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BENZOTHIAZOLE DERIVATIVES AS POTENTIAL ANTI-TUBERCULAR AGENT

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ABSTRACT

Benzothiazoles are a group heterocyclic scaffold which have a benzene ring and a nitrogen(N) and sulfur(S) groups present in the pentacyclic ring structure which in combination gives rise to Benzothiazole ring. This benzothiazole ring structure is a parent ring structure for many pharmacological activities as anti-tubercular, anti-microbial, anti-malarial, anti-inflammatory, anti-cancerogenic activity, anti-convulsant activity., etc. this class of heterocyclic moiety show some similarity with penicillin, carbapenems, cephalosporins classes as the functional group in the parent ring is similar but the atomic configuration is different. There are various uses of the benzothiazole ring but we are interested in anti-tubercular activity. In this article, there will be detail understanding of structural activity relationships of the parent ring and also there are variety of synthesis discovered but one very specific to it is discussed later.

KEYWORDS: Benzothiazole, anti-tubercular activity, anti-microbial activity, anti-malarial activity.

INTRODUCTION

Tuberculosis is a disease which overpowers to people who are suffering from economical stress, vulnerability, stigma, criticize and discrimination faced by the people since they are affected by it.[1,2] About a quarter of the world's population is affected with tuberculosis. It's a communicable disease that comes in top 10 causes of death in worldwide. In 2019, about 10 million people developed TB and 1.4 million people died.[3] The causative agent of this disease is *Mycobacterium Tuberculosis* and its strains discussed later in the part. Due to this, there was need to escalate the rate of research in order to suppress this tremendous infective and death rates. A new category of thiazoles were under the lights for its anti-tubercular activity and secured a better place amongst the other ant tubercular agents. Tuberculosis infection generally leads to four possible outcomes the very first is the Immediate clearance of the organism when it enters the body then Latent infectious stage, Primary disease and Reactivation diseases.[4]

the infection is developed only after small droplets of tubercle bacilli infiltrate the lung to reach alveolar spaces and spreads the infection. If the host is not able to defend itself and his defence system fails to eliminate the bacilli, the bacilli will eventually proliferate inside the alveolar macrophages and damage the cell. Because of this event the infected macrophages release cytokines and chemokines which attract other phagocytic cells, monocytes, alveolar macrophages and neutrophils which results in formation of *nodular granulomatous* structure inside the lung called as tubercle. If at this stage the bacterial growth is not controlled, there is enlargement of this tubercle leading to enter in the local lymph nodes which results in *lymphadenopathy*. This lesions caused during the expansion of the tubercle results in damage to lung parenchyma and lymph nodes which is also known as the *Ghon complex*.[5]

The bacilli continuous to grow until the CMI (cell-mediated immune) response is not into action (it takes two to six weeks of time to develop this CMI response)but till then, the lesions caused by the bacilli creates high amount of damage to the alveolar tissues and all the reactive oxygen atom, nitrogen containing intermediates and contents of cytotoxins (perforins, granzymes) may all chip in to the concretion of necrosis that characterize a tuberculous lesion. If the bacterial growth is still left unchecked then the spread of bacilli will disseminate the entire lung and create its millet seeds called as *miliary TB*. This miliary TB, is responsible for the spreading of disease to other healthy person. Death happen in 80 percent of the cases and remaining patients develop with the chronic disease or could also be recovered from the disease. Reactivation or reoccurrence of the Tuberculosis infection, results in proliferation of previously dormant bacterium miliary which were present at the time of primary infectious stage. This activation could be because of the immunosuppression which can trigger the latent infection to become operational.[5–7]

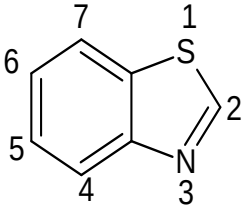
Bacterial Cell Component

The bacterial cell was is surprisingly very complex structure. The mycobacterium cell wall is not classified as gram positive nor gram negative because it neither show signs of gram positive or gram negative bacteria as such so, for this reason, acid fast staining is done to the bacteria. This acid fast staining helps the staining process to retain the coloured property by penetrating the dense lipid layer which allows it to stain the bacteria using the Ziehl-Neelsen staining which gives special pink colour stain known as carbon-fuchsin ,because of this the bacteria appears to be pink in colour. The cell wall component comprises of Mycolic acid, Arabinogalactans peptidoglycan known as mAGP complex. Mycolic acid being the outer most layer comprises of cord factor (synthesized by Ag85A,BC), high molecular weight R-alkyl-β-hydroxy fatty acids and esters of arabinogalactan. The benzothiazole and its derivatives are specially design to target the Mycolic acid layer and abrupt the normal functioning of the cell wall of mycobacterium tuberculosis.[8]

