

## A REVIEW ON BENZOTHIAZOLE AND ITS DERIVATIVES IN MEDICAL AND PHARMACEUTICAL FIELD

**ABSTRACT:** Benzothiazole is a molecule that has a wide range of different pharmacological activities. Literature reveals that benzothiazole with Sulphonamide increases the anti-inflammatory and antioxidant activity. Benzothiazole with oxadiazole shows the potent anthelmintic activity. Presence of an electron withdrawing group such as fluorine in the structure of benzothiazole exhibits anticancer activity of the drug.

**Keywords:** Benzothiazole, anisidine, pyrrolidine, *o*-phenylenediamine, benzophenone, anti-inflammatory, antioxidant, anthelmintic

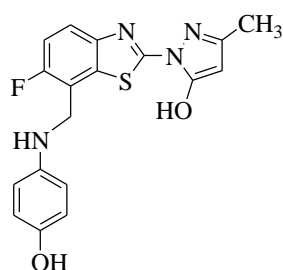
### INTRODUCTION

Benzothiazole is a most active lead molecule in the field of drug discovery for its wide range of pharmacological activity. Benzothiazole is a fused ring system containing one benzene and one thiazole ring. Thiazole ring contains sulphur and nitrogen which shows the potent antimicrobial activity. Addition of some new atom or ring at different position of benzothiazole enhances the activity. Substitution can be done by considering various factors like steric effect, lipophilicity, hydrophilicity, logP etc. Riluzole (6-trifluoromethoxy-2-benzothiazolamine) was found as a glutamate receptor antagonist in different biochemical and behavioural experiments. After that benzothiazole derivatives have been studied in expanded way to found a wide reactivity and broad spectrum of activity in the biological system. For e.g. Ethoxzolamide is a sulphonamide benzothiazole used as an inhibitor of carbonic anhydrase activity with diuretic act by decreasing reabsorption of water, sodium, potassium, bicarbonate ions and also used in glaucoma. Pramipexole is a benzothiazole containing drug use for the treatment of Parkinson's Disease (PD) as a dopamine agonist.

### BENZOTHIAZOLE DERIVATIVES

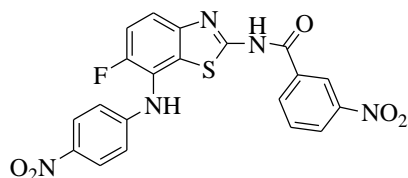
There are different types of benzothiazole derivatives with different pharmacological activity.

1. A Series of 1-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)-3-methyl-1*H*-pyrazol-5-ol derivatives were synthesized in four different phases containing different functional groups. Compound was synthesized by reacting 7-Chloro-6-Fluoro-Aniline with potassium thiocyanate and glacial acetic acid resulting in the formation of 7-Chloro-6-fluorobenzo[*d*]thiazol-2-amine. Then it was treated with hydrazine hydrate in ethylene glycol and concentrated hydrochloric acid. Then it was treated with ethyl acetoacetate in the presence of ethanol. Then 1-(7-chloro-6-fluoro-1,3-benzothiazole-2-yl)-3-methyl-1*H*-pyrazol-5-ol was treated with equimolar quantities of various substituted anilines like morpholine, piperazine aniline presence of 30ml N,N- dimethyl formamide (DMF). Benzothiazole substituted with anisidine, pyrrolidine, *o*-phenylenediamine on seventh position enhances the anti-microbial, anti-oxidant activities.



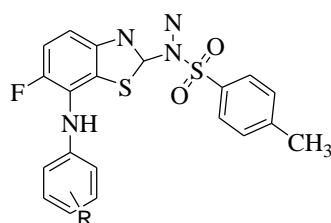
Antimicrobial activity was checked by using different bacterial and fungal strains and also by in-vitro disc-diffusion methods. Ciprofloxacin as a standard anti-bacterial and fluconazole as a standard anti-fungal drug was used. Anti-Convulsant activity of prepared compounds was evaluated by using Maximum Electroshock induced Seizures (MES). Antioxidant Activity was checked by *p*-NDA (*p*-Nitroso Dimethyl Aniline) Radical Scavenging Method.

