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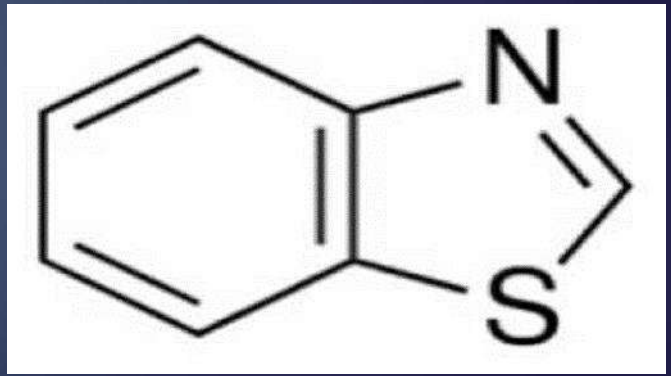
GRADUATION RESARCH

A Review on Recent Development and biological applications of benzothiazole derivative



Abstract

Benzothiozole (BTA) and its derivatives are the most important heterocyclic compounds, which arecommon and integral feature of a variety of natural products and pharmaceutical agents. BTA shows avariety of pharmacological properties, and its analogs offer a high degree of structural diversity that hasproven useful for the search of new therapeutic agents. The broad spectrum of pharmacological activityin individual BTA derivative indicates that, this series of compounds is of an undoubted interest. Therelated research and developments in BTA-based medicinal chemistry have become a rapidly developingand increasingly active topic. Particularly, numerous BTA-based compounds as clinical drugs have beenextensively used in practice to treat various types of diseases with high therapeutic potency. This worksystematically gives a comprehensive review in current developments of BTA-based compounds in thewhole range of medicinal chemistry as anticancer, antibacterial, antifungal, antiinflammatory, analgesic,anti-HIV, antioxidant, anticonvulsant, antitubercular, antidiabetic, antileishmanial, antihistaminic, anti-malarial and other medicinal agents. It is believed that, this review article is helpful for new thoughts inthe quest for rational designs of more active and less toxic BTA-based drugs, as well as more effectivediagnostic agents and pathologic probes.

Keywords: benzothiazoles, 2-aminobenzenethiol, green chemistry, condensation, cyclization, thioamide, CO2

Introduction

Benzotriazole is the simplest member of the class of benzotriazoles that consists of a benzene nucleus fused to a 1H-1,2,3-triazole ring. It has a role as an environmental contaminant and a xenobiotic. Benzotriazole occurs as an odourless, white to light tan, crystalline powder. 2) Tolyltriazole occurs as tan to light brown granules with a characteristic odour. Solubility: 1) Water: 1-5 g/l (at 23.7°C). Soluble in alcohol, benzene, toluene, chloroform, and dimethylformamide.[1]

Benzothiazole is a colorless, slightly viscous liquid with a melting point of 2°C and a boiling point of 227-228°C. The density of benzothiazole is 1.24 g/mL, and its molecular mass is 135.19 gmol−1. Benzothiazole has no household use. It is used in industry and research
Some benzothiazole derivatives are highly useful as insecticides and herbicides,
Benzothiazole is a natural product found in Psidium guajava, Zingiber mioga, and other organisms with data available. Benzothiazole is a metabolite found in or produced by Saccharomyces cerevisiae..[1]
Derivatives of 2-aminobenzothiazoles are reported to have diverse biological activities like cytotoxicity, anti-inflammatory, analgesic, anthelmintic, antiviral, antidiabetic, antimicrobial, antileishmanial, anticonvulsant, Alzheimer's disease, and calcium channel blocking
Some drugs derived from benzothiazole have been used in clinical treatment of various diseases, e.g ethoxzolomide serves as diuretic. Frentizole is used as an antiviral as well as immunosuppressive agent. ..[2]

benzothiazole has been identified as having great acute toxic activity against T. castaneum. However, a comprehensive evaluation of a new insecticide should include both direct toxic effects and sublethal effects

BZT exerts acute toxicity and is a respiratory irritant and dermal sensitizer. In a genetic toxicity assay BZT was positive in Salmonella in the presence of metabolic activation. BZT metabolism involves ring-opening and formation of aromatic hydroxylamines, metabolites with mutagenic and carcinogenic potential [3]

Benzotriazole is a specific corrosion inhibitor for copper and copper alloys. It is now widely used in industry to reduce the corrosion of these alloys under both atmospheric and immersed conditions.

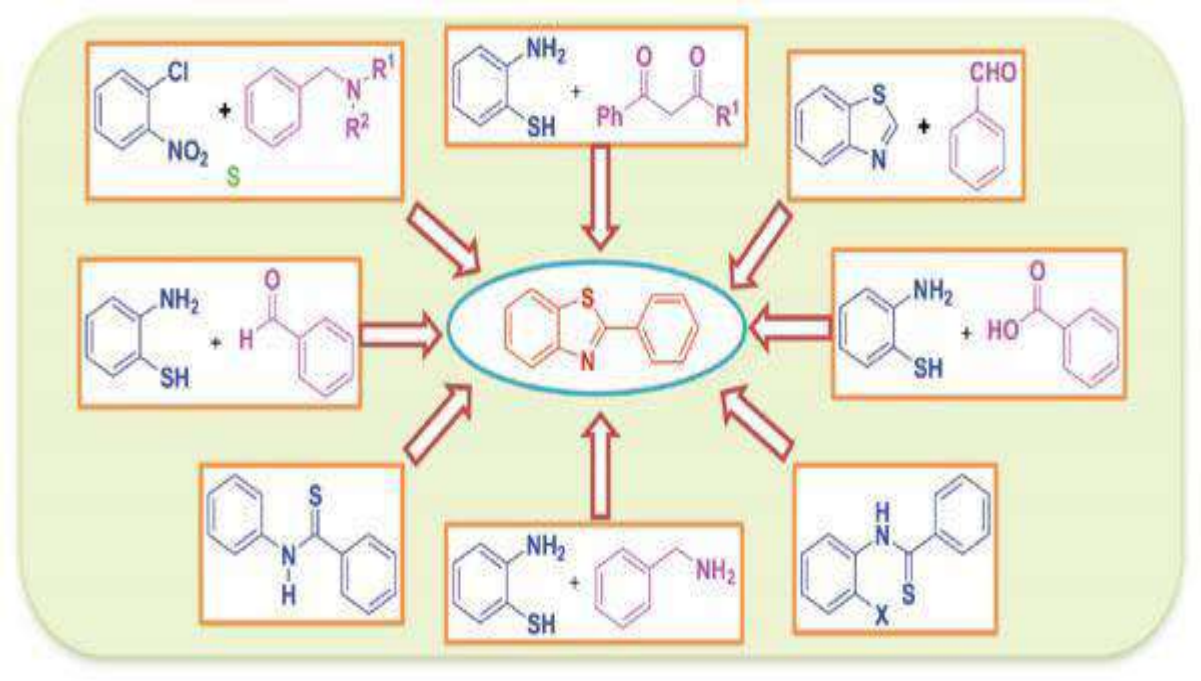
Benzothiazole nucleus is found to possess a large number of therapeutic agents are synthesized with the help of benzothiazole nucleus

number of biological activities such as anticancer, antimicrobial, antidiabetic, anti-inflammatory, antiviral, antileishmanial, and antiviral. Given below is a brief account related to various biological activities of benzothiazole derivatives.[4]

