DESAIN TURUNAN KALKON BERBASIS FURAN SEBAGAI SENYAWA ANTIKANKER BERDASARKAN PENAMBATAN MOLEKUL TERHADAP PROTEIN EGFR DAN HER2

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INTISARI

Penambatan molekul senyawa turunan kalkon furan sebagai agen antikanker terhadap protein EGFR (PDB ID: 1M17) dan HER2 (PDB ID: 3RCD) telah dilakukan. Kalkon berbasis furan berperan aktif dalam penghambatan kanker kulit (A431) dan kanker paru-paru (A549 dan A541). Sementara itu, protein EGFR merupakan salah satu protein yang mempengaruhi kanker seperti kanker prostat (PC-3) dan payudara (MCF-7) sedangkan protein HER2 berpengaruh terhadap kanker payudara (MCF-7) dan paru-paru (A-549). Penelitian ini dilakukan dengan tujuan untuk melakukan optimasi geometri senyawa turunan kalkon furan, serta mengetahui afinitas ikatan dan konformasi antara senyawa yang didesain dengan protein EGFR dan HER2 untuk mendapatkan agen antikanker.

Validasi basis set untuk metode optimasi geometri dilakukan dengan variasi basis set STO-3G, 3-21G, 6-31G, dan 6-311G. Basis set terbaik digunakan untuk optimasi geometri senyawa kalkon furan yang diusulkan. Setelah dioptimasi, senyawa usulan masing-masing ditambatkan terhadap protein EGFR dan HER2. Perangkat lunak yang digunakan yaitu Autodock Vina dengan nilai *exhaustiveness* 264. Untuk protein EGFR, ukuran *grid box* diatur sebesar 46 × 46 × 46 $Å^3$ dengan koordinat 21,697; 0,303; 52,093, sedangkan untuk protein HER2 ukuran *grid box* diatur sebesar 44 × 44 × 44 $Å^3$ dengan kordinat 12,48; 2,964; 28,015.

Berdasarkan perbandingan panjang ikatan, himpunan basis untuk metode optimasi geometri 6-311G DFT/B3LYP dipilih untuk optimasi geometri senyawa kalkon berbasis furan yang diusulkan. Hasil penambatan molekul menunjukkan senyawa usulan kalkon C ((*E*)-1-(4-klorofenil)-3-(furan-2-il)prop-2-en-1-on) direkomendasikan sebagai senyawa penghambat antikanker terbaik dari senyawa usulan lainnya baik terhadap protein EGFR maupun HER2. Pada EGFR, kalkon C memberi interaksi spesifik berupa Met769 dengan afinitas ikatan sebesar -6,9 kkal/mol sedangkan pada HER2, interaksi spesifik berupa Thr862 dengan afinitas ikatan sebesar -7,0 kkal/mol. Selain kalkon C, kalkon B ((*E*)-1-(4-aminofenil)-3-(furan-2-il)prop-2-en-1-on) juga direkomendasikan sebagai agen antikanker terhadap protein HER2 dengan interaksi spesifik Met801 dan afinitas ikatan sebesar -6,7 kkal/mol.

Kata kunci: antikanker; EGFR; HER2; kalkon berbasis furan; penambatan molekul

DESIGN OF FURAN-BASED CHALCONE DERIVATIVES AS ANTICANCER COMPOUNDS BASED ON MOLECULAR DOCKING STUDIES AGAINST EGFR AND HER2 PROTEINS

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ABSTRACT

Molecular docking of furan-based chalcone derivatives as anticancer agents to EGFR (PDB ID: 1M17) and HER2 (PDB ID: 3RCD) proteins has been carried out. Furan-based chalcone plays an active role in the inhibition of skin cancer (A431) and lung cancer (A549 and A541). Meanwhile, EGFR protein is one of the proteins that affect cancers such as prostate (PC-3) and breast (MCF-7) cancers while HER2 protein affects breast (MCF-7) and lung (A-549) cancers. This research was conducted with the aim of optimizing the geometry of furan-based chalcone derivatives, as well as finding the binding affinity and conformation between the proposed compounds with EGFR and HER2 proteins to obtain anticancer agents.

Validation of basis set for the geometry optimization method was carried out with variations of the basis sets STO-3G, 3-21G, 6-31G, and 6-311G. The best one was used for geometry optimization of the proposed furan-based chalcone compounds. After optimization, each of the proposed compounds was docked to EGFR and HER2 proteins. The software used is Autodock Vina, with an exhaustiveness value of 264. For EGFR protein, the grid box size is set at 46 × 46 × 46 $Å^3$ with coordinates 21.697; 0.303; 52,093, while for HER2 protein the grid box size is set at 44 × 44 × 44 $Å^3$ with coordinates 12.48; 2,964; 28,015.

Based on the comparison between the bond lengths, basis set 6-311G DFT/B3LYP was selected for the geometry optimization of the proposed furan-based chalcone compounds. The molecular docking results showed the proposed compound chalcone C ((E)-1-(4-chlorophenyl)-3-(furan-2-yl)prop-2-en-1-on) was recommended as the best anticancer inhibitor compound for both against EGFR or HER2 proteins. In EGFR, chalcone C gave a specific interaction in the form of Met769 with a binding affinity of -6.9 kcal/mol, while in HER2, the specific interaction was Thr862 with a binding affinity of -7.0 kcal/mol. Besides chalcone C, chalcone B ((*E*)-1-(4-aminophenyl)-3-(furan-2-il)prop-2-en-1-on) was also recommended as an anticancer agent against HER2 protein with Met801 as specific interaction and binding affinity of -6.7 kcal/mol.

Keywords: anticancer; furan-based chalcone; EGFR; HER2; molecular docking