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COMMON METHODS TO SYNTHESIZE BENZOTHIAZOLE DERIVATIVES AND THEIR MEDICINAL SIGNIFICANCE: A REVIEW

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Antimicrobial,
Anti-inflammatory,
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ABSTRACT

Recently, heterocyclic compounds analogues and their derivatives have attracted strong interest in medicinal chemistry due to their biological and pharmacological properties. The small and simple benzothiazole nucleus possesses numerous biological properties like - antitumor, antimicrobial, anti-inflammatory, anticonvulsant, and antidiabetic activities. These activities are also possessed by its substituted derivatives as well. The present review focuses on some commonly used easy procedures to synthesize the benzothiazole moiety and its derivatives, which comprise of different biological activities.

INTRODUCTION: The chemistry and biological study of heterocyclic compounds has been an interesting field for a long time in medicinal chemistry. A number of heterocyclic derivatives containing nitrogen and sulphur atom serve as a unique and versatile scaffolds for experimental drug design [1]. Benzothiazole is one of the most important heterocycle that has received overwhelming response owing to its diversified molecular design and remarkable optical, liquid and electronic properties [2].

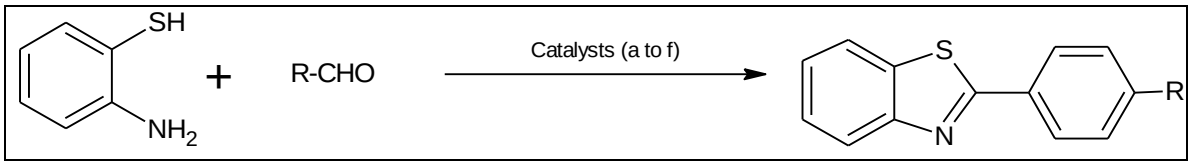
Benzothiazole consists of thiazole ring fused with benzene ring and possess multiple applications. In 1950s, a number of 2-aminobenzothiazoles were intensively studied as central muscle relaxants. Since then, biologist's attention was drawn to this series when pharmacological profile of Riluzole (6-trifluoormethoxy-2-benzothiazolamines, Rilutek), as a Glutamate neurotransmission inhibitor was discovered. After that benzothiazole derivatives have been extensively studied and found to have diverse chemical reactivity and broad spectrum of activity [3-7].

Due to these biological activities, the synthesis of benzothiazole is a considerable area of current discussion. The classical method involves condensation of *o*-aminothiophenols with substituted aldehydes [8-14], acyl chlorides, carboxylic acids [15-16] or esters, nitriles [17]. Other most commonly used methods include Pd/Cu/Mn/chloranil catalyzed cyclization of *o*-halothioformanilides [18-22]. The survey of literature related to benzothiazoles reveals the presence of this bicyclic ring system in various amine or terrestrial natural compounds, which have useful biological properties [23]. Benzothiazole derivatives possess a wide spectrum of biological applications such as antitumor [26-52], antimicrobial [54-83], schictosomicidal [84], anti-inflammatory [85-93], anticonvulsants [94-102], antidiabetic [103-108], antipsychotic [109] and diuretic [111] etc.

Given review is a brief account of some commonly used methods to synthesize benzothiazole derivatives and various structural alterations conducted on benzothiazole ring and preferential specificities imparted in their biological responses.

Some common routes to synthesis of substituted benzothiazole derivatives:

- **Condensation of *o*-aminothiophenol with aldehydes:** Treatment of o-aminothiophenols with substituted aldehydes affords the synthesis of 2-substituted benzothiazoles using different catalysts and reaction conditions.

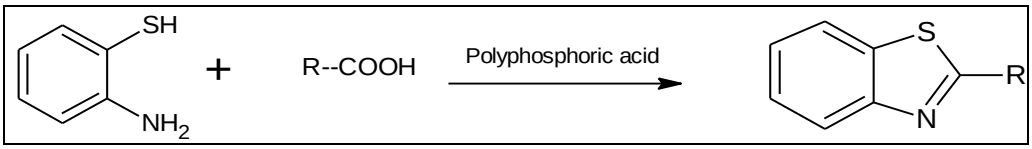


CONDENSATION OF *o*-AMINOTHIOPHENOL WITH ALDEHYDES

Catalysts (a-f):

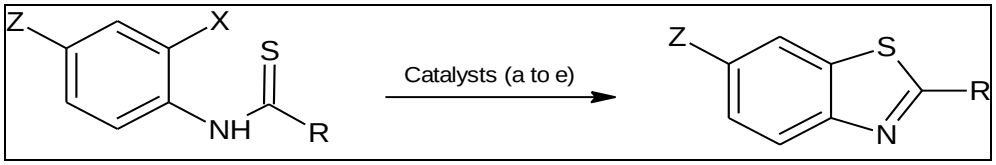
a. Montmorillonite,SiO_2/Graphite; Microwave, p-TsOH[8]
b. Diethyl bromophosphonate/*tert*-Butyl hypochlorite; acetonitrile [9]
c. Cerium (IV) ammonium nitrate [10]
d. H_2O_2/HCl system in ethanol [11]
e. AcOH/Air; Microwave/ Thermal Heating [12]
f. Baker's yeast, Dichloro methane [13]

- **Condensation of *o*-aminothiophenol with acids**: Treatment of 2-aminothiophenol and substituted aromatic acids in presence of Polyphosphoric acid provides a good method to synthesize 2-substituted benzothiazoles and gives a good yield [14-16].



CONDENSATION OF *o*-AMINOTHIOPHENOL WITH ACKDS

Cyclization of thioformanilides using different reagents: Substituted thioformanilides can be converted to 2-aminobenzothiazoles *via* intramolecular C-S bond formation/C-H functionalization utilizing various reagents and catalysts.

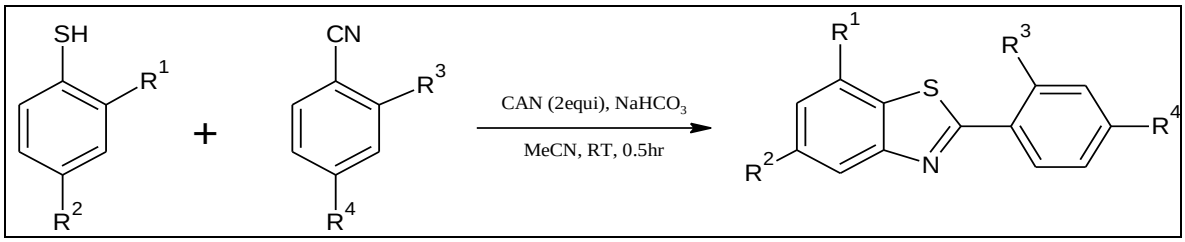


CYCLIZATION OF THIOFORMANILIDES USING DIFFERENT REAGENTS

Catalysts (a-e):

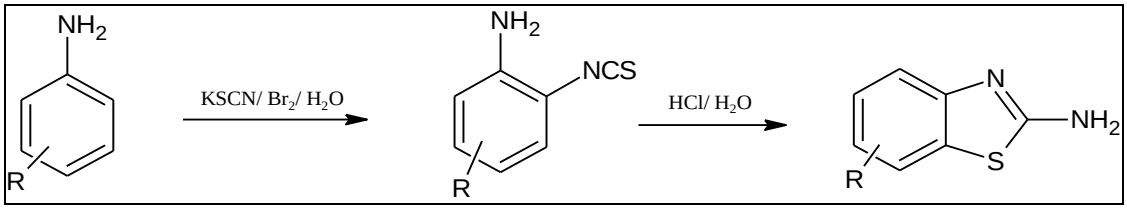
a. CuI; 1, 10-Phenanthroline, CS_2CO_3, reflux [18]
b. Manganese triacetate [20]
c. CS_2CO_3, Dioxane [21]
d. Photochemical cyclization induced by chloranil [19]
e. $Pd(PPh_3)_4/MnO_2$ system under an oxygen atmosphere [22]

- **Coupling between thiophenols and aromatic nitriles:** Thiophenols when treated with aromatic nitriles to affords a smooth reaction mediated by Ceric ammonium nitrate to give corresponding 2-arylbenzothiazoles in excellent yield [17].



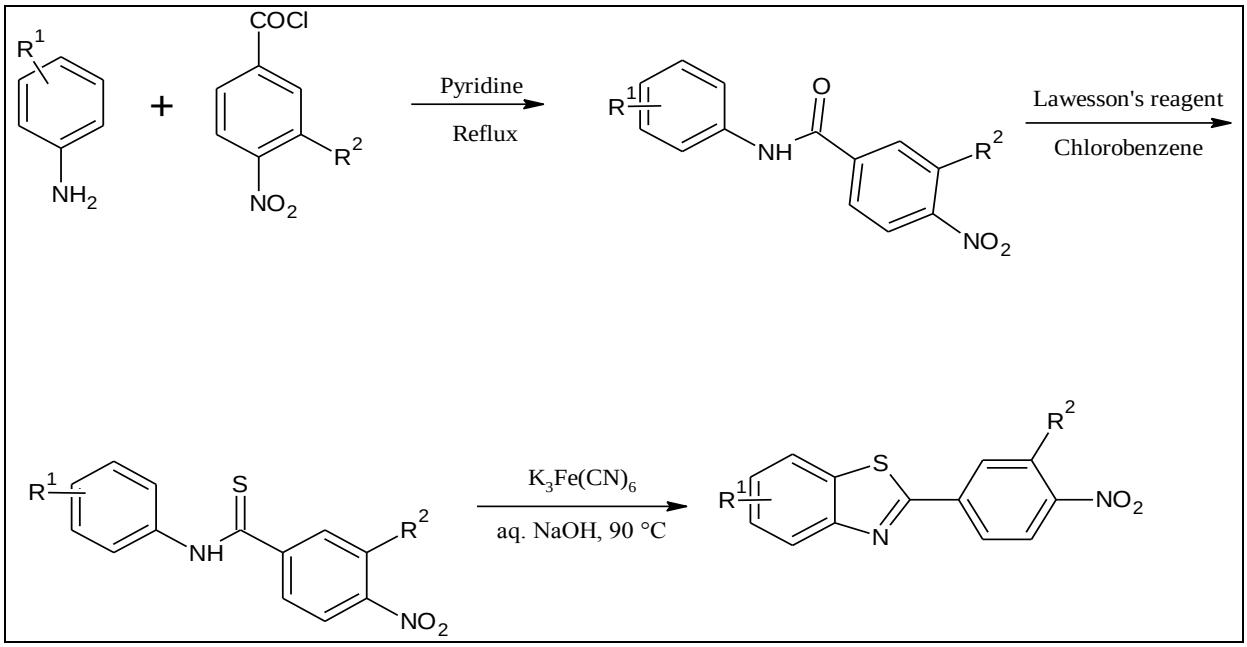
COUPLING BETWEEN THIOPHENOLS AND AROMATIC NITRILES

- **Synthesis using anilines**: Different substituted anilines when treated with KSCN in presence of glacial acetic acid to synthesize 2-substituted benzothiazoles [24].



