IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON SYNTHETIC STUDY OF BENZOTHIAZOLE DERIVATIVES

[1]Dinesh P. kawade, [2]Chetna R. Pardhi*, [3]Gitanjali R. Gadpayle, [4]Jitendra N. Bhalavi

[1]Associate professor, [2]student, [3]student, [4]student

[1]Department of pharmaceutical chemistry

Priyadarshini J.L.College of Pharmacy Nagpur, (MS) India

Abstract:

Benzothiazole is a fusion product of benzene and thiazole. An aromatic heterocyclic compound is benzothiazole containing five-membered 1,3-thiazole rings fused with benzene rings. Benzothiazole and its derivative have great significant in medicinal chemistry. 1,3-benzothiazole derivatives have considerable derivative shown in the research method of synthetic chemistry as well as medicinal chemistry because of their potent pharmacological activity. The current paper concise several synthetic methods utilized for synthesizing derivatives that act as Anti-inflammatory, Analgesic, Anti-tumor, Anti-viral, Anti-HIV and Anti-microbiological agents. Some derivatives of benzothiazole are used for the treatment of epilepsy, antidiabetic, anticancer, antiviral, anticonvulsant, and antioxidant. This review provides different reaction methods that are involved in the synthesis of benzothiazole derivative and also helps to understand the structure-activity relationship.

Keywords: Benzothiazole: Antiviral: Anti-HIV: Antitumor: Epilepsy

1.Introduction

Sulphur and nitrogen are both contain in heterocyclic compound of thiazole or 1,3-thiazole. In the moiety of thiazole, the numbering start from the Sulphur atom. The combination of benzene ring fused with 4th and 5th position of thiazole is the basic structure of benzothiazole.[1] Thiazole and benzothiazole play an essential role in the development of tremendous derivatives of benzothiazole which have different pharmacological activities. The derivatives of thiazole or benzothiazole are used in various diseases treatment.[2]

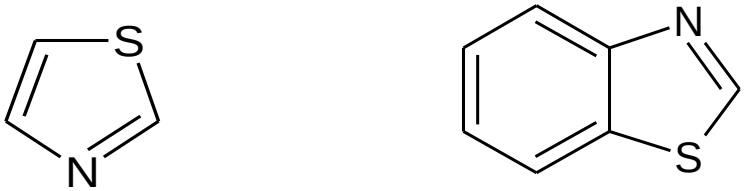
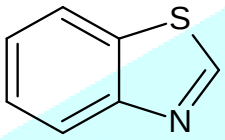


Figure1: Structure of A) Thiazole and B) Benzothiazole

Benzothiazole is a fusion product of benzene and thiazole. An aromatic heterocyclic compound is a benzothiazole containing five-membered 1,3-thiazole ring fused with a benzene ring.[3] Various marine or natural compounds have useful biological activities due to the presence of the benzothiazole ring. Benzothiazole is a colorless in nature, slightly viscous liquid, and its melting and boiling point of 2°C and 227-228°C respectively. Benzothiazole has an odor of sulfurous and meaty flavor. The bicycle has nine atoms and the substituent are attached by coplanar [4]

In the benzothiazole derivatives preparation, the different synthetic path has been developed. Recently the green synthesis or green chemistry advocates for the use of chemical technologies. Uses and production of raw materials, catalysts, solvents, and reagents reduce or stop the green synthesis methods. Human health, community safety, and the ecological environment are harmful by the products or by-products.[5] This review provides different reaction methods that are involved in the benzothiazole derivatives synthesis process and also helps to understand the structure-activity relationship [6]

1.1 Structure of Benzothiazole with their properties:[7]

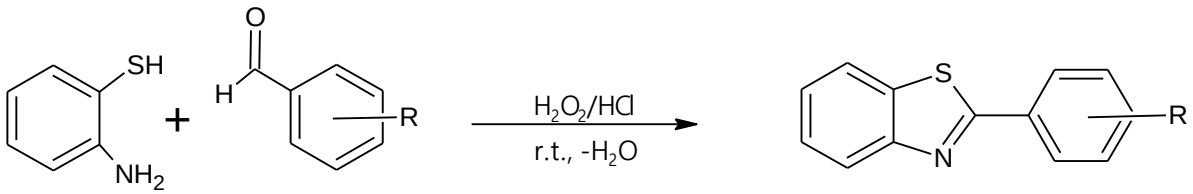


Molecular Formula:	C_7H_5NS
Formula Weight:	135.1863
Composition:	C(62.19%) H(3.73%) N(10.36%) S(23.72%)
Molar Refractivity:	40.57 ± 0.3 cm^3
Molar Volume:	106.2 ± 3.0 cm^3
Parachor:	288.4 ± 4.0 cm^3
Index of Refraction:	1.689 ± 0.02
Surface Tension:	54.2 ± 3.0 dyne/cm
Density:	1.272 ± 0.06 g/cm^3
Dielectric Constant:	Not available
Polarizability:	16.08 ± 0.5 $10^{-24}cm^3$

