8B - PHARMACEUTICAL CHEMISTRY

SYNTHESIS OF FLAVONE-BASED COMPOUNDS AS ROS-DEPENDENT APOPTOSIS INDUCERS IN COLORECTAL CANCER

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ABSTRACT

Apoptosis is essential for maintaining cell homeostasis. It hinders the cancer cells survival and excessive ROS can induce DNA damage in cancer cells, which lead to apoptosis. Therefore, targeting apoptosis may be a universal cancer therapeutic technique. Twelve flavone-based compounds were synthesised and characterised. All compounds were evaluated for cytotoxicity against four human cancer cell lines: kidney, breast, colorectal, and bladder cancer cells. Only compound 8 exhibited excellent cytotoxicity against all investigated cancer cell lines, with notably potent cytotoxicity against colorectal (SW620) cells (IC_{50}: 3.2 µM) and higher cytotoxicity than control (IC_{50}: 4.2 µM). Mechanistic analyses such as colony formation, cell cycle arrests and flow cytometry analyses demonstrated an increase in intracellular ROS-induced apoptosis in SW620 cells, which is a potential mode of action for compound 8. Western blot research confirmed the apoptotic mechanism of 8 by showing overexpression of c-PARP, BAD, BAK, and AMPK and downregulation of BCL-2 and AKT. Taken together, the data showed that 8 induces apoptosis by increasing ROS. According to this study, a 4-chloromethyl substituent at the C3-phenyl group may be required for 8's cytotoxicity since other para substituents are inactive. Therefore, structure-activity analysis of 8 in related proteins can be studied.

KEYWORDS:
Flavone-based compounds;
ROS-dependent;
Apoptosis;
Colon cancer.

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