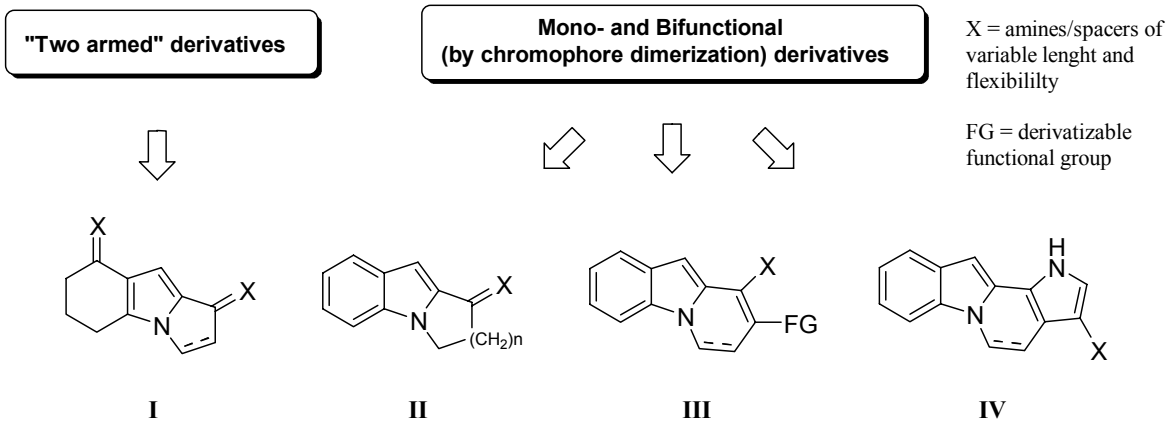
DESIGN AND SYNTHESIS OF NOVEL DNA BINDERS

Mario Sechi[a], Marco Derudas[a], Vanna Sanna[b], Roberto Dallocchio[c], Alessandro Dessì[c], Luciano Sannia[a], Giuseppe Paglietti[a], and Nouri Neamati[d]

[a]Dipartimento Farmaco Chimico Tossicologico, University of Sassari, 07100 Sassari, Italy
[b]Dipartimento di Scienze del Farmaco, University of Sassari, 07100 Sassari, Italy
[c]CNR-Istituto di Chimica Biomolecolare, sez. di Sassari, 07040 Li Punti, Italy
[d]Department of Pharmaceutical Sciences, University of Southern California, PSC 304BA, Los Angeles, CA 90089, USA

Design and development of nucleic acid targeted drugs is a challenging enterprise but real breakthroughs have been made in recent years [1]. 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. 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 [2], 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.



I **II** **III** **IV**

Herein, we report the synthesis of these new tricyclic and tetracyclic heteroaromatic systems and a first series of their derivatives as well as results of viscosimetry tritration and molecular dynamic 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 and will be presented.

[1] Demeunynck, M.; Bailly, C.; Wilson, W.D. *DNA and RNA Binders. From Small Molecules to Drugs*, Wiley-VCH, Weinheim; **2003**, Vol.1 and 2.
[2] Sechi, M., Mura, A.; Sannia, L.; Orecchioni, M.; Paglietti, G. *ARKIVOC* **2004**, (v), 97-106.