Advances In Benzothiazole Scaffold: A Review of Synthesis and Medicinal Significance

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ABSTRACT

*A large number of bioactive heterocycles have been synthesized and reported to exhibit a wide range of biological properties including anticancer, antimicrobial, antidiabetic, anticonvulsant, anti-inflammatory, antiviral, antitubercular activities. In recent years there have been some interesting developments in the biological activities of benzothiazole derivatives. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities. The heterocycles bearing benzothiazole nucleus were synthesized using One-pot synthetic approach, which involved One-pot condensation of 2-aminothiophenol with different aromatic aldehydes, alcohols and carboxylic acids. Microwave promoted Suzuki-Miyaura coupling approach and Catalytic synthetic methodology were also employed in this synthesis. This review does not only disclose facile synthetic methodologies to benzothiazoles nucleus and their Schiff bases but also their medicinal significance and structure activity relationship can be seen in **Graph 1.***
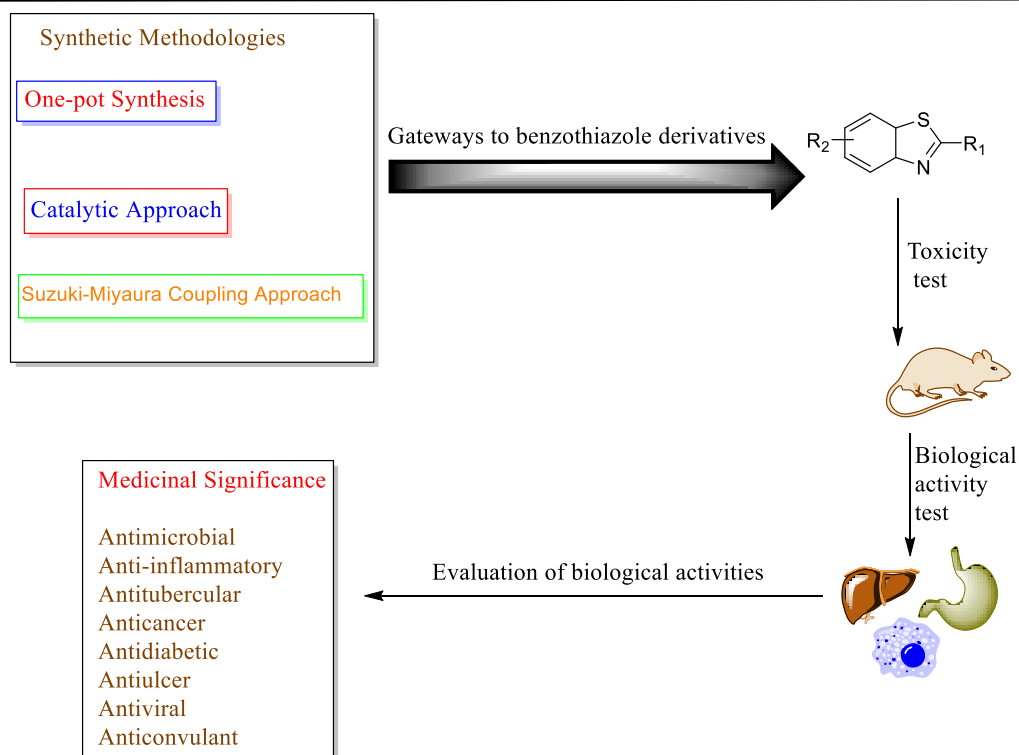
Graph 1 : Graphical abstract of Synthesis and medicinal significance of benzothiazole derivatives

INTRODUCTION

Benzothiazole are classes of organic compound characterized with the basic skeleton (C_7H_5NS). They belong to the family of bicyclic heterocyclic compounds having benzene nucleus fused with five-membered ring comprising nitrogen and sulfur atoms. 2-substituted benzothiazole has emerge in its usage as a core structure in the diversified therapeutically applications. The study of structure-activity relationship interestingly reveals that change of the structure of substituent group at C-2 position commonly results to change of its bioactivity. Benzothiazole and their Schiff bases are very important biological compound with reference to various biological activities such as antimicrobial [1-5], anticancer [6-9],anti-helmintic [10],anti-diabetic activities [11], anti-tubercular [12,13], anti-malaria [14], anticonvulsant [15-16], analgesic [17] ,anti-inflammatory [18], antitumor [19] anti-viral [20,21], anti-oxidant [22], anti-glutamate and anti-parkinsonism [23], muscle relaxant activities [24], neuroprotective [25], inhibitors of several enzymes [26].

Marine and terrestrial natural compounds where the original sources of benzothiazole ring system, which was widely used as vulcanization accelerators, antioxidants, plant growth regulators, anti-inflammatory agents, enzyme inhibitors, imaging reagents, fluorescence materials and electroluminescent device as a result of its highly pharmaceutical and biological activity [27-30]. They are widely found in bioorganic and medicinal chemistry with application in drug discovery [31]. Thus, Benzothiazole is a privileged bicyclic ring system with multiple applications. In the 1950s, a number of 2- amino benzothiazole derivatives were report as central muscle relaxants. Since then, medicinal chemists have not taken active interest in this chemical family. Biologist's attention was drawn to this series when the pharmacological profile of riluzole was discovered [32]. Riluzole (6- trifluoromethoxy-2-benzothiazolamine, PK-26124, RP- 25279, Rilutek) was found to interfere with glutamate neurotransmission in biochemical, electrophysiological, and behavioral experiments. After that benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity. Various benzothiazoles such as 2-aryl benzothiazole received much attention due to unique structure and its uses as radioactive amyloid imagining agents [33] and anticancer agents [34].

In last few years, it was reported that benzothiazole, its bioisosters and derivatives had antimicrobial activities against Gram-negative, Gram-positive bacteria (e.g. *Enterobacter, Pseudomonas aeruginosa, E. coli,* and *Staphylococcus epidermidis* etc.) and the yeast (e.g., *Candida albicans*). Benzothiazole nucleus as seen in **Figure 1** has wide applications in dyes such as thioflavin [35]. According literature, several works on benzothiazole derivatives have been reported, briefly describing the synthetic strategies and their biological activities of [36-39].
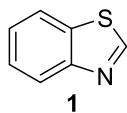
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Figure 1. Basic Structure of Benzothiazole

The basic structure of benzothiazole consist of benzene ring fused with 4, 5 position of thiazole. The IR spectrum of the compound showed absorption peak at $3344cm^{-1}$, $3025cm^{-1}$, $1630cm^{-1}$, $690cm^{-1}$ due to stretching of N-H, C-H, C=N, C-S [40]. The Structure Activity Relationship of the benzothiazole nucleus is summarized in **Figure 2** below.
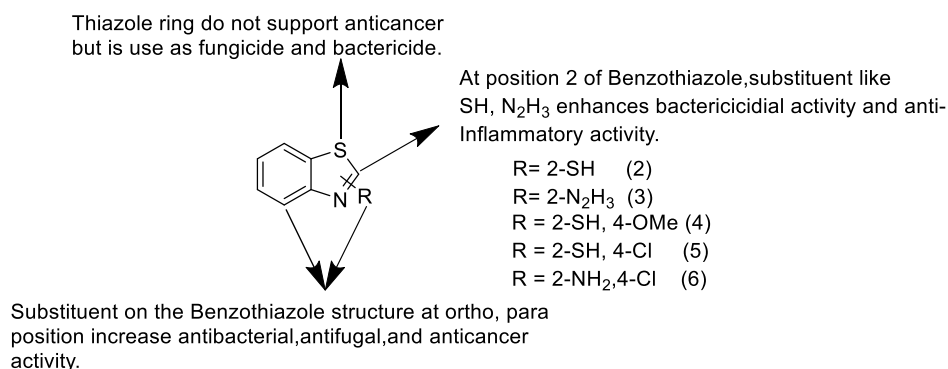
Thiazole ring do not support anticancer but is use as fungicide and bactericide.

At position 2 of Benzothiazole,substituent like SH, N_2H_3 enhances bactericicidial activity and anti-Inflammatory activity.

R= 2-SH   (2)
R= 2-N_2H_3 (3)
R = 2-SH, 4-OMe (4)
R = 2-SH, 4-Cl   (5)
R = 2-NH_2,4-Cl (6)

Substituent on the Benzothiazole structure at ortho, para position increase antibacterial,antifugal,and anticancer activity.

**Figure 2.** Structure Activity Relationship of Benzothiazole nucleus

Compounds (**2 and 3**) were found to exhibit bactericidal activity and anti-inflammatory [41]. Introduction of methoxy group ($-OCH_3$) at position 4 of 2-mercapto benzothiazole (**4**) was found to exhibit antibacterial activity [3]. The presence of electron withdraw group (-Cl) at position 4 of 2-mercaptobenzothiazole (**5**) increases antifungal activity [3]. Chloro substituted amino benzothiazole (**6**) is found to encourage sensitivity to cancer line compare to flouro substituted benzothiazole [42]. Heterocyclic rings, 1-acetyl-pyrazoline and thiazole do not support eminently for anticancer activity but is use as fungicide and bactericide.

Synthetic Approaches to Benzothiazole Derivatives (2)

To date, different methods have been developed for the preparation of benzothiazole derivatives, some of which includes:
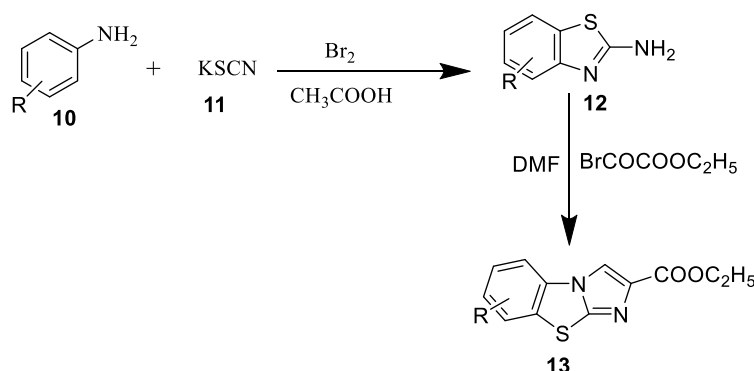
Synthesis of Benzothiazole from Aniline (2.1)

Murthi and Pathak (2008) reported the Synthesis of substituted 2-mercapto benzothiazole derivatives (**9**) with different substituents at 4, 5, and 6-position in the benzothiazole ring system and this is carried out in two steps; step 1 involved the conversion of substituted anilines (**7**) to its hydrochloride salts. Subsequently the Aniline hydrochloride salt (**8**) was then cyclized in step 2 to substituted 2-mercaptobenzothiazoles by reacting with carbon disulphide in presence of sulfur in an alkaline medium **Scheme 1** [3].
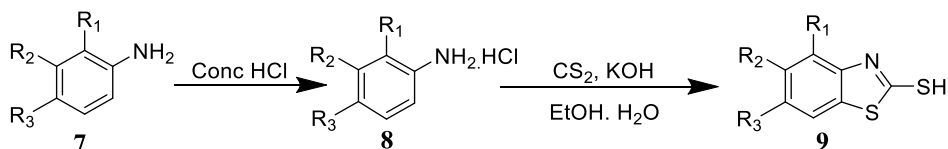
Scheme 1: Synthesis of 2-mercapto benzothiazole derivatives

Synthesis from Aniline and Potassium Thiocyanate (2.1.1)

Trapani, *et al.*, (1992) reported the synthesis of substituted 2-ethoxycarbonyl-imidazo benzothiazole derivatives (**13**), this was carried out by reacting different substituted aniline (**10**) and potassium thiocyanate (**11**) in presence of bromine in acetic acid to give the intermediate 2-amino substituted benzothiazole (**12**). Stoichiometric amount of (**12**) and ethyl 2-bromo-2-oxoacetate in dimethyl formamide were reacted to afford the targeted derivatives (**13**) **Scheme 2** [43].
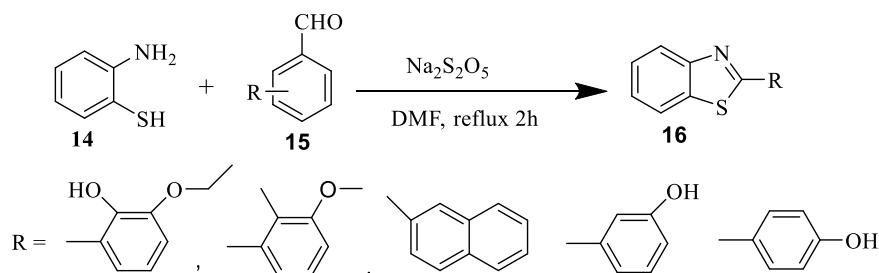
Scheme 2: Synthesis of 2-ethoxycarbonyl-imidazole benzothiazole derivatives

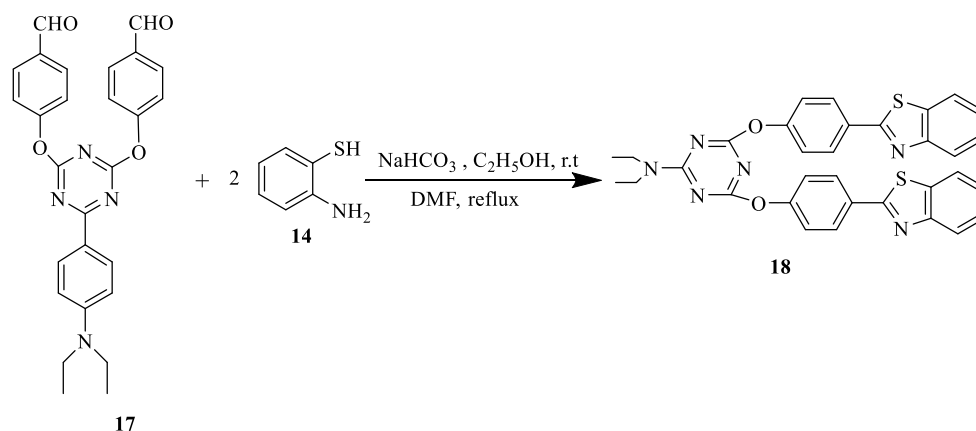**Synthesis of Benzothiazoles from 2-Aminothiophenol (2.2)**

Synthesis of benzothiazole from 2-aminothiophenol and different aromatic aldehydes (2.2.1)

Khan, *et al.,* 2011 reported an efficient method for the synthesis of 2-substituted benzothiazoles (16) of which high yield of 2-substituted benzothiazole (16) was obtained by condensation of 2-aminothiophenol (14) with different substituted aromatic aldehydes (15) in N,N-dimethylformamide (DMF) and sodium metabisulfite ($Na_2S_2O_5$) under reflux conditions of 2 hours **Scheme 3** [44].