. Banzothiazole make by condensation of 2-aminothiophenol and aldehydes and their derivatives using a mixture of H2O2/HCl as a catalyst in ethanol at room temperature

And the 2_aminothiophenol made by

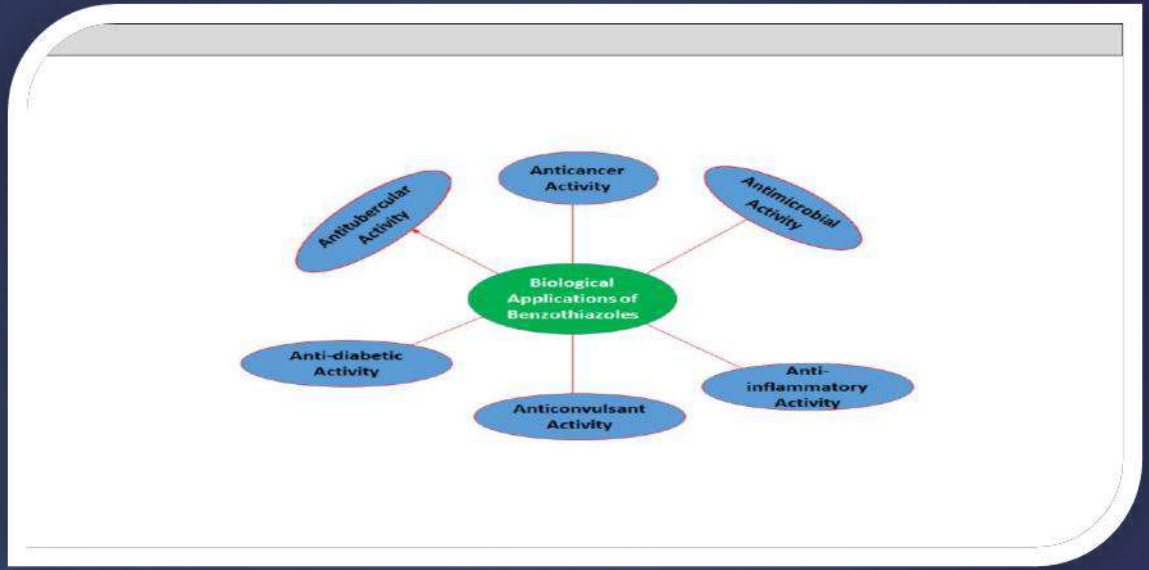
cyclisation of the corresponding arylthioureas in at least 85% strength sulfuric acid in the presence of catalytic quantities of bromine, hydrogen bromide, sodium bromide, potassium bromide or ammonium bromide at temperatures of from 2° to 120°.[5]



Benzothiazole Derivatives

Biological Aspects:

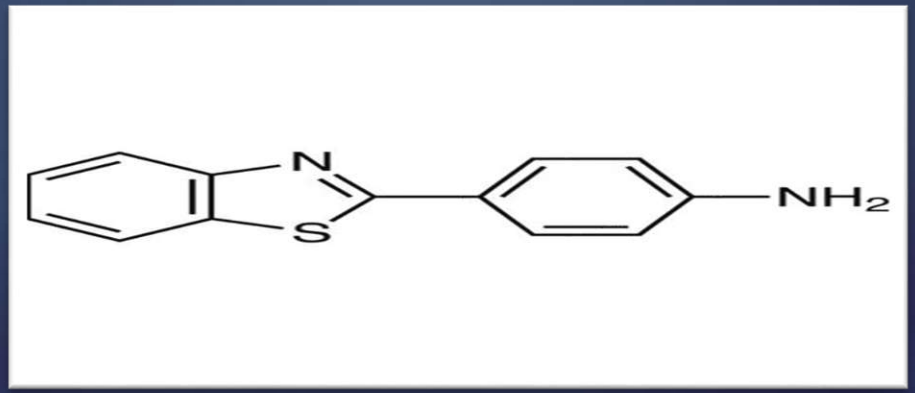
Benzothiazole nucleus is found to possess a number of biological activities such as anticancer, antimicrobial, antidiabetic, anti-inflammatory, antiviral, antileishmanial, and antiviral.



1.Anticancer Activity:

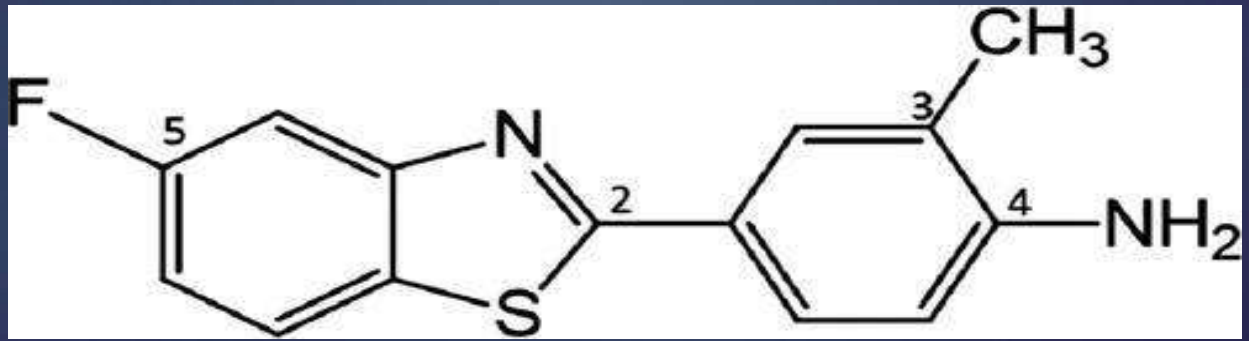
A series of potent and selective antitumor agents mostly from substituted 2-(4-aminophenyl) benzothiazoles were developed and examined, in vitro, their antitumor activity in ovarian, breast, lung, renal and colon carnicoma human cell lines [6]. Pyrimido benzothiazole and benzothiazolo quinoline derivatives [7], imidazo benzothiazoles [8] as well as, polymerized benzothiazoles [9] showed antitumor activity.

