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Synthesis and various biological activities of benzothiazole derivative: A review

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Abstract [1, 3, 4, 15]
Substituted 1, 3-benzothiazole derivatives are an important class of heterocyclic compounds. It is a combination of two rings six membered and five membered and both the rings are responsible for the therapeutic activity. Benzothiazole is a class of heterocyclic compound having two hetero atoms namely Sulphur and nitrogen. The analogues of benzothiazole and its derivatives have a significant role in research area especially in synthetic, medicinal and pharmaceutical chemistry because of its biological and pharmacological properties. Our study's major goal is to disseminate up-to-date knowledge regarding synthesised Benzothiazole analogues and related biological activity against a variety of disorders. The benzothiazole possesses a wide spectrum of biological activities such as antimicrobial, anticancer, antioxidant, anti-Inflammatory, anticonvulsant, antimalarial and some miscellaneous Activity. Hence, various methodologies have been Accomplished to synthesize benzothiazole compounds considering the purity, yield, and selectivity of the products.

Keywords: Benzothiazole derivative, heterocyclic compounds, biological

Introduction [1, 3, 4, 14, 15]

The field of medicinal chemistry is the one area of exploration that directly affects the health, weal, and development of people. Medicinal chemistry works at the boundary of synthetic organic chemistry and biology with top focus on medicine development. In particular, the study of heterocyclic chemistry is one of the most typical, but inversely important branches of organic chemistry, constituting one of the wide areas of exploration for further than a century. In recent times, there has been a growing interest pertaining to the conflation and natural progression of bioactive composites in the field of organic chemistry Benzothiazole is a heterocyclic compound having a thiazole ring. Thiazole having five membered ring fused with benzene gives the benzothiazole. The thiazoles and benzothiazoles are set up in a wide variety of bioactive moity's and natural products. The terrestrial and marine organism's microorganisms have been a prominent source of these heterocyclic. These naturally being secondary metabolites or polypeptides are frequently bioactive and a large bulk of Literature is being published related to their insulation, chemistry and biology. It's a taintless and slightly thick in nature with a boiling point of 227- 228 °C, the viscosity and molar mass of benzothiazole is1.644 gm/ ml and139.19 g/ spook independently. The numbering is starting from sulphur snippet.

A variety of synthetic pathways have been accomplished for the formation of benzothiazole derivatives

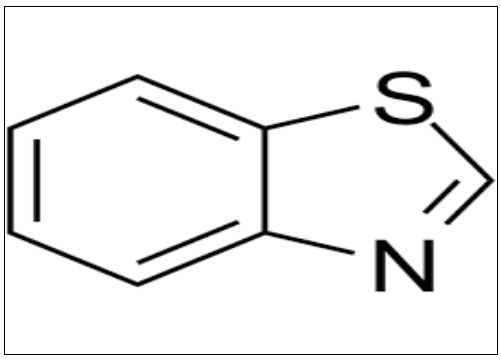
Benzothiazole and its derivations have been of great scientific Exploitation and interest as these are accompanied with nearly all the natural and pharmacological conditioning, like antibacterial, antiviral, antidepressant, analgesic, anticonvulsant, Antiprotozoal, antimalarial, anti-cancer, treat disinclinations, gene Modulating conditioning, anti-schizophrenia, anti- hypertension, Anti-inflammation, anti-HIV infections and numerous further.

From the literature check it easily knows that the Benzoheterocycles are veritably extensively distributed in colourful terrestrial and marine composites and are essential to life in colourful ways.

Structure and properties of benzothiazole: [2, 4, 7]

General properties

1. Molecular formula: C_7H_5NS
2. Molar mass: 135.1863gm/mol
3. Density: 1.24gm/cm^3
4. Melting point: 2^oC
5. Boiling point: 230^0C



Structure and activity relationship: [4, 2, 11]

1. There are several active sites in the structure of benzothiazole. Different derivatives are created when the benzothiazole molecule has different functional groups substituted at various sites. Positions 2, 4, 5, 6, and 7 are active sites for adding different substituents.
2. The activity of benzothiazole in its second position is strengthened by the thiol group, amino group, pyrazoline moiety, and phenyl with a lipophilic group, such as -NH_2, -OH, -CH_3, -Cl. Replacing of -H, -Cl and -F atom on 5^{th} position it increases the potency of the compound. In the sixth position, -OH, -OCH_3, and -CH_3 boost the compound's potency.
3. Introduction of methoxy group (-OCH3) at position 4 of 2-mercaptobenzothiazole increase antibacterial activity

and introduction of chloro group (-Cl) at same position increase antifungal activity.

