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In-silico investigation of new triazole derivatives as inhibitors of DPP4 enzyme

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***Abstract*—The dipeptidyl peptidase 4 (DPP4) is a serine protease enzyme that is present at the surface of all cells and body fluids. DPP4 plays an important role in glucose metabolism by cleaving a dipeptide from N-terminal of incretin hormones. Inhibition of DPP4 increases the activity of incretin hormones. Therefore, insulin production continues for a longer time. Due to the fact that incretin hormone-based therapies do not have some of common side effects of other antidiabetic drugs, recently, DPP4 inhibitors have been recognized as a new treatment for type2 diabetes. In this study, the inhibitory effect of three 1,2,3-triazole-5-carboximideamide derivatives on DPP4 enzyme was evaluated. For this purpose, molecular docking performed for three new inhibitors ([N-benzyl-4-phenyl-1H-1,2,3-triazole-5-carboximidamide]: compound 1, [N- (4-chlorophenyl) -4-phenyl-1H-1,2,3-triazole-5-carboximidamide]: compound 2, [N- (4-methylbenzyl) -4-phenyl-1H-1,2,3-triazole-5-carboximidamide]: compound 3) and sitagliptin as a lead compound using AutodockVina software and PDB code:6B1E. Then, molecular dynamic simulations for all complexes were performed in 70 ns by Gromacs software and Amber ff99SB/GAFF force field for protein/ligands, respectively. Then, structural parameters (RMSD, Rg and number of hydrogen bonds) and thermodynamic parameter (binding free energy) were investigated. To assess overall stability, the RMSD analysis of DPP4 enzyme respect to initial structure of enzyme was performed. This analysis showed that all simulated systems reached equilibrium within 25 ns and lasted 45 ns. The average value of RMSD indicated more stability of DPP4-sitagliptin complex (0.148 nm) relative to other complexes: DPP4-1 complex (0.179 nm), DPP4-2 complex (0.181 nm) and DPP4- 3 complex (0.192 nm). By calculating the binding free energy, it was found that the compound 1 has the most favorable binding free energy after sitagliptin. The binding free energy values for simulated complexes are as follows: DPP4-sitagliptin complex (-89.5 kcal/mol), DPP4-1 complex (-68.9 kcal/mol), DPP4-2 complex (-68.08 kcal/mol) and DPP4- 3 complex (-53.68 kcal/mol). Also, for all complexes, the major favorable contributors are van der Waals and electrostatic terms. In addition, compound 1 has the highest number of hydrogen bonds with the active site of the enzyme. These finding shows among the studied compound, compound 1 is the best inhibitor for DPP4.**

***Keywords*—Molecular docking, Molecular dynamics simulation, DPP4, T2D, 1,2,3-triazole-5-carboxamidamide**

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