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Synthesis of benzothiazoles and biologically active derivatives from 2-aminothiophenol- REVIEW-

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Abstract

In the new millennium, benzothiazole derivatives have attracted great interest in medicinal chemistry due to their pharmacological and biological properties. Benzothiazole nucleus possesses diverse biological properties such as antimicrobial, anticancer, antifungal, anthelmintic, antidiabetic and anticonvulsant activities. In this review, we expose the common procedures to synthesize benzothiazole and its derivatives, which comprise various biological activities.

Keywords: Benzothiazole, 2-aminothiophenol, Antimicrobial, Anticancer, Biological applications

1. Introduction

Benzothiazoles are found in a wide assortment of natural products and bioactive molecules with less toxic effects and their derivatives display enhanced activities, which has proven benzothiazole scaffold as one of the substantial moieties in medicinal chemistry. [1, 2]. Benzothiazole **(1)** is a heterocyclic aromatic compound with the formula C_7H_5NS. The basic structure consists of a benzene ring fused with 4 and 5 positions of thiazole as shown in Figure 1. Benzothiazole is one of the most attracted heterocycles due to its various molecular design and superb electronic, and optical properties [3].

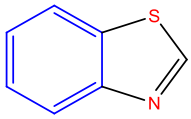

Figure 1: Structure of benzothiazole (1).

Benzothiazole is a weakly basis, slightly viscous colourless liquid that is insoluble in water but soluble in salts, forming a strong aqueous acid hydrochloride. Benzothiazole has a melting point of 2°C, a boiling point of 227–228°C, and a density of 1.238 g/mL at 25°C [4]. Many organic compounds, such as bleomycin, epoethylone A, lingapatili, and dolstatin, contain the benzothiazole moiety [5]. Due to their various biological activities benzothiazole moiety act as the core nucleus in various drugs such as ethoxazolamide (carbonic anhydrase inhibitor), zopolrestat which used for the treatment of overdue-stage diabetic complications including nephropathy and neuropathy) and riluzole (acts as anxiolytic) Figure 2

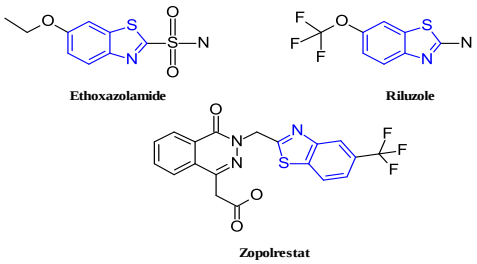

Figure 2: drugs containing benzothiazole moiety

Many medicinally significant compounds with antitumor, antibacterial, anti-inflammatory, anticonvulsant, and antidiabetic properties are derived from benzothiazole [6]. Various methods have been reported for the synthesis of benzothiazole. Among these methods is the condensation of 2-aminothiophenol with aldehydes, acids, oxalyl chloride, amines, alcohols, nitriles, ketones, diketons and β-ketoesters [7]. This report summarizes the biological activities of benzothiazole derivatives and shows current procedures and synthetic routes for producing them from the condensation of 2-aminothiophenol.

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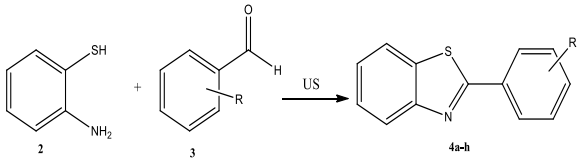
2. Synthesis of benzothiazole derivatives

2.1. Condensation of 2-aminothiophenol with aldehydes

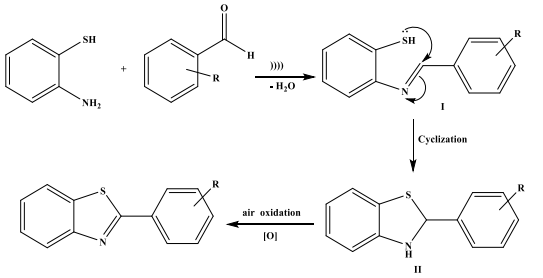
Benzothiazole derivatives (**4a-h**) can be obtained from condensation of 2-aminothiophenol (**2**) with various aromatic aldehydes (**3**) via ultrasonic irradiation in 20 min. at room temperature. Yields range from 65% to 83%. Compared with conventional methods [8], the advantages of this procedure of synthesizing benzothiazoles include simplicity, short reaction time, solvent and catalyst free reactions (Scheme 1),



R= H, 2-Cl, 3-Cl, 4-Cl, 2-F, 4-F, 4-Br, 4-OCH_3

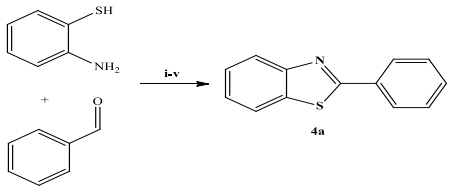
Scheme 1

A plausible mechanism of the formation of benzothiazole derivatives involves nucleophilic attack of 2-aminothiophenol on the benzaldehyde carbonyl group, leading to the formation of intermediate **I**. A subsequent cyclisation reaction yields intermediate **II**. Finally, air oxidation of intermediate **II** furnishes benzothiazole derivatives, as depicted in Scheme 2 [9].



Scheme 2

Various methods using nanoparticles as a catalyst have been reported for the synthesis of benzothiazole. In a study published in 2015, benzothiazole (**4a**) was synthesized using nickel oxide (NiO) Nano rods as catalyst and ethanol as solvent. The reaction mixture was agitated at 60°C for 4 h (Scheme 3) [10].



Scheme 3: Reaction conditions i) nano NiO,60°C, EtOH,4h ii) acetic acid, grinding, r.t.,15 min. iii) CO_2, MeOH70°C, 2h iv) zinc sulphide (NPs) and v) Co_3O_4 nano-flakes, r.t

Peng *et al.* reported the synthesis of 2-phenylbenzo[d]thiazole (**4a**) from compound (**2**) and benzaldehyde in the presence of acetic acid as catalyst using the mortar-pestle grinding method. This method is simple, with good functional group tolerance and a short reaction duration (Scheme 3) [11].

Xiao *et al*. reported the green and effective condensation of compound (**2**) and benzaldehyde in self-neutralising acidic CO_2-alcohol to afford compound (**4a**). In this reaction, CO_2 reacted with methanol to form alkyl carbonic acid, which catalysed the reaction of benzaldehyde and 2-aminothiophene to produce the target product (Scheme 3) [12].

