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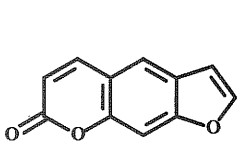
PYRROLO-FUSED HETEROCYCLES AS PHOTOCHEMOTHERAPEUTIC AGENTS

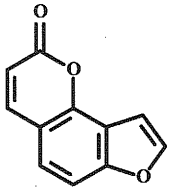
Virginia SPANÒ

Università di Palermo – Dipartimento Farmacochimico, Tossicologico e Biologico
Via Archirafi, 32 – 90123 Palermo
Dottorato di Ricerca in Scienze Farmaceutiche – Ciclo 2005-2006 (XX)

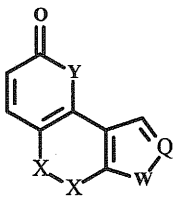
Psoralen **1** and Angelicin **2**, linear and angular furocoumarins, are photoactivable drugs which upon UVA irradiation, intercalate into DNA and photobind with it.[1] They are currently used in PUVA therapy for the treatment of various skin diseases such as psoriasis, vitiligo and tumors such as T-cell lymphoma when used in conjunction with long-wave (320-400 nm) ultraviolet light (UV-A). Recently the synthesis of their heteroanalogues were reported.[2]



1 Psoralen

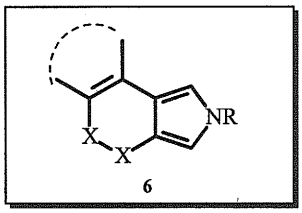


2 Angelicin



X-X= CH_2-CH_2 or CH=CH

3 Y=NH, W = N-R, Q=C-Me
4 Y=NH, W = C-R, Q=N-R
5 Y=S, W= N-R, Q=C-R



6

For many years the research group I work with, has focused the attention on the synthesis of polycyclic systems containing the pyrrole mojety endowed with biological activity and more recently the interesting field of photochemotherapy has been investigated. With the aim of preparing and studying new photoreactive agents with antiproliferative activity and decreased toxic side effects, thus it was reported the synthesis of the new ring systems pyrrolo[2,3-*h*]quinolin-2-one **3**, pyrrolo[3,4-*h*]quinolin-2-one **4** and thiopyrano[2,3-*e*]indol-2-one **5** whose derivatives showed higher cytotoxicity than 8-MOP (GI_{50} 0.4-16.4 μM, 1.1-15.0 μM and 0.2-17.0 μM respectively).[3]

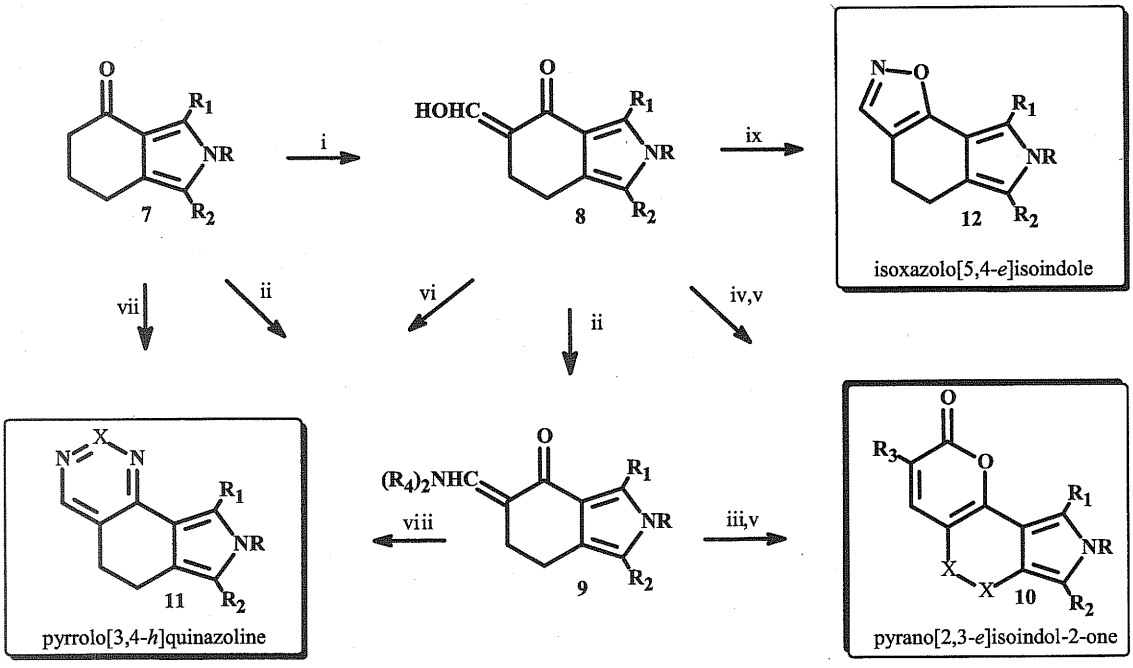
In this light considering the interesting results achieved in this field of research, it was planned for my project the synthesis of new ring systems of type **6** in which a six or a five membered ring was annelated to the isoindole moiety with the aim of evaluating their photochemotherapeutic activity. A first approach in this direction led us to investigate the synthesis and the biological activity of the new ring system *pyrano[2,3-e]isoindol-2-one* **10**, where pyrrole replaces the furane ring of Angelicin. The starting ketons **7** were conveniently prepared according to procedures reported in literature.[4] The first step of the synthetic pathway was the formylation of **7** with ethyl formate which led to the hydroxymethylene derivatives **8**. Enaminoketones **9** (R_4=Et) were successfully obtained by reacting these latter with diethylamine at room temperature, or directly by refluxing in toluene ketones **7** with an excess of *t*-butoxybis(dimethylamino)methane (TBDMAM) (R_4=Me). Reaction of enaminoketones **9** with the proper dialkyl malonate, used as solvent, afforded the desired tricyclic derivatives **10** (R_3=COOEt or COOMe, X-X= CH_2-CH_2) in moderate to good yields (30-73%). Alternatively, heating the hydroxymethylene derivatives **8** with (ethoxycarbonylmethylene)triphenilphosforane in TEG derivatives **10** (R_3=H) where obtained. Full aromatization of adducts **10** was accomplished with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing anhydrous benzene (X-X= CH=CH).

