University *of Ljubljana*
Faculty *of Pharmacy*

2nd Meeting of the Paul Ehrlich MedChem Euro-PhD Network

BOOK OF ABSTRACTS

9th-11th September 2012

Ljubljana, Slovenia

http://www.medchemeurophd2012.eu/

MARINE ALKALOIDS ANALOGUES AS KINASE INHIBITORS

B. Parrino[1]

[1]Dipartimento di Scienze e Tecnologie Molecolari e Biomolecolari (STEMBIO), Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy

Indole alkaloids have received a great deal of attention because of their broad spectrum of biological activities including antimicrobial, antiviral and antitumor properties (1,2).
Nortopsentins A-C, having a characteristic 2,4-bis(3'-indolyl)imidazole skeleton, showed *in vitro* cytotoxicity against P388 cells (IC_{50} 1.7-7.8 μg/ml). Their N-methylated derivatives exhibit a significant improvement in P388 activity compared to that of the parent compounds (IC_{50} 0.34-0.90 μg/ml) (3). In our previous work we reported the synthesis of two new series of bis-indolyl-5-membered heterocycles in which the imidazole moiety of nortopsentin was replaced by thiophene and pyrazole rings. Some of these compounds showed antiproliferative activity with GI_{50} values in the micro- and sub-micromolar range (4,5).
Considering the interesting results obtained for previous series, we synthesized 3-[2-(1*H*-indol-3-yl)-1,3-thiazol-4-yl)-1*H*-4-azaindole derivatives, in which the 4-azaindole ring substituted one indole system and the thiazole moiety replaced the imidazole nucleus of nortopsentin, in order to verify whether the aza-substitution to the indole system increases the antineoplastic activity.
For all synthesized compounds *in vitro* screen based on the sulforodamine B (SRB) assay was performed in order to study the antiproliferative effects of all the synthesized compounds. Four compounds consistently reduced the growth of all experimental models independent of *TP53* gene status, with IC_{50} values ranging from 2.20±0.13 to 19.36±2.63 μM, and were also able to inhibit CDK1 activity in a cell-free assay with IC_{50}<1 μM. Further results will be discussed.

REFERENCES

(1) Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. J. ***New bisindole alkaloids of the topsentin and hamacanthin classes from the Mediterranean marine sponge Rhaphisia lacazei.***. *J. Nat. Prod.* **2000**, *63*, 447 –451.
(2) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C.; Sim, C. J.; Jung, J. H. ***Cytotoxic bisindole alkaloids from a marine sponge Spongosorites sp.*** *J. Nat. Prod.* **2005**, *68*, 711 –715.
(3) Sakem, S.; Sun, H. H. ***Nortopsentins A, B,and C. Cytotoxic and antifungal imidazolediylbis[indoles]from the sponge Spongosorites ruetzleri.*** *J. Org. Chem.* **1991**, *56*, 4304-4307.
(4) Diana, P.; Carbone, A.; Barraja, P.; Montalbano, A.; Martorana, A.; Dattolo, G.; Gia, O; Dalla Via, L; Cirrincione, G. ***Synthesis and antitumor properties of 2,5-bis(3'-indolyl)thiophenes: analogues of marine alkaloid nortopsentin.*** *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2342-2346.
(5) Diana, P.; Carbone, A.; Barraja, P.; Martorana, A.; Gia, O.; Dalla Via, L.; Cirrincione, G. ***3,5-Bis(3'-indolyl)pyrazoles, analogues of marine alkaloid nortopsentin: synthesis and antitumor activity.*** *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6134-6137.