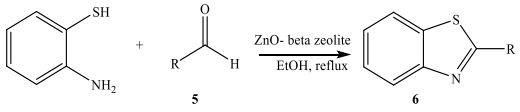
Arun *et al.* developed the reaction of compound (**2**) with benzaldehyde derivatives in the presence of zinc sulphide nanoparticles (NPs) derived from the waste stems of Trigonella foenum-graecum to achieve benzothiazoles (**4a**) in high yield with a short reaction time, solvent-free conditions, and recyclable catalyst (Scheme 3) [13].

Geetika *et al*. explored a one-pot synthesis of 2-phenylbenzo[d]thiazole (**4a**) by condensation of compound (**2**) and benzaldehyde in the presence of Co_3O_4 nano- flake using various solvents at room temperature. The reaction went to completion using Co_3O_4 nano- flake as catalyst as shown in table (Scheme 3) [14].

Optimization of reaction conditions for the synthesis of 2-phenyl-1,3-benzothiazole

Entry	Catalyst	Solvent	Time (min)	Yield (%)
1	Co_3O_4 NFs	EtOH (1 ml)	10	**92**
2	Co_3O_4 NFs	H_2O (1 ml)	10	**85**
3	Co_3O_4 NFs	THF (1 ml)	30	**55**
4	Co_3O_4 NFs	CH_2Cl_2 (1 ml)	30	**48**
5	Co_3O_4 NFs	Neat	5	**95**

Katkar *et al.* reported an effective and green method for the synthesis of benzothiazole derivatives (**6**) from compound (**2**) and various aldehydes (**5**) using ZnO-beta zeolite as a heterogeneous catalyst. Advantages of this procedure include high yield, simplicity, and reusability of the catalyst, as depicted in Scheme 4 [15].

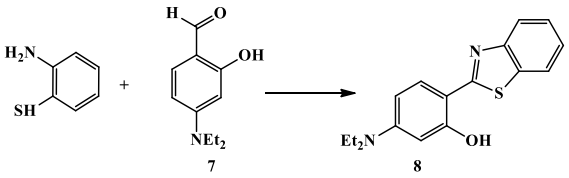


R= C_6H_5 ,4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$,4-OHC_6H_4 , 2-$NO_2C_6H_4$, 2-OHC_6H_4 , 2-ClC_6H_4 , 4-ClC_6H_4 , 4-$OMeC_6H_4$, 2-$OMeC_6H_4$, Furyl

Scheme 4

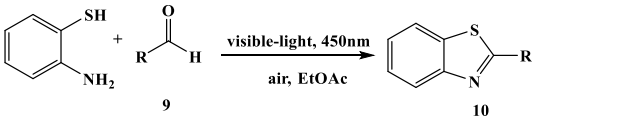
Padalkar *et al.* reported the synthesis and antimicrobial effect of benzothiazole derivatives. Reaction of *p-N,N*-diethylamino salicylaldehyde (**7**)

with compound (**2**) in ethanol and phosphorus trichloride at 60°C gave the corresponding compound (**8**), shown in Scheme 5 [16].



Scheme 5

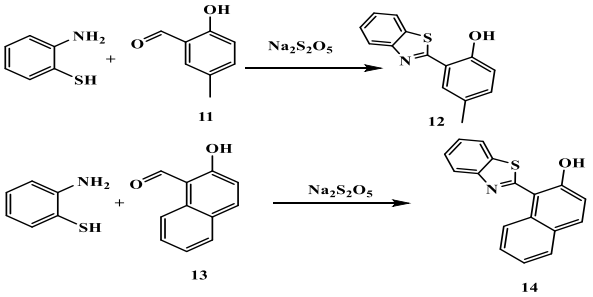
Linmaio *et al*. synthesised benzothiazoles (**10**) from compound (**2**) and various aldehydes (**9**) in ethyl acetate under photo irradiation (λ = 450 nm) in an air atmosphere (Scheme 6) [17].



R= ph, 2-Me-C_6H_4, 3-MeC_6H_4, 2OHC_6H_4, 4-$CF_3C_6H_4$,4-ACOC_6H_4, 3-indolyl, 2-thienyl, 2-furanyl, 2-napthyl

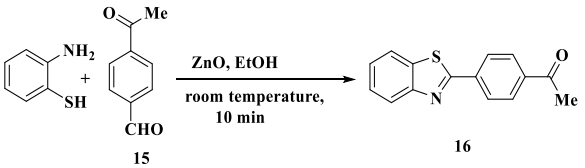
Scheme 6

Liu *et al.* synthesised compound (**12**) and (**14**) via condensation of 2-hydroxy-5-methyl-benzaldehyde (**11**) or 2-hydroxy-1-naphthaldehyde (**13**) with compound (**2**) and $Na_2S_2O_5$ in *N,N*-dimethylformamide (Scheme 7) [18].



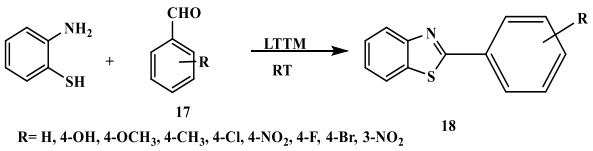
Scheme 7

Ravinaik *et al*. synthesized 1-(4-(benzo[d]thiazol-2-yl)phenyl)ethanone (**16**) by condensation of compound (**2**) with 4-acetylbenzaldehyde (**15**) in the presence of ZnO NPs at room temperature (Scheme 8) [19].



Scheme 8

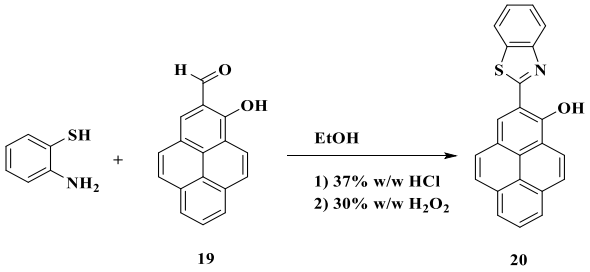
Patil *et al.* reported the synthesis of 2-substituted benzothiazole derivatives (**18**) by reacting compound (**2**) with diverse aromatic aldehydes (**17**) using oxalic acid dihydrate**:** proline low transition temperature mixture (LTTM) as green reaction medium at room temperature. This method is eco-friendly, gives a high yield and takes almost 2.5 h for completion (Scheme 9) [20].



R= H, 4-OH, 4-OCH_3, 4-CH_3, 4-Cl, 4-NO_2, 4-F, 4-Br, 3-NO_2

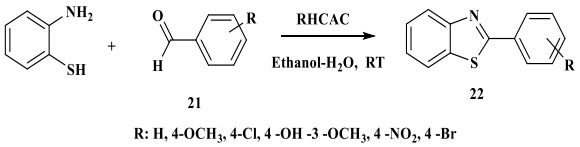
Scheme 9

Hu *et al*. synthesised 2-(benzo-thiazole -2-yl)pyren-1-ol (**20**) by reaction of 1-hydroxypyrene-2-carbaldehyde (**19**) with compound (**2**) in the presence of 37% HCl and 30% H_2O_2 stirred at room temperature for 1 h (Scheme 10) [21].



