SINTESIS, UJI AKTIVITAS ANTIOKSIDAN DAN ANTIKANKER, SERTA KAJIAN PENAMBATAN MOLEKUL TURUNAN HIDROKSIXANTON TERHADAP TOPOISOMERASE II

Nela Fatmasari
17/418586/PPA/05370

INTISARI

Telah dilakukan sintesis, uji aktivitas antioksidan dan antikanker, serta penambatan molekul turunan hidroksixanton terhadap enzim Topoisomerase II. Senyawa tersebut antara lain 1,3,8-trihidroksixanton (**HX1**); 1,6-dihidroksixanton (**HX2**); 1,5,6-trihidroksixanton (**HX3**); 1-hidroksi-5-kloroxanton (**HX4**) dan 1,6-dihidroksi-5-metilxanton (**HX5**).

Turunan hidroksixanton diperoleh melalui reaksi asilasi Friedel-Craft dan dehidrasi antara asam-2,6-dihidroksibenzoat dengan senyawa fenolat (flouroglusinol, resorsinol, pirogalol, 2-klorofenol dan 2-metilresorsinol) menggunakan reagen Eaton (CH_3SO_3H/P_2O_5). Proses reaksi yang dilakukan berupa refluks pada 80-85 °C selama 3 jam. Produk reaksi yang diperoleh kemudian dimurnikan dengan Kromatografi Lapis Tipis Preparatif (KLTP) menggunakan etil asetat:n-heksana rasio 1:1 (v/v) sebagai eluen. Konfirmasi struktur produk senyawa dilakukan menggunakan spektrometer FTIR, MS, ^{1}H dan ^{13}C-NMR. Uji antioksidan dilakukan terhadap turunan hidroksixanton menggunakan metode 1,1-difenil-2-pikrilhidrazin (DPPH), sedangkan uji antikanker menggunakan metode 3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazoinumbromida (MTT). Proses penambatan molekul menggunakan perangkat lunak Autodock Vina.

Produk turunan hidroksixanton yang diperoleh dari reaksi antara asam-2,6-dihidroksibenzoat dengan senyawa fenolat berupa padatan berwarna kuning dengan persen hasil senyawa **HX1**, **HX2**, **HX3**, **HX4** dan **HX5** masing-masing **s**ebesar 16,12; 33,33; 10,92; 11,11 dan 19,28%. Senyawa **HX1-HX5** memiliki aktivitas antioksidan dalam berbagai kategori. Senyawa **HX2** dalam kategori kuat (IC_{50} 79,68 µg mL^{-1}), **HX1**, **HX3** dan **HX5** dalam kategori sedang (IC_{50} 159,4; 128,0 dan 276,9 µg mL^{-1}), serta **HX4** dalam kategori lemah (IC_{50} 432,9 µg mL^{-1}). Senyawa **HX1-HX5** tidak bersifat selektif terhadap sel kanker uji. Senyawa **HX1** paling kuat aktivitas antikankernya terhadap sel MCF-7 (IC_{50} 45,00 µg mL^{-1}), tetapi senyawa tersebut juga besifat toksik terhadap sel Vero (IC_{50} 67,01 µg mL^{-1}). Interaksi antara senyawa **HX1** dengan Topoisomerase II pada penambatan molekul berupa ikatan hidrogen (DG F:13) dan *pi–pi stacked* (DA F:12 dan DC C:8).

Kata kunci: asam-2,6-dihidroksibenzoat, antikanker, antioksidan, fenolat, Topoisomerase II.

SYNTHESIS, ANTIOXIDANT AND ANTICANCER ACTIVITIES EVALUATION AS WELL AS MOLECULAR DOCKING STUDY OF HYDROXYXANTHONE DERIVATIVES TOWARD TOPOISOMERASE II

Nela Fatmasari
17/418586/PPA/05370

ABSTRACT

Synthesis, antioxidant and anticancer activities evaluation as well as molecular docking of hydroxyxanthone derivatives toward Topoisomerase II have been carried out. These compounds include 1,3,8-trihydroxyxanthone (**HX1**); 1,6-dihydroxy-xanthone (**HX2**); 1,5,6-trihydroxyxanthone (**HX3**); 4-chloro-1-hydroxy-xanthone (**HX4**) and 1,6-dihydroxy-5-methylxanthone (**HX5**).

The hydroxyxanthone derivatives were obtained through the Friedel-Craft acylation reaction and dehydration of 2,6-dihydroxybenzoic acid with phenolic compounds (phloroglucinol, resorcinol, pyrogallol, 2-chlorophenol, and 2-methyl-resorcinol) using Eaton's reagents (CH_3SO_3H/P_2O_5). The reaction was conducted by reflux at 80-85 °C for 3 h. The products were purified by thin layer chromatography using ethyl acetate and n-hexane 1:1 (v/v) as eluent. The chemical structures were confirmed by FTIR, MS, ^{1}H and ^{13}C-NMR spectrometers. Antioxidant test was conducted using 1-1-diphenylpicryl-2-hydarzyl (DPPH) method, while anticancer test was conducted using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) method. The molecular docking process was computed by AutoDock Vina.

The hydroxyxanthone derivatives were produced from the reaction between 2,6-dihydroxybenzoic acid and phenolic as yellow solids with percent yield of **HX1, HX2, HX3, HX4** and **HX5** were 16.12; 33.33; 10.92; 11.11 and 19.28%, respectively. The hydroxyxanthone derivatives have antioxidant activity in various categories. Compounds **HX2** was in the strong category (IC_{50} 79.68 µg mL^{-1}), compounds **HX1**, **HX3** and **HX5** were in the moderate category (IC_{50} 159.4; 128,0 and 276.9 µg mL^{-1}), and compound **HX4** was in the weak category (IC_{50} 432.9 µg mL^{-1}). The hydroxyxanthone derivatives (**HX1**-**HX5**) were not selective towards the tested cancer cell lines. Compound **HX1** has the strongest anticancer activity against MCF-7 cell (IC_{50} 45,00. µg mL^{-1}), but the compound was also toxic to Vero cell (IC_{50} 67.01 µg mL^{-1}). The interaction between compound **HX1** and the Topoisomerase II in the molecular docking was hydrogen bond (DG F:13) and pi-pi stacked (DA F:12 and DC C:8).

Keywords: 2,6-dihydroxybenzoic acid, anticancer, antioxidant, phenolic, Topoisomerase II