عنوان مقاله:

Chemoinformatic Design of Phthalazinone Analogues as Novel Dengue Virus NS۲B-NS۳ Protease Inhibitors with Enhanced Pharmacokinetics

محل انتشار:

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خلاصه مقاله:

Dengue fever is the most common and important arthropod-borne viral illness in humans. However, no effective medications or vaccinations exist to prevent this condition. The dengue viral (DENV) protease non-structural protein (NS) ۲B-۳ is a possible target for antiviral treatment. Based on the lead compound reported in our earlier study, eight phthalazinone analogues were designed using a structure-based drug design approach, which involved systematic alterations to the various positions of the benzyl ring bearing carbamate pharmacophore and carbamate terminal chain length of the lead. These compounds were also evaluated for in silico ADME properties and drug-likeness. The molecular docking scores of the design ligands were greater than the template's binding score, ranging from-۸.۹ to-۹.۶۰ kcal/mol, and also higher than those of the Ribavirin and the co-crystalized protease ligand, which were -۸.۹۰, -۶.۱۰, and -۸.۱۰ kcal/mol, respectively. All of the developed ligands satisfied Lipinski's requirements with good synthetic accessibility (۳.۰۷–۳.۴۱) and a better ADME profile than the template, indicating that they were highly bioavailable and simple to synthesize in the laboratory. Phthalazinone derivatives with higher binding scores (-۹.۰ to -۹.۶۰ kcal/mol) were designed and found to interact well with the DENV NS۲B-NS۳ protease. The compounds also have significantly improved pharmacokinetic and ADME properties compared to their parent template. The designed compounds could be used as a starting point for developing potent DENV NS۲B-NS۳ protease inhibitors with suitable pharmacokinetic .and ADME properties

کلمات کلیدی:

Dengue fever, Carbamate, ADME, Docking, DENV, Binding score