Desain Inhibitor *Pf*DHFR baru Berbasis Senyawa Turunan 4-benziloksi-2-trikloromethilkuinazolina: Pendekatan *Computer-Aided Drug Design*

Radite Yogaswara
21/489532/SPA/00826

INTISARI

Salah satu tantangan utama dalam pengembangan obat antimalaria adalah resistensi yang muncul akibat mutasi pada enzim *Plasmodium falciparum dihydrofolate reductase* (*Pf*DHFR), khususnya mutasi empat kali lipat (*quadruple mutant*) yang mengurangi efektivitas inhibitor konvensional. Senyawa turunan 4-benziloksi-2-trikloromethilkuinazolina (4b2tK) telah menunjukkan potensi sebagai kandidat inhibitor, namun kajian komputasi yang mengintegrasikan model hubungan kuantitatif struktur-aktivitas (HKSA) dua dimensi (2D) dan tiga dimensi (3D), penambatan molekul, simulasi dinamika molekul, serta prediksi profil farmakokinetik dan toksisitas belum tersedia secara komprehensif. Penelitian ini bertujuan mengembangkan dan mengoptimalkan senyawa 4b2tK sebagai inhibitor selektif terhadap enzim mutan *Pf*DHFR melalui pendekatan kimia komputasi terintegrasi.

Penelitian ini meliputi penyusunan dan validasi model HKSA-2D dan HKSA-3D menggunakan 27 turunan 4b2tK melalui metode MLR dan PLS, penambatan molekul pada *Pf*DHFR mutan dengan *Yasara Structure* (AMBER14), serta simulasi dinamika molekul 100 ns untuk menilai stabilitas kompleks. Prediksi ADME, *drug-likeness*, dan toksisitas dilakukan secara *in silico* menggunakan SwissADME. Hasil analisis menunjukkan bahwa model HKSA yang dibangun memiliki validitas statistik tinggi ($R^2_{training}$ = 0,94; R^2_{test} = 0,99; Q^2 = 0,87) dengan dukungan validasi eksternal dan uji Y-*randomization*. Tiga kandidat terbaik yaitu senyawa 4-[(quinolin-2-yl)methoxy]-2-(trichloromethyl)quinazoline (**S10**), 4-[(1H-indol-6-yl)methoxy]-2-(trichloro-methyl)quinazoline (**S23**), dan 3-methyl-4-(((2-(trichloromethyl)quinazolin-4-yl)oxy)methyl)phenol (**S64**) teridentifikasi memiliki aktivitas antimalaria tinggi dengan nilai IC_{50} prediksi < 2 µM, energi pengikatan kuat sebesar –9,87 kkal/mol, interaksi stabil dengan residu penting pada *Pf*DHFR, serta profil farmakokinetik dan *drug-likeness* yang baik dengan tingkat toksisitas sedang. Simulasi dinamika molekul mengonfirmasi kestabilan kompleks selama 100 ns, ditunjukkan oleh nilai RMSD < 2 Å dan energi ikatan yang konsisten. Senyawa **S10**, **S23**, dan **S64** terbukti memiliki afinitas kuat dan interaksi stabil dengan *Pf*DHFR mutan, didukung energi ikatan rendah serta profil ADME dan toksisitas yang baik, sehingga layak diajukan sebagai kandidat inhibitor antimalaria utama.

Kata kunci: HKSA, Penambatan Molekul, Simulasi Dinamika Molekul, ADME, *Pf*DHFR

Design of Novel *Pf*DHFR Inhibitors Based on 4-benzyloxy-2-trichloromethylquinazoline Derivatives: Computer-Aided Drug Design Approach

Radite Yogaswara
21/489532/SPA/00826

ABSTRACT

One of the major challenges in the development of antimalarial drugs is the emergence of resistance caused by mutations in the *Plasmodium falciparum* dihydrofolate reductase (*Pf*DHFR) enzyme, particularly the quadruple mutant, which diminishes the efficacy of conventional inhibitors. Derivatives of 4-benzyloxy-2-trichloromethylquinazoline (4b2tK) have demonstrated potential as candidate inhibitors; however, comprehensive computational studies integrating two dimensional (2D) and three dimensional (3D) quantitative structure activity-relationship (QSAR) models, molecular docking, molecular dynamics simulations, as well as pharmacokinetic and toxicity profile predictions, remain unavailable. This research aims to develop and optimize the 4b2tK compound as a selective inhibitor of mutant *Pf*DHFR through an integrated computational chemistry approach.

This study involves the development and validation of 2D-QSAR and 3D-QSAR models using 27 derivatives of 4b2tK through MLR and PLS methods, molecular docking against mutant *Pf*DHFR using Yasara Structure (AMBER14), as well as a 100 ns molecular dynamics simulation to evaluate complex stability. ADME prediction, drug-likeness evaluation, and toxicity assessments were performed in silico using SwissADME. The analysis results indicate that the constructed QSAR model exhibits high statistical validity ($R^2_{training}$ = 0,94; R^2_{test} = 0,99; Q^2 = 0,87), supported by external validation and Y-randomization. The three best candidates 4-[(quinolin-2-yl)methoxy]-2-(trichloromethyl)quinazoline (**S10**), 4-[(1H-indol-6-yl)methoxy]-2-(trichloro-methyl)quinazoline (**S23**), dan 3-methyl-4-(((2-(trichloromethyl)quinazolin-4-yl)oxy)methyl)phenol (**S64**) were identified as having strong antimalarial activity with predicted IC_{50} values < 2 µM, strong binding energy of –9.87 kcal/mol, stable interactions with key *Pf*DHFR residues, and favorable pharmacokinetic and drug-likeness profiles with moderate toxicity levels. The molecular dynamics simulation confirmed the stability of the complex over 100 ns, as indicated by an RMSD value < 2 Å and consistent binding energy. Compounds **S10**, **S23,** and **S64** demonstrated strong affinity and stable interactions with mutant *Pf*DHFR, supported by low binding energies and favorable ADME profiles and toxicities, indicating their potential as promising primary antimalarial inhibitor candidates.

Keywords: QSAR, Molecular Docking, Molecular Dynamics Simulation, ADME, *Pf*DHFR