2. Synthesis of Benzothiazole

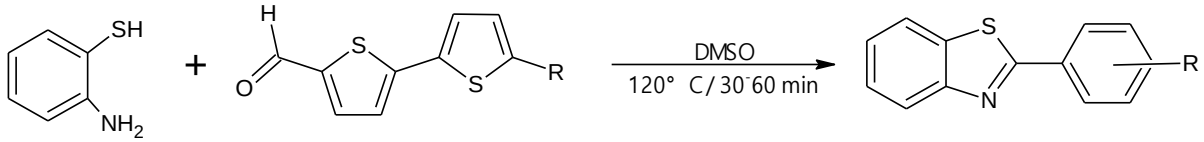
2.1 scheme 1

In synthesis of 2-phenylbenzothiazoles through condensation of 2-amino thiophenol with an aromatic aldehyde in presence of the H_2O_2/HCL system in ethanol. The synthesis proceeds under room temperature. Several solvents including acetonitrile, dichloromethane, 1,4-dioxane, and ethanol were investigated during this study. The best result was achieved using ethanol. Aldehyde bearing electron-donating and electron-withdrawing both substituents gave desired excellent yields of benzothiazole.[8]



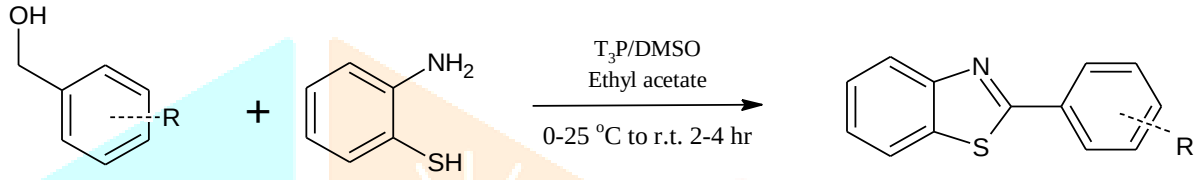
2.2 Scheme 2:

The condensation of 2-aminobenzothiazole with 5-aldehyde bisthiophene compounds in presence of dimethyl sulfoxide (DMSO) under reflux condition for 1hr to obtain 2-bisthiophene substituted benzothiazole products.[9]



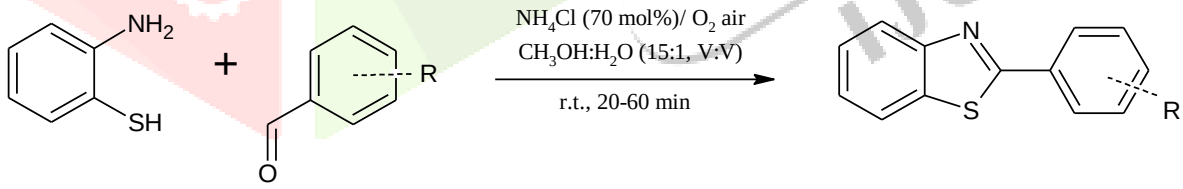
2.3 Scheme 3:

The oxidation of alcohols to aldehydes followed by cyclization with o-aminothiophenol and finally propylphosphonic anhydride (T3P) mediated dehydrogenation under mild reaction conditions (0–25°C). Closer look to the scope of reaction depicts that the reaction of o-aminothiophenol with variety of aromatic, aliphatic and heterocyclic substituents react well under these optimized reaction conditions and provides access to high yield of the product.[10]



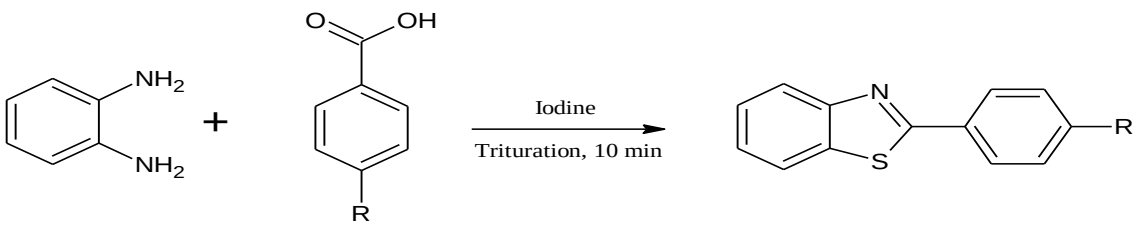
2.4 Scheme 4:

