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Synthesis of novel 1,2,4-oxadiazole topsentin analogs with antitumor activity

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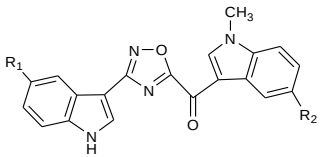
Marine environment is considered an unfailing source of compounds useful as a lead for the synthesis of new molecules of pharmaceutical interest, including some of the most potent antineoplastic agents yet discovered. Topsentins are relevant examples of marine alkaloids, isolated from the sponge *Spongosorites sp.*, with antitumor activity.[1,2] In this study we conveniently synthesized a new series of topsentin analogs with the aim to target pancreatic cancer.



R_1=R_2=R_3= H, Br, F, OCH_3

Figure 1. Structure of the new series of topsentin analogs

The inhibitory nature of new oxadiazole analogs (Fig.1) was examined in SUIT-2, CAPAN-1 and PANC-1 pancreatic cancer cell lines. All tested compounds showed promising antiproliferative activity at micromolar concentrations, against all the three pancreatic cancer cell lines, as confirmed by the range of IC_{50} values, from 0.4 to 7.14 μM. Cells exposed to oxadiazole compounds for 24 hours showed an increase of G2/M phase highlighting an additional induction of apoptotic cell death. Of note, the over-expression of *MMP-9* and *SNAIL2* genes suggests the induction of feedback mechanisms to counteract the anti-migration activity of these compounds, as assessed by the reduced cell migration of CAPAN-1 cells by 40-50%.

Our findings demonstrated the cytotoxic and anti-migration activities of new 1,2,4-oxadiazole topsentin analogs in several preclinical models of pancreatic cancer, supporting the use of this compounds as new anticancer agents.

Bibliografia

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