A comprehensive review on benzothiazole derivatives for their biological activities

Shubham Abrol, R. B. Bodla* and Chatinaya Goswami

Department of Pharmaceutical Chemistry, Delhi Pharmaceutical Science and Research University, New Delhi - 110017, New Delhi, India.

Keywords: Benzothiazoles, Anticancer, Antimicrobial, Antioxidant

Correspondence to Author:
R. B. Bodla
Assistant Professor, Department of Pharmaceutical Chemistry, Delhi Pharmaceutical Science and Research University, New Delhi - 110017, New Delhi, India.
E-mail: rameshbodla@gmail.com

ABSTRACT: Benzothiazole derivatives have a wide interest because of their diverse biological activities and clinical use. This bicyclic compound consists of a fusion of benzene nucleus with a five-membered ring comprising nitrogen and sulphur atoms. It is a vital Pharmacophore and privileged structure in medicinal chemistry and exhibits various useful therapeutic activities such as anti-tubercular, antimicrobial, antimalarial, anticonvulsant, anthelmintic, anti-inflammatory, anti-tumor, anti-diabetic, analgesic, neurodegenerative disorders, local brain ischemia, and central muscle relaxant activities. Moreover, it can be easily found in a range of marine or terrestrial natural compounds that have tremendous biological activities. Benzothiazoles have a promising biological profile and are easy to access which makes this pharmacophore an interesting molecule for designing new bioactive benzothiazole derivatives.

INTRODUCTION: Heterocyclic compounds containing oxygen, nitrogen and sulphur atoms have been identified to have the most significant biological activities. Benzothiazole is a heterocyclic aromatic compound. The compound is bicyclic which consists of a fusion of benzene with thiazole ring. It is an important pharmacophore as benzothiazole and its novel analogs have been found to have a wide variety of therapeutic activities in medicinal chemistry such as in anticancer, anti-HIV, antioxidant, anticonvulsant, trypanocidal agent, antitumor, antimicrobial, COX inhibitor, hypoglycemic, antidiabetic, antituberculosis, anti-urease and inhibitor of α-glucosidase. Benzothiazole is a six-membered bicyclic heteroaromatic compound in which benzene ring is fused to the 4- and 5-positions of thiazole ring. Benzothiazoles are found in marine as well as terrestrial natural compounds in a very less amount but have considerable pharmacological effects, where they act as aroma constituents of tea leaves and cranberries which are produced by fungi named Aspergillus clavatus and Polyporus frondosus. The fission yeast Schizosaccharomyces pombe is an important organism for the study of cellular biology.

As eukaryotes, these yeasts can be used to study processes that are conserved from yeast to humans but are absent from bacteria, such as organelle biogenesis or to study the mechanism such as transcription, translation and DNA replication, in which the eukaryotic components and processes are significantly different from their bacterial counterparts. The data can be calculated by DFT methods; its importance is given in various recent publications.
Various benzothiazole derivative such as 2-aryl benzothiazole is in the eyes of most scientists due to its diverse structure and its uses as radioactive amyloid imaging agents. It is reported that the isosters and derivatives of benzothiazole have antimicrobial activity against various types of gram positive and gram negative bacteria (e.g., *E. coli*, *Pseudomonas aeruginosa*, *Enterobacter Staphylococcus epidermis*, etc.). The various positions in the benzothiazole ring are indicated accordingly sulphur having 1 position as shown in the figure.

**Appearance:** Pellets large crystal, yellow in colour

**Melting Point:** 2 °C

**Boiling Point:** 227-228 °C at 765 mmHg

**LOGP:** 2.01

**Solubility:** Very soluble in ether, soluble in acetone, alcohol, carbon disulphide and slightly soluble in water.

![1, 3- Benzothiazole](image)

**Molecular Formula:** C₇H₅NS

**Molecular Weight:** 135.184 g/mol

**FIG. 1: TAUTOMERISM / NUMBERING IN BENZOTHIAZOLE**

Some of the marketed drugs having benzothiazole derivatives are shown in **Table 1**.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Marketed Drug</th>
<th>Company</th>
<th>Use</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pramipexole</td>
<td>Zydus Cadila</td>
<td>Parkinsons disease, restless legs syndrome</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Riluzole</td>
<td>Sun Pharmaceuticals</td>
<td>Amyotrophic lateral sclerosis</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ethoxzolamide</td>
<td>Pharmacia, Upjohn</td>
<td>Glaucoma, diuretic, duodenal ulcers</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Frentizole</td>
<td></td>
<td>Antiviral, an immunosuppressive agent</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Thioflavin T</td>
<td></td>
<td>Amyloid imaging agent</td>
<td></td>
</tr>
</tbody>
</table>

