

Synthesis of Imidazole-containing Derivative as New Potential anti-tubercular

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ABSTRACT

Imidazole, being a core molecule in many biological systems viz ; histidine, histamine and biotin and being an active component in several drug molecules like losartan, olmesartan, eprosartan and trifenagrel [15-16], has attracted attention in recent years. They play a central role in the process of discovery of drugs because of their wide range of chemical reactivity and manifold biological activities. Different substituted imidazoles are shown to be antibacterial, antiinflammatory, anticonvulsant, antiulcer, antiviral, antitumour, antioxidant and antitubercularagents. The synthesized compounds are found in good yield and highly sensitive compounds, 1-{3-[1-(4-Chloro-4H-pyrazol-3-ylmethyl)-piperidin-4-ylamino]-6-fluoro-3H-imidazol-5-yl}-ethanone is more reliable than streptomycine and shows 94.9% resistance power with MTB bacteria.

Keywords: - Imidazole Derivative, Mycobacterium tuberculosis, MTB Bacteria

INTRODUCTION

Tuberculosis (TB) is considered to be the most infectious disease with a sizable portion of the total world population infected with this disease. The above- mentioned proportion includes both latent and active patients. When the infected person does not produce any evident symptoms, the disease is said to be in latent form. While when the disease is with symptoms it is said to be the active form of disease. TB is a communicable and airborne bacterial disease caused by mycobacterium, which once inside the body can invade any system such as kidney, brain, spines etc. Bacteria causing TB, is a slow-growing bacteria and it grows best in an area where lot of blood and oxygen is available. Therefore, it generally attacks the lungs. TB is one of the disease which causes mass death worldwide. As per global TB report published in 2023, an estimated 10 million people were said to be affected with TB in which 90% were adult, 65% male and 10% people with HIV. Around 74% of the infected person worldwide are from Africa and 56% are from developing countries like India, Indonesia, Pakistan, and Bangladesh (Figure 1). Number of death due to TB is unacceptably higher than one can think [1].

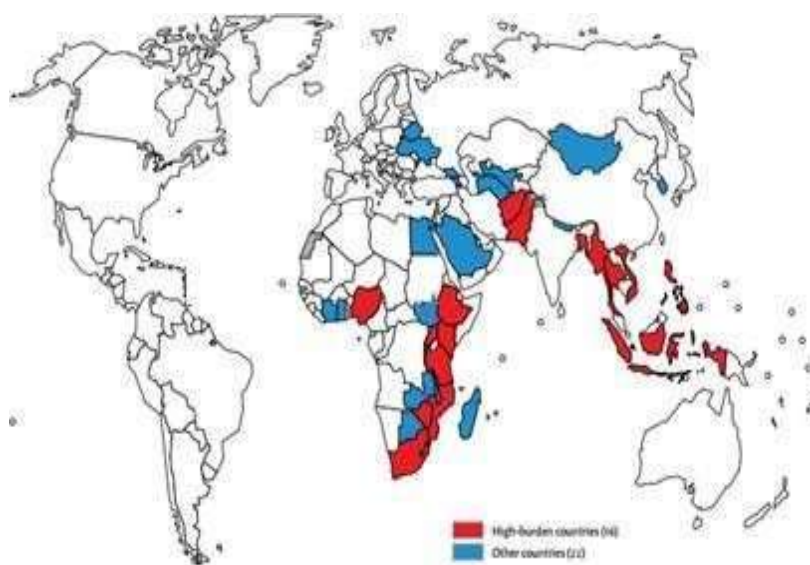


Figure 1: Countries with High Burden of TB

TB is one of the infectious diseases which can communicate from diseased person to another healthy person. The disease is airborne and major source of infection is a person suffering from pulmonary or laryngeal TB which expectorates bacilli. The most common way to get exposed to this disease is when one healthy person is near an infected person and the infected person either sneezes, coughs or through the transmission of respiratory secretions without taking precaution or preventive measures.