Scheme 10

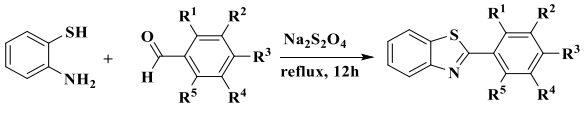
Asatkar *et al.* reported the synthesis of benzothiazole derivatives (**22**) by reacting compound (**2**) with diverse aromatic aldehydes (**21**) using rice husk-derived chemically activated carbon (RHCAC) as a catalyst in an aqueous medium at room temperature, achieving a high yield within a short time (Scheme 11) [22].



R: H, 4-OCH_3, 4-Cl, 4 -OH -3 -OCH_3, 4 -NO_2, 4 -Br

Scheme 11

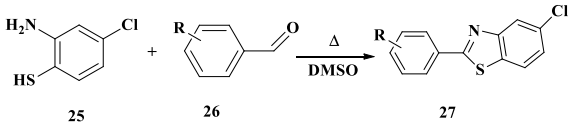
Djuidjea *et al.* synthesised benzothiazole derivatives (**24**) by condensing compound (**2**) with various aromatic aldehydes (**23**) using sodium hydrosulphite as catalyst in an aqueous medium (Scheme 12) [23].



R^1	R^2	R^3	R^4	R^5
H	H	H	H	H
OH	H	H	H	H
H	OH	H	H	H
H	H	OH	H	H
H	H	OCH_3	H	H
OH	H	OH	H	H
OH	H	H	OH	H
H	OH	OH	H	H
H	OH	OCH_3	H	H
H	OH	H	OH	H
OH	H	OH	OH	H

Scheme 12

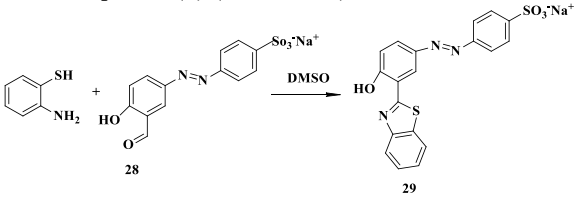
Manoharan *et al.* reported the synthesis of halogen substituted benzothiazole derivatives. 2-Amino-4-chloro benzenethiol (**25**) was reacted with aldehyde derivatives (**26**) in the presence of dimethyl sulphoxide (DMSO) to afford benzothiazole derivatives (**27**) (Scheme 13) [24].



R= 4-N(CH$_3$)$_2$, 2-OH -5Cl

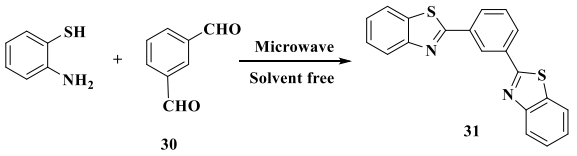
Scheme 13

Park *et al.* demonstrated the synthesis of benzothiazoles (**29**) by condensation of 5-(4-sulfophenylazo) salicylaldehyde sodium salt (**28**) with compound (**2**) (Scheme 14) [25].



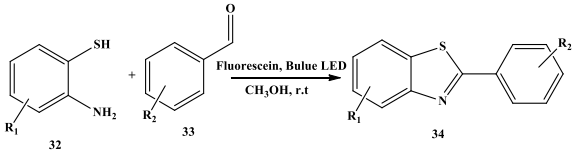
Scheme 14

Kaur *et al.* reported the synthesis of benzene-1,3-bis(benzothiazole) (**31**) via condensation of compound (**2**) with benzene-1,3-dicarbaldehyde (**30**) under microwave irradiation (Scheme 15) [26].



Scheme 15

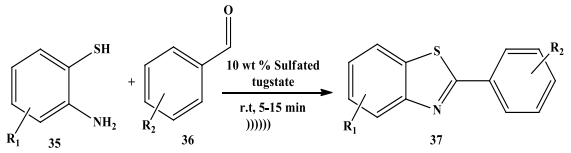
Wuji *et al.* synthesised benzothiazole derivatives (**34**) from compound (**32**) with an aromatic aldehyde (**33**), fluorescein as a photocatalyst, and a blue LED as the light source at room temperature for 3 h under a molecular oxygen atmosphere. The reaction was completed without using any metal catalyst with excellent yield (Scheme 16) [27].



R$_1$= 3-Cl
R$_2$= 2-Br, 3-Br,4-Br, 4-Cl, 4-F, 2-Me-,4-OMe

Scheme 16

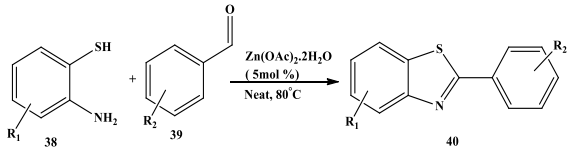
Ashok and co-workers investigated the rapid synthesis of benzothiazoles (**37**) by condensation of compound (**35**) with various aldehydes (**36**) in the presence of sulphated tungstate under ultrasound irradiation at room temperature. This efficient, environmentally friendly, solvent-free reaction is performed under mild conditions with excellent yield (Scheme 17) [28].



R$_1$= 4-Br
R$_2$= 2-Br, 3-Br, 4-Br, 4-Cl, 4-F, 2-Me, 4-OMe

Scheme 17

Kokane *et al.* reported a simple and solvent-free condensation of 2-substituted benzothiazoles (**40**) from compound (**38**) and substituted aromatic aldehydes (**39**) with Zn(OAc)$_2$.2H$_2$O as a catalyst at 80°C. The method offers several benefits including environmentally friendly catalysts that are inexpensive and easily accessible (Scheme 18) [29].

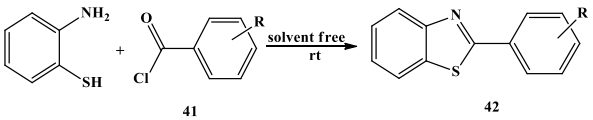


R$_1$= 5-Me, 5-Br, 5-CF$_3$
R$_2$= 4-Me, 4-OMe, 4-OH, 4-Cl, 4-F, 2-CN, 4-N(Me)$_2$

Scheme 18

2.2. Condensation of 2-aminothiophenol with benzoyl chlorides

Ziarani *et al.* synthesised benzothiazole derivatives (**42**) by reaction of compound (**2**) with aromatic benzoyl chlorides (**41**) in a solvent-free environment at room temperature, with a short reaction time and excellent yield (Scheme 19) [30].