**Synthesis and Biological Activities:**

**Several Methods for Synthesis and Pharmacological Properties of Substituted Benzothiazole Reported in the Literature:** Caleta I. *et al.* reported 2-amino-6-cyanobenzothiazole as antiproliferative agent ²⁴.
Trapani G. et al. reported substituted 2-aminobenzothiazole as anticonvulsant agents. \(^{25}\)

Yoshida M. et al. reported the synthesis and biological evaluation of benzothiazole derivatives as potent antitumor agents. \(^{26}\)

Flohr A. et al., reported 2-amino-4-methoxy-7-substituted benzothiazole as adenosine receptor ligands. \(^{27}\)

Das J et al., reported substituted 2-aminobenzothiazoles as protein tyrosine kinase inhibitors. \(^{28}\)

Jung B. Y. et al., reported synthesis and methods for 2-amino-6-methyl-benzothiazole and 2-amino-4-bromo-6-methyl-benzothiazole as antifungal agents. \(^{29}\)

Bhusari K. P. et al., reported substituted 2-(4-aminophenyl sulphonamide) benzothiazoles. \(^{30}\)

Nargund L. V. G. et al., reported 6-Fluoro (N-p-tolyl sulphonamide)-6-fluoro-7-substituted benzothiazoles as antibacterial activity. \(^{31}\)

Dave A. M. et al., reported the synthesis and antibacterial efficacy of halogenated phenothiazine derivatives by using substituted 2-aminobenzothiazoles. \(^{32}\)
Rana A. et al., reported N-[(6-substituted-1,3-benzothiazole-2-yl) amino] carbonothioyl]-2/4-substituted benzamides as anticonvulsant agents 33.

2. Synthesis:

Brewstar R. Q. and Dains F. B. obtained substituted 2-imino-benzothiazoles by direct thiocyanogenation 34.

Elderfield R.C. and Sort F. W. have synthesized substituted benzothiazole 35.

3. Some Other Method of Synthesis:

By Condensation Reactions: Condensation containing 2-aminothiophenol and aldehydes:-

Homogeneous Catalysis: Homogeneous catalysis may be defined as the chemical reaction in which the catalyst and the reactants are in the same phase. The reaction can occur both in the solid and gas phase.

Acid Catalysed Reaction: Guo with his fellow members reported the acid catalyzed homogeneous condensation reaction containing 2-aminothiophenol and substituted aldehyde in the presence of H2O2/HCl in ethanol at room temperature 36.

Base Catalysed Condensation: Maleki et al., using ammonium chloride as a base develops a method for the synthesis of 2-aryl benzothiazole by the condensation of 2-aminothiophenol with aromatic aldehydes. The solvent system used for this synthesis is methanol/water in the ratio 15:1 v/v at room temperature 40.

For comparative studies, various authors have chosen different solvents such as ethanol, acetonitrile, chloroform, dichloromethane, and water.

Mortimer synthesizes a series of novel 2-phenyl benzothiazoles by using 2-aminothiophenol and substituted benzaldehyde in ethanol (EtOH) 37.
But as far as the studies methanol/water is considered as the best solvent system.

Accordingly, ammonium chloride is used as a base because it is cheap and readily available and is also a metal-free reagent.

The major advantage is the use of PIFA which works both as Lewis acid and as an oxidant. Also it has wide substrate scope, short reaction time, microwave conditions and a good yield.

Dandia et al., demonstrated the synthesis of benzothiazoles by the condensation of 2-Phenyl-1H-indole-3-carboxaldehyde and 5-substituted -aminoothiophenols in piperidine or para-toluene sulfonic acid (p-TSA) in ethanol (EtOH) or N, N-dimethylformamide (DMF) under microwave irradiation for 3-6 min at 240W.

Paul et al., finds out an efficient method for the synthesis of 2-aryl benzothiazole by the condensation of 2-aminoothiophenol with B-Chlorocinnamaldehyde under microwave irradiation using para-toluene sulfonic acid (p-TSA). This reaction is meant to be environmentally friendly, fast, simple, general applicability, and accommodating a variety of substitution patterns are the main advantages.

Microwave Induced Condensation: Praveen with his colleagues demonstrated microwave induced condensation by using phenylodionium bis (trifluoroacetate) (PIFA) as an oxidant for cyclocondensation of 2-aminoothiophenol / 2-aminophenol using different aldehydes in ethanol at 80 °C, which then gives high yield oh benzothiazole and benzoazole derivatives.

