ejpmr, 2022, 9(1), 223-237

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A COMPREHENSIVE REVIEW ON BENZOTHIAZOLE

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Article Received on 15/11/2021 **Article Revised on 05/12/2021** **Article Accepted on 25/12/2021**

ABSTRACT

Benzothiazole is a heterocyclic compound possessing 5-membered ring containing sulphur and nitrogen at 1, 3-position connected with a benzene ring. Many authors adopted different schemes for synthesis of various benzothiazole derivatives and evaluated them for different activities. Numerous molecules that have benzothiazole skeleton shows anticancer, antibacterial, antifungal, anti-inflammatory, analgesic, anti-HIV, antioxidant, anticonvulsant, antitubercular, antidiabetic, antileishmanial, antihistaminic, antimalarial and other pharmacological activities.

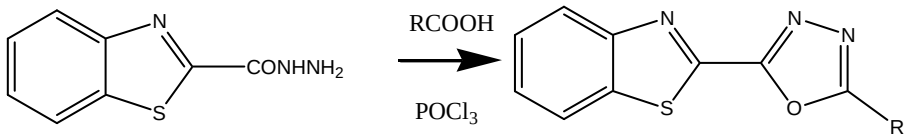
KEYWORDS: benzothiazole, antibacterial, antidiabetic.

INTRODUCTION

Benzothiazole is a heterocyclic compound which containing two hetero atoms sulphur and nitrogen. Benzothiazole possessing 5-membered ring containing sulphur and nitrogen at 1,3-position connected with a benzene ring. Benzothiazole includes various natural products and pharmaceutical agents. Benzothiazole and its derivatives shows numerous pharmacological effects that has useful information in the search of new therapeutic agents.[1] Among all the benzothiazole derivatives 2-substitued benzothiazole have been found to be more potent. Heterocyclic compounds analogues of benzothaizoles and derivatives possessing numerous biological and pharmacological activities such as anticancer, antibacterial, antifungal, antiinflammatory, analgesic, anti-HIV, antioxidant, anticonvulsant, antitubercular, antidiabetic, antileishmanial, antihistaminic, antimalarial.[2]

Mostly 2-aryl benzothiazole derivatives having anticancer and radioactive amyloid imaging properties. 2-aminobenzothaizole when fused with other heterocyclic moieties it shows good pharmacological action, toxicity lowering and anticancer activity.[3]

S.M. shanta kumar *et al.* (2009) reported the synthesis of some novel 2-(5-substituted-1, 3, 4-oxadiazole-2-yl)-1, 3- benzothiazole (1a-1j) derivatives by refluxing different aryl acids with benzothiazolyl carboxyhydrazide in the presence of phosphoryl chloride and evaluated their invitro antibacterial activity. A mixture of 1,3-benzothiazole-2-carboxyhydrazide, with appropriate aromatic acid in the presence of phosphoryl chloride (10 mL) was refluxed for 6-8 hours on water bath. After cooling the reaction mixture was poured with the help of stirring into crushed ice bath which shown in fig. 1. Then the solid compound was filtered, washed and recrystallized with ethanol to get the final products.(1a-1j) The *invitro* antibacterial activity of these synthesized compounds against gram positive and gram negative bacterial strains such as *Bacillus subtilis, Bacillus pumilus, Escherichia coli* and *Pseudomonas aureginosa*were evaluated The compound 1b, 1d, 1g and 1h have more antibacterial activities due to the presence of bromo group at meta position in 1b, chloro group at meta position in 1d, 2 chloro groups at meta position in 1g and nitro group at para and ortho position in 1h.[4]-[7]



1,3-benzothiazole-2-carboxyhydrazide

2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3- benzothiazole (3a-j)

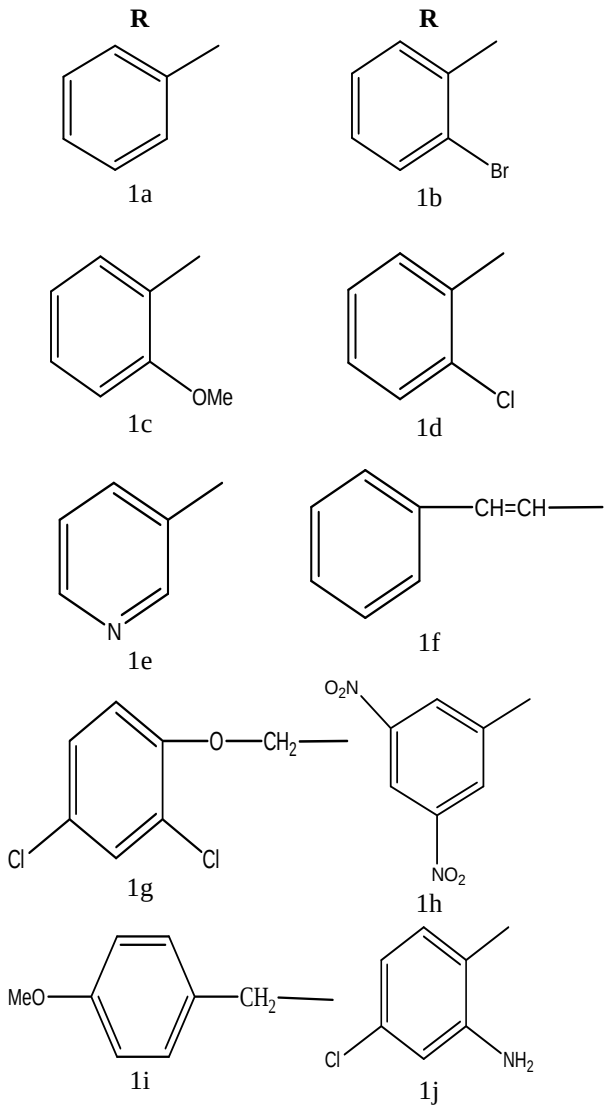
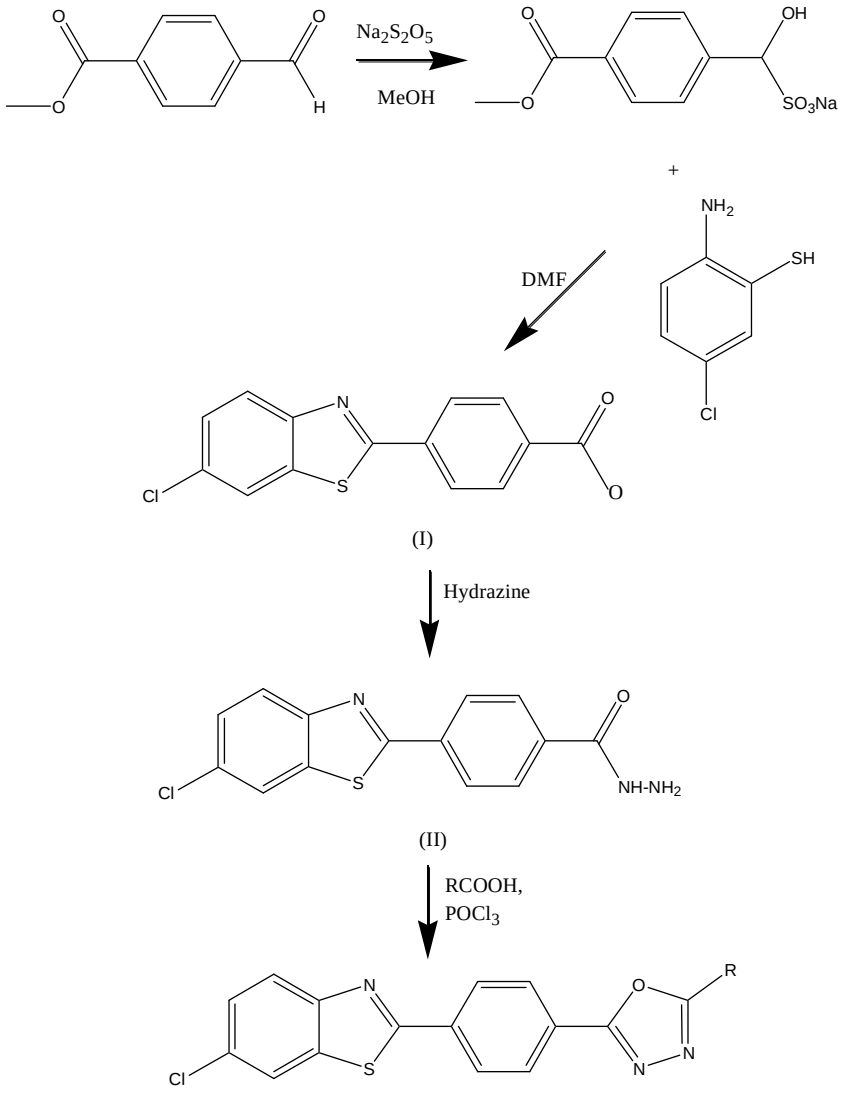


