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An Introduction to the Synthetic Method and Pharmacological Activity of Benzothiazole Nucleus: A Review

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ABSTRACT
Benzothiazole is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiazole 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 among the usually occurring heterocyclic nuclei in many marine as well as natural plant products. Benzothiazole is known to exhibit a wide range of biological properties including anticancer, antimicrobial, and antidiabetic, anticonvulsant, anti-inflammatory, antiviral, antitubercular activities.

KEYWORDS: Benzothiazole, Pharmacological activities, antimicrobial activity ,antiinflammatory activity , anti bacterial, anti fungal activity.

I. INTRODUCTION

Hantzsch and Waber first described Thiazolein 1887 and its structure confirmed by Popp in 1889. In thiazole, moiety numbering starts from the sulfur atom. The basic structure of benzothiazole is the combination of a benzene ring fused with 4, 5 positions of thiazole.

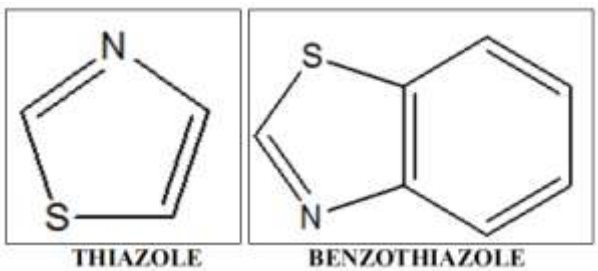
Thiazole is a heterocyclic compound. Thiazole ring is a five- member ring consists of one nitrogen and one sulfur atom in the ring. Thiazole and their analogs such as benzothiazole play an essential role as a template in the development of tremendous derivatives of thiazole which have different pharmacological activity and useful in the treatment of various disease **(1)**.

Benzothiazole is the combination of two rings, which contain the heterocycles thiazole and benzene. The core structure of thiazole and its pharmacologically and biologically active compounds are due to the presence of sulfur and nitrogen atoms present in the ring **(2)** .

Various marine or terrestrial natural compounds, which have useful biological activities is due to the presence of the benzothiazole ring **(3)** . Benzothiazole is a colorless, slightly viscous liquid with a melting point of 2 ºC and a boiling point of 227-228 °C. The density of benzothiazole is 1.238 g/ml (25 ºC). Benzothiazole has no household use. It is used in industry and research work purpose which are very beneficial for the development of the various pharmaceutical
compound **(4)** .

II. STRUCTURE OF BENZOTHIOZOLE:

The basic structure of benzothiazole consist of benzene ring fused with d face (4, 5position) of thiazole. The numbering in thiazole starts from the sulphur atom. **(5).**



THIAZOLE BENZOTHIAZOLE

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III. CHARACTERISTIC OF BENZOTHIAZOLE NUCLEUS:(5)

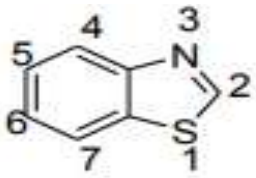
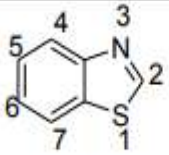
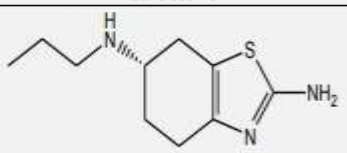
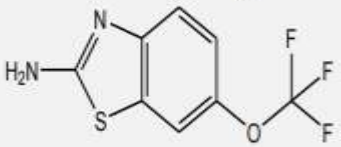
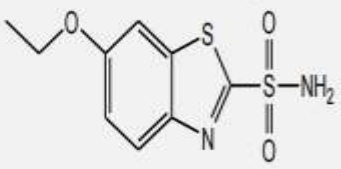


TABLE:1

Structure	
IUPAC Name	1,3-Benzothiazole
Molecular Formula	C_7H_5NS
Molecular Weight	136.19
Boiling Point	227-228^{O}C
Melting Point	2^{O}C
Density	1.644 g/ml
Physical appearance	colorless, slightly viscous liquid

