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BOOK OF ABSTRACTS

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Isoindolo[1,5]benzoxazepine as potential antitumor and/or antiviral agents

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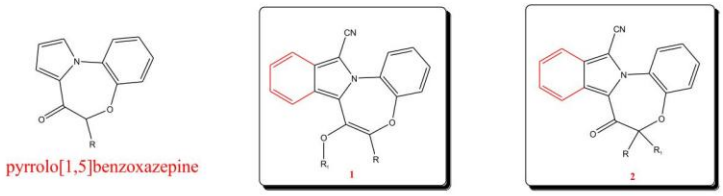
The benzodiazepine nucleus is a pharmacophoric scaffold, and many benzodiazepines have received great attention because of their wide range of therapeutic and pharmacological properties. In particular, the cytostatic effect of pyrrolo-benzoxazepine is widely reported. (1) Some pyrrolo[1,2-d][1,5]benzoxazepine (PBOX) compounds have been identified as novel microtubule-depolymerising agents (2) that possess the ability to potently induce apoptosis in several cancerous cell lines including, for example, K562 and MCF-7 cell line with minimal toxicity to normal peripheral blood mononuclear cells or bone marrow cells. (3) Moreover, PBOX show an anti-angiogenic activity targeting cells vasculature. In particular, in the Human Umbilical Vein Endothelial Cells (HUVEC) the formation of capillaries and the migratory activity of the cells is inhibited (IC50 = 0.06-0.70 μM). (4) The same pyrrolo[1,2-d][1,5]benzoxazepine ring system properly decorated also represents a new class of non-nucleoside inhibitors of reverse transcriptase (RT) of the immunodeficiency virus type 1 (HIV-1) that is capable of preventing cytopathogenicity in the T4 lymphocytes.
It has been identified that PBOX are able to bind the highly conserved part of the RT enzyme responsible for maintaining the primer terminus in the appropriate orientation for nucleophilic attack on an incoming dNTP showing an IC50 value of 0.036-10 μM. (5)
Considering the interesting results shown by the pyrrolo[1,2-d][1,5]benzoxazepine derivatives, the purpose of my project was the synthesis of the new isoindolo[1,2-d][1,5]benzoxazepine ring in order to evaluate whether the substitution of the pyrrole ring with an isoindole one could increase the antitumor and/or antiviral activity.
Isondolobenzoxazepine derivatives have also been functionalized with the ethyl or the acetyl group in the benzoxazepine ring, depending on whether the compounds have potential antiviral or antitumor activity, to obtain compounds of type 1 and 2.



R = phenyl, *p*-tolyl
R_1 = ethyl, acetyl

The biological screenings, in order to evaluate their antiproliferative and antiviral activity, are in progress.

References

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(3) See for example: D. M. Zisterer et al., J. Pharmacol. Exp. Ther. **2000**, 293, 48-59; M. M. Mc Gee et al., J. Pharmacol. Exp. Ther. 2001, 296, 31-40; M. M. Mc Gee et al., J. Biol. Chem. **2002**, 277, 18383-18389.
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