

Novel Anti-Tubercular Compounds Based on Substituted 1,3,4-Thiadiazole are on the Uptrend

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Tuberculosis (TB) is one of the greatest global health threats with about 8.6 million cases during 2012. The WHO estimated nearly 450,000 cases of multidrug-resistant tuberculosis (MDR-TB) in 2012 compared to 62,000 cases in 2011. With growing number of drug resistance problems, there is a need for discovering new anti-tubercular agents. Attempts by scientists around the globe are directing toward establishing structure-activity relationships between the drugs and their pharmacological activity as well as synthesizing new entities.

The *Mycobacterium tuberculosis* (*M. tuberculosis*) is responsible for this deadly disease that affects one-third of the world population. The Human Immunodeficiency Virus (HIV) may be another reason for the prevalence of TB, causing 50% of deaths among the HIV-infected patients due to co-infection with *M. tuberculosis*, thereby affecting the collapse of immune system. As per the statistics of WHO, two million people are likely to die every year with at least nine million people getting infected on a yearly basis. This has created interests among the scientists all around the world to develop new active forms of TB.

One of the most attractive antimicrobial drug targets is the bacterial fatty acid synthesis pathway (FAS-II). This has created much interest in recent years to develop novel chemical entities based on isoniazid (INH). Among the enzymes involved in FAS-II, the NADH-dependent enoyl acyl carrier protein reductase (ENR) encoded by *Mycobacterium* gene *InhA* is the key catalyst in mycolic acid biosynthesis. Several investigations from our group over the past decade have established that *InhA* is the primary molecular target for INH, which is a frontline drug for more than some 40 years that was used for treating TB. The INH-NADH adducts function as a potent inhibitor of *InhA* and other *InhA* inhibitors.

This editorial note presents a short overview of the progress made in developing novel types of compounds useful for the treatment of TB and these are evaluated in our laboratories through a series of experimental protocols. These new anti-TB drugs were synthesized based on 1,3,4-thiadiazoles as its analogs that are the well known antimicrobial agents due to the presence of toxophoric moiety, which exhibits a broad spectrum of biological activities. The recently developed pyrrolyl aryloxy thiadiazole derivatives as the effective anti-tubercular (anti-TB) have been well characterized and tested for their activities [1-5].

One of the design strategies for these newly developed anti-TB compounds is based on the hybridization. Azole derivatives have shown interesting anti-TB and antimicrobial activity, inhibiting the bacteria by blocking lipid biosynthesis and/or additional mechanisms. In our ongoing efforts of designing new entities, we have utilized the concept of hybridization between 1,3,4-thiadiazole and pyrrole moieties, to demonstrate that new anti-TB agents can be designed. In one of our study, 5-oxopyrrolidine was mapped with 1,3,4-thiadiazole moiety, whereas carboxamide was mapped with methoxy group (AOCH₂), while hydrophobic moieties like cyclohexyl and 3,5-dichlorophenyl were mapped with pyrrole and o/m/p substituted phenyl derivatives.

On the other hand, substitution in 2- and 5-positions of thiadiazole ring and the compounds obtained thereof showed high lipophilicity, hypothesizing that this property could facilitate the passage of these compounds through *M. tuberculosis* bacterial membrane. The new derivatives were synthesized following the Paal-Knorr pyrrole synthesis [1].

The computational strategies including three-dimensional quantitative structure-activity relationship (3D-QSAR) and molecular docking studies were performed on these as well as many other such compounds [1-5] that correlated well within silico analysis that are shown to be the potential target of pyrrolyl aryloxy thiadiazole derivatives. In all our recent studies, we have demonstrated Surflex-Docking and comparative molecular field analysis (CoMFA) for activity prediction of pyrrolyl aryloxy thiadiazole derivatives that exhibit in vitro anti-TB activity.

In another aspect of our study, we have developed polymeric carriers for INZ delivery under varying pH conditions and these results are quite encouraging to increase the release time of the drug. For instance, the coated Interpenetrating blend microparticles of chitosan and guar gum have effectively controlled released the INH in intestine [6]. Also, some novel pH- and temperature-responsive blend microspheres of sodium alginate and PNIPAAm-g-GG for controlled release of INZ have shown improved slow release profiles [7].

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Received March 27, 2015; Accepted March 29, 2015; Published April 05, 2015

Citation: Aminabhavi TM, Joshi SD (2015) Novel Anti-Tubercular Compounds Based on Substituted 1,3,4-Thiadiazole are on the Uptrend. *J Pharma Care Health Sys* 2: e129. doi:10.4172/2376-0419.1000e129

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