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BENZOTHIAZOLE - A MAGIC MOLECULE

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Benzothiazoles, Antimicrobial, Anticancer, Clinical trials

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ABSTRACT: Antimicrobial resistance has been called one of the world's most pressing public health problems. Addressing the issue of antimicrobial resistance is one of the most urgent priorities in the fields of public health today. Alarmingly, the development of resistance such as multi-drug resistance towards a number of antibiotics poses a challenge to the scientific community in the discovery of new therapies. Thus, there is a need to develop newer and effective molecules with high safety profile. Benzothiazoles are fused membered rings, which contain heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. Benzothiazole is an interesting pharmacophore exhibiting diverse pharmacological activities like antimicrobial, anticancer, anthelminthic, antidiabetic, antitubercular, anticonvulsant, antioxidant, anti-inflammatory, antifungal, antipsychotic *etc*. The present article extensively covers various procedures of synthesis of 2-substituted benzothiazole core and its analogs - by utilizing distinctive catalysts, solvent conditions, reactants immobilized on solid support and microwave irradiation. Variations in synthetic procedures are studied to explore chemo-selectivity of the reactions, in-expensive, eco-friendly, less time consuming procedure with easy and quick isolation of the products. Ongoing clinical trials of different benzothiazole derivatives, exploring additional pharmacological activities, are also included.

INTRODUCTION: Benzothiazoles are fused membered rings, which contain heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds [1]. Benzothiazoles consist of a 5-membered 1, 3-thiazole ring fused to a benzene ring. The nine atoms of the bicycle and the attached substituents are coplanar.

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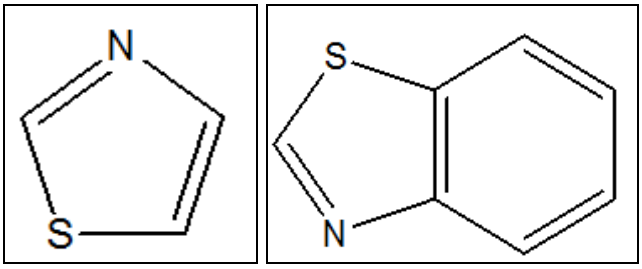
Benzothiazole derivatives have been intensively studied, as the pharmacophore is one of the privileged structures in medicinal chemistry. Benzothiazoles have emerged as a core structure for diversified therapeutic applications which include, antimicrobial, anticancer, anthelminthic, antidiabetic, antitubercular, anticonvulsant, anti-oxidant, anti-inflammatory, antifungal, anti-psychotic activities. They are also used in industry as vulcanisation accelerators. Various benzo-thiazoles such as 2-aryl benzothiazoles received much attention due to unique structure and its uses as radioactive amyloid imagining agents. Benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological properties [2].

It is reported that the isosteres and derivatives of benzothiazoles have antimicrobial activities against gram negative, gram positive bacterias (*e.g., E. coli*, *Pseudomonas aeruginosa*, *Entero bacter*, *Staphylococcus epidermis*, etc) and the yeast (*e.g. Candida albicans*).

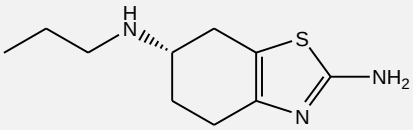
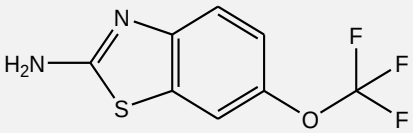
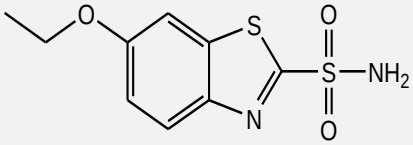
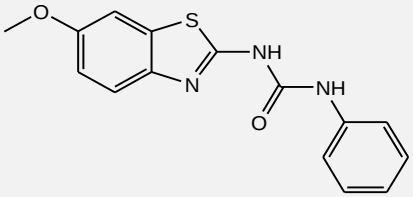
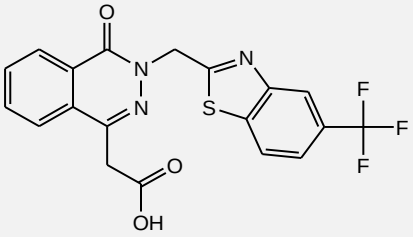
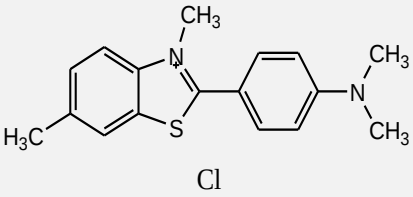
Structure: The basic structure of benzothiazole consist of benzene ring fused with d face (4, 5 position) of thiazole. The numbering in thiazole starts from the sulphur atom.



THIAZOLE **BENZOTHIAZOLE**

Some of the marketed drugs [3] having benzothiazole nucleus are shown in **Table 1**.

TABLE 1: MARKETED PREPARATIONS HAVING BENZOTHIAZOLE NUCLEUS

S. no	Marketed drug	Company	Use	Structure
1	Pramiprexole	Zydus cadila	Parkinsons disease, restless legs syndrome	
2	Riluzole	Sun pharmaceuticals	Amyotrophic lateral sclerosis	
3	Ethoxzolamide	Pharmacia, Upjohn, allergan	Glaucoma, diuretic, duodenal ulcers	
4	Frentizole	Not Available	Antiviral, immunosuppressive agent	
5	Zopolrestat	Not Available	Anti-diabetic	
6	Thioflavin T	Not Available	Amyloid imaging agent	

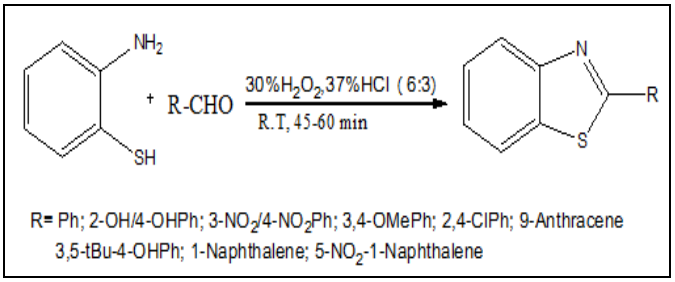
Methods of Synthesis:

By Condensation Reaction:

Condensation of 2-aminothiophenol with aldehydes:

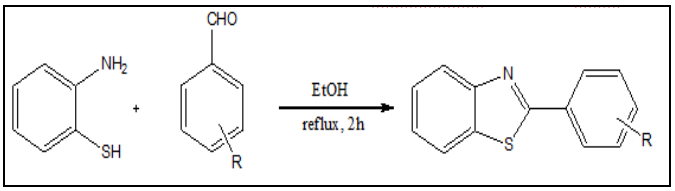
Homogenous Catalysis: Homogeneous catalysis is a catalytic reaction in which the catalyst is in the same phase as the reactants. Homogeneous catalysis applies to reactions in the gas phase and even in a solid phase

Acid Catalyzed Condensation: Guo and co-authors demonstrated the acid catalysed homogeneous condensation of 2-aminothiophenol and substituted aldehyde using H_2O_2 / HCl in ethanol at room temperature **(Scheme 1).** [4]



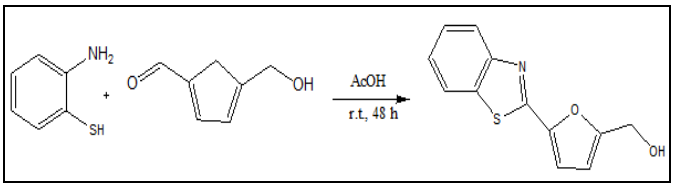
SCHEME: 1

Mortimer and colleagues synthesized a series of novel 2-phenylbenzothiazoles by the reaction of 2-aminothiophenol and substituted benzaldehydes in ethanol (EtOH) **(Scheme 2)** [5].



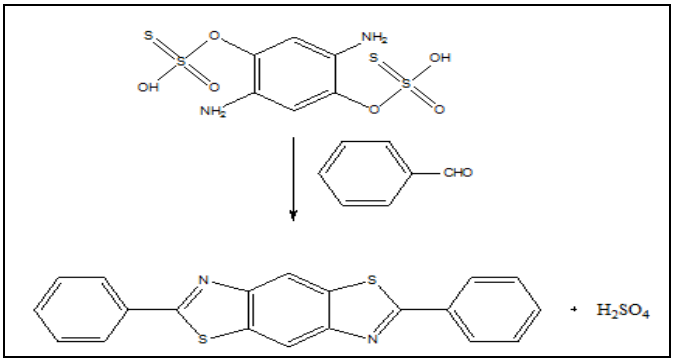
SCHEME: 2

Sattler and co-authors synthesized [5-(2,3-dihydro-1,3 benzothiazol-2-yl)oxolan-2-yl]methanol from the condensation of hydroxymethylfurfural (HMF) and 2 -aminobenzenethiol in the presence of acetic acid (AcOH). **(Scheme 3)** [6].



SCHEME: 3

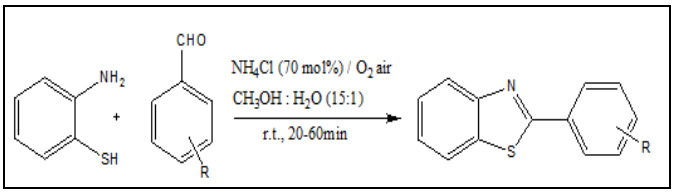
Perkin *et al.*, demonstrated the synthesis of benzobisthiazoles from benzaldehydes. Benz aldehydes when heated with *para*-phenylene diamine-2, 5- di- (thiosulfuric acid) formed a benzal derivative as an intermediate, which at higher temperature yielded the benzobisthiazole **(Scheme 4)** [7].



