounds with pyrazoline and thiazole substitution (2,3,4,5) were tending to have moderate anticancer activity. Heterocyclic rings, 1-acetyl-pyrazoline and thiazole do not support eminently for anticancer activity (2,3). Chloro substituted amino benzothiazoles were found to have encouraging sensitivity to cancer cell lines compared to fluro substituted benzothiazoles. [20]



1



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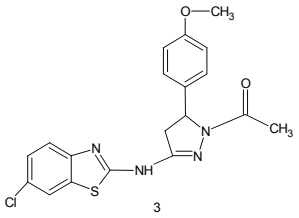

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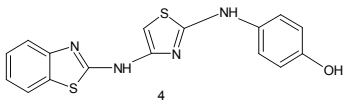

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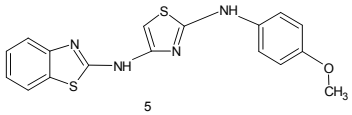
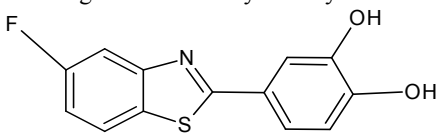


5

Minor modification of dihydroxyphenyl group, removal of fluro group or its replacement with other halogens had a profoundly dyschemotherapeuitic effect with respect to *in vitro* cancer cell growth inhibitory activity. [21]



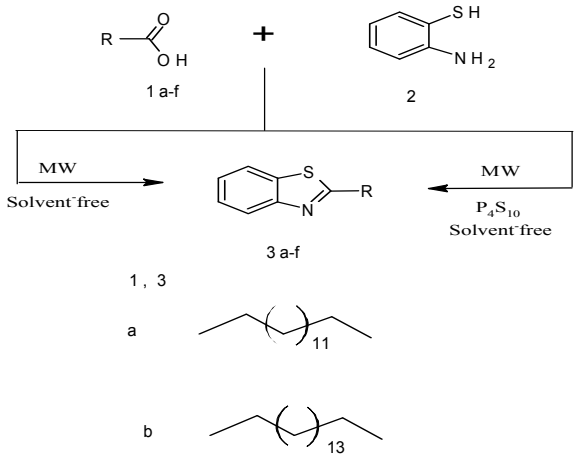
The thiazole ring has been extensively studied and it forms a part of vitamin B, penicillins and the antibacterial thiazoles. Given below is a brief account of various structural modifications done on benzothiazole ring and their associated biological activities.

**SYNTHESIS**

Many methods had been reported in literature. Some methods were listed in this study.

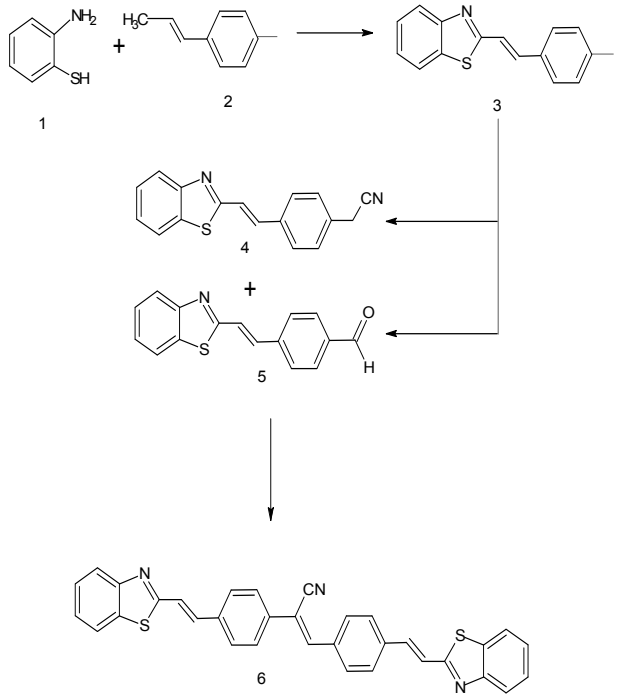
1) ***Scheme1:*** *Solvent free synthesis*

Synthesis of 2-substituted benzothiazoles by condensation of 2-aminothiophenol with various saturated and olefinic fatty acids under microwave in solvent free condition (path-A) with the use of catalyst $P_4S_{10}$ in (path-B), the reaction was successful in terms of yield and was completed within 3-4 min. [2]



