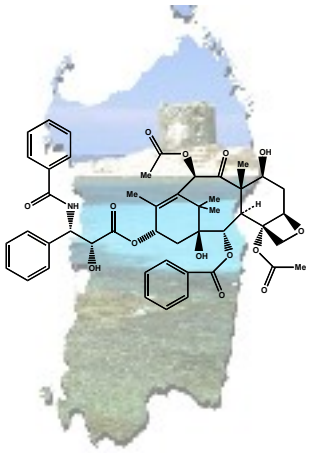
SardiniaChem2008

GIORNATA DI STUDIO DEDICATA ALLA CHIMICA ORGANICA DELLE MOLECOLE BIOLOGICAMENTE ATTIVE

30 Maggio 2008, Aula Magna della Facoltà di Scienze – Sassari



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DESIGN, SYNTHESIS, MOLECULAR MODELING AND ANTI-HIV 1 INTEGRASE ACTIVITY OF A SERIES OF PHOTOACTIVABLE DIKETO ACID-CONTAINING INHIBITORS AS AFFINITY PROBES

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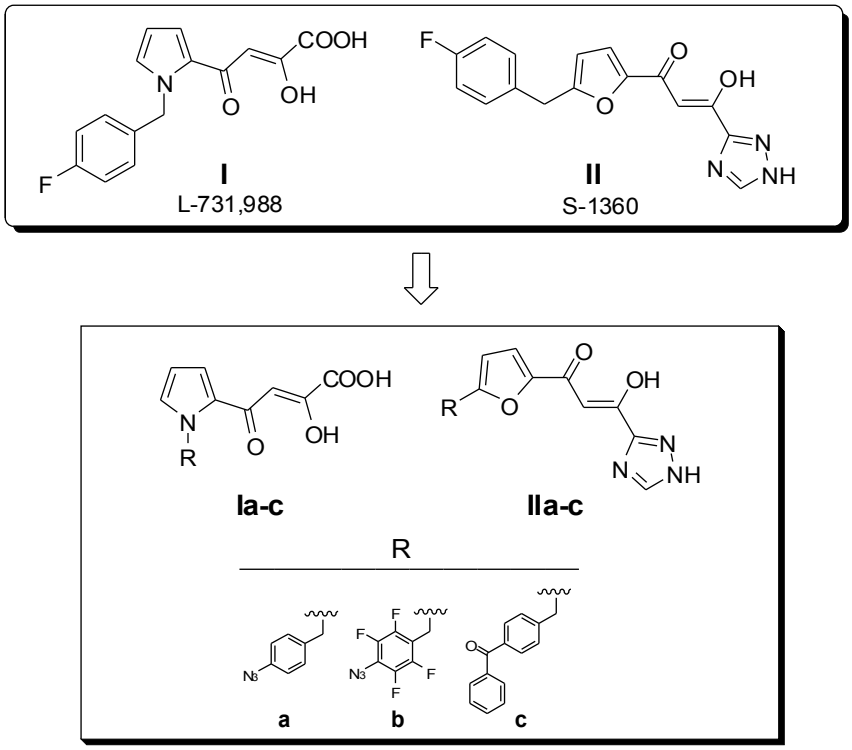
Photoaffinity Labelling (PL) is a powerful method in the chemical proteomic approach of protein functions [1-5]. This method is especially useful for the identification of ligand-binding sites of target proteins and for the investigation of ligand–receptor interactions. The use of affinity-labeled inhibitors to covalently modify the site of interaction and subsequent analysis of the protein have been very effective in providing useful informations about inhibitor binding for a multitude of therapeutic target proteins. Therefore, it could reasonably be applied in drug discovery and development processes.

For example, such approach can be used to obtain structural information detailing the association between the enzyme HIV-1 integrase (IN) and inhibitors under development. IN, the enzyme that mediates the insertion of viral DNA into the host genome, is an attractive and validated target for developing novel antiretroviral agents [6]. Application of PL to IN has elucidated a small number of inhibitor-binding sites to atomic resolution [7]. Recently, a class of compounds bearing a β-diketo acid (DKA) moiety, independently discovered by scientists from Shionogi & Co. Ltd. and Merck Research Laboratories, have emerged as the most promising lead in anti-HIV-1 IN drug discovery [8].In this context, to facilitate identification of DKA-binding sites, a series of photoactivable compounds, related to two potent diketo acid inhibitors (L-731,988 I, and S-1360 II), were prepared as DKA photoaffinity probes.

The photoprobes were tested for their ability to inhibit IN catalytic activity in in vitro assays employing purified enzyme. All tested compounds showed anti-IN activity in low micromolar concentration range. In cross-linking assays designed to measure disruption of substrate DNA binding, the photoprobes behaved similarly to a reference DKA inhibitor. Molecular modeling studies suggest that such derivatives interact within the IN active site in similar manner with respect to the parent diketo acid compound. Analogues **Ia-c** represent novel photoaffinity ligands, which may be useful in clarifying the HIV-1 binding interactions of DKA inhibitors.



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