Fig.1

Mohammed Gollapalli *et al.* (2019) gave the scheme for the synthesis of Benzothiazole based oxadiazolederivatives (2a-2w) from mixture of methyl 4-formylbenzoate and sodium metabisulfite in the presence of methanol gives sodium hydroxy (4-methoxycarbonyl)phenyl methane sulfonate intermediate (I). The intermediate (I) was reacted with 2-amino-5-chlorobenzothiol in the presence of dimethyl formamide which gives methyl 4-(6-chlorobenzo[d]thiazol-2-yl) benzoate intermediate (II). 4-(6-chlorobenzo[d]thiazol-2-yl)benzo hydrazide intermediate (III) was prepared by mixing intermediate II with hydrazine hydrate in the presence of methanol. Then intermediate (III) was reacted with substituted aromatic carboxylic acids in the presence of phosphorus oxychloride which gives benzothiazole based oxadiazole derivatives which are given in fig.2.

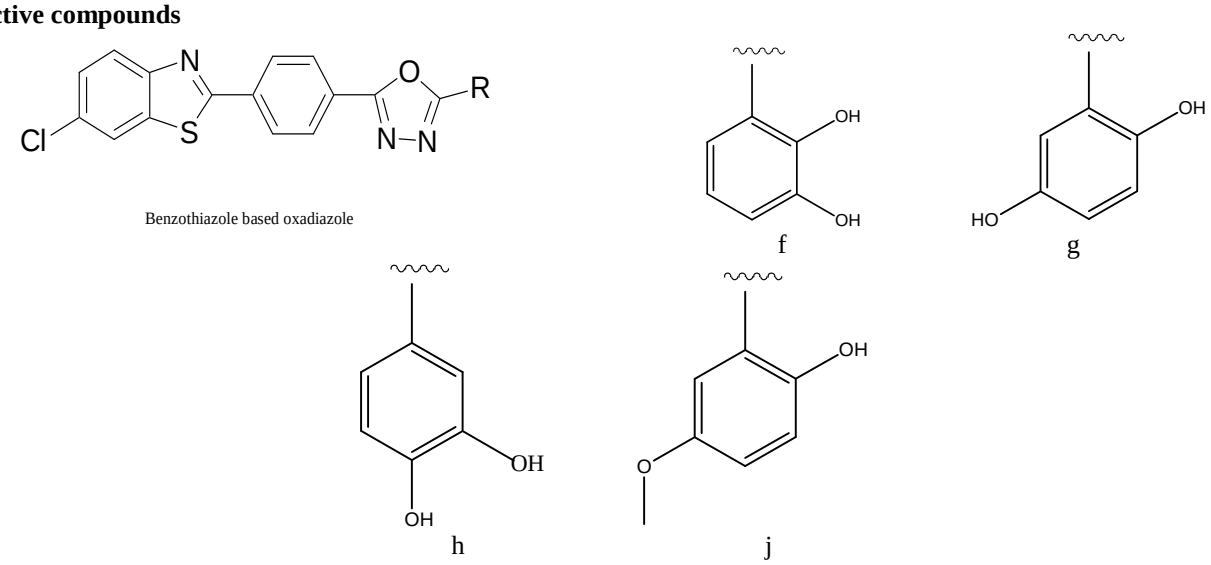
Molecular docking of these 23 synthesized compounds evaluated that compound 2f, compound 2g, compound 2h and compound 2j were most active compounds which showed several hydrophobic interactions with active site residues of α-glucosidase enzyme (fig.3) due to the presence of hydroxyl group at meta position in 2f, two hydroxyl group at ortho and meta position in 2g, two hydroxyl group at ortho and meta position in 2h and hydroxyl group at para and acetyl group at meta position in 2j.[8]-[10]



Benzothiazole based oxadiazole

Fig.2

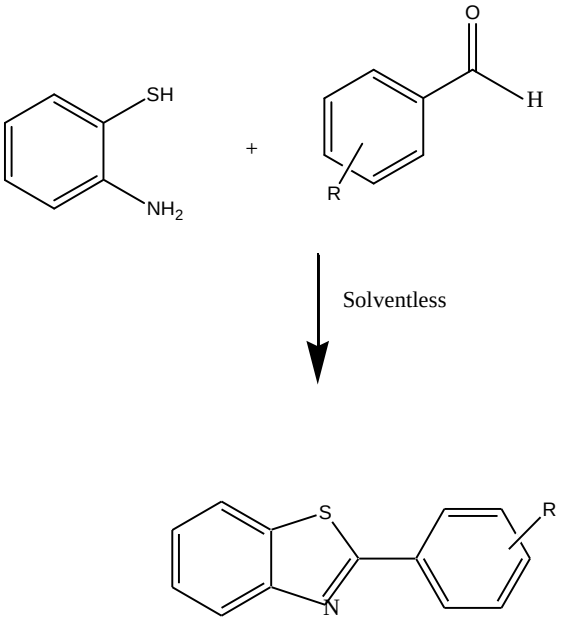
Active compounds



Benzothiazole based oxadiazole

Fig.3

Kan *et. al*. (2017) reported the reaction between 2-aminophenothiol and substituted benzaldehyde in the presence of ultrasound probe irradiation formed (3a-3i) benzothiazole derivatives which are shown in fig. 4. The yield of these synthesized compounds were ranging from 65 – 83%. The final synthesized compounds were purified by silica gel column chromatography (Hexane: Ethyl acetate = 9.5:0.5, v/v) except for compound i which was purified with a different solvent system (Hexane: Ethyl acetate = 8.5:1.5, v/v).[11]-[16]

