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Short communication

Synthesis, antimycobacterial screening and ligand-based molecular docking studies on novel pyrrole derivatives bearing pyrazoline, isoxazole and phenyl thiourea moieties

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ABSTRACT

We report here the synthesis, antibacterial and antitubercular evaluation of 61 novel pyrrolyl derivatives bearing pyrazoline, isoxazole and phenyl thiourea moieties. Molecular docking was carried out on enoyl ACP reductase from *Mycobacterium tuberculsosis* using Surflex-Dock, which is one of the key enzymes involved in type II fatty acid biosynthetic pathway of *Mycobacterium tuberculosis*, an attractive target for designing novel antitubercular agents. Docking analysis of the crystal structure of ENR performed using Surflex-Dock in Sybyl-X 2.0 software indicates the occupation of substituted pyrrolyl derivatives into hydrophobic pocket of InhA enzyme. Compounds **9b** and **9d** exhibited the highest antitubercular activity almost close to isoniazid (0.4 μg/mL) with a MIC value of 0.8 μg/mL. All other compounds showed the good activity with a MIC value of 6.25–100 μg/mL. The compounds were further tested for mammalian cell toxicity using human lung cancer cell-line (A549) and were nontoxic. Some compounds exhibited inhibition activities against InhA.

1. Introduction

Tuberculosis (TB) is a chronic disorder caused by five closely related mycobacteria such as *Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti and Mycobacterium canetti*. Among these, *Mycobacterium tuberculosis* (*M. tuberculosis*) by far the most causative agent for TB. TB is an infection caused by slow-growing bacteria in parts of the body having high level of blood and oxygen is often found in lungs, called pulmonary TB. The disease also spreads to other parts of the body, called as extra-pulmonary TB that may be latent or active. In other case, treatment of the active TB is more complex due to multi-drug resistance (MDR-TB), extensive-drug resistance (XRD-TB) and HIV infection. The MDR-TB is a type of TB which occurs once MTB strain turns resistant to the most efficient anti-TB drugs i.e. rifampin and isoniazid. In 2013, 0.45 million people developed MDR-TB worldwide and there were 0.21 million deaths resulting from MDR-TB. XDR-TB occurs when MTB strain is resistant to at least isoniazid and rifampin in addition to being resistant to one of the fluoroquinolones, as well as resistant to at least one of the second line injectable drugs i.e. amikacin, kanamycin or capreomycin. XDR-TB was found worldwide in 100 countries by the end of 2013. About, 9% of MDR-TB cases lead to XDR-TB which is related with higher mortality rate than MDR-TB. World Health Organization (WHO) estimated 9.0 million people with cases of TB in 2013 of which 1.5 million died and 360,000 of them were affected with HIV-positive. TB is a foremost public health problem in India. India accounts for one-fifth of the world TB incident cases. Every year about 2 million people in India develop TB, of which around 0.87 million are

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[1] Authors dedicate this work on the eve of retirement of Dr. K. V. S. N. Raju after 37 years of service at IICT, Hyderabad, India.

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infectious cases. Furthermore, it is estimated that yearly around 330,000 Indians die due to TB. The MTB generally attacks the lungs, spine, kidney, and brain. Therefore, if TB is not treated properly, it can be severe and fatal.

Over the past decades, several anti-tubercular (anti-TB) drugs have been developed see Fig. 1, but drug-resistance issue has not been solved. There is thus a tremendous need to develop new anti-TB drugs that are active against both acute and chronic growth phases of mycobacterium to stop all forms of drug resistant-TB [1,2]. In this perspective, many studies have been made on targeting the cell wall of mycobacteria.

Mycolic acid biosynthesis has been carried out [2] by numerous successive enzymatic cycles equivalent to Fatty Acid Synthase (FAS) systems viz., FAS I and II. Mycolic acid is a unique signature fatty acid, which is a core constituent of the mycobacterial cell wall present in fatty acid synthase system of *M. tuberculosis.* InhA, the enoyl acyl carrier protein reductase (ENR) from *M. tuberculosis* is the key enzyme for type II fatty acid synthesis (FAS II), which catalyses NADH-dependent reduction of 2-trans-enoyl-ACP (acyl carrier protein) to yield NAD+ and reduced enoyl thioester-ACP substrate, which in turn, helps the synthesis of mycolic acid.

Chalcone is a central core for many important biological compounds that are synthesized by aldol condensation reaction between substituted aryl ketones and aromatic aldehydes in the presence of sodium hydroxide as a catalyst. These undergo variety of chemical reactions to produce innumerable heterocyclic compounds that are used as intermediates to prepare drugs with therapeutic value. Literature reveals that chalcone derivatives from natural and synthetic analogs exhibit diverse pharmacological activities such as anti-TB, anti-inflammatory, anti-cancer, anti-neoplastic, anti-bacterial, anti-fungal, anti-malarial, anti-viral, anti-allergic and estrogenic [3–9]. On the other hand, isoxazole derivatives constitute a class of nitrogen and oxygen containing five membered heterocyclic compounds that are the important class of heterocyclic pharmaceuticals due to their wide spectrum of biological activities, including potent and selective antagonism of NMDA receptor [10], anti-HIV activity [11], anti-tuberculosis, anti-bacterial, antibiotic, anti-fungal, anti-cancer, ulcerogenic activities and also used as COX-2 inhibitors and anti-inflammatory drugs [12–16].

Pyrazolines have been widely used as anti-tubercular [17], anti-bacterial [18] and anti-cancer [19] agents, as these have a broad spectrum antimicrobial activity and hence, can be explored further. The most prominent compounds featuring pyrazoline nucleus are sulphaphenazole, ampyrone, phenazone and propylphenzone see Fig. 2a. Some of the reported pyrazoline skeletals which exhibit

Abbreviations: TB, Tuberculosis; MDR, Multi-Drug resistant; JATA, Japan Anti-Tuberculosis Association; NM4TB, New Medicines for Tuberculosis; iM4TB, Innovative Medicines for Tuberculosis.

Fig. 1. Milestone in TB drug research.