2-(4-Aminophenyl) benzothiazoles [10] (1) comprise a novel mechanistic class of antitumor agents. Their unusual activity was first recognized from the distinctive biphasic-dose response relationship shown in in vitro assays against sensitive breast tumor cell lines, e.g., MCF-7 and MDA-468. Potency against these breast lines and others was independent of the estrogen or growth factor receptor status of the cells. Introduction of methyl or halogen substituent into the 3’-position of the 2-phenyl group enhances potency and extends the spectrum of action to certain colon, lung, melanoma, renal and ovarianc cell lines.



6-Amidino-substituted-2-aminobenzothiazoles (2), N-methyl-2-(4-cyanostyryl) benzothiazolium, cyano-substituted-2-styryl benzothiazoles (3) and amidino and bis-amidino-Caleta et al [11, 12]. All new compounds were tested on cytostatic activities against malignant cell lines. The compounds exerted a different inhibitory effect, depended on concentration and type of the cells. The best inhibitory effect was achieved with compounds (3) and (4) with slight differences among them. All of them inhibited the growth of examined tumor cell lines and also normal fibroblasts. Other examined compounds exhibited a moderate inhibitory effect, depending on type of the cells.

Fluorinated analogues of 2-(4-aminophenyl) benzothiazoles have been synthesized which successfully block C-oxidation by Hutchinson et al17. 2-(4-Amino-3-methylphenyl)-5fluorobenzothiazoles (5) is the favored analogue for clinical consideration possessing enhanced efficacy in vitro and superior potencies against human breast and ovarian tumor xenografts implanted in nude mice.[13]



2.The antibacterial activities:

tested on S. aureus as Gram positive bacteria and E- coli as Gram negative bacteria are presented in Table 1 and Table 2. The screening of the synthesised compounds showed that some compounds inhibited the growth of both Gram negative and Gram positive bacteria organisms, only compound (2) showed inactive to the Gram negative organism Escherichia coli. Compound (3b) gave the best minimum inhibition concentration amongst the synthesised compounds, while the standard drug ampicillin showed better activities than the synthesised compounds. The possible mechanism of action of the synthesized compounds (3a and 3b) could be the 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 steps in the formation of dihydrofolic acid[14]. The mechanism of action could be as well via the inhibition of carbonic anhydrase activities. Sulphonamides inhibits carbonic anhydrase and dihydropteroate synthase activities [15]. The mechanism of action of the thiourea (1) and benzothiazole (2) derivative could be through the inhibition of protein tyrosine kinases [15]. 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.

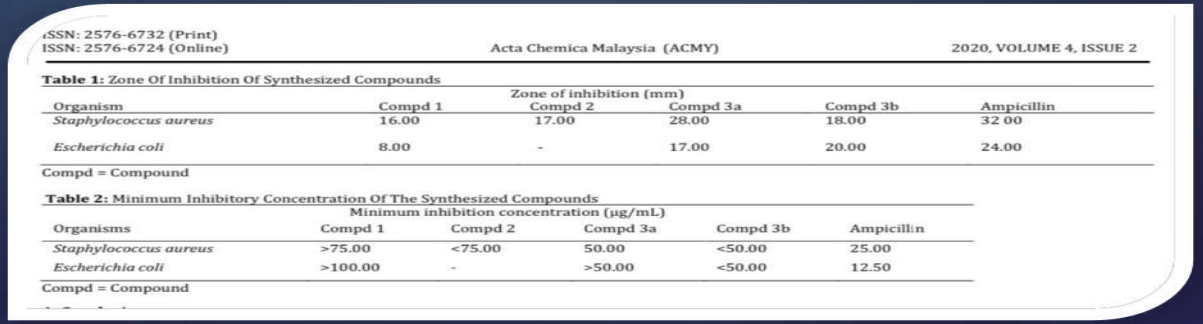


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Table 1: Zone Of Inhibition Of Synthesized Compounds

Organism	Zone of inhibition (mm) Compd 1	Compd 2	Compd 3a	Compd 3b	Ampicillin
Staphylococcus aureus	16.00	17.00	28.00	18.00	32 00
Escherichia coli	8.00	-	17.00	20.00	24.00

Compd = Compound

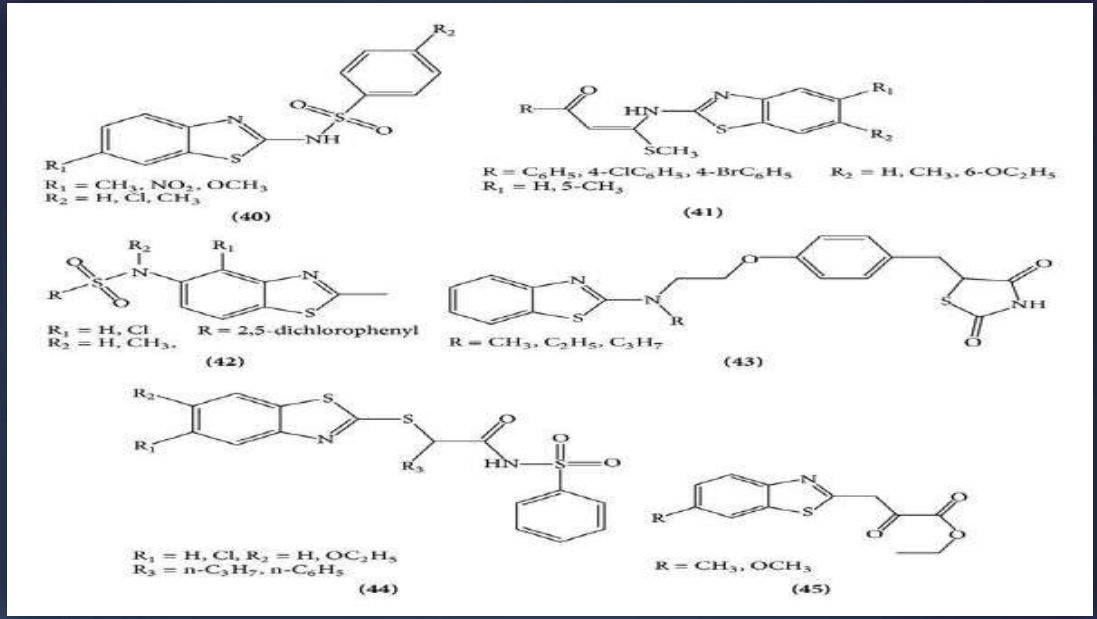
Table 2: Minimum Inhibitory Concentration Of The Synthesized Compounds