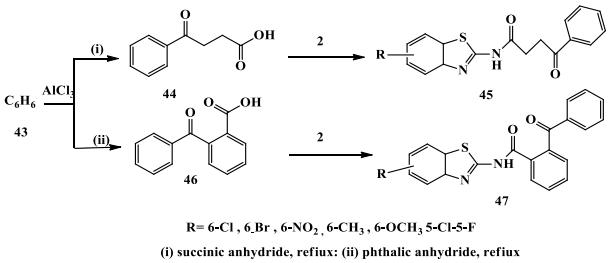


R= 2-Cl, 3-Cl, 2,4-Cl, 3-NO$_2$, 4-NO$_2$

Scheme 19

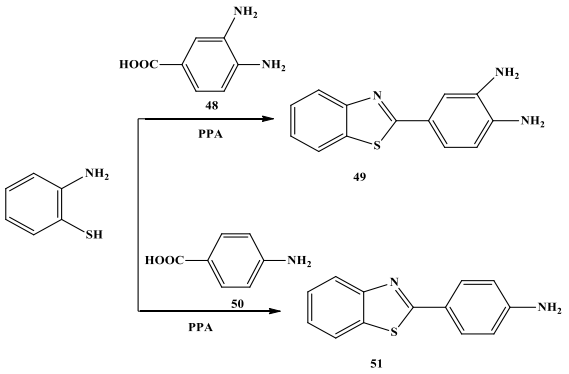
2.3. Condensation of 2-aminothiophenol with carboxylic acid

Hassan *et al.* reported the design, synthesis and evaluation of benzothiazole derivatives as anticonvulsant and neuroprotective agents. Synthesis of 4-oxo-4-phenylbutanoic acid (**44**) and 2-benzoyl benzoic acid (**46**) was achieved by acylation of benzene (**43**) with succinic anhydride and phthalic anhydride via a Lewis acid-catalysed Friedel-Crafts mechanism. Refluxing with 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide and hydroxybenzotriazole in the presence of dichloromethane, followed by the addition of compound (**2**) produced the desired amides (**45, 47**) (Scheme 20) [31].



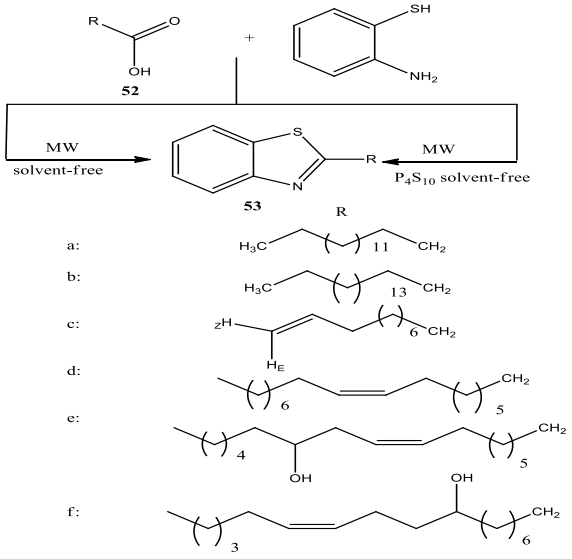
Scheme 20

Various substituted 4-(benzo[*d*]thiazol-2-yl) benzene-1, 2-diamine (**49**) and 4-(benzo[*d*]thiazol-2-yl) benzenamine (**51**) have been synthesised by Paczkowski *et al.* [32] and Singh *et al.* [33] via treatment of compound (**2**) with 3,4-diaminobenzoic acid (**48**) and/or *p*-aminobenzoic acid (**50**) in the presence of polyphosphoric acid (Scheme 21).



Scheme 21

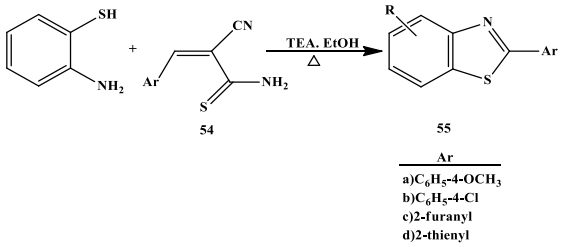
Under microwave irradiation in solvent-free medium or in the presence of P_4S_{10}, the treatment of compound (**2**) with several fatty acids (**52**) afforded the corresponding 2-substituted benzothiazoles (**53**) (Scheme 22) [34].



Scheme 22

2.4. Condensation of 2-aminobenzenthiol with aryl methylene cyanothioacetamide

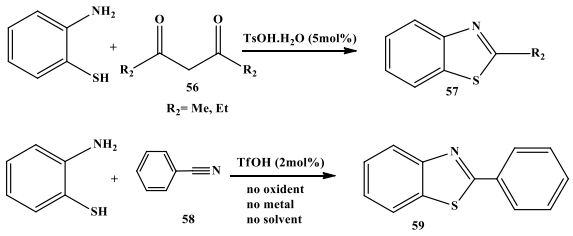
Elgemeie *et al.* reported the synthesis of 2-arylbenzothiazoles (**55**) by the condensation of compound (**2**) with various aryl methylene cyanothioacetamide (**54)** (Scheme 23) [35].



Scheme 23

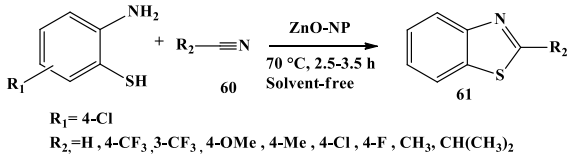
2.5. Cyclisation of 2-aminobenzenthiol with β-diketones and nitriles

Xiaoqiang *et al.* reported the synthesis of 2-substituted benzothiazoles (**57**) via the Brønsted acid-catalysed cyclization of compound (**2**) with *β*-diketones (**56**) under oxidant, transition-metal, solvent, and irradiation-free conditions. Also reported the synthesis of 2-substituted benzothiazoles (**59**) via the reaction of compound (**2**) with substituted nitriles (**58)** and trifluoromethane-sulphonic acid (TFOH) as Brønsted acid catalysis (Scheme 24) [36].



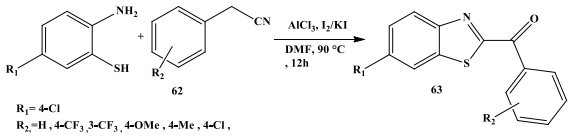
Scheme 24

Under solvent-free conditions, and ZnO NPs as a catalyst Dhawale *et al.* reported the synthesis of benzothiazole derivatives (**61**) via cyclization of compound (**25**) and aryl/alkyl nitriles (**60**) (Scheme 25) [37].