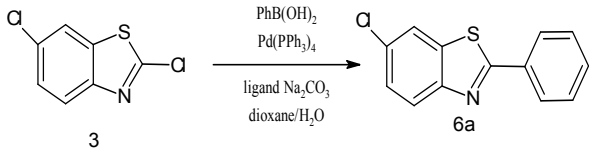
2) ***Scheme2:*** *Synthesis of cynosubstituted conjugated benzothiazoles*

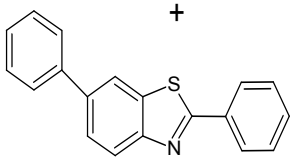
They explored synthesis of benzothiazole based organic nano-particles. The elaboration of conjugated system was performed by reacting equimolar quantities of 4 and 5 in dry THF and terbutyl alcohol at 50ºC while a small amount of terbutylammonium hydroxide was slowly dropped in mixture. [3]



3) ***Scheme3:*** *Suzuki-Miyaura coupling reaction*

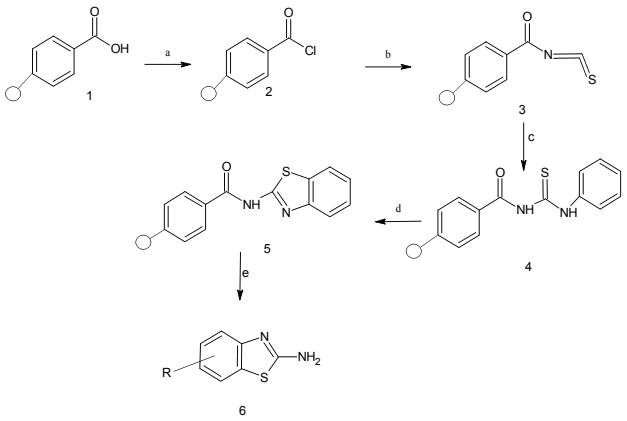
Development of microwave promoted Suzuki-Miyaura reaction 2-chlorobenzothiazole with phenyl boronic acid was carrid out using $Pb(PPh_3)_4$ as a catalyst. This reaction provides the adduct 6a with excellent regioselectivity. The bis adduct 2,6-diphenyl benzothiazole(7) by the catalysis of 2,6-dichloro benzothiazole with excess of phenyl boronic acid. [4]





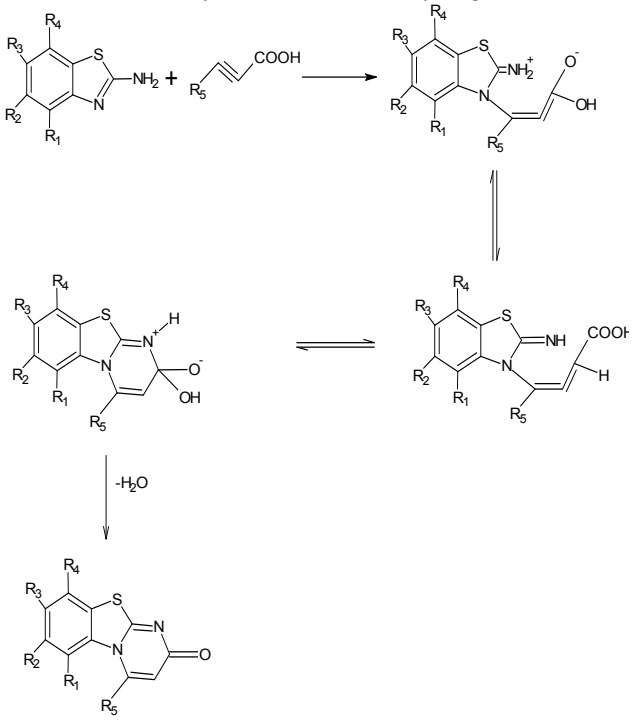
4) ***Scheme 4:*** *Solid phase synthesis-*

Conversion of resin bound isothiocynate 3 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. [5]



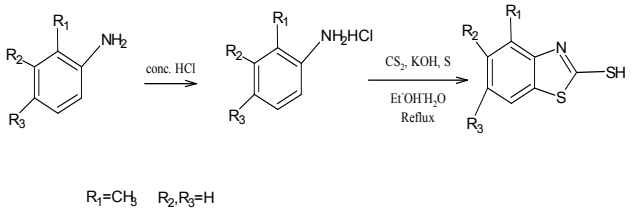
5) ***Scheme5***

Development of simple procedure to prepare a series of pyrimido[2,1-*b*]benzothiazoles by the conjugation addition of the imino nitrogen of 2-aminobenzothiazoles to alkyne β-carbon atom of acetylinic acid followed by ring closure. [6]



