Analisis Selektivitas Isoform Reseptor Adenosin secara In Silico = Selectivity Analysis of Adenosine Receptor Isoforms In Silico

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Abstrak

Adenosin trifosfat (ATP) berfungsi sebagai sumber energi pada berbagai aktivitas seluler, seperti modulasi pelepasan neurotransmitter, menyebabkan vasokonstriksi dan vasodilatasi pada arteri dan vena, dan meregulasi pelepasan sitokin proinflamasi. Aktivitas adenosin dimodulasi oleh reseptor adenosin yang termasuk ke dalam G-coupled protein receptors(GCPR). Reseptor adenosin memiliki empat isoform, yaitu A1, A2A, A2B, dan A3 yang terdistribusi dalam berbagai jaringan tubuh dan menarik untuk ditinjau selektivitasnya. Selektivitas reseptor sebagai target obat perlu dilihat untuk memastikan efek farmakologis yang ditimbulkan lebih spesifik. Penelitian ini dilakukan secara in silico untuk mengetahui selektivitas obat terhadap struktur kristal reseptor adenosin A1 dan A2A, serta struktur A2B dan A3 yang didapatkan melalui pemodelan homologi. Pemodelan homologi didapatkan dengan perangkat lunak SWISS-MODEL kemudian di evaluasi strukturnya melalui Plot Ramachandran di laman PROCHECK. Penambatan molekuler dilakukan di AutoDock dalam perangkat lunak PyRx. Penambatan molekuler divalidasi dengan cara redocking melalui AutoDock. Parameter yang diperhatikan adalah nilai RMSD kurang dari 2 Ã. Interaksi antara reseptor-ligan diamati melalui perangkat lunak LigPlot+ dan PyMOL. Selektivitas dianalisis melalui indeks selektivitas dengan perbandingan konstanta inhibisi dua subreseptor. Selektivitas ligan terhadap reseptor A1 berada pada rentang 0,85 – 136,07; reseptor A2A0,0073 – 1,18; reseptor A2B 2,49 – 180,83; dan reseptor A3 0,021 – 1,79. Ligan yang paling selektif terhadap masing-masing reseptor secara in silico adalah : reseptor A1 capadenoson, reseptor A2A tozadenant, reseptor A2B BAY 60-6583, dan reseptor A3 piclidenoson.

.....Adenosine triphosphate (ATP) functions as an energy source in various cellular activities, such as modulating neurotransmitter release, causing vasoconstriction and vasodilation in arteries and veins, and regulating the release of proinflammatory cytokines. Adenosine activity is modulated by adenosine receptors included in the G-coupled protein receptors (GCPR). Adenosine receptors have four isoforms, namely A1, A2A, A2B, and A3 which are distributed in various body tissues and are interesting to review their selectivity. The selectivity of receptors as drug targets needs to be seen to ensure that the pharmacological effects produced are more specific. This study was conducted in silico to determine the selectivity of drugs to the crystal structures of adenosine receptors A1 and A2A, as well as the structures of A2B and A3 obtained through homology modeling. Homology modeling was obtained using SWISS-MODEL software and then its structure was evaluated through the Ramachandran Plot on the PROCHECK page. Molecular docking was carried out in AutoDock in PyRx software. Molecular docking was validated by redocking through AutoDock. The parameters of interest were RMSD values less than 2 Ã . The interaction between receptor-ligand was observed through LigPlot+ and PyMOL software. Selectivity was analyzed through the selectivity index by comparing the inhibition constants of two subreceptors. The selectivity of ligands to the A1 receptor was in the range of 0.85 - 136.07; A2A receptor 0.0073 - 1.18; A2B receptor 2.49 - 180.83; and A3 receptor 0.021 - 1.79. The most selective ligands to each receptor in silico were: capadenoson A1

receptor, tozadenant A2A receptor, BAY 60-6583 A2B receptor, and piclidenoson A3 receptor.