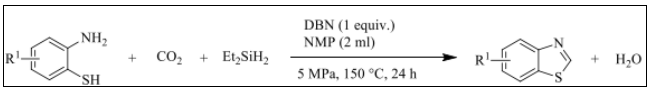
4. Mercapto group and hydrazine group on second position of benzothiazole shows activity for bactericidal and anti-inflammatory activity.
5. Presence of hydrophobic moieties in molecule is conductive for cytotoxic activity of benzothiazole derivatives against cancer cell lines. Benzothiazole containing amino, hydroxyl, and chloro group shows better activity against cancer.
6. In the second position, phenyl and substituted phenyl groups have anticancer, anti-TB, anticonvulsant, and anti-inflammatory properties. Anticonvulsant properties are given by halogen substituents, anti-Alzheimer activity is produced by -OCH3 substituents, and anti-inflammatory properties are provided by phenyl group substitutions.

Synthesis of benzothiazole: [5, 3, 6, 15, 14, 17, 20, 18]

1. Cyclization reaction

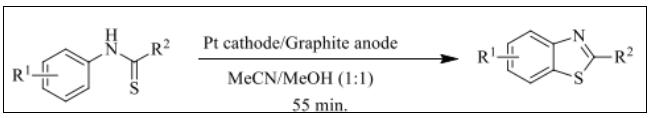
a. Cyclization of co$_2$ as raw material

The DBN catalysed synthesis of benzothiazoles from 2-aminothiophenols and CO2 via cyclization reaction in the presence of diethyl silane. Many benzothiazole derivatives were afforded in excellent yields. This work demonstrates that hydro silane played a crucial role in the preparation of benzothiazoles and successfully avoided the formation of benzothiazolines as by-products. This method gives an eco-friendly path for synthesizing benzothiazoles and their derivative.

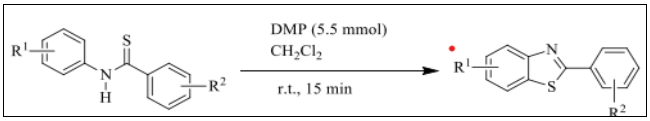


b. Cyclization of various substituted thioamides

In order to create moderate to good yield and high current performances from aryl thioamides, the supporting electrolyte-free electrochemical and catalyst-free synthesis of benzothiazoles utilizes a flow electrochemical reactor. The described methods for producing benzothiazoles in this technique were greatly improved by the straightforward scaling up of the reaction.



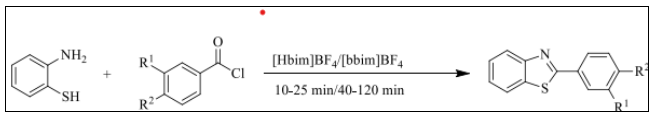
The cyclization method used to create benzothiazoles from sulfamide substrates. DMP was used as the catalyst while dichloromethane served as the reaction solvent during the reaction, which was conducted at room temperature. The method reveals that the novel oxidized benzothiazole chemical is produced in high yields by a thiol radical and that solid-phase synthesis is also capable of synthesizing combinatorial libraries of heterocycles. With this strategy, you may benefit from short reaction times, high activity levels, high yields, and gentle reaction conditions.



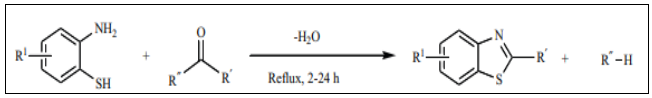
2. Synthesis of benzothiazole by condensation reaction

a. Condensation of 2-amionbenzenthiol with acyl chloride

An appropriate reaction media and promoters, BF_4 and BF_4 ionic liquid to synthesize 2-aryl benzothiazoles via condensation of aromatic acid chloride compounds with 2-aminobenzenethiol under moderate reaction conditions. Many novel ILs were synthesized and tested for these reactions in this research. The ambient reaction conditions, recyclability of non-volatile ILs, and the absence of catalysts make an eco-friendly methodology susceptible for scale-up