6) ***Scheme-6***

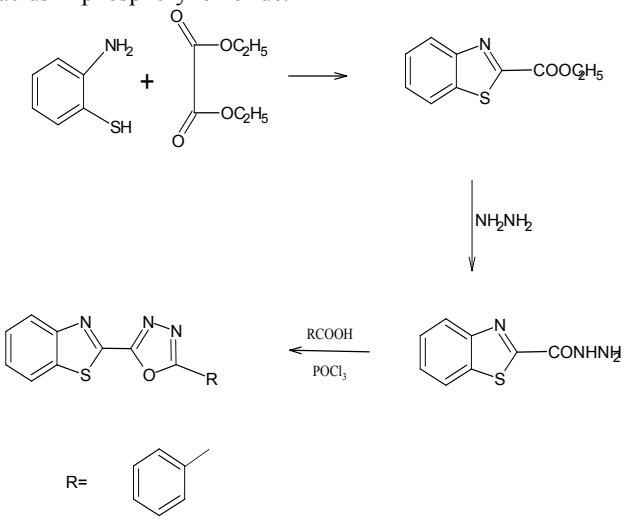
Synthesis of substituted 2-mercaptobenzothiazoles by varying substituents at 4, 5, and 6-position in the benzothiazole ring system. The synthesis of final compounds involves two steps- 1) Substituted anilines were converted to its hydrochloride salts. 2) This aniline hydrochloride salt was then cyclized to substituted 2-mercaptobenzothiazoles by reacting with carbon disulphide in presence of sulfur in an alkaline medium. [8]



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

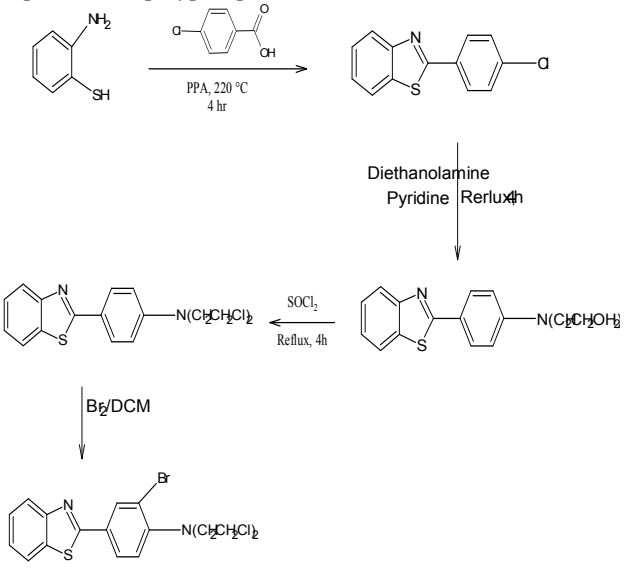
7) ***Scheme-7***

Synthesis of new 2-substitued benzothiazole derivatives by refluxing benzothiazolyl carboxyhydried with different arryl acids in phosphoryl chloride. [9]




8) ***Scheme-8***

Synthesis of 2-aryl substituted benzothiazole derivatives by refluxing o-aminothiophenols with substituted benzoic acids in presence of polyphosphoric acid at 220°C. [11]

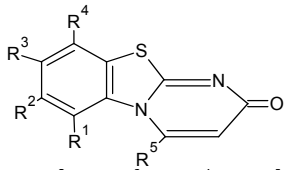



## BIOLOGICAL ACTIVITY

### 1) *Antimicrobial activity*

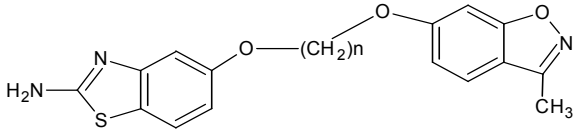
Microbes are causative agents for various types of disease like pneumonia, ameobiasis, typhoid, malaria, common cough and cold various infections and some severe diseases like tuberculosis, influenza, syphilis, and AIDS as well. Various approaches were made to check the role of benzothiazole moiety as antimicrobial agent from the discovery of molecule to the present scenario.