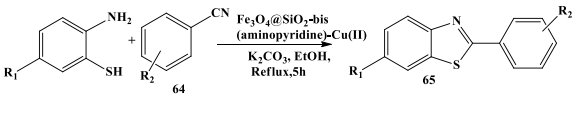
Scheme 25

Zhang *et al.* developed an efficient synthesis of 2-acylbenzothiazoles (**63**) in moderate to good yields by $AlCl_3$-mediated cyclisation and oxidation of compound (**25**) with arylacetonitriles (**62**) in DMF (Scheme 26) [38].



Scheme 26

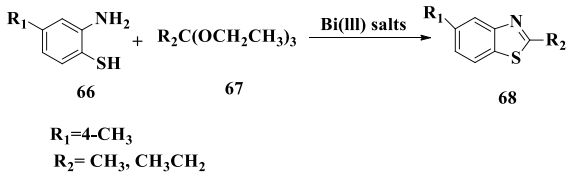
Zaid *et al*. synthesised benzothiazoles (**65**) by condensing compound (**25**) and benzonitriles (**64**) using novel copper catalysts derived from Fe_3O_4@SiO_2-bis(aminopyridine)-Cu(II) (Scheme 27) [39].



Scheme 27

2.6. Condensation of 2-aminothiophenol with orthoesters

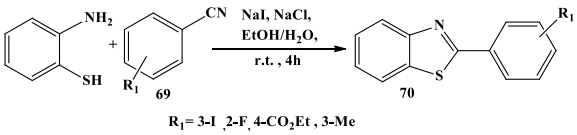
Balturk *et al.* synthesised 2-substituted benzothiazoles **(68)** by the treatment of compound **(66)** with *orthoesters* **(67)** in the presence of Bi (TFA) as catalyst in various solvents such as $ClCH_2CH_2Cl$, $CHCl_3$, CH_3OH and CH_3CN, and under solvent-free conditions at room temperature (Scheme 28) [40].



Scheme 28

2.7. Condensation of 2-aminothiophenol with isothiocyanate derivatives

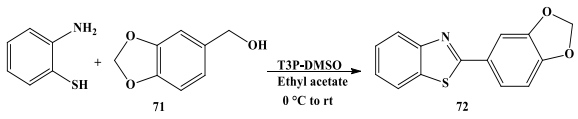
Mahmooda, Z. H. *et al*. reported the synthesis of benzothiazole derivatives (**70**) in moderate yields under metal-free conditions by condensation of compound (**2**) with isothiocyanate derivatives (**69**) using NaI and NaCl in aqueous ethanol at room temperature for 4 h (Scheme 29) [41].



Scheme 29

2.8. Condensation of 2-aminothiophenol with alcohol

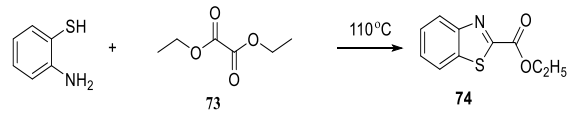
Raghavendra et al. reported one-pot operation cyclocondensation of compound (**2**) with Benzo[d][1,3]dioxol-5-yl-methanol (**71**) afford benzothiazole derivative (**72**) with excellent yield in the presence of T3P-DMSO (Scheme 30) [42].



Scheme 30

2.9. Condensation of 2-aminothiophenol with diethyl oxalate

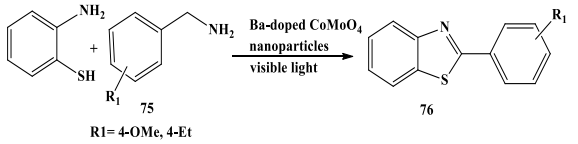
Mokhtar and coworkers reported efficient ethyl benzothiazole-2-carboxylate (**74**) formation from compound (**2**) with diethyl oxalate (**73**) upon heating at 110°C for 4 h (Scheme 31**)** [43]. In another report, Bhutani *et al.* reported the synthesis, molecular modelling analysis, and ADME prediction of benzothiazole-derived oxadiazole-Mannich bases, and evaluation of their antidiabetic activities. Ethyl benzothiazole-2-carboxylate (**74**) was synthesised by refluxing a mixture of compound (**2**) and diethyl oxalate (**73**) in water (Scheme 31) [44].



Scheme 31

2.10. Condensation of 2-aminothiophenol with amines

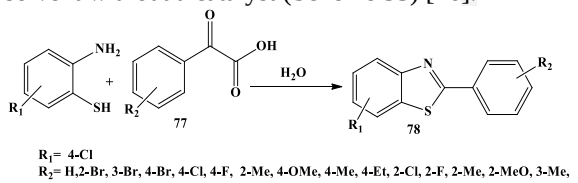
Benzenethiol derivatives (**76**) have been synthesized by Ramanjulu *et al*. [45] in good to excellent yields by condensation of compound (**2**) with different aryl methyl amines (**75**) using Ba-doped $CoMoO_4$ NPs under visible light irradiation in an air atmosphere (Scheme 32).



Scheme 32

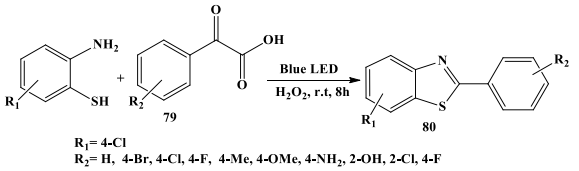
2.11. Condensation of 2-aminothiophenol with α-keto acids

Jian *et al*. reported a green method for the synthesis of benzothiazoles (**78**) via condensation of α-keto acids (**77**) with compound (**25**) in water as solvent without a catalyst (Scheme 33) [46].



Scheme 33

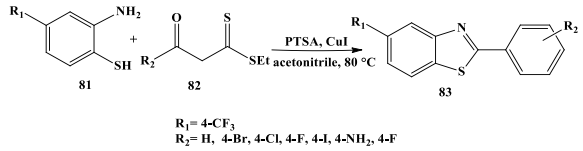
Under blue LED irradiation (λ = 435–445 nm) the treatment of compound (**25**) and α-keto acids in the presence of H_2O_2 afforded benzothiazoles (**80**) in moderate to good yields by Aparna et al. (Scheme 34) [47].



