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Simultaneous determination of meptazinol and its major metabolites by LC - MS/MS in human plasma

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An efficient and sensitive method based on liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS) has been developed for the simultaneous determination of meptazinol and its three metabolites, 7-oxomeptazinol (M1), 3-hydroxyethylmeptazinol (M2) and N-desmethylmeptazinol (M3), in human plasma. After enzymolysis and protein precipitation, chromatographic separation within 6.0 min was obtained from Welch Ultimate XB-C18 column using gradient elution. Meptazinol-d3 was used for the internal standard and the analytes were simultaneously determined by using the following [M+H]+ transitions: m/z 234.2→107.2 for meptazinol, m/z 248.2→107.1 for M1, m/z 250.1→107.1 for M2 and m/z 220.2→107.0 for M3. The calibration curves were prepared in the concentration ranges of 100-100000ng/mL for meptazinol, 5-5000ng/mL for M1, 5-500ng/mL for M2 and 50-20000ng/mL for M3. The relative errors ranged from -6.85% to 3.33%, -5.40% to 4.30%, -5.80% to 2.80% and -4.27% to 8.89% for meptazinol, M1, M2 and M3, respectively. This method has been successfully applied to the determination of meptazinol and its metabolites in plasma of eight healthy volunteers who had a single oral administration of 400 mg hydrochloride meptazinol capsule.

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The identification, binding mode and prospective chemical structural features of NS3 helicase inhibitors as potential anti-Zika virus drugs: Insights from comprehensive molecular and thermodynamic simulations

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The Zika virus has been ravaging South America over the past year, with recent reports showing dissemination of the virus on a global scale. Evolving modes of transmission have allowed the spread of the disease over continents, creating a pandemic status. Evidence on the virus has already been linked to irreversible chronic central nervous system (CNS) conditions. The concerns of the scientific and clinical community are the consequences of Zika viral mutations, thus suggesting the urgent need for viral inhibitors. Rapid rational drug design and discovery research is fundamental in the production of potent inhibitors to destroy the virus completely. Herein, using hybrid ligand virtual screening, shape similarity- and a pharmacophore-based approach, combined with molecular dynamics and post dynamics analysis were applied to identify potential new leads targeting the Zika NS3 helicase, with a detailed analysis of its binding modes. The top ranked compounds from the shape similarity-based library (L121, $\Delta G_{bind=}$ -28.7482 kcal/mol) and pharmacophore-based library (L542, $\Delta G_{bind=}$ -20.2271 kcal/mol) possess comparatively better binding affinities than the reference molecule, ivermectin (ΔG_{bind}= -18.0694 kcal/mol). Both top identified hits, L121 and L542 showed similar binding mode at the active site as the prototype, ivermectin. Hydrophobic and electrostatic interactions seemed to be the prominent binding forces that hold these ligands at the active binding site of the NS3 protein. A set of chemical structural features that can be used as a guide in the design of potential NS3 helicase inhibitors for not only Zika viral targets, but rather numerous flavivirus targets.

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