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Penapisan Virtual Senyawa Kandidat Inhibitor Enzim beta-ketoacyl-Acyl Carrier Protein (ACP) Synthase (KasA) dengan Fragment-Based Design untuk Terapi Tuberkulosis = Virtual Screening of beta-ketoacyl-Acyl Carrier Protein (ACP) Synthase (KasA) Inhibitor with Fragment-Based Design for Tuberculosis Therapy

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Abstrak

Tuberkulosis (TB) merupakan penyakit yang disebabkan oleh infeksi Mycobacterium tuberculosis (MTB). TB menular melalui udara dengan paru-paru sebagai target organ utama. Enzim beta-ketoacyl-Acyl Carrier Protein (ACP) synthase (KasA) berperan dalam biosintesis mycolic acid yang merupakan komponen pertahanan MTB. Thiolactomycin dipilih sebagai ligan inhibitor MTB. Penelitian ini bertujuan untuk menentukan struktur ligan hasil Fragment Based-Design yang memiliki potensi sebagai inhibitor enzim KasA pada MTB, memaparkan interaksi antara enzim KasA dengan ligan hasil modifikasi, dan menjelaskan proses farmakokinetika yang meliputi proses Absorpsi, Distribusi, Metabolisme, dan Ekskresi (ADME) maupun toksisitas pada ligan hasil modifikasi. Enzim didapatkan dari situs Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) dan ligan thiolactomycin dari situs PubChem. Penapisan sifat druglikeness terhadap ligan dilakukan melalui perangkat lunak OSIRIS DataWarrior. Perangkat lunak Molecular Operating Environment (MOE) 2014.09 digunakan untuk penapisan senyawa, penambatan molekul, dan modifikasi scaffold replacement terhadap thiolactomycin. Penambatan molekul dilakukan dengan metode penapisan virtual, rigid docking, dan induced-fit docking. Analisis terhada sifat ADMET dilakukan pada perangkat lunak OSIRIS DataWarrior dan Toxtree maupun situs pkCSM. Penelitian ini membuktikan bahwa senyawa hasil fragment-based design mampu menginhibisi enzim KasA didasarkan pada lima ligan terbaik dengan nilai RMSD, perubahan energi bebas Gibbs, dan pKi. Interaksi antara enzim KasA dengan ligan hasil fragment-based design terjadi pada asam amino Met213 dan Arg214. Selain itu, didapatkan senyawa 3063 dan 953 dengan sifat farmakologi terbaik.
.....Tuberculosis (TB) is a disease caused by infection of Mycobacterium tuberculosis (MTB). TB spreads via air transmission with lung as its primary target. beta-ketoacyl-Acyl Carrier Protein (ACP) synthase (KasA) enzyme acts in mycolic acid biosynthesis, which has a significant role in MTB virulence. Thiolactomycin was chosen as MTB ligand inhibitor. This research aims to define fragment-based design ligand structure that has a potential as KasA enzyme in MTB, define the interaction between KasA enzyme and modified enzyme, and describe pharmacokinetics process including Adsorption, Distribution, Metabolism, and Excretion as well as toxicity of the modified ligand. KasA enzyme was obtained from Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) and thiolactomycin ligand was downloaded from PubChem. Screening of ligand druglikeness was done using OSIRIS DataWarrior. Molecular Operating Environment (MOE) 2014.09 software was operated to screen, dock, and run scaffold replacement towards thiolactomycin. Molecular docking methods used were virtual screening, rigid docking, and induced-fit docking. ADMET analysis was done using OSIRIS DataWarrior and Toxtree software as well as pkCSM site. This research has proven that fragment-based design compounds were able to inhibit KasA enzyme based on the RMSD value, change of Gibbs free energy binding, and pKi of five

best ligands. Interaction between KasA enzyme and fragment-based design ligand occurred in Met213 and Arg214 amino acids. Meanwhile, compound 3063 and 953 were considered as best pharmacological compounds.