The microorganism causing this infection is a tiny bacterium which is hard to see through naked eye and is known as *Mycobacterium tuberculosis*. Chances to get infected with TB generally depend on the duration of exposure to this bacterium, so people at high risk are especially those who live or work with the infected person [2]. *Mycobacterium tuberculosis* is a group of species that include *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti* and *Mycobacterium canetti*, all these species are capable of causing TB in humans but it is generally caused due to *Mycobacterium tuberculosis*. Beside the above mentioned species several other species like *Mycobacterium leprae* cause leprosy and there are some non TB mycobacteria which can also cause some clinical manifestations similar to those like that of TB [3,4]. There are number of signs and symptoms which reveal the exposure to tubercular bacterium and a lot of them are self-reported which includes a cough, shortness of breath or difficulty of breathing (dyspnoea), night sweats, coughing up of blood (haemoptysis), chest pain and other symptomatic characters which can be observed are: e.g. anemia, tachycardia, an axillary temperature higher than that of 37⁰C, body mass index comparatively lower etc. [5, 6]. Exposure to *Mycobacterium tuberculosis* does not necessarily show positive sign and symptoms of TB and in most of the cases they do not transmit the infection, but pulmonary TB is a origin of *Mycobacterium tuberculosis* bacilli which can infect other part of the body like kidney, bone, skin etc. [7]. TB can be detected by locating *Mycobacterium tuberculosis* through laboratory diagnosis either by traditional methods like that of smear microscopic identification, culture and phenotypic identification[8].

Anti-TB drugs are classified into five groups based on evidence of efficacy, potency, drug class and experience of use [1]. All first line anti TB drug names has a standard three letter and/or a single letter abbreviation. The first line anti-TB drugs are ethambutol (EMB/E) [2, 3], isoniazid (INH/H) [4, 5], pyranamide (PZ/Z) [6-9], rifampicin (RIF/R) [10-13], and streptomycin (STM/S) [14-15] given for 6 months second line drugs (SLDs) are those that are less effective than the first line or have some side effect. The unavailability of a drug in many developing countries also makes it SLD. If the treatment fails as a result of bacterial drug resistance, or intolerance to one or more drug, SLDs are used. The SLDs are only used to treat disease that is resistant to first line therapy (i.e. extensively drug-resistant tuberculosis (XDR-TB) or multidrug resistant tuberculosis (MDR-TB) [16]. Further, the SLDs are divided into six classes; these are (i) aminoglycosides (amikacin/AMK, kanamycin/KM), (ii) polypeptides (capreomy-cin, viomycin, enviomycin) (iii) fluoroquinolones (ciprofloxacin/CIP, moxifloxacin/MXF, levofloxacin), (iv) thioamides (prothionamide, ethionamide), (v) cycloserine, and (vi) ter-izidone and p-ainosalicylic acid/PAS/P.

The third line drugs are either not very efficient or their effectiveness is not yet established. This includes rifabutin, macrolides: e.g., clarithromycin (CLR); linezolid (LZD); thin-acetazone (T); thioridazine; arginine; vitamin D; bedaquiline. Rifabutin is effective, but is not included on the WHO list because for most developing counties. It is impractically expensive [17]. WHO recommended directly observed treatment short Course (DOTS) anti-TB therapy involves the administration of four drugs: INH, RIF, PZA and EMB or SM. Treatment with these so called first line drugs is carried out initially over 2 months, leading to the destruction of bacteria in all growth stages, after which treatment continues with RIF and INH alone 4 months, where any residual dormant bacilli are eliminated by RIF and any remaining RIF-resistant mutants are killed by INH [18].

Namrata and co-workers [19] identified benzyloxy phenyl butenyl azoles as anti-TB agents. Trivedi et al. carried out synthesis of pyrazolo (3,4-d) pyrimidine derivatives and assessed antimycobacterial active-ities against Mtb using MABA. Compounds exhibited best results (1.2 mg/mL) when compared with first line drugs such as INH and RIP. SAR study reveals, the presence of 2-chloro-, 3-chloro-, 4-methyl- and 2-chloro-5-sulfonyl substitu-ents markedly enhances anti-TB activity [20].

An efficient domino approach for the synthesis of novel pyrrolo (2, 3, 4-kl) acridin-1-one derivatives has been established by Huiyuan et al. [21]. This reaction represents the first facile conversion of an isatin to a pyrrolo (2, 3,4-kl) acridin-1-one via a C-N bond cleavage reaction without the need for a multistep reaction process anti-tuberculosis drug induced Hespatoxicity was studied by Jaime R. and others. [22].

