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Thioguanine-based DENV-2 NS2B/NS3 protease inhibitors: Virtual screening, synthesis, biological evaluation and molecular modelling

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Abstract

Dengue virus Type 2 (DENV-2) is predominant serotype causing major dengue epidemics. There are a number of studies carried out to find its effective antiviral, however to date, there is still no molecule either from peptide or small molecules released as a drug. The present study aims to identify small molecules inhibitor from National Cancer Institute database through virtual screening. One of the hits, D0713 (IC₅₀ = 62 μM) bearing thioguanine scaffold was derivatised into 21 compounds and evaluated for DENV-2 NS2B/NS3 protease inhibitory activity. Compounds 18 and 21 demonstrated the most potent activity with IC₅₀ of 0.38 μM and 16 μM, respectively. Molecular dynamics and MM/PBSA free energy of binding calculation were conducted to study the interaction mechanism of these compounds with the protease. The free energy of binding of 18 calculated by MM/PBSA is -16.10 kcal/mol compared to the known inhibitor, panduratin A (-11.27 kcal/mol), which corroborates well with the experimental observation. Results from molecular dynamics simulations also showed that both 18 and 21 bind in the active site and stabilised by the formation of hydrogen bonds with Asn174.

Keywords

KeyWords Plus: DENGUE VIRUS PROTEASE; SERINE-PROTEASE; NS3 PROTEASE; ANTIVIRAL ACTIVITY; PEPTIDE-HYBRIDS; DISCOVERY; TYPE-2; IDENTIFICATION; OPTIMIZATION; FLAVONOIDS

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