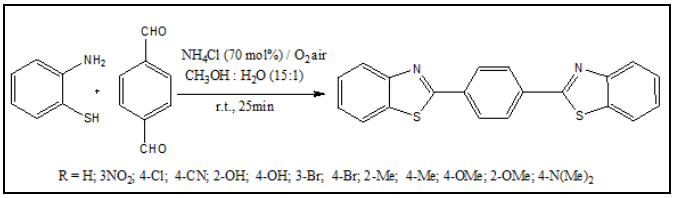
SCHEME: 4

Base Catalyzed Condensation: Maleki *et al.*, have developed a method for the synthesis of 2-arylbenzothiazole derivatives from condensation of 2-aminothiophenol with aromatic aldehydes using ammonium chloride as a catalyst in methanol/water (15:1 v:v) as a dual solvent system at room temperature **(Scheme 5a, b)** [8].

The chief advantage of this reaction is the use of ammonium chloride which is a cheap, metal-free and readily available reagent. For comparative study authors have used various organic solvents such as chloroform, ethanol, acetonitrile, dichloromethane and water. However, methanol / water have been observed as the best solvent system in terms of the yield.

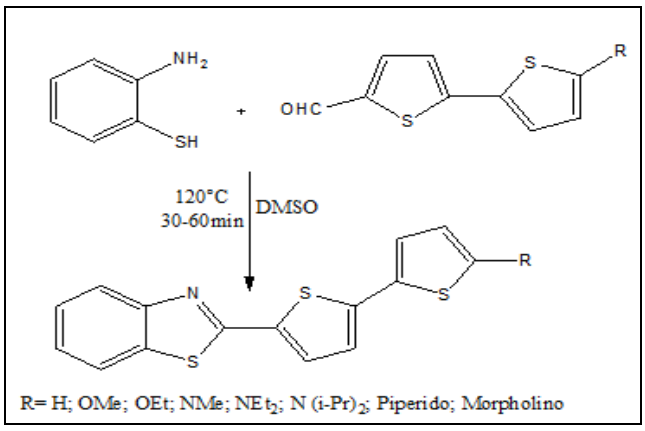


SCHEME: 5A



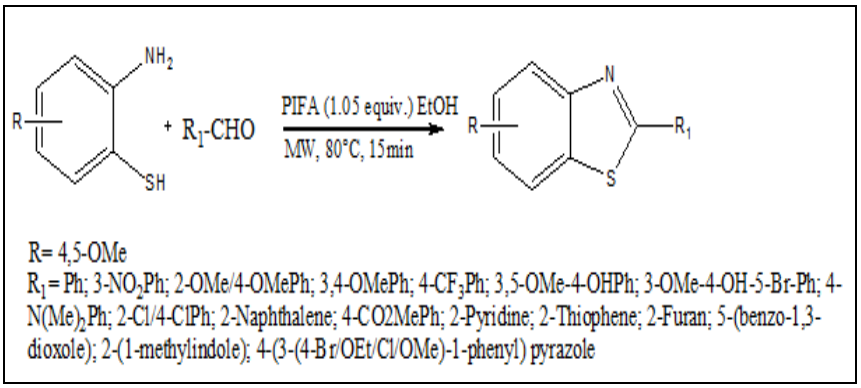
SCHEME: 5B

Solvent Catalyzed Condensation: Batista *et al.*, prepared Bithienyl-1, 3-benzothiazoles by employing the condensation of 2-amino benzenethiol and various 5-formyl-5'-alkoxy-bithiophenes or 5-formayl-5,-*N*,*N*-dialkylamino- 2, 2'-bithiophenes under the refluxing Dimethyl sulfoxide (DMSO) for 30-60 min **(Scheme 6)** [9].



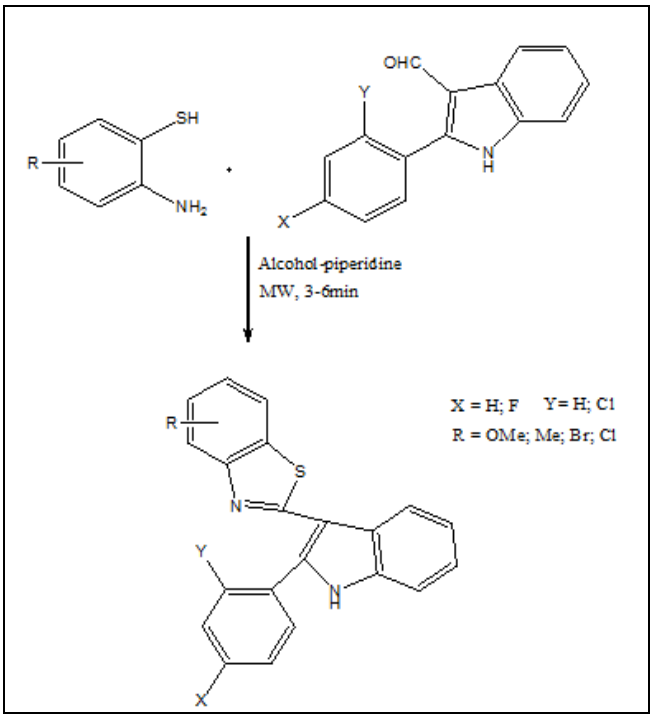
SCHEME: 6

Microwave-induced Condensation: Praveen and co-workers demonstrated microwave-assisted synthesis of benzothiazole and benzoxazole derivatives using phenyliodonium bis (trifluoroacetate) (PIFA) as an oxidant for the cyclocondensation of *2*-aminothiophenols / 2-aminophenols with different aldehydes in ethanol at 80 °C, which afforded high yield of the products **(Scheme 7)** [10]. Due to the cleavage of the heterocycles in the microwave irradiation, heterocyclic nucleus containing substituted aldehyde compounds such as pyridine, thiophene and furan allowed average yield. The major advantages of this method are the use of PIFA (which works both as a Lewis acid and as an oxidant), wide substrate scope, short reaction time, microwave condition and satisfactory yields.



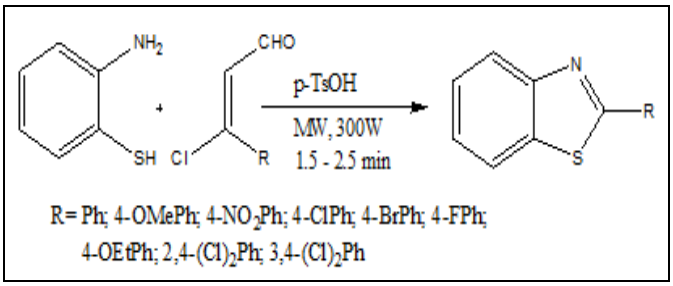
SCHEME: 7

Dandia *et al.,* reported the synthesis of benzothiazoles by the condensation of 2-phenyl-1*H*-indole-3-carboxaldehyde and 5-substituted 2-aminothiophenols in the presence of piperidine or *para* toluenesulphonic acid (p-TSA) in ethanol (EtOH) or *N*,*N*-dimethylformamide (DMF) solvent under microwave irradiation (MWI) for 3-6 min at 240 W **(Scheme 8)** [11].



SCHEME: 8

Paul *et al.,* demonstrated an efficient method for the synthesis of 2-arylbenzothiazoles by condensation reaction of *2*-aminothiophenol with β-chlorocinnam aldehydes under microwave irradiation (MWI) using *para*-toluenesulfonicacid (*p*-TSA) **(Scheme 9)** [12]. Operational simplicity, fast environmental friendly reaction, general applicability and accommodating a variety of substitution patterns are the notable advantages of this procedure.



SCHEME: 9

Heterogeneous Catalysis: In heterogeneous catalysis the catalysis occurs at the interface of two phases, typically gas-solid. It involves the use of a catalyst in a different phase from the reactants. Typical examples involve a solid catalyst with the reactants as either liquids or gases.

Acid Catalyzed Condensation: The methods of acid catalysed condensation are depicted in the

following schemes: Nalage *et al.*, demonstrated an efficient method for the synthesis of 2-arylbenzothiazole by condensation of different aldehydes and 2-aminothiophenol, in the presence of phosphorus pentoxide (P_2O_5) in methanol (MeOH) for 3–7 hr at room temperature. Phosphorous pentoxide acts as an acid catalyst **(Scheme 10, Method 1)** [13].

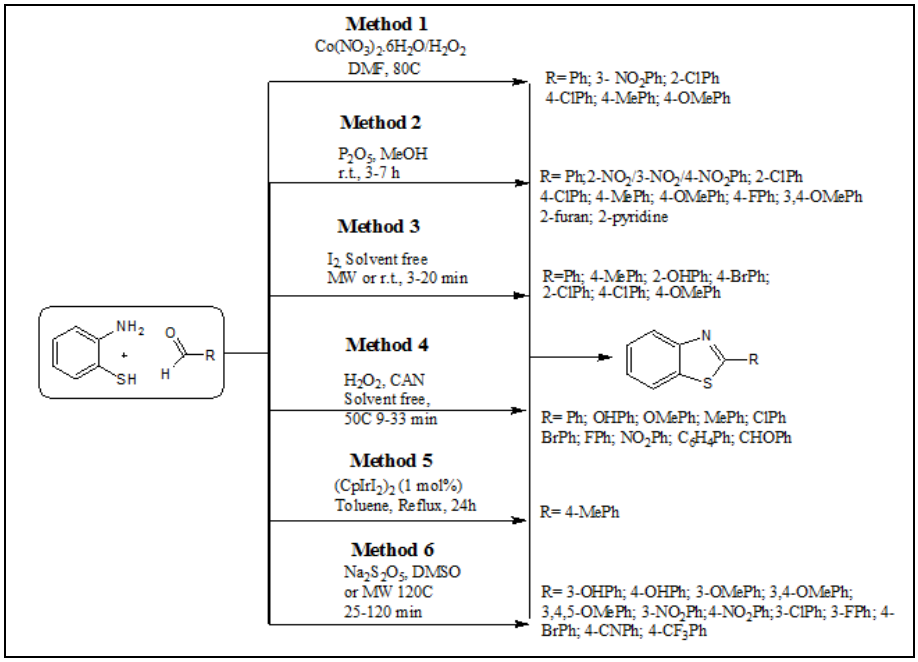
Chandrachood and colleagues demonstrated the synthesis of 2-arylsubstituted benzothiazoles, usuing cobalt nitrate ($Co(NO_3)_2{\cdot}6H_2O$)/ hydrogen peroxide (H_2O_2) as a catalyst **(Scheme 10, Method 2)** [14]. They have noticed the impact of temperature, change in reagent amount and change in solvent on the reaction and found the best outcomes utilizing cobalt nitrate and hydrogen peroxide in N,N-dimethylformamide (DMF).