Scheme 3: Synthesis of 2-substituted benzothiazole from 2-aminithiophenol and different aromatic aldehydes

Yamazaki, *et al.*, (2015) employed similar method for the synthesis of 4, 6-bis (4-[benzo[d]thiazole-2-yl) phenoxy)-N-N-diethyl-1,3,5-triazin-2-amine **(18).** This was achieved by initially treating aromatic aldehyde, ((diethylamino)phenyl)-1,3,5-triazine-2,4-diyl)bis-(oxy)) dibenzaldehyde (DIPOD) **(17)** with solution of $NaHSO_3$ in ethanol at room temperature and then subsequently added 2-aminothiophenol **(14)** in DMF under reflux conditions for 3 hours to afford targeted compound **(18)** in 74% yield **Scheme 4** [45]. Synthesis of benzothiazole from 2-aminothiophenol and substituted benzaldehyde with some modifications is common, as found in many literature reports **Scheme 4** [46,47].

Scheme 4: Synthesis of 4, 6-bis (4-[benzo[d]thiazole-2-yl) phenoxy)-N-N-diethyl-1, 3, 5-triazin-2-amine

A more similar approach has been employed for the synthesis of benzothiazole **(20)** from aryl aldehyde **(19)** and 2-aminothiophenol **(14).** This approach involves the reaction of the 2-aminothiaphenol **(14)** with 2-hydroxybenzaldehyde **(19)** in the presence of 30% H_2O_2 and cerium

ammonium nitrate (NH$_4$CeNO$_2$) in acetonitrile at 50°C **Scheme 5** [48,49]. Beside this, 2-substituted benzothiazoles **(20)** have also been synthesized from substituted aldehyde and 2-aminothiophenol in presence of various catalysts and reaction conditions such as montmorillonite, SiO$_2$/graphite, under microwave and p-TsOH [50], diethylbromophosphonate/t-butyl hypochlorite; acetonitrile [51], H$_2$O$_2$/HCl in ethanol [52], AcOH/air; microwave or thermal heating [53] and Baker's yeast, dichloromethane [54].
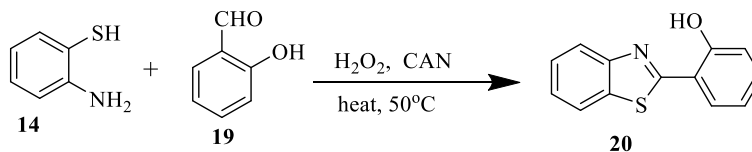
**Scheme 5: Synthesis of 2-(Benzo[d]thiazole-2-yl) phenol**

Synthesis of benzothiazoles from 2-aminothiophenol and different carboxylic acids (2.2.2)

You, *et al.*, (2009) reported a perculiar method for the synthesis of naphthyridine derivatives of benzothiazole (24). In this method, 2-aminothiophenol (14) undergoes cyclization on treatment with naphthyridine-3-carboxylic acid (21) in presence of polyphosphoric acid (PPA) at 170– 250°C and affords compound (22) in moderate yield. Consequently, intermediate (22) was nitrated to give intermediate, which is followed by reduction of compound (23) with Pd/C affording the final product (24) in 40–73% yield **Scheme 6** [55].

Y = C, N
Z = H,F,(S)-CH(CH$_3$)CH$_2$O-
R^1= H, Cl,NO$_2$, NH$_2$
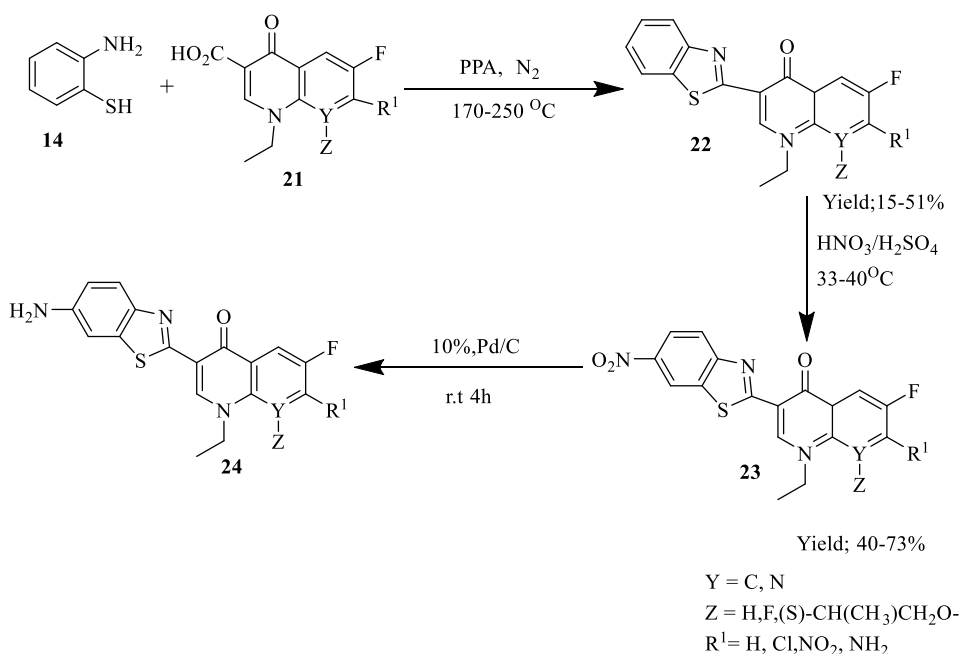
Scheme 6: Synthesis of naphthyridine derivatives of benzothiazole

Marques, *et al.*, (2013) reported the coupling of 2-aminothiophenol (14) with amino acid (or ester) (25) to give access to 2- substituted benzothiazoles (26). In this reaction, 2-aminothiophenol (14) was reacted with amino acid (or ester) (25) such as glycine ethyl ester and D-valine to give corresponding benzothiazole (27), in the presence of dehydrating agent such as PPA at 220°C within 4h **Scheme 7** [56]. It has also been observed that benzothiazoles are produced in a high yield when ethyl ester of amino acid is used as starting material instead of amino acid.

X-R$_1$ = CH$_2$ CH-(R)-iPr
Yield: 40- 50%
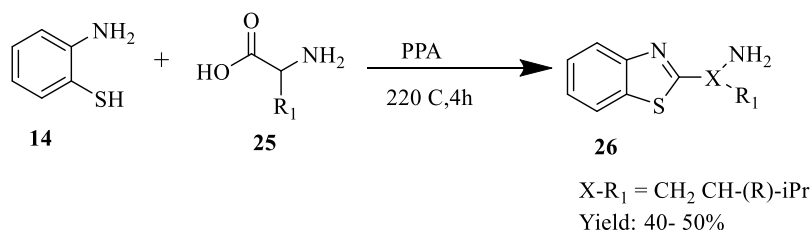
Scheme 7: Synthesis of benzothiazole from 2-aminothiophenol and amino acids

A convenient single step method for the synthesis of 2- aryl benzothiazoles (29) has been reported by utilizing substituted amino benzoic acid (27) and substituted 2-aminothiophenol (29) in the presence of PPA at higher temperatures [57,58]. Simultaneously, 4-nitrobenzoic acid (30) was utilized for synthesis of benzothiazole (29), and this was achieved by subsequent reduction of the compound (30) using Fe/NH$_4$Cl to afford compound (29) in 50-60% yield **Scheme 8**. It was also observed that electron withdrawing groups on the benzoic acid counterpart gave high yields of the product.
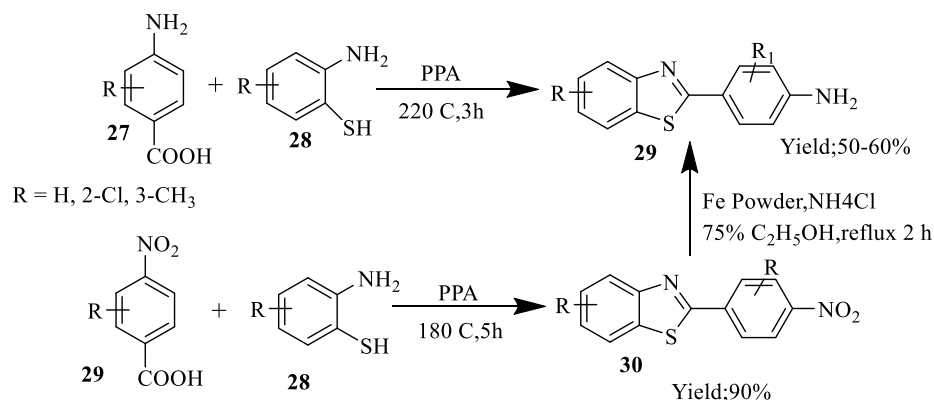
Scheme 8: Synthesis of 2-(4-nitrophenyl) Benzo[*d*]thiazole derivatives

**Synthesis of benzothiazole from 2-aminothiophenol and alcohols (2.2.3)**

There are few reports in literature where alcohols have been used as reactants in the starting material. Rangappa, *et al.*, (2011) reported the one-pot tandem approach for synthesis of benzothiazole (**32)** in which excellent yields, and was gotten using different of alcohols (**31**) and 2-aminothiophenol (**14**) without any oxidant. This process includes oxidation of alcohols to aldehydes followed by cyclization with (**14**) and finally propylphosphonic anhydride (T$_3$P) mediated dehydrogenation under mild reaction conditions (0–25°C). It has also be observed that the reaction of (**14**) with variety of aromatic, aliphatic and heterocyclic substituents reacts well under these optimized reaction conditions and provides access to high yield of the product **Scheme 9** [59].
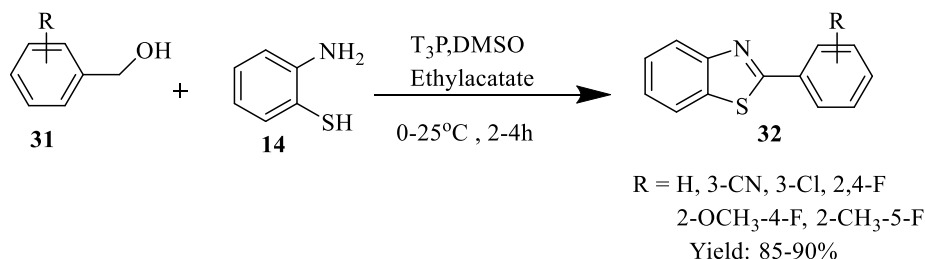
Scheme 9: Synthesis of Substituted 2-phenylbenzothiazole derivatives

Suzuki-Miyaura coupling reaction (2.3)

Heo, *et al.,* (2006) reported that microwave promoted Suzuki-Miyaura coupling of 2,6-dichlorobenzothiazole(**33**) with arylboronic acid. This reaction was promoted efficiently by heating the two reactant in a microwave, to produce 6-chloro-2-phenylbenzo[*d*]thiazole in a highly regioselective manner (**34**) which then serve as the reactant for preparing 4-(2-phenylbenzo[b]thiophene-6-yl) morphine (**35**) **Scheme 10** [34].
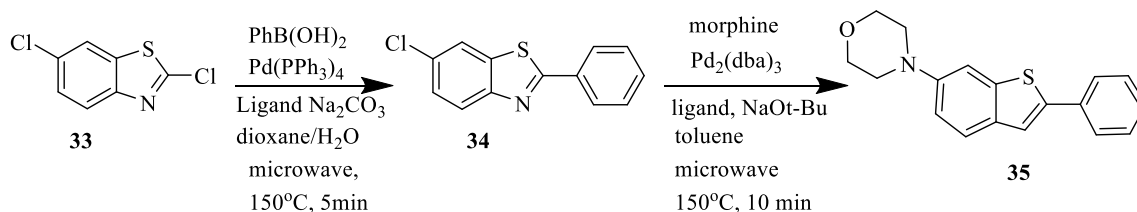
Scheme 10: Suzuki-Miyaura coupling reactions of 2,6-dichlorobenzothiazole with arylboronic acid

Synthesis of benzothiazole derivatives from hydrazine (2.4)

Latrofal, *et al.,* (1996) reported the synthesis of 1, 3, 4-triazolo benzothiazole (37) from 2-hydrazinylbenzothiazole (36), which was obtained by the hydrazinolysis of benzothiazole-2-thiol (2), and mixture of trimethyl orthoformate and silica gel in xylene **Scheme 11** [60].
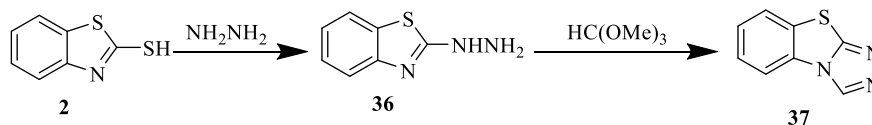
Scheme 11: **Synthesis of 1, 3, 4-triazolo benzothiazole**

Chemical Synthesis of Benzothiazole Derivatives (2.5)

Arun, *et al.,* (2010), reported the synthesis of N-(4, 5-dihydro-1H-imidazol-2-yl)-6-substituted-1,3-benzothiazol-2-amines (42a-c) and N-(1 H-benzimidazol-2-yl)-6-substituted-1,3-benzothiazol-2-amines 43(a-c). This was achieved by preparing 6-substituted-2 aminobenzothiazole (40) through condensation of p-substituted aniline (38) with ammonium thiocyanate (49) in the presence of bromine as a catalyst. This reaction was followed by, addition of an aqueous solution of sodium hydroxide, Carbon disulphide and methyl iodide to a well stirred ice solution of (40) in dimethyl formamide, after an interval of 30 minutes, and then stirred continually for 4 hours. The mixture was poured in ice cold water and the resulting solid N-(benzothiazole-2-yl)-1, 3-bis (methylthio) propan-2-imine (41) was washed with wat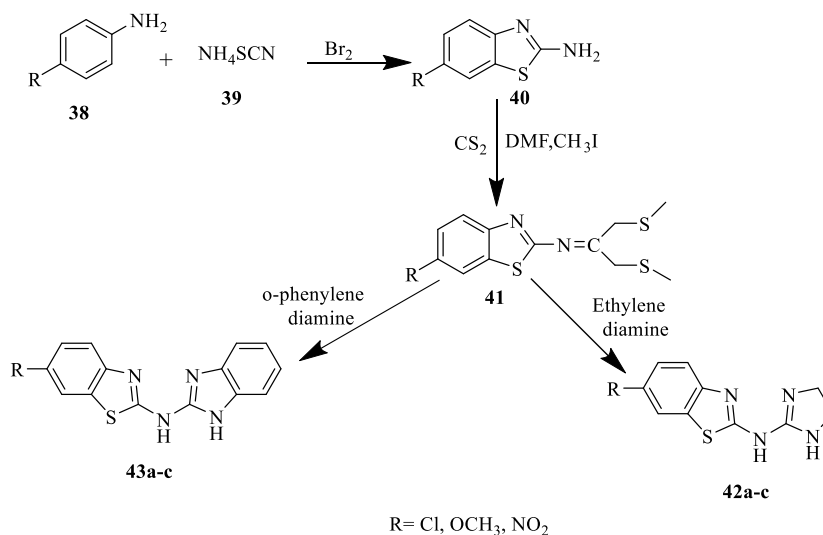er and recrystallized from aqueous ethanol. Ethylene diamine in dimethyl formamide and O-phenylene diamine in dimethyl formamide were then added to the resulting solid (41) and stirred at room temperature. The reaction mixture was reflux for 8 hours and then poured on crushed ice to get the targeted products 42(a-c) and 43(a-c) respectively **Scheme 12** [61] **Table 1.**

