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Novel Nitroimidazoles with promising anti-tubercular activity: Optimizing ADME/Tox properties to increase drug discovery success

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New compounds against tuberculosis are urgently needed to combat the crisis of drug resistance in tuberculosis (TB). We have identified a nitro-dihydro-imidazooxazole analog, IIIM-114 as a new anti-tubercular agent with a MIC of 0.06 μg/ml against H37Rv. The structural properties of the compound were studied using Schrodinger Software. Since, IIIM-017 followed Lipinski's and Verber's rule, based on these properties was chosen for further investigation. A rapid and sensitive liquid chromatography (LC) coupled to tandem mass spectrometry (MS-MS) and electrospray ionization (ESI) method was developed and validated for the quantification of IIIM-114 in mice plasma. The chromatographic separation was accomplished using a gradient mode and the mobile phase comprised of acetonitrile and 0.1% formic acid in water. The flow rate used was 0.6 ml/min on a C18e high performance Chromolith column. The MS-MS ion transitions used were 467>227.0, 467>338. The entire study was validated for accuracy, precision, linearity, range, selectivity, LLOQ, recovery and matrix effect in accordance with the FDA guidelines of method validation. The method was applied successfully to determine solubility, lipophilicity, microsomal stability and PK. Lipophilicity was determined experimentally as Octanol-PBS partition coefficient (log P) and the compound exhibited a log P of -0.08. The method was also applied successfully in determining microsomal stability wherein the compound was found to be very slightly metabolized by RLM. The pharmacokinetics was performed on male Balb/c mice at 5 mg/kg (p.o) and exhibited acceptable *in-vivo* pharmacokinetic parameters. Thus, IIIM based on acceptable drug-like properties should undergo further investigation.

Biography

Gurleen Kour is currently a PhD scholar and is currently working as a Senior Research Fellow (SRF) at Indian Institute of Integrative Medicine, Council of Scientific and Industrial Research, India. She is working under the guidance of Dr. Zabeer Ahmed, Principal Scientist at Indian Institute of Integrative Medicine, India. She is currently working in the areas of drug metabolism and pharmacokinetics of novel candidates with promising anti-tubercular activity for the selection of lead drug candidates. She has also published her work in Elsevier and American Chemical Society.

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