Organisms	Minimum inhibition concentration (µg/mL) Compd 1	Compd 2	Compd 3a	Compd 3b	Ampicillin
Staphylococcus aureus	>75.00	<75.00	50.00	<50.00	25.00
Escherichia coli	>100.00	-	>50.00	<50.00	12.50

Compd = Compound

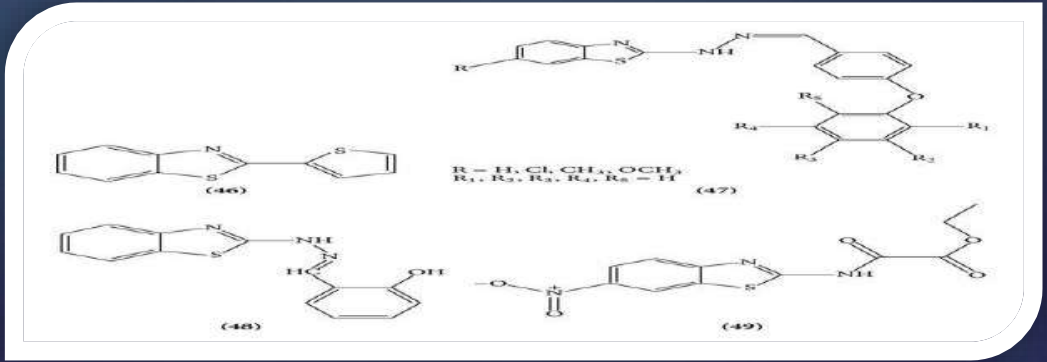
3.Antidiabetic Activity:

Diabetes mellitus is characterized by chronic hyperglycemia and belongs to a group of metabolic disorders with multiple etiologies. Recent estimates from the year 2000 indicate that there are 171 million people in the world with diabetes, and this is projected to increase to 366 million by 2030. There is thus a growing need for effective therapies to achieve optimal glycemic control in the management of diabetes. N-(6-substituted-1,3-benzothiazol-2-yl)benzenesulfonamide derivatives were synthesized and evaluated for their in vivo antidiabetic activity in a noninsulin-dependent diabetes mellitus rat model and also evaluated for 11-HSD1 and PTP-1B enzymes by Moreno-Díaz et al.[16]. A novel series of substituted (E)-3-(Benzo[d]thiazol-2-ylaminophenylprop-2-en-1-ones were synthesized and were evaluated for their antidiabetic activity by Patil et al[16]. Selective inhibitors of 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) have considerable potential as treatments for metabolic diseases, such as diabetes mellitus type 2 or obesity. Su et al. [16] reported the discovery and synthesis of a series of novel benzothiazole derivatives and their inhibitory activities against 11-HSD1 from human hepatic microsomes measured using a radioimmunoassay (RIA) method. Benzothiazole derivatives of thiazolidinones were synthesized by Jeon et al. [17] and assayed for activity on PPAR subtypes and inhibitory activity of NO production in lipopolysaccharide activated macrophages. Most of the compounds were identified as PPARγ agonist, indicating their potential as drug candidate for diabetes. A group of phenylsulfonamides were synthesized by Ammazzalorso et al. [17] and evaluated in vitro against the agonistic effect of GW7647; they showed an inhibitory effect on PPARa activation, with best compounds revealing a dose-dependent antagonistic profile.Navarrete-Vazquez et al. [18] prepared ethyl 2-(6-substituted benzo[d]thiazol-2-ylamino)-2-oxoacetate derivatives using a one-step reaction. The in vitro inhibitory activity of the compounds against protein tyrosine phosphatase-1B (PTP-1B) was evaluated. The compounds were evaluated for their in vivo hypoglycemic activity, showing significant lowering of plasma glucose concentration in acute normoglycemic model and oral glucose tolerance test similar to the effect exerted for hypoglycemic drug glibenclamide .


R1 = CH3, NO2, OCH3
R2 = H, Cl, CH3
(40)
R = C6H5, 4-ClC6H5, 4-BrC6H5
R1 = H, 5-CH3
R2 = H, CH3, 6-OC2H5
(41)
R1 = H, Cl
R2 = H, CH3,
R = 2,5-dichlorophenyl
(42)
R = CH3, C2H5, C3H7
(43)
R1 = H, Cl, R2 = H, OC2H5
R3 = n-C3H7, n-C6H5
(44)
R = CH3, OCH3
(45)

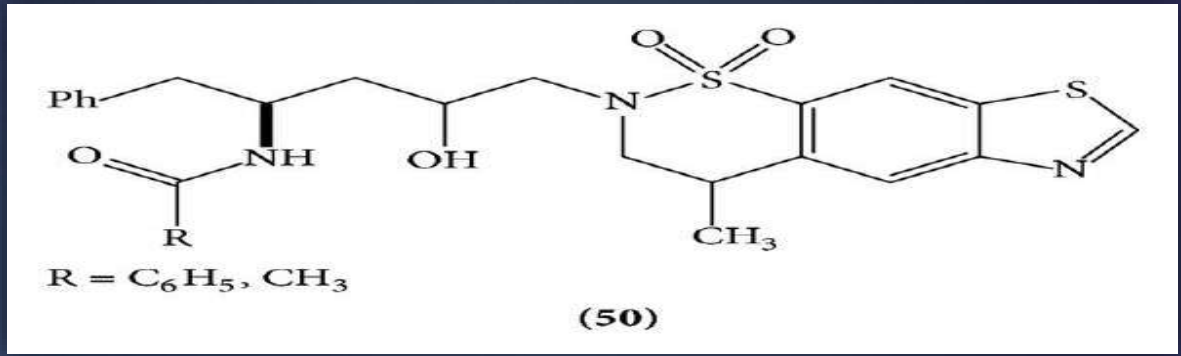
4.Antitubercular Activity:

Synthesis, characterization, DFT simulation, and biological assays of two new metal complexes of 2-(2-thienyl)benzothiazole—BTT are reported by Pereira et al. [19]. Both complexes showed a good activity against Mycobacterium tuberculosis. A series of structurally novel, substituted 2_2_4_aryloxybenzylidene hydrazinyl benzothiazole derivatives incorporating 2-hydrazinobenzothiazole and 4-(aryloxy)benzaldehyde were designed and synthesized using molecular hybridization approach by Telvekar et al. [19]. All the synthesized compounds exhibited promising activity (MIC 1.5–29.00 µg/mL) against Mycobacterium tuberculosis H37Rv strains using REMA. Derivatives of 2-hydrazinobenzothiazole have been synthesized for testing as antituberculous agents by Katz [19]. HisG is an ATP-phosphoribosyl transferase (ATPPRTase) that catalyzes the first step in the biosynthetic pathway for histidine. Among the enzymes in this pathway, only HisG represents a potential drug target for tuberculosis. To discover more potent and diverse inhibitors, virtual screening was performed by Cho et al. [20], and several of the hits contained a nitrobenzothiazole fragment, which was predicted to dock into the monophosphate-binding loop, and this binding mode was confirmed by crystallographic evidence.



5.Antiviral Activity:

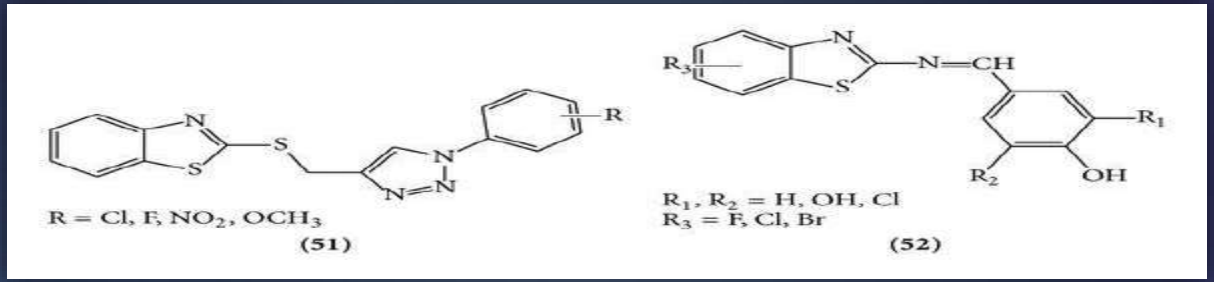
Nagarajan et al. [21] showed that the replacement of t-butylurea moiety by benzothiazole sulfonamide provided protease inhibitors with improved potency and antiviral activity since the inhibitors incorporated a variety of isosteres including the hydroxyethylurea at the protease cleavage site. Some of the compounds had shown good oral bioavailability and half-life in rats. The synthesis of benzothiazole derivatives led them to explore other heterocyclic compounds. During the course of their studies, they also developed an efficient synthesis of benzothiazole-6-sulfonic acid via a two-step procedure starting from sulfanilamide



(50)

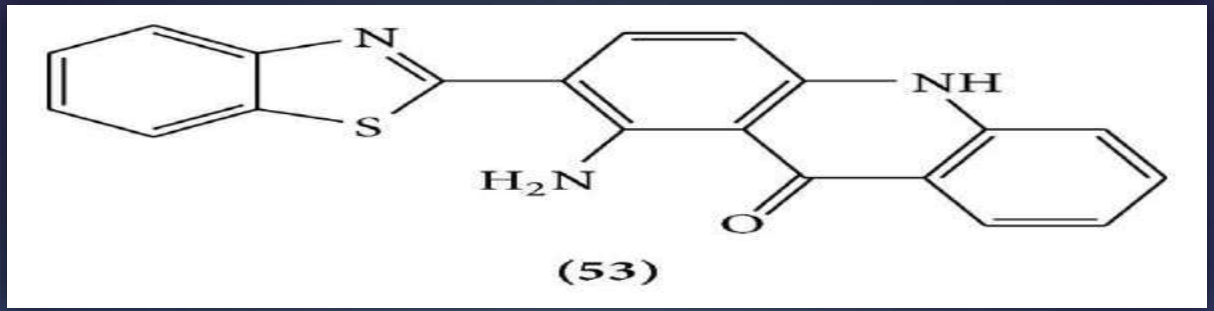
6.Ant-Inflammatory Activity:

A focused library of novel bis-heterocycles encompassing 2-mercaptobenzothiazole were synthesized using click chemistry approach by Shafi et al. [22]. The synthesized compounds have been tested for their anti-inflammatory activity by using biochemical cyclooxygenase (COX) activity assays and carrageenan-induced hind paw edema. Geronikaki et al. [22] synthesized several new thiazolyl/thiazolinyl/benzothiazolyl Schiff bases. The referred compounds were reported to act as lipoxygenase inhibitors affecting inflammation and/or psoriasis



7.Antileishmanial Activity:

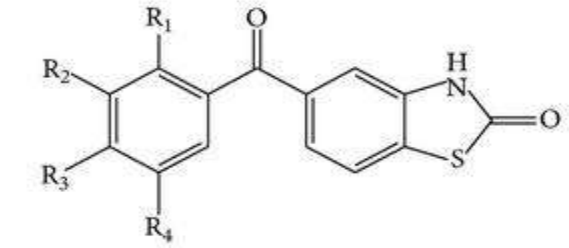
(1,3-Benzothiazol-2-yl)amino-9-(10H)-acridinone derivatives were synthesized by Delmas et al. [23] via a procedure based on the Ullman reaction and were assessed for their in vitro antileishmanial activity.



(53)

8.Antioxidant Activity:

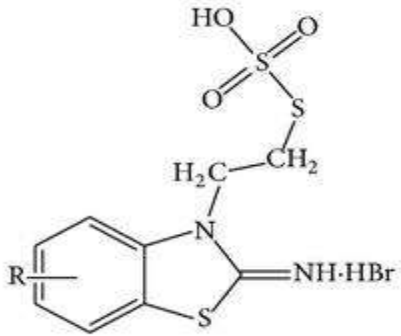
Tzanova et al. [24] described an efficient synthesis of three novel benzophenones containing 1,3-thiazol moiety . Their antioxidant power was evaluated in vitro and in three cell lines (the cancerous MCF7, and the noncancerous hTERT-HME1 mammary cells, and the H9c2 cardiomyoblastic cells). One analogue 5-(2,5-dihydroxybenzoyl)-2(3H)-benzothiazolone displayed an important antioxidant activity and low cytotoxicity and could decrease reactive oxygen species production generated by tert-butyl hydroperoxide (tBHP) in all three cell lines. Cressier et al. [25] reported the synthesis and characterization of new compounds derived from benzothiazoles and thiadiazoles . The radioprotective activity had also been evaluated in mice. Some of these compounds could be good radioprotectors.