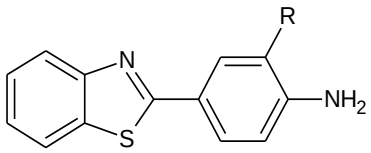
SYNTHESIS USING ANILINES

2-aryl substituted benzothiazoles can be synthesized using reaction of substituted anilines with nitrobenzoyl chloride in pyridine under reflux and further treatment with Lawesson's reagent and then cyclization of intermediate using Potassium ferricyanide [25].



Biological activities of benzothiazole derivatives:

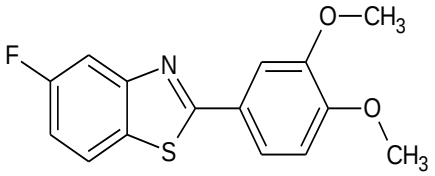
1. Anticancer Activity: Different substituted benzothiazoles showed antitumor activity. Mainly the 2-(4-aminophenyl) derivatives are especially potent. Stevens *et al* reported the *in-vitro* antitumor activity of a new series of alkyl-, halo-, cyano-, alkoxy- and hydroxy- substituted 2-(4-aminophenyl) benzothiazoles (**1.1-1.4**). Compound (**1.1**) showed the most potent growth inhibition against the ER+ (MCF-7 and BO) and ER- (MT-1 and MT-3) tumors [26-28].



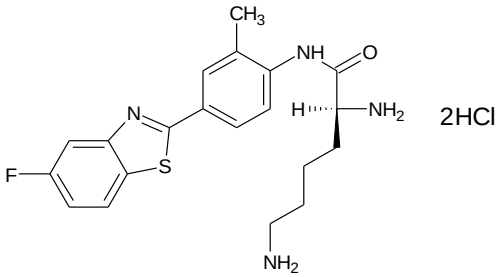
1.1 - 1.4

Structure no.	R group
1.1	CH_3
1.2	Br
1.3	I
1.4	Cl

Further aryl substituted 2-phenyl benzothiazoles (**1.5**) and L-lysyl and l-alanyl amide prodrugs of 2-(4-aminophenyl) benzothiazole (**1.6**) were found to possess exquisitely potent anti-proliferative activity [29-30].

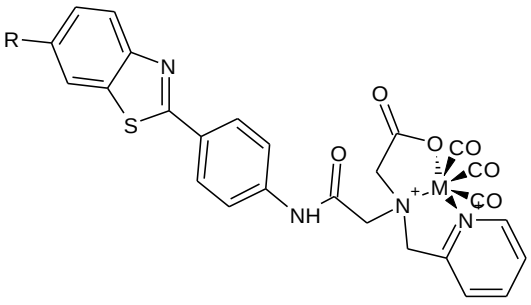


1.5



1.6

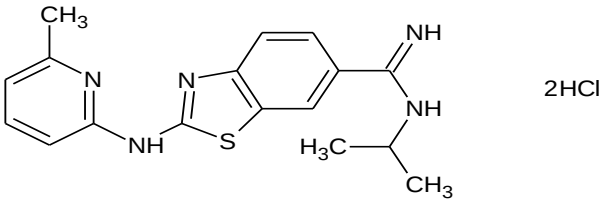
Maria Pelecanou *et al.,* prepared a series of Rhenium ($^{185/187}$Re) and Technetium-99m (^{99m}Tc) complexes of 2-(4'-aminophenyl) benzothiazole. The *in-vitro* evaluation of complexes **1.7 a & 1.7 b, 1.8 a & 1.8 b**, and *in-vivo* application of the ^{99m}Tc complexes (**1.7b**) and (**1.8b**) in MCF-7[a] tumor bearing SCID mice established the potential of these labeled 2-(4'-aminophenyl) benzothiazole derivatives for radiopharmaceutical applications [31].



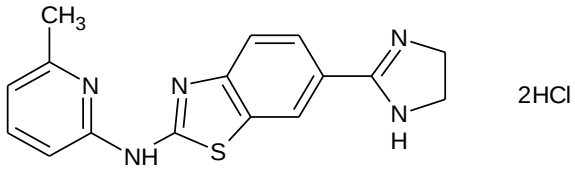
1.7, 1.8

Structure no.	R gp.	M
1.7a	H	Re
1.7b	H	^{99m}Tc
1.8a	CH_3	Re
1.8b	CH_3	^{99m}Tc

Antitumor evaluation of some novel cyano and amidino benzothiazole derivatives (**1.9**) and (**1.10**) was described by Kralj *et. al*. Almost all amidino derivatives showed noticeable anti-proliferative effect on several tumor cell lines while cyano derivatives showed considerably less pronounced activity due to poor solubility in aqueous cell culture[31,32].

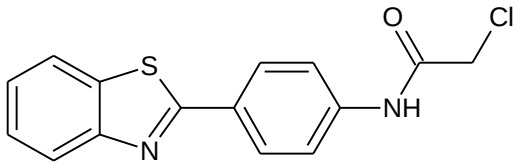


1.9

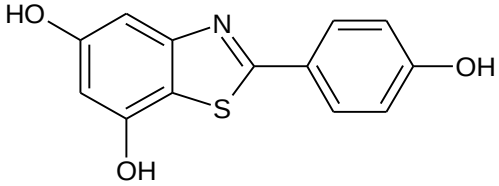


1.10

A series of 2-(4-acylaminophenyl) benzothiazoles (**1.11**) and polyhydroxylated 2-phenylbenzothiazoles (**1.12**) were screened for anticancer activity and found to be very active against breast MCF-7 and MDA 468 cells [33, 34].

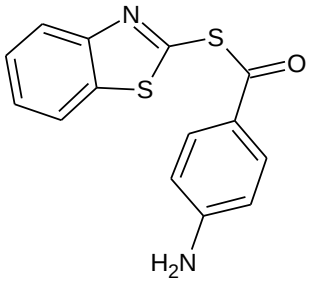


1.11

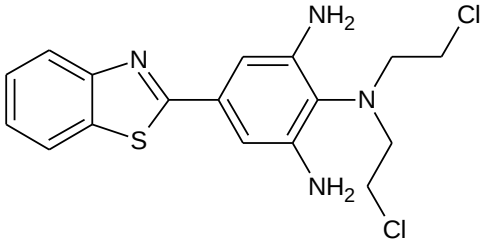


1.12

Devmurari *et al.,* prepared a series of seven substituted 2-phenyl benzothiazoles and substituted 1, 3-benzothiazole-2-yl-4-carbothioate derivatives. All synthesized novel compounds were screened for anticancer activity and compounds (**1.13**) and (**1.14**) showed very good anticancer activity [35].

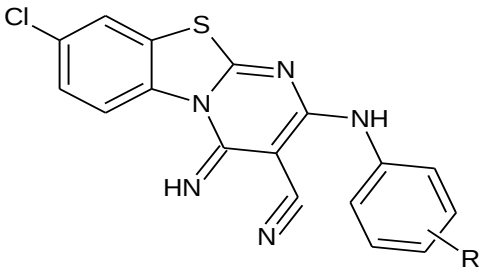


1.13

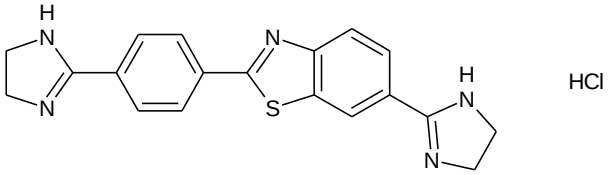


1.14

Substituted pyrimido (1.15) and cyano, dicyano, amidino and diamidino (**1.16**) and imidazole (**1.17** & **1.18**) substituted 2-phenylbenzothiazole derivatives were prepared and evaluated for *in-vitro* anticancer activity towards 60 human cancer cell lines [37, 38, 23].

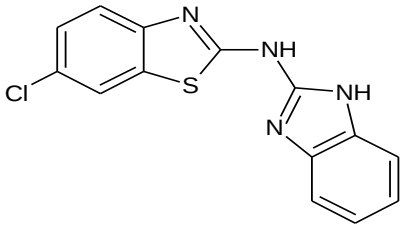


1.15



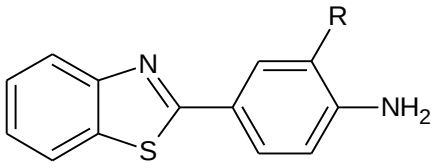
1.16

1.17 (R= Cl, OCH_3)



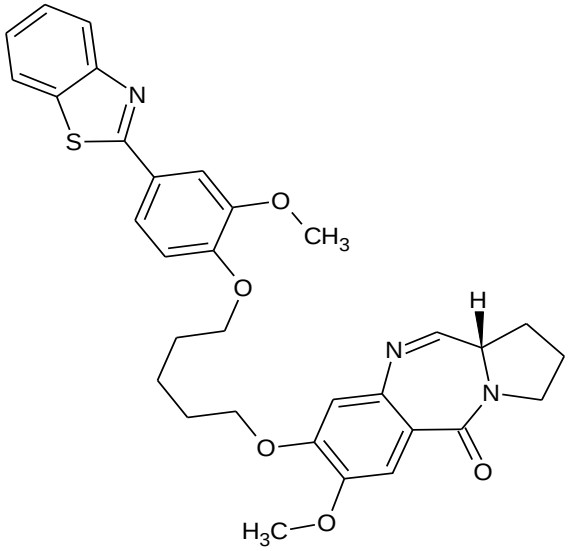
1.18

2-(4'-aminophenyl) benzothiazoles elicit biphasic growth inhibitory effects against number of human cancer cell lines. A series of 3'-substituted-2-(4'-aminophenyl)-benzothiazoles (**1.19**) were prepared by Bradshaw *et al* and when tested against MCF-7 and MDA 468 cell lines, revealed a unique profile of growth inhibition [39, 40].