Cerebrospinal fluid drug concentrations and the treatment of tuberculosis meningitis were studied by Gordon et al. [23]. In the substituted cinnolinepyrazole series, the compounds which are halogen mainly chloro, Bromo and Fluoro substituted were showed potent antibacterial, anti-inflammatory and antifungal activity then other compounds, especially chloro substituted compounds showed more potent anti-inflammatory activity among all the substituted cinnolinepyrazole compounds.

RESEARCH METHODOLOGY

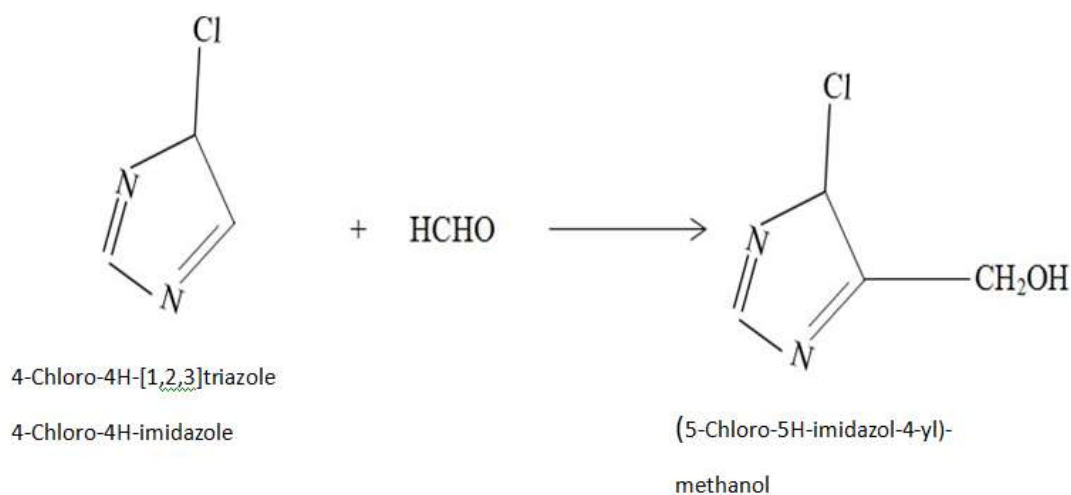
Synthesis of Imidazole Derivative

For the synthesis of imidazole derivative 4-Chloro-4H-[1,2,3]triazole 4-Chloro-4H- imidazole to react with the formaldehyde to produce (5-Chloro-5H-imidazol-4-yl)- methanol white powder. In next process (5-Chloro-5H-imidazol-4-yl)-methanol ($C_6H_5N_2Cl$) reacted with cyclohexamine in presence of H_2SO_4 to give 1-(5-Chloro-5H-imidazol-4-ylmethyl)-azepan-4-ylamine and finally 1-(5-Chloro-5H-imidazol-4-ylmethyl)-azepan-4-ylamine; compound with methane reacted with piperidine to give 1-{3-[1-(4-Chloro-4H-imidazole-3-ylmethyl)-piperidin-4-ylamino]-6-fluoro-3H-imidazol-5-yl}-ethanone.

