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MCD-017: Potential Candidate from the Class of Nitroimidazoles to Treat Tuberculosis

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Abstract : New chemotherapeutic compounds against multidrug-resistant Mycobacterium tuberculosis (Mtb) are urgently needed to combat drug resistance in tuberculosis (TB). Apart from in-vitro potency against the target, physiochemical properties and pharmacokinetic properties play an imperative role in the process of drug discovery. We have identified novel nitroimidazole derivatives with potential activity against mycobacterium tuberculosis. One lead candidates, MCD-017, which showed potent activity against H37Rv strain (MIC=0.5µg/ml) and was further evaluated in the process of drug development. Methods: Basic physicochemical parameters like solubility and lipophilicity (LogP) were evaluated. Thermodynamic solubility was determined in PBS buffer (pH 7.4) using LC/MS-MS. The partition coefficient (Log P) of the compound was determined between octanol and phosphate buffered saline (PBS at pH 7.4) at 25°C by the microscale shake flask method. The compound followed Lipinski's rule of five, which is predictive of good oral bioavailability and was further evaluated for metabolic stability. In-vitro metabolic stability was determined in rat liver microsomes. The hepatotoxicity of the compound was also determined in HepG2 cell line. In vivo pharmacokinetic profile of the compound after oral dosing was also obtained using balb/c mice. Results: The compound exhibited favorable solubility and lipophilicity. The physical and chemical properties of the compound were made use of as the first determination of drug-like properties. The compound obeyed Lipinski's rule of five, with molecular weight < 500, number of hydrogen bond donors (HBD) < 5 and number of hydrogen bond acceptors(HBA) not more then 10. The log P of the compound was less than 5 and therefore the compound is predictive of exhibiting good absorption and permeation. Pooled rat liver microsomes were prepared from rat liver homogenate for measuring the metabolic stability. 99% of the compound was not metabolized and remained intact. The compound did not exhibit cytoxicity in hepG2 cells upto 40 µg/ml. The compound revealed good pharmacokinetic profile at a dose of 5mg/kg administered orally with a half life (t1/2) of 1.15 hours, Cmax of 642ng/ml, clearance of 4.84 ml/min/kg and a volume of distribution of 8.05 l/kg. Conclusion : The emergence of multi drug resistance (MDR) and extensively drug resistant (XDR) Tuberculosis emphasize the requirement of novel drugs active against tuberculosis. Thus, the need to evaluate physicochemical and pharmacokinetic properties in the early stages of drug discovery is required to reduce the attrition associated with poor drug exposure. In summary, it can be concluded that MCD-017 may be considered a good candidate for further preclinical and clinical evaluations.

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