INDUCTION OF CELL GROWTH INHIBITION AND APOPTOSIS BY MULTISUBSTITUTED HYDROXYNAPHTHALENE CARBOXAMIDES IN CANCER CELL LINES

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Small molecules containing amide bond (-CONH-) became interesting model moieties for drug design since the amide group, which naturally occurs in many biological structures, facilitates the interaction of such a molecule with their cellular targets. One example of these model structures could be a group of salicylanilide derivatives with recently uncovered anticancer properties. Based on the similarity in the structure, a new group of salicylanilide analogs, hydroxynaphthalene carboxamides, were prepared. Our previous studies showed interesting findings of antiproliferative and pro-apoptotic effects induced by monosubstituted hydroxynaphthalene carboxamides. These results indicated that the biological effects of the compounds are related to the presence of electron-withdrawing substituents at *meta* or *para* positions. In this follow-up study, we decided to assess that effects induced by new multisubstituted hydroxynaphthalene carboxamides. Among the tested compounds, the disubstituted ones showed higher antiproliferative activity in cancer cell lines than their monosubstituted analogs and also higher than the derivatives with four or five anilide substituents. The cell growth inhibition of the most potent disubstituted compound was additionally demonstrated by induced accumulation of cancer cells in G1 cell cycle phase. Further analyses revealed mitochondrial membrane depolarization and increased production of mitochondrial superoxide in THP-1 cell line that was accompanied by a rapid decrease of cellular ATP levels and release of cytochrome C. Additional detection of increased caspase 3 activity and PARP cleavage might indicate induction of apoptosis in THP-1 cells. Taken together, our study showed that it is preferable to substitute the hydroxynaphthalene carboxamides by two electron-withdrawing groups on the anilide moiety rather than by one analogous group for the induction of antiproliferative effect and activation of apoptosis. Thus obtained results confirmed the previous findings indicating that the structure of hydroxynaphthalene carboxamides might represent an interesting model moiety for future drug design.

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