DESAIN TURUNAN PIRAZOLINA SEBAGAI SENYAWA ANTIKANKER KOLON BERDASARKAN ANALISIS HUBUNGAN KUANTITATIF STRUKTUR-AKTIVITAS TIGA DIMENSI (HKSA-3D) DAN PENAMBATAN MOLEKUL

Stephanus Satria Wira Waskitha
20/466494/PPA/06060

INTISARI

Kanker kolon merupakan salah satu penyebab utama kematian secara global. Turunan pirazolina merupakan senyawa yang memiliki berbagai aktivitas biologis, termasuk antikanker kolon. Desain turunan pirazolina sebagai senyawa antikanker kolon telah dilakukan berdasarkan analisis hubungan kuantitatif struktur-aktivitas tiga dimensi (HKSA-3D) dan penambatan molekul terhadap *epidermal growth factor receptor-tyrosine kinase* (EGFR-TK). Penelitian ini bertujuan untuk mendesain senyawa turunan pirazolina baru berdasarkan persamaan dan peta kontur HKSA-3D serta untuk mengetahui mekanisme penghambatan senyawa turunan pirazolina yang didesain terhadap EGFR-TK. Himpunan basis metode DFT/B3LYP yang tervalidasi, yaitu 6-311G, dipilih untuk melakukan optimasi model dari 23 senyawa turunan pirazolina. Model senyawa tersebut ditumpangtindihkan dan interaksinya terhadap *probe atom* dihitung untuk memperoleh deskriptor-3D sterik, elektrostatik, dan hidrofobik. Persamaan HKSA-3D dibangun menggunakan teknik *multiple linear regression* (MLR), *partial least square* (PLS), dan *k-nearest neighbor molecular field analysis* (kNN-MFA). Model persamaan HKSA-3D terbaik digunakan untuk mendesain 10 senyawa turunan pirazolina baru. Senyawa turunan pirazolina hasil desain kemudian ditambatkan terhadap EGFR-TK untuk mengetahui afinitas ikatan dan interaksi yang terbentuk.

Hasil penelitian menunjukkan bahwa persamaan HKSA-3D terbaik diperoleh menggunakan teknik MLR dengan persamaan pIC_{50} = –0,2490×(E755) – –0,0256×(E670) – 0,0143×(S198) – 0,0305×(E269) + 5,1936 dan dengan parameter statistika yaitu n = 18, r^2 = 0,810, q^2= 0,712, F_{test} = 13,860, r^2_{se} = 0,215, q^2_{se} = 0,265, r^2_{pred} =0,888, dan pred_r^2_{se} = 0,131. Persamaan tersebut digunakan untuk mendesain 10 senyawa turunan pirazolina baru dengan IC_{50} prediksi sebesar 3,473-10,900 µg/mL. Seluruh senyawa turunan pirazolina hasil desain berinteraksi secara stabil dan memiliki afinitas ikatan yang lebih rendah dibandingkan ligan *native* erlotinib dengan membentuk ikatan hidrogen, interaksi hidrofobik, dan elektrostatik khususnya terhadap residu asam amino Lys721. Penelitian ini diharapkan dapat menjadi referensi dalam mendesain senyawa turunan pirazolina sebagai senyawa antikanker kolon berdasarkan analisis HKSA-3D dan penambatan molekul.

Kata kunci: turunan pirazolina, antikanker kolon, HKSA-3D, penambatan molekul, EGFR-TK

DESIGN OF PYRAZOLINE DERIVATIVES AS ANTI-COLON CANCER COMPOUNDS BASED ON THREE-DIMENSIONAL QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (3D-QSAR) AND MOLECULAR DOCKING

Stephanus Satria Wira Waskitha
20/466494/PPA/06060

ABSTRACT

Colon cancer is one of the leading causes of death globally. Pyrazoline derivatives are compounds having various biological activities, including anti-colon cancer. Designing pyrazoline derivatives as anti-colon cancer compounds had been conducted based on three-dimensional quantitative structure-activity relationship (3D-QSAR) analysis and molecular docking against epidermal growth factor receptor-tyrosine kinase (EGFR-TK). This study aimed to design new pyrazoline derivatives based on the 3D-QSAR equation as well as its contour map and determine the mechanism of inhibition of the designed pyrazoline derivatives against EGFR-TK. The validated basis set of DFT/B3LYP method, 6-311G, was chosen to optimize the model of 23 pyrazoline derivatives. Those model compounds were aligned and their interactions with probe atoms were calculated to obtain steric, electrostatic, and hydrophobic 3D-descriptors. 3D-QSAR equations were built using multiple linear regression (MLR), partial least square (PLS), and k-nearest neighbor molecular field analysis (kNN-MFA) techniques. The best 3D-QSAR equation model was used to design 10 new pyrazoline derivatives. The designed pyrazoline derivatives were then docked against EGFR-TK to determine the binding affinity and the formed interactions.

The results showed that the best 3D-QSAR equation was obtained using the MLR technique with the equation of pIC_{50} = –0.2490×(E755) – 0.0256×(E670) – 0.0143×(S198) – 0.0305×(E269) + 5.1936 and its statistical parameters of n = 18, r^2 = 0.810, q^2= 0.712, F_{test} = 13.860, r^2_{se} = 0.215, q^2_{se} = 0.265, r^2_{pred} =0.888, and pred_r^2_{se} = 0.131. This equation was used to design 10 new pyrazoline derivatives with a predicted IC_{50} of 3.473-10.900 μg/mL. All of the designed pyrazoline derivatives interacted stably and had lower binding affinity than the native ligand erlotinib. This is due to the formation of hydrogen bonding, hydrophobic, and electrostatic interaction, especially with Lys721 amino acid residue. This research is expected to be a reference in designing pyrazoline derivatives as anti-colon cancer compounds based on 3D-QSAR analysis and molecular docking.

Keywords: pyrazoline derivatives, anti-colon cancer, 3D-QSAR, molecular docking, EGFR-TK