The reaction of 2-aminothiophenol with benzaldehyde. Especially, benzothiazole could be obtained at a high yield by this reacting in a methanol-water mixed solvent at room temperature for 1 hr. furthermore the study of the mechanism showed that NH_4CL activated benzaldehyde through hydrogen bonding and promoted the nucleophilic attack of benzaldehyde by the amino group of 2-aminobenzenethiol to obtain the target product.[11]



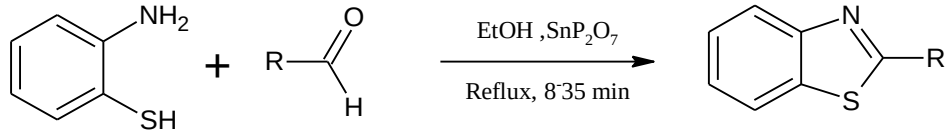
2.5 Scheme 5:

The molecular iodine was utilized in a one-pot, solid-phase, solvent-free reaction between 2-aminothiophenol and benzoic acid derivatives to obtain solid-phase, solvent-free reaction between 2-aminothiophenol and benzoic acid derivatives to obtain an excellent yield of benzothiazole derivatives for 10 min. Compared with polyphosphoric acid and-Br catalyzed microwave synthesis, the new method has a significantly reduced cost due to the fact that no additional chemicals and solvents are essential.[12]



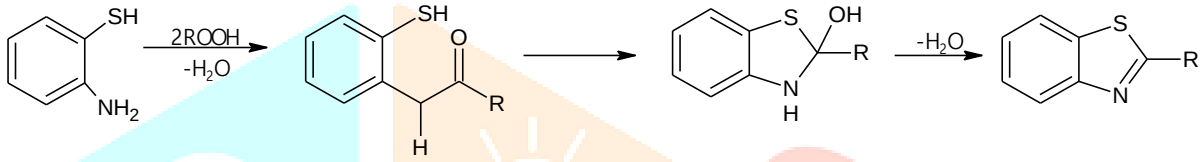
2.6 Scheme 6:

Green method for the benzothiazoles synthesis by a condensation reaction of 2-aminothiophenol with various aromatic aldehydes using SnP_2O_7 as a new heterogeneous catalyst. In this work, these high yields (87-95%) and vary short reaction times (8-35 min) were obtained; meanwhile the new catalyst collude be reused at least five times and without any degradation of its activity.[13]



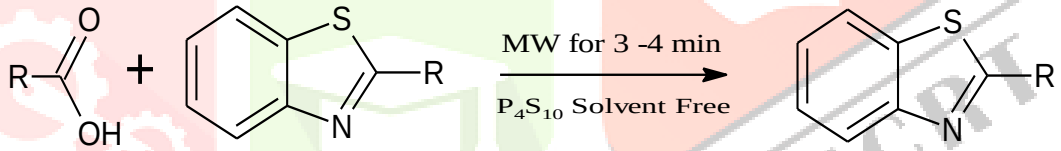
2.7 Scheme 7:

Benzothiazole is synthesized by cyclo condensation of O-Amidethiophenol with ATP 1 and carboxylic acid 2. The reaction involved heating and catalytic dehydration of the S-H group by an o-aryl-S cross-coupling protocol to the hydroxybenzothiazolidine ring to produce the benzothiazole derivatives.[14]



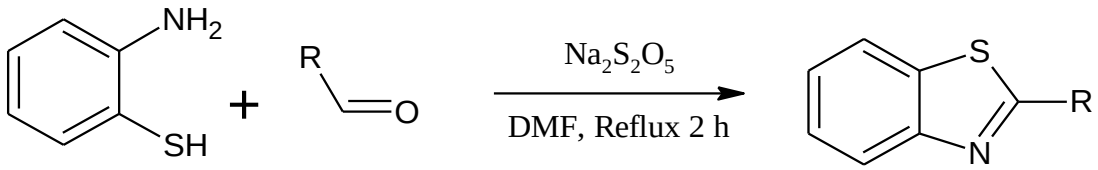
2.8 Scheme 8:

2-substituted benzothiazoles was synthesized by condensation of 2-aminothiophenol with various saturated olefinic fatty acids under microwave in solvent free condition with the use of catalyst P_4S_{10}. This reaction gives high yield and takes almost 3-4 min for competition of the reaction.[15]



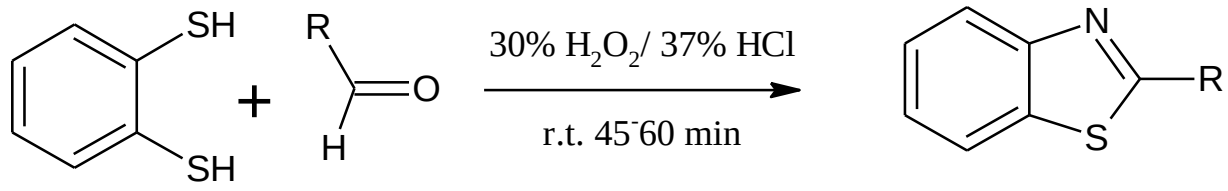
2.9 Scheme 9:

An efficient synthesis of 2-substituted benzothiazoles has been reported in high yield by condensation of 2-aminothiophenol and substituted aromatic aldehydes in N, N-dimethylformamide (DMF) and sodium metabisulfite ($Na_2S_2O_5$) under reflux condition of 2 hrs. [16]



2.10 Scheme 10:

The condensation of 2-aminothiophenol and aldehydes and their derivatives using a mixture of H_2O_2/HCl as a catalyst in ethanol at room temperature for 1 h. For a comparative study, a ratio of 1:1:6:3 of 2-aminothiophenol/aromatic aldehyde/H_2O_2/HCl was found to be optimum for the coupling. Furthermore, both aldehydes bearing electron-donating substituents and electron-withdrawing substituents could be used to obtain the desired benzothiazoles substituents and electron-withdrawing substituents could be used to obtain the desired excellent yields are the main advantages of this procedure.[17]



3. Pharmacological study

3.1 Antimicrobial activity:

The 2-arylbenzothiazole derivatives were tested against the gram-negative bacteria Escherichia coil and Moraxella catarrhalis and gram-positive bacteria staphylococcus aureus and Enterococcus faecalis. The results indicates that the presence of hydroxy or methoxy substituent at the C-2 position of the phenyl group was shown to not influence the antibacterial activity of the 2-phenyl substituted benzothiazole derivatives. The compound 1-5 gives good activity against Moraxella catarrhalis but is lower than Azithromycin. (MIC 0.06µg/ml).

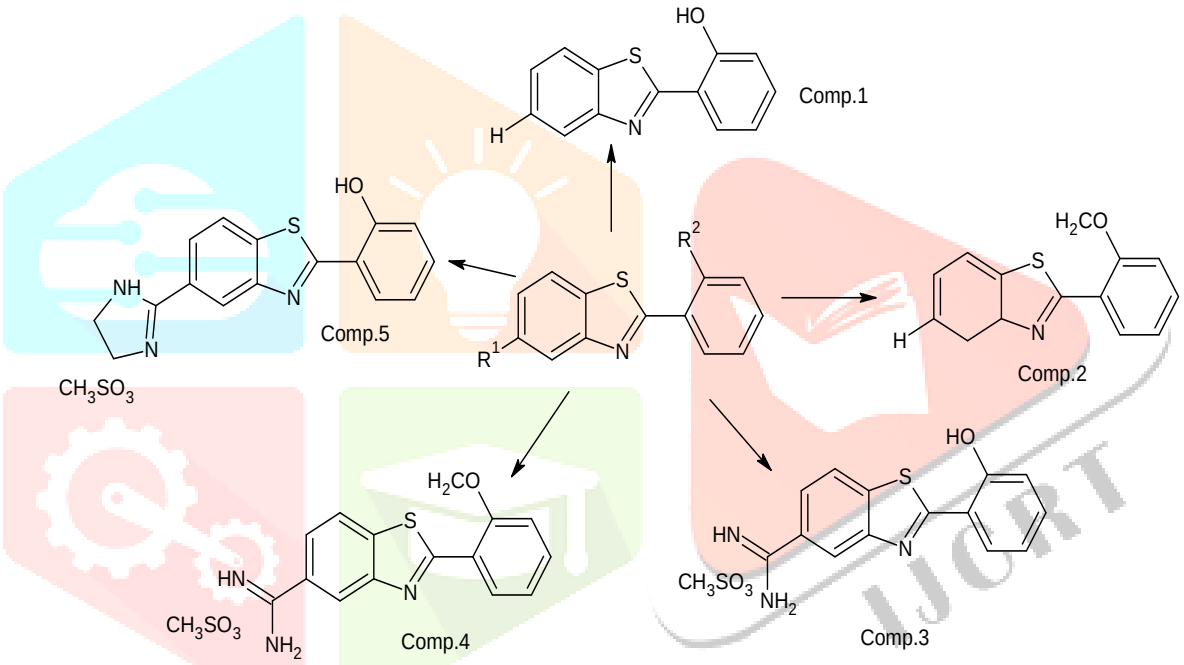


Figure 2. Derivatives of Antimicrobial activity.

3.2 Anticancer activity:

2-([1,3]-benzothiazole-2-yl)-acetonitrile derivatives were found to be most effective against human breast MCF-7 cancer cell line measured with SRB assay against cisplatin.