Rapid and effective condensation reactions of *2*-aminothiophenol with various aldehydes were carried out using iodine as a catalyst in solvent-free conditions, by Moghaddam *et al.*, to afford the corresponding 2-substituted benzothiazole derivatives in a relatively short time in excellent yields **(Scheme 10, Method 3)** [15].

Weekes *et al.*, have reported a simple, one-pot and high-yielding protocol for the substituted 2-phenylbenzothiazoles under both thermal and microwave (MW) conditions from the condensation of various benzaldehydes and *2*-aminothiophenol using sodium metabisulfite ($Na_2S_2O_5$) as a mild oxidant in dimethylsulfoxide (DMSO) at 120 °C **(Scheme 10, Method 4)** [16]. Here, less reaction time and simple isolation of product without column chromatography are the additional advantages. Authors also achieved excellent yield of product using dimethyl-formamide (DMF) at 90 °C as a solvent, though this reaction takes longer time (>2 h) because of the lower solubility of reaction components in DMF. However, DMSO is an efficient solvent for promoting this reaction, due to its optimal reagent dissolution and oxidizing agent properties.

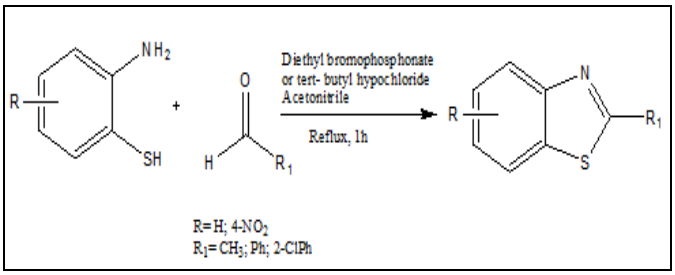
Synthesis of 2-(*para*-tolyl) benzothiazole by transition metal-Ir-catalyzed hydrogen-transfer reactions of 4-methylbenzaldehyde with *2*-aminothiophenol have suggested by Blacker and colleagues **(Scheme 10, Method 5)** [17].

The H_2O_2/Cerium ammonium nitrate (CAN) system as a novel and very efficient reagent for the convenient synthesis of benzothiazoles in good to excellent yields through the condensation of *2*-aminothiophenol and various substituted aryl aldehydes was described by Bahrami and co-authors **(Scheme 10, Method 6)** [18]. Short reaction time, easy and quick isolation method, excellent chemo selectivity and good yields are the main advantages of this procedure.



SCHEME: 10

2-substituted benzothiazole and benzoxazole were synthesized by the condensation of aldehydes with 2-aminothiophenol or 2-aminophenol respectively through a one-pot reaction by applying diethyl bromo phoshonate and tert-butyl hypochlorite (*t*-BuOCl) in acetonitrile (MeCN) by Patil *et al.*, **(Scheme 11)** [19].

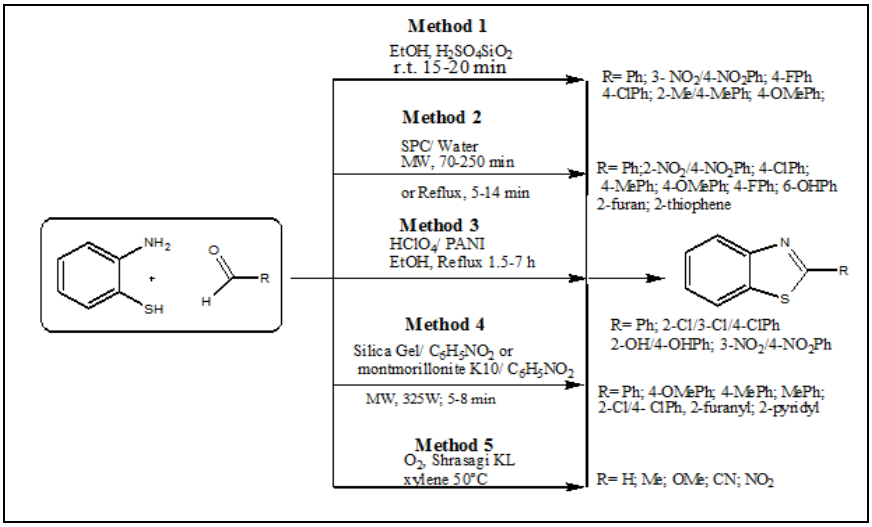


SCHEME: 11

Solid Supported Condensation: Maleki *et al.*, have suggested an efficient and improved catalyst, sulphuric acid immobilized on silica-gel ($H_2SO_4.SiO_2$) for the synthesis of 2-aryl benzothiazoles through condensation of various aldehydes and 2-aminothiophenol **(Scheme 12, Method 1)** [20]. Here, $H_2SO_4.SiO_2$ is an inexpensive, heterogeneous and stable catalyst possessing very high reactivity compared to unsupported H_2SO_4. The authors have examined the effect on the yield by employing different amounts of catalyst in various solvents but considerable growth of the reaction rate and improvement of the yield were observed when 5 mg of $H_2SO_4.SiO_2$ in ethanol (EtOH) was used.

Shokrolahi *et al.*, have reported the condensation of *2*-aminothiophenol with aldehyde using Sulfonated Porous Carbon (SPC) as a heterogeneous catalyst in water under reflux conditions and microwave irradiation to produce benzothiazole derivatives **(Scheme 12**, **Method 2)** [21]. Here, porous carbon materials can accomplish most of the required properties for a suitable catalyst support due to high surface areas and well-developed porosities. Authors have studied the optimization experiment using different amount of SPC for the condensation reaction in water by refluxing for 90 min or by microwave irradiation for 6 min. Use of 0.1g of SPC shows the best results under these reaction conditions. The reusability and recyclability of the catalyst (SPC) was checked under similar reaction conditions and was concluded that, for the three catalytic cycles, the yields and reaction times remained the same. This protocol had simple work set up, was environmentally benign, produced good yields, and had no requirement of extra oxidants and use of cheap catalyst compared to previously reported methods.

The synthesis of 2-substituted benzothiazoles efficiently in good yields by the reaction of 2-aminothiophenol and various aldehydes in the presence of a catalytic amount of perchloric acid-doped Polyaniline ($HClO_4$/PANI) under refluxing ethanol (EtOH) was reported by Alibeik *et al.*, **(Scheme 12, Method 3)** [22]. The superior characteristics of this catalyst are the low cost, simple recovery and efficient reusability. The authors have studied the reusability of the catalyst and the results showed that there were no considerable changes in the catalyst reactivity.



SCHEME: 12

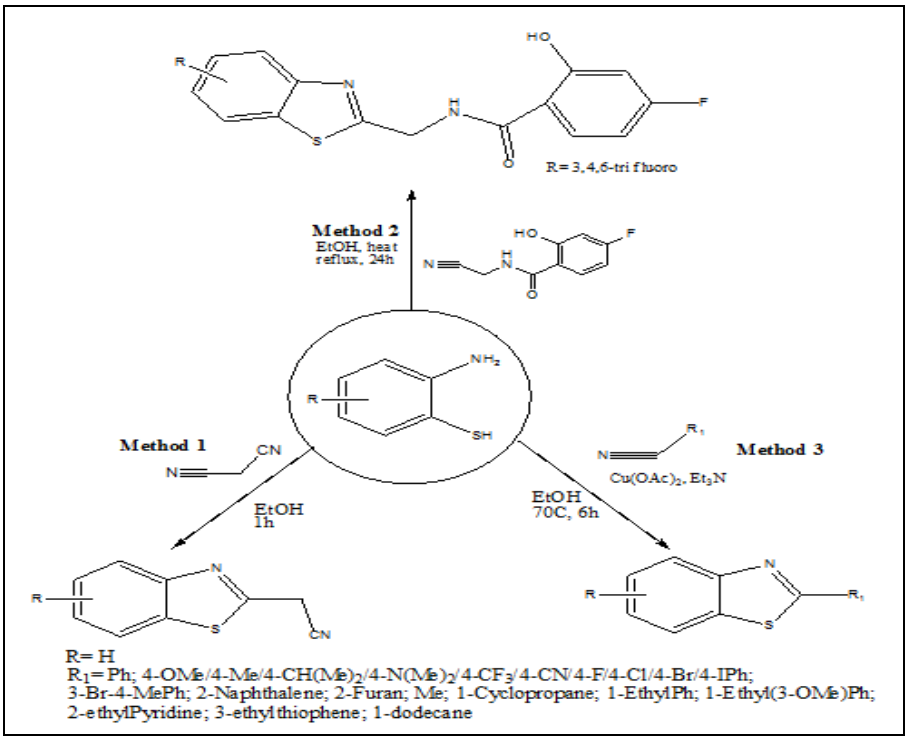
Alloum *et al.*, have presented the condensation of various aldehydes with 2-aminothiophenol on silica gel / nitrobenzene or montmorillonite K-10 / nitrobenzene under microwave irradiation (MWI) which afforded 2-arylbenzothiazoles in good yields with high purity **(Scheme 12, Method 4)** [23].