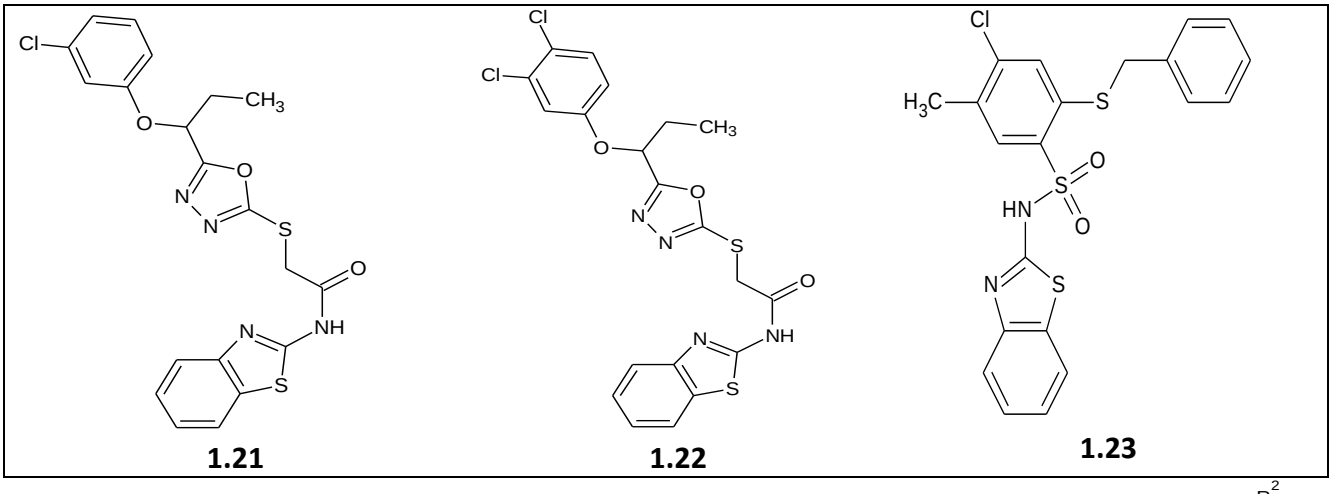
1.19

R= H, I, CH_3, Br & Cl



1.20

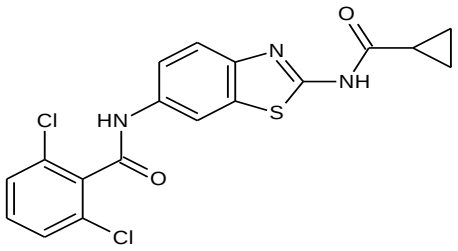
Benzothiazole linked pyrrolobenzodiazepine (**1.20**) and 1, 3, 4-oxadiazole-2-thione (**1.21** & **1.22**) conjugates showed significant effects on leukaemial cell lines [41, 42].



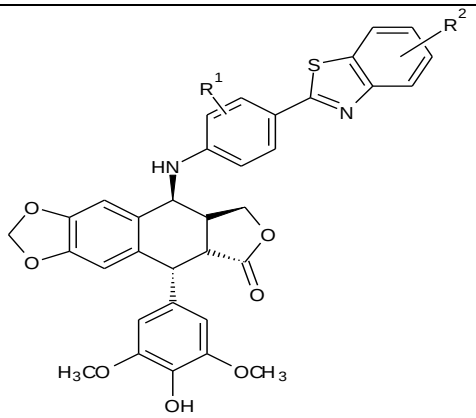
1.21 **1.22** **1.23**

N-(benzothiazol-2-yl) derivatives of 2-benzylthio-4-chloro-5-R^1-benzenesulfonamides were prepared and evaluated for activity and selectivity towards non-small cell lung cancer and melanoma cell lines. Compound (**1.23**) was found more potent due to high lipophilicity of CH_3 group as compared to CN or $CONH_2$ group [43].

A new series of 2,6-dichloro-N-[2-(cyclopropanecarbonyl-amino) benzothiazol-6-yl] benzamide (**1.24**) and fluorinated benzothiazole-substituted- 4- hydroxy cyclohexa- 2, 5- dienones (quinols) (**1.25**) was synthesized and found to possess good antitumor activity [44, 45].

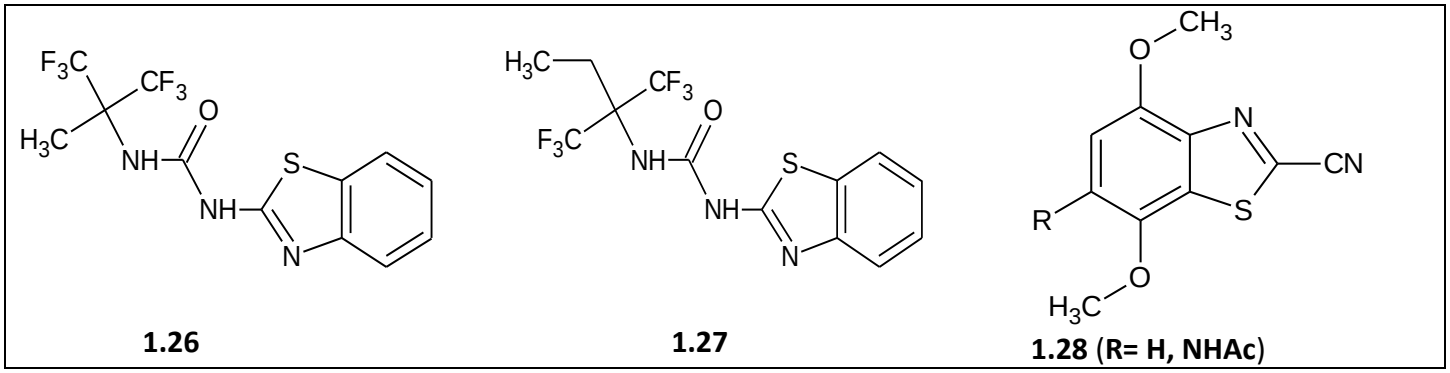


1.24



1.25

A number of N-bis-(triflouromethyl)-alkyl-N'-benzothiazolyl ureas were prepared and derivatives with an electron withdrawing substituent showed greater activity towards the tumor cell lines. The compounds (**1.26**) and (**1.27**) were found to have significant action on prostate, CNS, renal and leukaemial cancer cell lines [46].

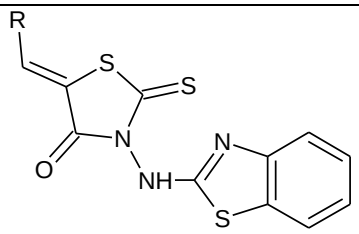


1.26 **1.27** **1.28** (**R= H, NHAc**)

Several novel 2-carbonitrile (**1.28**) and 4-thiazolidinone (**1.29**) benzothiazole derivatives were synthesized and screened for anticancer activity on leukaemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancer cell lines [47, 48].

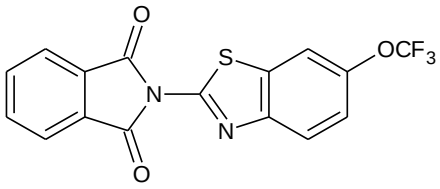
Benzothiazole containing phthalimide (**1.30**) were synthesized and found to exhibit *in-vitro* cytotoxic potential on human cancer cell lines [49].

A new series of benzothiazole substituted Quinol ethers and esters (**1.31**) were found to be active *in-vitro* against human colon and breast cancer cell lines [50].



1.29

R= 2-(4-OMe-$C_6H_4NHCOCH_2O$)-5-ClC_6H_5



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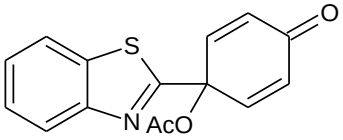
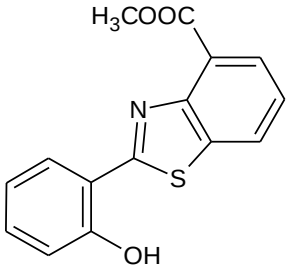


1.31

The cytotoxicity studies of test compounds 2-(substituted phenyl) benzothiazoles (**1.32**) was done against human A-549, BFTC-905, RD, MES-SA and HeLa carcinoma cell lines [51].

A new series of 2-(4-aminophenyl) benzothiazole derivatives with a cyano or alkynyl group at 3' position was prepared and evaluated for antitumor activity. The 5-flouro derivative (**1.33**) possessed *in-vitro* activity against MCF-7 and MDA-468 human cancer cell lines[52].



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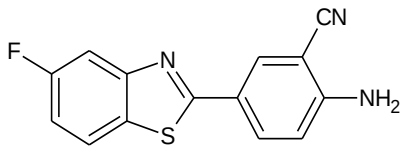
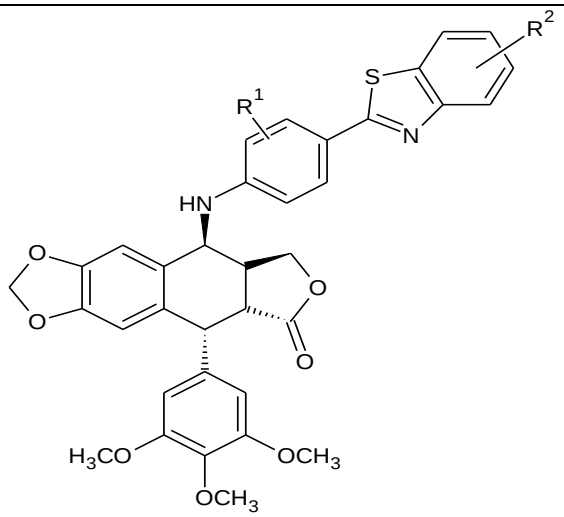


1.32

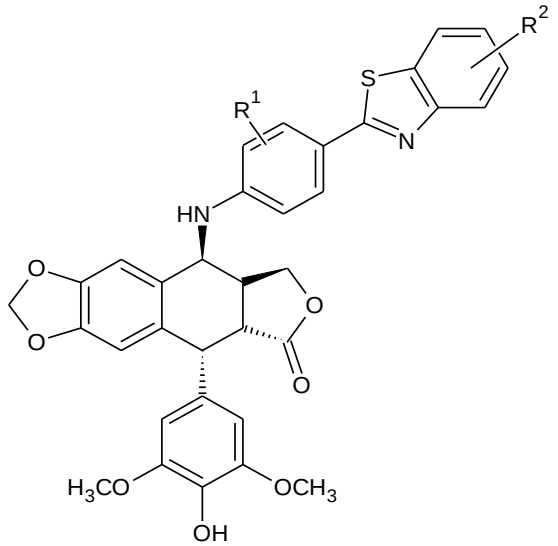
Kamal and co-workers synthesized benzothiazolo-4*β*-anilino-podophyllotoxin (**1.34**) and benzothiazolo -4*β*-anilino4 -*O*-demethylepipodophyllotoxin (**1.35**) cogeners and screened some compounds for cytotoxicity studies against human cancer cell lines and DNA Topoisomerase-II inhibitory activity [53].



