Biological evaluation of new 1,2,4-oxadiazole topsentin analogs as anticancer agents

by Barbara Parrino | Daniela Carbone | Stella Cascioferro | Btissame El Hassouni | Godefridus J. Peters | Girolamo Cirrincione | Elisa Giovannetti | Patrizia Diana | Dipartimento STEBICEF, Università degli Studi di Palermo, Via Archirafi 32, 90123, Palermo, Italy | Dipartimento STEBICEF, Università degli Studi di Palermo, Via Archirafi 32, 90123, Palermo, Italy. Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, De Boelelaan 1117, 1081HV Amsterdam, The Netherlands | Dipartimento STEBICEF, Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy | Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, De Boelelaan 1117, 1081HV Amsterdam, The Netherlands | Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, De Boelelaan 1117, 1081HV Amsterdam, The Netherlands | Dipartimento STEBICEF, Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy | Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, De Boelelaan 1117, 1081HV Amsterdam, The Netherlands | Dipartimento STEBICEF, Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy

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Introduction

Marine environment is considered an inexhaustible source of compounds useful as a lead for the synthesis of new molecules of pharmaceutical interest. Topsentins are relevant examples of marine alkaloids, isolated from the sponge Spongosorites sp., with antitumor activity.[1,2] In order to improve the outcome of pancreatic cancer, in this study we synthesized a new series of topsentin analogs with the aim to obtain new anticancer agents against this disease.

Methods

The role of our new analogs (Fig.1) in the inhibition of cell growth and migration, as well as in the modulation of cell cycle and in the induction of the apoptosis was examined in SUIT-2, CAPAN-1 and PANC-1 pancreatic cancer cell lines. The inhibition of cancer cell proliferation was determined by the SRB assay and IC_{50} values have been derived using a non-linear regression analysis with the GraphPad Prism software. The analysis of apoptosis induction and the cell cycle progression have been performed by flow cytometry, while cell migration

has been examined using the in vitro scratch wound healing assay. In order to evaluate the capability to modulate the epithelial to mesenchymal transition (EMT), we evaluated the modulation of gene expression of key EMT determinants using a specific Real-Time PCR analysis on the total mRNA extracted from PANC-1 and CAPAN-1 cells exposed to the new oxadiazole compounds.

Results

All compounds tested in the present study resulted active 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 mM. As far as concerned the effects on cell cycle, a G2/M phase increase has been registered in SUIT-2 cells after treatment with oxadiazole compounds. Induction of apoptotic death following treatment with new derivatives suggests that they may orchestrate a potential axis of autophagy and apoptosis in SUIT-2, CAPAN-1 and PANC-1 cells which can, in turn, facilitates cellular destruction. Furthermore, the treatment with the two most cytotoxic analogs (for 24 hours at 5 mM) reduced the cell migration of CAPAN-1 cells by 40-50%. 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 wound healing, in particular in CAPAN-1 cells.

Conclusions

Our findings demonstrated the cytotoxic and anti-migration activities of neo-synthetic compounds against several preclinical models of pancreatic cancer, supporting further studies to evaluate these compounds as anticancer agents against this tumor type.

References

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