Scheme 34

2.12. Condensation of 2-aminothiophenol with β-oxodithioesters

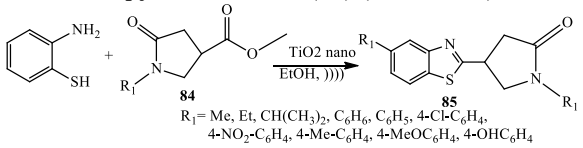
Arindam *et al*. synthesised 2-substituted benzothiazoles (**83**) with good to excellent yields from compound (**81**) and β-oxodithioesters (**82**) utilising p-toluene sulphonic acid (PTSA) and CuI in acetonitrile with stirring for 24 h at 80°C (Scheme 35) [48].



Scheme 35

2.13. Condensation of 2-aminothiophenol with esters

Benzothiazole-linked pyrrolidin-2-one have been synthesized by Ammar et al [49]. Methyl 1-benzyl-5-oxopyrrolidine-3-carboxylate (**84**) with compound (**2**) in a TiO_2 nanostructure under ultrasonic irradiation afforded 4-(Benzothiazol-2-yl)-1-substituted pyrrolidin-2-one (**85**) (Scheme 36)



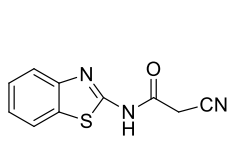
Scheme 36

3. Biological applications

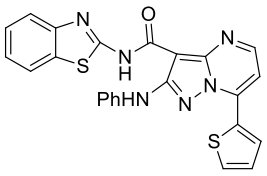
Benzothiazoles have been linked to compounds with a variety pharmacological activity.

3.1. Antimicrobial *activity*

Bondock *et al.* described the synthesis and antibacterial activity study of novel benzothiazole analogue-containing thiazole, thiophene, and pyrazole derivatives. In vitro tests on compound (**86**) and compound (**87**) reveals significant antibacterial activity [50].

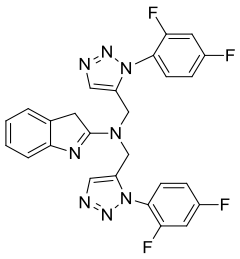


86

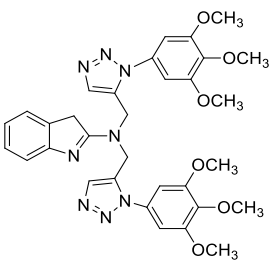


87

Singh *et al.* reported the synthesis and antimicrobial activity of novel benzothiazole moieties. Compound (**88**) showed potent antibacterial activities, while compound (**89**) showed potent antifungal activities [51].

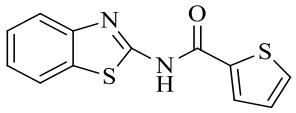


88



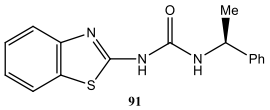
89

Gurram and Azam designed, synthesised and biologically evaluated novel *N*'-(1,3-benzothiazol-2-yl)-arylamide derivatives as antibacterial agents. Compound (**90**) exhibited high activity against *Staphylococcus aureus* ATCC 43300, with a minimum inhibitory concentration (*MIC*) of 15.0 μM [52].

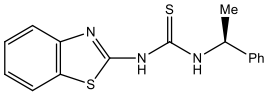


90

In a different study, new chiral urea/thiourea derivatives bearing benzothiazole moieties were synthesized and their antimicrobial activity was assessed [53]. The compounds benzothiazole-urea (**91**) and benzothiazole-thiourea (**92**) were found to be only effective against *S. aureus* and *Bacillus cereus.*

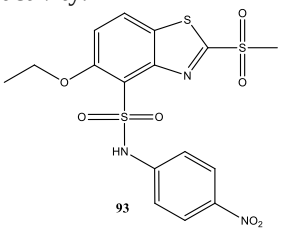


91

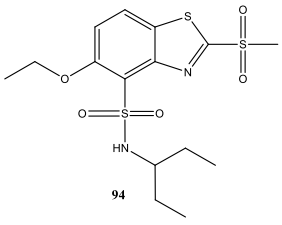


92

Lad et al. [54] synthesised and evaluated novel 4-substituted methylsulfonylbenzothiazole derivatives (**93**) and (**94**) which showed potent antibacterial activity.



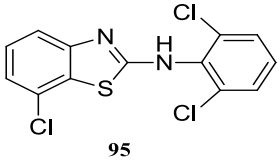
93



94

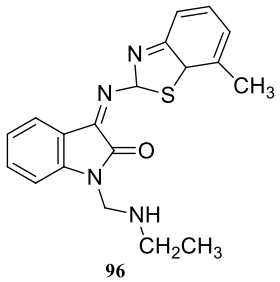
3.2. Anticancer activity

Noolivi and coworkers synthesised 7-chloro-*N*-(2,6-dichlorophenyl) benzo[*d*]thiazol-2-amine (**95**), which inhibited the HOP-92 non-small cell lung cancer cell line [55].



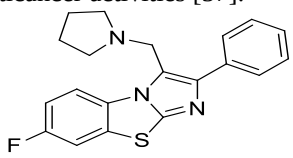
95

Solomom *et al.* reported the design and synthesis of the isatin-benzothiazole group, and compound (**96**) showed potent anti-breast cancer activity [56].



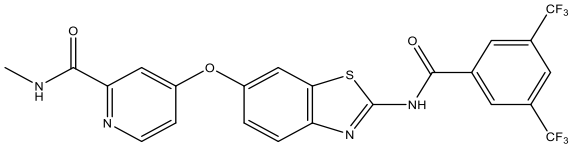
96

3-(pyrrolidinomethyl)-2-phenyl-7-fluoro-imidazo[2,1-*b*]benzothiazole (**97**) have been synthesized by Kumbhare *et al.* which exhibit potential anticancer activities [57].



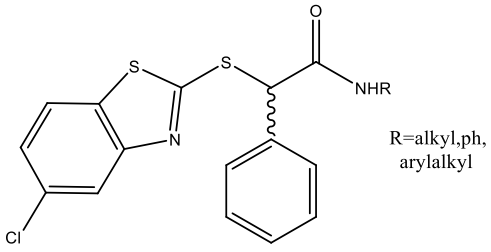
97

Ammazzalorso *et al.* reported antiproliferative effect of the compound (**98**) [58].



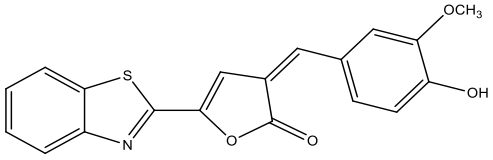
98

Benzothiazol amides (**99**) with PPARα displayed antiproliferative effect against pancreatic and colorectal cancer [59].



