(P002)

Apoptosis induction and activation of the mitogen-activated protein kinase pathway in human U-937 leukaemia cells by the synthetic flavanone 6-methoxy-2-(naphtalen-1-yl)-chroman-4-one.

[a]Francisco Estévez, [a]Ester Saavedra, [a]Henoc Del Rosario, [b]Ignacio Brouard, [c]Judith Hernández-Garcés, [c]Celina García, [a]José Quintana, [h] , [i]

[a]University of Las Palmas de Gran Canaria.
[b]IPNA-CSIC.
[c]University of La Laguna.

Chalcones (1,3-diphenyl-2-propen-1-ones) are biosynthetic precursors of flavonoids and some of them are potential anticancer agents. In this communication we report the synthesis of a new series of chalcones and their corresponding flavanones as well as their antiproliferative activity against the human tumour cell line U-937. This series of chalcone derivatives was characterized by the presence of a naphthalene ring as the second aryl system - which was kept unaltered. The structure-activity relationship of these chalcone derivatives and their corresponding cyclic compounds was investigated by the introduction of different substituents (methyl, methoxy, benzyloxy, chlorine) or by varying the position of the methoxy or benzyloxy groups on the A ring. The chalcone containing the methoxy group at 5' position of the A ring and its corresponding flavanone were the most cytotoxic compounds, with IC50 values of 2.8 ± 0.2 µM and 1.3 ± 0.2 µM, respectively. Synthetic flavanone was as cytotoxic as the antitumor agent etoposide against human leukaemia cells, but human peripheral blood mononuclear cells were more resistant than leukaemia cells to the cytotoxic effects of the flavanone. This compound induced (i) G2-M cell cycle arrest, (ii) apoptosis which was blocked by overexpression of the anti-apoptotic protein Bcl-2, and (iii) phosphorylation of p38 MAPK, extracellular-signal regulated kinases and c-jun N-terminal kinases / stress-activated protein kinases (JNK/SAPK) following different kinetics. Moreover, cell death was attenuated by the inhibition of mitogen-activated extracellular kinases and JNK/SAPK and was independent on reactive oxygen species generation.