$R_1 = R_2 = R_4 = H; R_3 = OH$
$R_1 = R_4 = H; R_2 = R_3 = OH$

$R_1 = R_4 = OH; R_2 = R_3 = H$

(54)

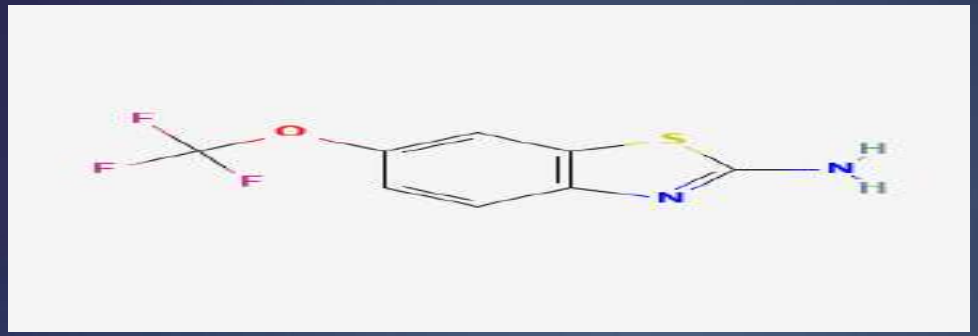


$R = H, CH_3, OCH_3$

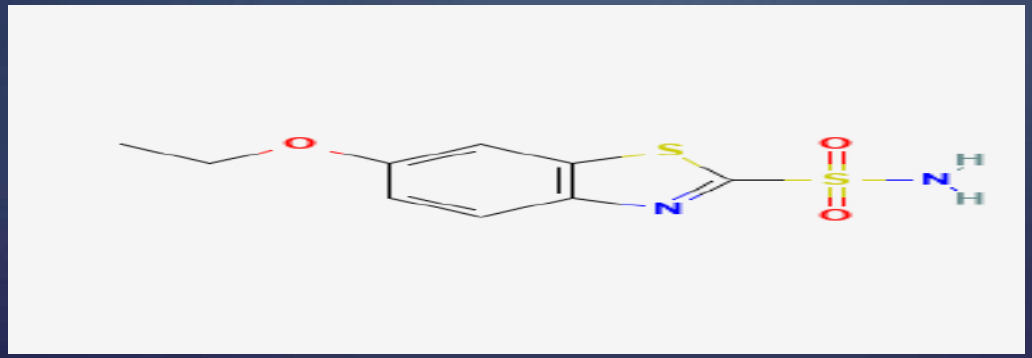
(55)

Drug containing benzothiazole

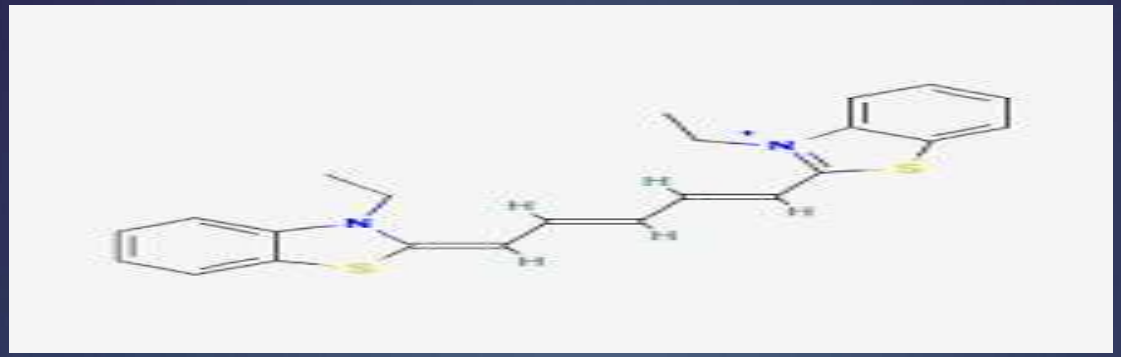
Riluzole : A glutamate antagonist used to treat amyotrophic lateral sclerosis.[27]



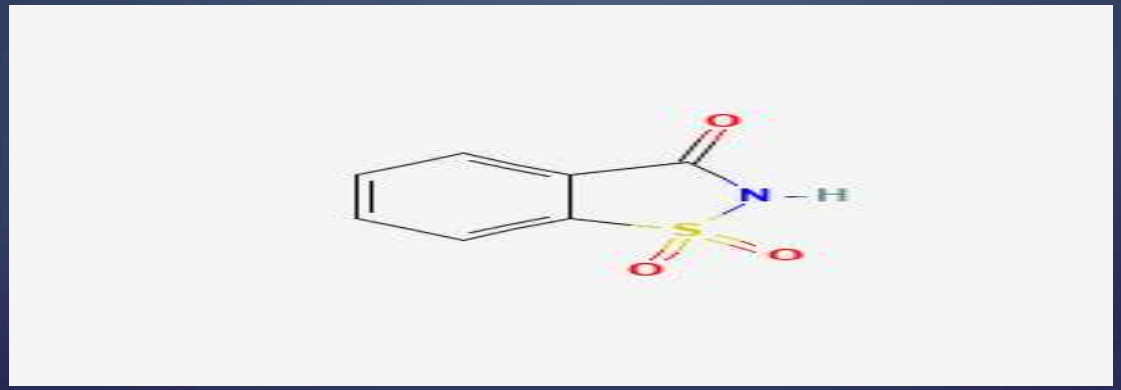
Ethoxzolamide : For use in the treatment of duodenal ulcers, as a diuretic, and in the treatment of glaucoma, and may also be useful in the treatment of seizures associated with epilepsy.[27]



