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Selective pro-apoptotic activity of novel bis-lawsone derivatives on human cancer cells via the induction of reactive oxygen species

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Recent studies have shown that many types of cancer cells have increased levels of reactive oxygen species (ROS) and enhanced antioxidant capacity as an adaptation to intrinsic oxidative stress, suggesting that cancer cells are more vulnerable to oxidative insults. Selective induction of apoptosis in cancer cells barring the normal cells is considered to be an effective strategy to combat cancer. In the present study, a series of 22 synthetic 3,3'-(aryl/alkyl-methylene)bis(2-hydroxynaphthalene-1,4-dione) bis-lawsone derivatives were assayed for their pro-apoptotic activity in six different cell lines. Out of these 22 test compounds, 1j was found to be the most effective in inducing apoptosis in human glioma cells (CCF-4) among the different cell lines used in the study. 1j contains a trifluoromethyl group (-CF3), a strong electron-withdrawing group. This kind of fluorinated moieties in heterocyclic compound are believed to interfere with the lipophilicity, metabolic stability and bioavailability of the compounds. In this study, 1j derivative showed very less toxicity to the normal kidney cells compared to cisplatin, a well-known chemotherapeutic agent. This compound was observed to induce apoptosis in the glioma cells by inducing the caspase dependent apoptotic pathways via ROS and downregulating the PI3K/AKT/mTOR pathway. Estimation of different oxidative stress markers also confirms the induction of oxidative stress in 1j exposed cancer cells. The toxicity of 1j compound toward cancer cells was confirmed further by analysing mitochondrial membrane potential and cell cycle progression. In addition, this compound also exhibited significant anti-tumor activity in S180 sarcoma bearing mice. Moreover different histopathological and biochemical studies also revealed that 1j did not induce significant level of toxicity in the vital organs. These studies not only identified a novel anticancer drug candidate but also will help to understand the metabolism of ROS and its application in cancer treatment.

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