1.34

R^1= H, 2'-Cl, 3'-CH_3, 3'-Br

R^2=6-OCH_3, 6-F, 4-Cl, 4, 6-dichloro



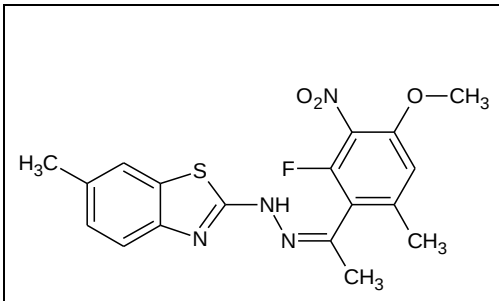
1.35

R^1= H, 2'-Cl, 3'-CH_3, 3'-Br

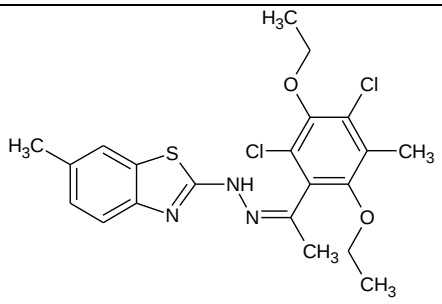
R^2=6-OCH_3, 6-F, 4-Cl, 4, 6-dichloro

2. Antimicrobiological Activity: Microbes are causative agents for various types of severe diseases and infections like ameobiasis, typhoid, malaria, common cold, cough, tuberculosis, influenza, syphilis, AIDS etc. To verify the role of benzothiazoles as antimicrobial agents, several approaches have been made.

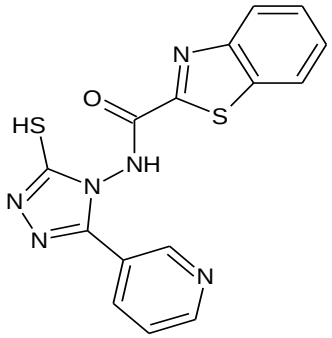
(a) Antibacterial and antifungal activity: Some 2-substituted benzothiazoles (**2.1**), (**2.2**) and 4-(2'-substituted benzothiaoles)- 5- mercapto- 3-(substituted)- 1, 2, 4-triazole derivatives (**2.3**) were examined against *E. coli* and *S. aureus* for antibacterial activity and *Candida albicins* and *Aspergillus niger* for antifungal activity. Most of the compounds showed promising results for both activities [54, 55].



2.1

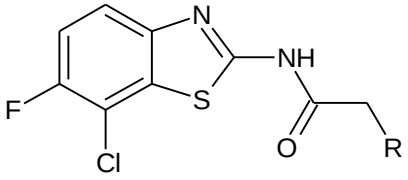


2.2



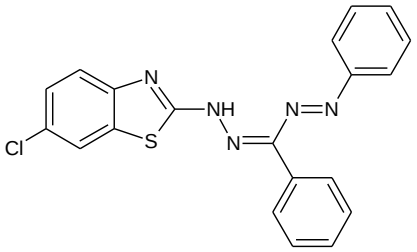
2.3

A series of fluoro, chloro2-(*α*-subsituted aryl amino acetamido) benzothiazoles (**2.4**) and 2-[1-aryl azo] methyleneimino- 6- chloro benzothiazole derivatives (**2.5**) were prepared and showed significant antibacterial activity when examined against *B. subtilis, S. typhi, E. coli* and *S. aureus* bacterial strains [56, 57].



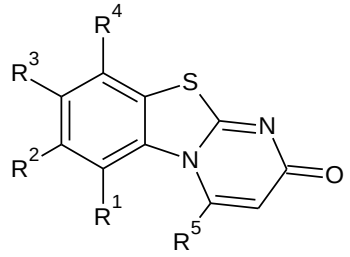
2.4

R= *p*-Bromo/ nitro/ methyl aniline

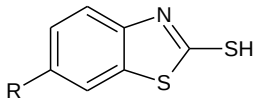


2.5

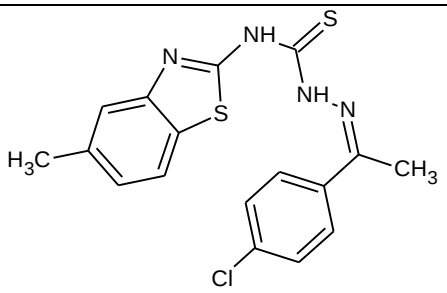
Substituted pyrimido [2, 1-b] benzothiazoles (**2.6**), (**2.7**) and low molecular weight 2- mercapto benzothiazole derivatives (**2.8**), (**2.9**) and fluoro benzothiazole incorporated with 1, 3, 4-thiadiazole were found active against *E. coli*, *B. subtilis*, *P. typhii* and *S. aureus*, *Candida albicans* and *Aspergillus niger* [58-60].



2.6 (R^1=H, R^2=Me, R^3=H, R^4=Me, R^5=Ph)
2.7 (R^1=H, R^2=Cl, R^3=H, R^4=H, R^5= 1-Pentyl)

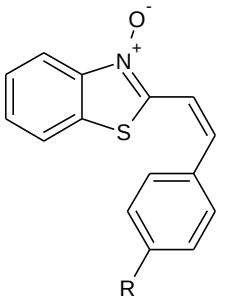


2.8 (R= CF_3)
2.9 (R=NO_2)

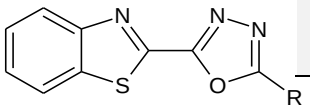


2.10

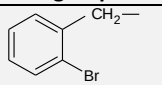
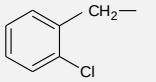
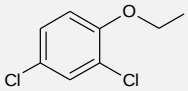
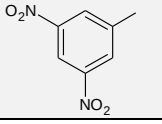
N-2-Benzothiazolylthiourea derivatives (**2.10**) and 2-styrylbenzothiazole-N-oxides (**2.11**) had been screened and found to have good antimicrobial activities against Gram-positive and Gram-negative bacteria such as *S. aureus, P. aeruginosa* and *E. coli* and a yeast (*C. albicans*) and a mould (*Microsporum gypseum*) [61, 62].



2.11



2.12

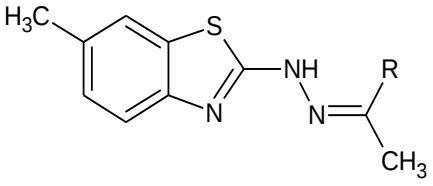
Structure No.	R group
2.12a	
b	
c	
d	

R= N, N- dimethyl amine, imidazole, benztriazole

2- (5- substituted- 1, 3, 4- oxadiazole- 2- yl)- 1, 3- benzothiazoles (**2.12 a, b, c, d**) were found to have good *in-vitro* antibacterial activity against Gram positive and Gram negative bacterial strains such as *B. subtilis, B. pumilus, E. coli and P. aeruginosa* [63].

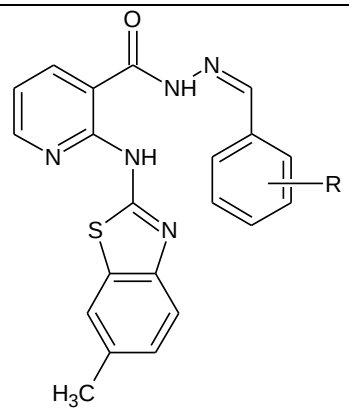
Alang *et al* synthesized seven new derivatives of 2- substituted benzothiazole (**2.13**) and found them a good antibacterial agent against Gram positive bacteria (*S. aureus, S. epidermidis*) and Gram negative bacteria (*P. aeruginosa* and *E. coli*) [64].

A new series of compounds 2-[(6-methyl-1, 3- benzothiazol- 2- yl) amino]- N- [2- (substituted phenyl/ furan- 2- yl)- 4- oxo- 1, 3- thiazolidin- 3-yl] nicotinamides, (**2.14 & 2.15**) were prepared and examined to possess good *in-vitro* antimicrobial activity against two Gram positive (*S. aureus, S. pyrogens*), two Gram negative (*E. coli, P. aeruginosa*) bacteria and three fungal species (*C. albicans, A. niger, A. clvatus)* [1].



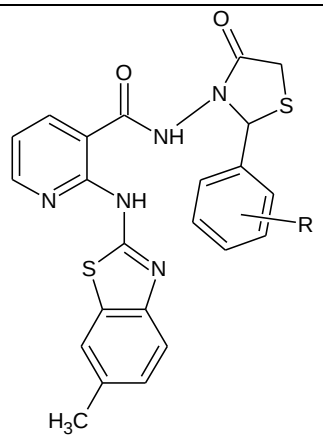
2.13

R= 2''- Chlorophenyl, *p*-hydroxyphenyl, 2''- hydroxyphenyl and 2'', 5''-dihydroxyphenyl



2.14

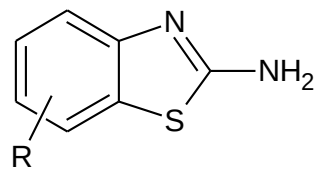
R=H, 2-Cl, 4-Cl, 2-NO_2, 3-NO_2, 4-OH, 4-OMe, 3-OMe-4-OH, 3-OMe-4-OH-5-NO_2 and 2-furyl



2.15

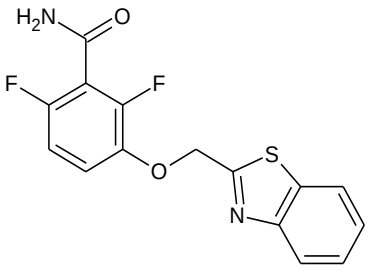
R=H, 2-Cl, 4-Cl, 2-NO_2, 3-NO_2, 4-OH, 4-OMe, 3-OMe-4-OH, 3-OMe-4-OH-5-NO_2 and 2-furyl

Some new 2-amino substituted benzothiazoles (**2.16**) were synthesized and evaluated for *in-vitro* antifungal activity against fungal strains such as *C. albiacns, A. niger and A. flavus* [65].

