

Pyrrole Analogs as Novel Organic Molecules to Combat Tuberculosis

Joshi SD and Aminabhavi TM*

Department of Pharmaceutical Chemistry, SET's College of Pharmacy, Dharwad, 580 002, India

*Corresponding Author: Tejraj M. Aminabhavi, Department of Pharmaceutical Chemistry, S.E.T's College of Pharmacy, Dharwad, 580002, India, Tel: 09449821279; E-mail: aminabhavit@gmail.com

Received date: Jul 23, 2016; Accepted date: Jul 26, 2016; Published date: Jul 29, 2016

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Editorial

Synthetic organic chemists are the most imaginative scientists as they keep developing novel molecules that have immense applications in medicinal chemistry for curing many diseases. In bioengineering area, organic semiconductors have created a major breakthrough as biosensors, organic conducting polymers or even thermally stable polymers have applications in aerospace engineering etc. All these achievements are the attributes of their heterocyclic nature exhibiting a variety of properties.

In the past decade, we have been actively involved in developing novel organic structures exhibiting essential biological characteristics that help to cure many diseases. One such attributes is in the area of alleviating the problem of a deadly diseases such as tuberculosis (TB), which is regarded as one of the severe universal problems. TB is a communicable disease that spreads through air and caused by different strains of mycobacteria, primarily by the Mycobacterium tuberculosis and the disease affects mainly lungs in addition to other parts of the human body. The disease is responsible for the second foremost reason of death worldwide and is a major cause of death particularly in HIV patients. World Health Organization (WHO) estimates that nearly nine million people that were affected with TB in 2013, of which 1.5 million died and 360,000 of them were found to be HIV-positive. This suggests that TB is more aggressive with the diminishing of body immune mechanism.

What steps were taken by the scientists to overcome this deadly disease? In the past, even though organic chemists have developed quite a few anti-tubercular (anti-TB) drugs have been developed; nevertheless, drug-resistance aspect has not been completely resolved. This has created a tremendous gap in our scientific knowledge and scientists around the world have been curious 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.

Pyrrole, a five membered heterocyclic compound, has been reported for its various chemotherapeutic activities. Pyrrole is found in the animal and plant empire because of its involvement as the heme and vitamin B₁₂ in animal cells and as a subunit of chlorophyll in plant cells. It was first isolated in 1857 from the products of bone pyrolysis and identified as a biologically relevant compound after when it was recognized as a structural fragment of heme and chlorophyll. Even before 1950s, pyrrole and its various derivatives were found to exhibit in vitro antitubercular activity, but intense research efforts were not pursued. Lupin company was the first to synthesize a chain of pyrrole derivatives, one of which (LL3858) is presently in clinical development for the treatment of TB.

The chemistry of pyrroles has fascinated many researchers due to their varying biological activities and their potential as biological and

pharmacological agents. This prompted us to develop novel pyrrole derivatives that have immense applications as anti-TB agents. In our major research efforts on developing anti-TB drugs, we have designed novel entities based on pyrrole as a template in our synthetic protocol [1,2]. Our investigations include the well-designed molecular modeling studies in conjunction with our own laboratory experiments [3-4].

In our ongoing efforts to synthesize new potential inhibitors of InhA enzyme bearing pyrrole, aryloxy and -C=N-NHCO- bridge have been used as core fragments compared to PT70 and TCL [5-7]. We then have synthesized these along with 2D and 3D-QSAR studies [8,9]. During our studies on Paal-Knorr and Williamson ether reactions on amine and phenol, we have focused our attention on pyrrole with aryloxy/ethoxy/propoxy fragments as the core structures of the newly designed inhibitors. Molecules containing aryloxy/ethoxy/propoxy and pyrrole as structural fragments have been widely explored. We also have reported a quantitative pharmacophore mapping tool that is valuable to identify physicochemical and structural requirements for ligand binding and biological activity aspects along with the molecular docking investigations on 1-(4-(2/3-aryloxyethoxy/propoxy)phenyl)-1H-pyrroles as inhibitors of InhA and M. tuberculosis [10]. Some examples are given in Figure 1.

