Penapisan berbasis framakofor untuk menemukan inhibitor host retikulum endoplasma alpha-glukosidase II sebagai terapi dengue = Virtual screening based on pharmacophore to discover host endoplasmic reticulum alpha-glucosidase II inhibitor as dengue therapy / Elsafira Ariavianti

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Abstrak

ABSTRAK
Dengue merupakan salah satu penyakit serius pada manusia yang disebabkan oleh infeksi virus dengue (DENV). Namun, pengembangan senyawa antiviral DENV sering menghadapi masalah dikarenakan belum ada obat yang efektif menangani semua jenis serotipe DENV. Penghambatan melalui host enzim virus yang terlibat dalam siklus hidup DENV dapat menjadi pendekatan potensial dalam penemuan obat dengue dan juga menghindari resisten antiviral. Host retikulum endoplasma (RE) alpha-gukosidase II adalah salah satu target enzim dalam host RE DENV yang berperan penting dalam pelipatan glikoprotein DENV. Dalam penelitian ini digunakan sekitar 67.609 senyawa bahan alam yang telah diketahui aktivitas biologisnya dari pangkalan data InterBioScreen (IBS) sebagai kandidat inhibitor host RE alpha-gukosidase II. Proses penapisan untuk mendapatkan inhibitor terbaik dilakukan melalui tiga tahap simulasi penambatan molekul yaitu virtual screening, rigid docking, dan flexible docking. Titik farmakofor untuk proses penapisan diperoleh dari analisis Protein-Ligand Interaction Fingerprint (PLIF) menggunakan delapan protein alpha-glukosidase II dengan ligan yang berbeda-beda. Berdasarkan proses penapisan tersebut, sebanyak 32 ligan memiliki nilai Root Mean Square Deviation (RMSD) dan Gbinding yang diinginkan, dan lima ligan memiliki interaksi molekul paling baik untuk menghambat host RE alpha-glukosidase II sebagai target enzim. Sifat farmakologi kelima ligan dianalisis melalui uji ADME-Tox menggunakan perangkat lunak Toxtree, SwissADME, admetSAR, dan pkCSM. Ligan terbaik yaitu STOCK1N-86400 memiliki sifat farmakologi terbaik, interaksi hidrogen terbanyak dengan asam amino penting Asp564, Asp640, dan Met565 pada situs aktif host RE alpha-glukosidase II, dan Gbinding paling rendah dibandingkan standar. Hasil simulasi dinamika molekul juga menunjukkan ligan tersebut stabil pada suhu 310K.
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ABSTRACT
Dengue is one of the crucial diseases in human caused by dengue virus (DENV) infection. However, the development of DENV antiviral is often facing a problem because no effective drug to treat infection caused by all DENV serotypes. The inhibition of enzyme host of virus involved in DENV life cycle can be a potential approach in dengue drug discovery, and also avoiding antiviral resistance. Host endoplasmic reticulum (ER) alpha-glucosidase II is one of the enzymes target in host DENV ER that plays an important role in the DENV glycoprotein folding. In this research, about 67.609 natural products that have been known for their biological activities were acquired from InterBioScreen (IBS) database as candidate host alpha-glucosidase II inhibitor. The screening process was done by three protocol of molecular docking simulation: virtual screening, rigid docking, and flexible docking. Pharmacophore features in screening were obtained from Protein-Ligand Interaction Fingerprint (PLIF) analysis using eight -glucosidase II proteins with

different ligands. Based on that screening process, about 32 ligands have a desirable value of Root Mean Square Deviation (RMSD) and Gbinding, and five ligands have a good molecular interaction to inhibit host ER alpha-glucosidase II as enzyme target. Pharmacological properties of the five ligands were analyzed through ADME-Tox test using Toxtree, SwissADME, admetSAR, and pkCSM software. The best ligand, STOCK1N-86400 has the best pharmacological properties, the highest number of hydrogen interaction with critical amino acids Asp564, Asp640, and Met565 in host ER alpha-glucosidase II active site, and the lower Gbinding from standard. The result of molecular dynamic simulation also showed that ligand is stable at a temperature of 310 K.