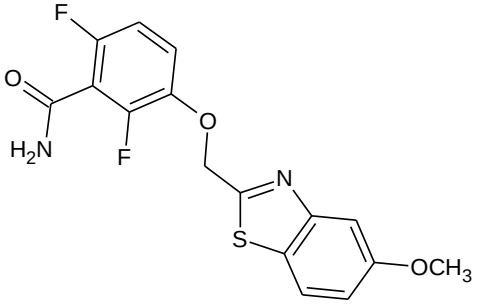


2.16

R= 6-COOH, 4/6/7-NO_2, 6-Br/Cl, 4, 6- di NO_2

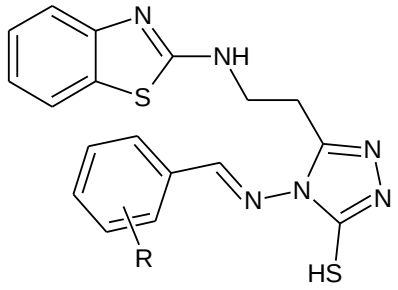


2.17



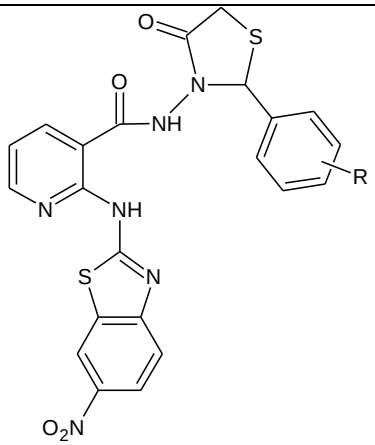
2.18

Alkyl derivatives of 3-methoxy benzamide substituted with heterocyclic systems were found to be potent anti-staphylococcal agents with a good to moderate inhibition of essential bacterial cell division protein FtsZ. Agents (**2.17**) and (**2.18**) were revealed as most active as antibacterial against *S. aureus* [66]. Newer Schiff bases of benzothiazole derivatives (**2.19**) and thiazolidinones incorporated benzothiazoles (**2.20 & 2.21**) exhibited moderate antibacterial activity against Gram positive (*S. aureus* and *S. pyrogenus*), Gram negative bacteria (*E. coli* and *P. aeruginosa*) and Fungi (*C. albicans*, *A. niger* and *A. clavatus*). The results demonstrated that compounds with a 4-hydroxy, 4-dimethylamino and 3, 4-dimethoxy group on the aromatic ring showed good antibacterial activity [67, 68].



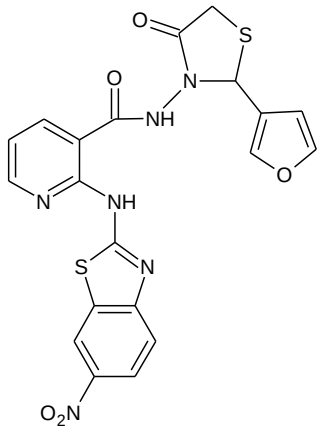
2.19

R=4-OH, 2-Cl, 4-N(CH$_3$)$_2$ and 3, 4-OCH$_3$



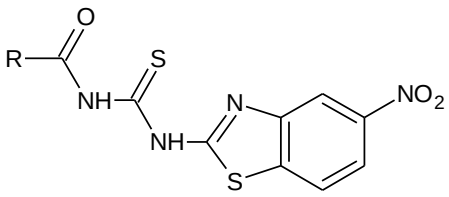
2.20

R= H, 2-Cl, 4-Cl, 2-NO$_2$, 3-NO$_2$, 4-OH, 4-OCH$_3$, 3-OCH$_3$-4-OH, 3-OCH$_3$-4-OH-5-NO$_2$



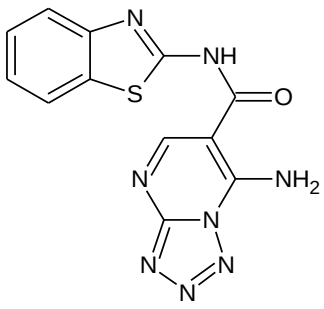
2.21

Antimicrobial evaluation of some thiourea derivatives (**2.22**), pyrazole, isoxazole and pyrimidine derivatives of benzothiazole was carried out and 7-amino-n-(benzothaizol-2-yl)- tetrazolo [1, 5-a]pyrimidine- 6-carboxamide (**2.23**) was found to be most potent against *B. subtilis* and *B. thuringiensis* (Gram positive), *E. coli* and *P. aeruginosa* (Gram negative) bacteria and *Botrytis fabae* and *Fusarium oxysporum* fungal strains [69, 70].

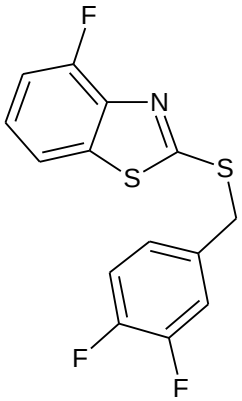


2.22

R=4-nitrophenyl, 2-thiophene, phenyl, n-butyl



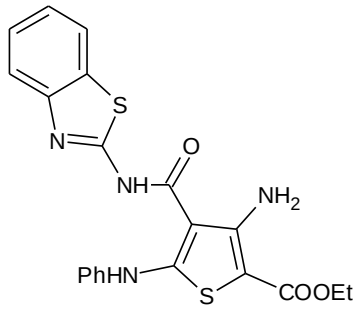
2.23



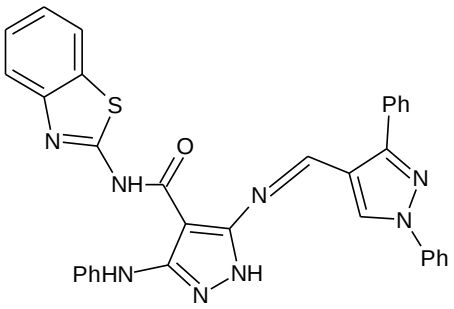
2.24

2-(3, 4-Difluoro-benzylsulfanyl)-4-fluoro benzothiazole (**2.24**) exhibited most interesting antifungal activities against *R. solani*, *B. cinereapers* and *D. gregaria* among a series of polyfuorinated 2-benzylthiobenzothiazoles [71].

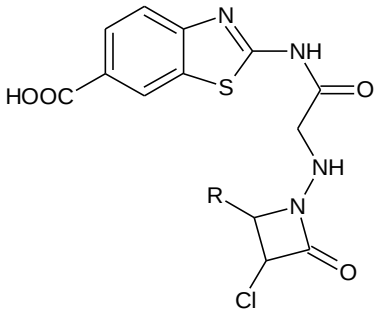
Further thiazole, thiophene and pyrazole derivatives of benzothiazole were prepared and examined for antibacterial and antifungal. The test compounds (**2.25**) and (**2.26**) showed good potency towards *S. aureus* and *S. pyrogenes* that was equal to Chloramphenicol [72].



2.25



2.26

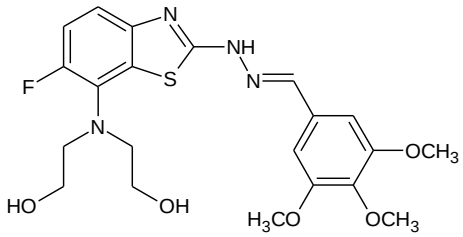


2.27

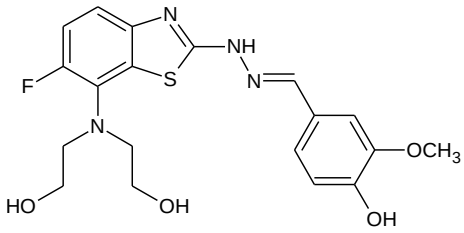
R= 2-ClC_6H_4, 4-Clc_6H_4, 3- $NO_2C_6H_4$ and 4-$NO_2C_6H_4$

Antibacterial and antifungal activity of oxoazetidine derivatives (**2.27**) and nitrogen mustards of fluoro benzothiazoles was determined against *S. aureus, B. subtilis, C. tropicans, A. niger* and *F. heterosporium*. The nitrogen mustards (**2.28**), (**2.29**) showed excellent inhibition at a conc. of 50 µg/0.1ml [73, 74].

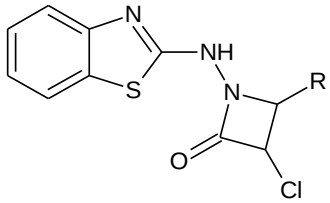
2-(4-substituted aryl-3-chloro-2-oxo-azetidine)-2-imino benzothiazoles (**2.30**) were prepared and evaluated for *in-vitro* antibacterial against *B. subtilis, E. coli, S. aureus, K. pneumoniae* and antifungal activity against *A. niger, A. flavus, F. oxisporium* and *T. viride* [75].



2.28



2.29

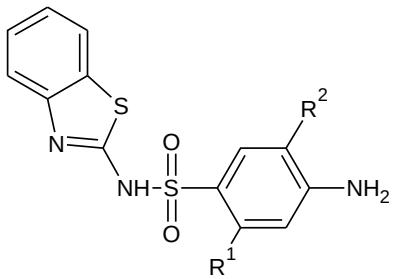


2.30

R= C_6H_5, 2/3/4-ClC_6H_4, 2/3/4-Br, C_6H_4, 2/3/4-OCH_3, C_6H_4, 2/3/4-NO_2, C_6H_4 and 4, 4'-$(CH_3)_2NC_6H_4$

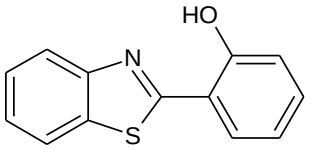
(b) **Anti-tubercular activity:** Some 4-Amino-N-(1,3-benzothiazol-2-yl) benzenesulphonamide derivatives were prepared and found to have good *in-vitro* Antimycobacterial activity (**2.31**) against *$H_{37}Rv$* strain of *mycobacterium tuberculosis* and other derivatives (**2.32**) and (**2.33**) were also found active as antibacterial and antifungal agents [76].

