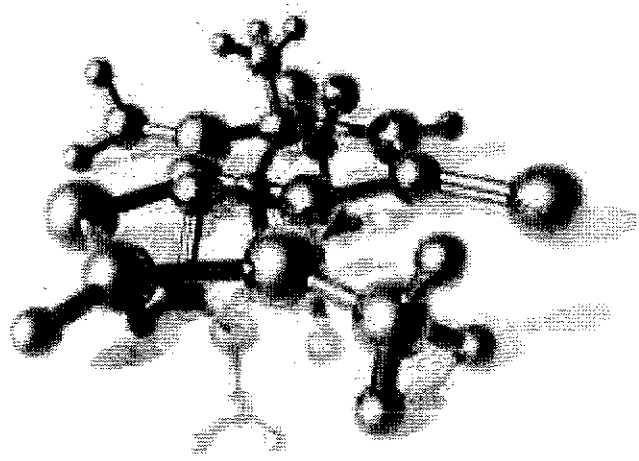
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

6° MEETING

NUOVE PROSPETTIVE IN CHIMICA FARMACEUTICA

Hotel Atlantic
Lungomare della Libertà, 15
Riccione (RN)
15 - 17 APRILE 2012



^{7}N ^{15}P ^{6}C ^{9}F 6

ANTITUMOR ACTIVITY OF 2,5-BIS-(3'-INDOLYL)-PYRROLES, DEAZA-ANALOGUES OF NORTOPSENTINS

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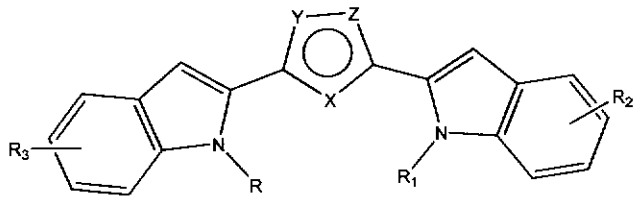
Marine indole alkaloids represent an important class of compounds because of their potent biological properties, such as antimicrobial, antiviral and antitumor activities.[1] In particular, **Nortopsentins** having a characteristic 2,4-bis(3'-indolyl)imidazole skeleton, isolated from Spongosorites ruetzleri, exhibited in vitro cytotoxicity against P388 cells (IC_{50} values: 4.5–20.7 μM). Their N-methylated derivatives showed a significant improvement in P388 activity compared to that of the parent compounds (IC_{50} values 0.8–2.1 μM).[2] Due to the interesting biological activities various analogues were synthesized.[3] We have recently reported the synthesis and the antitumor activity of new series of bis-indolyl-5-membered heterocycles of type **1-4** in which the imidazole moiety of nortopsentin was replaced by thiophene, pyrazole, isoxazole, and furan rings. Some of these compounds showed antiproliferative activity against a wide range of human tumor cell lines with GI_{50} values from micromolar to sub-micromolar concentrations.[4] In our attempts to search for new antitumor compounds, we synthesized 2,5-bis-(3'-indolyl)-pyrroles of type **5**, in which a pyrrole ring substituted the central imidazole ring of Nortopsentin. Compounds tested by the NCI showed GI_{50} values at micromolar concentrations. The most active compounds showed selectivity towards bladder cancer cell lines and cell lines derived from melanoma. Moreover we investigated the in vivo efficacy in nude mice by using the bladder cancer xenograft BXF 1218 and the melanoma MEXF 276. Results will be discussed.



Nortopsentins X=N; Y=CH; Z=NH, NMe; R=H, Me; R_1=H, Me; R_2=H, Br; R_3=H, Br ; **1**: X=S; Y=Z=CH; R=H, Me; R_1=H, Me, SO_2Ph; R_2=R_3=H, Me, OMe, Cl, Br; **2**: X=CH; Y=N; Z=NH, NMe; R=R_1=Me; R_2=R_3=H, Me, OMe, Cl, Br ; **3** X=CH; Y=N; Z=O; R=R_1= Me; R_2=R_3=H, Me, OMe, Cl, Br; 4: X=O; Y=Z=CH; R= R_1= Me; R_2=R_3=H, Me, OMe; **5**: X=N; Y=Z=CH; R= R_1= Me; R_2=R_3=H, Me, OMe, Cl, Br

References

[1] a) J. Shin, Y. Seo, K. W. Cho et al. *J. Nat. Prod.* **1999**, 62, 647-649; b) A. Casapullo, G. Bifulco, I. Bruno et al. *J. Nat. Prod.* **2000**, 63, 447–451; c) B. Bao, Q. Sun, X. Yao et al. *J. Nat. Prod.***2005**, 68, 711–715; [2] S. Sakemi, H. H. Sun, *J. Org. Chem.* **1991**, 56, 4304–4307; [3] a) X.-H. Gu, X.-Z. Wan, B. Jiang, *Bioorg. Med. Chem. Lett.* **1999**, 9, 56–572; b) B. Jiang, X.-H. Gu, *Bioorg. Med. Chem.* **2000**, 8, 363 –371; c) B. Jiang, X. Xiong, C. Yang, *Bioorg. Med. Chem.* **2001**, 9, 1149–1154; [4] a) P. Diana, A. Carbone, P. Barraja, A. et al. *Bioorg. Med. Chem. Lett.* **2007**, 17, 2342–2346. b) P. Diana, A. Carbone, P. Barraja et al. *Bioorg. Med. Chem. Lett.* **2007**, 17, 6134 – 6137; c) P. Diana, A. Carbone, P. Barraja et al. *Bioorg. Med. Chem.* **2010**, 18, 4524–4529.