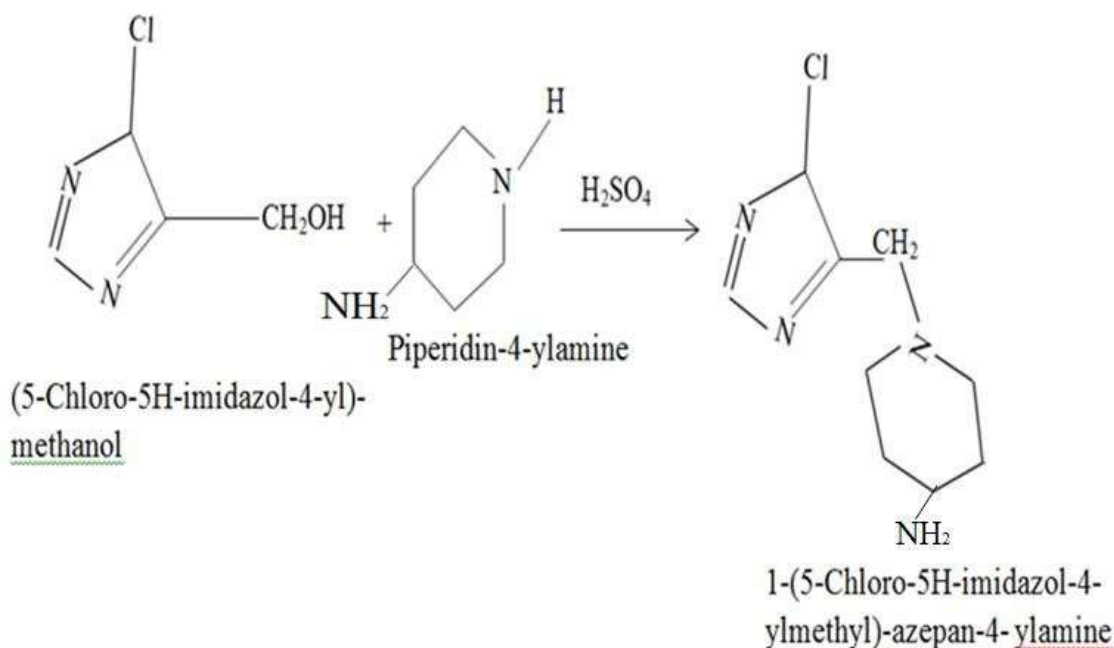
For the synthesis of imidazole derivative in scheme 1 we used imidazole and HCHO for synthesis of chloro derivative than the chloro derivative reacted with piperidin derivative in scheme 2 and we get intermediate and further it reacted with imidazole to give final derivative with yield of 10.6 gm.

1-{3-[1-(4-Chloro-4H-imidazole-3-ylmethyl)-piperidin-4-ylamino]-6-fluoro-3H-imidazol-5-yl}-ethanone

Scheme-I



Scheme-II



Scheme-III

1-(5-Chloro-5H-imidazol-4-ylmethyl)-azepan-4-ylamine; compound with methane

1-{3-[1-(5-Chloro-5H-imidazol-4-ylmethyl)-piperidin-4-ylamino]-6-fluoro-3H-imidazol-5-yl}-ethanone

Compound

RESULT AND DISCUSSION

The synthesized compound are found in good yield and highly sensitive compounds 1-{3-[1-(5-Chloro-5H-imidazol-4-ylmethyl)-piperidin-4-ylamino]-6-fluoro-3H-imidazol-5-yl}-ethanone occurs as 10.6 gm.

1-{3-[1-(4-Chloro-4H-imidazole-3-ylmethyl)-piperidin-4-ylamino]-6-fluoro-3H-imidazol-5-yl}-ethanone is compared with dose of streptomycin is represent in table.

Table: Efficiency of Compound with Dose of Streptomycin

S. No.	Dose of streptomycin	Streptomycin % efficiency	Compound (IV) % efficiency
1	0.2 µg/ml	76.7	77.48
2	0.5 µg/ml	77.3	77.98
3	1.0 µg/ml	78.35	79.18
4	1.5 µg/ml	79.24	80.30
5	2.0 µg/ml	79.37	80.97
6	2.5 µg/ml	80.29	81.72
7	3.0 µg/ml	84.34	85.99
8	3.5 µg/ml	85.38	86.42
9	4.0 µg/ml	85.27	87.19
10	5.5 µg/ml	86.32	89.98
11	6.0 µg/ml	88.36	90.43
12	6.5 µg/ml	90.36	91.19
13	7.0 µg/ml	92.44	93.29
14	7.5 µg/ml	93.39	93.92
15	8.0 µg/ml	94.37	94.99
16	8.5 µg/ml	94.49	95.72
17	9.0 µg/ml	94.66	95.76

Graphical represent of Compound with Dose of Streptomycin Efficiency

CONCLUSION

Imidazole compounds is very effective and capable to reduce problem and side effects of gastro, severe neurotoxicity, peripheral neuropath, central nervous system, ototoxicity, Hypotoxicity etc.

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