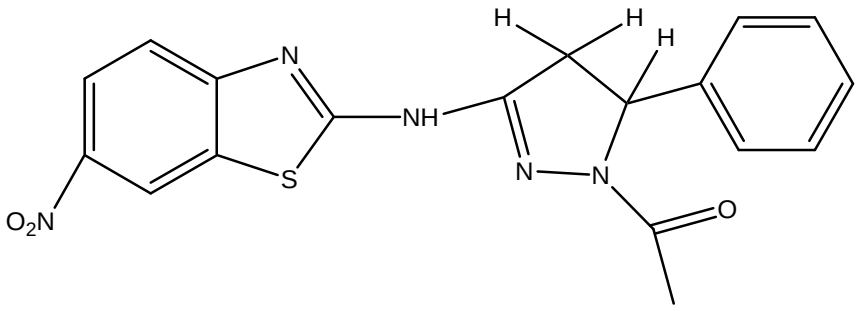


Compounds	R
3a	H
3b	2-Cl
3c	3-Cl
3d	4-Cl
3e	2-F
3f	4-F
3g	4-Br
3h	4-$CH(CH_3)_2$
3i	4-OCH_3

Fig.4

Usman Abdul fatai *et. al.*(2017) reported 37 amino-benzothiazole derivatives by *In silico* studies which include Quantitative structure-activity relationship (QSAR) and molecular docking studies having anticonvulsant activity. The QSAR studies of synthesized compounds was performed by Genetic function approximation (GFA) of Material studio software version8. With the help of Autodock version 4.0 of pyrx software the molecular docking of ligands (aminobenzothiazolederivatives) with the receptor ($GABA_{AT}$) was performed. Amnerkar and Bhusari, et.al. (2010) synthesized amino-benzothiazole derivatives and these derivatives were used for molecular docking.

From 37 synthesized amino-benzothiazole derivatives, 29 compound was the most active compound which is given in fig.5. The molecular docking studies of 29 compound shown the the best binding affinity of -9.1 kcal/mol was bounded by hydrophobic pockets of amino residues among all the synthesized compounds due to the presence of nitro group at meta position. The aminobenzothiazole derivatives will bind tightly to $GABA_{AT}$ gives high binding affinity of -9.1 kcal/mol and inhibit the enzyme through amino acid residues.[17]-[22]



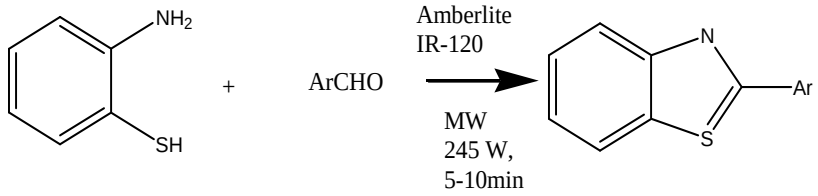
1-[3-(6-Nitro-benzothiazol-2-ylamino)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-ethanone

Fig. 5

Mohit Chhabra *et. al.* (2015) delivered the scheme for the synthesis of 2-arylbenzothiazole derivatives. 2-aminothiophenol was reacted with substituted benzaldehyde in the presence of Amberlite IR-120 which is used as a solid support and acid catalyst under microwave conditions give 2-arylbenzothiazole

derivatives (4a-4e) which are shown in fig. 6. Compounds 4b, 4d and 4e showed the maximum antimicrobial and anticancer activity due to presence of halogen functional group on benzothiazole ring. The presence of fluorine atom which is electronegative group in Compound 4d at para position having high cytotoxicity activity. The antimicrobial activity of the synthesized 2-arylbenzothiazole derivatives showed adverse effect when the electron donating group such as methyl, hydroxyl, methoxy present on benzene ring.

To evaluate the antimicrobial activity of synthesized derivatives two strains were used *Staphylococcus aureus* and *Bacillus subtilis*. The cytotoxicity activity of all the synthesized compounds was evaluated usingstandard 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) bioassay.[23]

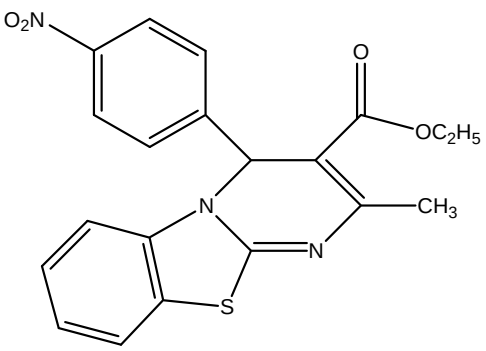


Compounds	Ar
4b	2-chlorobenzaldehyde
4d	4-fluorobenzaldehyde
4e	2-bromobenzaldehyde

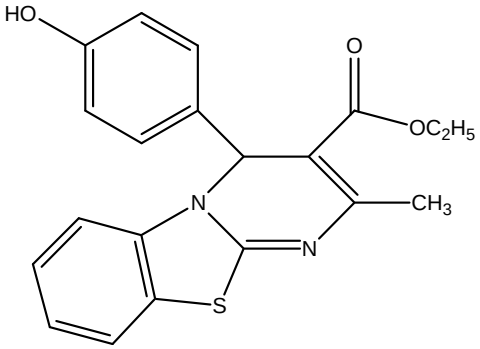
Fig.6

Synthesis of 4H-pyrimido[2,1-b][1,3]benzothiazole derivatives(5a-5h) was reported by Pramod K. Sahu *et.al*. (2011). They synthesized it by mixture of substituted aldehyde, ethyl acetoacetate, and 2-amino benzothiazole were heated in solvent-free conditions using aluminum chloride as a catalyst at temperature 60–70˚C which is shown in fig. 7. (One-pot three-component reaction)

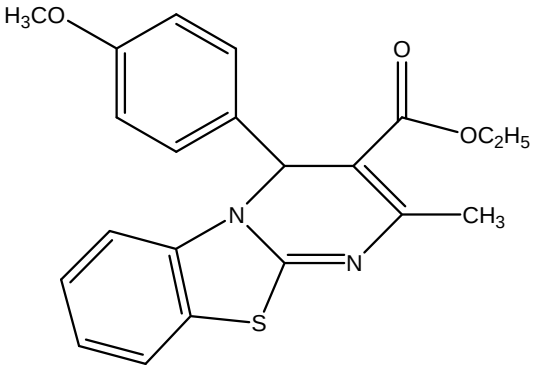
These compounds shows antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus aureus*. Compounds 5c, 5d, 5f, 5g, and 5h have shown maximum activity against all bacterial strains due to presence of 1-dimethylaminealdehyde in 5c, 1-nitroaldehyde in 5d, 1-hydorxyaldehyde in 5f, 1-methoxyaldehyde in 5g, and 3,5-dichloroaldehyde in 5h as their starting material.[24]-[28]