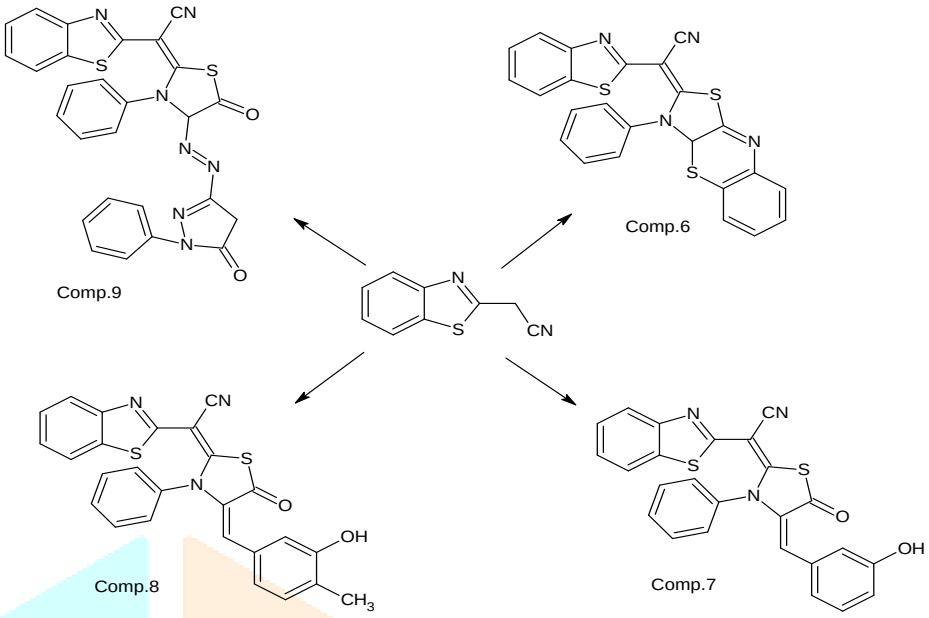


Figure 3. Derivatives of Anticancer activity.

3.3 Anti-oxidant activity:

The benzothiazole hydrazide compound show better activities compared with the benzothiazole carbohydrazide derivatives. The in-vitro antioxidant assay of pyrazole-conjugated benzothiazole derivatives gives almost similar activities. The compound has -OH group on N-phenyl group conjugated with pyrazole and marked superior activity in the series.

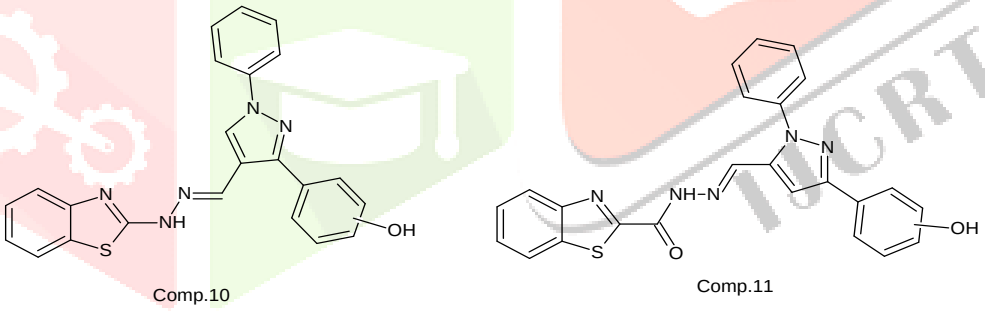


Figure 4. Derivatives of Anti-oxidant activity.

3.4 Anti-tubercular activity:

The highly infectious disease. Tuberculosis (TB) is commonly caused by mycobacterium tuberculosis. The synthesized compound was active against M. tuberculosis at 100µg/ml. The synthesized compound p-CH3 and p-cl (in hydrazine derivative) showed excellent activity. The structure-activity relationship study reveals that the compounds with electron-donating groups exhibit superior activity in both the series. The compound with hydrazine linked shows superior activity than the carbohydrazide linked benzothiazole with pyrazole derivatives.