IV. MARKETED PREPARATIONS HAVING BENZOTHIAZOLE NUCLEUS (5)

TABLE:2

S. no	Marketed drug	Company	Use	Structure
1	Pramiprexole	Zydus cadila	Parkinsons disease, restless legs syndrome	
2	Riluzole	Sun pharmaceuticals	Amyotrophic lateral sclerosis	
3	Ethoxzolamide	Pharmacia, Upjohn, allergan	Glaucoma, diuretic, duodenal ulcers	

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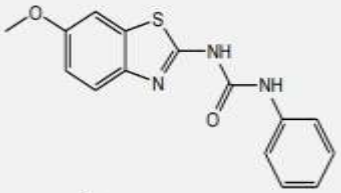
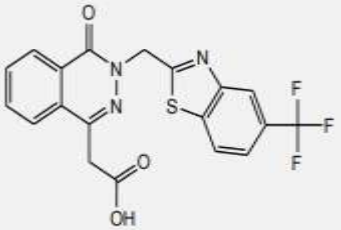
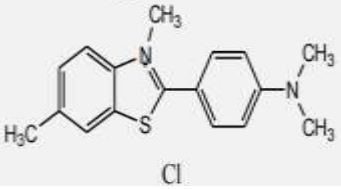
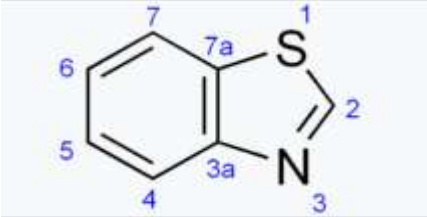
4	Frentizole	Not Available	Antiviral, immunosuppressive agent	
5	Zopolrestat	Not Available	Anti-diabetic	
6	Thioflavin T	Not Available	Amyloid imaging agent	

V. CHEMISTRY AND STRUCTURE ACTIVITY RELATIONSHIP



The basic structure of benzothiazole consist of benzene ring fused with 4, 5 position of thiazole. The IR spectrum of the compound showed absorption peak at 3344cm-1, 3025cm-1, 1630cm-1, 690cm-1 due to stretching of N-H, C-H, C=N, C-S.**[6]**

Structure Activity Relationship Study:

1. Presence of hydrophobic moieties in molecule is conductive for cytotoxic activity of benzothiazole derivitives against cancer cell lines. The amino, hydroxyl, and chloro group containing benzothiazole shows better anticancer activity.**[7]**

2. The substituents at second position of benzothiazole ring like mercapto group and hydrazine group are responsible for marked bactericidal activity and anti-inflammatory activity.**[8]**

3. Introduction of methoxy group (-OCH3) at position 4 of 2- mercapto benzothiazole increase antibacterial activity and introduction of chloro group (-Cl) at same position increase antifungal activity. **[9]**

4. Anticancer activity of compounds are due to substituent at position 2nd of amino benzothiazole. Compounds with pyrazoline and thiazole substitution were tending to have moderate anticancer activity.[2, 14, 15, 19] Heterocyclic rings, 1-acetyl-pyrazoline and thiazole do not support eminently for anticancer activity. Chloro substituted amino benzothiazoles were found to have encouraging sensitivity to cancer cell lines compared to fluro substituted benzothiazoles.**[10]**

VI. SYNTHESIS OF BENZOTHIOZOLE:

i) Solvent free synthesis

2-substituted benzothiazoles (Fig 3) was synthesized by condensation of 2-aminothiophenol with various saturated olefinic fatty acids under microwave in solvent free condition with the use of catalyst P4S10. This reaction gives high yield and

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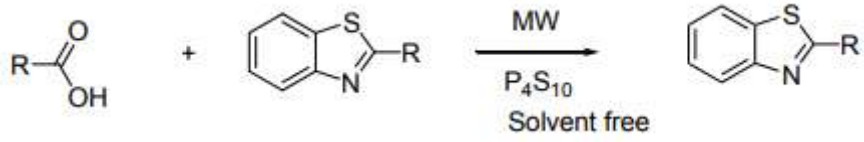
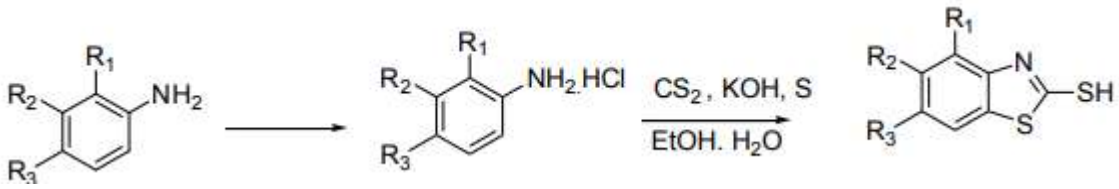
takes almost 3-4 min for completition of the reaction. [11]

