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GIORNATA DI STUDIO DEDICATA ALLA CHIMICA ORGANICA DELLE MOLECOLE BIOLOGICAMENTE ATTIVE

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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 catalyzes 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 combined 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.