Heterogeneous Catalysis: Heterogeneous catalysis is defined as the reaction in which the catalyst and the reactants are in the opposite phase. In these type of reactors, the catalysts are mainly in the solid form while the reactants are in liquid or gas.
**Acid Catalysed Condensation:** These type of acid catalyzed reaction are followed in these reactions:-

Nalage et al., finds out an efficient method for the synthesis of 2-aryl benzothiazole by condensation of different types of aldehydes and 2-aminothiophenol. This reaction takes place in the presence of phosphorus pentoxide (P$_2$O$_5$) (act as an acid catalyst) in methanol for 3-5 hrs at room temperature$^{45}$. Chandrachood et al. finds out an alternative method for the synthesis of 2-aryl substituted benzothiazole using cobalt nitrate (Co(NO$_3$)$_2$ 6H$_2$O)/Hydrogen peroxide (H$_2$O$_2$) as a catalyst. From this, they come to know the importance of temperature, change in reagent amount, change in solvent found the best outcome in Dimethyl-formamide (DMF)$^{46}$.

Blacker et al., synthesize 2-(para-tolyl) benzothiazole by transition metal-Ir catalysed hydrogen transfer reaction of 4-methyl benzaldehyde with 2-aminothiophenol$^{48}$. Use of Hydrogen peroxide/Cerium ammonium nitrate (CAN) founds out to be the most novel and very efficient reagent for the synthesis of benzothiazole. This reaction was described by Bahrami$^{49}$ in which condensation of 2-aminothiophenol with variously substituted aryl aldehydes takes place. This process provides a very high yield product.

A one pot reaction by condensing aldehyde with 2-aminothiophenol or 2-aminophenol for the synthesis of 2-substituted benzothiazole and benzoxazole in the presence of diethyl bromo phosphate and tert-butyl hypochlorite (t-BuOCl) in acetonitrile (MeCN). This reaction is given by Patil et al.$^{50}$

Moghaddam et al., finds out the most effective and rapid technique which also includes a high yield of the product by using condensation reaction of 2-aminothiophenol with various aldehydes in the presence of iodine as a catalyst. This reaction is a solvent-free reaction$^{47}$. A second method for the synthesis of benzothiazole derivative was reported by Shokrolahi et al., in which the condensation of 2-aminothiophenol with aldehyde using Sulfonated Porous Carbon (SPC) as a heterogeneous catalyst in water under microwave conditions$^{52}$.

**Solid Support Condensation:** Maleki with his colleagues suggested an efficient method for the synthesis of 2-aryl benzothiazoles through condensation of various aldehydes and 2-aminothiophenol$^{51}$ by using improved catalyst sulphuric acid immobilized on silica gel (H$_2$SO$_4$.SiO$_2$). The H$_2$SO$_4$.SiO$_2$ used her is the inexpensive, heterogeneous and stable catalyst that has a very high reactivity as compare to unsupported H$_2$SO$_4$. The authors examined various catalysts with different solvents found out that 5 mg of H$_2$SO$_4$.SiO$_2$ in ethanol is considerably the best.
Albeik et al., have suggested the synthesis of 2-substituted benzothiazole efficiently in good yield by the reaction between 2-aminothiophenol and various aldehydes by using perchloric acid doped polyaniline (HClO₄/PANI) under refluxing ethanol as a catalyst.

Alloum et al., reported the condensation of various aldehydes with 2-aminothiophenol on silica gel/nitrobenzene or montmorillonite K-10/nitrobenzene under microwave irradiation which gives 2-aryl benzothiazole in good yield with considerable high purity.

Condensation of 2-Aminothiophenols with Nitrile: Mokhier et al., have reported the synthesis of 2-cyanomethyl benzothiazole by the condensation of 2-aminothiophenol and malonodinitrile in the presence of glacial acetic acid as a catalyst.

The synthesis of 4-fluoro-2-hydroxy-N(4,5,7-trifluorobenzothiazol-2-ylmethyl)benzamide using N-cyanomethyl-4-fluoro-2-hydroxy-benzamidine and 2-amino-4,5,7-trifluorothiophenol hydrochloride in refluxing ethanol (EtOH) for 24 h was reported by Zandt with his colleagues.

Sun et al., reported the synthesis of 2-substituted benzothiazole via condensation of 2-aminobenzenethiols with a wide range of nitriles containing different functional groups by using copper acetate as a catalyst.

Condensation of 2-aminothiophenol with Ester: Khalil et al., have suggested that an amino ester and the selected 2-substituted aromatic amines such as 2-aminothiophenol was condensed to form 2-substituted benzothiazole. This reaction takes place in the presence of Poly Phosphoric Acid (PPA) at 160 °C for 3 h followed by neutralization with aq ammonia.