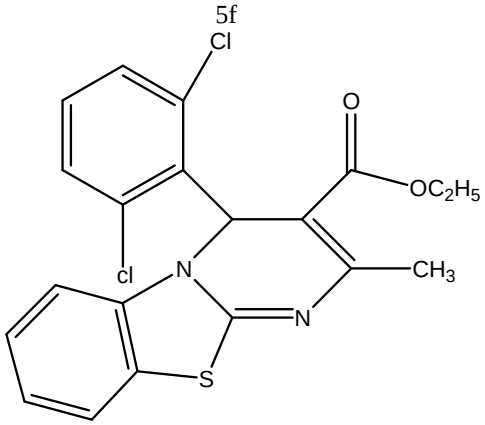
5d



5f



5g



5h

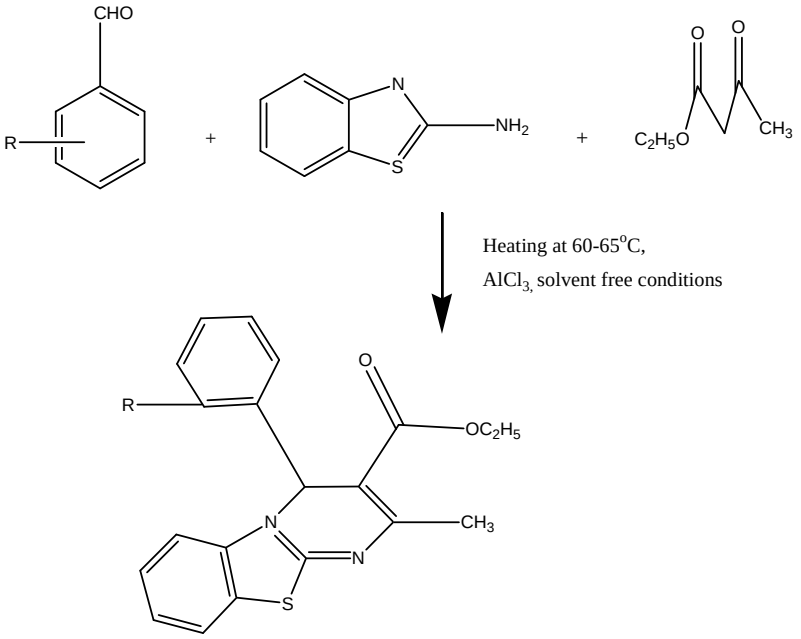


Fig.7

Akhilesh Gupta *et.al.*(2019) reported the scheme for the synthesis of novel methoxy substituted benzothiazole derivatives (6a to 6i) by the treatment of 3-chloro-4-methoxyaniline with potassium thiocyanate in the presence of bromine and ammonia gives intermediate I (4-chloro-5-methoxybenzo[d]thaizol-2-amine). Further intermediate I was reacted with substituted benzoyl chloride generates intermediate II (N-(4-chloro-5-methoxybenzo[d]thaizol-2-yl)benzamide. Then the intermediate II was treated with substituted anile gives the final product which are given in fig.8.

These novel synthesized novel methoxy substituted benzothiazole derivatives were screened for their antifungal activity against *Aspergillus niger*. Compound 6e and 6f showed maximum antifungal activity against *Aspergillus niger* due to presence of 3-nitro group in 6e and nitro group at 4th position in 6f.[29]-[30]

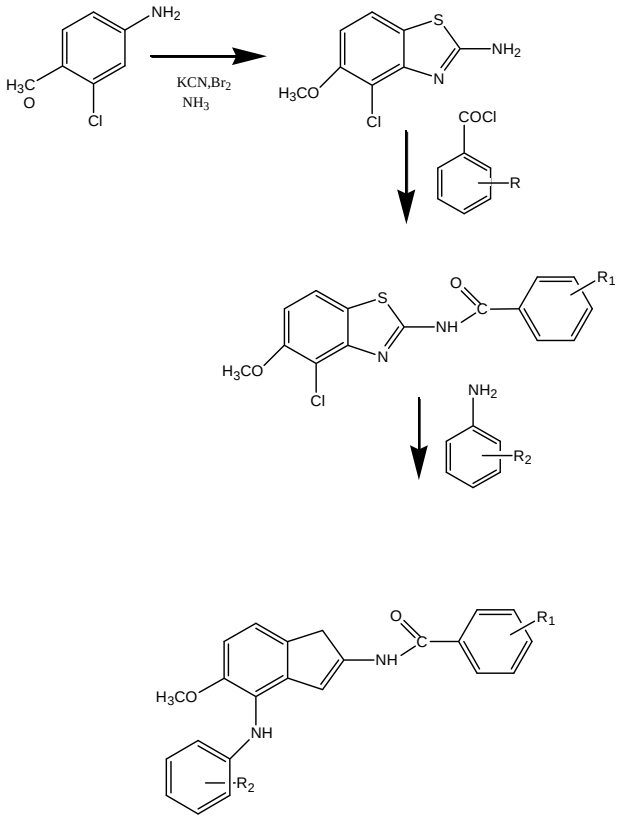
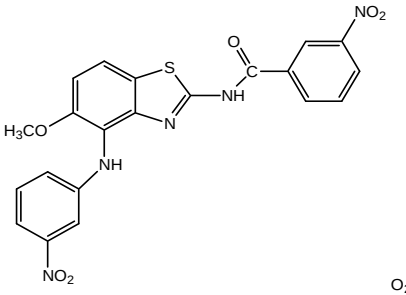
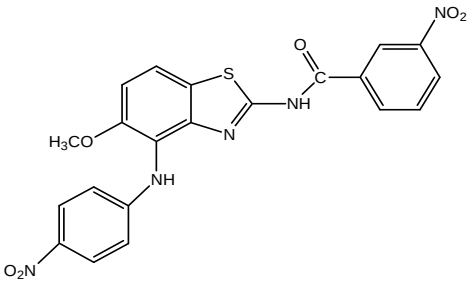


Fig.8



6e



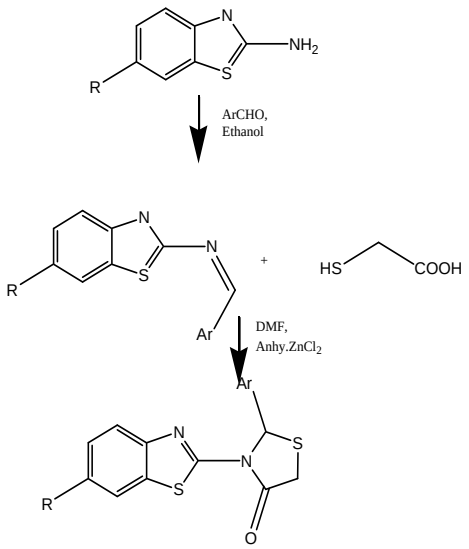
6f

Deepak Pareek *et. al.*(2010)planned the scheme for synthesis of 2-aryl 3-(-6-substituted benzothiazolyl)-1,3-thiazolidine- 4-ones derivatives (7a-7l) from a mixture of 2-amino-substituted benzothiazole and substituted aromatic aldehydein the presence of ethanol which are shown in fig.9.

