EUROPEAN FEDERATION FOR MEDICINAL CHEMISTRY
SOCIETÀ CHIMICA ITALIANA - DIVISIONE DI CHIMICA FARMACEUTICA

European School of Medicinal Chemistry

(XXXIII Advanced Course of Medicinal Chemistry and
"E. Duranti" National Seminar for PhD Students)

2013

Urbino, July 7-12

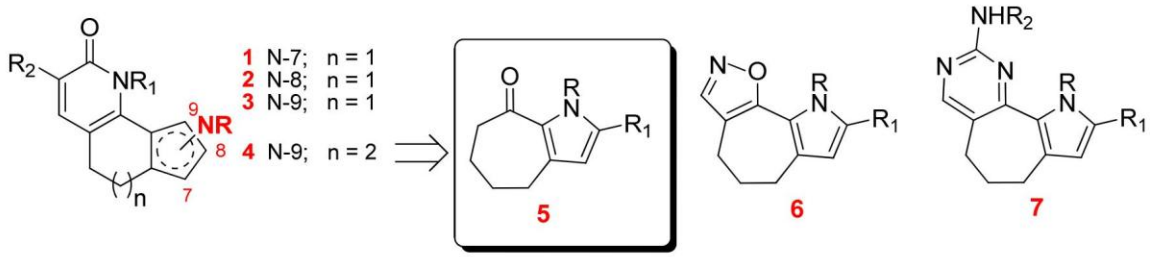
PROCEEDINGS OF PhD STUDENT POSTER SESSION

CYCLOHEPTAPYRROLO SYSTEMS WITH ANTITUMOR PROPERTIES

Daniele GIALLOMBARDO

Dipartimento di Scienze e Tecnologie Biologiche Chimiche e Farmaceutiche (STEBICEF)
Università degli Studi di Palermo – Via Archirafi, 32 – 90123 Palermo (Italy)
Dottorato di Ricerca in Scienze Farmaceutiche – Ciclo XXIV

The photodynamic therapy (PDT) is an interesting therapeutic option for the treatment of various tumors, including carcinomas of the esophagus and lung. It requires systemic administration of a photosensitizing agent (PS), followed by irradiation of the tumor with light of proper wavelength in accordance to the absorption spectrum of the PS. PDT is a rapidly expanding field, and is becoming widely recognized as a valuable treatment option, expecially for localized tumors. Up to date it is used for the treatment of skin diseases like psoriasis, vitiligo, cutaneous T-cell lymphoma (CTCL), and it has also been applied to T-cell mediated autoimmune diseases (progressive systemic sclerosis, lupus erythematosus, pemphigo vulgaris and AIDS).[1] The NCI has approved the use of a linear furocumarin, 8-methoxypsoralen (8-MOP), as photosensitizer for the treatment of T-cell lymphoma and it is still in clinical trials also for Hodgkin and non-Hodgkin lymphomas.



During the past years, our research group, studied different classes of compounds with antitumor properties. Among these pyrrolo[2,3-*h*]quinolin-2-one **1**, pyrrolo[3,4-*h*]quinolin-2-one **2** and pyrrolo[3,2-*h*]quinolin-2-one **3** showed very promising photosensitizing properties in some cases with higher cytotoxicity than 8-MOP (GI_{50} 0.4-16.4 μM, 1.1-15.0 μM and 0.2-7.4 μM respectively).[2] Moreover they usually localize in mitochondria producing reactive oxygen species (ROS) responsible of the cellular death. Additionally, the class of pyrrolo[3,2-*h*]quinolin-2-one **3** demonstrated a great potential in the modulation of long term side effects, as they do not induce DNA damage at variance of 8-MOP. This result is of extraordinary importance to cover this products with an international patent.[2]

In this light, it was planned for my project, the syntheses of new ring systems *tetrahydropyrrolo [3',2':6,7]cyclohepta[1,2-b]pyridin-9(1H)-one* of type **4** with the aim of evaluating the effect on the photochemotherapeutic activity of the expansion of the central ring on the tricyclic systems.

Ketones **5**, suitable substrates for our purpose, were functionalized on the nitrogen atom and subjected to the synthetic pathway leading to the desired products **4**. The evaluation of phototoxicity of the new derivatives at different UV-A doses is in progress.

Ketones **5** were used as scaffold for other reaction of cyclization, leading to the *tetrahydropyrrolo[2',3':3,4]cyclohepta[1,2-d][1,2]oxazole* ring system **6**. The [1,2]oxazole nucleus is part of many drugs with antitumor activity. Among these diaryiloxazoles showed strong growth inhibitory activities against human cancer cell lines showing in some cases very high antitubulin activity [3].