Scheme 12: Synthesis of N-(4, 5-dihydro-1H-imidazol-2-yl)-6-substituted-1, 3-benzothiazol-2-amines (42a-c) and N-(1 H-benzimidazol-2-yl)-6-substituted-1, 3-benzothiazol-2-amines

Table 1: Physical properties of compound (41a-c, 42a-c and 43a-c)

Compounds	R	Molecular Formula	Melting point °C
41a	Cl	$C_{10}H_9C_lN_2S_3$	180-184
41b	OCH₃	$C_{11}H_{12}N_2OS_3$	159-161
41c	NO₂	$C_{10}H_9N_3O_2S_3$	216-219
42a	Cl	$C_{10}H_9C_lN_4S$	230-234
42b	OCH₃	$C_{11}H_{12}N_2OS$	196-199
42c	NO₂	$C_{10}H_9N_5O_2S$	216-218
43a	Cl	$C_{14}H_9C_lN_4S$	250-255
43b	OCH₃	$C_{15}H_{12}N_4OS$	150-153
43c	NO₂	$C_{14}H9N_5O_2S$	272-275

Samuel, *et al.,* (2021) reported the synthesis of benzothiazole derivatives of sulphonamide 49(a-b). In this synthetic procedure, a solution of

diphenylamine (44) and ammonium thiocynate (39) in methanol was stirred at room temperature until the salt dissolved and become light brown in colour. On completion of the reaction which was monitored with thin layer chromatography, H_2SO_4 was added until the pH of the solution was 2. The orange colour precipitate obtained was filtered with suction pressure and crystallized with water to yield the product N-(biphenyl-4-yl) thiourea (45). A freshly prepared solution of bromine gas, chloroform at the temperature of $0^{\circ C}$ to $-5^{\circ C}$ was then added to well cooled solution of 45 in chloroform to obtain a solution of 2-amino-6-phenylbenzothiazole (46). After evaporation of the solvent, 46 was washed with water and recrystallized to obtain cream colour crystal with mp $158^{\circ C}$ and yield 64%. A solution of (47) in chloroform was added to a well stirred solution of benzosulphonyl chloride (47) in chloroform and para-toulenesulphonyl chloride (48) in chlorofom separately. The reaction mixtures were then reflux for 30 minutes. The chloroform was removed by evaporation and the residues were treated with dilute hydrochloric acid. The reaction mixtures were boiled at $45^{\circ C}$, decolourised with activated charcoal and filtered and a hot $NaHCO_3$ was then added to the filtrate and stirred. The complete reactions were ascertained by litmus paper which showed no color change. The crude white products 49(a-b) were filtered upon cooling and washed with methanol and recrystallize with 1:1 chloroform/ methanol mixture **Scheme 13** [62].
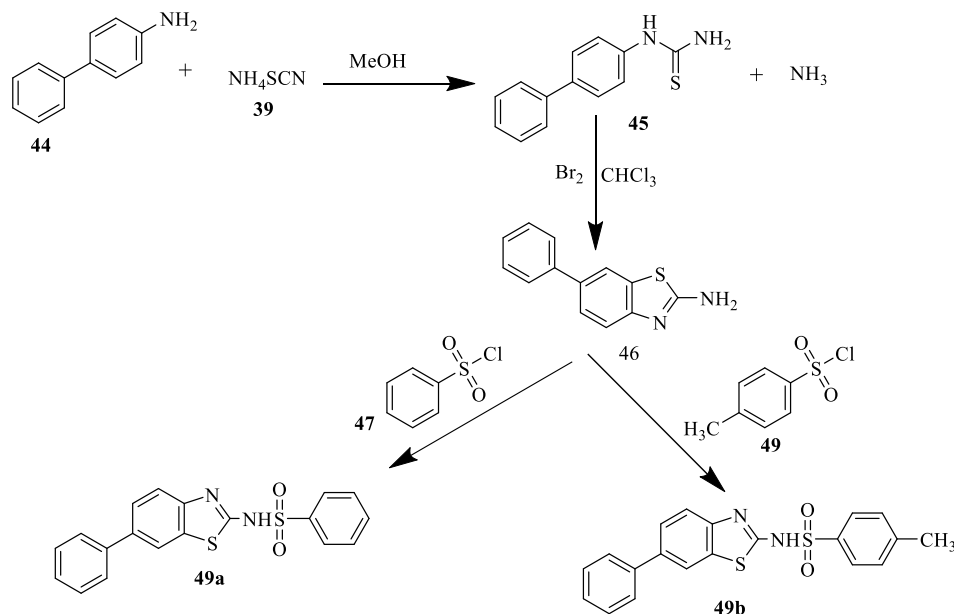
Scheme 13: Synthesis of benzothiazole derivatives of sulphonamide

Shafi, *et al.,* (2012) reported the synthesis of 2-mercaptobenzothiazole and 1, 2, 3-triazole based bis-heterocyclic compounds. This was achieved by reacting benzothiazole-2-thiol (**2**) with propargyl bromide (**50**) in dioxane in the presence of triethylamine to obtained compound (**51**) which was then treated with aromatic azides (**52**) using click chemistry, to afforded final product **53(a-d) Scheme 14** [63].

53a: $R^1 = Cl$; $R^2 = H$
53b: $R^1 = H$; $R^2 = F$
53c: $R^1 = H$; $R^2 = Br$
53d: $R^1 = H$; $R^2 = NO_2$
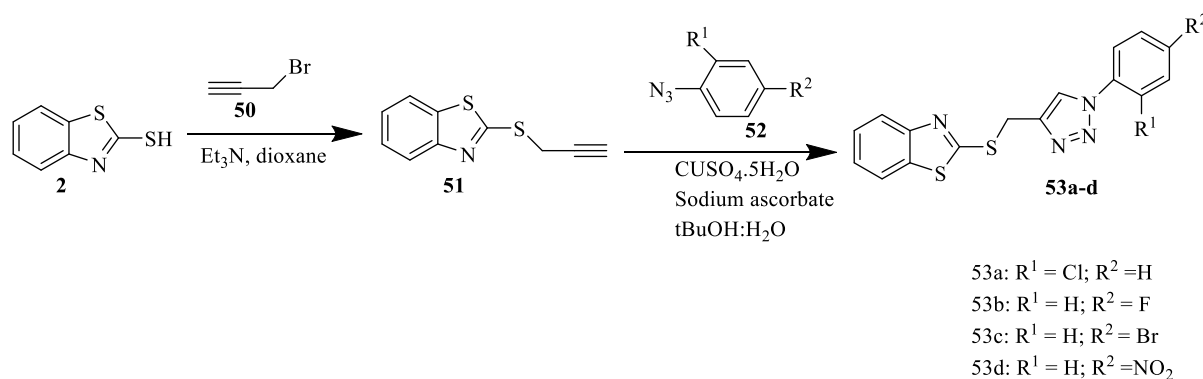
Scheme 14: Synthesis of 1, 2, 3-triazole based bis-heterocyclic compounds

Vrushali *et al.*, (2015) reported the synthesis of 2-amino-6-methoxy benzothiazole derivative. In this synthetic procedure, 6-methoxy-1,3-benzothiazol-2-amine (54) in dry acetone was dissolved and potassium carbonate was added, the reaction mixture was irradiated for 120 seconds and then ethyl chloroacetate was added and the reaction mixture was stirred and irradiated for another 180 seconds, the reaction mass was then neutralized by using glacial acetic acid and then extraction was done by using diethyl ether. The completion of the reaction was monitored by thin

layer chromatography and the compound ethyl [(6-methoxy-1,3-benzothiazol-2-yl)amino]acetate (55) was obtained. Compound (55) was then dissolved in ethanol treated with mixture of hydrazine hydrate and hydrochloride solution and reflux for 6 hours. The reaction was cooled, poured into ice water, and a solid product 2-[(6-methoxy-1,3-benzothiazol-2-yl)amino]acetohydrazide (56) was obtained, which is then filtered, dried, and recrystallized from ethanol **Scheme 15** [64].
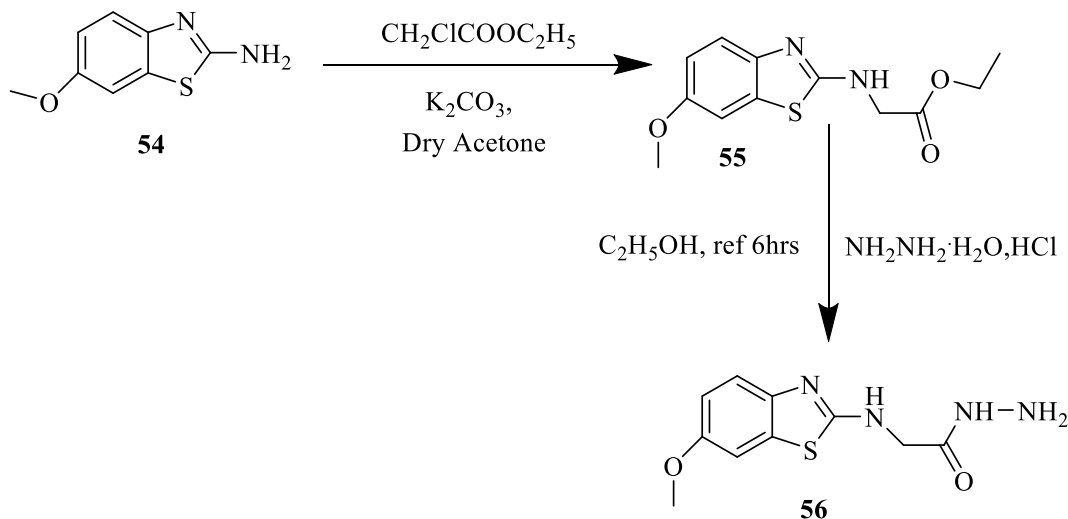
Scheme 15: Synthesis of hydrazino benzothiazole