These all synthesized compounds were screened for their *in vitro* antibacterial activity against *Escherichia coli, Klebsiella species, Micrococcus lutius and Staphylococcus aureus*. 7a and 7l showed higher antibacterial activity against *Escherichia coli.*

7a, 7g, 7l gave potent antifeedant activity against larvae of *Spodoptera litura.*

7a, 7b, 7e, 7g, 7h exhibited good acaricidal activityagainst *Tetranychus urtica*.[31]



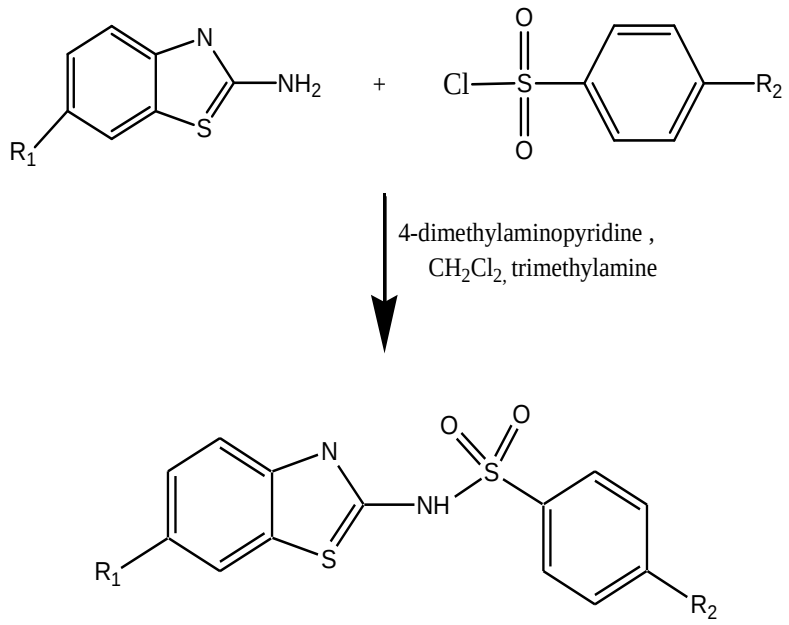
Compounds	R	Ar
7a	Cl	C_6H_5
7b	Cl	o-C_6H_4OH
7e	OC_2H_5	C_6H_5
7g	OC_2H_5	*p*-$C_6H_4OCH_3$
7h	OC_2H_5	*p*-C_6H_4Cl
7l	CH_3	*p*-C_6H_4Cl

Fig.9

Synthesis of N-(6-substituted-1,3-benzothiazol-2-yl)benzenesulfonamides (8a-8h) was done by Hermenegilda Moreno-Diaz *et. al.* (2008) from 2-amino-6-substituted benzothiazoles by coupling reactionwith arylsulfonyl chlorides, in the presence of 4-dimethylaminopyridine as a catalyst and triethylamine which are shown in fig.10. with the help of non-insulin-dependent diabetes mellitus rat model the synthesized compounds were evaluated for their *invivo* antidiabetic activity. All synthesized derivatives were *in vitro* evaluated as 11b-hydroxy-steroid dehydrogenase type 1 (11β-HSD1) inhibitors by molecular docking program Genetic Optimization for Ligand Docking (GOLD).

Compound 8c showed maximum *in vivo* antidiabetic activity due to presence of unsubstituted position 4 of benzenesulfonamide. The *invivo* antidiabetic screening of compound 8f showed higher antidiabetic activity due to presence of methyl group at position 4 of benzenesulfonamide. Compound 8d having substitution at p-position with nitro group showed higher antidiabetic activity.

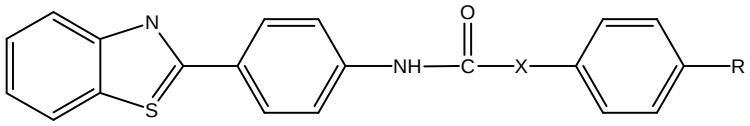
Compound 8c and 8d showed higher affinity for 11β-HSD1 due to presence of methoxy group attached at position 5 of the benzothiazole ring in both compounds.[32]



Compounds	R_1	R_2
8c	$-OCH_3$	-H
8d	$-OCH_3$	$-NO_2$
8f	$-OCH_2CH_3$	$-CH_3$

Fig.10

Kayhan Bolelli *et. al.*(2011) synthesized novel 2-[4-(4-substitutedbenzamido/phenylacetamido)phenyl]benzothi azolesderivatives by reaction between 2-(4-aminophenyl)benzothiazole in the presence of sodiumbicarbonate, and ether. The antimicrobial activity of these synthesized derivatives was measured against *Klebsiella pneumoniae* RSKK 574, *Pseudomonas aeruginosa* ATCC 25853, *Escherichia coli* ATCC 25922, *K. pneumoniae* isolate, as Gram-negative bacteria, *Bacillus subtilis* ATCC 6633, *Staphylococcusaureus* ATCC 25923, as Gram-positive bacteria. Compound 9d showed higher activity against *Staphylococcus aureus* in which rifampicin and ofloxacin used as a standard drug. Compounds 9i and 9k gives the maximum antibacterial activity against *Bacillus subtilisin* which ampicillin trihydrate, gentamicinsulfate, rifampicin used as a reference drugs which are given in fig.11.[33]-[35]

