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**Penambatan Molekul dan Skrining Virtual Hasil Kajian Hubungan Kuantitatif Struktur-Aktivitas Turunan
5-Benzilidenatiazolidin-2,4-dion sebagai Kandidat Antidiabetes**
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PENAMBATAN MOLEKUL DAN SKRINING VIRTUAL HASIL KAJIAN HUBUNGAN KUANTITATIF STRUKTUR-AKTIVITAS TURUNAN 5-BENZILIDENATIAZOLIDIN-2,4-DION SEBAGAI KANDIDAT ANTIDIABETES

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INTISARI

Telah dilakukan penambatan molekul dan skrining virtual terhadap hasil kajian hubungan kuantitatif struktur-aktivitas (HKSA) 20 turunan 5-benzilidenatiazolidin-2,4-dion (BTZD) baru sebagai inhibitor DPP4 antidiabetes. Data pergeseran kimia spektra NMR BTZD digunakan dalam validasi himpunan basis metode DFT/B3LYP. Deskriptor dihitung dengan himpunan basis tervalidasi. Model persamaan HKSA disusun dengan regresi linier berganda (MLR). Model divalidasi dan digunakan dalam desain senyawa usulan. Validasi metode penambatan molekul melalui penambatan ulang sitagliptin-DPP4 dilakukan setelah preparasi protein dan ligan. Metode tervalidasi digunakan pada penambatan molekul senyawa usulan. Afinitas ikatan dan interaksi residu asam amino dianalisis. Fitur farmakofor diambil dari senyawa referensi berupa obat komersial dan usulan hasil HKSA teruji penambatan molekul serta digunakan pada skrining virtual.

Model HKSA terbaik, yaitu $\log_{10} IC_{50}$ = -62,924 + (53,842 × qC4) + (40,073 × qC5) + (21,371 × qS9) + (54,342 × qC10) + (-56,381 × HOMO) dengan n = 20; R^2 = 0,928; SEE = 0,301; F_{hit}/F_{tab} = 12,189; PRESS = 1,265. Tujuh senyawa usulan antidiabetes baru dari HKSA dengan aktivitas lebih baik berhasil didesain. Ikatan hidrogen Glu205 atau Glu206 tidak terbentuk pada usulan HKSA. Fitur farmakofor senyawa komersial dan senyawa usulan HKSA berdampak baik terhadap interaksi senyawa usulan hasil skrining virtual. Setidaknya satu ikatan hidrogen Glu205 atau Glu206 ditemukan pada senyawa usulan skrining virtual. Senyawa 34 dinyatakan sebagai yang terbaik karena terdapat ikatan hidrogen Glu205 dan Glu206 serta afinitas ikatan yang baik sebesar -10,040 kcal mol^{-1}. Senyawa 34, yaitu *N*-(4-asetamidofenil)-2-((4-amino-5-(1,4,5,6-tetrahidrosiklopenta[*c*]pirazol-3-il)-4H-1,2,4-triazol-3-il)tio)asetamida.

Kata kunci: 5-benzilidenatiazolidin-2,4-dion, DPP4-i, farmakofor, HKSA, penambatan molekul

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MOLECULAR DOCKING AND VIRTUAL SCREENING OF RESULTS FROM THE STUDY ON QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP OF 5-BENZYLIDENETHIAZOLIDINE-2,4-DIONE DERIVATIVES AS ANTIDIABETIC CANDIDATES

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ABSTRACT

Molecular docking and virtual screening were performed based on the quantitative structure-activity relationship (QSAR) study of 20 novel 5-benzylidenethiazolidine-2,4-dione (BTZD) derivatives as antidiabetic DPP4 inhibitors. Chemical shift of NMR spectra data BTZD were used to validate the DFT/B3LYP basis set. Descriptors were calculated using the validated basis set. The QSAR model was constructed using multiple linear regression (MLR). The model was validated using statistical parameters and applied in the design of proposed compounds. Validation of the molecular docking method through re-docking of sitagliptin-DPP4 was performed after the preparation of the protein and ligand. The validated method was applied to the molecular docking of the proposed compounds. Binding affinities and amino acid residue interactions were analyzed. Pharmacophore features were extracted from reference compounds including commercial drugs and proposed compounds designed by QSAR validated through molecular docking also used in virtual screening.

The best QSAR model was $\log_{10} IC_{50} = -62.924 + (53.842 \times qC4) + (40.073 \times qC5) + (21.371 \times qS9) + (54.342 \times qC10) + (-56.381 \times HOMO)$ with $n = 20$; $R^2 = 0.928$; $SEE = 0.301$; $F_{cal}/F_{tab} = 12.189$; $PRESS = 1.265$. Seven new antidiabetic compounds proposed by QSAR with improved activity were successfully designed. The proposed compounds by QSAR did not form hydrogen bonds with Glu205 or Glu206. The pharmacophore features of commercial compounds and proposed compounds designed by QSAR had a positive impact on the interactions of the proposed compounds resulting from virtual screening. At least one Glu205 or Glu206 hydrogen bond was found in the proposed compounds from virtual screening. Compound 34 was identified as the best candidate because it contains Glu205 and Glu206 hydrogen bonds also exhibits a good binding affinity of -10.040 kcal mol^{-1}. Compound 34 was N-(4-acetamidophenyl)-2-((4-amino-5-(1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)thio)acetamide.

Keywords: 5-benzylidenethiazolidine-2,4-dione, DPP4-i, molecular docking, pharmacophore, QSAR