A REVIEW ON BENZOTHIAZOLE DERIVATIVES AND THEIR BIOLOGICAL SIGNIFICANCES

ABSTRACT: Benzothiazole is a molecule that has a wide range of pharmacological activities. The addition of a fluorine atom into the structure of benzothiazole enhances the various activities of the drug as the alteration of hydrogen or oxygen atom from a carbon bond by a fluorine atom improves desirable pharmacological properties such as greater biological half-life, higher ability to bind with the targeted receptor, and also enhances the lipophilic character of the drug. The special property that makes fluorine a very important molecule in the drug discovery includes a very small radius of the fluorine atom, a higher attacking power towards electrons, and a very low polarizability of the fluorine atom. Literature reveals that strong electron-attacking groups like fluorine in the structure of benzothiazole can exhibit anticancer activity of the drug, benzothiazole with Sulphonamide or with beta-lactam ring enhances the anti-inflammatory and antioxidant activity. Benzothiazole with oxadiazole shows potent anthelmintic activity. [1-5]

Keywords: Benzothiazole**,** oxadiazole, sulphonamide, anthelmintic

INTRODUCTION

Benzothiazole is the 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 sulfur and nitrogen which shows potent antimicrobial activity. The addition of some new atom or ring at different positions of benzothiazole enhances the activity. Substitution can be done by considering various factors like steric effect, lipophilicity, hydrophilicity, logP, etc. Riluzole, a fluorine-containing drug was found as a blocker of glutamate receptors in different biomedical and behavioral studies. After that, the different derivatives of benzothiazole molecules were studied in a much-expanded way to find a wide application and activity in the biological system. E.g. Ethoxzolamide is a sulphonamide benzothiazole used as an inhibitor of carbonic anhydrase activity with a diuretic act by decreasing reabsorption of water, sodium, potassium, and

bicarbonate ions and also used in glaucoma. Pramipexole is a benzothiazole-containing drug used for the treatment of Parkinson's disease (PD) as a dopamine agonist.

BENZOTHIAZOLE DERIVATIVES WITH DIFFERENT PHARMACOLOGICAL ACTIVITIES:

In this review paper, I have given different types of benzothiazole derivatives with different pharmacological activities along with their structures.

ANTI-MICROBIAL ACTIVITY

1. Different derivatives of 1-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)-3-methyl-1*H*-pyrazol-5-ol were synthesized. Firstly the compound 7-Chloro-6-Fluoro-Aniline was treated with KSCN and glacial acetic acid (CH_3COOH) to get 7-Chloro-6-fluorobenzo[*d*]thiazol-2-amine.Then it was treated with hydrazine hydrate in ethylene glycol and concentrated hydrochloric acid. Then 7-Chloro-6-fluorobenzo[*d*]thiazol-2-amine was reacted with ethyl acetoacetate in presence of C_2H_5OH. Then 1-(7-chloro-6-fluoro-1,3-benzothiazole-2-yl)-3-methyl-1*H*-pyrazol-5-ol was treated with different substituted anilines like morpholine, piperazine aniline with DMF. The substituted benzothiazole with anisidine, pyrrolidine, *and o*-phenylenediamine in the 7^{th} position shows better anti-microbial activities.

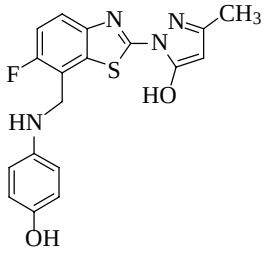

Figure:1-Benzothiazole derivatives with anti-microbial activity

Antimicrobial activity was studied by using different bacterial strains like *B.subtilis, S.aureus, K.pneumonia, and E.coli* with a concentration 25, 50, and 100 µg/ml, and anti-fungal activity was studied using *A. flavus* and *A.niger* with a concentration of 100 and 150 µg/ml. Ciprofloxacin was used as a standard anti-bacterial drug and fluconazole was used as a standard anti-fungal drug. Anti-Convulsion activity of the synthesized compounds was

performed for studies by Maximum Electroshock induced Seizures. Antioxidant Activity was studied by a radical scavenging method using *p*-Nitroso Dimethyl Aniline.

2. Different benzothiazole derivatives with ß-lactam group such as 3-chloro-1-(7-chloro-6-fluoro-4-nitrobenzo[*d*]thiazol-2-yl)-phenylazetidin-2-one and their derivatives were synthesized. The synthesized compound 3-chloro-1-(6-fluoro-4-nitro-7-(substituted phenylamino)benzo[*d*]thiazol-2-yl)-4-trimetoxyphenyl azetidine-2-one was found to have potent antibacterial activity.

Figure: 2 Benzothiazole derivatives with anti-microbial activity

The antibacterial activity was studied against *S.aureus* and *B.subtilis, E.coli,* and *P. aeruginosa* and the above-synthesized compound showed interesting effects on the selected microorganisms.