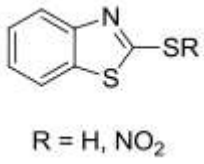
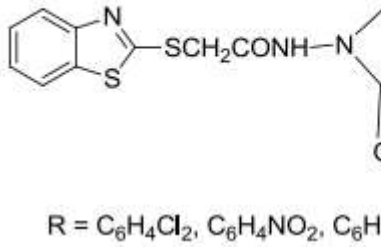


ii) Cyclization

Synthesis of substituted 2-mercapto benzothiazoles (Fig 4) by varying substituent's at 4, 5, and 6-position in the benzothiazole ring system. The synthesis of final compounds involves two steps- 1) Substituted anilines were converted to its hydrochloride salts. 2) This aniline hydrochloride salt was then cyclized to substituted 2-mercaptobenzothiazoles by reacting with carbon disulphide in presence of sulfur in an alkaline medium. [12]



VII. PHARMACOLOGICAL ACTIVTIY OF BENZOTHIAZOLE DERIVATIVES-

S.No.	Chemical Name/Structure	Activity	Author and Year
1	 R = H, NO_2	Antibacterial Agents	Mahran et al(2018)[13]
2	 R = $C_6H_4Cl_2$, $C_6H_4NO_2$, C_6H 2-(Substituted benzal hydrazino carbomyl methyl thio)benzothiozoles	Antimicrobial Activity	Trivedi et al et al (1992)[14]

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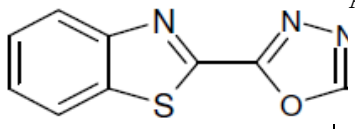
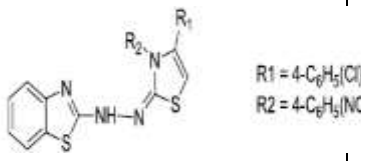
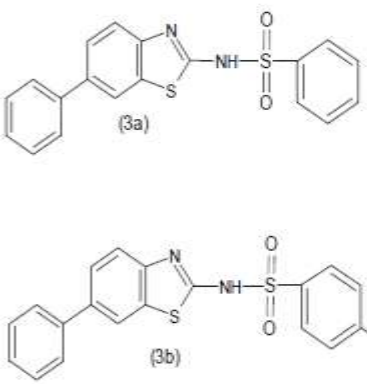
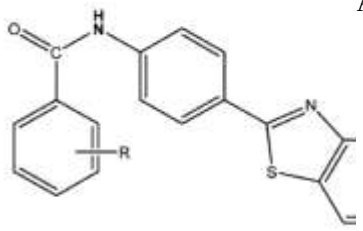
3	 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3-benzothiazole	Antimicrobial Activity	S.M. Shantakumar et al (2009)[15]
4	 	Antimicrobial and antiparasitic activity	Saeed .S (2015)[16]
5	 N-(biphenyl-4-yl)thiourea (a) and 2-amino-6-phenylbenzothiazole(b)	Antibacterial Activities	Chinyere B. C. Ikpaet al(2020) [17]
6	 N-(4-(benzo[d]thiazol-2-yl)phenyl)-styrene-amides	Antibacterial Activities	Meenakshi Singh et al(2014)[18]
7		Antitubercular Agents	Venugopala et al.(2018)[19]