Kawashita and co-workers have disclosed a simple and direct synthesis of 2-arylbenzothiazole by the aid of activated carbon (Shirasagi KL) **(Scheme 12, Method 5)** [24].

Condensation of 2-Aminothiophenols with Nitrile: Mokhir *et al.*, have mentioned the synthesis of 2-cyanomethyl benzothiazole from the condensation of 2--aminothiophenol and malonodinitrile in the presence of glacial acetic acid **(Scheme 13, Method 1)** [25]. The suspension of 2-cyanomethyl benzothiazole in iso-propanol and water containing potassium nitrite (KNO_2) was further treated with conc. HCl to yield benzothiazolyl cyanoxime, which is good multidentate ligand for co-ordination chemistry.

Zandt and colleagues have reported the synthesis of 4-fluoro-2-hydroxy-*N* (4, 5,7-trifluorobenzothiazol-2-ylmethyl)-benzamide using *N*-cyanomethyl-4-fluoro-2-hydroxy-benzamide and 2-amino-4,5,7-trifluorothiophenol hydrochloride in refluxing ethanol (EtOH) for 24 h **(Scheme 13, Method 2)** [26].

Copper acetate catalysed formation of 2-substituted benzothiazoles in excellent yields via condensation of 2-aminobenzenethiols with wide range of nitriles containing different functional groups was developed by Sun *et al.*, **(Scheme 13, Method 3)** [27]. Optimization of the reaction conditions explored that the optimal catalytic conditions consist of $Cu(OAc)_2$ (10mol %) and Et_3N (1.0 equiv.) in ethanol (EtOH) at 70 °C for 6 hr gives best results in terms of yield.



SCHEME: 13

Condensation 2-aminothiophenole with Ester: Khalil *et al.*, have surveyed that an amino ester and the selected 2-substitued aromatic amines such as 2-aminothiophenol was condensed in the presence of poly phosphoric acid (PPA) at 160 °C for 3 h followed by neutralization with aq. ammonia to yield corresponding 2-substituted benzothiazole **(Scheme 14, Method 1)** [28].

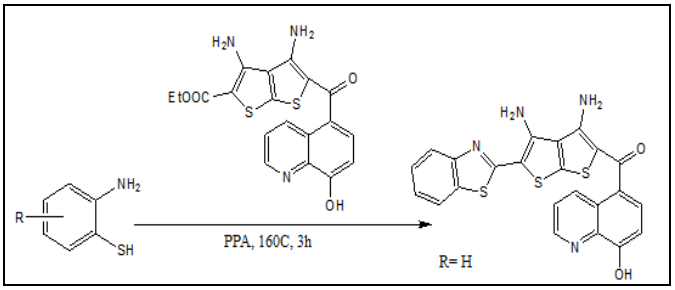
Manfroni *et al.*, have synthesized the 5-substituted ethyl-2-(benzothiazol-2-yl) acetate by the condensation of various substituted 2-aminothiophenol and ethyl cyanoacetate at 120 °C, which afforded high yield of the products **(Scheme 14, Method 2)** [29].

Reddy *et al.*, have investigated the distinctive formation of trifluoroacetonyl benzothiazole by condensation of *2*-aminophenol with trifluoroacetyl ketene diethyl acetal under microwave irradiation (MWI) in toluene for 8 min **(Scheme 14, Method 3)** [30].

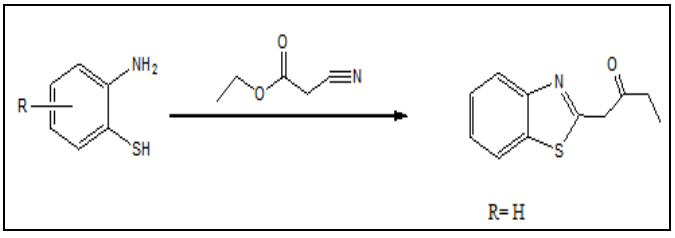
Shantakumar *et al.*, have presented some new banzothiazole derivatives by the reaction of benzothiazolyl carboxyhydrazide with variant aryl acids using phosphoryl chloride ($POCl_3$) **(Scheme 14, Method 4)** [31].

The convenient, flexible, connective and efficient preparation of various benzothiazole derivatives by the condensation of substituted anilines with functionalized 2-esters in good to excellent yields under mild conditions was established by Bastug and colleagues **(Scheme 14, Method 5)** [32].

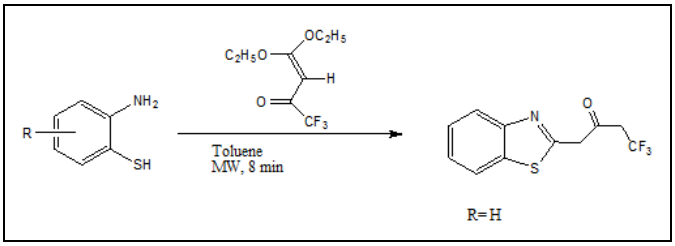
The development of new libraries of multifunctional sites containing heterocycles is the versatility of this protocol. Broad range of substituted 2-esters was prepared using the modified Pinner sequences which widen the scope of this condensation.



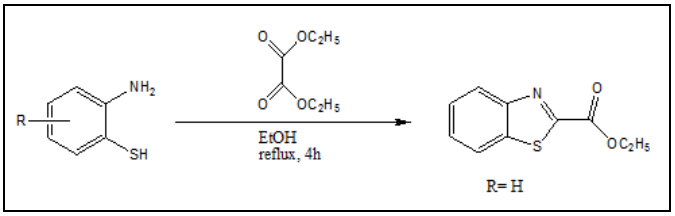
METHOD: 1



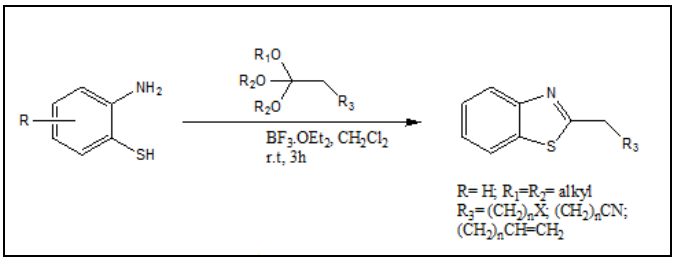
METHOD: 2



METHOD: 3



METHOD: 4

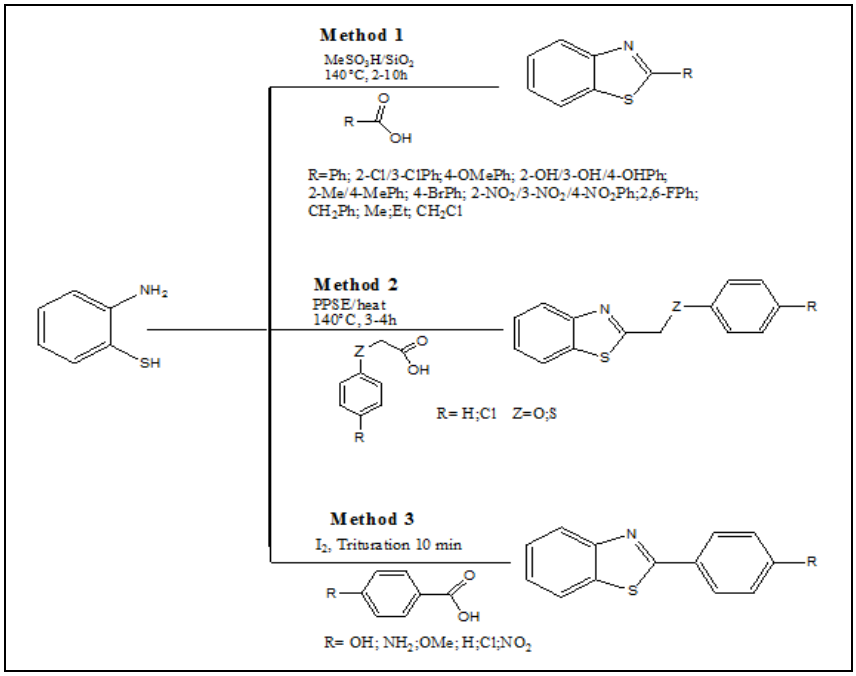


METHOD: 5
SCHEME: 14

Condensation of *2*-aminothiophenol with Acid: Sharghi *et al.*, have indicated an efficient, one-pot and high yielding procedure for the synthesis of 2-substituted benzothiazoles from the *2*-aminothiophenol and different aliphatic or aromatic carboxylic acids in novel methane sulfonic acid / silica gel ($MeSO_3H/SiO_2$) at 140 °C for 2-12 h **(Scheme 15, Method 1)** [33]. Silica gel was recovered and reused many times without loss of its efficiency.

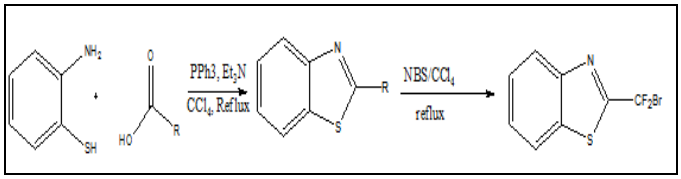
Yildiz *et al.*, have reported the viable methodology for the synthesis of various 2-substituted benzothiazoles from 2-aminothiophenols and corresponding carboxylic acids refluxing in trimethylsilylpolyphosphate ester (PPSE) at various temperatures and time to afford various derivatives in excellent yield **(Scheme 15, Method 2)** [34].