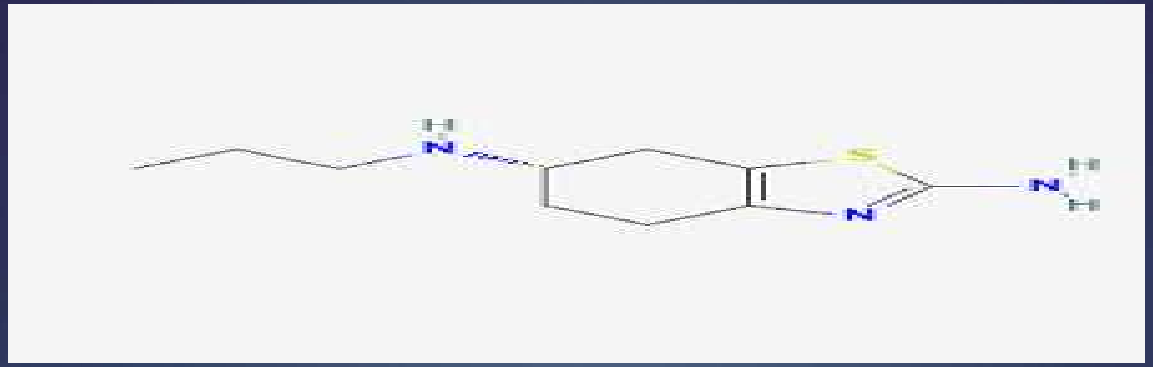
Dithiazanine : Dithiazanine is a highly potent anthelmintic, introduced in 1959 for the treatment of strongyloid worms and whipworms. However, its use is severely limited due to its toxicity.[27]



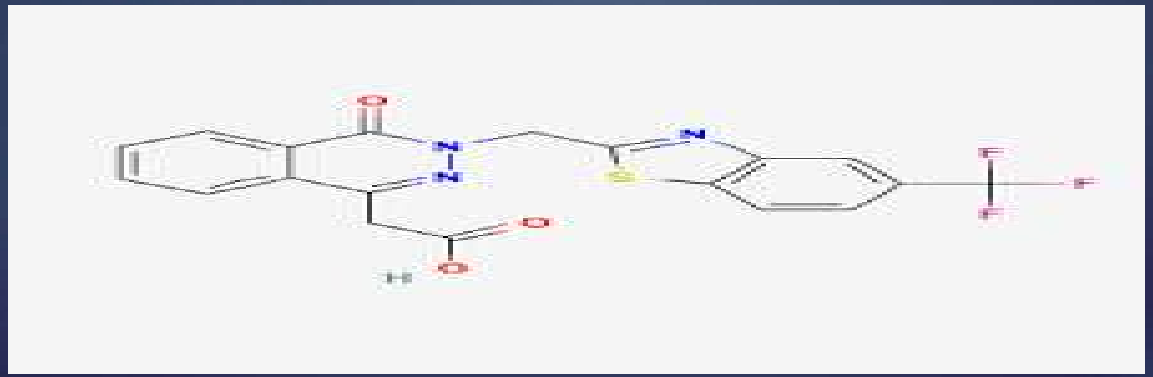
Saccharin : non-nutritive artificial sweetener for sweetening foods and drinks.[27]



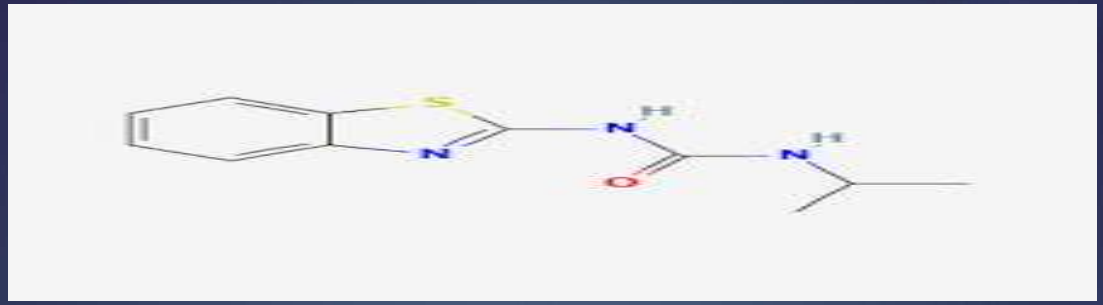
Pramipexole : non-ergot dopamine agonist used to treat the signs and symptoms of idiopathic Parkinson's disease and Restless Legs Syndrome (RLS).[27]



Zopolrestat (CP73850) : a potent, orally active aldose reductase (AR) inhibitor. Zopolrestat is used for the research of diabetic complications.[27]



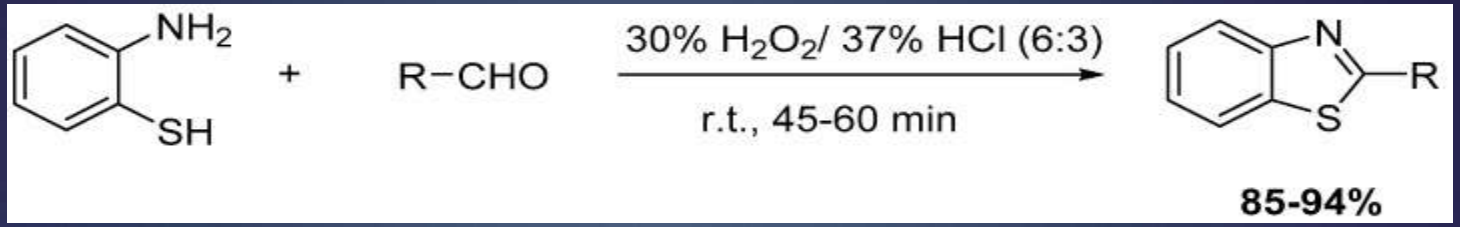
Bentaluron : a fungicide used mainly as a wood preservative.[27]