Having in hand the key intermediates **8** and **9**, which are versatile synthons as they can react with a variety of dinucleophiles, we decided to study the synthesis of the new ring system *pyrrolo[3,4-h]quinazolin-2-one,* an heteroanalogue of the pyrroloquinolinone ring **4** i which an additional nitrogen atom replaces the α-carbon of the pyridone ring. The quinazoline nucleus is of great interest because it is the scaffold of many antitumor drugs mainly acting as tyrosine kinase receptors (RTK); overexpression of these receptors is found in a number of cancers (e.g. breast, ovarian, colon, prostate).[5] Leading examples are the anticancer agent Tarceva (OSI 774/CP358,774) which is in Phase III clinical trials and the clinically approved anticancer agent Iressa (ZD1839).[6] Fused tricyclic pyrazolo- and pyrrolo-quinazoline showed GI_{50} values in the nanomolar range in the inhibition of (VEGFR).[7] Additionally lipophilic

inhibitors of the dihydrofolate reductase (DHFR) containing the quinazoline ring are used for neoplastic diseases.[8] Our synthetic approach for the synthesis of the mentioned ring system **11** consisted on the annelation of the pyrimidine ring on the isoindole moiety using hydroxymethylene isoindoles **8** as building blocks. Thus reaction of **8** with urea, as dinucleophile, in refluxing anhydrous ethanol afforded the tricyclic derivatives **11** (X=CO) (30-62%). The same ring system **11** (X=CH) (30-65%) was obtained refluxing ketones **7** in formamide with tris-(formylamino)-methane whereas reaction of the enaminoketons **9** with guanidine nitrate afforded the 2-amino substituted derivatives **11** (X=C-NH_2) (40-84%).

We further investigated annelation on the isoidole moiety to achieve the new ring system *isoxazolo[5,4-e]isoindole* **12**. The isoxazole nucleus is part of many drugs with antitumor activity. Among these diaryilisoxazoles showed strong growth inhibitory activities against human cancer cell lines. Moreover pteridine compounds containing the isoxazole moiety are active as dihydrofolate reductase (DHFR) inhibitors. These compounds showed growth *in vitro* inhibitory activities against breast (MCF7), lung (NCI-H460) and central nervous system (SF-268) cell lines.[9]

Ring closure on the hydroxymethylene building blocks **8** was easily achieved with hydroxylamine hydrochloride, in ethanol to give the desired derivatives **12** (40-72%). All derivatives of the new ring systems will be subjected to screenings to evaluate the photochemoterapeutic activity as well as the antiproliferative activity against a panel of human tumor cell lines.



(i) HCOOEt, benzene; (ii) $HNEt_2$, benzene or TBDMAM, toluene; (iii) $CH_2(COOEt)_2$ or $CH_2(COOMe)_2$ (X-X= CH_2-CH_2); (iv) $Ph_3PCH_2CO_2Et$, TEG (X-X= CH_2-CH_2); (v) DDQ, benzene (X-X= CH=CH); (vi) $CO(NH_2)_2$, ethanol; (vii) $(HCONH)_3CH$, formamide; (viii) $H_2NC(=NH)NH_2.HNO_3$, ethanol; (ix) $NH_2OH.HCl$, ethanol.

References:

[1] Comber, M.F. et al. *Synthesis* **1992**, 731; [2] Rodighiero, P. et al. *J. Med. Chem.* **1996**, *39*, 1293; [3] Barraja, P. et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2809; Barraja, P. et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2291; Barraja, P. et al. *Bioorg. Med. Chem.*, **2006**, *14*, 8712; [4] Spreitzer, H. et al. *Chem. Ber.* **1990**, *123*, 413; Clezy, P.S. et al. *Aus. J. Chem.* **1977**, *30*, 1337; Gabbutt, C.D. et al. *J. Chem. Soc. Perkins Trans. 1* **2002**, 2779; [5] Mtsuno, K. et al. *J. Med. Chem.* **2002**, *45*, 4513; Hennequin, L.F. et al. *J. Med. Chem.* **2002**, *45*, 1300; [6] Hunt, J.T. et al. *J. Med. Chem.* **2004**, *47*, 4054; Moyer, J.D. et al. *Cancer Res.* **1997**, *57*, 4838; [7] Palmer, B.D. et al. *J. Med. Chem.* **1997**, *40*, 1519; [8] Kuyper, L.F. et al. *J. Med. Chem.* **1996**, *39*, 892; [9] Sun, C.-M. et al. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1078; Chauhan, P.M.S. et al. *Bioorg. Med. Chem.* **2005**, *13*, 3513; Kaffy, J. et al. *Bioorg. Med. Chem.* **2006**, *14*, 4067.