David, *et al*., (2018) reported the synthesis of benzothiazole derivatives bearing carboxamide and sulphonamide functionalities. In this synthetic procedure, sodium carbonate was added to a solution of amino acids 58(a-h) in water with continuous stirring until all the solutes dissolved. The solution was cooled to -5$^{\circ C}$ and the appropriate benzenesulphony chloride 57(a-c) was added in four portions over a period of 1h. The slurry was further stirred at room temperature for 4 hours. The progress of the reaction was monitored using thin layerchromatograohy plate. Upon completion, the mixture was acidified using aqueous hydrochloric acid to pH of 2. The crystals was then filtered via suction and washed with pH 2.2 buffer. The pure products 59(a-l) were dried over self-indicating fused silica gel in a desiccator. Appropriate benzenesulphonamides 59(a-f) was dissolved in sodium hydroxide in a round bottom flask; benzoyl chloride (60) was then added to the solution and stirred at room temperature. The reaction progress was monitored by thin layer chromatography to the disappearance of the benzenesulphonamide spot. Upon completion, the solution was transferred into a beaker containing crushed ice and then acidified to pH 3 with concentrated hydrochloric acid. The solid was collected via suction filtration and transferred into a beaker containing tetrachloromethane (CCl$_4$) and covered with watch glass and boiled for 10 minutes. The mixture was allowed to cool slightly and then filtered. The products 61(a-f) obtained were washed with CCl$_4$ and dried over fused self-indicating silica gel in a desiccators. To a suspension of the substituted benzenesulphonamide 61(a-f) 62 (g-i) in dry toluene equipped with Dean-Stark apparatus for azeotropic removal of water, was added 2-amino-benzothiazole (2) and boric acid at room temperature and then refluxed for 6 hours. On completion (as monitored by thin layer chromatography), the amide products were precipitated out from the reaction mixture by adding n-hexane. The carboxamides 62(a-l) were obtained via suction filtration, washed with n-hexane and dried over fused silica gel or concentrated using rotary evaporator and dried over vacuum in the case of oily products **Scheme 16** [65].
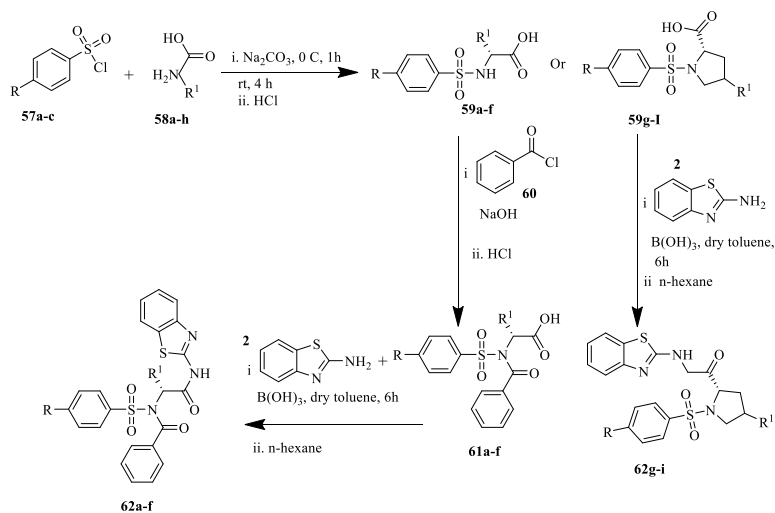
Scheme 16: Synthesis of benzothiazole derivatives bearing carboxamide and sulphonamide functionalities
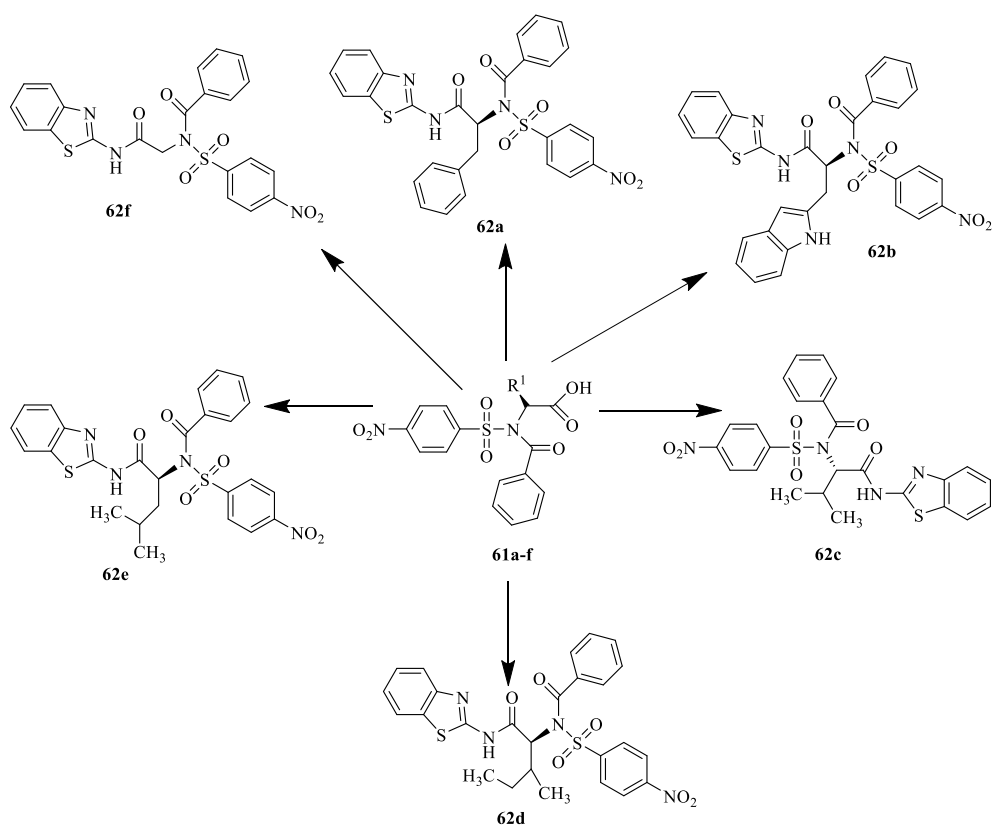
Scheme 16.1: N-benzolated benzene sulphonamide derivatives 62 (a-f)
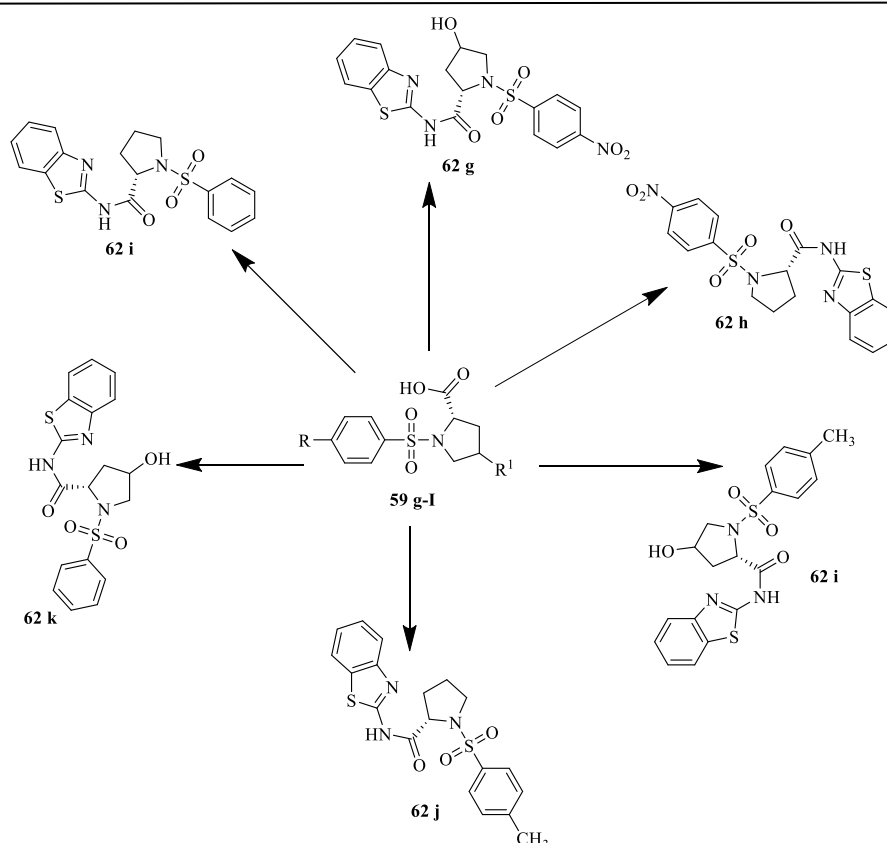
Scheme 16.2: Proline derivatives of Benzenesulphonamide 62(a-l)

Sarkar, *et al* (2018) reported the synthesis of benzothiazole derivatives of azetidinones. The intermediate 2-amino-5-fluorobenzothiazole (66) was prepared by reaction of 4-fluoro substituted aniline (65) and potassium thiocyanate in glacial acetic acid with bromine as catalyst. The 2-amino-5-fluorobenzothiazole (66), absolute ethanol, anhydrous potassium trioxocarbonate (IV) and ethyl chloroformate (67) were mixed at $0^{\circ C}$ - $5^{\circ C}$. The mixture was heated for 7-8 hours at $60^{\circ C}$- $70^{\circ C}$ .The solution was filtered, and the solvent was evaporated under reduced pressure to obtain the product (68) as a solid,which was recrystallized using ethanol. The resulting product Ethyl (5-fluorobenzothiazole-2-yl) carboxamate (68) was treated with hydrazine hydrate and then dissolved in ethanol. The reaction mixture was refluxed for 5 hours and cooled to room temperature. The separated products (69) were filtered, and the residue was washed wit ethanol and recrystalized using ethanol. The resulting product N-(5-fluorobenzothiazole-2-yl) carbohydrazide (69) was dissolved in absolute ethanol and substituted benzaldehyde was added and refluxed for 3 h and then the solvent was removed under reduced pressure to yield Schiff base (70). To a solution of Schiff base in N, N-dimethylformamide (DMF), chloroacetylchloride and triethyl amine were mixed and stirred for 24 hours. The reaction mixture was poured into cooled water and the liberated compound was extracted using chloroform. Evaporation of the compound afforded the corresponding azetidinones (71) **Scheme 17** [66].
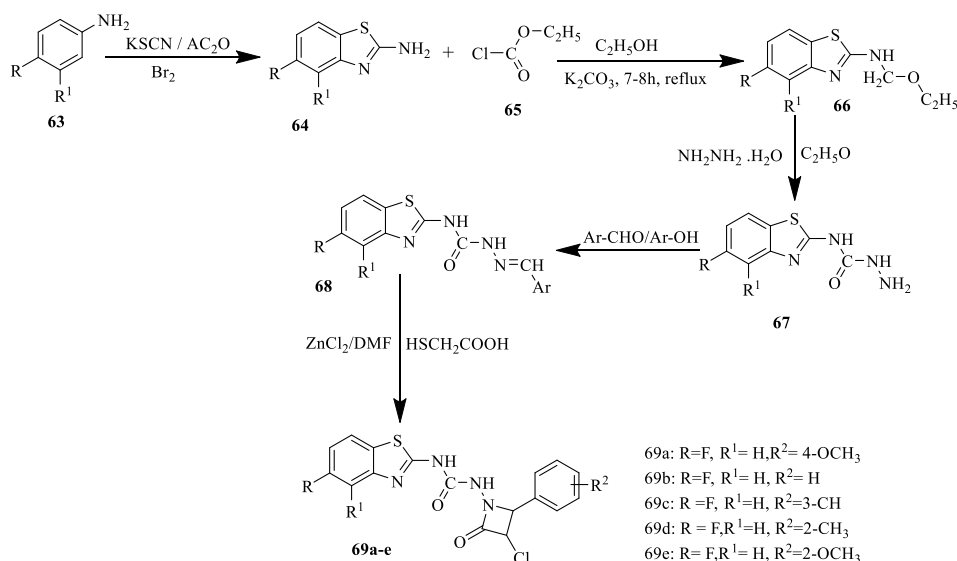
Scheme 17: Synthesis of benzothiazole derivatives of azetidinones
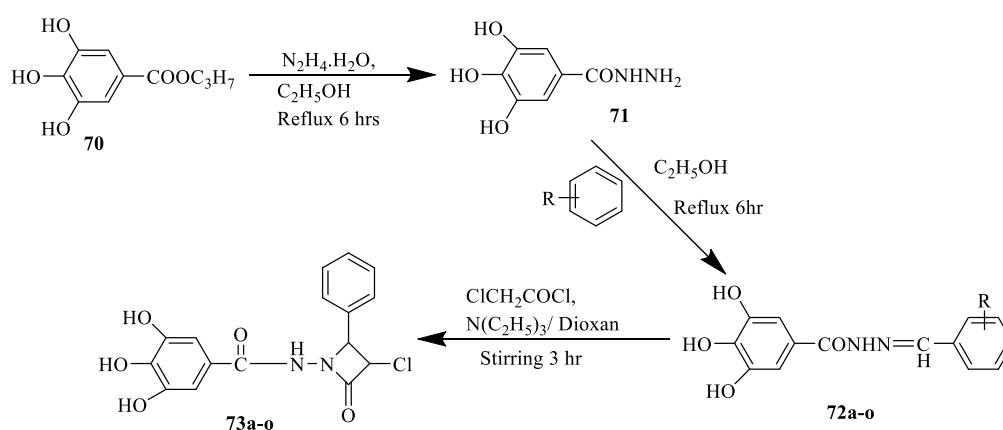
Scheme 18: Synthesis of Novel Trihydroxybenzamido azetine-2-one derivatives

Previously,in the year 2011 derivatives of azetidinone **73(a-o)** of promising anti-tubercular activity were prepared by IIango and Arun kumar. Propyl gallate (**70**) in ethanol and hydrazine hydrate were refluxed for 6 hours. The excess of solvent was distilled off under reduced pressure using a pump. The cold residual mass was washed with distilled water, filtered and dried. The crude product obtained was recrystallised from methanol to yield galloylhydrazine (**71**).An equimolar quantities of the galloylhydrazide (**71**) and various aromatic aldehydes in ethanol were refluxed for 6 hours. The completion of the reaction was monitored on silica gel G precoated TLC plates using hexane and ethyl acetate (1:1) as an eluent and observed under UV light. The resultant mixture was poured into ice cold water. The crude Schiff bases were washed, filtered, dried and recrystallised from ethanol to yield N-substituted arylidene galloyl hydrazide (**72**). The mixture of N-substituted arylidenegalloylhydrazide (**72**) and triethylamine were dissolved in 1,4-Dioxan and a well stirred cold solution of chloroacetylchloride was added drop wisely for 20 minutes, then the mixture was concentrated, cooled and then poured into ice cold water, filtered off and recrystallized from methanol to yield the product 4-Aryl-3-chloro-N-3,4,5-trihydroxy benzamido)-2-azetidinones **73(a-o) Scheme 18** [67] **Table 2**.

| Compound	R	Color	Molecular weight	% yield	Melting point	Retention factors value
73a	H	Dull white	348.1	64	221	0.63
73b	2-OH	Pale yellow	364.7	68	198	0.78
73c	2-OH-3-OCH3	White	394.7	68	217	0.72
73d	3-OH	White	364.7	62	206	0.69
73e	4-OH	Pale yellow	364.7	72	228	0.83
73f	2-Cl	Light Brow	382.1	71	243	0.56
73g	3-Cl	Pale yellow	382.1	63	211	0.41
73h	2-NO$_2$	White	393.7	66	215	0.49
73i	3-NO$_2$	White	393.7	66	224	0.75
73j	4-NO$_2$	White	393.7	73	231	0.8
73k	4-N-(CH$_3$)$_2$	White	391.8	61	234	0.66
73l	3,4,5-(OCH$_3$)$_3$	Pale brown	438.8	69	241	0.71
73m	3,4,-(OCH$_3$)$_3$	Pale brown	408.7	66	203	0.81
73n	4-OCH$_3$	Pale yellow	378.7	73	218	0.48
73o	4-Cl	Pale yellow	382.1	72	204	0.54

Nuray, *et al.,* (2017) reported the synthesis of 2- substituted benzothiazole derivatives **77(a-b)**. In this synthetic procedure, sodium hydroxide (NaOH) was added to powerfully stirred solution of cis- bicycle [3-2-0] hept-2-en-6-one (**74**) and substituted aldehydes (**75**). The resulting solution

was stirred for 4 hours at room temperature. Chloroform was added to the mixture and the organic phase was washed, dried with sodium sulfate and filtered, and the solid compound (**76**) was recrystallised in ethyl acetate/n-hexane (1:9). The obtained compound 76(a-b) was then reacted with 2-amino-thiophenol in ethanol in the presence of *p*-toluenesulphonic acid. The mixture was refluxed for 10 hours, and the reaction was monitored by TLC and then cooled. Chloroform was added to the reaction mixture and the organic phase was washed, dried with sodium sulphate and filtered .The final products **77(a-b)** were purified by chromatography with hexane and an increasing amount of ethyl acetate (0-15%) yielding a waxy solid **77(a-b) Scheme 19** [68].
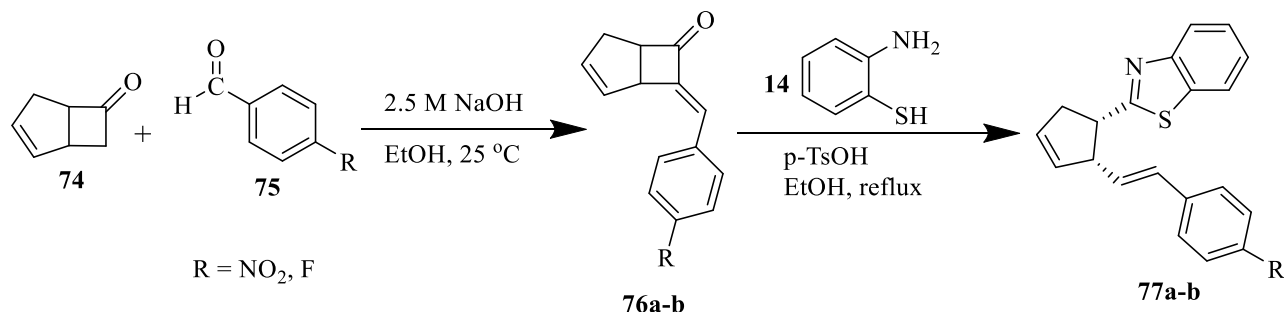
**Scheme 19: Synthesis of cyclopent-3-en-1-ylbenzothiazole derivatives**

Shi, *et al.,* (2012) reported the synthesis of benzothiazole-2-thiol derivatives **85(a-c)**.This was achieved by reacting substituted aromatic amines **80(a-c)** with 2-chloroacetyl chloride (**81**) in the presence of potassium carbonate to obtained compound **82(a-c).** The resulting compounds **82(a-c)** were then reacted with 6-aminobenzothiazole-2-thiol (**83**) to afford compounds (**84a-c**). Compounds **85(a-c)** were finally treated with 2-chloroacetyl chloride (**81**) in the presence of triethylamine to obtain compound **85(a-c)** in 70-90% yield **Scheme 20** [69].

