Abstract

A range of substituted 1H-indole-2,3-diones (isatins) was synthesized to assess their capability to inhibit caspases and prevent apoptosis in Jurkat T cells. The key steps in the synthesis of such molecules involved electrophilic substitution of the C-5 position of the isatin nucleus (if necessary), N-alkylation, Wolff-Kishner reduction of the C-3 carbonyl group and finally, Knoevenagel condensation. The design and synthesis of such potential inhibitors was guided by SAR studies of peptide based inhibitors such as “Q-VD-O-Ph”, as well as small-molecule inhibitors based upon the isatins scaffold. Previously, 3-(2,6-difluorobenzylidene)-5-nitroindolin-2-one has been shown to inhibit apoptosis in human Jurkat T cells at 5 μM activity. Herein, it is shown that by increasing the functionality of such oxindole derived inhibitors from two points of variability (e.g., 1-(2,6-difluorobenzyl)-3-((pyridin-4-yl)methylene)indolin-2-one), to three points of variability by adding an electron-withdrawing group such as a chlorine atom at the C-5 position, the potency of the molecules against apoptosis was approximately increased up to 2-fold. Several other 3-substituted benzylidene derivatives were tested against human Jurkat T cells and were found to be active at micromolar concentrations.