Benzothiazole as an Anti-Tubercular Agent

The first line drugs as chemotherapeutics for the treatment of tuberculosis is the Isoniazid and Ethambutol, which inhibits the synthesis of the Mycolic acid and abrupt the synthesis of bacterial cell wall. A wide range of multi drug therapy (MDRTB) is also used in the treatment of the TB but there is always a resistance developed by the bacteria against the drugs used in the treatment respectively. Hence there is always an need to develop a new drug against the mycobacterium tuberculosis and its strains. Benzothiazole show wide range of interesting biological activities and therapeutically important for many diseases other than tuberculosis, such as, antimicrobial, antimalarial, anticonvulsant.[1,9] various neurodegenerative disorders etc. This moiety can be isolated from various sources such as marine and terrestrial habitat.[2,10]

Chemistry



The benzothiazole ring moiety belongs to the family of bicyclic heterocyclic compound having the functional groups as Nitrogen(N) and sulfur(S) atoms . The substitution on the second position of the ring results in increase hydrophobicity and activity which is required for penetration in *mycobacterium tuberculosis* and results in good anti-tubercular activity.[10] The benzothiazole group is used as a pharmacophore part, when the drug containing this parent ring is involved in drug-receptor binding. The benzothiazole backbone has resulted in great results for anti-tubercular activity.[11] The structural activity studies at second position and the fluorine group on the fifth position in the parent ring gave very interesting results of the ring which attracted more number of researchers to develop new compounds with benzothiazole as a parent ring.[12–14]

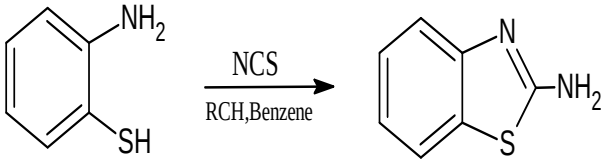
In 1887, August Wilhelm Von Hofmann, contributed to the synthesis of benzothiazole with substitution on the second position on the ring which showed great activity. Few synthesis including the Hofmann synthesis have been included in this review article for better understanding and clarification of the topic.

Synthesis

The synthesis of benzothiazole as an conventional method and much straight forward method is the condensation of the ortho-amino thiophenol with aromatic aldehyde, carboxylic acid, acyl chloride or nitrile compounds used, the problem with this method is that the ortho-amino thiophenol are used which are readily oxidize and prevents the formation of many 2-arylbenzathiazoles[15]. The other methods used in the laboratories (Jacobsen cyclization) and some new methods developed are discussed in this review article further,

Hoffmann Method

In this method, A.W. Hofmann tried to synthesize 1-mercapto benzothiazole using sulfhydryl derivative of thiocarbanilide with carbon disulphide on ortho-amino phenol. The product obtained after this reaction was subjected to recrystallization to obtain a pure compound of 2-amino benzothiazole (melting point:- 179°C). The reaction of amino thiophenol and phenyl isothiocyanate with Benzene as a catalyst gives 2-anilino benzothiazole.[2,4,16]



Jacobsen and Frankenbacher Cyclisation

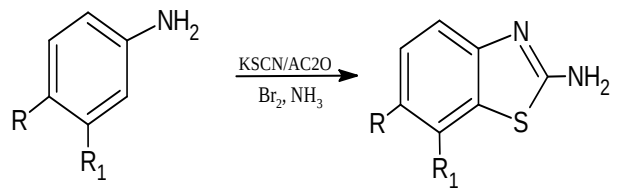
In 1886, Jacobsen and Frankenbacher synthesized the 2-substituted benzothiazole compound using azobenzene with carbon disulphide heating the whole content in a sealed and air tight tube at 250°C for 5-6 hrs. they generated the same product with the melting point of 174°C and reported this synthesis and cyclization process using potassium ferricyanide with sodium hydroxide.[16–19]

Sibaji Sarkar Method

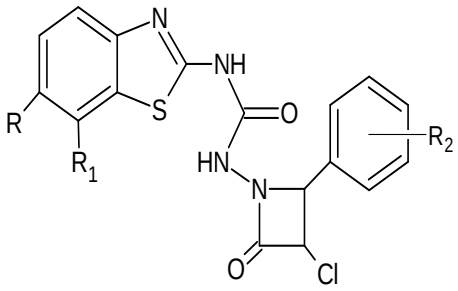
In 2019, Sibaji Sarkar[4] developed a new technique to synthesize benzothiazole and have added various substitutions on the second position of the parent ring that is on benzothiazole ring. The reaction was based on trial and error as the substitution on the second position was fully supported for Anti-Tubercular activity. This

reaction was further carried containing azetidinone ring for its novel activity against *Mycobacterium tuberculosis*.

In this reaction, Substituted aniline was considered to be the starting material which when reacted with potassium thiocyanide resulted in the intermolecular cyclization and resulted in the fused five membered ring with benzene ring resulting in our parent compound Benzothiazole.[4,19–21]



In the further synthesis of the benzothiazole ring structure, there were different modifications done to the parent ring which is given or stated as A6-10 compounds. This number justify the few modifications on the substituted (-R) groups on the starting material. The changes on the R group was kept constant as Fluorine atom and on the R_1 position Hydrogen atom was kept constant. The substitution was made at the R_2 position as mentioned in the later part in this topic. The above reaction after various reaction intermediates gives out the final structure to which the substitution was applied, the final structure is mentioned below



The further treatment on R_2 position on the ring gave the resulted compound as mentioned below.[4]