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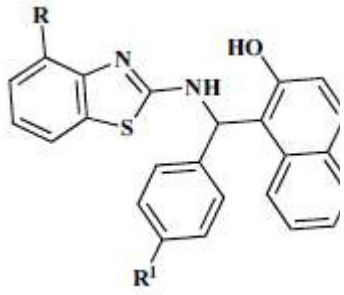
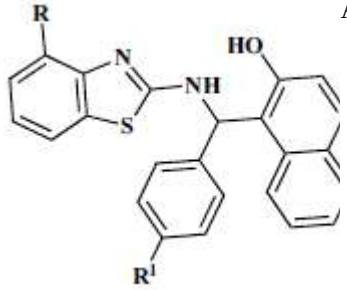
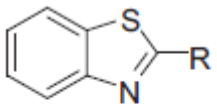
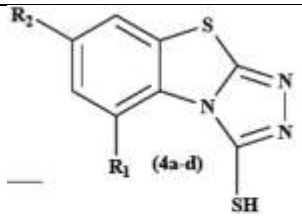
	 1-(((4-Substituted benzo[d]thiazol-2-yl)amino)(4-substituted) methyl) naphthalen-2-ol		
8		Antitubercular Agents	Bhat and Belagali(2019)[20]
9	 **14:** R = 2-EtPh **15:** R = 4-HOPh 2-substituted benzothiazoles	Antimicrobial Activity	M. Henary et al(2013)[21]
10	 a R_1=CH_3, R_2=H b R_1=H, R_2=CH_3 c R_1=H, R_2=Br d R_1=H, R_2=NO_2	Antitubercular Agents	Mamatha et al(2020)[22]

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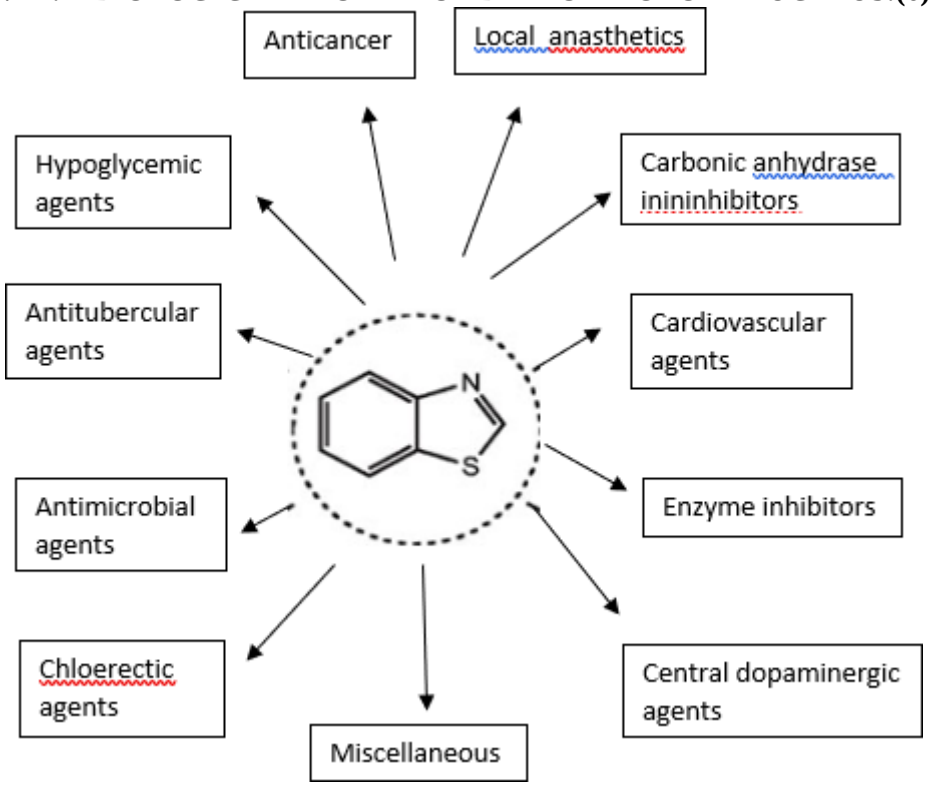
VIII. BIOLOGICAL PROFILE OF BENZOTHIOZOLE NUCLEUS:(6)



IX. CONCLUSION-

The present study has provided the basic idea regarding the introduction, chemistry,characteristic properties, reactivity and synthesis of Benzothiazole derivatives.

The review also provides general concept regarding the pharmacological activities of Benzothiazole derivatives .

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