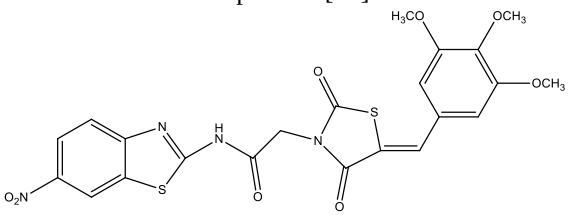
99

Asif *et al.* prepared benzothiazole analogue-containing furanone (**100**) exhibiting potent anticancer activity [60].

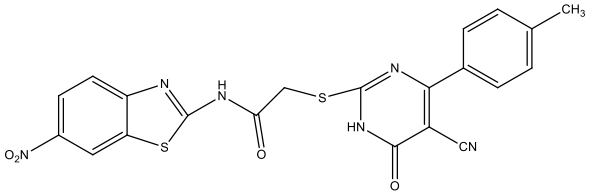


100

Mohammad *et al.* prepared of series of 2-aminobenzothiazole hybrids linked to thiazolidine-2,4-dione and cyanothiouracil derivatives, and studied their anticancer effect against three cancer cell lines (HCT-116, HEPG-2 and MCF-7). Compounds (**101**) and (**102**) showed potent effect against a breast cancer cell line with IC_{50} values of 6.11 and 10.86 µM. Sorafenib (SOR) is an established medicinal product [61].

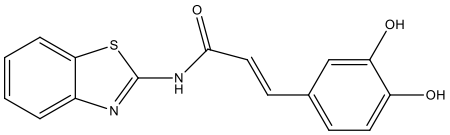


101



102

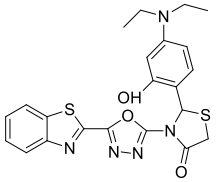
Riccardo *et al*. synthesised compound (**103**) that inhibits both Colo-38 human melanoma cells and HaCat immortalised human keratinocytes. Compound (**103**) showed excellent effect and selectivity toward human melanoma cells, and is a good antioxidant [62].



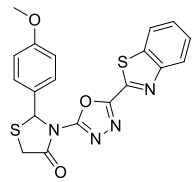
103

3.3. Antidiabetic activity

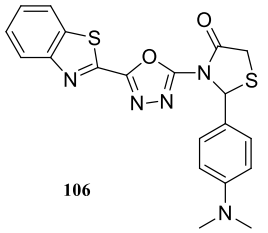
Bhutani *et al.* reported the synthesis and evaluation of a novel series of 3-[5-(benzo[*d*]thiazol-2-yl)-1,3,4-oxadiazol-2-yl]-2-substituted thiazolidine 4-one derivatives as PPARα agonists and *α*-glucosidase inhibitors. Compounds (**104, 105** and **106**) were potent antidiabetic agents [63].



104

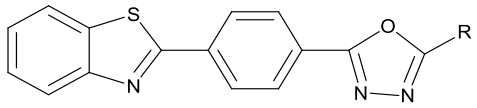


105



106

Gollapalli *et al.* synthesised benzothiazole-based oxadiazole derivatives (**107**) that displayed potent *α*-glucosidase inhibitor [64].

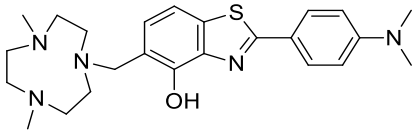


107

R= 4-OHC$_6$H$_5$, 2,4-(OH)$_2$C$_6$H$_3$, 3-NO$_2$, 4-OCH$_3$, 3-OH

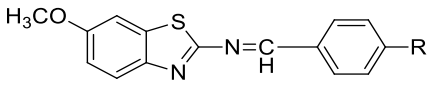
3.4. Amyloid imaging agents in Alzheimer's disease (AD)

Huang *et al.* reported the synthesis of compound (**108**) as an amyloid cascade for treatment of AD [65].



108

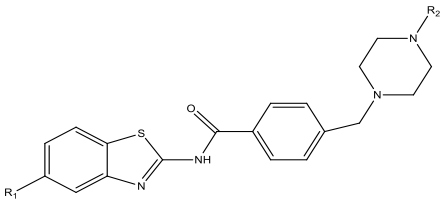
Gan *et al.* synthesised a series of benzothiazole Schiff bases and evaluated them as amyloid imaging agents in AD since they targeted *β*-amyloid plaques. Compound (**109**) exhibited high binding affinity towards amyloid plaques in AD brain. [66].



R= N(CH$_3$)$_2$, CH$_3$O , OH

109

Karaca *et al.* reported the synthesis and biological activity analysis of novel benzothiazole derivatives (**110**) as dual acetylcholinesterase (AChE)-monoamine oxidase B (MAO-B) inhibitors in the treatment of AD. Benzothiazoles derivatives (**110**) exhibited significant activity against AChE and MAO-B enzymes, and the capacity to prevent the formation of beta-amyloid plaques accumulating in the brain of AD patients [67].

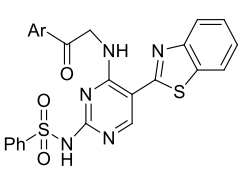


110

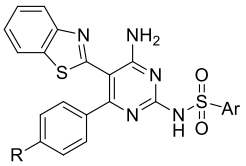
R$_1$= H, OMe
R$_2$= Me, Et, CH$_2$ CCH$_2$, CH$_2$ CH$_2$N(CH$_3$)$_2$

3.5. Antiviral activity

Azzam *et al.* reported the synthesis and antiviral effect of substituted 2-pyrimidylbenzothiazoles incorporating either sulphonamide or amino groups in the C2 position of the pyrimidine ring. Compounds (**111, 112**) were the most effective against HSV-1, and showed inhibitory activity against the Hsp90α protein [68].



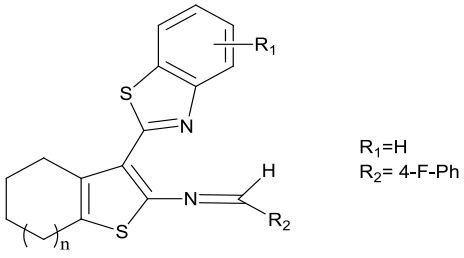
111



112

Ar	R
4-CH$_3$-C$_6$H$_4$	H
4-CH$_3$-C$_6$H$_4$	F
4-CH$_3$-C$_6$H$_4$	Cl

Ke *et al.* reported the synthesis of compounds containing substituted benzothiazole (**113**) possessing potent antiviral activity [69].

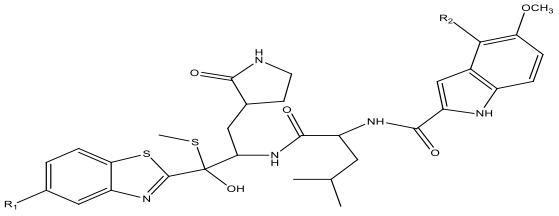


R$_1$=H
R$_2$= 4-F-Ph

n= 0,1

113

Xiaohui *et al*. reported that benzothiazolyl ketone (**114**) was a potential anti-coronavirus agent [70].

