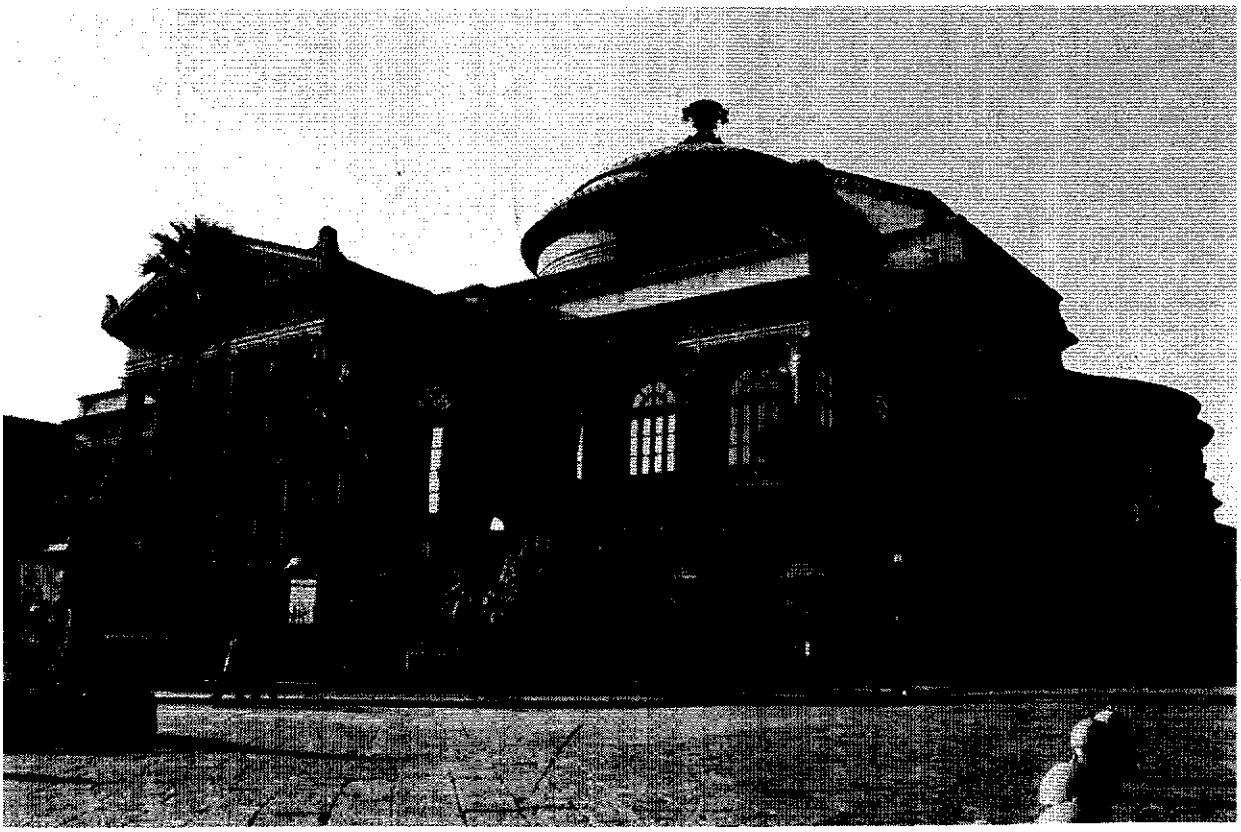
Società Chimica Italiana

EFMC
European Federation
for Medicinal Chemistry

21ST NATIONAL MEETING ON MEDICINAL CHEMISTRY



BOOK OF ABSTRACTS

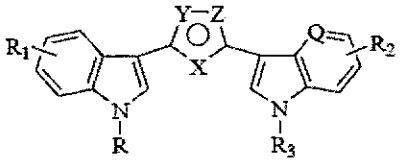
Palermo July 17 – 20, 2012

3-[2-(1*H*-Indol-3-yl)-1,3-thiazol-4-yl)-1*H*-4-azaindole a new series of Kinase Inhibitors

Barbara Parrino

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

Marine indole alkaloids have emerged as an important structural class because of their great variety of biological activities including antimicrobial, antiviral and antitumor properties. 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) [1]. We have recently reported two new series of bis-indolyl-5-membered heterocycles in which the imidazole moiety of nortopsentin was replaced by thiophene **1** and pyrazole **2** rings. Some of these compounds showed antiproliferative activity against a broad spectrum of human tumor cell lines with GI_{50} values in the micro- and sub-micromolar range [2,3]. Many other analogues of the marine nortopsentins such as 2,4-bis(3'-indolyl)thiazoles **3**, in which the heterocyclic core of the system is constituted by thiazole ring, have been synthesized. These derivatives possessed strong inhibitory activity against a wide range of human tumor cell lines [4]. In the attempt of looking for novel antitumor compounds, we thought it was interesting to synthesize 3-[2-(1*H*-indol-3-yl)-1,3-thiazol-4-yl)-1*H*-4-azaindole derivatives **4**, 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.



Nortopsentins X = N, Y = NH, Z = CH

1 X = S, Q = Y = Z = CH; **2** Q = X = CH, Y = N, Z = NR_4;
3 X = N, Y = S, Q = Z = CH; **4** Q = X = N, Y = S, Z = CH

We used an *in vitro* screen based on the sulforodamine B (SRB) assay to study the antiproliferative effects of all the synthetized compounds **4** in a panel of cell lines with different histologic origin, including breast cancer, androgen-independent prostate cancer, pancreatic carcinoma and peritoneal mesothelioma. Cells were exposed to 0.05-50 μM of each compound for 72 h. 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. Moreover, treatment with the most active compound, which induced the greatest *in vitro* inhibition of CDK1 (IC_{50}=0.66 μM), also reduced the cyclin B1-associated CDK1 kinase activity (as evaluated by phosphorylation of the histone H1) in a peritoneal mesothelioma cell line. A 4-fold and 3-fold increase in caspase-9 and caspase-3 (as assessed by hydrolysis of the specific fluorogenic substrates), respectively, was also observed in cells treated with the same compound compared to untreated cells. Overall, our results demonstrate that 3-[2-(1*H*-indol-3-yl)-1,3-thiazol-4-yl)-1*H*-4-azaindole **4** derivatives show antiproliferative activity, and suggest the opportunity to further develop them as anti-CDK chemotherapeutic agents.

[1] Sakem, S.; Sun, H. H. *J. Org. Chem.* 1991; 56:4304-4307. [2] Diana, P.; Carbone, A.; Barraja, P.; Montalbano, A.; Martorana, A.; Dattolo, G.; Gia, O; Dalla Via, L; Cirrincione, G. *Bioorg. Med. Chem. Lett.* 2007; 17:2342-2346. [3] Diana, P.; Carbone, A.; Barraja, P.; Martorana, A.; Gia, O.; Dalla Via, L.; Cirrincione, G. *Bioorg. Med. Chem. Lett.* 2007; 17:6134-6137. [4] Jiang, B.; Gu, X-H. *Bioorg. Med. Chem.* 2000; 8:363-371.