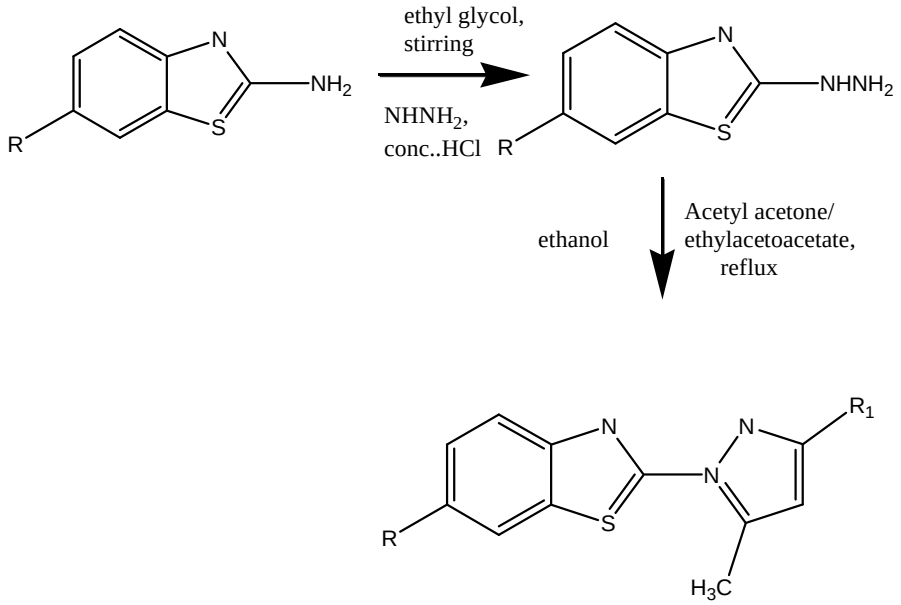


Compounds	X	R
9d	-	C_2H_5
9i	CH_2	Br
9k	CH_2	OCH_3

2-[4-(4-substitutedbenzamido/phenylacetamido)phenyl]-benzothiazole derivatives

Fig.11

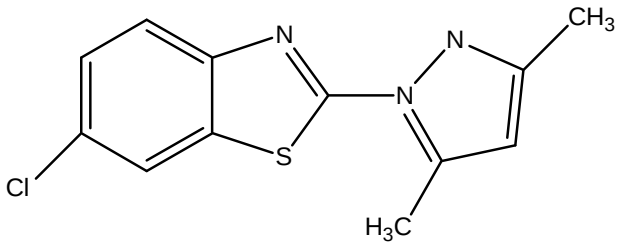
Smita Pawar *et. al.* (2019) planned the scheme for the synthesis of 6-Substituted 2-(3-substituted 5-Methyl 1H-Pyrazol-1yl) benzothiazole derivatives 10a-10j. Intermediate 6-Substituted 2-hydrazino benzothiazole was obtained by reacting 6-Substituted 2-amino benzothiazole in the presence of ethylene glycol, hydrazine and concentrated hydrochloric acid. Then this intermediate was reacted with acetyl acetone & ethylacetoacetate in the presence of ethanol to get final product which is shown in fig.12 which shows antimicrobial activity.



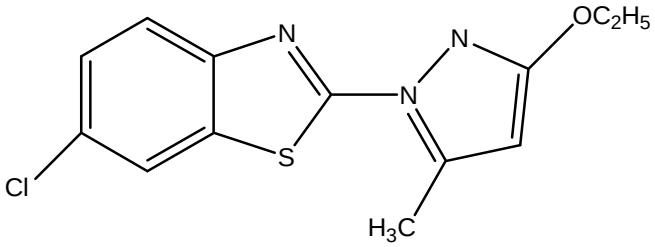
6-Substituted
2-(3-substituted,5-methyl1H-pyrazol-1-yl)benzo[d]thiazole

Fig. 12

Among all the synthesized compounds 10c and 10d showed maximum antibacterial and antifungal activities against gram-positivebacteria *B. subtilis* (ATCC 6633) *S. aureus*(ATCC 9144) and gram-negative bacteria *E. coli* (ATCC 25922) and *P. Aeruginosan* in which Ciprofloxacin and fluconazole were used as astandard for antibacterial activity and for antifungal activity.[36]-[39]



10c



10d

Manavendra K. Singh *et. al.*(2012)prepared benzothiazole 1, 2, 3-triazole analogs (11a to 11t) using 2-aminobenzothiazole and propargyl bromide in the presence of potassium carbonate in dry acetone gives intermediate I (benzothiazol-2-yl-di-prop-2-ynyl-amine) then this interemediate reacted with substituted aromatic azides to get the final product which is given in fig. 13. Synthesized compounds (11a to 11t) were screened for their antibacterial activity against Gram+ bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*), Gram - bacteria (*Salmonella typhi, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Shigella boydii*) & evaluated their antifungal activity against *Candida tropicalis, Candida albicans, Candida krusei, Cryptococcus neoformans.*

Compounds 11b and 11c showed potent antibacterial activity against *E. faecalis*due to presence of 3-chloro-4-fluoro and 4-chlorosubstituted on benzenering. 11e containing 2,4-difluorosubstituted benzene showed maximumpotency against all strains.

The compound 11a revealed the good antifungal activity against *Aspergillusniger* and *A. fumigatus*in which fluconazole is used as standard drug. The compound 11 n showed potent activity against all the strains used to evaluate the antifungal activity.[40]

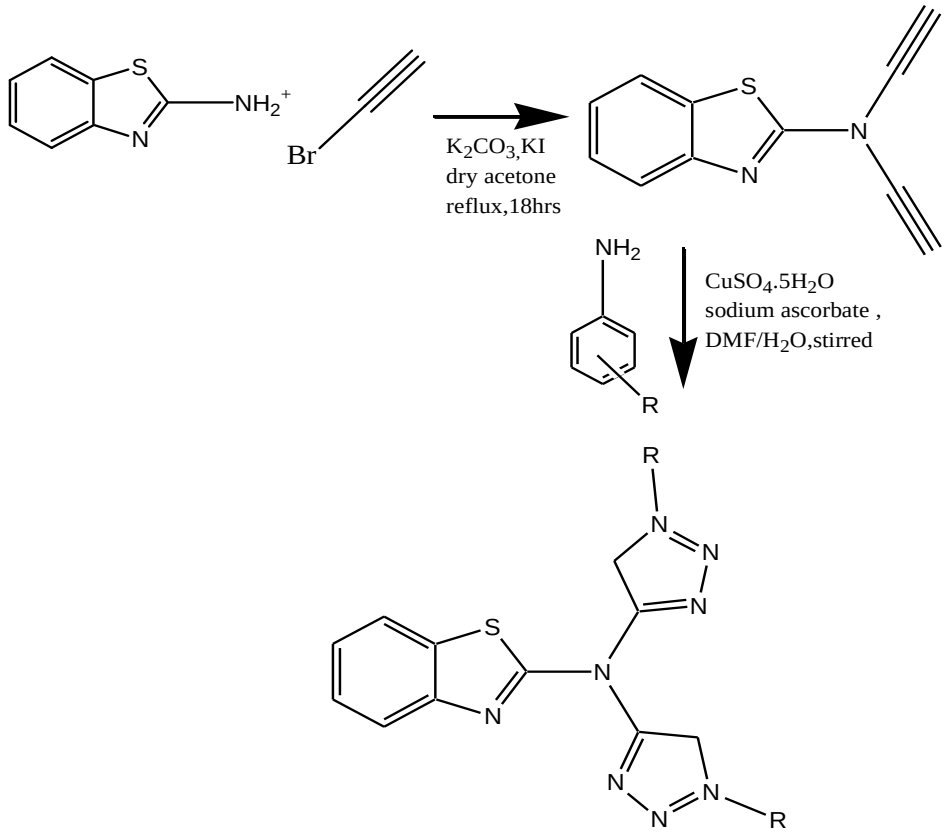
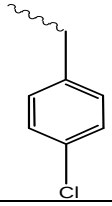
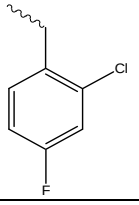
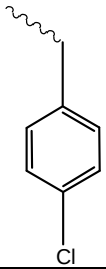
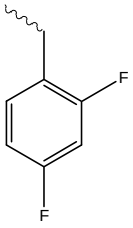
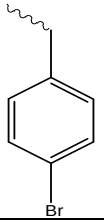
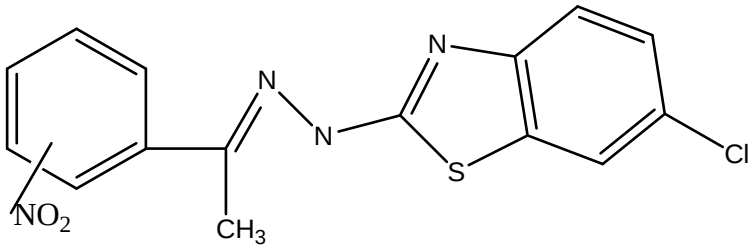


