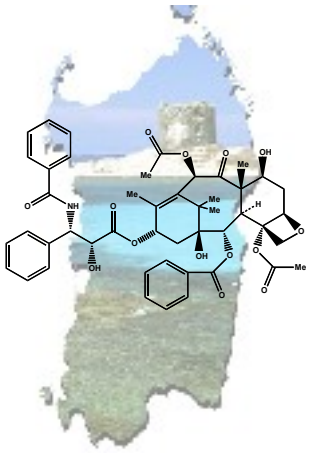
SardiniaChem2008

GIORNATA DI STUDIO DEDICATA ALLA CHIMICA ORGANICA DELLE MOLECOLE BIOLOGICAMENTE ATTIVE

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



Comitato Scientifico:
Giampaolo Giacomelli, *Univ. Sassari*; Giovanna Delogu *CNR Sassari*; Salvatore Cabiddu, *Univ. Cagliari*; PierPaolo Piras, *Univ. Cagliari*

Comitato Organizzatore:
Andrea Porcheddu, *Univ. Sassari*; Roberto Dallocchio, *CNR Sassari*;
Stefania De Montis *Univ. Cagliari*

Sponsor
hanno contribuito alla realizzazione del convegno:

UNIVERSITA' di Sassari-Dipartimento di Chimica; UNIVERSITA' di Sassari-Facoltà di Scienze MFN; CNR-Istituto di Chimica Biomolecolare, Sassari; UNIVERSITA' di Cagliari; SAPIO s.r.l.; SIGMA-ALDRICH s.r.l.; CARLO ERBA Reagenti; MEDINLAB s.r.l.; VWR International s.r.l.

FROM LIGAND TO COMPLEXES. PART 2. REMARKS ON HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 INTEGRASE INHIBITION BY B-DIKETO ACID METAL COMPLEXES

Mario Sechi,[a] Mauro Carcelli,[b] Dominga Rogolino,[b] Emilia Fisicaro,[c] Carlotta Compari,

[c] Mariano Biemmi,[c] Fabrizio Carta,[d] Christoph Sotriffer,[e] Martin Sippel,

[e]Laith Q. Al-Mawsawi,[f] Nouri Neamati[f]

[a]*Dipartimento Farmaco Chimico Tossicologico, Università di Sassari, Via Muroni 23/A, 07100 Sassari, Italy*

[b]*Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica, and* [c]*Dipartimento di Scienze Farmacologiche, Biologiche e Chimiche Applicate, Università di Parma, Parco Area delle Scienze 17/A, 43100 Parma, Italy*

[d]*School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK*

[e]*Institut für Pharmazie und Lebensmittelchemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany*

[f]*Department of Pharmaceutical Sciences, University of Southern California, School of Pharmacy, 1985 Zonal Avenue, PSC 304, Los Angeles, CA 90089, USA*

HIV-1 integrase (IN) is an essential enzyme for viral replication and a validated target for the development of drugs against AIDS [1,2]. Several IN inhibitors were identified through in vitro inhibition assays with recombinant IN and among them the β-diketo acid class of compounds showed the most promising results. After about 15 years of study, one compound (Raltegravir, MK-0518), a diketo acid-based derivative, has been approved in therapy [3]. 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.

In a previous work [4] we reported results about the coordination ability of the diketo acid pharmacophore, and discussed on the anti-HIV-1 IN activity of a series of synthesized β-diketo acid metal complexes. We demonstrated that the diketo acid functionality chelates divalent metal ions in solution giving complexes with metals in different stoichiometric ratios. We also postulated that the diketo acids act as complexes in their active form, and the difference in activities is related to the complexes they preferentially form in solution.

Herein, a further extension of this study is reported. In particular, a new set of complexes with different stoichiometry was synthesized, and a series of potentiometric measurements were conducted for two diketo acids as model ligands in the presence of other divalent metal ions in order to outline a speciation model. The first X-ray solved structure of a diketo acid metal complex is presented.

Moreover, we tested the obtained complexes for anti-HIV 1 IN activity. Furthermore, detailed docking studies were conducted in order to investigate the mode of binding of the free ligands compared with their metal complexes on the active site.

---

1) Neamati, N. *Exp. Opin. Invest. Drugs* **2001**, *10*, 281-296.

2) Pommier, Y.; Johnson A. A.; Marchand, C. *Nature Rev. Drug Discovery* **2005**, *4*, 236-48.

3) Wang, Y., Serradell, N., Bolos, J, Rosa, E. *Drugs Fut.* **2007**, *32*, 118-122

3) Sechi, M.; Bacchi, A.; Carcelli, M.; Compari, C.; Duce, E.; Fisicaro, E.; Rogolino, D.; Gates, P.; Derudas, M.; Al-Mawsawi, L. Q. and Neamati, N. *J. Med. Chem.* **2006**, *46*, 4248-60.