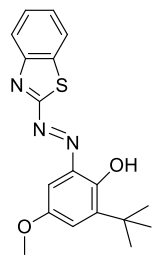


114

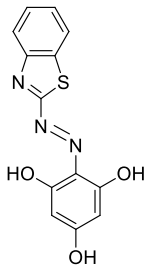
3.6. Antioxidant activity

In a study by Prakash *et al.*, 2-(benzo[*d*]thiazol-2-yldiazenyl)-6-(tert-butyl)-4-methoxyphenol (**115**)

and 2-(benzo[*d*]thiazol-2-yldiazenyl) benzene-1,3,5-triol (**116**) showed remarkable antioxidant activity [71].

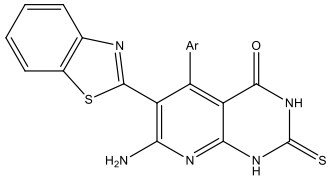


115

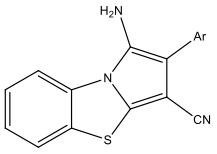


116

Al-Mutairi *et al*. reported the synthesis novel 2,3-dihydropyrido[2,3- d]pyrimidin-4-one (**117**) and pyrrolo[2,1-b][1,3]benzothiazoles (**118**) showed strong antioxidant activity [72].

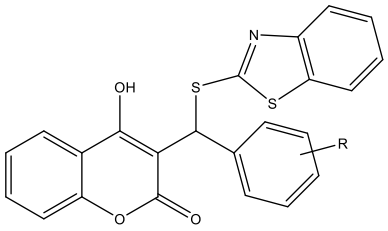


117



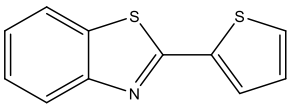
118

Kadam, *et al.* synthesised 3-[(1,3-benzothiazol-2-ylsulfanyl)(phenyl)methyl]-2*H*-chromen-4-ol derivatives (**119**) that proved to be good antioxidants [73].



119 R= H, Br, Cl, OMe, OH, Me

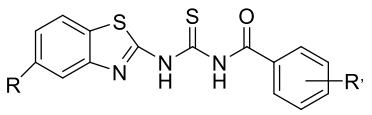
Djuidje *et al.* reported the synthesis of benzothiazole containing thiophene (**120**) that showed a good antioxidant effect [74].



120

3.7. Analgesic and anti-inflammatory activities

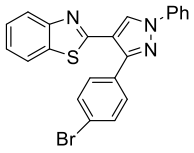
Siddiqui *et al.* reported the synthesis of benzothiazole benzamide derivatives (**121**) that exhibited potent analgesic and antidepressant activities [75].



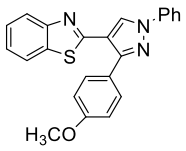
121

R	R'
F	H
Br	2-Cl
F	2-Cl
Br	4-Cl
OCH_3	4-OCH_3

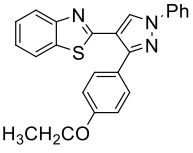
Praveen *et al.* reported the synthesis of substituted benzothiazoles (**122, 123** and **124**) possessing potent analgesic activities [76].



122

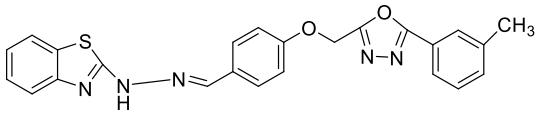


123



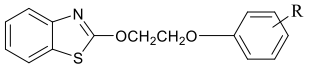
124

Zheng *et al.* synthesised novel benzothiazole derivatives bearing a 1,3,4-oxadiazole group, and evaluated their antioxidant and anti-inflammatory activities. Compound (**125**) showed good anti-inflammatory and antioxidant activities [77].

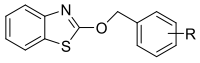


125

He *et al.* reported the synthesis of a series of benzothiazoles and evaluated their anti-inflammatory and analgesic activities. Among the synthesised compounds, (**126**) and (**127**) showed excellent anti-inflammatory and analgesic activities [78].



126

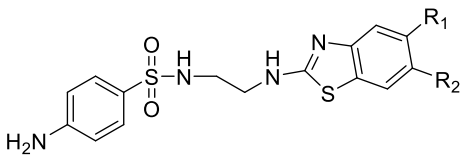


127

R:H, 2,4-F_2,4-F, 2,4-Cl_2 4-Cl, 2,4-Br_2, 4-Br

3.8. Antitubercular activity

Raju *et al.* reviewed the various biological activities of some derivatives of benzothiazole (**128**) exhibiting promising antitubercular activity against *Mycobacterium tuberculosis* [79].

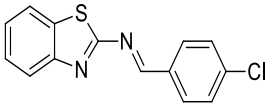


128

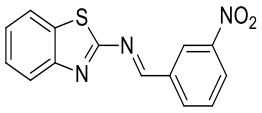
R_1 , R_2 = H
R_1= Cl, R_2=H
R_1= Cl,R_2= F

3.9. Antimalarial activity

Thakkar and co-worker's synthesised compound (**129**) and (**130**) which exhibited antimalarial activity [80].



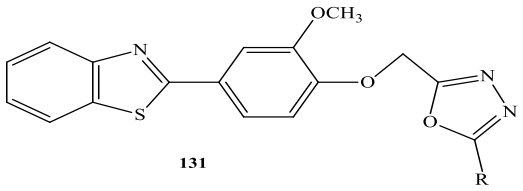
129



130

3. 10. Antiepileptic agents

Chauhan *et al*. designed and synthesised benzothiazole derivatives (**131**) with anticonvulsant potential. *In vivo* and *in silico* studies confirmed that compounds (**131**) were potent antiepileptic agents [81].



131

R= 4-ClC_2H_4, 4-$NO_2C_6H_4$, 4-OHC_6H_4, 3,5 $DiNO_2$ C_6H_3, 4-$MeOC_6H_4$, DiC_6H_5 CH_2

4. Conclusions

The present review presents the multiple synthesis approaches and biological function of benzothiazole derivatives with diverse biological and pharmacological properties. These compounds include antimicrobial, anticancer, antidiabetic, and AD amyloid imaging agents, as well as anti-inflammatory, antiviral, analgesic, antimalarial, antioxidant and antitubercular compounds. A wide variety of pharmacological medications are being developed, and benzothiazole derivatives represent promising therapeutic leads.

5. Conflicts of interest

The author declares no conflict of interest

6. References

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