Molecular iodine was employed by Gupta and co-workers in a one-pot, solid-phase, solvent free and microwave assisted reaction of *2*-aminothiophenol and various benzoic acids to obtain high yield of various benzothiazole derivatives, compared to polyphosphoric acid (PPA) and [pmim] Br catalyzed microwave assisted reactions **(Scheme 15, Method 3)** [35]. The reaction was completed within 10 min and requires a very small amount of iodine. The authors have studied that this new protocol has lower cost with compare to PPA and [pmim] Br, because no additional chemicals and solvents are essential during this transformation. This protocol is an inexpensive, solvent-free and less time consuming.



SCHEME: 15

An efficient and one-pot synthesis of 2-trifluoro- and 2-difluoromethyl substituted benzothiazole derivatives in excellent yields by the condensation reaction of trifluoroacetic acid and difluoroacetic acid with commercially available 2-aminobenzenethiols, respectively, was examined by Ge and co-workers **(Scheme 16)** [36].



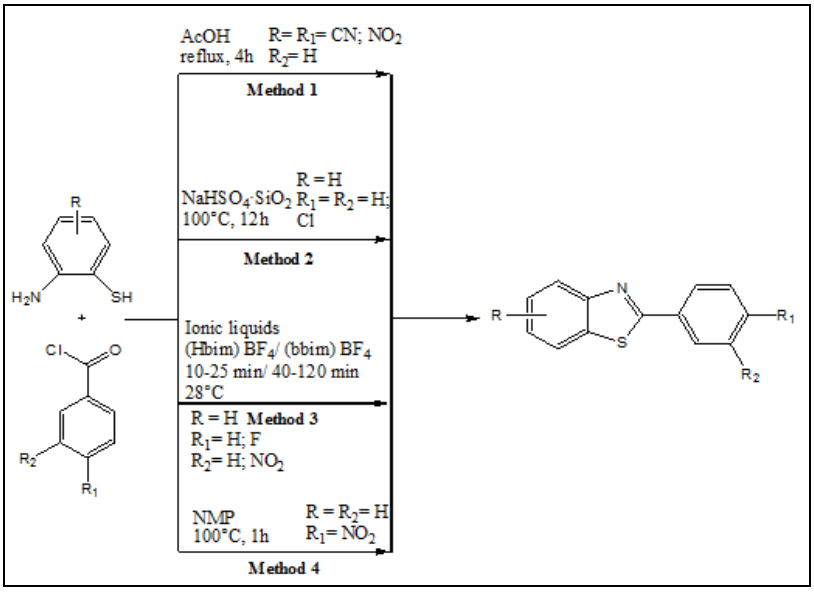
SCHEME: 16

Condensation with Acyl Chloride: Racane *et al.*, have reported that the bis-nitrile and nitro-nitrile derivatives of 2-phenylbenzothiazole were prepared by the condensation reaction of cyano or nitro-substituted 2-aminobenzothiole with commercially available 4-cyano or 4-nitrobenzoylchloride, respectively, under reflux condition in acetic acid (AcOH) for 4 hr **(Scheme 17, Method 1)** [37].

An efficient and environment friendly catalyst $NaHSO_4$-SiO_2 promoted solvent-free synthesis of library of benzothiazole derivatives by the condensation reaction of various acyl chlorides with 2-aminothiophenol was developed by Kumar and co-workers **(Scheme 17, Method 2)**[38]. This reaction is heterogeneous in nature, so the catalyst can be easily recovered by simple filtration. The use of nontoxic, inexpensive, easily available, reusable and green catalyst makes the reaction protocol inexpensive and eco-friendly. $NaHSO_4$-SiO_2 catalyst can be used four times with consistent yield, which shows importance of its use in the large scale operations and industry. Authors have also investigated the effect of time, temperature and solvent on the reaction. From this study they have concluded that best results were obtained, when $NaHSO_4$-SiO_2 refluxing at 100 °C for 12 hours, without use of any solvent.

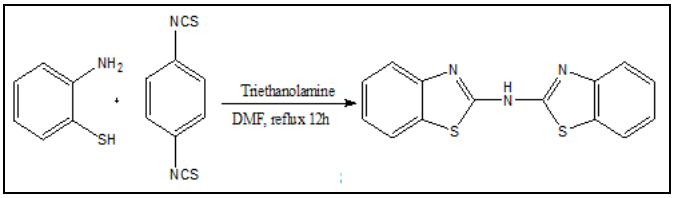
Nadaf and co-workers developed a novel one-pot regioselective synthesis of 2-aryl benzothiazoles by condensation of 2-aminothiophenol and substituted benzoyl chloride using 1-butylimidazolium tetraflouroborate ([Hbim]BF_4) and 1,3-di-*n*butylimidazoliumtetrafluoroborate ([bbim]BF_4) ionic liquids (ILs) as reaction media at room temperature in excellent yields **(Scheme 17, Method 3)** [39]. Ambient reaction conditions, absence of a catalyst and recyclability of the non-volatile ILs makes this protocol green and environment-friendly.

Karlsson *et al.*, have given a minor change in the condensation reaction of 2-aminothiophenol with 4-nitrobenzoyl chloride by applying *N*-methyl-2-pyrrolidone (NMP) as an oxidant at 100 °C for 1 hr to give 2-(4-nitrophenyl)benzothiazole **(Scheme 17, Method 4)** [40].



SCHEME: 17

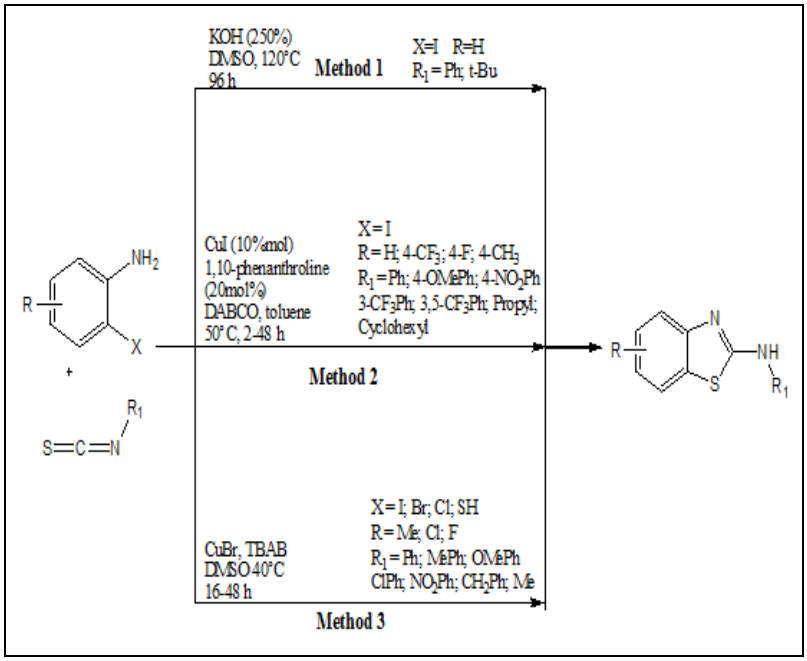
Condensation with Isothiocyanate: El-Sharief and colleagues have introduced an exclusive condensation reaction of 1, 4-phenylenedi-isothiocyanate with *2*--aminothiophenol to produce *N,N'*-Bis(benzothiazole-2-yl)-benzene-1,4-diamine using triethanolamine / *N,N*-dimethylformamide (TEA/ DMF) as a reaction media **(Scheme 18)** [41].



SCHEME: 18

Cano *et al.,* described the reaction of equimolecular amounts of 2-iodoaniline and various isothiocyanato derivatives in presence of combination of dimethyl sulfoxide (DMSO) and an excess of potassium hydroxide (KOH) at 120 °C for 96 hr, which afforded *N*- substituted benzothiazol-2-amine derivatives **(Scheme 19, Method 1)** [42].

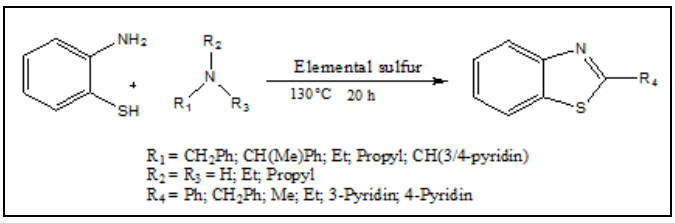
Ding *et al.,* demonstrated Copper (I)-catalysed reaction of 2-iodobenzenamine with isothio-cyanates under mild conditions for the synthesis of 2-substituted benzothiazoles. **(Scheme19, Method 2)** [43].



SCHEME: 19

High efficiency, mild reaction conditions and experimental ease are the key features of this method. Authors have applied various ligands and base in different solvents for optimization of the reaction condition by means of good yield and time. From that study, they have concluded that the best results were obtained, when the reaction of 2-iodoaniline and phenyl isothiocyanates catalysed by CuI(I) (10 mol%) in the presence of ligand (1,10-phenanthroline) and base (1,4-diazabicyclo[2.2.2]octane) (DABCO) in toluene at 50 °C. Guo *et al.,* have reported a ligand and base-free, copper-catalyzed reaction of 2-halobenzenamine derivatives with various isothiocyanates using copper(I)bromide (CuBr) and tetra-n-butyl ammonium bromide (TBAB) as the promoter at 40 °C, afforded various 2-aminobenzothiazoles in moderate to excellent yields **(Scheme 19, Method 3)** [44].

Condensation of 2-aminothiophenol with Aryl Amines: A novel, efficient, solvent-free, catalyst-free and metallic contaminants free chemoselective oxidative coupling of various alkylamines and substituted 2-mercaptoaniline for the synthesis of substituted benzothiazoles using elemental sulphur was developed by Nguyen and co-authors **(Scheme 20)** [45].