78a:80a:82a:83a: R = Cl
78b:80b:82b:83b: R = Br
78c:80c:82c:83c: R= Me
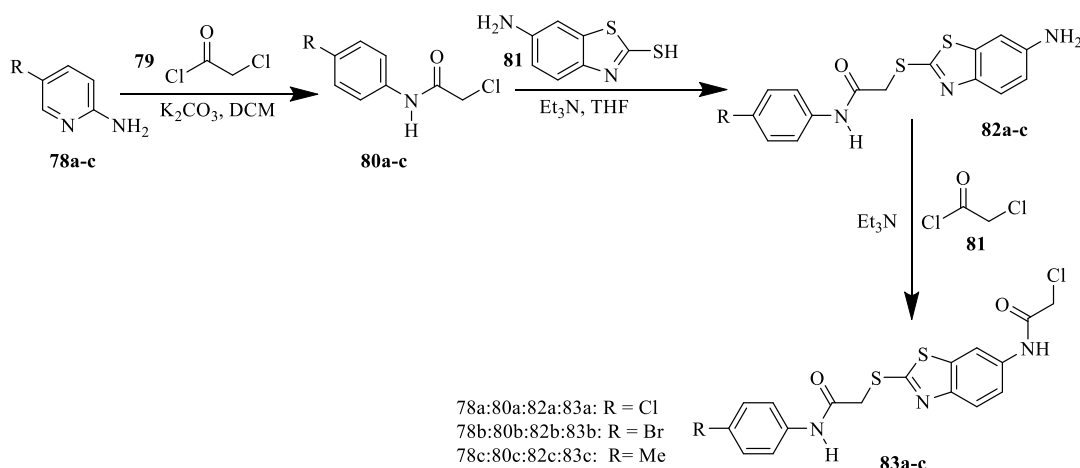
Scheme 20: Synthesis of benzothiazole-2-thiol derivatives

Sunil, *et al.,* (2017) reported the synthesis of some benzothiazole-2-thiol derivatives. In this synthetic procedure, a mixture of hydrochloric acid and water were added to substituted aniline (**86**) in a round bottom flask. The solution was heated for about 30 minutes and then cooled at room temperature. Ammonium thiocyanate was further added to the reaction mixture, refluxed for 4 hours and then cooled. The precipitate obtained (**87**) was filtered, washed with water, dried and crystallize from ethanol. A mixture of the compound (**87**), potassium hydroxide in water, and carbon disulphide in the presence of sulphur and absolute ethanol was heated under reflux for 2 hours at 280°C-285°C and 600-700 psi pressure. The reaction mixture was cooled, filtered and the filtrate was acidified with dilute hydrochloric acid, the product (**88**) obtained was collected and recrystaillized from ethanol. The compound 2- mercaptobenzothiazole (**88**) obtained and ethyl chloroacetate in dry acetone in the presence of potassium trioxocarbonate (iv) was refluxed for 10 h and the reaction mixture was poured into ice and neutralized with dilute hydrochloric acid. The solid (**89**) obtained was then washed several times with water and recrystallized from chloroform. The compound ethyl-2-benzothiazole carboxylate (**89**) obtained and ethanol was dissolved in a clean dry round bottomed flask, and hydrazine hydrate was added drop by drop with constant stirring and the mixture were refluxed for 8 h and then cooled to room temperature to form the product (**90**). The mixture of the compound (**90**), different aromatic aldehydes (**91**), and absolute ethanol was refluxed for 3 hours.The solvent was evaporated and the residue was recrystallized from ethanol to get the crystallized product (**92**). A mixture of the compound (**92**) and mercapto acetic acid in N, N-dimethylformamide (DMF) containing a pinch of anhydrous zinc chloride was then refluxed for 8 hours. The reaction mixture was then cooled and poured into ice-cold water.

The resulting solid (**93a-i**) was filtered, washed several times with water and then crystallized from DMF **Scheme 21** [70].
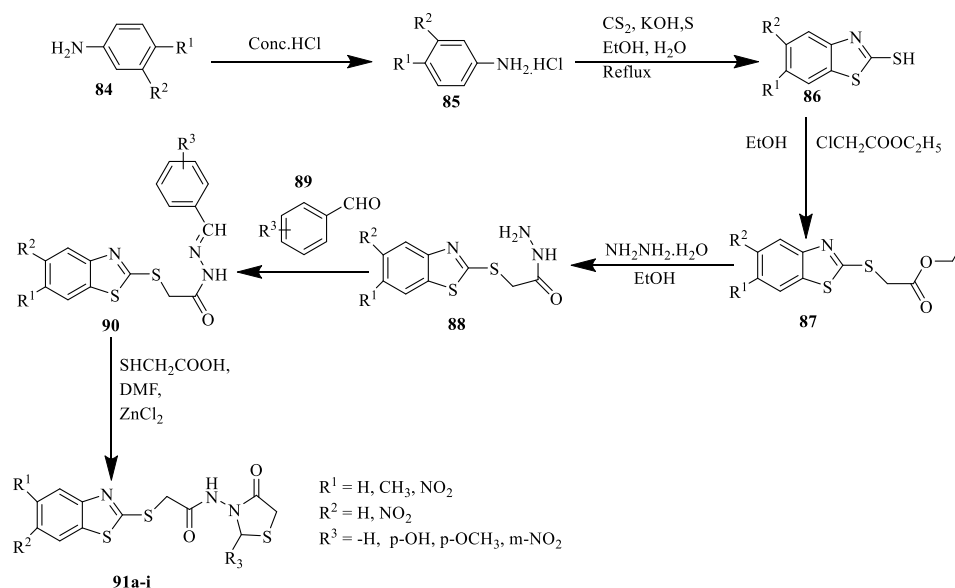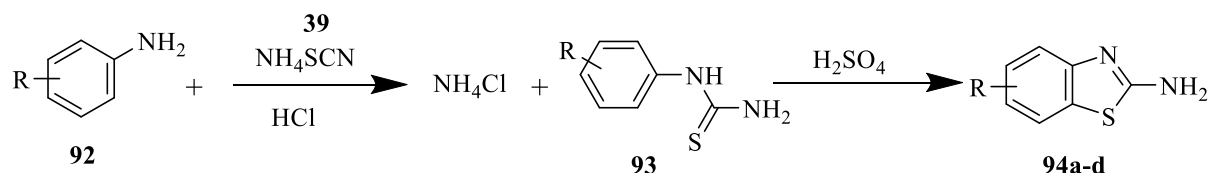

Scheme 21: Synthesis of acetamide derivatives of benzothiazole

Table 3: Physicochemical properties of the synthesized derivatives (91a-i)

Compound	Molecular Formula	Molecular Weight	Melting point in °C	% Yield	Retention factor
91a	$C_{19}H_{17}N_3O_2S_3$	415.55	168-170	62.5	0.58
91b	$C_{19}H_{17}N_3O_3S_3$	431.55	188-189	68.7	0.62
91c	$C_{20}H_{19}N_3O_3S_3$	445.58	210-212	72.3	0.64
91d	$C_{19}H_{16}N_4O_4S_3$	460.55	276-278	76.2	0.72
91e	$C_{18}H_{14}N_4O_4S_3$	446.52	165-167	59.5	0.63
91f	$C_{18}H_{14}N_4O_5S_3$	462.52	184-186	63.2	0.68
91g	$C_{19}H_{16}N_4O_5S_3$	476.55	207-209	69.1	0.71
91h	$C_{18}H_{13}N_5O_6S_3$	491.52	273-275	74.8	0.78
91i	$C_{18}H_{14}N_4O_4S_3$	446.52	161-163	56.8	0.61
91j	$C_{18}H_{14}N_4O_5S_3$	462.52	179-181	61.3	0.69
91k	$C_{19}H_{16}N_4O_5S_3$	476.55	202-204	67.7	0.7
91l	$C_{18}H_{13}N_5O_6S_3$	491.52	269-271	71.9	0.77

Thube, *et al.,* (2021) reported the synthesis of 2-substituted benzothiazole derivatives. In this reaction, an equimolar quantities of substituted anilines (92) and ammonium thiocyanate (39) were dissolved in ethanol containing concentrated hydrochloric acid and kept for 30 minutes to afford substituted, 1-phenylthiourea (93). Concentrated H_2SO_4 acid was then added to (93), and the reaction mixture was refluxed and the completion of the reaction was monitored using thin layer chromatography. The precipitate was washed with cold water to make it acid free, then it was dried and recrystallized to obtain 2-amino benzothiazole derivatives 94(a-d) **Scheme 22** [80]. Para substituted chloroacetanilide derivative (96a-c) was also prepared by dissolving substituted anilines (92) in glacial acid and saturated solution of sodium acetate, chloroacetyl chloride(95) was added to this mixture drop wise with stirring, and the reaction was monitored by thin layer chromatography. After half an hour a white precipitate was obtained. The precipitate was filtered, dried and recrystallized from alcohol to afford the product 96(a-c) **Scheme 23** [89]. Finally, equimolar quantities of substituted 2-aminobenzothiazole (94a-d) and para substituted chloroacetanilide 96(a-c) were dissolved in dry 1, 4-dioxane, and triethylamine was added to this mixure. The reaction mixture was then monitored by thin layer chromatography. It was then cooled, poured into a crushed ice to obtain the solid precipitates of 2-substituted benzothiazole derivatives 97(a-j) **Scheme24** [71] **Table 4.**

Scheme 22: Synthesis of 2-substituted benzothiazole derivatives
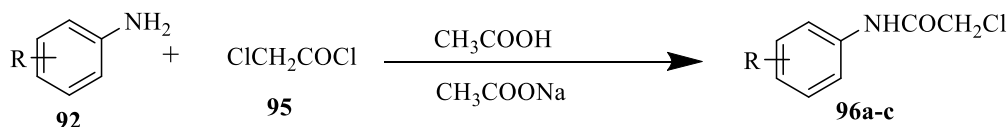
Scheme 23: Synthesis of 2-chlorophenylacetamide derivatives
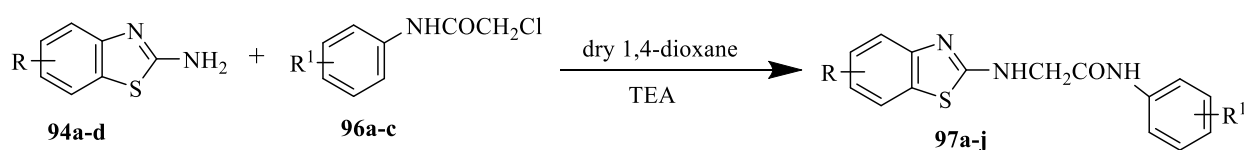
Scheme 24: Synthesis of 2-substituted benzothiazole derivatives

Table 4: Physicochemical properties of the synthesized compound (97a-j)

Compound	R^1	R	Molecular Formula	Molecular weight	Melting point(°C)	% Yield	Retention factor Values
97a	6-Br	4-Br	$C_{15}H_{11}N_3OSBr$	441.02	165-166	50.01	0.68
97b	6-Br	4-NO$_2$	$C_{15}H_{11}N_4O_3SBr$	407.11	124-126	73.74	0.62
97c	6-NO$_2$	4-NO$_2$	$C_{15}H_{11}N_5O_5S$	373.22	99-101	70.57	0.6
97d	6-Br	4-Cl	$C_{15}H_{11}N_3OSBrCl$	396.63	150-152	82.55	0.72
97e	6-NO$_2$	4-Br	$C_{15}H_{11}N_4SO_3Br$	407.12	109-111	80.61	0.69
97f	5-Cl	4-Cl	$C_{15}H_{11}N_3SOCl_2$	352.21	152-155	82.56	0.63
97g	5-Cl	4-NO$_2$	$C_{15}H_{11}N_4SO_3Cl$	362.72	150-152	66.12	0.67
97h	5-NO$_2$	4-Cl	$C_{15}H_{11}N_4SO_3Cl$	362.72	155-157	65	0.66
97i	5-NO$_2$	4-Br	$C_{15}H_{11}N_4SO_3Br$	407.11	110-113	67.12	0.62
97j	5-NO$_2$	4-Cl	$C_{15}H_{11}N_5SO_5$	373.31	125-127	56.25	0.68

Mariappan, *et al.,* (2012) reported the synthesis of the N-(5-chlorobenzothiazol-2-yl)-2-(substituted amino) acetamide **102(a-j)**. This was achieved by adding potassium thiocyanate (KSCN) and 4-chloroaniline **(98)** to a required amount of chilled glacial acetic acid and place in a freezing mixture. The solution was stirred mechanically with drop wise addition of Br$_2$ in glacial acetic acid at such a rate that the temperature does not rise above 5°C.The stirring was continued for an addition 3 hours at 0-10 °C and the separated hydrochloride salt was filtered, washed with acetic acid and dried. It was dissolved in hot water and neutralized with aqueous ammonia solution (25%). The resulting precipitate was filtered, washed with water and recrystallized from methanol to obtain pure 6- chloro-1, 3-benzothiazol-2-amine (**99**). An equimolar quantity of compound (**99**) and chloroacetyl chloride in sufficient quantity of chloroform were then refluxed in the presence of K$_2$CO$_3$ for about 10 h. The excess solvent was removed in a vacuum and the residue thus obtained was washed with 5% NaHCO$_3$ and the crude product (**100**) was dried and recrystallized from ethanol to furnish white crystal. Different secondary and primary amine (**101**) was added to the solution of the compound (**100**) in absolute alcohol. The mixture was refluxed on water bath for 4-6 hours and the completion of the reaction was checked by TLC. The crude product **102(a-c)** thus obtained was filtered, dried and recrystallized from aqueous alcohol **Scheme 25** [72] **Table 5.**
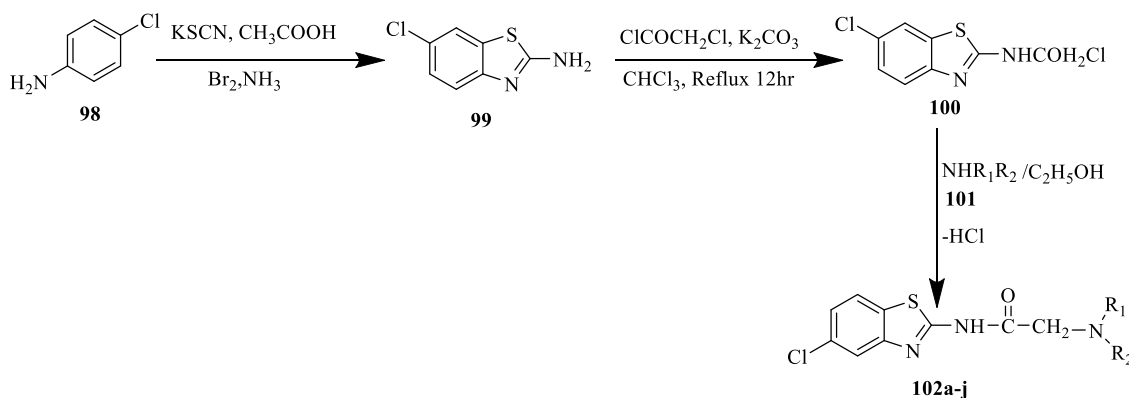
Scheme 25: Synthesis of the N-(5-chlorobenzothiazol-2-yl)-2-(substituted amino) acetamide derivatives

