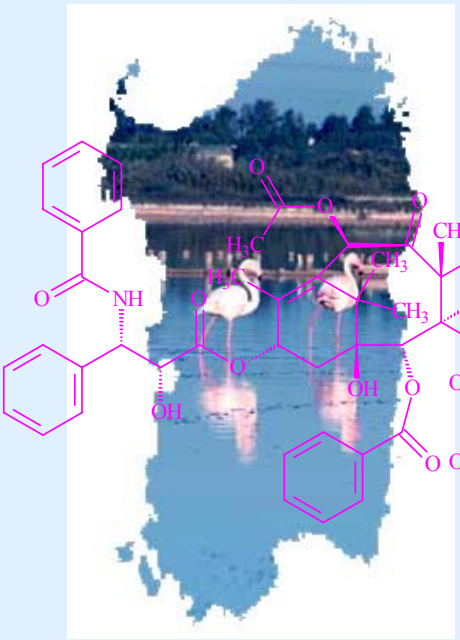
SardiniaChem 2006

GIORNATA DI STUDIO DEDICATA ALLA CHIMICA ORGANICA DELLE MOLECOLE BIOLOGICAMENTE ATTIVE

5 Giugno 2006, Complesso Universitario di Monserrato, Cagliari



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SYNTHESIS OF BIS-AMIDES AND HYDRAZIDE-CONTAINING DERIVATIVES OF MALONIC ACID AS HIV-1 INTEGRASE INHIBITORS

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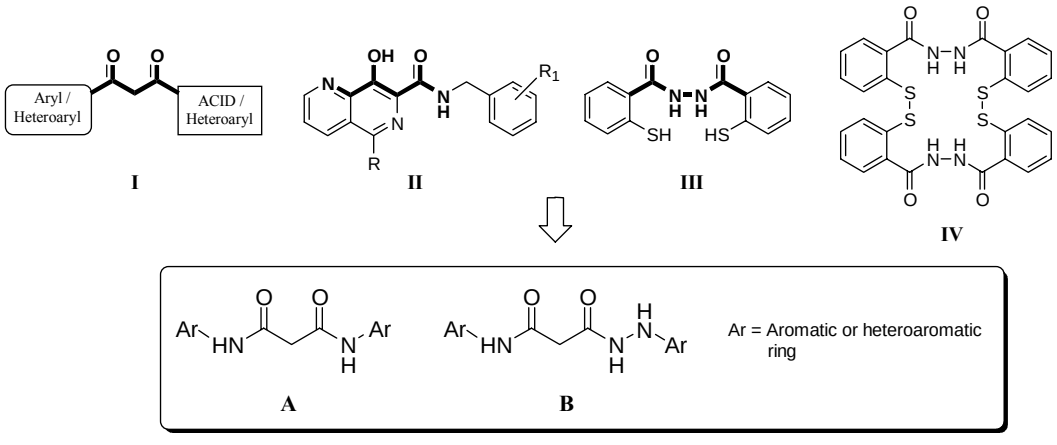
Integration of retroviral DNA into host chromosomes is an essential step in the viral life cycle. For HIV-1 this process is mediated by integrase (IN), one of the three enzymes encoded in the viral genome, which catalizes two coordinated biochemical reactions referred to as 3'-processing and strand transfer [1]. Because IN does not have a human homologue, it is one of the most promising targets in AIDS research.

In the past several years, numerous compounds with diverse structural features have been reported as IN inhibitors [2]. In particular a number of compounds bearing a diketo acid moiety (**I**), and more recently a class of naphthyridine carboxamide derivatives (**II**), were discovered as new selective and potent inhibitors [3].

With the aim to identify novel and/or unified putative pharmacophore required for activity we selected and formally combinated the main structural motifs of **I** and **II** together to the hydrazide fragment of compounds **III** and **IV**, previously reported [4] as new class of selective IN inhibitors having antiviral activity. Also, the possibility to generate a potential metal chelating pharmacophore has been considered. With this in mind, we designed two sets of symmetrical and unsymmetrical bis-amides and hydrazide derivatives of malonic acid of general structure **A** and **B**.



Synthesis and anti-IN activities of title compounds will be presented.

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[1] Asante-Appiah, E.; Skalka, A.M. *Adv. Virus Res.* **1999**, *52*, 351-369.
[2] Neamati, N. *Expert. Opin. Ther. Pat.* **2002**, *12*, 709-724.
[3] Johnson, A.A.; Marchand, C.; Pommier, Y. *Curr. Top. Med. Chem.* **2004**, *4*, 671-686.
[4] Neamati, N.; Lin, Z.; Karki, R.G.; Orr, A.; Cowansage, K.; Strumberg, D.; Pais, G.C.G., Voigt, J.H.; Nicklaus, M.C.; Winslow, H.E.; Zhao, H.; Turpin, J.A.; Yi, J.; Skalka, A.M.; Burke, T.R.Jr., Pommier, Y. *J. Med. Chem.* **2002**, *45*, 5661-5670.