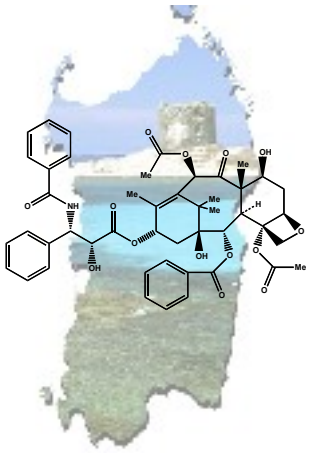
SardiniaChem2008

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.

SINGLE AMINO ACID SUBSTITUTION IN HIV-1 INTEGRASE CATALYTIC CORE CAUSES A DRAMATIC SHIFT IN INHIBITOR SELECTIVITY

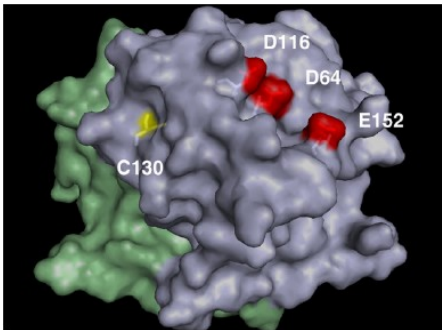
Laith Q. Al-Mawsawi,[a] **Mario Sechi**,[b] Nouri Neamati[a]

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

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

HIV-1 integrase (IN) mediates the insertion of viral cDNA into the cell genome, a vital process for replication. This step is catalyzed by two separate DNA reaction events, termed 3'-processing (3'-P) and strand transfer (ST). The second step, ST, is the concerted transesterification reaction that results in the insertion of this DNA product within the host genome [1]. Using this in vitro method we present here the activity of six small molecule IN inhibitors from five different structural classes tested against wild type (WT) IN, a soluble double mutant (F185K/ C280S) protein (SM), and two other IN mutants containing an additional substitution at position C130 (Ala and Ser).

We show that the six inhibitors display a selectivity shift towards preferential ST inhibition over the 3'-P activity of IN when a single serine is substituted at position C130 [2]. Even though IN utilizes the same active site for both reactions, this finding suggests a distinct conformational dissimilarity in the mechanistic details of each IN catalytic event.



1) Brown, P.O. (1997) Integration. In: Retroviruses (Coffin, J.M., Hughes, S.H. and Varmus, H.E., Eds.), pp. 161–203, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

2) Al-Mawsawi, L. Q.; Sechi, M.; Neamati, N. *FEBS Letters* **2007**, *581*, 1156.