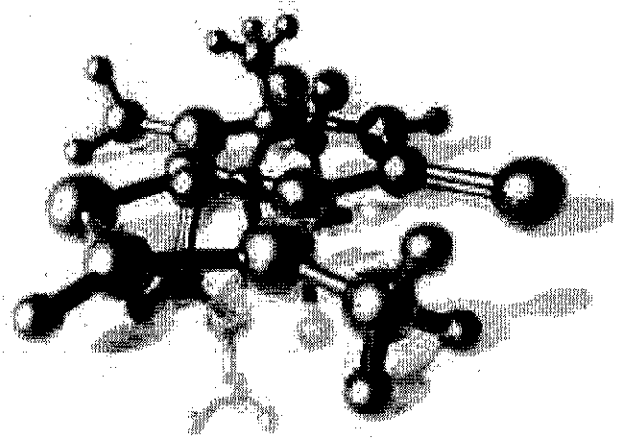
ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

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

PYRAZOLO[3,4-*h*]QUINOLIN-2-ONES WITH PHOTOBIOLOGICAL PROPERTIES

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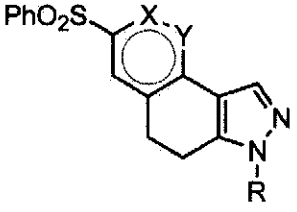
Angelicin, and its linear congener (psoralen) are photoactivable drugs which, upon irradiation with UVA light generate covalent bonds with thymine bases of DNA.[1] Considering our interest in the pyrrole chemistry, in the past years we have focused our attention of heteroanalogues of angelicin reporting the synthesis of the new ring systems pyrroloquinolin-2-ones, which showed in some cases higher cytotoxicity than 8-MOP (8-methoxypsoralen) used as reference drug.[2-5] We now report the synthesis of the *pyrazolo[3,4-h]quinolin-2-one* ring system in which a pyrazole is fused to the quinolinone moiety, with the aim of evaluate the influence on the antiproliferative activity of the substitution of pyrrole ring with pyrazole. Several pyrazolo[3,4-*h*]quinolin-2-one derivatives of type **1** were isolated and further subjected to methylation giving either the 1-methyl pyrazoloquinolin-2-ones **2** and the 2-methoxypyrazoloquinolines of type **3**. Cytotoxicity was determined against 6 human tumor cell lines: K-562, Jurkat, HL-60, A-431, A-549, LoVo and MCF-7. Interestingly, at variance of the previous series of pyrroloquinolinones some compounds showed activity already in the dark reaching the low micromolar range. In particular pyrazoloquinolin-2-ones **1,2** exhibited higher selectivity against carcinoma cell lines A-431, A-549 and MCF-7 whereas the 2-methoxy derivatives **3** reduced cell viability mainly in the Jurkat cell line. Moreover, the phototoxicity of these derivatives was studied and many derivatives presented a clear UVA-dose decrease in cell survival, the most active compounds being the 2-methoxypyrazoloquinolines of type **3** with GI_{50} values reaching the low micromolar range.



1 Y=NH, X=CO
2 Y=NMe, X=CO
3 Y=N, X=OMe

References
[1] Dall'Acqua, F; Viola,G. In *Photobiology for the 21th century*, Coohil TP, Valenzeno D P Eds. Valdenmar: Overland Park, KS, **2001**, 325.
[2] Barraja, P.; Diana, P.; Montalbano, A. et al. *Bioorg. Med. Chem.* **2006**, 14, 8712–8728.
[3] Barraja, P.; Caracausi, L.; Diana, P. et al. *Bioorg. Med. Chem.* **2010**, 18, 4830–4843.
[4] Barraja, P.; Cirrincione, G.; Dall'Acqua, F. et al. **2011**, WO 2011013159; *Chem. Abstr.* **2011**, 154, 182251.
[5] Barraja, P.; Diana, P.; Montalbano, A. et al. *Bioorg. Med. Chem.* **2011**, 19, 2326–2341.