Gupta S *et al* [6] 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 acytylenic acid followed by ring closure and synthesized compounds are studied for antimicrobial activity against *E. coli* and *Enterobacter* as test organisms at conc 100µg per disc using vancomycine and meropenam as standard drug.

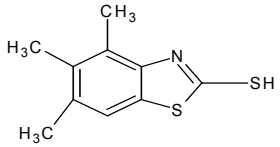


$R^1$= H, $R^2$=Cl, $R^3$=H, $R^4$=H, $R^5$=Ph.

Kumbhare RM *et al* [7] synthesized new benzothiozole and benzisoxazole from 2-amino 5/6-hydroxybenzothiazole, 6-hydroxy-3-methyl-1, 2-benzisoxal and different dihaloalkanes and screened for their antimicrobial activity against *Staphylococcus aureus,* and *E. coli* by disc diffusion method and anti fungal activity against *Aspergillus flavus,* and *Candida albicans.* Ciprofloxacin (10µg/ml) and fluconazole (10µg/ml) were used as standard drug for antibacterial and antifungal activity respectively.

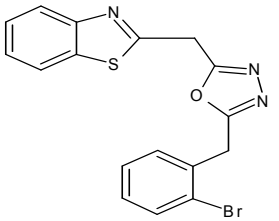


Murthi Y, *et al* [8] synthesized some new 2-mercaptobenzothiazoles and coreleted the effect on antimicrobial potency by varying the substituents in benzene part of the benzothiazole ring system. Anti-microbial screening was performed against *E. coli, S. aureus, C. albicans* and antifungal activity against *Aspergillus flavus* and *Candida albicans* at conc. 100µg/ml using agar plate Kirby-Bauer disc diffusion method in DMF as solvent. Ofloxacine (100µg/ml) and griciofulvin (100µg/ml) were used as standard drug for antibacterial and antifungal activity respectively

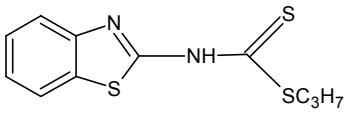


R=$OCH_3$, $R_2$,$R_3$=H

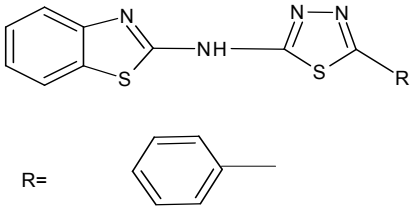
Rajeeva B, *et al* [9] synthesized some new 2-substituted benzothiazole derivatives by refluxing benzothiazolylcarboxyhydrazide with different aryl acids in phosphoryl chloride and screened the derivative for antimicrobial activity against *B. subtilis, E. coli and P. aeruginosa* by disc diffusion method at conc. 100µg/ml. The activity was compared to antibiotic ciprofloxine.



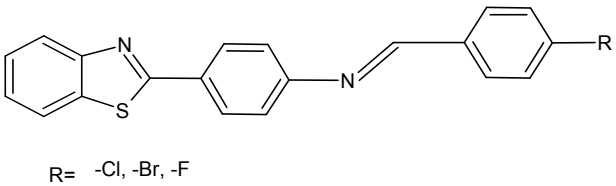
Maharan M, *et al* [10] synthesized series of benzothiazole-2-yl-dithiocarbamates along with copper complexes *via* reaction of suitable alkyl or heteroaryl halide with sodium salt of benzothiazole-2-yl-dithiocarbamic acid followed by complexation with copper sulphate and selected derivatives checked for their schistosomicidal activity against *Schistosoma mansoni*.



Amir M *et al* [23] synthesized 1, 3, 4-thiadiazole and imidazolline derivatives containing benzothiazole and screened for both antibacterial and antifungal activity using cup-plate agar diffusion method. Ofloxacine (50µg/ml) and ketokonazole (50µg/ml) were used as std. drug for antibacterial and antifungal activity respectively. Anti-microbial screening was performed against *E. coli, S. aureus, C. albicans* and antifungal activity against *Aspergillus flavus* and *Candida albicans*.

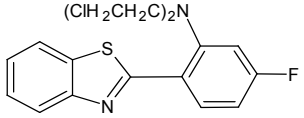


Nagarjuna A *et al* [24] synthesized benzothiazole substituted thiazolidinone. Compounds were tested against pathogenic bacteria *P. mirabilis, S. Aureus* and *S. typhi* by disc diffusion method. Streptomycin was used as standard drug.