2. First 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole was synthesized, then 7-chloro-6-fluoro-2-(3-nitro phenyl)-carboxamido-(1,3)-benzothiazole was prepared by stirring a solution of triethylamine and 2-amino-7-chloro-6-fluoro benzothiazole. After that 7-(4 nitro anilino)-6-fluoro-2-(3-nitro phenyl) carboxamido (1,3)benzothiazole was prepared by refluxing for 2-4 hours in oil bath with a mixture of 7-chloro-6-fluoro-2-(3 nitro phenyl) carboxamido(1,3)benzothiazole and *p*-nitro aniline in equimolar quantities in dimethyl formamide. In vitro anthelmintic activity was screened against earthworms' *perituma posthuma*.



The above compound showed the significant effect with compared to standard drug albendazole.

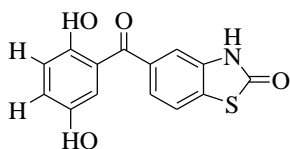
3. 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole was synthesized first, then 7-chloro-6-fluoro-2-hydrazinyl(1,3)-benzothiazole was synthesized by using hydrazine hydrate and concentrated HCl. Then synthesized compound was treated with potassium carbonate and formic acid to produce 8-chloro-7-fluoro-1,9a-dihydro-[1,2,4]-triazole-[3,4-b][1,3]-benzothiazole. Then the compound 8-chloro-7-fluoro-1,9a-dihydro-[1,2,4]-triazole-[3,4-b][1,3]-benzothiazole was refluxed with *p*-toluene sulphonamide in presence of pyridine to get 8-chloro-7-fluoro-1-[4methylphenyl]sulphonyl-1,9a-dihydro-[1,2,4]-triazolo-[3,4b][1,3]-benzothiazole. Finally the compound was refluxed with primary or secondary aromatic amine in presence of N,N-dimethyl formamide to get different derivatives. Benzothiazole substituted with morpholine, pyrrolidine and ansidine on seventh position enhances the anti-microbial, anti-inflammatory and antioxidant activity.



Anti-bacterial, anti-fungal activity was screened using different microbial strains

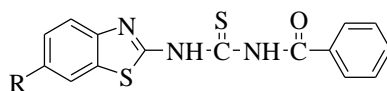
4. In the first step the Friedel–Crafts acylation of activated benzenes such as anisole , veratrole , and 1,4-dimethoxybenzene was performed with freshly prepared 4-chloro-3-nitrobenzoyl chloride in dichloromethane in the presence of AlCl<sub>3</sub> as a catalyst. Then reduction of the nitro group in compounds was accomplished with tin(II) chloride, then These compounds underwent smooth cyclization with ethyl potassium xanthate in dimethylformamide (DMF) as solvent to afford 5-aryloxy-2(3H)-benzothiazolethiones replacement of the thione group by a carbonyl group and demethylation of aryl methyl ethers to afford the desired hydroxyl substituted benzophenones. Benzophenones containing a

benzothiazolone moiety exhibit a wide pharmacological activity. They act as anti-inflammatory agent and can also inhibit COX pathway. They are also having a strong antioxidant property.



The ferric reducing antioxidant power (FRAP) method was used for assessing the antioxidant potential of derivatives. The cytotoxicity of benzophenone derivatives was tested on the cancerous MCF7 and the non-cancerous hTERT-HME1 mammary cell lines and it showed an effective antioxidant property with no cytotoxicity.