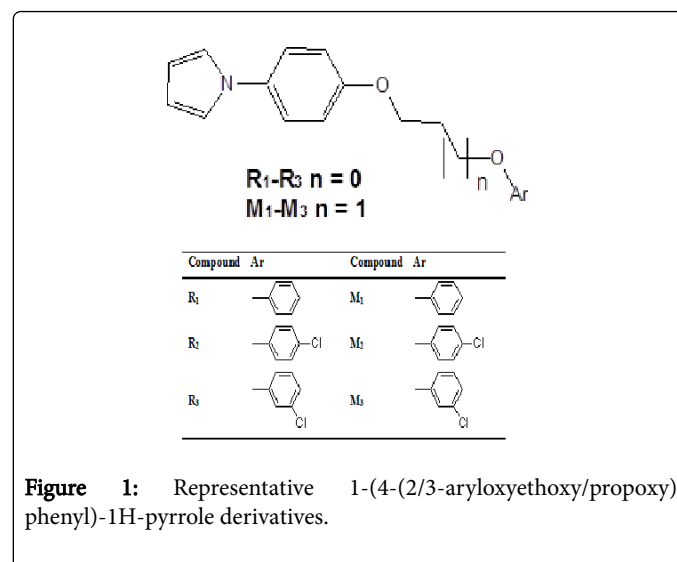
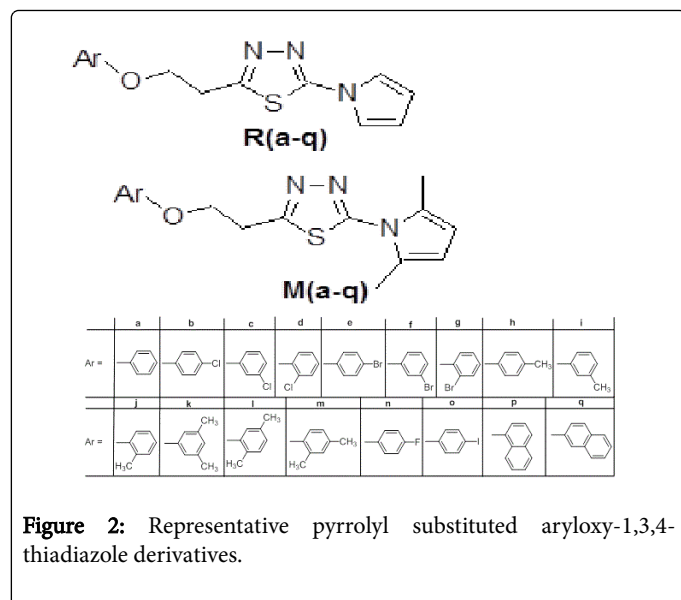


Figure 1: Representative 1-(4-(2/3-aryloxyethoxy/propoxy)phenyl)-1H-pyrrole derivatives.

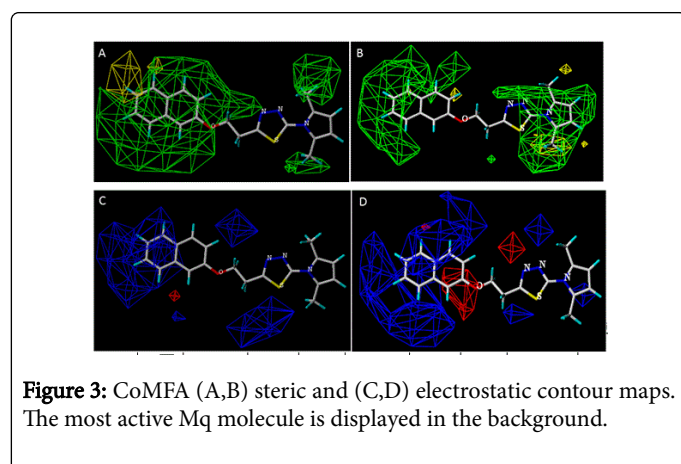
In another feature, our study involved the synthesis of novel pyrrolyl hydrazones and their copper complexes and characterized using analytical and spectral techniques to show that tetrahedral geometry for Cu(II) complexes exhibit biological activities. Biological activities of hydrazones have been assessed to understand the role of metal ion on their biological activity and the effect of pyrrolyl hydrazones. In vitro

an anti-TB activity against *M. tuberculosis* of the metal complexes exhibited the highest anti-TB activity that is quite close to rifampicin drug [11].

We also developed sixty-eight novel pyrrolyl substituted aryloxy-1,3,4-thiadiazoles synthesized by three-step optimization process (see typical examples in Figure 2).



Three-dimensional quantitative structure-activity relationships (3D-QSAR) were established for pyrrolyl substituted aryloxy-1,3,4-thiadiazole series of InhA inhibitors using comparative molecular field analysis (CoMFA) as shown in Figure 3. In vitro testing of ligands using biological assays substantiated the efficacy of ligands that were screened through in silico methods. [12].



Our investigations gave us enough confidence to summarize that the chemistry of pyrroles is versatile and exhibit a much larger promise in a number of areas than many other similar class of compounds. Most of the substitutions to the parent moiety were explored in order to evaluate pharmacological and biological profiles of pyrroles, many of which have shown promising activities.

All this does not come to a round table closure, but science grows indefinitely. There are still much broader possibilities and avenues that are to be explored further on this versatile and promising moiety as the amount of diverse molecular targets are existing for pyrroles. The exploitation of such compounds is growing in the field of medicinal chemistry at a much rapid pace to solve the human health and hygienic problems. Finally, we find that the docking studies have much similarity for those calculated from quantum packages used earlier [13,14].

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