Design, synthesis and docking studies of Flavokawain B type chalcones and their cytotoxic effects on MCF-7 and MDA-MB-231 cell lines

ABSTRACT

Flavokawain B (**1**) is a natural chalcone extracted from the roots of *Piper methysticum*, and has been proven to be a potential cytotoxic compound. Using the partial structure of flavokawain B (FKB), about 23 analogs have been synthesized. Among them, compounds **8**, **13** and **23** were found in new FKB derivatives. All compounds were evaluated for their cytotoxic properties against two breast cancer cell lines, MCF-7 and MDA-MB-231, thus establishing the structure–activity relationship. The FKB derivatives **16** (IC_{50} = 6.50 ± 0.40 and 4.12 ± 0.20 μg/mL), **15** (IC_{50} = 5.50 ± 0.35 and 6.50 ± 1.40 μg/mL) and **13** (IC_{50} = 7.12 ± 0.80 and 4.04 ± 0.30 μg/mL) exhibited potential cytotoxic effects on the MCF-7 and MDA-MB-231 cell lines. However, the methoxy group substituted in position three and four in compound **2** (IC_{50} = 8.90 ± 0.60 and 6.80 ± 0.35 μg/mL) and **22** (IC_{50} = 8.80 ± 0.35 and 14.16 ± 1.10 μg/mL) exhibited good cytotoxicity. The lead compound FKB (**1**) showed potential cytotoxicity (IC_{50} = 7.70 ± 0.30 and 5.90 ± 0.30 μg/mL) against two proposed breast cancer cell lines. It is evident that the FKB skeleton is unique for anticancer agents, additionally, the presence of halogens (Cl and F) in position 2 and 3 also improved the cytotoxicity in FKB series. These findings could help to improve the future drug discovery process to treat breast cancer. A molecular dynamics study of active compounds revealed stable interactions within the active site of Janus kinase. The structures of all compounds were determined by ^{1}H-NMR, EI-MS, IR and UV and X-ray crystallographic spectroscopy techniques.

Keyword: Chalcone synthesis; Breast cancer cell lines; SARs; Anti-cancer; Flavokawain B derivatives