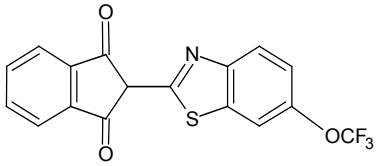


2) ***Anti-cancer activity***

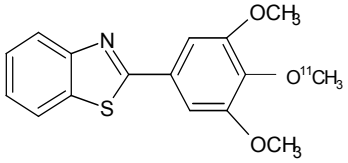
Kini S, *et al* [11] refluxed o-aminophenols with substituted benzoic acid in presence of polyphosphoric acid at higher temperature to get aryl substituted benzothiazoles and evaluated them against Human Cervical Cancer cell lines as anticancer drugs.



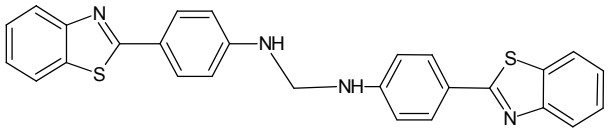
Stanton HLK, *et al* [12] synthesized benzothiazole containing phthalimide and studied their anti-cancer activity on human carcinoma cell lines.



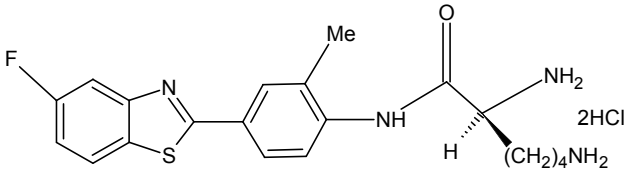
Wang M *et al* [13] synthesized carbon 11 labeled fluorinated 2-aryl benzothiazoles used for protein emission tomography (PET) to image tyrocinekinese in cancer.



Gupta S *et al* [14] synthesized benzothiazole derivatives and evaluated for *in vitro* cytotoxic activity against HL-60 and U-937 cell lines using 5-flurouracil, and cisplatin as std. drug. *In silico* pharmacokinetic study revealed that benzothiazole dimere were free from teratoginicity, irritation and sensitivity properties than monomers. The QSAR study showed that increase in hydrogen donor count is conductive for cytotoxic activity of benzothiazole derivatives against HL-60 cell lines.

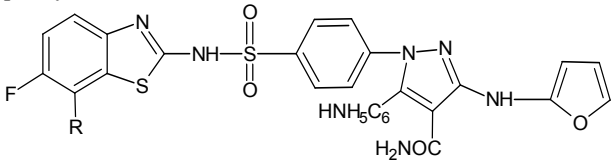


Hutchinson I *et al* [27] have been synthesized Fluorinated analogues of 2-(4-aminophenyl) benzothiazoles which successfully block C-oxidation. Fluorinated benzothiazole analogue 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F203, NSC 703786) (1d), exhibit selective and potent anticancer activity. 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, NSC710305), (1e) is under phase I clinical trials at the United Kingdom.



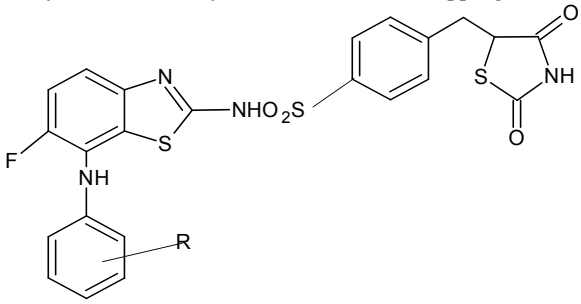
**3)** ***Anthelmentic activity***

Sreenivasa M *et al* [15] synthesized fllurobenzothiazole comprising sulfonamide pyrazole derivitives. They screened synthesized for anthelmentic activity by using earthworms (*Peritumaposthum*). Albendazole was used as standard drug. The compounds were evaluated by time taken for complete paralysis and death of worms.



**4)** ***Anti-diabetic activity***

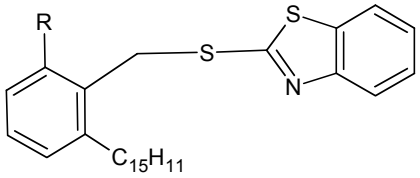
Pattan S *et al* [16] synthesized 2-amino[5`(4-sulphonylbenzylidine)-2,4-thiazolidnedione]-7-chloro-6-flurobenzothiazole series and screened for their antidiabetic activity on albino rat by alloxan induced tail tipping method.