Katz *et al* synthesized some derivatives of 2-hydrazinobenzothiazole (**2.34)** and evaluated them for anti-tuberculous activity [77].

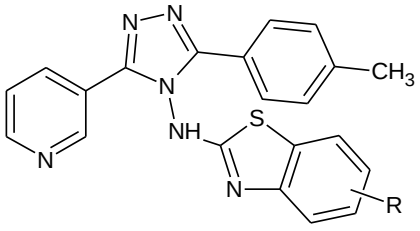


2.31

(R^1= Cl, R^2= COOH), 2.32 (R^1= Br, R^2= OCH_3) 2.33 (R^1= Cl R^2= CH_3)



2.34

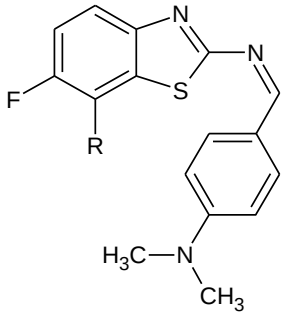


2.35

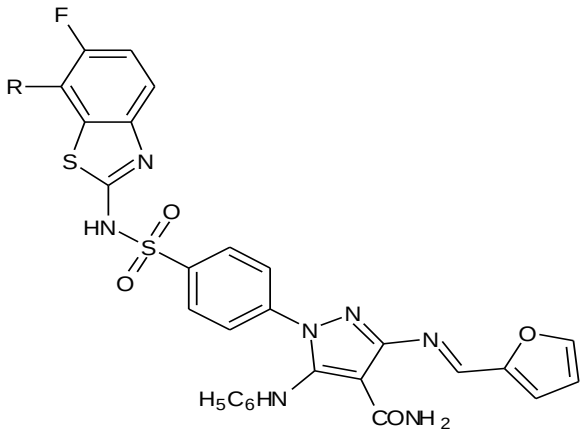
R=6-F, 6-CH_3, 4-CH_3, 6-Br, 6-OCH_3, 4-NO_2, 6-NO_2, 4-Cl, 6-Cl & 5, 6-di Cl

Triazole anlogs of benzothiazole (**2.35**) were synthesized and screened for anti-tubercular activity against *M. tuberculosis* $H_{37}Rv$ strain and antimicrobial activity against some Gram positive and negative bacteria and fungal species. The 4-Cl analogue with MIC 25 µg/ml was revealed better anti-tubercular agent than Rifampicin (MIC 40 µg/ml) [78].

(c) Antihelmentic activity: Some fluoro benzothiazole Schiff bases (**2.36**) and sulfonamido pyrazole derivatives of fluorobenzothiazoles (**2.37**) were prepared and examined for anthelmintic activity against earthworm *Perituma posthuma*. Some of the analogs showed significant activity [79, 80].

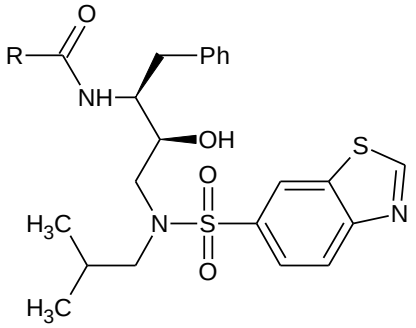


2.36, R= *o, m, p*-nitro aniline; o*, m, p*-chloro aniline

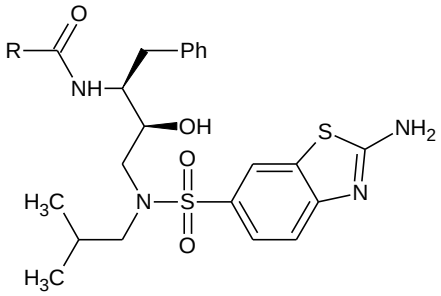


2.37, R= o,m,p-chloro; o,m,p- nitro aniline; Aniline, PABA; morpholine, piperazine; Dimethylamine, diphenylamine

(d) Antiviral activity: HIV-1 protease inhibition was observed with novel Benzothiazolesulfonamides (**2.38**) and (**2.39**) with an IC_{50} value in 2-3nM range. The carbamate analogues were found to be better antiviral and inhibitors of HIV-1 Protease [81].



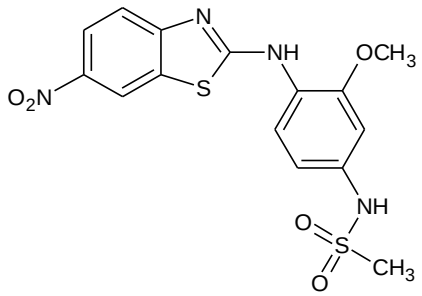
2.38



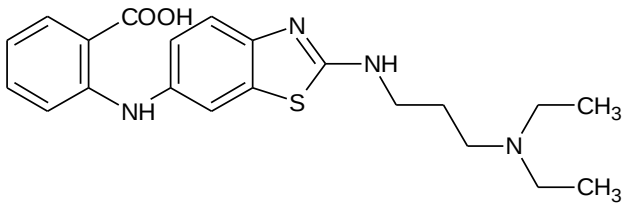
2.39

R=3-pyridylmethoxy, 5-thiazolylmethoxy and 3-tetrahydrofuranyloxy

(e) Antimalarial activity: Antimalarial activity of 2-substituted-6- nitro and 6-amino benzothiazoles and their anthranilic acids were carried out on *W2* and *3D7* strains of *P. falciparum*. The results revealed the potency of compounds (**2.40**) and (**2.41**) as the antimalarial agents of clinical and biological research [82].



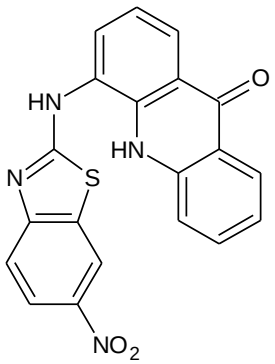
2.40



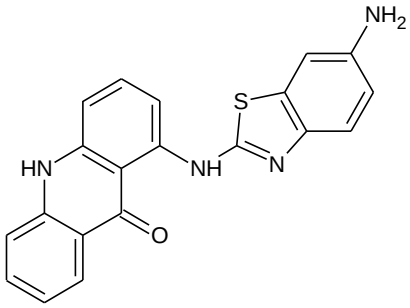
2.41

(f) Antileshmanial and Antischistosomicidal activity: Acridone derivatives of benzothiazole were synthesized and evaluated for antileshmanial activity towards *Leishmania promastigotes*. Two derivatives, 4-(6- nitro- benzothiazol-2- ylamino)- 10H- acridin- 9-one (**2.42**) and 1-(6-amino-benzothiazol-2-ylamino)-10-H-acridine-9-one (**2.43**) revealed a selective antileishmanial activity. The prersence of a 6-amino benzothiazole group on position 2-amino chain and a 6-nitro benzothiazole group on position 4 amino chain was found essential for antiamastigote properties [83].

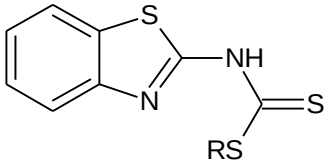
A series of benzothiazol-2-yl-dithiocarbamates (**2.44**) and their copper complexes was prepared and evaluated for their *in-vitro* Schistosomicidal activity against *Schistosoma mansoni*. The copper complexes showed an activity similar to Praziquantel with 100% worm mortality at 10 µg/ml [84].



2.42



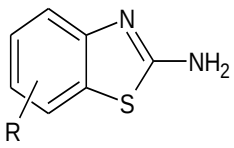
2.43



2.44

R= C_3H_7, $CH_2C_6H_5$, CH_2COOEt, *m*-nitro pyridine

3. Anti-Inflammatory Activity: In the recent years, a large number of benzothiazole based anti-inflammatory agents have been synthesized. Venkatesh *et al.* synthesized some novel 2-amino benzothiazole derivatives and evaluated them for anti-inflammatory activity. Test compounds (**3.1**) showed significant anti-inflammatory activity and it was noted that when the 2-amino benzothiazole is substituted at 4 or 5 positions with electron withdrawing groups like Cl, NO_2, OCH_3 increase in anti-inflammatory activity was found [85].

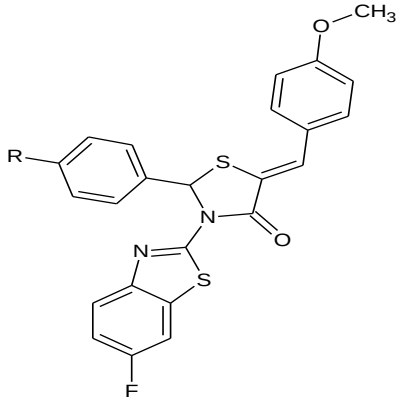


3.1

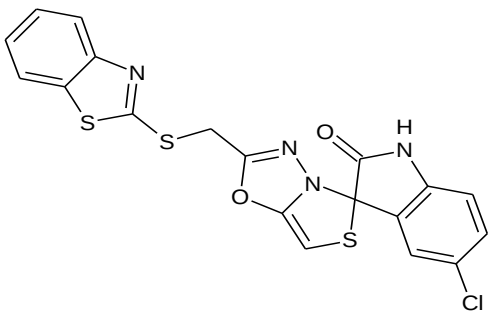
Structure no.	R group	Structure no.	R group
3.1 a	H	d	6-NO_2
b	5-Cl	e	6/4-methoxy
c	6-Cl	f	6-Br

A new series of 2-substituted benzothiazole derivatives was prepared by Shashank and co-workers. All synthesized compounds were evaluated for anti-inflammatory activity and (**3.2**) and (**3.3**) were found to be the most active among the series. The maximum activity may be due to presence of –F and –OCH_3 groups. The same series of compounds also showed good anticancer activity [86].

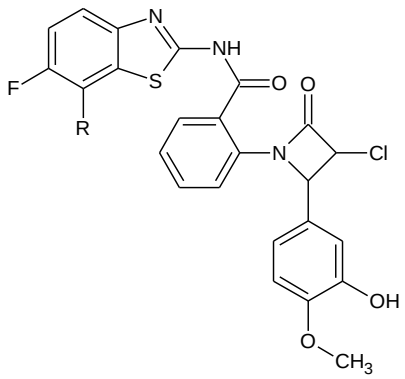
Kumar *et al* prepared 2'-((benzo[d]thiazol-2-ylthio)-methyl)spiro[indoline-3, 5'-thiazolo[4, 3-b][1, 3,4]-oxadiazol]-2-ones and examined them for anti-inflammatory action. (**3.4**) was the most potent anti-inflammatory agent [87].