Table 5: Physicochemical properties of the synthesized compound (102a-j)

Compound	-NR$_1$R$_2$	Yield (%)	Melting point (°C)
102a	Dimethylamino	80	196-199
102b	Diethylamino	73	190-192
102c	Diethanolamino	85	201-202
102d	Morpholino	83	156-158
102e	Piperidino	77	193-195
102f	4-fluoroanilino	67	198-200
102g	3-chloroanilino	61	193-195
102h	4-pyridino	68	190-193
102i	2-pyridino	61	167-169
102j	4-sulfanilido	69	204-206

Petal, *et al.,* (2013) reported the synthesisof benzothiazole-2-amine derivatives 104(a-j).In this synthetic procedure, 2-aminobenzothiazole (36) in dry pyridine was refluxed with 2-(4-nitrophenyl)-5-(pyridine-3-yl)-1,3,4-oxadiazole (103) or 2-(4-chlorophenyl)-5-(pyridine-3-yl)-1,3,4-oxadiazole (103) to get the respective benzothiazole-2-amine derivatives **Scheme 26** [73].

R = NO$_2$, Cl
R^1= a) 6-F, b) 6-Br, c) 6-NO$_2$, d) 6-CH3, e) 6-OCH$_3$, f) 6-Cl, h) 4-NO$_2$, i) 5-Cl, j) 4-Cl
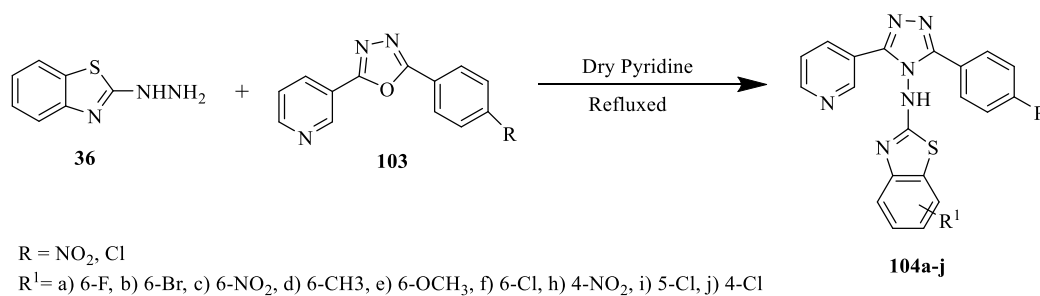
Scheme 26 : Synhesis of *N*-(3-(pyridin-3-yl)-5-(*p*-tolyl)-4*H*-1,2,4-triazol-4-yl)benzohiazol-2-amine derivatives

Montalvao, *et al.,* (2016) reported the synthesis of (4-amino-5-(benzo[d]thiazole-2-yl)-arylsulfoamides **109(a-b)**. In this synthetic procedure, benzothiazole-2-yl-acetonitrile (**105**) was allowed to react with N,N-dimethylformamide dimethyl acetal (**106**) in ethyl alcohol at room temperature for 10 minutes to get the 2-(benzo[d]thiazole-2-yl)-3-(dimethylamino)acrylonitrile (**107**). This intermediate (**107**) was further reacted with N-arylsulfonated guanidine (**108**) in the presence of potassium hydroxide and dioxane for 2 hours to give the synthesized compound **109(a-b)** **Scheme 27** [98].

a) Ar = C_6H_5, b) Ar = 4-CH_3-C_6H_4
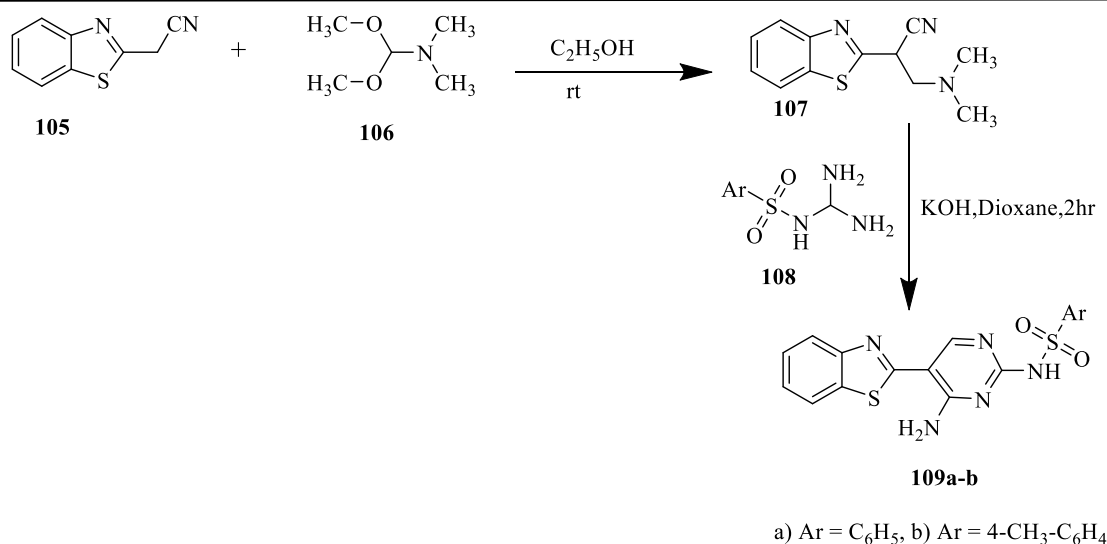
Scheme 27: Synthesis of (4-amino-5-(benzothiazole-2-yl-arylsulphonamides

Masssari, *et al.,* (2010) reported the synthesis of ethyl-7-(4-(benzothiazole-2-yl)piperazin-1-yl)-1-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**115**).This was achieved by treating ethyl-2-(2,6-dichloronicotinoyl)-3-(dimethylamino)acrylate (**110**) with methylamine in a diethylether/ethanol mixture to yield ethyl-2-(2,6-dichlorobenzoyl)-3-(dimethylamino)acrylate (**111**).This was followed by cyclization of the precursor (**111**) in the presence of potassium carbonate in N,N-dimethylformamide (DMF) to obtain Ethyl,7-chloro-1-methyl-4-oxo-1,4-dihydroquinoline-3-carboxtlate (**112**) . The intermediate product (**112**) was then condensed with 1-(benzothiazol-2-yl)piperazine (**113**) in N,N-dimethylformamide (DMF) to furnish ethyl-7-(4-(benzothiazole-2-yl)piperazin-1-yl)-1-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (**114**) which was then hydrolyzed in alkaline medium to afford the final product (**115**) **Scheme 28** [75].
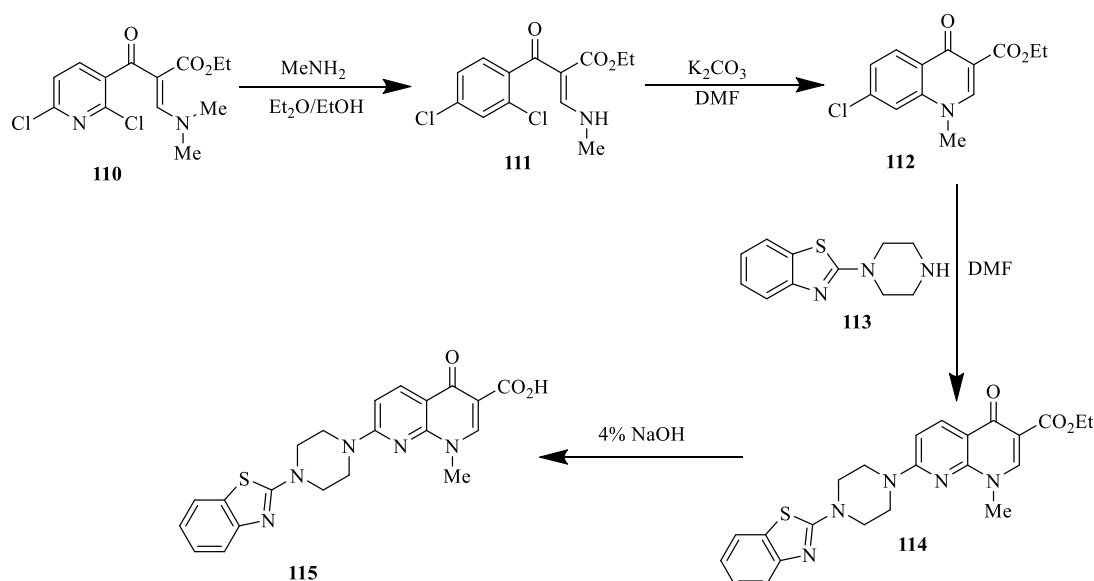
Scheme 28: Synthesis of 7-(4-(benzothiazol-2-yl)piperazin-1-yl)-1-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

Jonckers, *et al.,* (2012) reported the synthesis of 2-substituted benzothiazole derivatives bearing carboxamide functionality (**122a-b**). In this synthetic procedure, a commercially available epoxide (**116**) was treated with an excess of isobutylamaine in isopropanol to yield tertiarybutl-3-hydroxy-4-(isobutylamino)-1-phenylbutan-2-yl)carbamate (**117**). Compound **117** was then coupled with a benzothiazole-6-carboxylic acid (**118**) using o-(7-azabenzotriazol-1-yl)-N,N,N',N-tetramethyluronium hexafluorophosphate (HATU) as an activating agent in the presence of triethylamine to afford 2-substituted benzothiazole derivatives bearing carboxamide functionality**119(a-b)** with protected amino group**,** the subsequent treatment of which with trimethylsilyl chloride and sodium iodide converted the protected amino group to a reactive primary amine **120(a-b)**. In the final step, a triethylamine-mediated coupling of compounds **120(a-b)** with 2,5-dioxopyrrolidin-1-yl thiazol-5-ylmethyl carbonate

(**121**) furnished final products (**122a-b**) in approximately 85% yield **Scheme 29** [76].
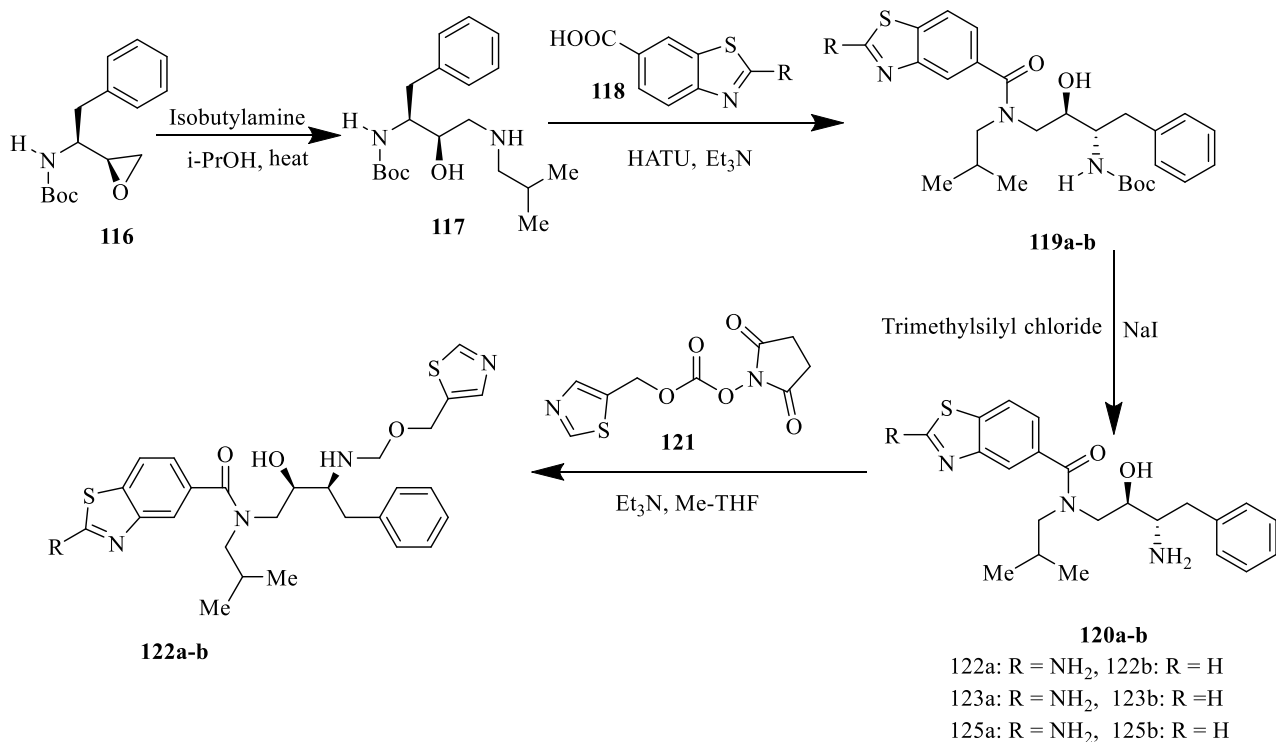
Scheme 29 : Synthesis of 2-substituted benzothiazole derivatives bearing carboxamide functionality

