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Design and synthesis of novel mycobacterial ATP synthase inhibitors against both replicating and non-replicating *M. tuberculosis*

In recent years, tuberculosis (TB) chemotherapy is dependent on drugs targeting bacterial metabolism with bactericidal action having no effect on dormant or latent or metabolically inactive bacilli that target cell division. The ATP synthase is a ubiquitous enzyme in energy metabolism due to its involvement in the generation of sufficient amount of ATP and/or in generating a proton motive force (PMF) in mycobacteria during adverse conditions of low oxygen environment and nutrient deficiency. This pivotal role of ATP synthase is targeted by the diarylquinoline TMC207 that kills *Mycobacterium tuberculosis*. Utilizing the state-of-the-art medicinal chemistry approach the quinoline class of aryl-sulfonamides has been identified as potent, orally bioavailable and selective mycobacterial ATP synthase inhibitors. Among a series of compounds synthesized which were effective in vitro on ATP synthase, the lead compound [N-(7-chloro-2-methylquinolin-4-yl)-N-(3-((diethylamino) methyl)-4-hydroxyphenyl)-2,3-dichlo-r obenzene sulfonamide] exhibited excellent selectivity (mycobacterium ATPase IC_{50} = 0.51 µM, mammalian ATPase IC_{50} >100 µM, and selectivity >200) and is also active in the hypoxic culture of non replicating *M. tuberculosis* at 100 µg/mL (32-fold of its MIC) as compared to positive control isoniazid [approximately 0.2 log10 reduction in CFU at 5 lg/mL (50-fold of its MIC)]. Docking of the best compound on homology modeled ATP synthase revealed the participation of the protonated tertiary amine and hydroxyl group to interact with the carboxylate oxygen of Glu61 that is similar to TMC207. The study provides a deep understanding about the structural requirements for ATP synthase inhibitors helpful in the discovery of novel chemical entities.

Biography

Anil K Saxena is actively involved in the domain of Medicinal Chemistry & CADD, drug discovery and development research. He has 45 years of research experience with 200 research publications, 19 reviews/articles in books and/monographs, 72 patents and has delivered >180 invited lectures, chaired >45 sessions. He is Fellow of Royal Society of Chemistry, UK, Editorial Board Member of different prominent journals like, *Medicinal Chemistry Research, SAR* and *QSAR in Environmental Research*, online International journal *ARKIVOC*, and Patent Evaluator: Current Drugs, UK. He is also series Editor for book series *"Topics in Medicinal Chemistry"* published by Springer Verlag.

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