Fig. 13

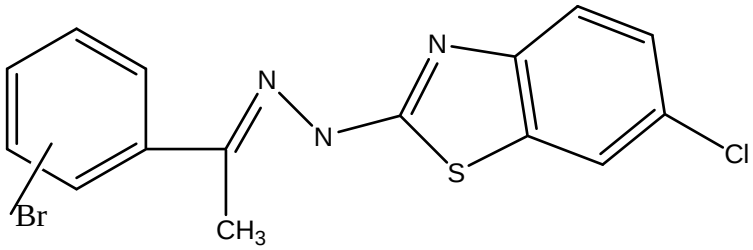
Table no. 1: Most active 1,2,3-triazole benzothiazole derivatives.

Compounds	R	Compounds	R
11a		11b	
11c		11e	
11n			

1, 3-benzothiazole-2-yl-hydrazone derivatives (12a-12j) were prepared by Vivek Asati *et.al.*(2011) showed *in vitro* antimicrobial activity. These synthesized compounds were showed their antimicrobial activity by using four pathogenic bacterial strains, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas alkaligenes* and three fungal strains *Aspergillus niger*, *Rhizopus oryzae* and *Candida albicans* were used. Due to the presence of electron releasing group (CH_3) at R_1 position and electron withdrawing group (NO_2, Br) at position R_2 in compounds 12a and 12b showed good antimicrobial activity against *A. niger* and *C. albicans*among all the synthesized compounds.[41]



12a



12b

Ayyadurai Jerad Suresh*et. al*. (2017) delivered the scheme for synthesis of Imino-3-(6-substitutedbenzo[d]thiazol-2-yl) thiazolidin-4-one derivatives which is shown in fig.14.

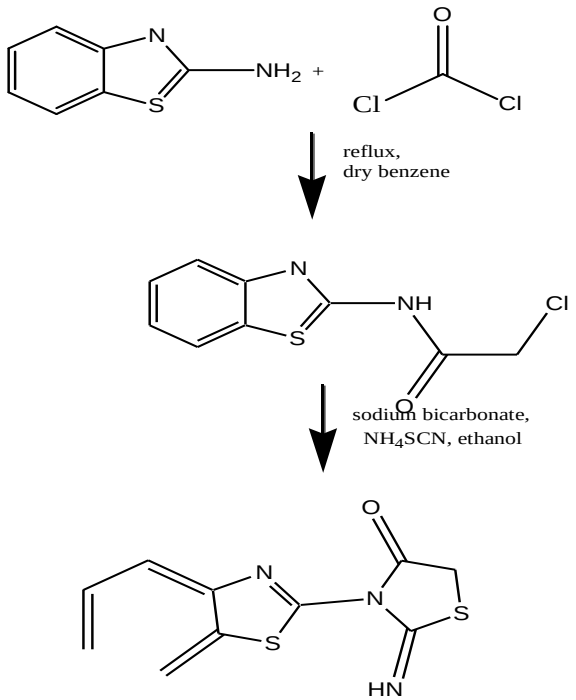


Fig.14

These all synthesized compounds were docked by AutoDock against Glutamine Synthetase I to evaluate their Anti Tubercular activity.[42]

Novel 2-[3-(substituted phenyl)-4-formylpyrazol-1-yl]-6-chloro benzothiazole derivatives (13a-13g) have been synthesized by Deepa Chauhan *et. al.*(2015) showed antibacterial activity. These derivatives were synthesized by reacting the substituted hydrazones aromatic ketones with 6-chloro benzothiazol-2-yl hydrazine under microwave irradiation through Vilsmeier-Haack reaction which is shown in fig.15. These synthesized compounds were evaluated for their antimicrobial activity against gram positive bacteria [*Staphylococcus aureus*(ATCC-25923)] and gram-negative bacteria [*Escherichia coli* (ATCC25922), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella 234neumonia* (MTCC-432)] by measuring zone of inhibition. Due to presence of of electron withdrawinggroups (Cl, Br, NO_2) on 4-position of phenyl ring in compounds 13a, 13b and 13g gives higher antibacterial activity.[43]

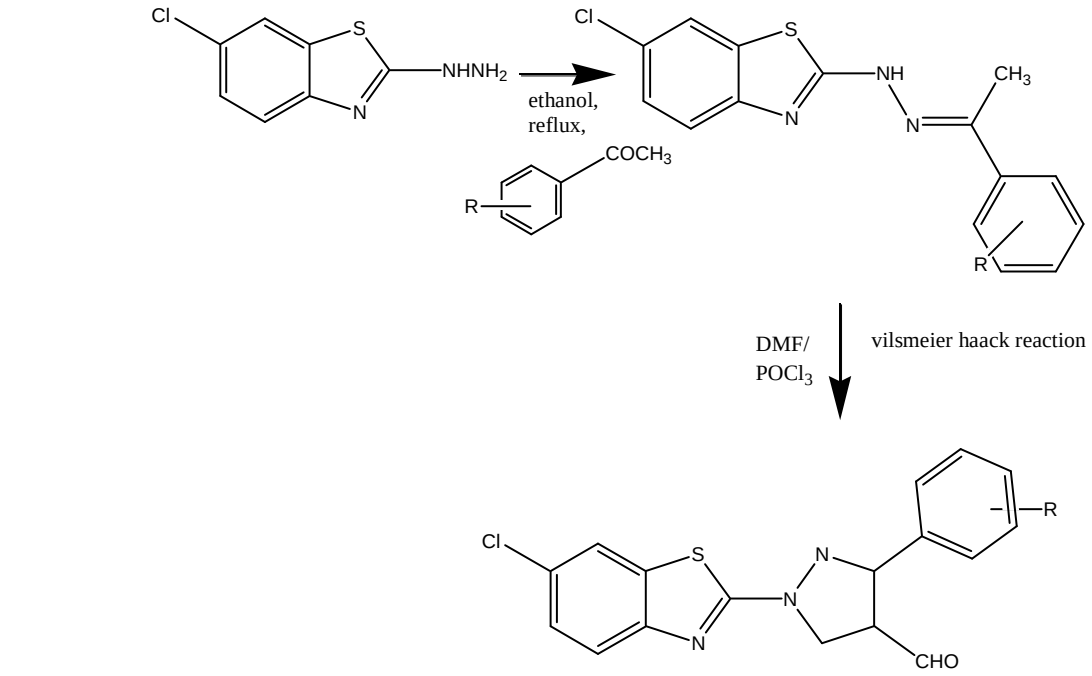
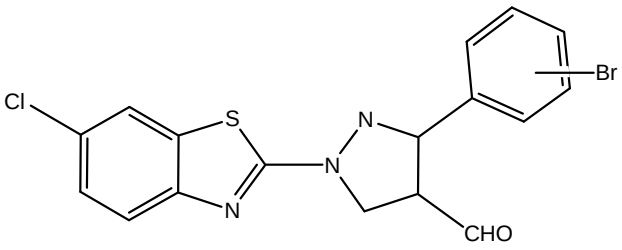
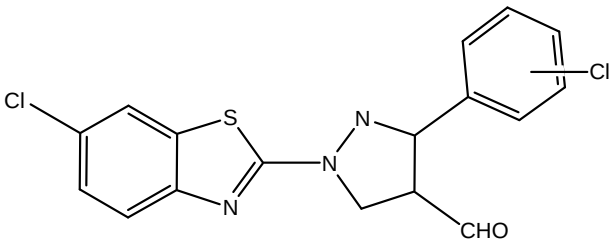