Ugale, *et al*., (2012) reported the synthesis of quinazoline substituted benzothiazoles 123(a-c). This was achieved by heating substituted 2-aminobenzothiazoles 126(a-c) and 6-bromo-2-ethyl-4H-benzo[1,3]oxazin-4-one (127) under reflux in dry pyridine to afford the product 128(a-c) **Scheme 28** [77].

a:128a: R^1 = H; R^2 = H
b:128b:R^1 =Cl; R^2 = H
c: 128b; R^1 =H; R^2= OMe
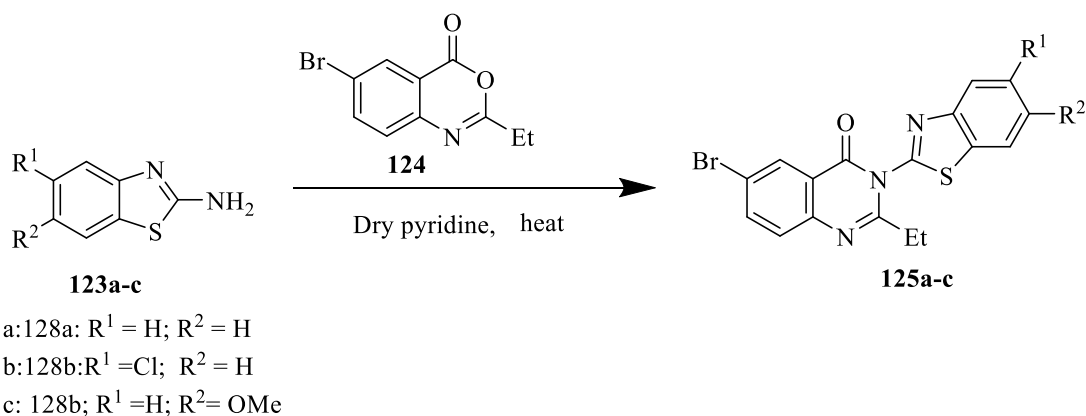
Scheme 30: Synthesis of quinazoline substituted benzothiazoles

Medicinal Significance of Benzothiazole Scaffold (3)

Benzothiazoles and their Schiff bases have shown a remarkable biological activity. The thiazole ring itself has been used as fungicide and bactericide. Some of the remarkable biological activities include:

Antimicrobial activity (3.1)

Microbes are causative agents for various types of disease like pneumonia, ameobiasis, typhoid, malaria, common cough and cold various infections and some severe diseases like tuberculosis, influenza, syphilis, and AIDS as well. An antimicrobial agent reduces or blocks the growth and multiplication of bacteria According to Merriam-webster Online Dictionary [78].These agents are among the most common and often injudiciously used therapeutic drugs worldwide [79], and consequently resulted in emergence of antibiotic-resistant pathogens. Antibacteria resistance is a global public health problem that has hampered the effective prevention and treatment of wide range of bacteria diseases [80-81]. Antibacteria resistance is aggravated by the misuse or overuse of antibacterial agents in people and animal [82]. Some bacteria are multidrug resistant and the major examples

are *Staphylococcus aureus* and *Escherichia coli* [82]. One of the WHO strategies for the control of antimicrobial resistance is to encourage investment in new medicine research and development [83].In accordance with this recommendation many research team are engrossed in the synthesis of new antimicrobial drug with better efficacy and lower toxicity [81-84].The most exploited derivatives are sulphonamides, thiourea and benzothiazole [85].Various approaches were made to check the role of benzothiazole moiety as antimicrobial agent.

Arun, *et al.,* (2010), reported antibacterial activity of N-(4,5-dihydro-1H-imidazol-2-yl)-6-substituted-1,3-benzothiazol-2-amines (**42a-c)** and N-(1 H-benzimidazol-2-yl)-6-substituted-1,3-benzothiazol-2-amines(**43a-c).** These compounds were tested using in-vitro assay against pathogenic *Escherichia coli*, *Klebsiella* specie, *Micrococcus luteus* and *Staphyloccus aureus*. The result was compared with some standard drugs like Novobiocin, Kanamycin and Amikacin. In the case of *Escharichia coli,* compound **42a**, **42c** and **43a** exhibited higher activity at 200 µg/ml while the rest of the compounds showed moderate activity. In case the of *Klebsiellia*, compound **42a, 42c** and **43a** show higher activity than the rest of the compound. In the case of *Micrococcus luteus* and Staphylococcuc *aureus*, compound **42a, 42c** and **43c** showed higher activity than the rest of the compounds [61]

Samuel, *et al.,* (2021) reported the antibacterial activity of benzothiazole derivatives of sulphonamide (**49a-b).**The experiment was conducted using in-vitro agar well diffusion techniques .The result showed that some of the compounds inhibit the growth of both Gram negative and Gram positive bacteria organisms, only compound (**45**) showed inactive to the gram negative organism *Escherichia coli*. Compound (**49b**) gave the best minimum inhibition concentration amongst the synthesized compounds, while the standard ampicillin showed better activities than the synthesized compounds. The possible mechanism of the action of the synthesized compounds (**49a and 49b**) could be competitive inhibition of the enzyme dihydropteroate synthase that catalyze the reaction of p-aminobenzoic acid with 7,8-dihydro-6-hydroxymethylpterin-pyrophosphate to form dihydropteroic acid which is one of the step in the formation of dihydrofolic acid. The mechanism of action could be well via inhibition of carbonic anhydrase activities. Sulphonamides inhibit carbonic anhydrase and dihydropteroate synthase activities. The mechanisms of action of the thiourea (**45**) and benzothiazole (**46**) derivative could be through the inhibition of protein tyrosine kinases. The compounds had reduced activities against the Gram negative organism (*E.coli*) and this could be attributed to the presence of efflux pump that reduce intracellular concentration of drug in Gram negative organism [62].

Table 6: **Zone of inhibition of the synthesized Compounds in (mm)**

Organisms	Compound45	Compound46	Compound49a	Compound49b	Ampicillin
Staphyloccus aureus	16	17	28	18	32
Escharichia coli	8	-	17	20	24

Table 7: Minimum Inhibitory Concentration of the synthesized Compounds in (µg/mL)

Organisms	Compound45	Compound46	Compound49a	Compound49b	Ampicillin
Staphyloccus aureus	>75.00	<75.00	50	<50.00	25
Escharichia coli	>100.00	-	>50.00	<50.00	12.5

Anti-inflammatory activity (3.2)

Inflammation is part of the body's immune response to stimuli. It is beneficial because it initiates healing processes. However, it is of concern because inflammation can be self-perpetuating creating more inflammation response to existing inflammation as reported by medical news [86]. Inflammatory diseases are widely prevalent world over and inflammation remains a common and poorly controlled disease which is life threatening in extreme form of allergy, autoimmune diseases, and rejection of organs transplanted [87]. Chronic inflammation has linked to a variety of diseases include cardiovascular diseases, cancer, diabetes, arthritis, Alzheimers disease, pulmonary disease, etc [87].

Non-steroidal anti-inflammatory drugs (NSAIDs) are drug class that provides analgesic, antipyretic, and anti-inflammatory effects. The most prominent members of this group are aspirin, ibuprofen, naproxen, diclofenac and indomethacin. Non-steroidal anti-inflammatory drugs (NSAIDs) exert their analgesic effect by peripheral inhibition of prostaglandin (PG) through inhibition of the cyclooxygenase (COX) enzymes, which catalyzes the conversion of arachidonic acid into the PG [88]. However, PG has a dual function, mediation of inflammation and [89] and cytoprotection against HCl [90] in the stomach and intestine. Long term use of NSAIDs for the treatment of pain and inflammation may lead to

gastrointestinal (GI) disorders and renal toxicity [91]. The work of Caughey, *et al* [92] and Varas-Lorenzo *et al* [93] has associated NSAIDs use with increased risk stroke. Various approaches have been made to check the role of benzothiazole moiety as anti-inflammatory agent.

Shafi, *et al.,* (2012) reported anti-inflammatory activities of 2-mercaptobenzothiazole and 1,2,3-triazole based bis-heterocyclic compounds(**53a-d**). The compounds (**53a-d**) were tested using biochemical cyclooxygenase (COX) activity assays and carrageenan-induced hind paw edema. The result showed that compound **53a** exhibit selective COX-2 inhibition with an IC_{50} ratio of 0.44 of COX-2/COX-1 and displayed a better in vivo anti-inflammatory activity profile compared with the industry standard, ibuprofen. Compound **53a** showed increased analgesic activity compared with ibuprofen when tested using Writhing method. Importantly, the synthesized compound **53a-d** displayed no gastric ulceration which has been a major downside to the clinical use of ibuprofen [63].

Arun, *et al.,* (2010), reported the anti-inflammatory activities of the novel compound (**42a-c** and **43a-c**). The synthesized compounds and reference drug (phenylbutanone) were examine for their anti-inflammatory activity. The pharmacological results of the synthesized compounds were reported in (**Table 8**). All the compounds showed anti-inflammatory activity ranging from 22.2 – 26.5% at the dose of 50 mg/kg body weight. The results obtained clearly infer that compound **42a** shows the highest Anti-inflammatory activity with respect to the other compounds. Compounds **42b, 43a,** and **43b** showed moderate activity and compound **42c** and **43c** show less activity [61].

Table 8: Anti-inflammatory activity (% inhibition) of the compounds (42a-c, 43a-c and phenyl butanone).

Compound	% Inhibition (50 mg/kg body weight)
42a	26.5
42b	24.5
42c	22.7
43a	25.5
43b	24.7
43c	22.2
Phenyl butanone	38.9

Vrushali, *et al.,* (2015) reported the anti-inflammatory activity of compound (55 and 56). The compound (**55, 56**) was tested using in-vitro assay. The study reveals that the activity of the synthesized compound (**56**) under test was satisfactory as compared to that of standard(Sodium Dichlofenac). That is the hydrazine derivatives were found to be potent enough to suppress haemolysis. However, the % inhibition of haemolysis in case of Sodium Dichlofenac (DFS) treated with RBC's was high as compared to that of the % inhibition provided by the synthesis compound (**56**). However hydrazine compound (**56**) showed better result as compared to the intermediate (**55**) [64]

Table 9: Anti-inflammatory results with % inhibition.

Concentration	Standard	%inhibition	Compound55	%inhibition	Compound56	%inhibition
6.25	0.183	94.89	0.37	68.8	0.415	76.61
12.5	0.097	95.22	0.357	68.89	0.305	82.81
25	0.054	96.12	0.314	73.52	0.301	83.04
50	0.021	97.23	0.272	77.06	0.294	83.44
100	0.011	99.82	0.255	78.49	0.288	83.77
Positive control	1.186		1.186		1.186	

David, *et al.,* (2018) reported the anti-inflammatory activities of compounds (**62a-l**). The result shows that all compounds except **62c** and **62i** caused less than 50% reduction of oedema at 1 h, 2 h and 3 h (**Table 10**).The most pronounced anti-inflammatory activity among the compounds was **62c**. The percentage reduction of reduction of **62c** and **62i** was higher than that of indomethacin at 1h, 2h, and 3h. The structure-activity relationship (SAR) showed that the indole ring of compound **62c** was more effective in reducing oedema than that of benzene ring of **62b**.Among the prolines (**62g-l**), compound **62i** was active derivate possessing anti-inflammatory activity better than indomethacin. Substitution at four –position of the proline was shown to enhance anti- inflammatory activity. The trend of the anti-inflammatory activity showed that compound **62g > 62h**, **62i > 62j**, and **62k > 62n**.Compound **62a** was the most active derivative among the aliphatic amino acid derivatives (**62a, 62d-f**), indicating that the higher the alkyl group β to the carboxamide, the lower the activity. The trend observed was **62a>62f>62e>62d**. The presence of electron withdrawing group at the para position of the benzenesulphonamide decreased the anti-inflammatory activity as evident with compounds **62g** and **62h** being lower than

that of **62i** and **62j**. However, electron withdrawing group still showed better activity than unsubstituted ring, **62g-h** > **62k-l** showing that the presence of a substituent at the four-position of the benzene ring enhanced anti-inflammatory activity [65].

Table 10: Anti-inflammatory activities of compound 62a-l (Percentage inhibition of oedema formation)

Compound	0.5 h	1 h	2 h	3 h
62a	32.31	7.06	7.03	12.96
62b	49.23	42.35	43.75	38.89
62c	52.31	72.01	76.36	80.09
62d	26.15	5.88	9.38	16.05
62e	27.62	17.65	14.84	1.85
62f	30.77	18.82	20.31	21.6
62g	27.62	7.06	8.59	16.05
62h	24.62	23.53	0.78	2.47
62i	41.54	64.04	73.02	78.12
62j	27.69	16.47	14.84	13.58
62k	26.15	5.88	8.28	16.67
62l	13.85	2.35	8.59	13.58
Indomethacin	56.93	63.53	64.84	63.58

Anti-tubercular Activity (3.3)

Tuberculosis (TB) is a fatal contagious disease caused by infection with *Mycobacterium tuberculosis* but also with *M. bovis* and *M .africanum,* which can affect almost any tissue or organ of the body, the most common site of infection of the disease is the lungs as reported by medical news [94]. Various approaches were made to check the role of benzothiazole moiety as antitubercular agent.

Sarkar, *et al* (2018) reported the antitubercular activity of compound (**69a-e)** against *Mycobacterium tuberculosis.* The compound (**69a-e)** was tested using in-vitro assay. Each of the compounds was dissolved in dimethylsulpoxide (DMSO). The in-vitro screening indicates that all the analogues exhibit significant anti-tubercular activity compared to that of the reference drugs isoniazid and rifampicin. These results indicate that compound **69e** is more active than the other compounds, perhaps because of their low partition coefficient and consequently, the low penetration ability through the mycobacterium cell wall [66].

Table 11: The in vitro screening data of compound (69a-e) indicating their anti-tubercular activity

Compound	25μg/mL (%Growth)	50μg/mL (%Growth)	Minimum inhibition concentration (MIC)
69a	0%	0%	25μg/mL
69b	100%	100%	50μg/mL
69c	100%	0%	50μg/mL
69d	100%	100%	50μg/mL
69e	100%	0%	50μg/mL
Isoniazid	0	0	25μg/mL
Rifampicin	0	0	25μg/mL

IIango and Arunkumar (2011) reported the antitubercular activity of **73(a-o)** against *Mycobacterium tuberculosis*. The result revealed that compound **73f, 73g, 73k** and **73o** showed minimum inhibitory concentration (MIC) values equivalent to that of the reference standard, isoniazid. Compound **73a, 73c, 73j** and **73n** exhibited moderate activity, while other compounds less active [67].