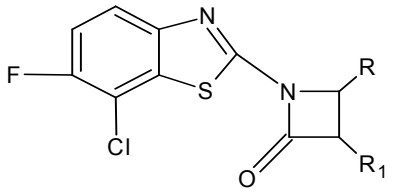
**5)** ***Cyclooxygenase inhibitor activity***

Pyrazolones and pyrazolinones rank among the more venerable 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 display anti-inflammatory activity.

Parmshivappa R *et al* [17] synthesized a series of 2-[(2-alkoxy-6-pentadecylphenyl) methyl] thio-1-H-benzimidazoles/ benzothiazole from anacardic acid (pentadecyl salicylic acid) and investigated their ability to inhibit human cyclooxygenase enzyme-2.

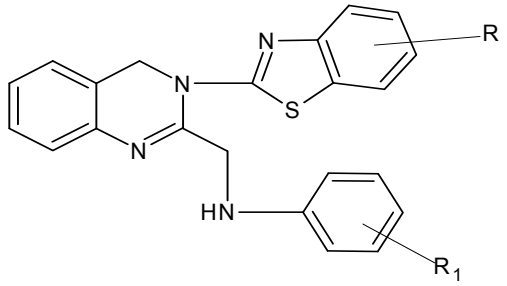



Gurupadayya B. *et al* [25] synthesized azatidin-2-ones and thiazoline-4-ones encompassing benzothiazole derivatives and evaluated for anti-inflammatory activity using carrageenan induced rat hind paw oedema method. Diclofenac sodium used as standard drug.




R= H $R_1 = C_6H_5$

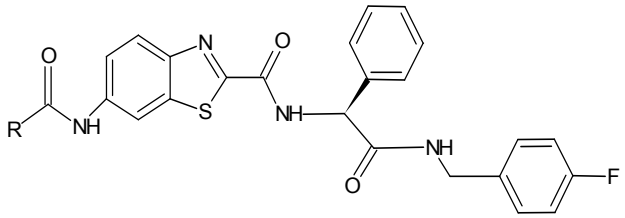
Srivastava N *et al* [26] synthesized 3-(6-substituted-1, 3-benzothiazole-2-yl) 2[{(4-substituted phenyl) amino} methyl] quinazoline-4(3H)-ones derivatives and tested for anti-inflammatory activity at the dose of 200mg/kg in acute-inflammatory models in rats. Diclofinac sodium used as standard drug.




R= Cl $R_1 = CH_3$

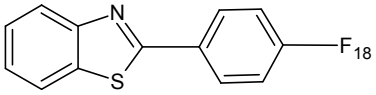
**6)** ***MTP Inhibition activity***

Chi B *et al* [18] synthesized triamide derivatives based on benzothiazoletemplet. A series of these compounds showed potent enterocyte-specific microsomal triglyceride transfer protein (MTP) inhibitors. Inhabitation of MTP by small molecules, therefore lead to reduction in plasma triglycerides and cholesterol level.




**7)** ***Amyloid imaging agent in Alzheimers disease***

Serdons K *et al* [19] F-labeled 2-(4′-fluorophenyl)-1-3-benzothiazoles. They evaluated it as amyloid imaging agent in Alzheimers disease in comparison with [$^{11}$C]PIB ($^{11}$C labeled 6-hydroxy-2-(4"-N- [$^{11}$C] methylaminophenol)-1,3-benzothiazole and showed excellent characteristics comparable with those of [$^{11}$C]PIB, namely good affinity for amyloid plaques present in human Alzheimers disease.




The reviewed substituted benzothiazoles had shown wide spectrum of biological activities. The substituted mercapto benzothiazole and 2-amino 5/6-hydroxybenzothiazole have significant antibacterial activity. Significant anticancer activity was displayed by pthalmide containing benzothiazole derivatives and benzothiazole diamers.

Good anti-diabetic activity was shown by 2-amino [5` (4-sulphonylbenzylidine)-2, 4-thiazolidnedione]-7-chloro-6-flurobenzothiazole series whereas series of 2-[(2-alkoxy-6-pentadecylphenyl) methyl] thio-1-H- benzothiazole showed good COX-2 inhibiation activity. The biological profile of these benzothiazoles represents much progress with regards to the older compounds.

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