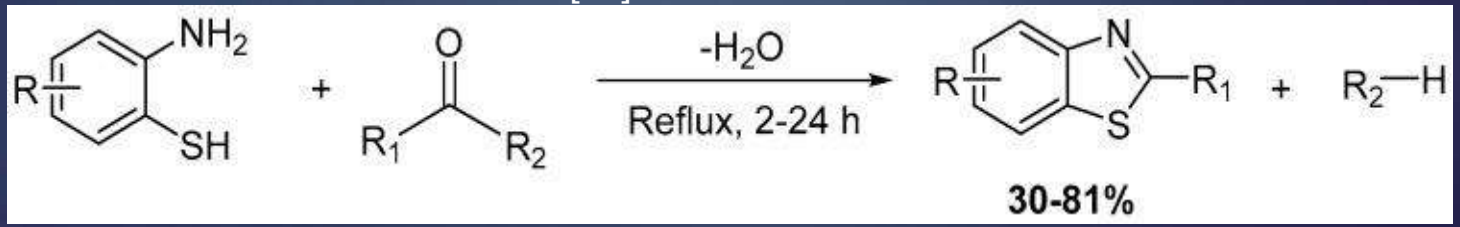
Synthesis of Benzothiazoles

1. By Condensation Reaction

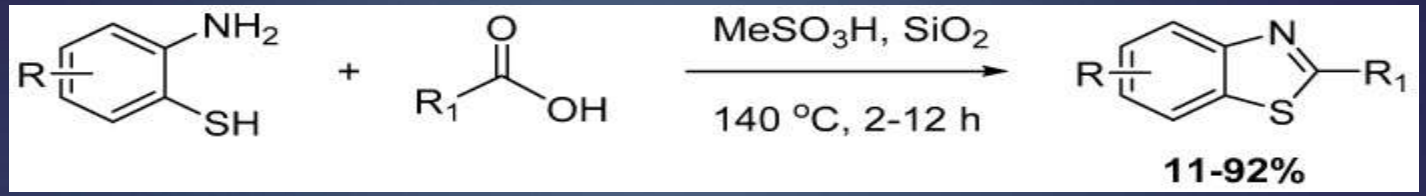
a.Condensation of 2-Aminothiophenol with Aldehydes condensation of 2-aminothiophenol and aldehydes and their derivatives using a mixture of H2O2/HCl as a catalyst in ethanol at room temperature for 1 h. [28]



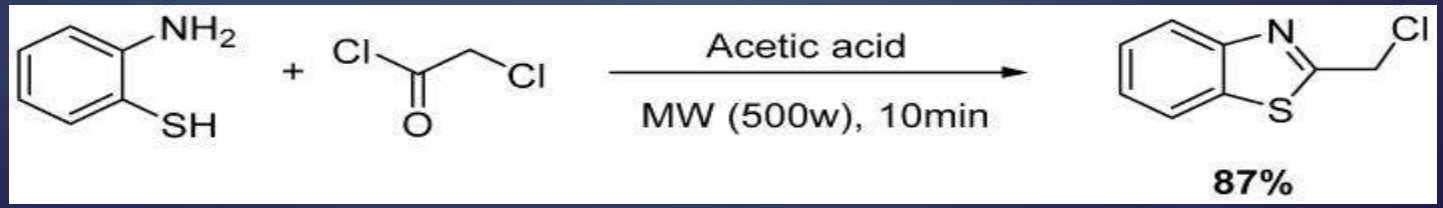
b.Condensation of o-aminobenzenethiol with ketones The condensation of ortho-aminobenzenethiol and its derivatives with representative ketones to yield 2,2-disubstituted benzothiazolines has been investigated by Elderfield and colleagues]. Notably, pyrolysis of benzothiazoline could yield a 2-substituted benzothiazole and eliminate hydrocarbons under reflux conditions.[29]



c.Condensation of 2-aminobenzenethiol with aliphatic or aromatic carboxylic acids have investigated a high-yielding method for the synthesis of a series of 2-substituted benzothiazole compounds by the condensation of 2-aminobenzenethiol with different kinds of aliphatic or aromatic carboxylic acids . The novel heterogeneous mixture of methanesulfonic acid and silica gel was developed to be an expeditious medium for the condensation reaction of aromatic and aliphatic carboxylic acids with 2-aminothiophenol for the synthesis of 2-substituted benzothiazoles. In addition, silica could be reused multiple times without reducing the yield. Simplicity, use of widely available and diverse carboxylic acids, and easy handling of the reaction conditions are among the benefits of this method. [30]



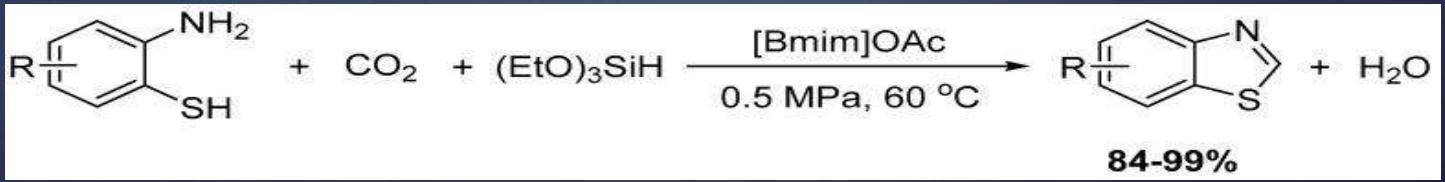
d.Condensation of 2-aminothiophenols with chloroacetyl chloride found that 2-chloromethyl-benzothiazole could be obtained from the condensation of 2-aminothiophenols with chloroacetyl chloride in acetic acid under microwave irradiation for 10 min. Compared with the traditional methods, the microwave-assisted procedures were efficient and environmentally friendly, with less time and high yield.[31]



2. By Cyclization

a. Cyclization of thiobenzamides at room temperature have investigated a general method for the intramolecular cyclization of thiobenzamides to benzothiazoles via aryl radical cations as reactive intermediates under mild conditions. In this method, the usage of phenyliodine(III) bis(trifluoroacetate) (PIFA) in trifluoroethanol or cerium ammonium nitrate (CAN) in aqueous acetonitrile was to promote cyclization within 30 min at room temperature in moderate yields. [32]

b. Cyclization of 2-aminobenzenethiols with CO2 and hydrosilane at 0.5 MPa the cyclization of 2-aminobenzenethiol compounds with CO2 and hydrosilane to produce a series of benzothiazoles was discovered by our group under mild conditions using acetate-based ionic liquid as a catalyst in high yields [33]



Conclusion

The above discussions, it is clearly shown that the structural BTA ring plays an important role in medicinal chemistry and the related research has been being unusually active subjects.[34]
A large amount of work has been made toward BTA-based medicinal chemistry. Numerous outstanding achievements revealed that BTA-based compounds possess extensively potential application as medicinal drugs, and diagnostic agents. In particular, a large number of BTA- based compounds as clinical anticancer, antibacterial, antifungal, antiinflammatory, analgesic, anti-HIV, antioxidant, anticonvulsant, antitubercular, antidiabetic, antileishmanial, antihistaminic agents, and soon have been successfully developed, marketed, and exten- sively used in the clinic in preventing and treating various types of diseases with low toxicity, high bioavailability, and good biocom- patibility and curative effects.[34]
All these have strongly suggested the infinite potentiality of BTA derivatives in medicinal field.[34]

benzothiazoles are molecules that have several uses and functions with a therapeutic ability in a group of diseases such as cancer, diabetes and others, a diuretic drug (Ethoxolamide), an anti- Parkinson's disease drug (Pramipexole), and a treatment for Alzheimer's disease (Thioflavine). , the production of a good drug by conducting a lot of research, and this indicates the existence of successful conditions for the medicinal substance.[34]

Thank you