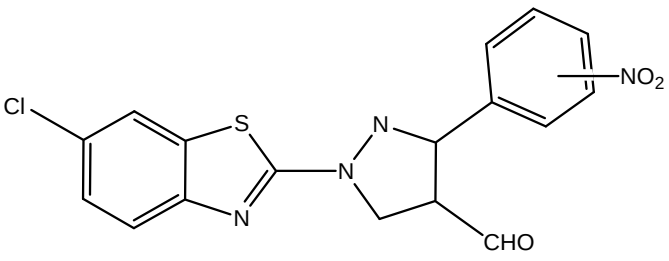
Fig.15



13a



13b



13g

Da-Qing Shi *et.al.*(2010)reported the synthesis of 2-arylbenzothiazolederivatives by reacting the titanium chloride with suspension solution of samarium powder in solvent tertrahydrofuran (THF) under dry nitrogen (N_2) atmosphere through bis-(2-(4-methylbenzalamino)phenyl)disulphide to get final product which is shown in fig.16.[44]

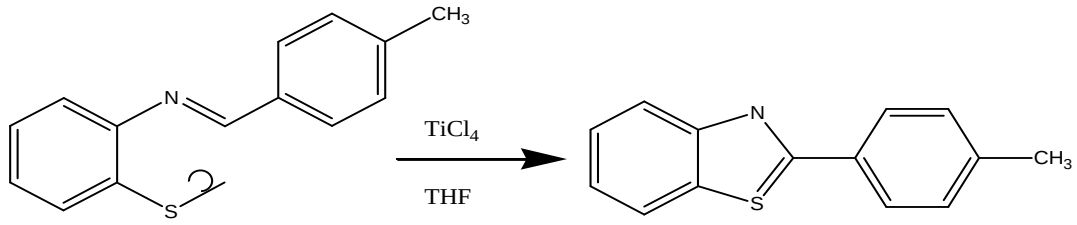


Fig.16

Ashok V. Borhade *et.al.*(2016)reported the synthesis of 2-arylbenzothiazole derivatives (14a-14i) by calcinized eggshell through solvent free conditions using mortar and pestle which is given in fig.17.[45]

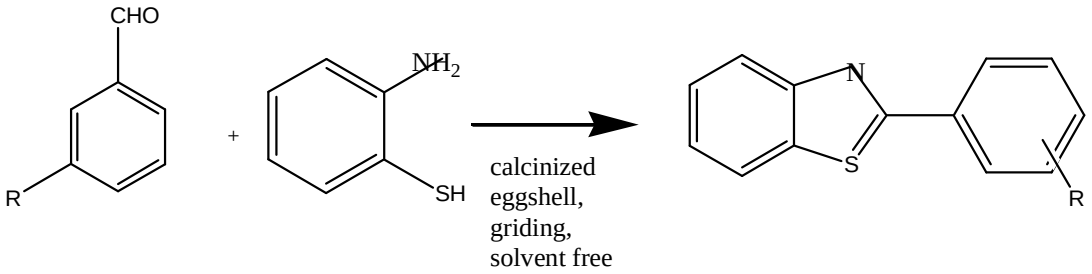


Fig. 17

Rahul Bhat*et. al.*(2017)reported the synthesis of 2-substituted benzothiazole derivatives (15a-15q) by the reaction between 2-aminothiophenol and substituted aryl aldehydes in the presence of citric acid through conventional method and microwave irradiated method which are shown in fig.18.[46]

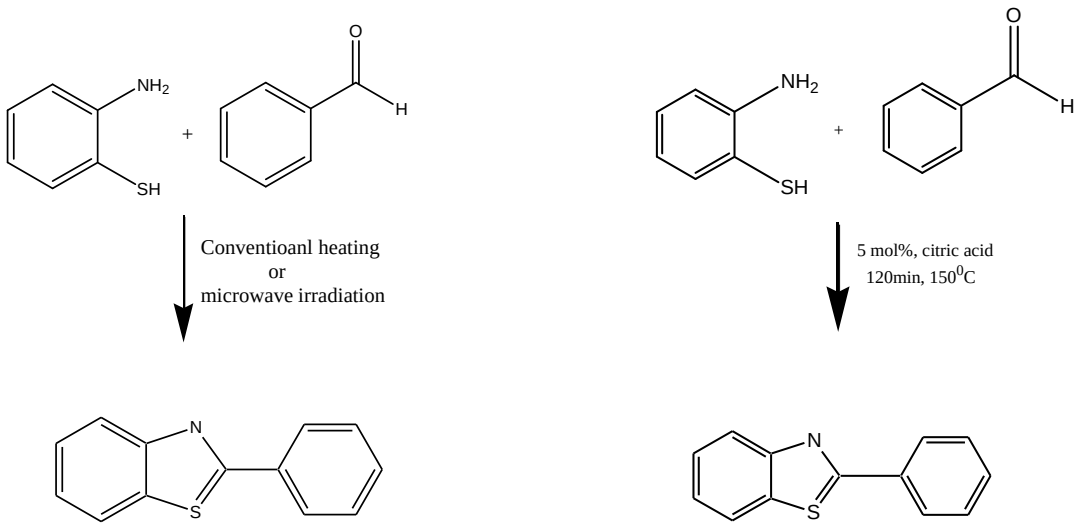


Fig. 18

CONCLUSION

This review attempts to represent the various benzothiazole portions. Benzothiazole is a heterocyclic molecule that has a wide range of biological properties and is currently being synthesised due to its powerful actions. As a result, various efficient and appealing methods for the synthesis of benzothiazole derivatives have been discovered. It is critical to develop simple and effective procedures for synthesising benzothiazole derivatives from obvious and commonly available sources.

Future trends

- Green chemistry relies heavily on benzothiazole. Green chemistry promotes the use of chemical technologies and procedures to decrease or eliminate the usage and manufacture of dangerous raw materials, catalysts, solvents, reagents, products, or

by-products to human health, community safety, and the environment. As a result, it's crucial to look at environmentally safe synthetic approaches for making benzothiazoles.

- The moiety benzothiazole shows promise as a molecular target for a variety of applications. In the sphere of medicine, for example, scaffold may yield more promising results. This knowledge is expected to lead to the creation of new synthetic techniques as well as the design of better molecules with improved biological characteristics and selectivity.

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