International Journal of Pharmaceutical Sciences and Research
Manforni et al., have reported the synthesis of 5-substituted ethyl-2-(benzothiazol-2-yl) acetate by condensing substituted 2-aminothiophenol and ethyl cyanoacetate at 120 °C 59, which afforded a high yield of products.

Condensation of 2-aminothiophenol with Acid: Sharghi et al., have suggested an efficient, one-pot reaction which produces a high yielding synthesis of 2-substituted benzothiazoles from the 2-

Condensation with Acyl Chloride: Nadaf and coworkers developed a novel technique in which they use 1-butylimidazolium tetra fluoroborate ([Hbim]BF₄) and 1,3-di-nbutylimidazoliumtetra-fluoroborate ([bbim]BF₄) ionic liquids (ILs) as reaction media for the synthesis of 2-aryl benzothiazoles by condensation of 2-

A small change in the above reaction was done by Karlsson et al., in which condensation of 2-aminothiophenol with 4-nitrobenzoyl chloride takes place by applying N-methyl-2-pyrrolidone (NMP) as an oxidant 64. This reaction takes place at 100 °C for 1 h to give 2-(4-nitrophenyl) benzothiazole.
**Condensation with Isothiocyanate:** El-Sharief and coworkers synthesize N,N'-Bis(benzothiazole-2-yl)-benzene-1,4-diamine by the condensation reaction between 1,4-phenylenediisothiocyanate and 2-aminothiophenol using triethanolamine/TEA/DMF (N,N-dimethylformamide) as a reaction media.

![Condensation with Isothiocyanate](image)

**Condensation of 2-aminothiophenol with ketone:** Elderfield and colleagues describe a method in which reaction takes place between 2-aminothiophenol with various ketones to yield 2,2-disubstituted benzothiazolines, which when pyrolysis yield 2-substituted benzothiazoles.

Kreysa and co-workers have synthesized a novel technique which includes the reaction between 2-aminobenzenethiol and benzyl methyl ketone to yield 2-methyl benzothiazole.

![Condensation of 2-aminothiophenol with ketone](image)

**Cyclization Reactions:** Rey and colleagues define cyclization of thioformanilides propelled by chloranil under irradiation in 1,2-Dichloroethane (DCE) and toluene at 80 °C for the synthesis of 2-substituted benzothiazoles. Another method of cyclization given by Downer et al. includes the conversion of thiobenzamides to benzothiazoles through aryl radical cation as a reaction intermediate. This reaction includes phenylidione (III)bis (trifluoroacetate) (PIFA) in trifluoroethanol or cerium ammonium nitrate (CAN) in aqueous acetonitrile which in turn increases the cyclization to complete within 30 min at room temperature.
### Biological Activities:

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Biological activity</th>
<th>Derivatives</th>
<th>Structure</th>
<th>Activity against</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Antimicrobial</td>
<td>Pyrimido benzothiazole&lt;sup&gt;70&lt;/sup&gt;</td>
<td><img src="image1.png" alt="Image" /></td>
<td>E. coli, Enterobacter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiazolidinone&lt;sup&gt;71&lt;/sup&gt;</td>
<td><img src="image2.png" alt="Image" /></td>
<td>P. mirabilis, S. aureus, S. typhi</td>
</tr>
<tr>
<td>2</td>
<td>Anticancer</td>
<td>Aryl substituted benzothiazole&lt;sup&gt;72&lt;/sup&gt;</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Human cervical cancer cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benzothiazole containing pthalamide&lt;sup&gt;73&lt;/sup&gt;</td>
<td><img src="image4.png" alt="Image" /></td>
<td>Human carcinoma cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benzothiazole derivative&lt;sup&gt;74&lt;/sup&gt;</td>
<td><img src="image5.png" alt="Image" /></td>
<td>HL-60 and U-937</td>
</tr>
<tr>
<td>3</td>
<td>Anthelmintic</td>
<td>Fluorobenzothiazole comprising sulphonamide pyrazole derivative&lt;sup&gt;75&lt;/sup&gt;</td>
<td><img src="image6.png" alt="Image" /></td>
<td>Earthworms--</td>
</tr>
<tr>
<td>4</td>
<td>Cyclooxygenase inhibitor</td>
<td>2-[(2-alkoxy-6-pentadecylphenyl)methyl]thio-1-H benzothiazole&lt;sup&gt;76&lt;/sup&gt;</td>
<td><img src="image7.png" alt="Image" /></td>
<td>Cyclooxygenase enzyme-2</td>
</tr>
<tr>
<td>5</td>
<td>Antiinflammatory</td>
<td>Azatidine-2-ones and thiazoline-4-ones encompassing benzothiazole derivative&lt;sup&gt;77&lt;/sup&gt;</td>
<td><img src="image8.png" alt="Image" /></td>
<td>Carrageenan-induced rat hind paw edema method. Diclofenac sodium as standard drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-(6-substituted-1,3-benzothiazole-2-yl)2[(94-substituted phenyl)amino]methyl] quinazoline-4(3H)-ones&lt;sup&gt;78&lt;/sup&gt;</td>
<td><img src="image9.png" alt="Image" /></td>
<td>Inflammatory model in rats. Diclofenac sodium as standard drug</td>
</tr>
<tr>
<td>6</td>
<td>MTP inhibition</td>
<td>Triamide derivative based on benzothiazole template&lt;sup&gt;79&lt;/sup&gt;</td>
<td><img src="image10.png" alt="Image" /></td>
<td>Enterocyte specific microsomal triglyceride transfer protein inhibitor</td>
</tr>
<tr>
<td>7</td>
<td>Amyloid imaging agent in Alzheimers disease</td>
<td>F-labeled 2-(4’-fluorophenyl)-1,3-benzothiazoles&lt;sup&gt;80&lt;/sup&gt;</td>
<td><img src="image11.png" alt="Image" /></td>
<td>Good affinity for amyloid plaque</td>
</tr>
<tr>
<td>8</td>
<td>Anti diabetic activity</td>
<td>N-(6-substituted-1,3-benzothiazol-2-yl)benzene sulphonamide derivative&lt;sup&gt;81&lt;/sup&gt;</td>
<td><img src="image12.png" alt="Image" /></td>
<td>Noninsulin-dependent diabetes mellitus rat model and evaluated for 1-HSD1 and PTP-1B enzymes</td>
</tr>
</tbody>
</table>
(E)-3-(Benzo[d]thiazol-2-ylamino)phenylprop-2-en-1-ones

Novel benzothiazole derivative

Benzothiazole derivatives of thiazolidinones

etyl 2-(6-substituted benzo[d]thiazol-2-ylamino)-2-oxoacetate derivative

9 Antitubercular
2-(2-(4-aryloxybenzylidene)hydrazinyl)benzothiazole derivative

10 Antiviral
Benzothiazole 71

11 Anti-leishmanial
(1,3-Benzothiazol-2-yl)amino-9-((10H)-acridinonederivative

12 Antioxidant
Benzophenones containing 1,3-thiazol/5-(2,5-dihydroxybenzoyl)-2(3H)-benzothiazolone

Benzothiazole in Clinical Trials:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Conditions</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riluzole</td>
<td>Spinocerebellar ataxia type 2</td>
<td>Phase 3&lt;sup&gt;99&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Inflammation Fatigue</td>
<td>Phase 4&lt;sup&gt;90&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Social anxiety disorder</td>
<td>Phase 2 and 3&lt;sup&gt;91&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PTSD</td>
<td>Phase 1&lt;sup&gt;92&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Parkinson disease</td>
<td>Phase 4&lt;sup&gt;93&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder</td>
<td>Phase 4&lt;sup&gt;94&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Extrapyramidal syndrome</td>
<td>Early phase 1&lt;sup&gt;95&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Parkinson disease</td>
<td>Phase 3&lt;sup&gt;96&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dexamipexole</td>
<td>Major depression disorder</td>
<td>Phase 2&lt;sup&gt;97&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
CONCLUSION: The present review article, therefore, highlights the use of benzothiazole derivatives and conclude that they have a marked biological activity. The biological properties of the nucleus include anticancer, anti-inflammatory, anti-diabetic, antiviral, antitubercular, antioxidant.

Hence, this unique molecule must serve as future therapeutic leads to developing various biological agents. It is anticipated that this study would give rise to the design of better molecules which can enhance biological properties and specificity.

ACKNOWLEDGEMENT: The authors are thankful to Dr. Ramesh Bodla, Mr. Ravikant and Ms. Shikha Thakur, Ms. Shruti and Mr. Ritesh for their motivational support and guidance.

CONFLICT OF INTEREST: Declared None

REFERENCES:


23. Ahmad K, Malik MS and Syed MAH: Therapeutic potential of benzothiazoles a patent review 2010-2014.


E-ISSN: 0975-8232; P-ISSN: 2320-5148
How to cite this article: Abrol S, Bodla RB and Goswami C: A comprehensive review on benzothiazole derivatives for their biological activities. Int J Pharm Sci & Res 2019; 10(7): 3196-09. doi: 10.13040/IJPSR.0975-8232.10(7).3196-09.