INTISARI

Riset penemuan dan pengembangan obat merupakan sebuah proses yang mahal, memakan waktu, dan berisiko. Pendekatan dalam riset penemuan obat menjadi sangat krusial guna meminimalisasi risiko kegagalan dalam penelitian. *Computer-Aided Drug Design* (CADD) terbukti telah memberikan kontribusi penting bagi riset pengembangan obat, salah satunya *molecular docking*. Efikasi senyawa kurkumin yang potensial sebagai obat sedang terhambat dalam pengembangannya karena bioavailabilitasnya yang rendah. Profil farmakokinetika memiliki peran penting dalam bioavailabilitas suatu obat. Senyawa analog kurkumin sedang banyak dikembangkan guna memperbaiki sifat farmakoniketikanya. Penelitian ini dilakukan untuk mengkaji interaksi analog 2,5-Dibenzilidensiklopentanon tertarget P-glikoprotein dan enzim CYP2D6.

Metode yang dilakukan untuk mengkaji interaksi senyawa adalah *molecular docking* menggunakan perangkat lunak MOE melalui proses validasi pose dan validasi skoring. Data skor *docking* dan interaksi senyawa uji dengan residu kunci asam amino digunakan sebagai dasar penentuan pose logis. Selanjutnya, skor *docking* yang dihasilkan digunakan untuk menghitung nilai pIC_{50} melalui persamaan kurva baku *scoring*.

Proses *docking* dilakukan menggunakan protokol *docking* tervalidasi melalui validasi pose dan validasi skoring dengan nilai R^2 kurva regresi mencapai 0,8203. Berdasarkan hasil *docking* sederhana terhadap P-glikoprotein, diamati beberapa parameter yang menjadi dasar pemilihan pose logis yaitu skor *docking*, interaksi ligan-reseptor, dan kemiripan posisi geometri ligan uji terhadap *native ligand.* Senyawa analog 2,5-Dibenzilidensiklopentanon terbukti berpotensi menghambat aktivitas transporter P-glikoprotein pada situs aktif ikatan yang sama dengan *native ligand* Elacridar dengan konformasi L-*shape* atau membentuk rantai panjang yaitu pada senyawa uji dengan kode B2, B4, B6, B8, B9, B10, B11, B12, B15, dan B16. Sedangkan aktivitas inhibisi senyawa uji terhadap enzim CYP2D6 diamati melalui interaksi dengan asam amino, pose ligan secara geometris, dan skor *docking* yang dikonversi menjadi nilai IC_{50} prediktif. Konversi nilai skor *docking* menjadi profil pIC_{50} menunjukkan bahwa beberapa senyawa tergolong memiliki potensi aktivitas inhibisi tinggi dengan nilai IC50 <1µM yaitu pada senyawa uji dengan kode B1 (PGV-0), B6, B7, B11, B12, B13, dan B14.

Kata kunci: 2,5-Dibenzilidensiklopentanon, *molecular docking*, P-glikoprotein, CYP2D6, residu kunci

ABSTRACT

Research on drug discovery and development is a costly, time-consuming, and risky process. The approach in drug discovery research is crucial to minimize the risk of failure in research. Computer-Aided Drug Design (CADD) has proven to be a significant contributor to drug development research, one of which is molecular docking. The efficacy of curcumin compounds, which have potential as drugs, is hindered in their development due to their low bioavailability. Pharmacokinetic profiles play a crucial role in the bioavailability of a drug. Analog compounds of curcumin are being developed to improve their pharmacokinetic properties. This study was conducted to examine the interactions of the targeted analog compound 2,5-Dibenzylidene-cyclopentanone with P-glycoprotein and the enzyme CYP2D6.

The method used to examine the compound Interactions was molecular docking using MOE software through pose validation and scoring validation processes. Docking score data and compound interaction with key amino acid residues were used as the basis for determining logical poses. Furthermore, the docking scores generated were used to calculate the pIC_{50} value through a standard scoring curve equation.

The docking process was carried out using validated docking protocols through pose validation and scoring validation with a R^2 value of regression curve 0,8203. Based on the results of simple docking against P-glycoprotein, several parameters were observed that formed the basis for selecting logical poses, namely docking scores, ligand-receptor interactions, and the similarity of the test ligand geometric positions to the native ligand. The analog compound 2,5-Dibenzylidene-cyclopentanone was found to potentially inhibit P-glycoprotein transporter activity at the same binding active site as the native ligand Elacridar with an L-shape conformation or forming a long chain, specifically in test compounds with codes B2, B4, B6, B8, B9, B10, B11, B12, B15, and B16. Meanwhile, the inhibitory activity of the test compound against the enzyme CYP2D6 was indicated by interactions with amino acids, geometric ligand poses, and docking scores converted into predictive IC_{50} values. Converting docking score values into pIC_{50} profiles showed that several compounds were classified as having high inhibitory activity potential with IC_{50} values < 1µM, specifically in test compounds with codes B1 (PGV-0), B6, B7, B11, B12, B13, and B14.

Keywords: 2,5-dibenzylidenesiclopentanone, molecular docking, P-glycoprotein, CYP2D6, key residue