Penapisan virtual berbasis farmakofor, penambatan molekul dan simulasi dinamika molekuler inhibitor histone deacetylase kelas IIA dari database herbal Indonesia = Pharmacophore based virtual screening molecular docking and molecular dynamic simulation of histone deacetylase class IIA inhibitor from Indonesian herbal database / Linda Erlina

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Abstrak

Senyawa yang berperan sebagai inhibitor HDAC kelas IIa telah banyak dikembangkan sebagai obat antikanker, antiinflamasi, penyakit Huntington, human papiloma virus dan antidiabetes. Senyawa inhibitor HDAC antara lain golongan hydroxamic acid, peptida siklik, asam alifatik dan benzamide. Metode yang digunakan untuk mencari senyawa inhibitor HDAC kelas IIa salah satunya adalah melalui pendekatan farmakofor 3D berbasis ligan. Senyawa aktif HDAC4 dan HDAC7 dibuat ke dalam dataset training dan test untuk pembuatan dan validasi model farmakofor 3D berbasis ligan menggunakan LigandScout 4.09.1. Model farmakofor terbaik digunakan untuk penapisan virtual terhadap database herbaldb. Senyawa hit yang diperoleh selanjutnya dilakukan penambatan molekul menggunakan AutoDock4Zn, simulasi dinamika molekuler dan perhitungan nilai MMGB/PBSA menggunakan AMBER12. Berdasarkan hasil validasi model farmakofor 3D berbasis ligan, dipilih model farmakofor terbaik yaitu model 6 dan 10 HDAC4 dan model 1 HDAC7. Berdasarkan hasil penapisan virtual diperoleh 6 senyawa hit yaitu artocarpesin, avicularin, dimboa glucoside, eriodictin, luteolin dan mirabijalone c. Proses simulasi dinamika molekul selama 10ns menunjukan bahwa senyawa yang memiliki aktivitas terbaik yaitu senyawa artocarpesin HDAC4 , mirabijalone c dan eriodictin HDAC7. Asam amino esensial HDAC4 meliputi Asp196, Asp290 dan His198 untuk interaksi ZBG. Asam amino esensial HDAC7 meliputi Asp707, Asp801 dan His709 untuk interaksi ZBG. .....Currently, compounds as the inhibitor of HDAC class IIa are developed as anticancer, antiinflammation, Huntington disease, human papilloma virus and antidiabetes. Inhibitor compounds of HDAC are mainly divided into hydroxamic acid, cyclic peptide, aliphatic acid and benzamide. 3D pharmacophore ligand based approached was used to found inhibitor compounds of HDAC class IIa. Active compounds of HDAC4 and HDAC7 were divided into training and test dataset for build and validation of 3D pharmacophore ligand based models using LigandScout 4.09.1. The best pharmacophore model, was used for virtual screening against herbaldb database. After this steps, hit compounds would be docking using AutoDock4Zn, molecular dynamic simulation, and MMGB PBSA calculation score using AMBER12. Based on the results of 3D model validation pharmacophore based ligand, selected models are models of best pharmacophore 6 and 10 HDAC4 and model 1 HDAC7. Based on the results of virtual screening, 6 hit compounds were obtained such as artocarpesin, avicularin, dimboa glucoside, eriodictin, luteolin and mirabijalone c. Molecular dynamics simulation process for 10ns indicate that the compound has the best activity are artocarpesin for HDAC4, mirabijalone c and eriodictin for HDAC7. Essential amino acids for HDAC4 include Asp196, Asp290 and His198 for ZBG interactions. Essential amino acids for HDAC7 include Asp707, Asp801 and His709 for ZBG interaction.