3. During the last decade it was reported that benzothiazole, benzoxazole, and benzimidazole derivatives substituted at position 2 and 5 has an antimicrobial activity on various microorganisms such as *E. aerogenes, P.aeruginosa, C. albicans* ctc. A series of different 2,2'-(2-(2-benzylidenehydrazinyl)-6-fluorobenzo[*d*]thiazol-7-ylazanediyl)diethanol derivatives were synthesized by reacting 2-(2-substitutedbenzylidenehydrazinyl)-7-chloro-6-fluorobenzo[*d*]thiazole with diethanolamine, for checking their antimicrobial activities against *S. aureus, B.subtilis, E. coli,* and *P.aeruginosa* using ampicillin as a standard antimicrobial drug.

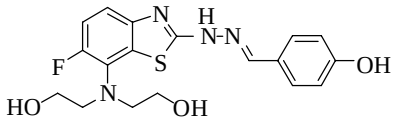

Figure: 3 Benzothiazole derivatives with anti-microbial activity

The above synthesized compound has shown potent antimicrobial activity against the standard drug.

ANTHELMINTIC ACTIVITY

4. First 7-chloro-6-fluoro -(1, 3)-benzothiazole-2-amine was synthesized, then 7-chloro-6-fluro-2-(3-nitro phenyl)-carboxamido-(1,3)-benzothiazole was prepared using 7-chloro-6-fluoro benzothiazole-2-amine and triethylamine. After that 7-(4-nitroanilino)-6-fluro-2-(3-nitro phenyl)-carboxamido-(1,3)-benzothiazole was prepared by refluxing for 2-4 hours with a mixture of 7-chloro-6-fluro-2-(3 nitro phenyl)carboxamido(1,3)benzothiazole and *p*-nitro aniline in DMF. In vitro, anthelmintic activity was screened against earthworms' *perituma posthuma*.

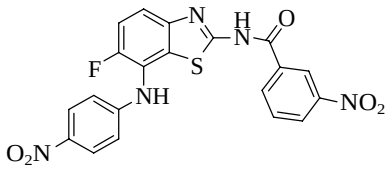

Figure: 4 Benzothiazole derivatives with anthelmintic activity

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

5. The synthesized benzothiazole derivative of o-substituted,6-methoxybenzothiazole-2-carbamate shows the most potent anthelmintic activity. Ethyl-2-(2-aminobenzothiazol-6-yloxy) acetate with hydrazine hydrate was treated to prepare 2-(2-aminobenzothiazol-6-yloxy)acetohydrazide. Then 2-(2-aminobenzothiazol-6-yloxy)acetohydrazide was refluxed with carbon disulfide and potassium hydroxide in ethanol for getting an oxadiazolethiole derivative. 5-Substituted sulfanyl-[1,3,4]-oxadiazolyl derivatives were prepared by reacting 1,3,4-oxadiazole-5-thiol derivatives with alkyl or aralkyl halide in K_2CO_3/DMF. substituted sulfanyl derivatives and methyl chloroformate were used to prepare 6-[(5-(alkyl- or aralkylsulfanyl)-[1,3,4]-oxadiazol-2-yl)methoxy]benzothiazole-2-carbamates. Then aryl isothiocyanates undergo cyclization into triazole derivatives. Finally 2-amino-6-[(5-(4-substituted phenacyl sulfanyl)-[1,3,4]-oxadiazol-2-yl)methoxy]-benzothiazoles were further

treated with methyl chloroformate to get methyl-6-[(5-(4- substituted phenacyl sulfanyl)-[1,3,4]-oxadiazol-2-yl)methoxy]-benzothiazole-2-carbamates.

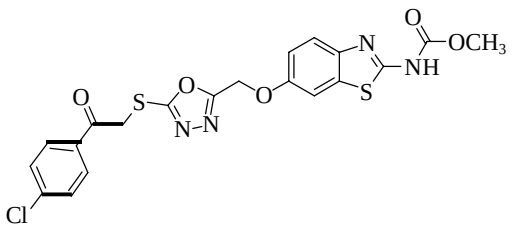

Figure:5 Benzothiazole derivatives with anthelmintic activity

Anthelmintic activity of the above compound was evaluated against *paramphistomum sp.* and it shows high paramphistomicidal activity.

