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Designing antitubercular agents exploring Mycobactin biosynthetic patway

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Developing newer antitubercular agents having novel chemical scaffold targeting novel proteins is essential to face the threat due to MDR and XDR tuberculosis. Mycobactin is a hexadentate ligand secreted by the tubercular bacilli to overcome the iron stress that it experiences once inside the host cell. Inhibiting any enzyme in the biosynthetic pathway will be novel approach in developing a newer chemotherapeutic agent against tuberculosis. Our group is working on mimics of phenyloxazoline portion of mycobactin. We identified, 3-(2-hydroxyphenyl)-5-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (1) as a potential inhibitor of Mycobacterium tuberculosis under iron stressed condition (Bioorg Med Chem Lett, 2008, 18(8):2662-8). We hypothesize that this compound as a putative inhibitor of phenyloxazoline synthetase, an enzyme in the mycobactin biosynthetic pathway catalysing the condensation/cyclization salicylic acid and serine. Compound 1 is a racemic mixture and their component isomers were found to be equipotent in nature (unpublished data). Further modification at the 1N of pyrazoline replacing the –C(=S)-NH2 group with –C(=O)-NH2, –C(=NH)-NH2 and –C(=O)-CH3 resulted in the reduction/loss of activity (unpublished data). With this background, analogue of compound 1 with different substitutions on the phenyl ring at 5th position of pyrazoline were designed, synthesized and evaluated for the antitubercular activity under iron stress using Mycobacterium smegmatis. Compounds were also subjected to in vitro cytotoxicity studies. Potent compound from this series is currently under screening against Mycobacterium tuberculosis and we are also planning for similar studies against resistant strains of Mycobacterium tuberculosis.

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