Modifikasi Oseltamivir sebagai Penghambat Neuraminidase Virus Influenza A Subtipe H1N1 melalui Docking dan Simulasi Dinamika Molekul

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Abstrak

Resistansi terhadap oseltamivir yang baru-baru ini dialami oleh virus pandemik 2009 menjadi masalah utama sejak munculnya resisten pada virus tersebut. Mutasi H274Y pada framework neuraminidase menyebabkan oseltamivir resisten terhadap strain H1N1. Penelitian ini bertujuan memodifikasi oseltamivir sebagai penghambat neuraminidase dalam melawan virus influenza A subtipe H1N1. 1232 ligan oseltamivir modifikasi dirancang berdasarkan sifatsifat residu asam amino pada sisi katalitik neuraminidase. Molekul-molekul ligan dan oseltamivir dan zanamivir sebagai ligan standar didocking berdasarkan pada energi terendah sebagai energi pengikatan dan interaksi ikatan pada sisi katalitik. Interaksi tiga ligan terbaik dievaluasi pada keadaan terhidrasi menggunakan simulasi dinamika molekul pada dua temperatur. Hasil docking menunjukkan ligan AD3BF2D (N-[(1S,6R)-5-amino-5- {[(2R,3S,4S)-3,4-dihydroxy-4-(hydroxymethyl) tetrahydrofuran-2-yl]oxy}-4- formylcyclohex-3-en-1-yl]acetamide-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate) memiliki energi pengikatan dan interaksi yang lebih baik dibandingkan ligan standar. Energi pengikatan yaitu -7,8885 kkal/mol dan memiliki 10 ikatan hidrogen sebagai interaksi terhadap sisi katalitik neuraminidase. Ligan AD3BF2D memiliki interaksi yaitu ikatan hidrogen dengan residu sisi katalitik sebagai afinitas ligan AD3BF2D terhadap neuraminidase pada simulasi dinamika molekul. Pada akhir simulasi temperatur 300 K terbentuk ikatan hidrogen dengan Glu278. Pada akhir simulasi temperatur 312 K terbentuk ikatan hidrogen dengan Glu278, Arg293, dan Arg293. Perbedaan konformasi enzim selama simulasi menunjukkan pengaruh adanya pelarut dan inhibitor. Hasil diatas menunjukkan bahwa ligan AD3BF2D dapat digunakan sebagai kandidat penghambat neuraminidase untuk melawan virus influenza A subtipe H1N1.

.....The emergence of oseltamivir resistance 2009 pandemic virus remains a major concern, since widespread oseltamivir resistance has been observed in seasonal H1N1 viruses recently. The H274Y neuraminidase mutation on the framework residue confers oseltamivir resistance on the currently circulating H1N1 strain. This research is focused on modification of oseltamivir functional groups as neuraminidase inhibitor to against influenza A virus subtype H1N1. 1232 oseltamivir modified ligands were designed base on properties of amino acid residues in catalytic site of neuraminidase. All molecules and oseltamivir as standard ligands were docked based on the lowest energy as the binding energy and the interaction binding to the catalytic site were analyzed. Three of the best ligands interaction were evaluated in the hydrate state using molecular dynamics simulations at two different temperatures. The docking result showed that AD3BF2D ligand (N-[(1S,6R)-5-amino-5-{[(2R,3S,4S)-3,4- dihydroxy-4-(hydroxymethyl) tetrahydrofuran-2-yl]oxy}-4-formylcyclohex-3-en-1- yl]acetamide-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate) has better values than oseltamivir as standard. Binding energy is -7.8885 kcal/mol and able to form 10 hydrogen bonds to the catalytic site of neuraminidase. AD3BF2D has interaction to form hydrogen bond with residue in catalytic site as the affinity of AD3BF2D ligand to the neuraminidase in molecular dynamics simulation. At the end simulation temperature of 300 K hydrogen bond was formed with Glu278 and at the end

simulation temperature of 312 K three hydrogen bonds were formed with Glu278, Arg293 and Arg293. Different conformation of enzymes which occur during simulation showed the dynamic behaviour of the presence of solvent and inhibitor. The results show that AD3BF2D ligand can be used as the candidate of neuraminidase inhibitor to against influenza A inhibitor virus subtype H1N1.