SINTESIS, UJI SITOTOKSISITAS DAN STUDI PENAMBATAN MOLEKUL SENYAWA XANTIL-SINAMAT SEBAGAI AGEN ANTIKANKER

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INTISARI

Penelitian ini dilakukan untuk mengembangkan struktur senyawa turunan xanton menggunakan konsep *hybridization*. Penelitian ini juga bertujuan untuk mempelajari potensi senyawa *hybrid* sebagai agen antikanker. Penelitian ini dilakukan melalui beberapa tahap: 1) sintesis senyawa hidroksixanton, 2) sintesis senyawa xantil-sinamat, 3) uji sitotoksisitas secara *in vitro* dan 4) studi penambatan molekul.

Sintesis seri senyawa hidroksixanton dilakukan melalui reaksi asilasi-siklisasi senyawa turunan asam benzoat (asam salisilat dan asam 2,4-dihidroksibenzoat) dengan senyawa turunan fenol (floroglucinol dan resorsinol). Berdasarkan hasil sintesis, didapatkan senyawa 1,3-dihidroksixanton (**3a**), 1-hidroksixanton (**3b**) dan 1,3,6-trihidroksixanton (**3c**) dengan rendemen berturut-turut sebesar 48,25; 11,79 dan 15,39%. Ketiga senyawa ini kemudian digunakan sebagai bahan dasar sintesis senyawa *hybrid* xantil-sinamat. Sintesis seri senyawa xantil-sinamat dilakukan melalui reaksi esterifikasi antara seri senyawa hidroksixanton (**3a**–**c**) dengan sinamoil klorida. Berdasarkan hasil sintesis, didapatkan senyawa 3-hidroksixanten-1-il sinamat (**4a**), xanten-1-il sinamat (**4b**), 1,3-dihidroksixanten-6-il sinamat (**4c**) dan 3,6-dihidroksixanten-1-il sinamat (**4d**) dengan rendemen berturut-turut sebesar 15,92; 10,09; 17,91 dan 12,70%. Struktur senyawa hasil sintesis tersebut telah dikonfirmasi menggunakan spektrometer FTIR, DI-MS, LC-MS, ^{1}H- dan ^{13}C-NMR.

Uji sitotoksisitas senyawa hasil sintesis dilakukan secara *in vitro* pada sel kanker T47D, HeLa, A549 dan WiDr, serta sel normal (Vero). *Hybridization* molekul xanton dengan asam sinamat meningkatkan selektivitas senyawa xanton (IS = 2,75–209,03). Senyawa **4c** memiliki potensi yang baik sebagai obat kanker kolon, menunjukkan aktivitas medium (IC_{50} = 14,80 ± 8,22 µg/mL) terhadap sel kanker WiDr. Dari hasil studi penambatan molekul, diketahui kompleks antara xantil-sinamat dan EGFR yang terbentuk lebih stabil dibandingkan senyawa hidroksixanton dan erlotinib. Senyawa **4d** dipilih sebagai senyawa dengan prediksi interaksi paling baik terhadap EGFR dengan nilai ΔG sebesar -8,37 kkal/mol dan Ki sebesar 0,74 µM.

Kata kunci: xanton, xantil-sinamat, sintesis, antikanker, penambatan molekul

SYNTHESIS, CYTOTOXICITY TEST AND MOLECULAR DOCKING STUDY OF XANTHYL-CINNAMATE COMPOUNDS AS ANTICANCER AGENTS

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ABSTRACT

This study was conducted to develop the structure of xanthone-derived compounds using the concept of hybridization. This research also aims to study the potential of hybrid compounds as anticancer agents. The research was carried out in several stages: 1) synthesis of hydroxyxanthone compounds, 2) synthesis of xanthyl-cinnamate compounds, 3) *in vitro* cytotoxicity assays and 4) molecular docking studies.

Synthesis of hydroxyxanthone compounds was performed via acylation-cyclization of benzoic acid derivatives (salicylic acid and 2,4-dihydroxybenzoic acid) with phenol derivatives (phloroglucinol and resorcinol). Compounds 1,3-dihydroxyxanthone (**3a**), 1-hydroxyxanthone (**3b**) and 1,3,6-trihydroxy-xanthone (**3c**) were obtained in 48.25, 11.79 and 15.39% yield, respectively. These compounds were then used as a precursor for synthesizing xanthyl-cinnamate hybrid compounds. Synthesis of xanthyl-cinnamate compounds was performed via esterification of hydroxyxanthones (**3a**–**c**) with cinnamoyl chloride. Compounds 3-hydroxyxanthen-1-yl cinnamate (**4a**), xanthen-1-yl cinnamate (**4b**), 1,3-dihydroxyxanthen-6-yl cinnamate (**4c**) and 3,6-dihydroxyxanthen-1-yl cinnamate (**4d**) were obtained in 15.92, 10.09, 17.91 and 12.70% yield, respectively. The structures of the all-synthesized compounds were confirmed using FTIR, DI-MS, LC-MS, ^{1}H- and ^{13}C-NMR spectrometers.

In vitro cytotoxicity assays of the synthesized compounds were evaluated against cancer cells T47D, HeLa, A549, and WiDr, as well as normal cells (Vero). The molecular hybridization of xanthone with cinnamic acid increased the selectivity of xanthone compounds (SI = 2.75–209.03). Compound **4c** was chosen as a potential drug for colon cancer, as this compound has moderate activity (IC_{50} = 14.80 ± 8.22 µg/mL) against the WiDr cell lines. From the molecular docking studies, it was known that the complex between xanthyl-cinnamate and EGFR formed was more stable than those hydroxyxanthone compounds and erlotinib. Compound **4d** was chosen as the compound with the best-predicted interaction with EGFR with a binding energy value of -8.37 kcal/mol and a Ki value of 0.74 µM.

Keywords: xanthone, xanthyl-cinnamate, synthesis, anticancer, molecular docking