ANTI-INFLAMMATORY ACTIVITY

6. 7-chloro-6-fluoro-(1,3)-benzothiazole-2-amine was synthesized first, then 7-chloro-6-fluoro-2-hydrazinylbenzothiazole was synthesized using hydrazine hydrate and concentrated HCl. Then synthesized compound was treated with K_2CO_3 and formic acid for getting 8-chloro-7-fluoro-1,9a-dihydrol-(1,2,4)-triazole-(3,4b)(1,3)-benzothiazole.Then the compound 8-chloro-7-fluoro-1,9a-dihydrol-(1,2,4)-triazole-(3,4b)(1,3)-benzothiazole was refluxed with *p*-toluene sulphonamide in pyridine to prepare 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 a primary or secondary aromatic amine in DMF in search different derivatives. Benzothiazole substituted with morpholine, pyrrolidine, and ansidine in the 7th position shows better anti-inflammatory activity.

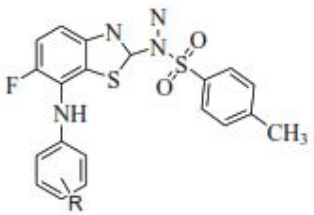

Figure: 6 Benzothiazole derivatives with anti-inflammatory activity.

ANTI-OXIDANT ACTIVITY

7. Friedel–Crafts acylation of benzenes such as anisole, veratrole, and 1,4-dimethoxybenzene was performed using 4-chloro-3-nitrobenzoyl chloride with CH_2Cl_2 and $AlCl_3$ as a catalyst. Then tin(II) chloride was used for the reduction of the nitro groups. Cyclization of these compounds undergoes ethyl potassium xanthate ($CH_3CH_2OCS_2K$) in DMF. Then replacement of the thione group was done by a carbonyl group and the demethylation of aryl methyl ethers was also done for getting benzophenones with hydroxyl groups. Benzophenones containing a benzothiazolone moiety exhibit a wide pharmacological activity. They act as an anti-inflammatory agent and can also inhibit the COX pathway. They are also having strong antioxidant properties.

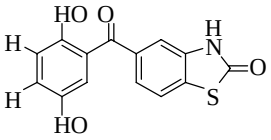

Figure: 7 Benzothiazole derivatives with antioxidant activity

The ferric-reducing antioxidant power method was used for studying the antioxidant activity of the synthesized compounds. The cytotoxic effect of the drug had also been tested on MCF7 and hTERT-HME1 mammary cell lines and it showed an effective antioxidant property with no cytotoxicity.

8. N-(7-chloro-6-fluorobenzo[d]thiazol-2-yl)acetamide was treated with various substituted aromatic aldehydes to get N-(7-chloro-6-fluorobenzo[d]thiazol-2-yl)-3-substituted phenyl acrylamide.

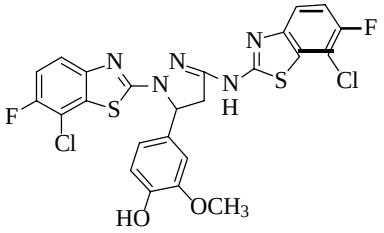

Figure: 8 Benzothiazole derivatives with antioxidant activity

Finally the compound N-(7-chloro-6-fluorobenzo[d]thiazol-2-yl)-3-substituted phenyl acrylamide was refluxed with 7-chloro-6-fluoro-2-hydrazinylbenzo[*d*]thiazole to get the novel targeted compound. The above-synthesized compound had shown the most potent antioxidant activity. The anti-oxidant activity was checked by ferric ion reduction and DPPH methods.

ANTI-CONVULSANT ACTIVITY

9. 1,3-benzothiazole-2-amines with substitution at position 6 were synthesized by treating aryl amines with KSCN. After that substituted benzoic acid and thionyl chloride were treated to produce substituted benzoyl iso-thiocyanate. Finally, we reflux 6-substituted-1,3-benzothiazol-2-amines and substituted benzoyl isothiocyanates to get N-[(6-substituted-1,3-benzothiazole-2-yl)amino]carbonothioyl-2/4-substituted benzamides. The synthesized compound has shown an effective anticonvulsant activity with no neurotoxicity.

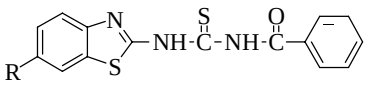

Figure: 9 Benzothiazole derivatives with anti-convulsion activity

CNS depressant study was performed by the forced swim pool method and rota rod test. And a maximal electroshock test was performed for anticonvulsant activity.

ANTI-CANCER ACTIVITY

10. Indole, isatin, benzothiazole, oxadiazole, etc., are the most common nitrogen and sulfur-containing heterocyclic compounds, and they have shown anticancer activities. Among them, benzothiazole shows anticancer activity by inhibiting different receptors like tyrosine kinase, aurora kinase, topoisomerase, etc. the percentage of growth inhibition of all the synthesized compounds were evaluated at a concentration of 10, 50, and 100 μM against lung (A-549), prostate (PC-3), leukemia (THP-1), and colon (Caco 2) cancer cell lines using paclitaxel, mitomycin-C, and 5-fluorouracil as standard and fluorine substituted benzothiazole exhibit most potent activity against leukemia in compare to non-fluorinated derivatives.

