Biological evaluation of a novel nitroimidazo-oxazole derivative, IIIM-MCD-019 against Mycobacterium tuberculosis and its in vivo efficacy


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Background: One of the nitroimidazo-oxazole derivatives, IIIM-MCD-019 discovered in-house was assessed for detailed biological activities against various strains of Mycobacterium tuberculosis. Further, in-vitro studies such as synergistic activity, intracellular MIC, time kill kinetics, cell cytotoxicity, microsomal stability and pharmacokinetics were performed. In-vivo efficacy of the compound was tested alone and in combination.

Methods & Materials: MIC was determined against H37Rv, mono-resistant as well multidrug resistant (MDR) isolates and streptomycin starved M. tuberculosis (ss18b). Synergistic studies were performed with rifampicin, isoniazid and ethambutol using microdilution checkerboard assay. Time kill of the compound was performed at MIC to 8X MIC against M. tuberculosis H37Rv. Intracellular MIC was performed in macrophage J774 cell lines using RPMI-1640 media. Cell cytotoxicity of the compound was assessed on HepG-2 cell lines using glucose and galactose containing media to identify mitochondrial cytotoxicity. Microsomal stability of the compound was performed using rat liver microsomes. PK parameters were assessed in mice by standard protocols and In-vivo efficacy was assessed in intranasal model using Balb/c mice for 4 weeks.

Results: IIIM-MCD-019 exhibited an MIC ranged between 0.12-0.25 μg/ml for all strains except for NRP which is streptomycin starved. When combined with rifampicin, isoniazid and ethambutol individually, it showed synergistic effect with rifampicin and isoniazid and additive effect with ethambutol and it has intracellular MIC of 1μg/ml. Time kill studies show that killing rate of this compound is comparable to the best in class drug candidate i.e. delamanid (OPC-67683). The compound did not exhibit cytotoxicity either in glucose or in galactose and found to be ≥ 99% stable in rat liver microsomes. Pharmacokinetic profile in terms of Cmax & AUC0-1 also shows 1.5 times increase (Cmax of 0.54 μg/ml and of 7.42 μg/ml h) compared delamanid. In in-vivo model, the compound showed 1 log reduction in cfu wrt early control and better efficacy when combined with combination of rifampicin and isoniazid.

Conclusion: IIIM-MCD-019 is a novel compound from nitroimidazo-oxazole scaffold and has a potent antiTB properties. The compound has shown better PK profile than the drug candidate, however further optimization of structure is required to achieve better in-vivo efficacy.

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