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Insight parameter drug design for human β -tryptase inhibition integrated molecular docking, QSAR, molecular dynamics simulation, and pharmacophore modelling studies of α -keto-[1,2,4]-oxadiazoles
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Abstract

Dengue hemorrhagic fever (DHF) is severe dengue with a hallmark of vascular leakage. β -tryptase has been found to promote vascular leakage in DHF patients, which could be a potential target for DHF treatment. This study aims to develop a theoretical background for designing and selecting human β -tryptase inhibitors through computational studies. Thirty-four α -keto-[1,2,3]-oxadiazoles scaffold-based compounds were used to generate 2D-QSAR models and for molecular docking studies with β -tryptase (PDB Code 4A6L). In addition, molecular dynamics (MD) simulation and molecular mechanics generalised born surface area (MM-GBSA) analysis on the binding of the reported most active compound, compound 11e, towards β -tryptase were performed. Finally, a structure-based pharmacophore model was generated. The selected 2D-QSAR models have statistically proven good models by internal and external validation as well as the y-randomization test. The docking results of compound 11e showed lower CDOCKER energy than the 4A6L co-crystallised ligand and a similar binding pattern as the 4A6L co-crystallised ligand. From molecular dynamics simulation, 4A6L in compound 11e bound state has RMSD below 2 Å throughout the 500 ns simulation, indicating the docked complex is stable. Besides, MM-GBSA analysis suggested the 4A6L-compound 11e docked complex (-66.04 Kcal/mol) is structurally as stable as the 4A6L-native ligand co-crystallized structure (-66.84 Kcal/mol). The best pharmacophore model identified features included hydrogen bond acceptor, ionic interaction, hydrophobic interaction, and aromatic ring, which contribute to the inhibitory potency of a compound. This study supplied insight and knowledge for developing novel chemical compounds with improved inhibition of β -tryptase. Communicated by Ramaswamy H. Sarma. © 2023 Informa UK Limited, trading as Taylor & Francis Group.

Author Keywords

docking; molecular dynamics; pharmacophore; QSAR; β -tryptase inhibitors

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