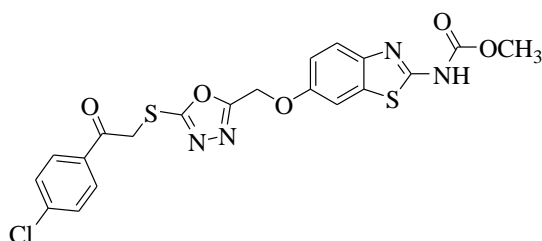
5. The 6-substituted-1,3-benzothiazole-2-amines **1e6** were synthesized by reacting aryl amines with potassium thiocyanates. 2/4-Substituted benzoyl iso-thiocyanate were obtained by reacting substituted benzoic acid and thionyl chloride. Final compounds N-[(6-substituted-1,3-benzothiazole-2-yl)amino]carbonothioyl}-2/4-substituted benzamides were synthesized by refluxing 6-substituted-1,3-benzothiazol-2-amines and 2/4-substituted benzoyl isothiocyanates. The synthesized N-[(6-substituted-1,3-benzothiazole-2-yl)amino]carbonothioyl}-2/4-substituted benzamides have shown effective anticonvulsant activity with no neurotoxicity.



The rota rod test was used to evaluate neurotoxicity. CNS depressant study was performed by the forced swim pool method. Maximal electroshock test was performed for anticonvulsant activity

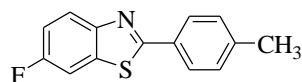
6. The synthesized benzothiazole derivative of o-substituted,6-methoxybenzothiazole-2-carbamate shows most potent anthelmintic activity. 2-(2-aminobenzothiazol-6-yloxy)acetohydrazide was prepared by heating ethyl 2-(2-aminobenzothiazol-6-yloxy)acetate with hydrazine hydrate. Acid hydrazide was refluxed with CS<sub>2</sub> and KOH in ethanol to yield oxadiazolethiole derivative which tautomerized to thione. 5-Substituted sulfanyl-[1,3,4]-oxadiazolyl derivatives were prepared in better yields, following a procedure for the

regioselective alkylation of hydrazones by stirring a mixture of 1,3,4-oxadiazole-5-thiol derivative 2 and an equimolar amount of selected alkyl or aralkyl halide in K<sub>2</sub>CO<sub>3</sub>/DMF. 6-[(5-(alkyl- or aralkylsulfanyl)-[1,3,4]-oxadiazol-2-yl)methoxy]benzothiazole-2-carbamates were synthesized by stirring a mixture of substituted sulfanyl derivatives and methyl chloroformate. substituted aryl isothiocyanates under various reaction conditions, led to direct cyclization into corresponding triazole derivatives. Finally 2-amino-6-[(5-(4-substituted phenacylsulfanyl)-[1,3,4]-oxadiazol-2-yl)methoxy]-benzothiazoles were further reacted with methyl chloroformate to achieve the intended methyl 6-[(5-(4- substituted phenacylsulfanyl)-[1,3,4]-oxadiazol-2-yl)methoxy]-benzothiazole-2-carbamates.

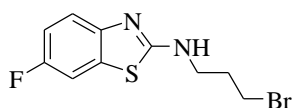


Anthelmintic activity of the synthesized compound was evaluated against rumen flukes (*paramphistomum*) and the above compound shows the high paramphistomicidal activity.

7. The derivatives of substituted 2-phenyl-1,3-benzothiazole has potent anti breast-cancer activity.

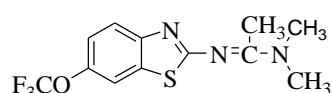


8. Fluorine substituted benzothiazole exhibits most potent activity against leukemia in compare to non-fluorinated derivatives.



Benzothiazole that has bearing a strong electron-withdrawing group like fluorine at position-6, improves the cytotoxic activity against particular cancer cell lines. The given synthesized structure has shown the most potent activity

9. A synthesized 6-trifluoromethoxy benzothiazole derivative has shown an effective neuroprotective activity in brain diseases like disorders like Alzheimer's (AD) and Parkinson's (PD).



