DESIGN, SYNTHESIS OF FLAVOKAWAIN B DERIVATIVE AND THEIR CYTOTOXIC EFFECTS ON MCF-7 AND MDA-MB-231 CELL LINES

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ABSTRAK

Kanser adalah antara punca kematian di mana kanser payudara merupakan kanser yang kedua terbanyak di kalangan wanita di seluruh dunia. Rawatan kanser dengan ubat kanser, kemoterapi dan radiasi yang biasa digunakan telah menyebabkan kesan yang tidak diingini pada pesakit. Oleh itu, kalkon dengan pelbagai manfaat farmakologi seperti anti-kanser, anti-mitosis, dan lain-lain, telah mendapat perhatian sebagai subjek penyelidikan. Derivatif kalkon flavokawain B yang mengandungi kumpulan metoksi, dimetoksi, trimetoksi, bromo, kloro, floro, metil, metiltio, nitro, hidroksil dan dimetilamino pada benzaldehida telah disintesis melalui kaedah kondensasi Claisen-Schmidt menggunakan pemangkin alkali; sebatian yang disintesis dicirikan dengan menggunakan spektrofotometri Ultraungu-Nampak (UV-Vis), spektroskopi Infrared (FTIR), Kromatografi Gas-Spektrometri Jisim (GC-MS) dan spektroskopi Resonans Magnetik Nuklear (NMR); dan dinilai untuk kesitotoksikan mereka terhadap sel kanser payudara dengan menggunakan asai MTT. Antara 22 sebatian yang disintesis, dua sebatian **80** dan **91** telah ditemui sebagai analog flavokawain B yang baru dan beberapa sebatian menunjukkan aktiviti anti-kanser yang bagus berikutan had nilai, IC_{50} adalah kurang daripada 30 μg/mL. Sebatian tersebut adalah kalkon **4** (7.70 ± 0.30 μg/mL), **5** (8.90 ± 0.60 μg/mL), **75** (12.30 ± 1.40 μg/mL), **79** (6.50 ± 0.40 μg/mL), **80** (7.12 ± 0.80 μg/mL), **82** (9.70 ± 0.70 μg/mL), **84** (5.50 ± 0.35 μg/mL), **85** (8.43 ± 0.40 μg/mL), **44** (13.30 ± 3.10 μg/mL) dan **90** (6.50 ± 0.35 μg/mL) yang menunjukkan aktiviti anti-kanser yang baik terhadap MCF-7. Kalkon **4** (5.90 ± 0.30 μg/mL), **5** (6.80 ± 0.45 μg/mL), **75** (18.10 ± 1.10 μg/mL), **79** (4.12 ± 0.20 μg/mL), **80** (4.04 ± 0.30 μg/mL), **81** (9.50 ± 0.60 μg/mL), **82** (8.30 ± 0.56 μg/mL), **84** (5.50 ± 0.40 μg/mL), **85** (7.22 ± 0.70 μg/mL) dan **44** (17.10 ± 2.15 μg/mL) yang menunjukkan aktiviti anti-kanser yang baik terhadap MDA-MB-231, serta sebatian **79** dan **80** didapati lebih aktif daripada ubat rujukan doksorubisin (5.05 ± 0.20 μg/mL). Kajian perhubungan struktur-aktiviti menunjukkan bahawa sitotoksik yang bertambah baik ditunjukkan oleh derivatif flavokawain B dengan kumpulan halogen, diikuti oleh derivatif flavokawain B dengan kumpulan metoksi terutamanya ketika penggantian terjadi pada kedudukan 2 dan 3 di cincin aromatik B.

ABSTRACT

Cancer is among the cause of death whereof breast cancer is the second leading cause of cancer death among women worldwide. Cancer treatment with standard anti-cancer drug, chemotherapy and radiation have caused unwanted side effects in the patient. Therefore chalcone with many pharmacological benefits such as anti-cancer, anti-mitotic, etc., has gained attention as a subject of research. Flavokawain B derivative chalcones bearing methoxy, dimethoxy, trimethoxy, bromo, chloro, fluoro, methyl, methylthio, nitro, hydroxyl and dimethylamino groups on benzaldehyde were synthesized via Claisen-Schmidt condensation method using base catalyst; the synthesized compounds were characterized by using UV-Visible, Fourier Transform Infrared spectrophotometry (FTIR), Gas Chromatography-Mass Spectrometry (GC-MS) and Nuclear Magnetic Resonance (NMR) spectrometry and evaluated for their cytotoxicity against breast cancer cell line by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay *in vitro*. Among 22 synthesized compounds, two compounds, **80** and **91** have been discovered as new flavokawain B analogs and some compounds showed good anti-cancer activity following the cut-off point value, IC_{50} is less than 30 μg/mL. The compounds are chalcone **4** (7.70 ± 0.30 μg/mL), **5** (8.90 ± 0.60 μg/mL), **75** (12.30 ± 1.40 μg/mL), **79** (6.50 ± 0.40 μg/mL), **80** (7.12 ± 0.80 μg/mL), **82** (9.70 ± 0.70 μg/mL), **84** (5.50 ± 0.35 μg/mL), **85** (8.43 ± 0.40 μg/mL), **44** (13.30 ± 3.10 μg/mL) and **91** (6.50 ± 0.35 μg/mL) that exhibited good anti-cancer activity against MCF-7. Chalcone **4** (5.90 ± 0.30 μg/mL), **5** (6.80 ± 0.45 μg/mL), **75** (18.10 ± 1.10 μg/mL), **79** (4.12 ± 0.20 μg/mL), **80** (4.04 ± 0.30 μg/mL), **81** (9.50 ± 0.60 μg/mL), **82** (8.30 ± 0.56 μg/mL), **84** (5.50 ± 0.40 μg/mL), **85** (7.22 ± 0.70 μg/mL) and **44** (17.10 ± 2.15 μg/mL) showed good anti-cancer activity against MDA-MB-231 as well as compound **79** and **80** was discovered to be more active than the reference drug doxorubicin (5.05 ± 0.20 μg/mL). Structure-activity relationship study suggested that significantly improved cytotoxicity was shown by halogenated flavokawain B, followed by methoxylated flavokawain B, particularly when substitution occurred at position 2 and 3 in ring B.