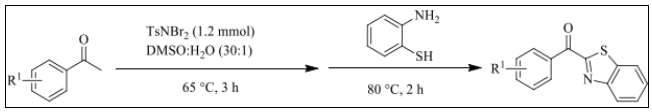


b. Condensation of 2-amionbenzenthiol with aldehyde



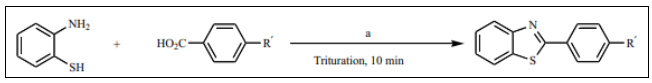
In the presence of acacia concinna as a biocatalyst, the microwave radiation accelerated the synthesis of 2-aryl-benzothiazoles from various types of aryl aldehydes and 2-aminothiophenol. The current technique differs from the conventional method in that it is more ecologically friendly, requires less reaction time, is solvent-free, and produces great yields of the required compounds**.**

c. Condensation of 2-aminobenzenthizole with ketone



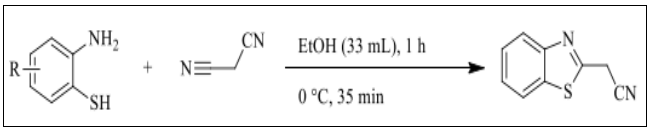
One-pot synthesis of benzothiazoles under metal-free conditions. The reaction proceeded with the treatment of aryl methyl ketones with 2-aminothiophenol. Preliminary mechanistic studies revealed that aromatic ketones initially react with $TsNBr_2$ in DMSO. Moreover, the condensation of 2-aminothiophenol with the crude reaction mixture, followed by Michael addition and oxidative dehydrogenation sequence, gives 2-acylbenzothiazoles.

d. Condensation of 2-amionbenzenthizole with acid

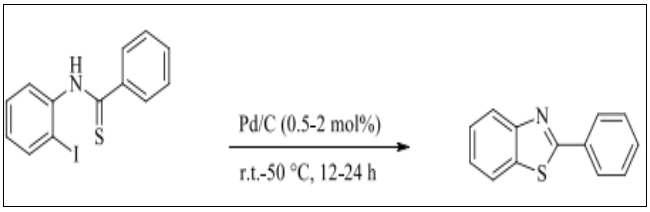


molecular iodine was utilized to achieve a highly economical and good yield of benzothiazole derivatives in a one-pot, solvent-free, and solid-phase condensation of ortho-amino thiophenol with benzoic acid derivatives for 10 minutes. The novel approach significantly reduces cost by 17-fold when compared to polyphosphoric acid and Br catalysed microwave synthesis because no additional chemicals or solvents are required for the reaction. The benefits of using iodine are that it is nonselective, low-priced, requires a shorter reaction time, and can be carried out under solvent free conditions.

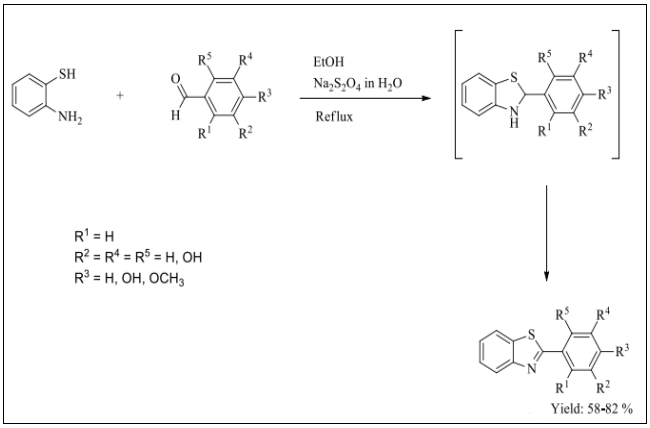
e. Condensation of 2-aminobenzenthizole with nitrile
synthesized 2-cyanomethyl benzothiazole via condensation of ortho-amino thiophenol with malonodinitrile in the presence of glacial acetic acid. In the subsequent step, conc. HCl was added dropwise to a mixture of 2-cyanomethyl benzothiazole in isopropanol and water for the formation of 2-benzothiazolylcyanoxime, which is a strong multidentate ligand for chemical coordination.



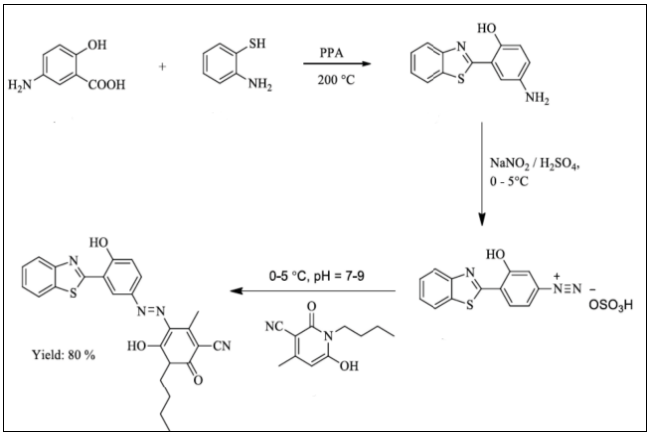
3. Other methods
a. 2-substituted benzothiazoles were produced by cyclizing o-iodothiobenzanilide derivatives at room temperature using Pd/C as the catalyst. The method requires very mild conditions, is high yielding, additive-free, and ligand-free.