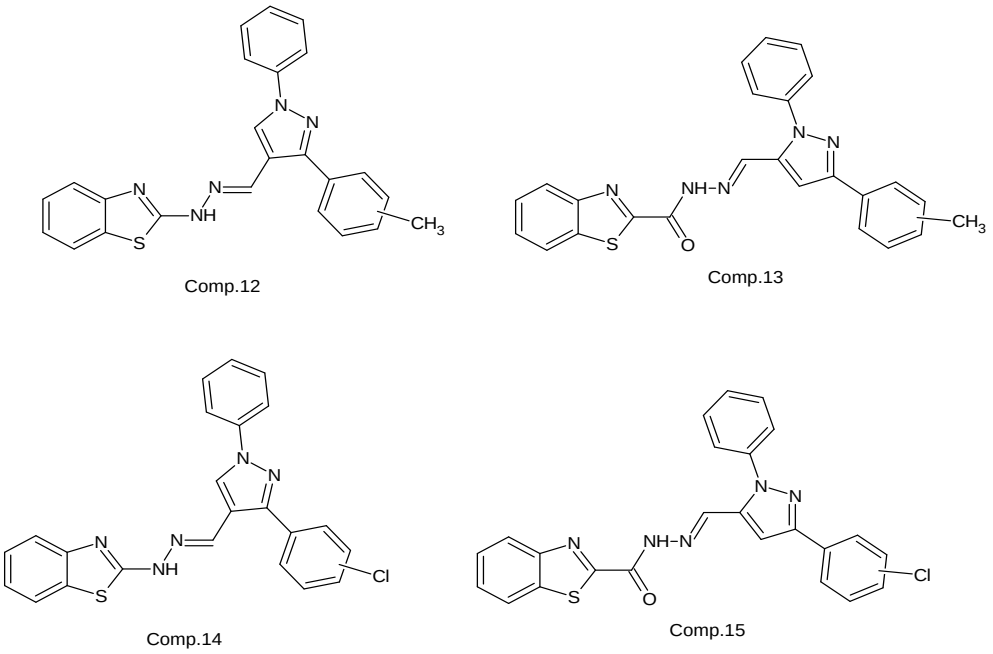


Figure 5. Derivatives of Anti-tubercular activity.

3.5 Anticonvulsant activity:

The evaluation of anticonvulsant activity and neurotoxicity of synthesized compounds were using the MES and rotarod test. The compound 2,4-triazole-3-thiol gives the best anticonvulsant activity. The compound 5i and 5j show the most potent activity with ED50 value.

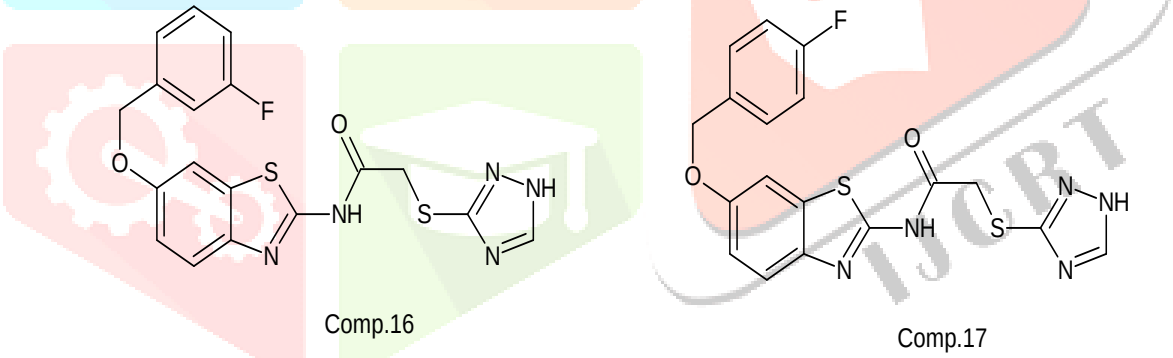
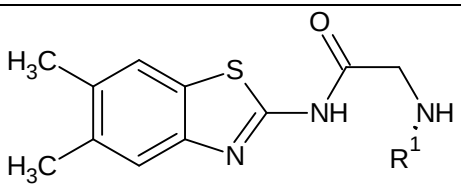
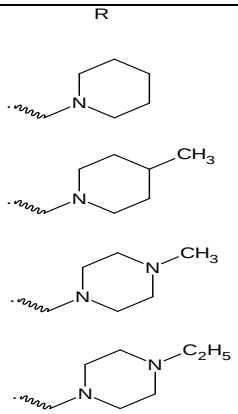
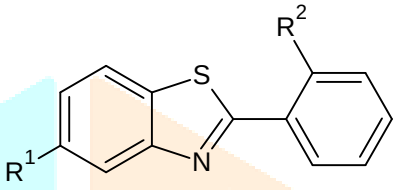
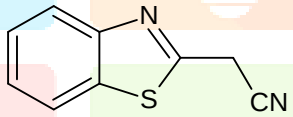
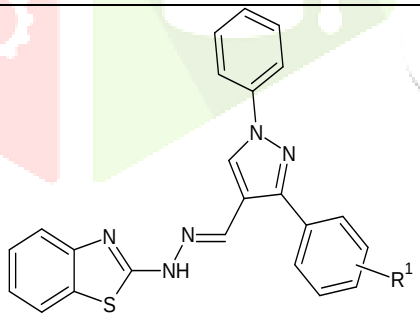
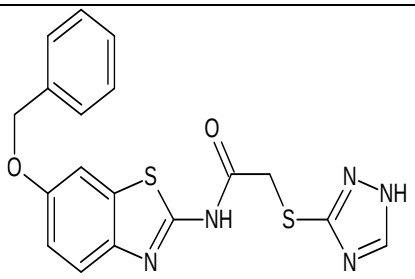
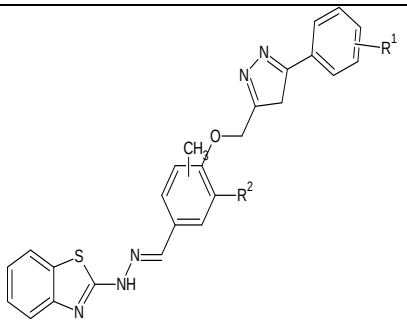
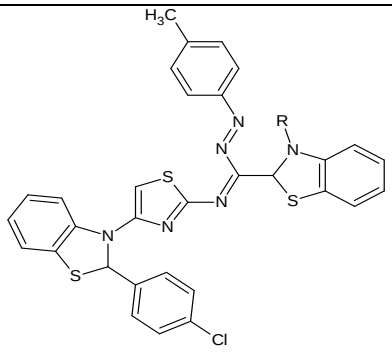


