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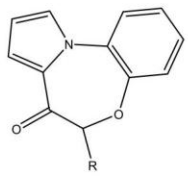
ISOINDOLO[1,5]BENZOXAZEPINES AS POTENTIAL ANTITUMOR AND/OR ANTIVIRAL AGENTS

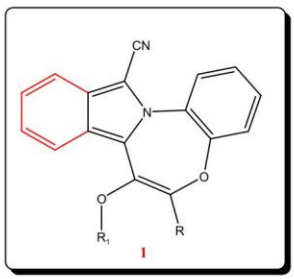
Cristina CIANCIMINO

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

Benzoxazepines are well-known for their potential biological effects such as antitumor and antiviral activity. 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, Jurkat T-lymphoma cell line, highly resistant chronic myeloid leukaemia (CML) K562 cell line and breast carcinoma 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 (IC_{50} = 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 a part of the β12-β13 hairpin, the so called "primer grip", with three highly conserved residues F227, W229 and L234, responsible for maintaining the primer terminus in the appropriate orientation for nucleophilic attack on an incoming dNTP. Mutations in this region significantly compromise RNA- and DNA-dependent DNA polymerase activities of RT.[5] The PBOX are able to bind exactly this part of the enzyme showing an IC_{50} value of 0.036-10 μM.[6]
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**.



pyrrolo[1,5]benzoxazepine



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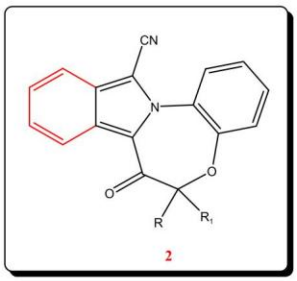

2

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

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

References:

1. See for example: M. Diaz-Gavilan et al., *Biorg. Med. Chem. Lett.*, **2008**, *18*, 1457-1460; L.C. Lopez-Cara et al., *Eur. J. Med. Chem.*, **2011**, *46*, 249-258; N. Blaquiere et al., WO 2011/036280 A1.
2. J.M. Mulligan et al., *Mol. Pharmacol.*, **2006**, *70*, 60-70.
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; M.M. Mc Gee et al., *J. Pharmacol. Exp. Ther.*, **2004**, *310*, 1084-1095.
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5. See for example: H. Pelemans et al., *Mol. Pharmacol.,* **2000,** *57,* 954-960; B.M. Wohrl et al., *J. Biol. Chem.,* **1997**, *272,* 17581-17587.
6. C. Fattorusso et al., *J. Med. Chem.,* **2005,** *48,* 7153-7165.