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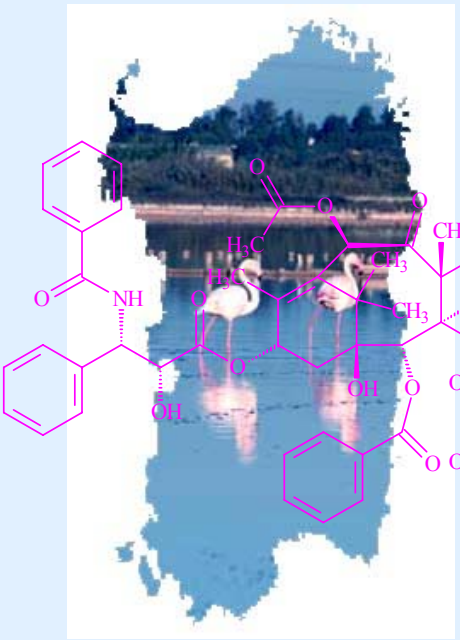

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FROM LIGAND TO COMPLEXES: INHIBITION OF HIV-1 INTEGRASE BY β-DIKETO ACID METAL COMPLEXES

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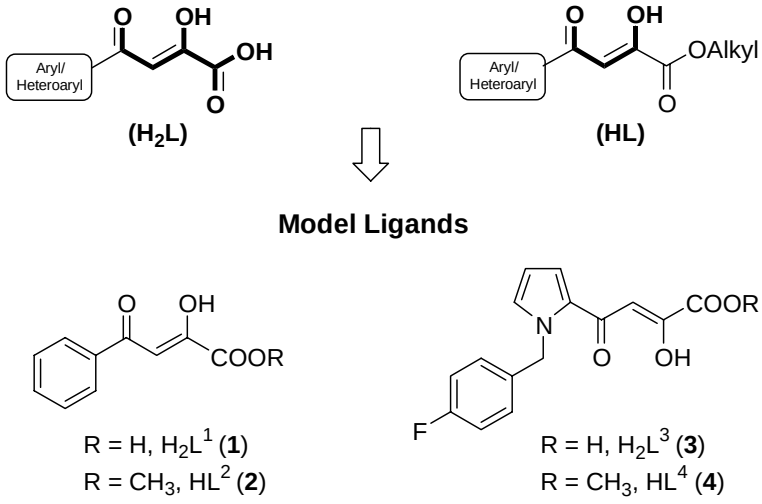
HIV-1 Integrase (IN) is an attractive and validated target for developing novel antiretroviral agents. [1-3]. Because of its vital role in the viral replication cycle, with no human counterpart of the enzyme known, the addition of an IN inhibitor to existing components of antiretroviral therapy is expected to improve the outcome of therapy by potential synergism, without exacerbating toxicity issues.

In the past several years, a plethora of compounds with diverse structural features have been reported as IN inhibitors [4]. Several of them inhibit both the viral enzyme and viral replication in cell-based assays as well as in animal models. However, as of today, no inhibitor of HIV-1 IN has been approved. Recently, a class of compounds bearing a β-diketo acid 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 [5]. It is believed that the β-diketo acid pharmacophoric motif could be involved in a functional sequestration of one or both divalent metal ions, which are critical cofactors at the enzyme catalytic site [6]. This would subsequently block the transition state of the IN-DNA complex. In this scenario, it is of paramount importance to acquire information about the mode of action of diketo acids, which could then be useful in the design of new compounds as IN inhibitors.

Starting from the hypothesis that these inhibitors are able to coordinate ions in solution before interacting on the active site, a series of potentiometric measurements have been performed to understand the coordination ability of the diketo acid pharmacophore towards the biologically relevant ion Mg^{2+}. Moreover, by using β-diketo acid/ester (**1-4**) as model

ligands with a set of divalent metal ions (Mg, Mn, Ni, Co, Cu, Zn), we obtained a series of complexes and tested them for anti-HIV-1 IN activity. Results demonstrate that the diketo acid functionality chelates divalent metal ions in solution and complexes with metals in different stoichiometric ratios are isolated. We postulate that the diketoacids act as complexes in their active form. In particular, they predominantly form species such as Mg_2L^{2+} and Mg_2L_2 (derived from diketo acids **1** and **3**, H_2L), and MgL^+ and MgL_2 (derived from diketo esters **2** and **4**, HL) at physiological pH. Furthermore, the synthesized mono- and dimetallic complexes inhibited IN at a high nanomolar to low micromolar range, with metal-dependency in the phenyl-diketoacid series. Retrospective analysis suggests that the electronic properties of the aromatic framework influence the metal-chelating ability of the diketo acid system. Therefore, the difference in activities is related to the complexes they preferentially form in solution, and these findings are important for the design of a new generation of IN inhibitors.



1) De Clercq, E. Strategies in the design of antiviral drugs. *Nature Rev. Drug Discovery* **2002**, *1*, 13-25.
2) De Clercq, E. New approaches toward anti-HIV chemotherapy. *J. Med. Chem.* **2005**, *48*, 1297-1313.
3) Neamati, N. Structure-based HIV-1 integrase inhibitor design: a future perspective. *Exp. Opin. Invest. Drugs* **2001**, *10*, 281-296.
4) Neamati, N. Patented small molecule inhibitors of HIV-1 integrase: a ten-year saga. *Expert Opin Ther Pat* **2002**, *12*, 709-724.
5) Pais, G. C. G.; Burke, T. R. Novel aryl diketo-containing inhibitors of HIV-1 integrase. *Drugs Future* **2002**, *27*, 1101-1111.
6) Pommier, Y.; Johnson A. A.; Marchand, C. Integrase inhibitors to treat HIV/AIDS. *Nature Rev. Drug Discovery* **2005**, *4*, 236-248.