Table 12: Anti-tubercular activities of compound 78(a-o)

Compound	R	Minimum inhibitory concentration values in (µg/ml)
73a	-H	2.8
73b	-2-OH	50.3
73c	-2-OH-3-CH$_3$	3.7
73d	-3-OH	50.3
73e	-4-OH	34.2
73f	-2-Cl	0.76
73g	-3-Cl	0.57
73h	-2	17.1
73i	-3	34.8
73j	-4	1.2
73k	-4-N-(CH$_3$)$_2$	0.62
73l	-3,4,5-(OCH$_3$)$_3$	23.4
73m	-3,4,-(OCH3)$_2$	31.4
73n	-4	2.8
73o	-4-Cl	0.83
Isoniazid		0.56

Anticancer Activity (3.4)

Nuray, *et al.,* (2017) reported anticancer activities of compound (77a-b). Different concentration (5, 25, 50, 75 and 100 µM) of these compounds were used to treated PANC- 1 cells for 48 hours and the cytotoxicity effects of these compounds (77a and 77b) on PANC – 1 human pancreatic cancer cells was determined by the MTT assay. PANC – 1 cell were also treated with increasing concentrations of the synthesized compound (77a and 77b) to determine whether the compounds induced apoptosis. The study showed that the synthesized compound (77a and 77b) have anti-proliferative effects against PANC -1 cell and reduced cell viability. These compounds (77a and 77b) also induced apoptosis of pancreatic cells and at the same time reduced the activity of SOD and GPx and reduced TAC [68].

Shi, *et al.,* (2012) reported the anticancer activity of compounds (83a-c). These compounds (83a-c) were evaluated against various cancer cell lines. The result shows that compound 83b demonstrated promising activity against SKRB-3 human breast cancer cells (IC$_{50}$ = 1.2 nM), SW620 colon cancer cells (IC$_{50}$ = 4.3 nM), A549 (IC50 = 44 nM) and HepG2 hepatic carcinoma cells (IC50 = 48 nM) as well induced apoptosis in HepG2 cancer cells [69].

Anti- Diabetic Activity (3.5)

Diabetes mellitus is an endocrinological and metabolic disorder with an increasing global prevalence and incidence. High blood glucose levels are symptomatic of diabetes mellitus as a consequence of inadequate pancreatic insulin or poor insulin-directed mobilization of glucose by target cells [95].

Sunil, *et al.,* (2017) evaluated the antidiabetic activity of compound (91a-l). The result revealed that compound 91d at 350 mg/kg exerted maximum glucose lowering effects whereas 91c showed minimum glucose lowering effects [70].

Table 13: Antidiabetic activity of compound **91(a-l)**

Treatment (350mg/kg b.wp.o)					% reduction in blood glucose
	0th day	7th day	14thday	21st day	0
Normal control	105.09±1.2	102±0.3	102±0.9	100±1.2	0
Diabetic positive control	274±1.3	274±1.6	271±1.4	270±1.9	0
Glibenclamide 10 mg/kg	278±2.1	219±.4	168±1.8	95±1.7	65.82%

91a	274±1.4	243±2.8	206±1.3	158±2.3	42.33%
91b	271±2.7	235±3.1	191±0.8	144±3.3	46.86%
91c	270±1.9	246±2.7	199±1.9	161±1.5	40.37%
91d	279±3.6	274±1.5	242±2.5	102±1.8	63.44%
91e	281±2.8	238±2.9	192±1.3	149±4.1	46.97%
91f	272±1.7	254±3.2	205±1.6	159±2.9	41.54%
91g	283±1.3	230±2.5	174±1.4	110±3.1	61.13%
91h	281±4.2	235±2.7	179±1.5	114±2.6	59.43%
91i	276±3.4	250±2.2	210±0.5	165±3.2	40.21%
91j	273±1.6	240±2.6	192±2.2	136±2.4	50.18%
91k	269±2.8	244±2.3	199±1.9	146±2.1	45.72%
91l	274±1.5	242±2.5	186±1.1	123±1.8	55.10%

Thube, *et al.,* (2021) reported the antidiabetic activity of compound (97a-j).All the synthesized derivatives were screened for their antidiabetic activity using alloxan induced method. Estimation of glucose, cholesterol and triglyceride levels were carried out, and it was found that compound 97d exhibited significant antidabetic activity. Compounds 97f, 97b, and 97a possess a moderate antidiabetic activity [71].

Table 14: Effect of compound (97a-j) on Blood glucose level data

Drug	Blood glucose level mg/dl (Mean±SEM)				
	0 day	3days	6days	9day	12day
Control	107.7±2.1	108.5±1.8	107.5±2.9	108.6±2.1	108.8±1.3
Diabetic Control	363.0±2.5	361.2±2.8	361.7±2.4**	361.3±2.3**	360.1±1.4
Standard	361.1±3.9	215.7±2.4**	151.1±3.2**	122.3±4.3**	101.2±2.2**
97a	357.0±2.6	235.2±3.2**	155.3±4.9**	132.4±4.7**	119.3±3.6**
97b	354.7±2.8	230.2±2.5**	154.7±3.8**	128.1±2.5**	115.4±2.1**
97c	353.0±2.2	277.4±3.9**	204.3±4.3**	160.6±2.4**	135.3±3.6**
97d	363.3±3.5	225.2±1.7**	150.4±3.5**	119.9±2.1**	102.8±1.8**
97e	382.8±4.4	272.1±2.6**	208.3±5.3**	170.5±4.1**	142.7±4.3**
97f	366.8±2.3	220.2±2.9**	152.8±3.2**	126.3±3.1**	110.5±2.3**
97g	368.8±3.2	240.3±2.1**	157.5±2.1**	139.5±2.1**	121.3±3.4**
97h	349.7±2.5	284.3±5.1**	210.1±3.3**	180.6±2.9**	145.2±4.5**
97i	350.7±4.9	275.5±4.9**	236.8±4.3**	190.8±3.7**	152.8±5.1**
97j	357.7±4.5	274.3±3.8**	239.6±5.3**	198.6±4.3**	155.0±6.9**

Table 15: Effect of compound (97a-j) on Blood Cholesterol level data

	Cholesterol level mg/dl (Mean±SEM)		
Drug	0 day	6 day	12 day
Control	139.3±6.1	138.4±5.3	139.5±6.7

Diabetic Control	346.3±6.1	347.3±5.4	346.4±5.9
Standard	348.5±2.1	189.4±5.1**	131.3±2.5**
97a	346.4±3.3	198.3±2.9**	134.5±2.5**
97b	342.±5.5	193.5±3.3**	133.4±3.1**
97c	341.8±6.8	262.2±4.9**	156.6±2.4**
97d	349.9±5.5	190.8±1.6**	132.6±3.9**
97e	351.6±3.8	131.4±3.2**	139.7±2.5**
97f	349.5±1.0	192.4±4.3**	131.6±5.3**
97g	348.4±4.5	216.5±1.1**	160.8±2.5**
97h	352.3±3.3	201.9±2.5**	162.2±4.4**
97i	354.3±2.3	234.1±3.5**	133.4±6.4**
97j	355.9±2.8	239.2±2.2**	131.3±2.8**

Table 16: Effect of compound (97a-j) on Blood Trigyceride level data

	Triglyceride level mg/dl (Mean±SEM)		
Drug	0 day	6 day	12 day
Control	120.4±9.8	121.5±8.8	120.3±9.6
Diabetic Control	251.5±7.5	252.5±6.8	251.7±7.1
Standard	249.4±8.4	188.5±7.1**	121.5±6.5**
97a	248.5±7.5	222.5±8.0**	130.2±7.5**
97b	246.9±8.4	190.4±7.2**	126.2±3.8**
97c	248.8±7.8	206.3±6.8**	115.2±7.6**
97d	246.6±8.5	191.7±6.7**	124.3±6.9**
97e	254.4±9.8	204.5±5.9**	125.4±8.6**
97f	248.4±7.0	192.9±7.5**	120.5±7.4**
97g	251.6±6.5	205.4±6.1**	147.5±3.5**
97h	253.2±5.3	212.5±7.5**	142.4±5.4**
97i	257.3±6.3	219.6±8.5**	139.6±6.4**
97j	254.4±5.8	221.8±9.0**	140.8±7.8**

Mariappan, *et al.,* (2012) reported the antidiabetic activities of N-(6-chlorobenzothiazol-2-yl)-2-(substituted amino) acetamide **102(a-j)** .The LD_{50} values of these compounds **102(a-j)** were also estimated to be in the range of 100-1000 mg/kg b.w, and the results revealed that all the synthesized compounds **102(a-j)** exhibited anti-diabetic response at the end of ten days. It has been found that oral administration of the synthesis compounds **102c, 102d, 102e**, and **102j** caused a more significant reduction in blood glucose than other compounds in diabetic rats. However, the compound **102d** at 100 mg/kg b.w. exerted maximum glucose lowering effects. The maximum glucose lowering effects of compound **102d** was seen to be due to the presence of heterocyclic amine (morphine) [72].

Table 17: Effect of compound (102a-j) on Blood glucose level data

Treatment (100mg/kg b.w p.o)	Blood glucose level mg/dl (Mean±SEM)		
	0 day	**5th day**	**10th day**
Diabetic Control	274.2±1.6	272.2±1.8**	270.5±1.7**
Glibenclamide 20 mg/kg	272.8±1.6	213.6±1.35**	114.0±1.6**

102a	274.7±1.9	235.5±1.65**	139.5±1.6**
102b	273.2±1.9	232.7±2.23**	140.3±1.4**
102c	262.5±4.01	228.0±2.03**	132.0±2.7**
102d	268.5±1.70	231.3±1.72**	130.8±2.42**
102e	266.3±2.9	228.3±2.38**	136.0±2.3**
102f	267.5±3.2	230.7±2.42**	144.2±1.9**
102g	270.7±2.8	231.5±2.47**	148.2±2.3**
102h	271.7±2.6	232.2±3.0**	143.2±1.6**
102i	271.7±2.5	233.8±2.2**	135.7±2.5**
102j	262.5±4.02	227.7±2.7**	132.5±1.18**

All the values were expressed as (Mean±SEM) (n=6). *$p < 0.05$ and ** $p < 0.01$

Antiulcer Activity (3.6)

Arun, *et al.,*(2010) also evaluated the antiulcer activities of the novel compounds (42a-c and 43a-c). All the synthesized compounds showed good activity as compared with standard drug (ranitidine). Compounds 42a, 42c, 42a, and 42c showed good activity while compound 42b showed moderate activity in Aspirin Induced Ulcer (ASP). The synthesized compound were also tested for Ethanol Induced Ulcer, it was observed that compounds 42a, 42b and 42c showed moderate activity while compounds 43a, 43b, and 43c showed less activity [61].

Antiviral Activity (3.7)

A virus is a very infectious agent that replicate only inside the living cells of an organism. Viruses infect all types of plants, animals, and microorganisms also, like bacteria [96]. Viral infections are considered to be one of the major threats to the health of human being. Virus infections take place due to globalization and unexpected climate changes [97]. A good number of unknown varieties of viruses maybe responsible for total infection cases. These viruses come to the picture when they show some symptoms to the host [98]. Despite the development of many molecules as antiviral, they are unable to satisfy the requirement criteria to treat the viral infection and drug resistance of current viruses. That is why it is still need of newer vaccines, diagnostic agents and antiviral molecules [99]. Considering the fact that benzothiazole moiety has versatile applications, several research findings have reported many biological activities of heterocycles containing this moiety, including antiviral effect against various species of viruses [100]. Based on the oustanding physical and chemical properties of benzothiazole moiety, many researchers have tried to synthesize various benzothiazole derivatives that show potent antiviral effects against various strain of viruses [101].

Petal, *et al.,* (2013) reported the antiviral activity of compounds (104a-j). The compounds(104a-j) were evaluated against Human Immune Virus (HIV). The result shows that all the compound (104a-j) are active against Human Immune Virus (HIV) [73].

Montalvao, *et al.,* (2016) reported the antiviral activity of compounds (112a-b). The compounds (104a-j) were evaluated against Herpes Simple Virus. The result reveal that compounds (112a-b) show potent antiviral activity against Herpes Simple Virus. They are also Hsp90α inhibitors with broad spectrum antiviral activity [74].

Masssari, *et al.,* (2010) reported the antiviral activity of compound (115). The compounds (104a-j) were evaluated and the result show that the synthesized compound (115) is a potential inhibitor of the HIV-1 Tat-mediated transcription, and also exhibit antiviral activity in HIV-infected cells. Compound 115 displayed EC_{50}=0.03 μg/mL and 0.02 μg/mL with HIV-1 and HIV-2 metal-lothionein 4 (MT-4) cells [75].

Jonckers, *et al.,* (2012) reported the antiviral activity of the Compounds (122a-b).The Compounds (122a-b) were evaluated as pharmacokinetic enhancers of HIV protease inhibitors [76].

3.8   Anticonvulsant Activity

Ugale, *et al*., (2012) reported the anticonvulsant activity of compounds (125a-c). The compound (125a-c) was evaluated as anticonvulsant agents by maximal electroshock and PTZ induced seizure methods. The result revealed that compound 125a showed remarkable activity against tonic seizure, whereas compound 125c showed promising results against clonic seizure. Significantly none of the synthesized compounds (125a-c) exhibited neurotoxicity or hepato-toxicity [77].

CONCLUSION (4)

From this literature review, it can be concluded that benzothiazoles and their Schiff bases have shown a wide range of medicinal value. It is a versatile nucleus in the field of medicinal chemistry. Hence this unique molecule must serve as future therapeutic leads of developing various

biological agents. Benzothiazole scaffold's wide applications is not only limited to the field of medicinal chemistry but also finds relevance in other aspects of chemistry.

Jiang, *et al.,* (2017) revealed that benzothiazole scaffold is always viewed as fluorophore and recognition moiety in structure of fluorescent probes, playing essential role on provision of fluorescence signal and binding sites [102]. According to Doner, *et al.,* (2011) organic compounds bearing heteroatoms with high electron density such as phosphorus, sulphur, nitrogen and oxygen etc are considered adsorption centers and are effective as corrosion inhibitors [103]. Going further, Hojat, *et al.,* (2019) reported the corrosion inhibition of carbon steel immersed in a 1 M HCl solution using benzothiazole derivatives [104].

In conclusion, although many works have been done on benzothiazole and their Schiff bases, yet further research is needed in this class of heterocycles due to its wide application, especially in the field of medicinal chemistry, pharmaceutical industry and other production industries. This review also discloses different methods of synthesizing benzothiazole and their Schiff bases which could invariable give good grounds to the researchers in the area of organic, pharmaceutical and medicinal chemistry to propose and develop a new reaction scheme bearing benzothiazole scaffold.

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