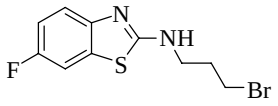

Figure:10 Benzothiazole derivatives with anti-cancer activity

Benzothiazole which has a strong electron-attacking atom like fluorine at the 6th position enhances the cytotoxic activity. The given synthesized structure has shown the most potent activity among the synthesized compounds.

11. The Difluorovinyltaxoids possess a notable higher potency against different cancer cell lines of the human breast, ovary, colon, and pancreas compared to the standard drug paclitaxel against breast cancer cell lines MCF-7 and an MDR cancer cell line NCI/ADR because of an appreciative half-life of the fluorine isotope ^{18}F. The ability of these new-generation fluoro taxoids exemplified here, to critically damage cancer stem cells (CSC) indicates the advantages of using these fluoro taxoids for tumor-targeted drug delivery systems (TTDDSs), as well as drug combinations and Nano formulations.

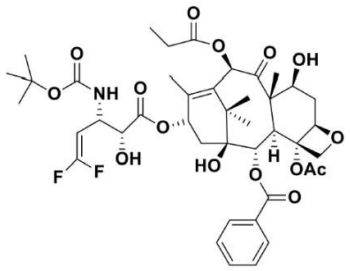

Figure: 11 fluorinated compounds with anti-cancer activity

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

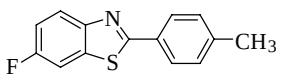

Figure: 12 Benzothiazole derivatives with anti-cancer activity

12. Benzothiazole has become a very important lead compound for its various pharmacological activities including antitumor activity. A wide range of research to modify benzothiazole nuclei with antitumor activities has been carried out over years. In this review article, the following compound shown here has good cytotoxic activity against Colo-205 and A549 cell lines while using PMX 610 as a standard drug.

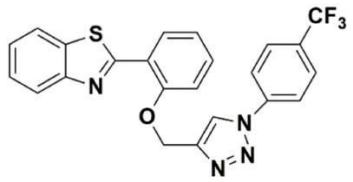

Figure: 13 Benzothiazole derivatives with anti-inflammatory activity

ANTI-ALZHEIMER ACTIVITY

13. A synthesized 6- Benzothiazole with trifluoromethoxy group at position 6 derivative has shown an effective neuroprotective activity in brain diseases like disorders like Alzheimer's (AD) and Parkinson's (PD).

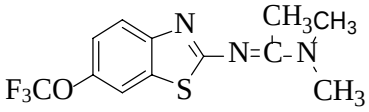

Figure: 14 Benzothiazole derivatives with anti-Alzheimer activity

14. Aggregated β-amyloid (Aβ) has been associated with the development of Alzheimer's disease (AD). A series of benzothiazole-containing agents for amyloid imaging of AD were developed in the last few years. Among them, the most specific and widely used amyloid imaging ligand is [^{11}C] 2-(4-(methylamino) phenyl)-6-hydroxybenzothiazole. But ^{11}C has a very short half-life (20.38 minutes), to overcome this problem ^{18}F-labeled benzothiazole derivatives had synthesized and it shows a better advantage over the ^{11}C molecules and it also shows more clear contrast images. By following the [^{18}F]fluoroethylation process three different ^{18}F-labeled benzothiazole derivatives had been synthesized such as [^{18}F]2-(4-

(methylamino)phenyl)-6-(2-fluoroethoxy)benzothiazole, [^{18}F]2-((2-(2-fluoroethoxy)-4-amino)phenyl)benzothiazole and [^{18}F]2-(3-((2-fluoroethoxy)-4-amino)phenyl)benzothiazole.

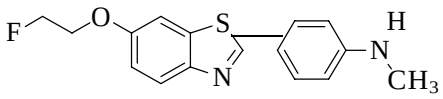

Figure: 15 Benzothiazole derivatives with anti-Alzheimer activity

The ^{18}F-labeled, 2-(4-(methylamino)phenyl)-6-(2-fluoro ethoxy)benzothiazole shows excellent activity for amyloid imaging concerning lipophilicity, brain entry, and brain clearance in normal SCID mice.

CONCLUSION:

Literature reveals that benzothiazole is a very important lead molecule that can be used for different types of drug discovery and development in the pharmaceutical and medicinal field. The presence of nitrogen and sulfur is helpful in its antimicrobial activity. Sulphonamide with benzothiazole increases anti-inflammatory and antioxidant activity. Benzothiazole with oxadiazole shows potent anthelmintic activity. An electron-attacking group like fluorine in the structure of benzothiazole can exhibit the anticancer activity of the drug. So, Benzothiazole moiety can be a greater choice for researchers for new drug discovery and development with a wide pharmacological activity.

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