## CONCLUSION:

Literature reveals that benzothiazole is a very important lead molecule that can be used for different types of drug discovery and development in pharmaceutical and medicinal field. The presence of nitrogen and sulphur is helpful in its antimicrobial activity. Sulphonamide with benzothiazole increases the anti-inflammatory and antioxidant activity. Benzothiazole with oxadiazole shows the potent anthelmintic activity. Presence of an electron withdrawing group such as fluorine in the structure of benzothiazole exhibits anticancer activity of the drug.

## REFERENCES:

- B. M. Gurupadayya, Ch. Sambireddy, M. N. Purohit, and G. V. Pujar. Synthesis and Pharmacological Evaluation of 7-chloro-6-fluoro-2-(5-aminoxazol/thiazol-2-aryldenylamino)benzo(1,3)thiazoles, J. Sci. Res. 2011; 3 (1):121-128.
- D. R. S. Reddy, L. P. Raparla, Karakavalasa. Pradeep, S. M. Ahmed and Sindhura J. Synthesis, analytical characterization, antimicrobial, antioxidant and anticonvulsant evaluation of some novel 6-fluorobenzothiazole substituted pyrazole analogues, IJPC 2013; 03 (04):72-81
- P. Naresh, P. Pattanaik and B. Rajeshwar. Synthetic Characterization and Antioxidant Screening of Some Novel 6 Fluorobenzothiazole Substituted [1, 2, 4] Triazole Analogues, Int. J. Pharma Sci. 2013; 3(2): 170-174.

- P. Naresh, P. Pattanaik, R. L. Priyadarshini, D. R. Reddy. Synthetic Characterization & Antimicrobial Screening of Some Novel 6-Fluorobenzothiazole Substituted [1, 2, 4] Triazole Analogues, *Int. J. Pharm. Res. and Health Sci.* 2013; 1 (1):18-25
- T.Tzanova, M.Gerova, O.Petrov,M.Karaivanova,D.Bagrel . Synthesis and antioxidant potential of novel synthetic benzophenone analogues. *Eur. J. Med. Chem.* 2008, 1–7
- N. Pathak, E.Rathi, N. Kumar<sup>1</sup>, S. G. Kini, C. M. Rao. Review on Anticancer Potentials of Benzothiazole Derivatives, *Mini-Reviews in Medicinal Chemistry*, 2020; 20:12-23
- A. Irfan *et al.* Review article, Benzothiazole Derivatives as Anticancer Agents, *J. Enzyme Inhib. Med. Chem.* 2020; 35(1): 265–279
- A. Catalano *et al.* Benzothiazole-Containing Analogues of Triclocarban with Potent Antibacterial Activity, *Antibiotics.* 2021; 10:803.
- X. Su *et al.* Benzothiazole derivatives as novel inhibitors of human 11 $\beta$ -hydroxysteroid dehydrogenase type 1 , *Mol. Cell. Endocrinol.* 2006; 248: 214–217.
- M. M. E. Omar , A. O. M. Aboulwafa,A. D. A. E. Issa, M. S. M. El-Shoukrofy ,A. M. E. Amra and I. M. El-Ashmawyc . Design, facile synthesis and anthelmintic activity of new O-substituted 6 methoxybenzothiazole-2- carbamates. Part II, *Med. Chem. Commun.*, 2017; 8: 1440-1451
- R. Liu *et al.* Hydride-induced Meisenheimer complex formation reflects activity of nitro aromatic antituberculosis compounds, *RSC Med. Chem.*, 2021; 12: 62-72.
- T. Al-Harthy , W. Zoghaib and R. A. Jalil . Review on Importance of Fluorine in Benzazole Compounds, *Molecules* 2020; 25, 4677
- J. A. Morales-Garcia *et al.* Biological and Pharmacological Characterization of BenzothiazoleBased CK-1 $\delta$  Inhibitors in Models of Parkinson’s Disease, *ACS Omega* 2017; 2: 5215–5220
- A.Gupta, S.Rawat. Synthesis and anti-inflammatory study of novel fluorobenzothiazole derivatives, *J. Chem. Pharm. Res.*, 2010, 2(5): 244-258