b. Sodium hydrosulphite as a catalyst to synthesize 2-arylbenzothiazoles unsubstituted on the benzothiazole ring by condensation of 2-aminothiophenol and benzaldehydes in ethanol. The same procedure, without the catalyst, yielded a mixture of benzothiazolines and benzothiazoles. As a result, Na2S2O4 increased the oxidation of the intermediates.



c. The intermediate is created by cyclizing 5-aminosalisycyclic acid with 2-aminothiophenol to create new azo conjugated benzothiazole dyes. The intermediate was treated with concentrated H2SO4 and sodium nitrite (NaNO2) at 0–5 °C, and then coupled with compound at 0–5 °C while maintaining a pH of 7-9, to produce the diazonium salt solution. High yields of the anticipated new heterocyclic dyes were produced through effective synthesis.



Pharmacological activities of benzothiazole: [3, 8, 9, 10, 12, 13, 16, 18, 19]

1. **Anti-microbial activity:** In recent decades, problems with multi-drug resistant microorganisms have reached an alarming level in many countries around the world. Resistance to a number of antimicrobial agents (b-lactam antibiotics, macrolides, quinolones and vancomycin) among a variety of clinically significant species of bacteria is becoming increasingly important global problem. Despite numerous attempts to develop new structural models in the search for more effective antimicrobials, BTA derivatives still remain as one of the most versatile class of compounds against In order to increase our understanding of molecules, microorganisms are useful substructures. Much research has revealed that BTA derivatives as antimicrobial drugs possess significant potential.

2. **Anti-diabetic activity:** Diabetes mellitus is a group of metabolic ailments distinguished by high blood sugar rising from defects in insulin secretion, insulin action, or both The eyes, kidneys, nerves, heart, and blood arteries are among the many organs whose long-term damage, abnormalities, and failure are linked to the chronic hyperglycaemia of diabetes. Various infective steps are involved in the development of diabetes. This ranges from autoimmune destruction of the β-cells of the pancreas with resulting insulin scarcity to irregularities that result in opposition to insulin action. The basis of the irregularities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action effect from insufficient insulin discharge and/or decreased tissue acknowledgement to insulin at added points in the complex pathways of hormone action. When two abnormalities coexist in the same patient, such as deterioration of insulin discharge or defects in insulin action, it is usually difficult to determine which one, if either, is the underlying cause of hyperglycaemia. When utilized as a parent molecule to create novel compounds that can be used as antidiabetic medicines, benzothiazole is such a flexible moiety. Benzothiazole has many advantageous physical and chemical characteristics that could be helpful in designing new antidiabetic drugs.

3. **Anti-fungal activity:** Benzothiazole-ringed compounds are crucial for biological action. It is thus necessary to develop simple and eco-friendly synthetic methods. In agriculture, benzothiazoles are used for control and prevention of phytopathogenic fungi found in soil, which affect crops.

4. **Anti-oxidant activity:** The ability of an antioxidant to capture free radicals is its primary quality. In biological systems, there are a multitude of sources of highly reactive free radicals and oxygen species. These free radicals can cause degenerative diseases and can oxidize proteins, lipids, nucleic acids, or DNA. Since phenolic acids, polyphenols, and flavonoids scavenge free radicals such peroxide, hydroperoxide, and lipid peroxyl, they prevent the oxidative processes that cause degenerative illnesses. According to several clinical trials, the antioxidants found in fruits, vegetables, tea, and red wine are the primary reasons for these foods' effectiveness in lowering the prevalence of chronic diseases like heart disease and some malignancies. Miller and Rigelhof have extensively researched and reported on the free radical scavenging properties of antioxidants in food. Numerous antioxidants, both natural and synthetic, have been suggested for the treatment of human diseases. Hence, considerable attention has been devoted for the development of techniques for measurement of antioxidant activity. A unique class of medicinal chemicals with a variety of biological functions is the benzothiazole family. The majority of substances that demonstrated both strong fluorescence characteristics and the ability to bind to cellular structures were widely employed as fluorochromes. Numerous pharmacological studies of recently synthesized benzothiazole derivatives have shown intriguing pharmacological activity since the 1990s. After learning about Riluzole pharmacological characteristics, biologists became interested in this series. Riluzole (6-trifluoromethoxy-2-benzothiazolamine) was found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioural experiments.

