Desain senyawa penghambat ER-Alfa Analog Kurkumin TetrahidroIndazol, Sintesis, dan Uji Sitotoksik Terhadap Beberapa Sel Kanker = Design of ER-Alpha inhibitor compounds, Tetrahydro-Indazole Analogs of Curcumin, Synthesis, and Its Cytotoxic Assay Against Some Cancer Cells

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Abstrak

Analog Kurkumin Indazol merupakan senyawa analog berpotensi dikembangkan sebagai antikanker. Penelitian ini bertujuan untuk memperoleh senyawa baru analog kurkumin tetrahidro-indazol yang mempunyai akivitas penghambatan antikanker yang selektif. Penelitian diawali skrining in silico 186 senyawa disain didasarkan pada penapisan model farmakofor dan terpilih 14 senyawa, dilanjutkan penambatan molekular menghasilkan 10 senyawa hit. Kemudian dilakukan sintesis dengan reaksi kondensasi Clasein-Schmidth, dihasilkan enam analog indazole baru dari kurkumin dan dievaluasi aktivitas sitotoksiknya menggunakan uji proliferasi metil tiazolil tetrazolium terhadap sel kanker MCF-7, HeLa, WiDr, dan Vero. Struktur senyawa dikarakterisasi dengan FTIR, NMR, dan spektral massa. Hasil penelitian menunjukkan bahwa senyawa yang disintesis lebih aktif terhadap sel WiDr dibandingkan dengan sel MCF-7 dan HeLa. Aktivitas sitotoksik senyawa 3b, 3c, 3d, 5a terhadap sel WiDr lebih aktif dibandingkan kurkumin dan tamoxifen. Evaluasi lebih lanjut terhadap sel Vero (sel normal) untuk menentukan selektivitasnya menunjukkan beberapa senyawa hasil sintesis lebih selektif (nilai IS > 2) dibandingkan tamoxifen dan doksorubisin (nilai SI < 2,00). Tiga senyawa (3a, 3b, dan 3c) menunjukkan IS tinggi terhadap sel WiDr yaitu 3,74, 5,27, dan 4,39. Di antara senyawa yang disintesis, 3b menunjukkan aktivitas sitotoksik tertinggi, terutama terhadap garis sel WiDr (IC50 = 27,20 M) dengan selektivitas yang sangat baik (SI = 5,27).
.....Indazole Analogs of Curcumin is an analog compound that has the potential to be developed as an anticancer. This study aims to obtain a new compound analogue of curcumin tetrahydro-indole which has selective anticancer inhibitory activity. The research began with the design of the curcumin analog compound tetrahydro-indazole in silico based on a pharmacophore model and 14 compounds were selected, then continued molecular docking to produce 10 hit compounds. Then the synthesis was carried out using the Clasein-Schmidth condensation reaction and produced a series of six novel indazole analogs of curcumin and evaluated their cytotoxic activity against MCF-7, HeLa, WiDr, and Vero cells. The structure of the compound was characterized by FTIR, NMR, and mass spectral. The results showed that the synthesized compound was more active against WiDr cells than MCF-7 and HeLa cells. The cytotoxic activity of compounds 3b, 3c, 3d, 5a against WiDr cells was more active than curcumin and tamoxifen. Further evaluation of Vero cells to determine their selectivity showed that some of the compounds synthesized were more selective (SI value>2) than tamoxifen and doxorubicin. Three compounds (3a, 3b, and 3c) showed high SI against WiDr cells, namely 3.74, 5.27, and 4.39. Among the synthesized compounds, 3b showed the highest cytotoxic activity, especially against the WiDr cell line (IC50 = 27.20 M) with excellent selectivity (SI = 5.27).