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BOOK OF ABSTRACTS

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Synthesis and biological evaluation of cycloheptapyrrolo systems

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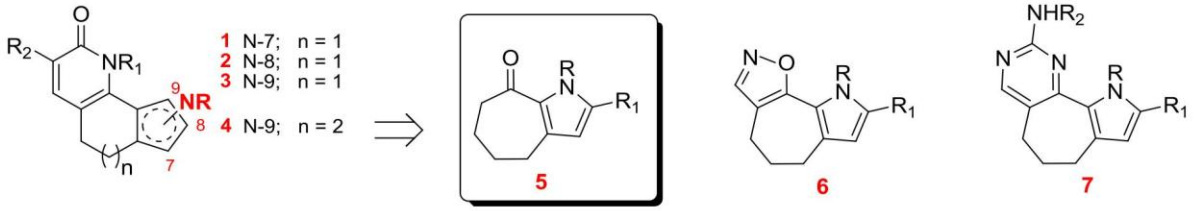
The photodynamic therapy (PDT) is an interesting therapeutic option for the treatment of several tumors. It requires systemic administration of a photosensitizing agent (PS), followed by irradiation of the tumor with light of proper wavelength in accordance to the absorption spectrum of the PS. During the past years, our research group, studied different classes of compounds with antitumor properties. Among these compounds of type 1, 2 and 3 showed very promising photosensitizing properties in some cases with higher cytotoxicity than 8-MOP, the photosensitizer used for the treatment of T-cell lymphoma. 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 (1). In this light, it was planned the syntheses of new ring systems tetrahydropyrrolo [3',2':6,7]cyclohepta[1,2-b]31yridine-9(1H)-one of type 4 with the aim of evaluating the effect of the expansion of the central ring on the tricyclic systems. The phototoxicity of the new derivatives will be discussed.



Ketones 5 were used as key synthons for further cyclization reactions leading to the tricyclic systems 6 and 7. The [1,2]oxazole core was previously introduced by us 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 (GI50 0.03-52.4 μM) (2). Thus, we annelated the [1,2]oxazole ring on ketones 5 obtaining a number of derivatives of the new ring system tetrahydropyrrolo[2',3':3,4]cyclohepta[1,2-d][1,2]oxazole 6. These latter were submitted to NCI of Bethesda to evaluate the antiproliferative activity against a panel of 60 human tumor cell lines. Early results indicated a good potential of this class of compounds, showing growth inhibitory activity reaching the nanomolar range.

Moreover, we conveniently prepared tetrahydropyrrolo[3',2':6,7]cyclohepta[1,2-d]pyrimidin-2-amines 7. In fact, the pyrimidine nucleus is of great interest, being the scaffold of many antitumor drugs as strong inhibitors of cyclin dependent kinases (CDKs) and Polo-like kinase 1 (Plk1) (3). Biological screenings are in progress to evaluate their antiproliferative activity and their possible interaction with the kinases mentioned before.

References

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