Sr no.	Numbering	R_2 substitution	Nomenclature
1	A6	4- OCH_3	N-[3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl] -N'-(6-fluoro-1,3-benzothiazol-2-yl)urea
2	A7	H	N-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-N'-(6-fluoro-1, 3-benzothiazol-2-yl)urea
3	A8	3-CH_3	N-[3-chloro-2-(3-methylphenyl)-4-oxoazetidin-1-yl]-N'-(6-fluoro-1,3-benzothiazol-2-yl)urea
4	A9	2-CH_3	N-[3-chloro-2-(2-methylphenyl)-4-oxoazetidin-1-yl]-N'-(6-fluoro-1,3-benzothiazol-2-yl)urea
5	A10	2-OCH_3	N-[3-chloro-2-(2-methoxyphenyl)-4-oxoazetidin-1-yl]-N'-(6-fluoro-1,3-benzothiazol-2-yl)urea

Anti-Tubercular Activity

The in-vitro biological assessment is carried out to evaluate the potential or activity of the drug compounds produced by Sibaji Sarkar et al., against the *Mycobacterium Tuberculosis* and to get the best suitable structure with high Anti-Tubercular activity. The test compounds were screened under the Lowenstein-Jensen method and the test strain of mycobacterium tuberculosis was used H37Rv strain(MTCC 200).[4,10,22] The medium was created by using Eggs aseptically(500ml),the content was then subjected to filtration process using a sterile muslin cloth, the mineral salt solution(containing 1.2g potassium phosphate,0.12g magnesium sulphate, 0.3g magnesium citrate, 1.8g/L asparagine,6 mL glycerol and 300mL of distilled water) and 4 ml of sterilized malachite green solution(2.0%) was added and mixed uniformly. The following mixer was dissolved using 1.5 ml DMSO solution and also used as diluting media and diluted to obtain 2000µg/ml of stock solutions. The 25µg/ml and 50µg/ml concentrations were made and an aliquot of 0.5 ml with 5 ml of Lowenstein-Jensen medium was transferred into McCartney bottles(opacity was adjusted by addition of sterile distilled water as per requirement) and was subjected into the vortex mixer, and was subjected to Inspissation process successively three times. The bottles were incubated for 3 days at the temperature of 75-80°C so that the contents inside the bottle gets solidify to prevent any misinterpretation while recording the data. This modified compounds were tested against the effectiveness on *Mycobacterium Tuberculosis* with assuming standard as Isoniazid and Rifampicin.[4,23,24]

Procedure for Inoculation

The inoculation was done in the screw cap test tubes, 1µg/ml of standard suspension diluted with 0.2 ml of inoculums and were subjected to incubation at 37°C in a slant position and the screw caps were tightened after 24-48hr because to allow the evaporation of the inoculum and then were subjected to incubation. The readings were noted after 28th and 56th day after inoculation process. The results after incubatory period was predicted by counting the magnification on slants and calculating the growth rate of *Mycobacterium Tuberculosis*.[4,25]

DISCUSSION

The in-vitro data received after conducting TLC, IR and ^{1}H NMR to the resulted compounds were confirmed by

elemental analysis and showed that, all compounds have the ability to inhibit the growth of *Mycobacterium Tuberculosis* at minimal inhibitory concentration. From the compounds A6- A10 the A6 compound was found to be more active or effective against *Mycobacterium Tuberculosis* H37Rv strain(MTCC 200). It showed zero percentage of growth in the following concentrations of 25 µg/ml and 50µg/ml of compound A6(N-[3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-N'-(6-fluoro-1,3-benzothiazol-2yl)urea).The methoxy group on the 4^{th} position of phenyl ring with the fluorine group at 6^{th} position substituted as (R) showed maximum activity. The indicated compounds showed significant Anti-Tubercular activity and the activity was compared with the reference drugs, Isoniazid and Rifampicin. The other compounds were not able to show desired activity because of their low penetration ability into the bacterium cell wall and poor partition coefficient. This data were consistent throughout the experimentation which resulted in Benzothiazole as a good anti-tubercular agent.

CONCLUSION

The benzothiazole parent ring structure belongs to a very important class of heterocyclic structure. with its wide range of biological and highly potent activities ,benzothiazole could be the key for the future synthesis of new drugs and hence all the researchers have diverted their attention to the benzothiazole synthesis and evaluation on its various pharmacological activities in different fields such as Anti-convulsant , Anti-tubercular, Anti-microbial, Anti-malarial, Anti-inflammatory, Anti-cancerogenic activity, etc. Several methods have been developed to synthesize this heterocyclic structure but out of which Sibaji Sarkar et.al., have developed a recent method with a modification on the benzothiazole which shows potent Anti-tubercular activity. The compound, N-[3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]-N'-(6-fluoro-1,3-benzothiazol-2-yl)urea shows good activity but with further research and various substitution could be the ideal drug for the treatment of tuberculosis. There were various methods developed on contrary to each other and had its own advantages and disadvantages over the period of time. However, there is a lot more scope in advancements for this compound in the future or as the research advances. the Nitrogen, Sulfur and carbon structure holds the very special place in the nature and could be beneficial to future.

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