Figure 6. Derivatives of Anticonvulsant activity.

Table 1. Pharmacological activities and derivatives of Benzothiazole.

Sr. No.	Authors	Compound	Derivatives	Activities
1	Umide Demir Ozkay, Ceren Kaya, Ulviye Acar Cevik; 2017.			Antidepressant activity. [18]
2	Livio Racane, Lucija Pticek, Marko Klobucar;2020		R^1 R^2 H_2 - OH NO_2 OCH_3	Antimicrobial activity, Antioxidative activity, Antitumor agent. [19]
3	Lamia W. Mohamed, Azza T. Taher, Mamdouh M. Ali;2016			Anticancer activity.[20]
4	Mahesh Bhat & Shiddappa Lagamappa Belagali;2017		R^1 CH_4 -Cl	Anti-tubercular activity, Anti-oxidant activity, Anti-microbial [21]
5	Da-Chuan Liu, Hong-Jian Zhang, Chun-Mei Jin; 2016		Fluro group at para and meta position of benzene ring.	Anti-convulsant activity [22]

6	Xian-Jing Zheng, Chun-Shi Li, Ming-Yue Cui, 2020		R^1 R^2 2-Cl H_2 2,4-di-Cl H_2 2-Br H_2	Anti-inflammatory activity and Anti-oxidant activity.[6]
7	Gajendra Kumar and N. P. Singh		R -Cl $-OCH_3$	Anti-inflammatory activity and Analgesic activity.[23]

4. Conclusion:

In this review, the plethora of research subscribed benzothiazole derivatives to indicates a wide spectrum of pharmacological activities exhibited. The new generation of benzothiazole biological profile would represent the further development of medicinal agents. Benzothiazole derivatives are focused on screening pharmacological activities such as Anti- bacterial, Anti-viral, anticancer, anticonvulsant, antitubercular, antimicrobial, antioxidant etc.

Benzothiazole derivatives identify molecules to deliver other pharmacologically active heterocyclic active heterocyclic nuclei and show potent biological activity. The investigated report in this review positively suggests the possibility to develop a lead compound to come out new chemical entities (NCEs) of benzothiazole having potential biological activity. On the one hand, an increasing effort is the structural modification by the introduction of the benzothiazole ring into available drugs and focused more on new structural benzothiazole containing compounds with novel mechanism of action. The electron-rich benzothiazole ring with a large conjugated system is an attractive molecular skeleton, which is not only easily modified by various type of functional groups but also employed to combine with other bioactive fragment to afford more active compounds with remarkable physicochemical properties.

Compliance with ethical standards Acknowledgments

I am thankful to the people, who contributed generously their time to prepare this review paper. We would also like to thank and express our gratitude to HOD and the teaching staff of Priyadarshini J. L. College of Pharmacy, Nagpur.

Disclosure of conflict of interest

The authors declare that there are no conflicts of interest.

5. References:

[1] Subhash Banerjee, Soumen Payra and Arijit Saha, 2017, A Review on the synthesis of Benzothiazole Derivatives, Current Organocatalysis, 164-181.

[2] Ashish Srivastava, Abhinav Prasoon Mishra, Suresh Chandra, 2019, Benzothiazole Derivatives: A review of its pharmacological importance in the synthesis of lead, IJPSR, 10, 1553-1566.

[3] Akhilesh Gupta and Swati Rawat, 2010, Synthesis and Cyclization of Benzothiazole : Review, JCPR, 3(1), 13-23.