In our group, the [1,2]oxazole core was introduced in a tricyclic system containing the pyrrole moiety, obtaining the *[1,2]Oxazolo[4,5-g]indole* system, which showed activity in the micromolar - nanomolar range (GI_{50} 0.03-52.4 μM).[4] Thus, we annelated the [1,2]oxazole ring on ketones **5** through a versatile route allowing the preparation of a number of derivatives of the new ring system **6** which have been submitted to NCI of Bethesda to evaluate the antiproliferative activity against a panel of about 60 human tumor cell lines divided into 9 subpanels (breast, ovaries, lung, colon, CNS, melanoma, leukemia, kidney, prostate). Early results indicated a good potential of this class of compounds showing growth inhibitory activity reaching the nanomolar range. Further results will be discussed.

On continuing our studies on tricyclic systems, we set the synthesis of *tetrahydropyrrolo [3',2':6,7] cyclohepta[1,2-d]pyrimidin-2-amine* **7**. The pyrimidine nucleus is of great interest, being the scaffold of

many antitumor drugs, and compounds that incorporate such moiety have recently emerged as inhibitors of cyclin dependent kinases (CDKs)[5] and Polo-like kinase 1 (Plk1).[6] Overexpression of these kinases is found in a lot of number of cancers, in fact they are recognized to be key components in the control of the cycle cell progression with important roles on the mitotic entry, centrosome duplication, bipolar mitotic spindle formation, transition from metaphase to anaphase, cytokinesis and maintenance of genomic stability.

Given this results of considerable importance, it was planned the synthesis of this new class of compound **7**, starting from our intermediates of type **5**, in which, in only two steps, the pyrimidine ring was anellated to the indole moiety bearing the proper decoration with the aim to obtain the best interactions with the above mentioned kinases. Biological screenings are in progress to evaluate their antiproliferative activity and their possible interaction with the kinases mentioned before.

References:

1. See for example: Rook, A. A. *NY Acad Sci.* **1991**, *636*, 209-216; Gollnick, H.P.; Owsianowski, M.; Taube, K. M.; Orfanos, C.E. *J. Acad. Dermatol.* **1993**, *28*, 122-124.

2. Barraja, P.; Diana, P.; Montalbano, A.; Dattolo, G.; Cirrincione, G.; Viola, G.; Vedaldi, D.; Dall'Acqua, F. *Bioorg. Med. Chem.*, **2006**, *14*, 8712-8728; Barraja, P.; Diana, P.; Montalbano, A.; Carbone, A.; Viola, G.; Basso, G.; Salvador, A.; Vedaldi, D.; Dall'Acqua, F.; Cirrincione, G.; *Bioorg. Med. Chem.*, **2011**, *19*, 2326-2341; Barraja, P.; Caracausi, L.; Diana, P.; Carbone, A.; Montalbano, A.; Cirrincione, G.; Brun, P.; Palu, G.; Castagliuolo, I.; Dall'Acqua, F. *Bioorg. Med. Chem.* **2010**, *18*, 4830-4843; Dall'Acqua, F.; Cirrincione, G.; Barraja, P.; Salvador, A. PCT Int. Appl. **2011**, WO 2011013159.

3. Sun, C. M.; Lin, L. G.; Yu, H.J.; Cheng, C. Y.; Tsai, Y. C.; Chu, C. W.; Din, Y. H.; Chau, Y. P.; Don, M. J. *Bioorg. Med. Chem. Lett.*, **2007**, *17*, 1078-1081; Kaffy, J.; Pontikis, R.; Carrez, D.; Croisy, A.; Monneret, C.; Florent, J. C. *Bioorg. Med. Chem.*, **2006**, *14*, 4067-4077

4. Barraja, P.; Caracausi, L.; Diana, P.; Spano V.; Montalbano, A.; Carbone, A.; Parrino, B.; Cirrincione G.; *Chem. Med. Chem,* **2012**, *7*, 1901 – 1904.

5. Traquandi G.; Ciomei M.; Ballinari D.; Casale E.; Colombo N.; Croci V.; Fiorentini F.; Isacchi A.; Longo A.; Mercurio C.; Panzeri A.; Pastori W.; Pevarello P.; Volpi D.; Rousell P.; Vulpetti A.; Brasca M.G. *J. Med. Chem.,* **2010**, 53, 2171-2187.

6. Beria, I.; Ballinari, D.; Bertrand, J.A.; Borghi, D.; Bossi, R.T.; Brasca, M.G.; Cappella, P.; Caruso, M.; Ceccarelli, W.; Ciavolella, A.; Cristiani, C.; Croci, V.; De Ponti, A.; Fachin, G.; Ferguson, R.D.; Lansen, J.; Moll, J.K.; Presenti, E.; Posteri, E.; Perego, R.; Rocchetti, M.; Storici, P.; Volpi, D.; Valvasina, B. *J. Med. Chem.,* **2010**, 53, 3532-3551.