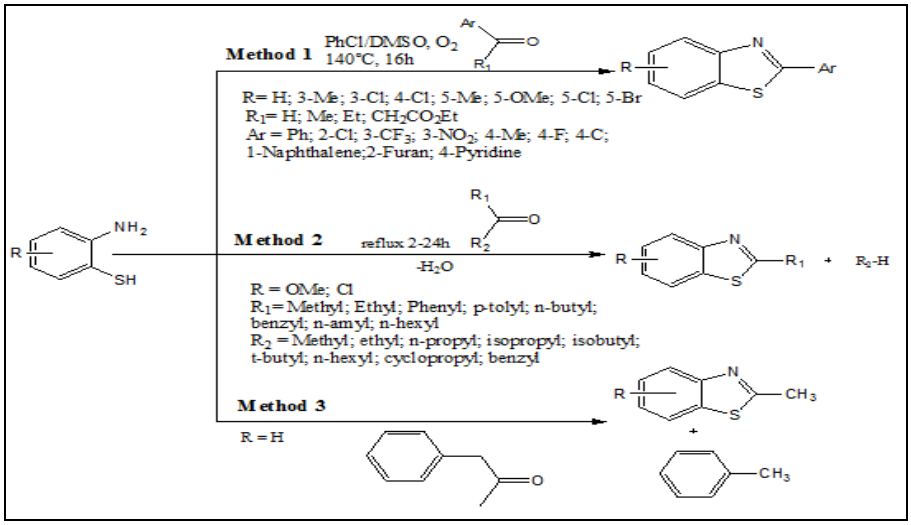
SCHEME: 20

The present method has valuable advantages such as easy availability of all reaction components including sulphur and the remarkably simple and catalyst-free reaction conditions at moderate temperature.

Condensation of 2-aminothiophenol with Ketones: Liao *et al.*, have developed an inexpensive and an efficient formation of various 2-aryl benzothiazoles from substituted 2-aminobenzenethiols and various aryl ketones using molecular oxygen as oxidant under metal-free and I_2-free conditions in a mixture of dimethyl sulfoxide (DMSO) / chlorobenzene (ClC_6H_5), to afford high yields of the products **(Scheme 21, Method 1)** [46]. Solvent played an important role in this transformation. Functional groups such as methyl (CH_3), methoxy (OCH_3), fluoro (F), chloro (Cl), bromo (Br) and nitro (NO_2) groups were all well endured during the study of the optimized reaction conditions.

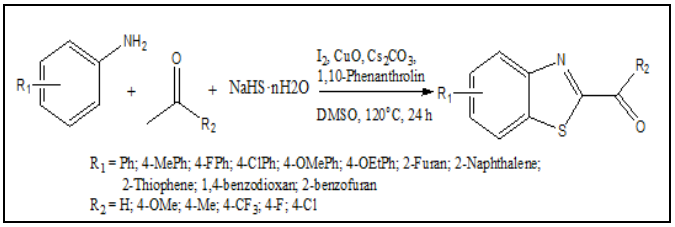
The reaction of various derivatives of 2-aminobenzenethiol with various ketones to yield 2,2-disubstituted benzothiazolines, which converted into 2-substituted benzothiazoles by the pyrolysis with the elimination of concomitant hydrocarbon under reflux condition, have examined by Elderfield and colleagues **(Scheme 21, Method 2)** [47].

Kreysa and co-workers have investigated a new protocol for the synthesis of 2-methylbenzothiazole using benzyl methyl ketone and 2-amino benzenethiol **(Scheme 21, Method 3)** [48].

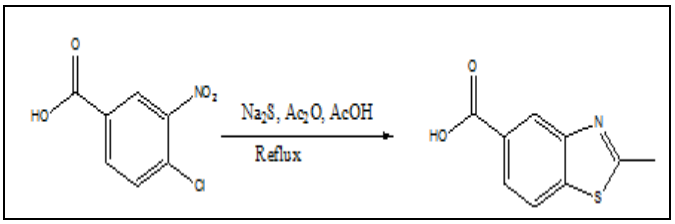


SCHEME: 21

Xue and co-authors have reported the condensation reaction of simple and readily available aromatic ketones with substituted anilines by employing $NaSH.nH_2O$ and CuO/CuI in the presence of base (Cs_2CO_3) and ligand (1,10-phenanthrolin) in dimethyl sulfoxide (DMSO) at 120 °C for the preparation of 2- acylbenzothiazoles **(Scheme 22)** [49].



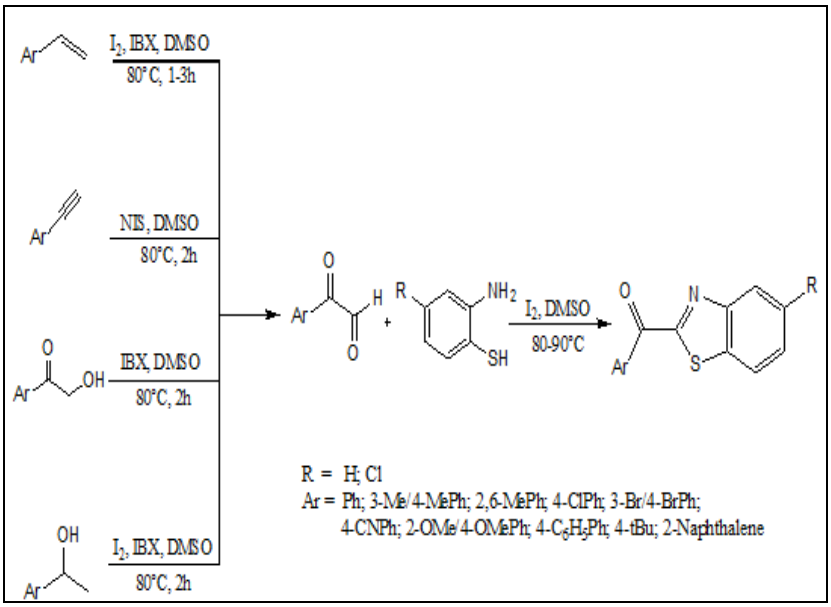
SCHEME: 22



SCHEME: 23

Condensation of 2-haloaniline with Sulfide: Klar and co-authors have developed method of synthesis of 2-methylbenzothiazole-5-carboxylic acid from 4-chloro-3-nitro benzoic acid in a one-pot reaction using sodium sulfide (Na_2S) in the presence of acetic anhydride (Ac_2O) and acetic acid (HOAc) **(Scheme 23)** [50].

Miscellaneous Reactions: A variety of 2-acylbenzothiazoles were synthesized by Zhu et al. from multiform substrates arylethenes, arylacetylenes, 2-hydroxyaromatic ketones and 1-arylethanol *via* four distinct pathways. They converted these substrates into aryl substituted glyoxal *in situ*, which condensed with various 2-aminothiophenol in one-pot metal-free reaction **(Scheme 24)** [51]. This synthetic approach embodied four specific reaction pathways. For optimisation of reaction conditions, the authors have carried out this reaction in the presence of various oxidants and additives in dimethyl sulfoxide (DMSO). However, the excellent reaction conditions for this reaction turned out to be styrene (1.1 mmol) and *2*-aminobenzenethiol (1.2 mmol) using iodine/ 2-iodobenzoic acid (I_2/ IBX, 2.0 mmol/ 1.5 mmol) in DMSO at 80 °C. Arylethenes, 2-hydroxy-aromatic ketones and 1-arylethanol follow the same optimal procedure, but arylacetylenes occur in good yield using *N*-iodosuccinimide (NIS) as catalyst.



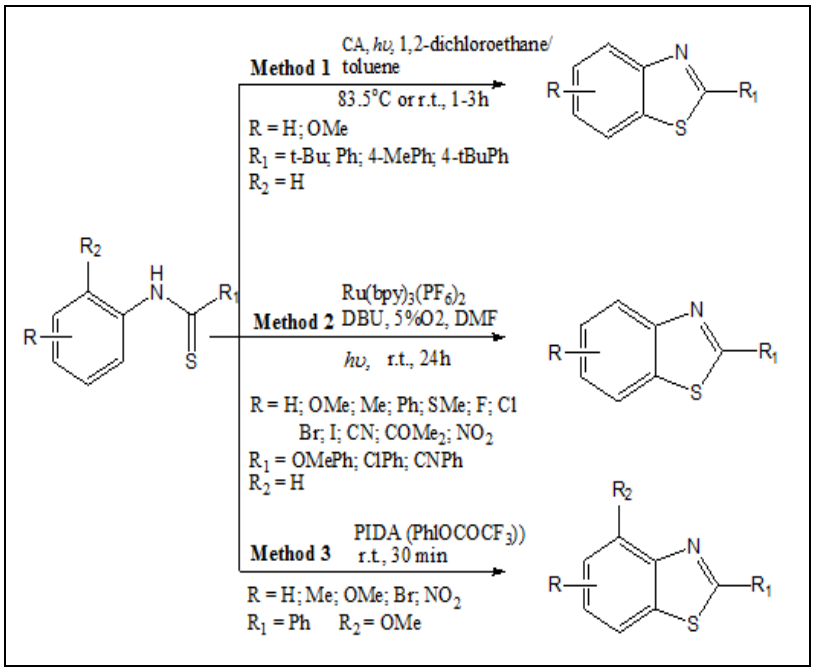
SCHEME: 24

By Cyclization Reaction: Wide range of derivatives of benzothiazole was synthesized by the cyclization of various substituted thioformanilides using different reagents and novel methods. Rey and co-authors have investigated a simple and affordable methodology for the synthesis of 2-substituted benzothiazoles by the photochemical cyclization of thioformanilides propelled by chloranil under irradiation in 1,2-dichloroethane (DCE) and toluene at 80 °C **(Scheme 25, Method**

1) [52]. The key step of the reaction mechanism was hydrogen atom abstraction from thiobenzamide by triplet chloranil.

