In-vitro and in-silico evaluations of heterocyclic-containing diarylpentanoids as Bcl-2 inhibitors against LoVo colorectal cancer cells

ABSTRACT

In the present study, we investigated the in-vitro anti-cancer potential of six diarylpentanoids against a panel of BRAF- and KRAS-mutated colorectal cancer cell lines including T84, SW620, LoVo, HT29, NCI-H508, RKO, and LS411N cells. Structure-activity relationship study suggested that the insertions of tetrahydro-4H-thiopyran-4-one and brominated phenyl moieties are essential for better cytotoxicity. Among the evaluated analogs, 2e has been identified as the lead compound due to its low IC50 values of approximately 1 μM across all cancer cell lines and high chemotherapeutic index of 7.1. Anti-proliferative studies on LoVo cells showed that 2e could inhibit cell proliferation and colony formations by inducing G2/M cell cycle arrest. Subsequent cell apoptosis assay confirmed that 2e is a Bcl-2 inhibitor that could induce intrinsic cell apoptosis by creating a cellular redox imbalance through its direct inhibition on the Bcl-2 protein. Further molecular docking studies revealed that the bromophenyl moieties of 2e could interact with the Bcl-2 surface pocket through hydrophobic interaction, while the tetrahydro-4H-thiopyran-4-one fragment could form additional Pi-sulfur and Pi-alkyl interactions in the same binding site. In all, the present results suggest that 2e could be a potent lead that deserves further modification and investigation in the development of a new Bcl-2 inhibitor.

Keyword: Diarylpentanoids; Colorectal cancer; Cytotoxicity; Anti-proliferative; Cell cycle; Apoptosis; Bcl-2 inhibitor; Molecular docking