3.2 (R=Cl), 3.3 (R=OCH_3)



3.4

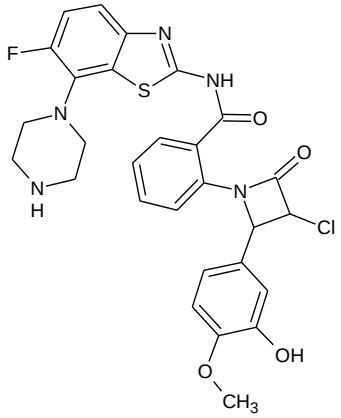


3.5

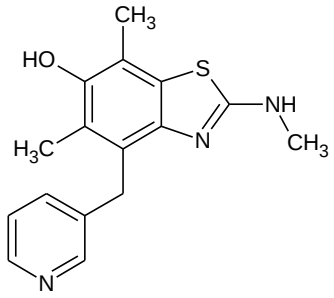
R=o/m- toluidine, m-chloroaniline

Various substituted 4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-flouro-7'-substituted (1, 3) - benzothiazol-2'-yl)-amido-2-phenyl]-3-chloro azetidin-2-one were synthesized and evaluated for anti-inflammatory activity. Among tested compounds (**3.5**) and (**3.6**) showed significant activity [88].

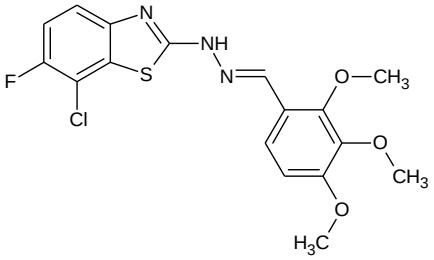
A series of 3-pyridylmethyl-substituted-2-amino-6-hydroxy benzothiazoles (**3.7**) and 7-chloro-6-flouro-N (substituted hydrazones)-benzothiazoles (**3.8**) was synthesized and tested for anti-inflammatory activity. Test compound (**3.7**) imparted a dual inhibitory action against leukotriene B_4 and thromboxane A_2, which was a result of direct action on 5-lipoxygenase and TXA_2 synthetase [89, 90].



3.6



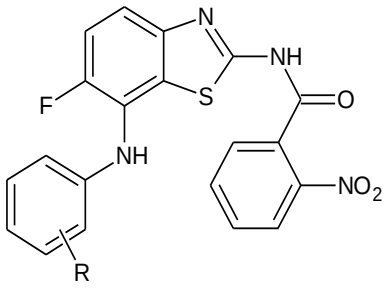
3.7



3.8

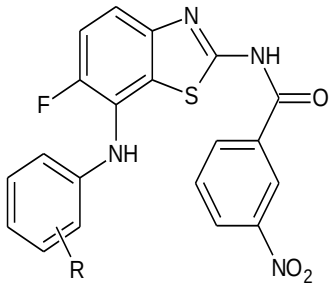
Synthesis of N-{6-fluoro-7-(substituted)-amino]-1, 3-benzothiazole-2-yl}-2/3/4-nitrobenzamides derivatives was carried out and screened for anti-inflammatory activity. The compounds (**3.9**), (**3.10**) were found to exhibit 70-78% inhibition in carrageenan induced paw oedema model in comparison to the standard Diclofenac (80%) [91].

2-Amino-heteroaryl-benzothiazole-6-anilides were discovered and evaluated for the anti-inflammatory activity. The 2-aminopyridyl analogue and 2-aminopyrimidinyl analogue (**3.11**) were identified as potent *lck* inhibitors with excellent cellular activities against T-cell proliferation [92].



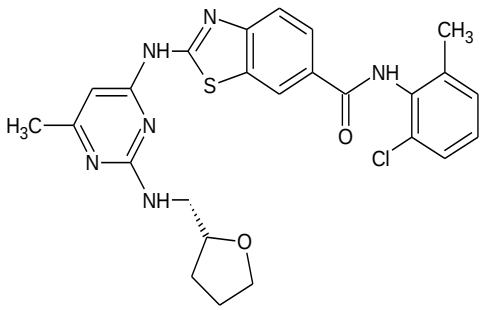
3.9

R=2,3,4-NO_2



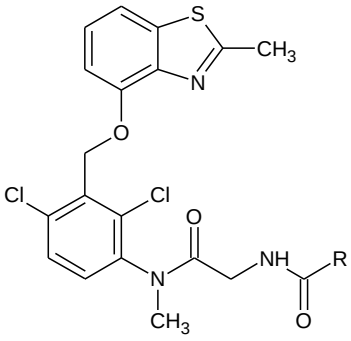
3.10

R=2-CH_3, 3- CH_3, 3-NO_2



3.11

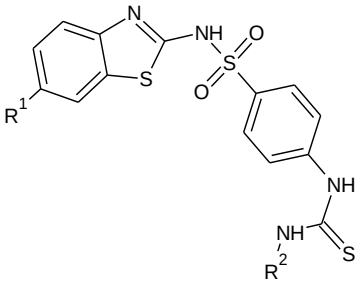
Anti-inflammatory activity of O-substituted-4-benzothiazoles (**3.12**) was determined and most of the derivatives were found potent inhibitors of Bradykinin B_2 receptor. The findings revealed that the 2-methyl group is an essential requirement for highly efficient antagonism of Bk B_2 receptor [93].



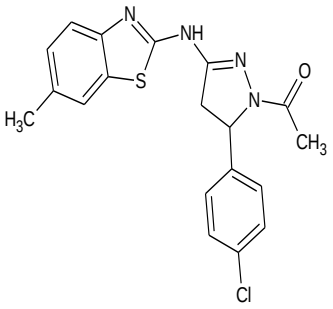
3.12

Structure no.	R group
3.12 a	-CH=CH-C_6H_5-(p-CH_3)
b	-CH=CH-C_6H_5-(p-CF_3)
c	-CH=CH-C_6H_5-(m-OCH_3)
d	-CH=CH-(2-furyl)
e	-CH=CH-$CH=CH_2$
f	-O-CH_2-C_6H_5

4. Anticonvulsant Activity: For anticonvulsant activity, a large number of benzothiazole derivatives were evaluated and found to possess significant activity against various types of seizures. In search of potent anticonvulsants containing benzothiazole moiety, a series of N-(6-substituted-1, 3-benzothiazol-2-yl)-4-{[(subsituted amino) carbonothioyl] amino} benzene sulfonamides (**4.1**) and prop-2-eneamido and 1-acetyl-pyrazolin derivatives of aminobenzothiazole (**4.2**) were synthesized and most of the compounds were active as anticonvulsants in MES and PTZ induced seizures [94, 95].



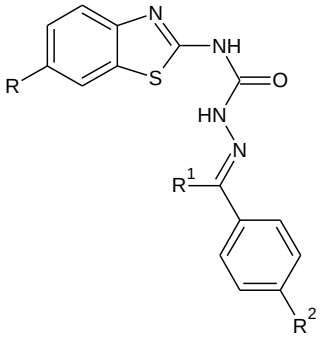
4.1



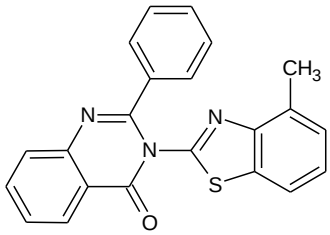
4.2

Structure no.	R^1	R^2
4.1 a	F	CH_3
b	F	C_2H_5
c	Cl	CH_3
d	Cl	C_2H_5
e	OCH_3	CH_3

A series of 1, 3-benzothiazol-2-yl semicarbazones (**4.3**) and 2-phenyl-3-(substituted benzothiazole-2-yl)-4[3H]-quinazolinone (**4.4** & **4.5**) was developed and evaluated against (MES) induced seizures and toxicity studies [96, 97].



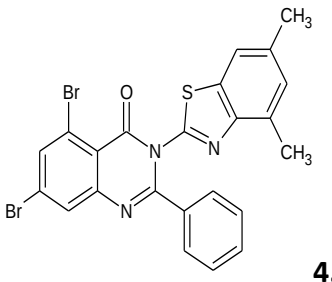
4.3



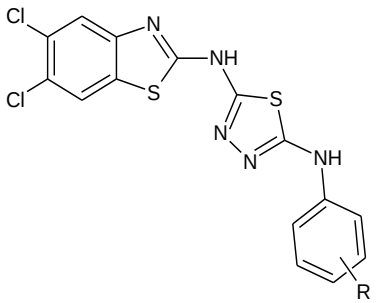
4.4

Structure no.	R	R^1	R^2
4.3 a	Cl	CH_3	H
b	CH_3	CH_3	NO_2
c	OCH_3	CH_3	NO_2
d	OCH_3	C_6H_5	H

Substituted 4-(*m*-hydroxy-*p*-methoxy phenyl)-1-[(6'-flouro-7'substituted (1, 3)-benzothiazole-2'-yl) amido-2-phenyl]-3-chloro azetidin-2-ones (**4.6**) and benzothiazol-2-yl thiadiazole derivatives (**4.7**) showed significant activity against PTZ and MES induced seizures [98, 99].



4.5

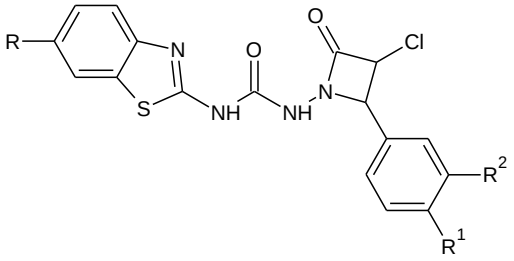


4.7

R= 4-Br, 3-Cl

4.6, R= *o,m,p*-nitroaniline; *o, m, p*-chloroaniline; aniline; *o, m, p*-anisidine; PABA

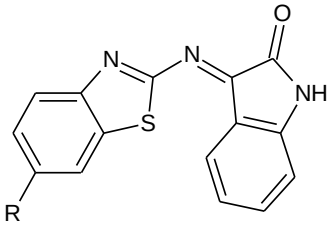
Anticonvulsant activity and toxicity studies of oxazetidin derivatives of benzothiazole (**4.8**) and isatin (indol-2, 3-dione) Schiff's bases (**4.9**) was carried out by Siddqui *et al*. Both of the compounds were found to exhibit 100% protection against MES induced seizures [100, 101].



