

SINTESIS SENYAWA TURUNAN KHALKON DAN FLAVON DARI ANISALDEHID DAN VERATRALDEHID, PENAMBATAN MOLEKUL SERTA UJI AKTIVITAS SITOTOKSIK TERHADAP CELL LINES HELA, WIDR DAN T47D

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INTISARI

Senyawa turunan khalkon dan flavon diketahui memiliki aktivitas sitotoksik terhadap sel kanker. Penelitian ini bertujuan untuk mensintesis senyawa 2-hidroksi-4'-metoksikhalkon (ST1a), 2-hidroksi-3',4'-dimetoksikhalkon (ST1b), 2,4-dihidroksi-3',4'-dimetoksikhalkon (ST1c), 4'-metoksiflavon (ST2a), 3',4'-dimetoksiflavon (ST2b) dan 7-hidroksi-3',4'-dimetoksiflavon (ST2c) yang berpotensi memiliki aktivitas sitotoksik terhadap *cell lines* kanker HeLa, WiDr dan T47D. Senyawa yang disintesis memiliki substituen metoksi yang berasal dari anisaldehyd dan veratraldehyd. Pada penelitian ini dilakukan 3 tahap penelitian yaitu sintesis tiga senyawa turunan khalkon yaitu ST1a, ST1b dan ST1c melalui reaksi kondensasi *Claisen-Schmidt* dari senyawa hidroksiasetofenon dan anisaldehyd atau veratraldehyd dengan menggunakan katalis KOH. Sintesis turunan flavon yaitu ST2a, ST2b dan ST2c dilakukan melalui siklisasi oksidatif senyawa turunan khalkon dengan menggunakan iodin dalam pelarut dimetil sulfoksida (DMSO). Senyawa hasil sintesis dianalisis strukturnya dengan FTIR, GC-MS, ^1H NMR dan ^{13}C NMR. Uji aktivitas sitotoksik senyawa hasil sintesis dengan menggunakan metode MTT assay (3-(4,5-dimetiltiazol-2-il)-2,5 difeniltetrazolium bromida) terhadap *cell lines* kanker HeLa, WiDr, dan T47D. Selanjutnya dilakukan penambatan molekul terhadap protein *Epidermal Growth Factor Receptor* (EGFR) menggunakan bantuan program Chimera 1.13, autodock tools 1.5.6 dan Discovery studio 2017. Prediksi sifat Absorpsi, Distribusi, Metabolisme, Ekskresi, dan Toksisitas (ADMET) dilakukan menggunakan program web pkCSM online.

Hasil penelitian menunjukkan bahwa ST1a, ST1b dan ST1c telah teridentifikasi dan diperoleh rendemen berturut-turut 68,29; 70,16 dan 71,31%. Selanjutnya senyawa sintesis ST2a, ST2b dan ST2c telah diidentifikasi dan diperoleh rendemen berturut-turut 75,39; 60,76 dan 50,33%. Hasil uji aktivitas sitotoksik menunjukkan bahwa senyawa ST1a dan ST1c menghambat *cell lines* kanker HeLa, WiDr dan T47D dengan nilai IC_{50} ST1a berturut-turut 15,11; 24,39; dan 45,75 $\mu\text{g/mL}$, sedangkan nilai IC_{50} ST1c berturut-turut yaitu 9,47; 6,83 dan 7,5 $\mu\text{g/mL}$. Indeks selektivitas (IS) ST1a terhadap HeLa, WiDr dan T47D sebesar 9,48; 6,09 dan 3,25 sedangkan indeks selektivitas ST1c berturut-turut 6,85; 9,5 dan 8,65. Hasil uji penambatan molekul senyawa hasil sintesis terhadap protein EGFR menunjukkan bahwa adanya interaksi ikatan hidrogen Met769 dan Cys773. Senyawa sintesis ST1a-c dan ST2a-c menunjukkan adanya interaksi ikatan hidrogen dengan Met769. Hasil uji menggunakan program pkCSM online menunjukkan bahwa senyawa ST1b, ST1c dan ST2c dapat diserap baik oleh tubuh, dapat didistribusikan dalam tubuh, dapat diekskresikan dan memiliki toksisitas yang relatif rendah.

Kata kunci : khalkon, flavon, sitotoksitas, penambatan molekul, ADMET

SYNTHESIS OF CHALCONE AND FLAVONE DERIVATIVES FROM ANISALDEHYDE AND VERATRALDEHYDE, MOLECULAR DOCKING, AND CYTOTOXICITY ASSAYS ON HELA, WIDR AND T47D CELL LINES

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ABSTRACT

Chalcone and flavone derivative compounds are known to have cytotoxic activity against cancer cells. This research aimed to synthesize 2-hydroxy-4'-methoxychalcone (ST1a); 2-hydroxy-3',4'-dimethoxychalcone (ST1b); 2,4-dihydroxy-3',4'-dimethoxychalcone (ST1c); 4'-methoxyflavone (ST2a); 3',4'-dimethoxyflavone (ST2b); and 7-hydroxy-3',4'-dimethoxyflavone (ST2c) which have the potential of cytotoxicity against HeLa, WiDr, and T47D cancer cell lines. The synthesized compound has methoxy substituents derived from anisaldehyde and veratraldehyde. In this research, 3 stages of research were carried out, namely the synthesis of three chalcone derivative compounds, namely ST1a, ST1b, and ST1c, through the Claisen-Schmidt condensation reaction from hydroxy acetophenone and anisaldehyde or veratraldehyde compounds using a KOH catalyst. The synthesis of flavone derivatives, namely ST2a, ST2b, and ST2c, was carried out through oxidative cyclization of chalcone derivative compounds using iodine in dimethyl sulfoxide (DMSO) solvent. The structure of the synthesized compounds was analyzed using FTIR, GC-MS, ¹H NMR, and ¹³C NMR. Test the cytotoxic activity of the synthesized compound using the MTT assay method (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide) against HeLa, WiDr, and T47D cancer cell lines. Next, molecular docking was carried out on the Epidermal Growth Factor Receptor (EGFR) protein using the Chimera 1.13 program, Autodock tools 1.5.6, and Discovery Studio 2017. Prediction of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties was carried out using the online pkCSM web program.

The results showed that ST1a, ST1b, and ST1c had been identified, and yields of 68.29, 70.16, and 71.31% were obtained. Furthermore, the synthetic compounds ST2a, ST2b and ST2c were identified and obtained yields of 75.39; 60.76 and 50.33%. The results of the cytotoxic activity test showed that ST1a and ST1c compounds inhibited the HeLa, WiDr and T47D cancer cell lines with IC₅₀ values for ST1a respectively 15.11; 24.39; and 45.75 µg/mL, while the IC₅₀ ST1c values were 9.47; 6.83 and 7.5 µg/mL. The selectivity index (IS) of ST1a against HeLa, WiDr and T47D was 9.48, 6.09 and 3.25, while the ST1c selectivity index was 6.85, 9.5 and 8.65. The results of the molecular docking test of the synthesized compound on the EGFR protein show that there is a hydrogen bond interaction between Met769 and Cys773. The synthetic compounds ST1a-c and ST2a-c showed hydrogen bond interactions with Met769. Test results using the online pkCSM program show that compounds ST1b, ST1c, and ST2c can be well absorbed by the body, distributed in the body, excreted, and have relatively low toxicity.

keywords: chalcone, flavone, cytotoxicity, molecular docking, ADMET