Another aerobic visible-light promoted photo redox catalytic formation of 2 substituted benzothiazoles have accomplished by Cheng *et al.*, *via* radical cyclization of thioanilides without metal involvement except the sensitizer **(Scheme 25, Method 2)** [53]. Various catalyst and solvents were applied for optimization of the reaction conditions and the results showed that tris(bipyridine) ruthenium(II) hexafluorophosphate $(Ru(bpy)_3(PF_6)_2)$ works as an optimal catalyst and *N,N*-dimethyl formamide (DMF) works as an optimal solvent for this new protocol. Visible-light as the reaction driving force, molecular oxygen as the terminal oxidant and water as the only by-product are the salient features of this protocol.

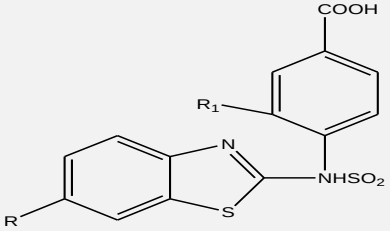
Downer *et al.*, have introduced a new and applicable protocol for the intramolecular cyclization of thiobenzamides to benzothiazoles through the aryl radical cations as reactive intermediates **(Scheme 25, Method 3)** [54]. The protocol uses phenyliodine (III)bis(trifluoroacetate) (PIFA) in trifluoroethanol or cerium ammonium nitrate (CAN) in aqueous acetonitrile to enhance the cyclization within 30 min at room temperature, which afforded moderate yield of the products.

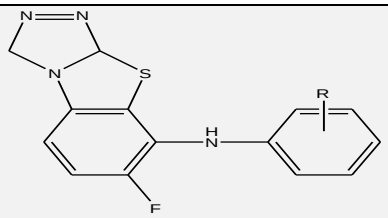
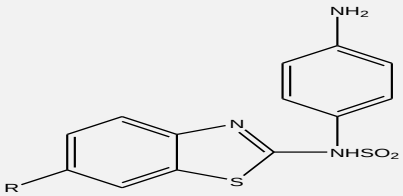
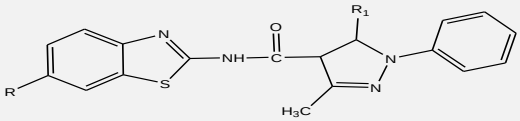
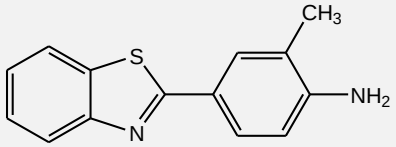
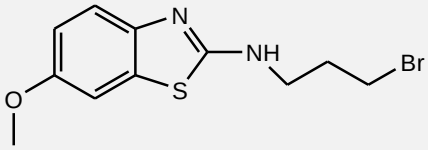
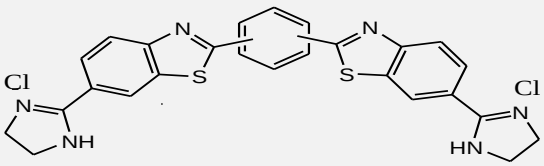
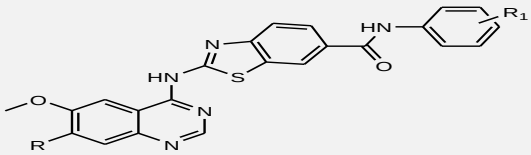
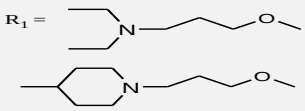
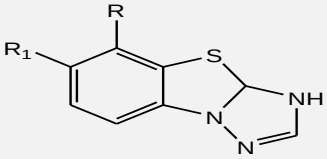


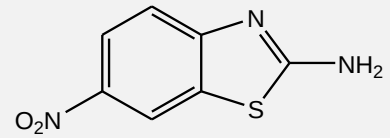
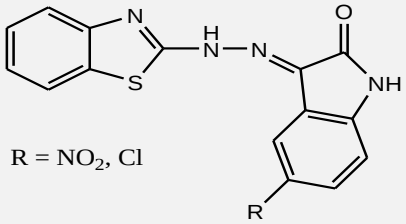
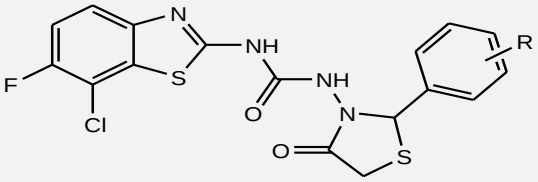
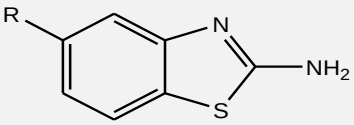
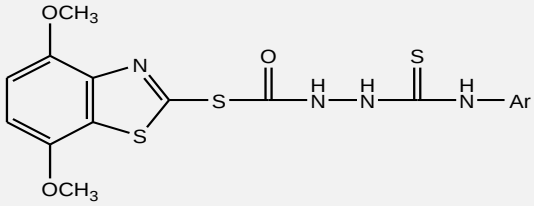
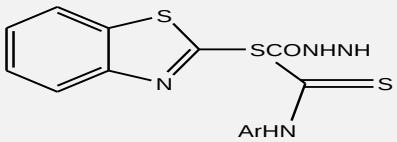
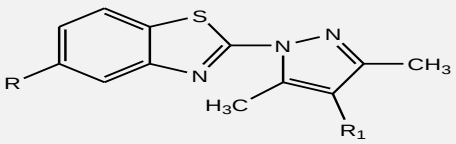
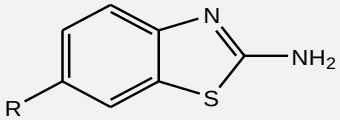
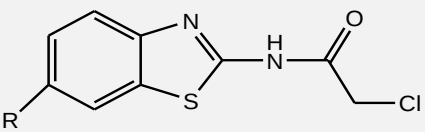
SCHEME: 25

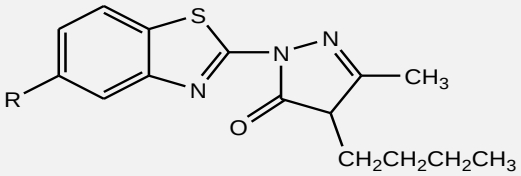
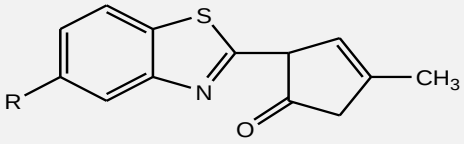
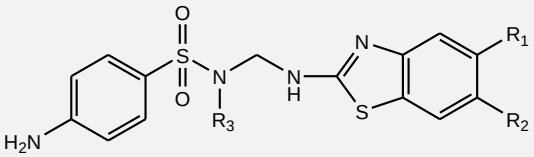
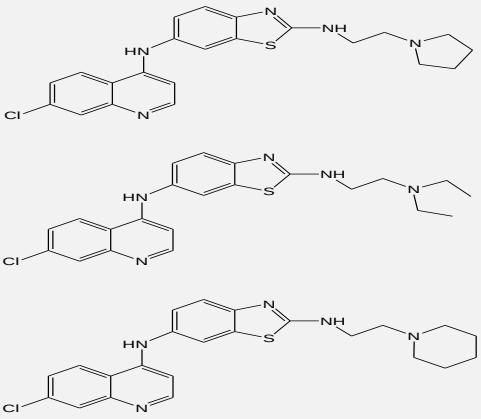
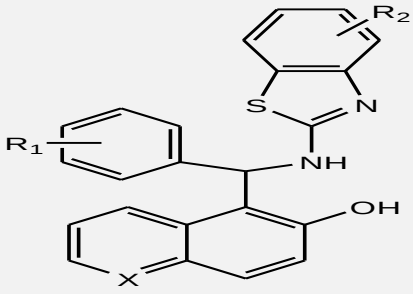
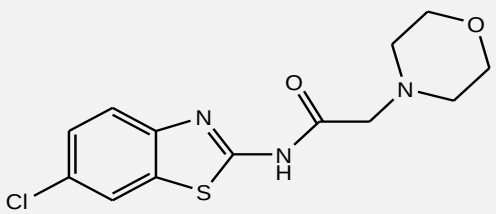
Pharmacological Activities: Benzothiazole nucleus is present in the drugs which possess numerous biological activities and is studied by researchers with interest. **Table 2** covers benzothiazole derivatives which have shown different pharmacological activities.

TABLE 2: PHARMACOLOGICAL ACTIVITIES OF BENZOTHIAZOLE DERIVATIVES

Pharmacological activity and derivative	Structure	Activity
2-(substitutedphenylsulfonamido)-6-substituted Benzothiazoles	 R = Cl, Br, CH_3, OCH_3 R_1 = I, CH_3, NH_2	*Bacillus subtilis, Salmonella typhi, S. dysentery* [55]