4.8

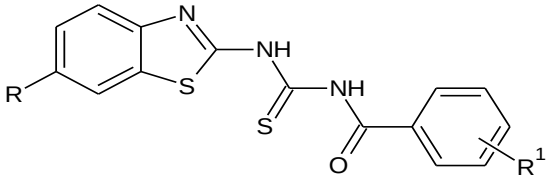
Structure no.	R	R^1	R^2
4.8 a	F	OH	H
b	CH_3	OH	H
c	CH_3	OCH_3	OCH_3

A series of 1, 3-benzothiazol-2-yl benzamides (**4.10**) was prepared by Siddiqui *et al* and carried out anticonvulsant, neurotoxicity and CNS depressant studies. Most of the compounds were found active in MES and PTZ screen with none of them neurotoxic or hepatotoxic. The compounds bearing the groups like F, CH_3, OCH_3 at the 6-position of benzothiazole ring with H, 2-Cl, 4-Cl substituted distant phenyl ring showed most excellent activity in MES and scPTZ tests [102].



4.9

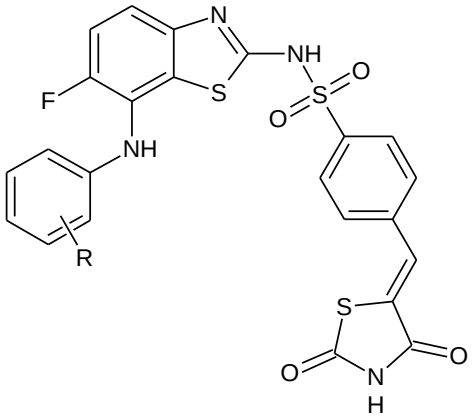
R=H, $N(CH_3)_2$, OCH_3



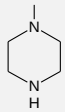
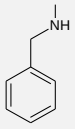
4.10

R= Br, Cl, F, NO_2, CH_3, OCH_3, R^1= H, 2-Cl, 4-Cl, 4-OCH_3

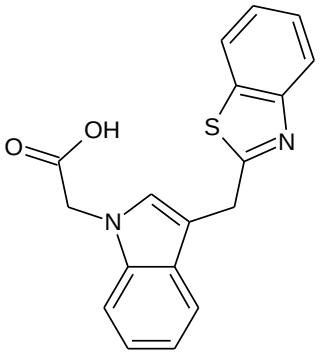
5. Anti-Diabetic Activity: In order to find potent anti-diabetic agents, several approaches had been made. Some of these approaches also led to synthesis of some benzothiazole based anti-diabetic agents. A series of 2-amino[5'(4-sulphonylbenzylidine)-2, 4-thiazolidinone]-7-chloro-6-flouro benzothiazoles were synthesized and examined for anti-diabetic activity. All the compounds of series (**5.1 a-f**) showed promising anti-diabetic activity [103].



5.1

Structure no.	R gp.
5.1 a	H
b	*m*-NO_2
c	*p*-COOH
d	
e	
f	

Zandt *et al.* prepared a novel series of conjugated indole-N-acetic acid with substituted benzothiazoles. All test compounds were evaluated for anti-diabetic activity and (**5.2 a-l**) were found most active compounds that inhibited aldose reductase with an IC_{50} of 5-12 nM and (**5.2b**) was most promising agent with IC_{50} 5 nM [104].

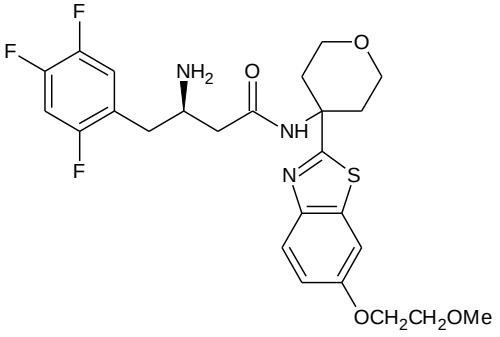


5.2

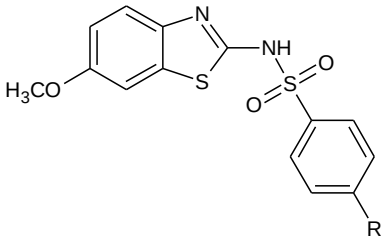
Structure no.	Substituents	Structure no.	Substituents
5.2 a	5'-F	**5.2 g**	5-morpholino, 4'-F, 5'-F, 7'-F
b	4'-F, 5'-F, 7'-F	**h**	6-F, 4'-F, 5'-F, 7'-F
c	2-CH_3, 4'-F, 5'-F, 7'-F	**i**	6-Cl, 4'-F, 5'-F, 7'-F
d	2-Cl,4'-F,5'-F,7'-F	**j**	7-F, 4'-F, 5'-F, 7'-F
e	5-CH_3,4'-F, 5'-F, 7'-F	**k**	7-Cl, 4'-F, 5'-F, 7'-F
f	5-OCH_3,4'-F, 5'-F, 7'-F	**l**	7-CH_3, 4'-F, 5'-F, 7'-F

A series of dipeptidyl peptidase inhibitors IV for the treatment of type 2 diabetes was synthesized and evaluated. The compound (3R)-3-amino-4- (2, 4, 5-trifluorophenyl)- N- {4- [6- (2- methoxyethoxy)- benzothiazol- 2- yl] tetrahydropyran- 4- yl}butanamide (**5.3**) was found to reduce the blood glucose level to a significant extent in an oral glucose tolerance test [105].

Anti-diabetic activity of novel N-(6-substituted-1, 3-benzothiazol-2-yl) benzenesulfonamides derivatives was determined on a NIDDM rat model. The compounds (**5.4**) and (**5.5**) were found to be potent inhibitor of 11β-hydroxy steroid dehydrogenase type-1 and showed 38-53% inhibition at 10μM concentration [106].

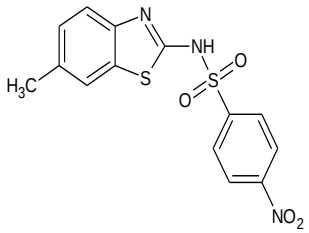


5.3

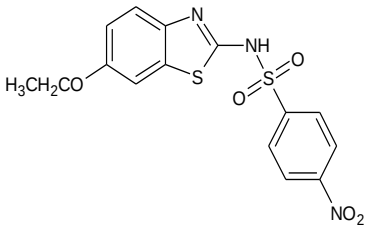


5.4 (R=H), 5.5 (R= NO_2)

Further, Paoli and co-workers prepared a small library of 2-arylsulfonyl aminobenzothiazoles and screened them for protein tyrosine phosphatase 1B inhibition. The most active compounds (**5.6**), (**5.7**) were observed rapid reversible inhibitors of PTP-1B and significantly lowered plasma gluose concentration[107].

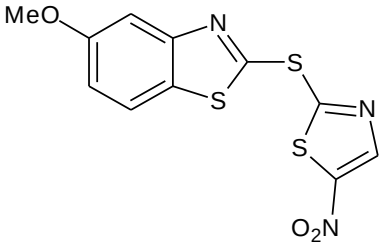


5.6

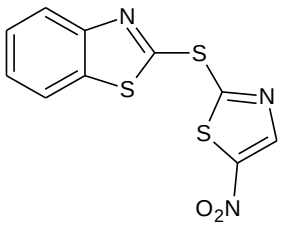


5.7

The novel 2-(5-nitrothiazol-2-ylthio) benzo [d] thiazole derivatives were discovered and screened for their ability to inhibit *c-Jun-N-terminal kinase*. The compounds (**5.8**) and (**5.9**) demonstrated good *in-vivo* activity in a diabetic model of insulin resistance[108].

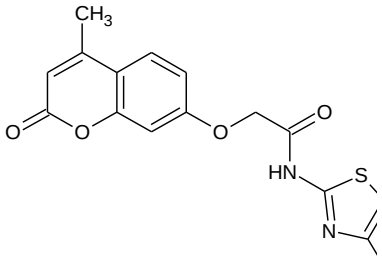


5.8

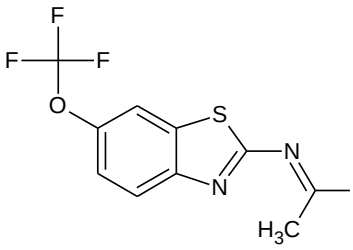


5.9

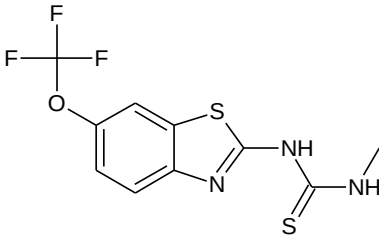
6. Miscellaneous Activities: In spite of all these activities, benzothiazoles are also active as antipsychotic agents (**6.1**), neuroprotective agents (**6.2**) and (**6.3**) and diuretic (**6.4**). Benzothiazole nucleus was found to possess a significant atypical behavior and a good potency to block 5-HT receptors and a good ability of fully antagonizing Glutamate release [109-111].



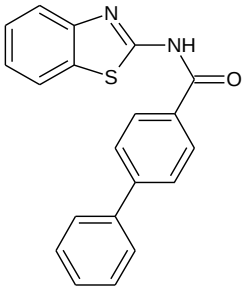
6.1



6.2



6.3



6.4

CONCLUSION: This review shows that 2-substituted benzothiazoles own a wide spectrum of biological activities. The benzothiazole substituted quinol ethers and esters, substituted 2-(4-amino phenyl) benzothiazoles and 2-carbonitrile, 4-thiazolidinone and and phthalimide linked benzothizoles are having specifically awesome antitumor activity. Significant antibacterial activity is displayed by some novel triazole, oxadiazole and pyrimidine derivatives of benzothiazoles. Various 2-substituted benzothiazoles are found to have potent anti-inflammatory activity. An interesting anticonvulsant activity is demonstrated by a number of azetidine2-one and semicarbazone analogues of benzothiazole. The 2-hydrazino benzothiazoles are found to be active as antitubercular agents, whereas biphenyl benzothiazole-2-carboxamide is showing carbonic anhydrase inhibitory action.

The biological profiles of this new generation of benzothiazoles represent much progress with regard to older compounds.

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