[4] A. Srivastava, A. P. Mishra, S. Chandra, and A. Bajpai, 2019, Benzothiazole derivatives: A review on its pharmacological importance towards the synthesis of lead, IJPSR, 1553-1566.

[5] Akif Hakan Kurt Lokman Ayaz, Furkan Ayaz, 2022. A review on the design, synthesis, Structure-activity relationship of benzothiazole derivatives against hypoxic tumors**.**

[6] Xiang Gao, Jiao Liu, Xin Zuo, 2020 Recent Advances in the synthesis of benzothiazole Compounds related to green chemistry. Molecules 25, 1657.

[7] Rosa M. F. Batista, Susana P.G. Costa, 2004, Synthesis of new fluorescent 2-(2',2''-Bithienyl)-1,3-benzothiazoles, Elsevier, 45, 2825-2828.

[8] Hong Yun Guo, Ji Chao Li, and You Le Shang, 2009, A Simple and efficient synthesis of 2-substituted benzothiazoles catalyzed by H_2O_2/HCl, Elsevier,1408-1410.

[9] Rosa M. F. Batista, Susana P.G. Costa and M. Manuela, 2004, Synthesis of new Fluorescent 2-(2', 2''-bithienyl)-1,3-benzothiazoles, Elsevier, 2825-2828.

[10] G. M. Raghavendra, A.B. Ramesha, C. N. Revanna, K. N. Nandeesh, K. Mantelingu, K. S. Rangappa, Tetrehedron Lett, 2011;52: 5571-55.

[11] Maleki, B; Salehabadi, H. Ammonium Chloride; as a mild and efficient catalyst for the Synthesis of some 2-arylbenzothiazoles and bisbenzothiazole derivatives. *Eur J. Chem* 2010, 1, 377-380

[12] Gupta, S.D.; Singh, H.P.; Moorthy, N. Iodine-Catalyzed, One-Pot, Solid-Phase Synthesis of Benzothiazole Derivatives. Synth Commun. 2007, 37, 4327–4329.

[13] Merroun, Y.; Chehab, S.; Ghailane, T.; Akhazzane, M.; Souizi1, A.; Ghailane, R. Preparation of tin-modified mono-ammonium phosphate fertilizer and its application as Heterogeneous catalyst in the benzimidazoles and benzothiazoles synthesis. *Reac Kine. Mech cat*. 2019, 126,249-264.

[14] Efren V. Garcia-Baez, Itzia I. Padilla-Martínez, 2021, Benzothiazoles from Condensation of *o*-Aminothiophenoles with Carboxylic Acids and Their

Derivatives: A Review, Molecules, 26(21): 6518.

[15] Amnekar N, Bhusari K. Preliminary anticancer activity of some prop-2-enemido, Thiazole and 1-acyl-pyrazoline derivatives of aminobenzothiazoles. Digest Journal of nanomaterials and Biostructures, 2010; (5): 177-184.

[16] K. M. Khan, F.Rahim, S. A. Halim, M. Khan, S. Perveen, Zaheer-ul-Haq, M. A. Mesaik, M. I. Choudhary, Bioorg. Med. Chem, 2011; 19: 4286-4294.

[17] Guo, H.Y.; Li, J.C.; Shang, Y.L. A simple and efficient synthesis of 2-substituted benzothiazole catalyzed by H2O2 /HCl. Chin. Chem. Lett. 2009, 20, 1408–1410.

[18] Umide Demir Ozkay, Ceren Kaya, Ulviye Acar Cevik, 2017, Synthesis and Antidepressant activity profile of some novel benzothiazole derivatives, Molecules, 1490.

[19] Livio Racine, Lucija Ptacek, Marko Klobucar,2020, Green synthesis and biological Evaluation of 6-substituted-2-(2-hydroxy/methoxy phenyl) benzothiazole derivatives as Potential antioxidant, antibacterial and antitumor agents, Elsevier,95.

[20] Lamia W. Mohamed, Azza T. Taher, Mamdouh M. Ali, 2016, Synthesis and cytotoxic The activity of certain benzothiazole derivatives against human MCF-7 cancer cell line, 532.

[21] Mahesh Bhat & Shiddappa Lagamappa Belagali, 2017, Synthesis, characterization and Biological screening of pyrazole-conjugated benzothiazole analogs, Future Medicinal Chemistry,0138.

[22] Da-Chuan Liu, Hong-Jian Zhang, Chun-Mei Jin, 2016, Synthesis and biological evaluation of novel benzothiazole derivatives as potential anticonvulsant agents, Molecules, 21, 164.

[23] Gajendra Kumar and N. P. Singh, 2021, Synthesis, anti-inflammatory and analgesic Evaluation of thiazole/oxazole substituted benzothiazole derivatives, Elsevier, 107.