Benzothiazolo triazole derivatives	 R= O–NO_2, H, O–Cl	*S. aureus, E. coli* and *C. ablican* [56]
6-fluoro-7-(substituted)-2-(*N*-p-anilinosulfonamido) benzothiazoles	 R = o–nitroanilino, m–nitroanilino, p–nitroanilino, o–chloroanilino, m-chloroanilino,p-chloroanilino, anilino, morpholino, piperazino, dimethylamino	*S. aureus, S. albus* and *C.ablicans* [57]
Benzothiazolyl carboxamido pyrazoline derivatives	 R = Cl, CH_3, R_1 = C_6H_5, o-$CH_3C_6H_4$, p-$OCH_3C_6H_4$	*S. aureus, E. coli, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Proteus mirabilis* [58]
Substituted 2- (4-aminophenyl) benzothiazoles		Ovarian, breast, lung, renal and colon carnicoma human cell line [59]
(3-bromo-propyl)-(6-methoxy-benzothiazol-2-yl)amine		Pancreatic cancer cell lines [60]
amidino derivatives of phenylene-bisbenzothiazoles		Human cancer cell lines [61]
4-benzothiazole-amino-quinazolines	 R = 2-Cl, 6-CH_3, 2,4,6-OCH_3 	Human cancer cell lines [62]
8-fluoro-9-substituted benzothiazolo (5,1-b) -1, 3, 4-triazole	 R = aniline, o–nitroanilino, m–nitroanilino, p–nitroanilino, o–methylanilino guanidine, hydrazine, p–methylanilino, diphenylamino, 2–carboxyanilino, 4-carboxyanilino ,morpholino, piperzino. R_1 = F ,Br	Perituma Posthuma [63]

substituted 2-amino-benzothiazoles		Eudrilus eugeinae, Megascoplex konkanensis [64]
3-(2-hydrazinobenzothiazole)-substituted indole-2-one	 R = NO_2, Cl	Comparable to standard drug; Albendazole [65]
1-[2-(substituted phenyl)-4-oxothiazolidin-3-yl]-3-(6-fluoro-7-chloro-1,3-benzothiazol-2-yl) ureas	 R = 3-CH_3, 2-OCH_3	Perituma Posthuma [66]
Substituted-2-benzothiazolamines	 R=CH_3 ,C_2H_5, n-prop, i-prop, n-but, n-pent, t-pent, $OCHF_2$, CF_3, OC_2H_5, CF_3, 4-OCF_3, 5-OCF_3, 7-OCF_3	Phenyltetrazolone induced convulsions [67]
2-(-4-arylthiosemicarbazido carbonylthio)- benzothiazoles		Phenyltetrazolone induced convulsions [68]
benzothiazoles containing sulphonamide derivative	 Ar = C_6H_5, o-$CH_3C_6H_4$, m-$CH_3C_6H_4$, p-$CH_3C_6H_4$, o-$OCH_3C_6H_4$, p-$CH_3C_6H_4$, p-ClC_6H_4, p-BrC_6H_4	Electroshock and phenyl tetrazolone induced seizures [69]
2- (3 *H*) -benzothiazolone derivatives	 R= H, CH_3, OCH_3, Cl, F, NO_2 R_1= H, CH_3, C_2H_5, i-C_3H_7, Br, CH_2COOH	Phenyl tetrazolone induced convulsions [69]
2-amino-6-substituted benzothiazole	 R = H, CH_3, OCH_3, F, Cl	Selective COX-2 Inhibition [70]
2-chloro-acetyl-amino-6-substituted benzothiazole	 R = H, CH_3, OCH_3, F, Cl	Selective COX-2 Inhibition [70]

2- (4'-butyl-3', 5'-dimethylpyrazol-1'-yl)- 6-substituted benzothiazoles	 R= H, CH_3, OCH_3, Cl, F	Inhibit human cycloxygenase-2 enzyme (COX-2) [71]
4-butyl-1-(6'-susbtituted-2'-benzothiazolyl) -3-methylpyrazol-5-ones	 R= H, CH_3, C_6H_5, p-ClC_6H_4	Inhibit human cycloxygenase-2 enzyme (COX-2) [71]
(a) N'-(benzo[d]-thiazol-2-yl aminomethyl)sulfanilamide (b) N'-(5-chlorobenzo-[d]thiazol-2-yl aminomethyl) sulfanilamide (c) N'-(5-chloro-6-Fluorobenzo[d]thiazol-2-yl aminomethyl) sulfanilamide (d) N'-(5-chlorobenzo[d]thiazol-2-ylaminomethyl)-N0-(pyramidin-4-yl)-sulfanilamide	 (a): R_1 = H, R_2 = H, R_3 = H (b): R_1 = Cl, R_2 = H, R_3 = H (c): R_1 = Cl, R_2 = F, R_3 = H (d): R_1 = Cl, R_2 = H, R_3 = $C_4H_3N_2$	M. tuberculosis H37 RV strains [72]
Amodiaquine analogues		Antiplasmodial activity against W2 and K1 chloroquine resistant strains of Plasmodium falciparum [73]
2,6-substituted and 2,4-substituted-benzo[d]thiazoles	 (a) : X =CH, R_1 = 4-OH, R_2 = 6-Cl (b) : X =CH, R_1 = H, R_2 = 6-Cl (c) : X = CH, R_1 = 4-NO_2, R_2 = 6-Cl (d) : X = N, R_1 = 4-OCH_3, R_2 = 6-Br (e) : X = CH, R_1 = 4-OCH_3, R_2 = 4-CH_3	Anopheles arabiensis [74]
N-(6-chlorobenzo[d]thiazol-2-yl)-2-morpholinoacetamide		Maximum glucose lowering effects comparable to the standard drug glibenclamide [75]

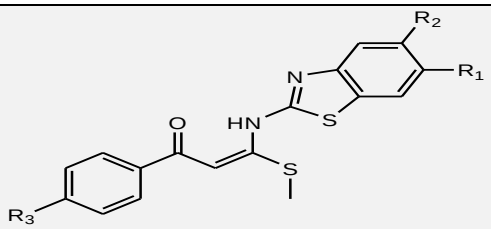
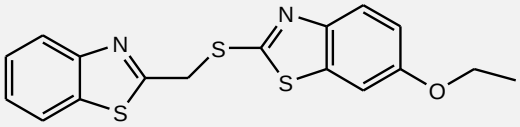
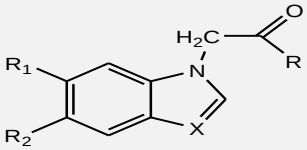
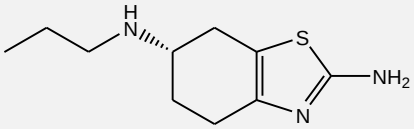
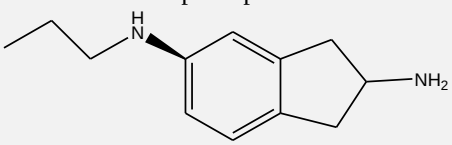
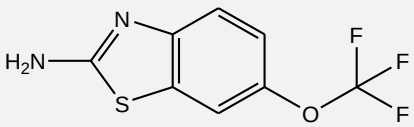
(E)-3-(benzo[d]thiazol-2-ylamino) phenylprop-2-en-1-ones	 R_1 = H, CH_3, $OC2H_5$ R_2 = H, CH_3 R_3 = Br, Cl, F, CH_3, OCH_3	show appreciable antidiabetic activity [76]
6-ethoxy substituted benzothiazoles		enhance the rate of glucose uptake in L6 myotubes in AMPK-dependent manner [77]
2-piperazinyl benzothiazoles	 X = S, O R_1= H, Cl R_2= H, CH_3 , C_6H_5-CO, (oCl-C_6H_4-CO) R = 1-morpholinyl, 1-pyrrolidinyl diethylamino, OCH_3, OC_2H_5	psychotropic diseases *e.g.*, anxiety, depression and schizophrenia [78]

TABLE 3: BENZOTHIAZOLES IN CLINICAL TRIALS

Drug	Indication	Clinical trial
Pramipexole 	Binge Eating Disorder	Phase 3 [79]
	Cocaine Addiction	Phase 1 [80]
	Cocaine Abuse	
	Cocaine Dependence	
	Amyotrophic Lateral Sclerosis	Phase 2 [81]
	Early Parkinson's Disease	Phase 4 [82]
	Bipolar Disorder	Phase 4 [83]
	Tourette Syndrome	Phase 2 [84]
	Fibromyalgia	Phase 2 [85]
	Alzheimer's Disease	Phase 2 [86]
	Major Depressive Disorder	Phase 4 [87]
	Restless Legs Syndrome	Phase 4 [88]
Dexpramipexole 	Hypereosinophilic Syndrome	Phase 2 [89]
	Chronic Sinusitis With Nasal Polyps and Eosinophilia	Phase 2 [90]
	Amyotrophic Lateral Sclerosis	Phase 1 [91]
	Fragile X Syndrome	Phase 4 [92]
	Post-traumatic Stress Disorder (PTSD)	Phase 1, Phase 2 [93]
	Depression	Phase 2 [94]
	Autism Spectrum Disorders	Phase 2, Phase 3 [95]
	Adult Solid Neoplasm,	Phase 1 [96]
Riluzole 	Recurrent Melanoma, Stage IIIA Skin Melanoma, Stage IIIB Skin Melanoma, Stage IIIC Skin Melanoma	
	Obsessive-compulsive Disorder (Ocd)	Phase 2 [97]
	Obsessive-Compulsive Disorder, Autism Spectrum Disorder, Autism, Asperger Disorder, Developmental Disorder	Phase 2 [98]
	Cervical Spondylotic Myelopathy	Phase 3 [99]

Cerebellar Ataxia	Phase 2, Phase 3 [100]
Melanoma (Skin)	Phase 2 [101]
Major Depressive Disorder	Phase 2 [102]
Social Anxiety Disorder, Performance Anxiety	Phase 2, Phase 3 [103]
Spinal Muscular Atrophy (SMA)	Phase 2, Phase 3 [104]
Huntington Disease	Phase 3 [105]
Mood, Memory Deficit	Phase 4 [106]
Tourette Syndrome	Phase 4 [107]
Multiple Sclerosis	Phase 2 [108]
Multiple System Atrophy, Progressive Supranuclear Palsy	Phase 3 [109]

CONCLUSION: Benzothiazole is a versatile class of heterocyclic compounds which exhibits a variety of biological activities. Many procedures for their synthesis have been developed among which the condensation of 2-aminothiophenols with various acids/ aldehydes/ ketones/ nitriles/ esters is widely used. A large number of benzothiazoles have been developed in recent years possessing appreciable anti-tubercular, antimicrobial, antimalarial, anticonvulsant, anthelmintic, analgesic, anti-inflammatory, antidiabetic and anticancer activities. This comprehensive review will be highly useful to the researchers working in this area. They can discover better and easy ways of synthesis with enhanced yield, purity in shorter span of time. They can further explore this class to increase the ambit of existing biological activity profile.

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