5. **Anti-cancer activity:** Intensive research on benzothiazole ring system is going on to identify novel lead compounds to fight against different cancers, and few recent trends in this field are briefly explained to understand the anticancer potential of Benzothiazole derivatives by assessing the effects of various substitution. The role of benzothiazole moiety in oncology was assessed during the development and screening of tyrosine kinase inhibitors during the late 20th century. In the year of 1994, Stevens *et al*. synthesized a series of 2-phenylbenzothiazoles derivatives bearing polyhydroxy groups and screened them against various cancer cell lines (MCF-7, Colon cancer and squamous carcinoma cell lines) which overexpress the Epidermal Growth Factor Receptor (EGFR) to assess the activity of compounds against tyrosine kinase receptor. Simultaneously, they computed the estrogen activity of benzothiazole derivatives as they were found as the structural analogues of 2-phenylindoles. The synthesized compounds had shown significant and selective cytotoxicity against breast cancer cell line (MCF-7) and it concluded that the antitumor activity of compounds is not allied with tyrosine kinase receptors.

6. **Anti-Alzheimer activity:** K. Serdons reported a 6-hydroxy-2-(40-aminophenyl)-1,3-benzothiazole performed radiolabelling with carbon-11 and investigated there In-vivo and *In-vitro* properties. Specific binding to amyloid plaques was demonstrated in vitro using post-mortem brain homogenates of AD patients; transgenic AD mice brain sections and post-mortem human AD brain sections. The potential for the three structural analogues as tracer agents for *In-vivo* visualization of amyloid plaques in AD patients is very high. Yuli Xie 84 investigates the relationship between benzothiazole derivatives and the enzymes Ab-binding alcohol dehydrogenase (ABAD) and amyloid beta peptide (Ab), which has recently been linked to the pathophysiology of Alzheimer's disease.

7. **Anti-convulsant activity:** N-(6-methoxybenzothiazol-2-yl)-4-oxo-4-phenylbutanamide a valuable pharmacophore in the investigation of agents controlling seizures and intoxication in epilepsy. This compound, after administration, improved the GABA level substantially and also decreased the development of ACR mediated neurotoxicity. There is also a need for more molecular and clinical research to establish its efficacy and mode of action during epilepsy. And many of benzothiazole derivative shows anti-convulsant activity.

8. **Anti-inflammatory activity:** The ability of several types of 2-[(2-alkoxy-6-pentadecylphenyl) methyl] Thoi]-1 H -benzimidazoles, benzothiazoles, and benzoxazoles to inhibit human enzyme cycloxygenase-2 (COX-2) was investigated. 2-(4'- butyl-3',5'-dimethylpyrazol-1'-yl)-6-substituted benzothiazole and 4-butyl-1-(6'-susbtituted-2'-benzothiazolyl)-3-methylpyrazol-5-ones and were found to display significant anti-inflammatory activity.

9. **Anti-tubercular activity:** For anti-tubercular efficacy, 2(Substituted Aryl Amino)-5, 6- disubstituted/6-substituted (1, 3) benzothiazoles are used.

10. **Local anaesthetic:** alkyl/aryl amino propionyl 2-amino benzothiazole and 2-amino (substituted) benzothiazole and 2-(alkylamino acyl imino) 3-methyl benzothiazolines shows local anaesthetic activity.

11. **Cardiovascular agent:** Synthesis of amino derivatives of 4, 5, 6, 7-tetrahydro benzothiazoles for cardiovascular activity. substituted 2-phenyl benzothiazoles for calcium channel blocking activity.

12. **Enzyme inhibitor:** Sulphonamide benzothiazole derivatives as topical carbonic anhydrase inhibitors. benzothiazole hydroxy urease as inhibitors of 5-lipoxygenase enzyme. The development of Triticum aestivum is controlled by synthetic 3-(2-alkoxy carbonyl-ethyl)-2-benzothiazolinones.

Conclusion

Benzothiazoles are fused membered rings, which contain heterocycles bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. Benzothiazole is an interesting pharmacophore exhibiting diverse pharmacological activities like antimicrobial, anticancer, anthelminthic, antidiabetic, antitubercular, anticonvulsant, antioxidant, anti-inflammatory, antifungal, antipsychotic etc. The present article extensively covers various procedures of synthesis of 2-substituted benzothiazole core and its analogues – by utilizing distinctive catalysts, solvent conditions, reactants immobilized on solid support and microwave irradiation. Variations in synthetic procedures are studied to explore chemo-selectivity of the reactions, in-expensive, eco-friendly, less time-consuming procedure with easy and quick isolation of the products. Ongoing clinical trials of different benzothiazole derivatives, exploring additional pharmacological activities, are also included.

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