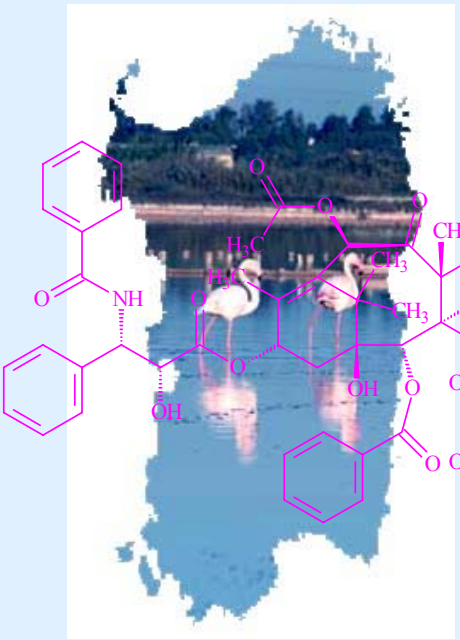
SardiniaChem 2006

GIORNATA DI STUDIO DEDICATA ALLA CHIMICA ORGANICA DELLE MOLECOLE BIOLOGICAMENTE ATTIVE

5 Giugno 2006, Complesso Universitario di Monserrato, Cagliari



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HANNO CONTRIBUITO ALLA REALIZZAZIONE DEL CONVEGNO:

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DESIGN AND SYNTHESIS OF NOVEL DNA BINDERS

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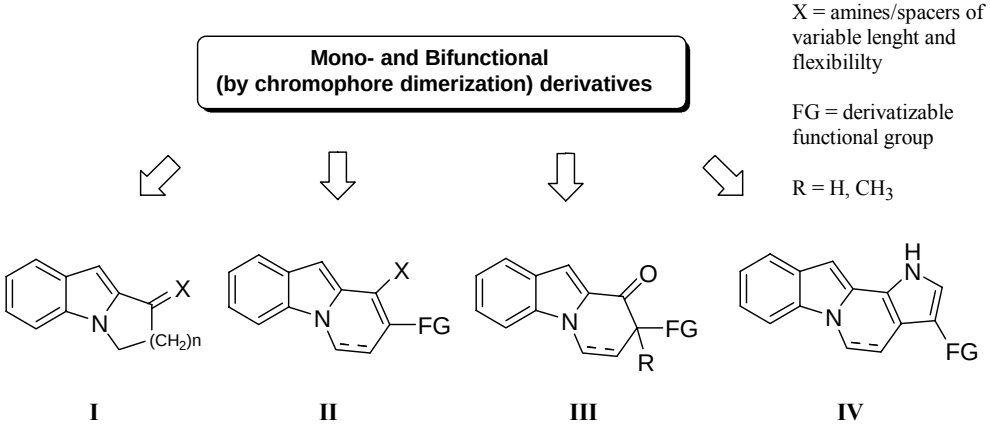
Design and development of nucleic acid targeted drugs is a challenging enterprise but real breakthroughs have been made in recent years[1-3]. Since DNA plays a fundamental role in normal cellular physiology and pathophysiology, it represents one of the most important molecular target of several chemotherapeutic drugs [4]. In particular, the discovery of nonpeptide-based DNA interactive drugs constituted one of the major goal. In fact, such agents offer the potential to interact with their intended target without falling hostage to cellular peptidases [1,3]. In this context, molecular recognition of DNA by polycyclic heterocycles having a planar structure bearing appropriate side chains have been widely investigated.

In the course of our work aimed at developing novel heterocycles of pharmaceutical interest, we designed and synthetized several templates as potential substrate in drug design. In particular, by adopting different strategies, we obtained a set of condensed ring systems (**I**-**IV**) as versatile structural platforms to be functionalized as possible DNA-interactive agents by intercalation and/or reversible enzyme inhibition such as topoisomerases, poly(ADP-ribose) polymerase-1 (PARP-1), and telomerase [5].



Herein, we report the synthesis of these new tricyclic and tetracyclic heteroaromatic systems and a first series of their derivatives as well as docking studies performed to investigate a possible DNA-binding mode of some model compounds.

Also, preliminary antiproliferative activity and other biological properties of these compounds are currently under investigation.

[1] Hurley, L.H. *Advances in DNA Sequence-Specific Agents*. Jai Press Inc., Greenwich, CT, **1992**, Vol.1
[2] Turner, PR; Denny, W.A. *Curr. Drug Targets.* **2000**, *1*, 1-14
[3] Graves, D.E.; Velea, L.M. *Curr. Org. Chem.* **2000**, *4*, 915-929
[4] Demeunynck, M.; Bailly, C.; Wilson, W.D. *DNA and RNA Binders. From Small Molecules to Drugs*, Wiley-VCH, Weinheim; **2003**, Vol.1 and 2
[5] Hurley, L.H. *Nat. Rev. Cancer* **2002**, *3*, 188-200.