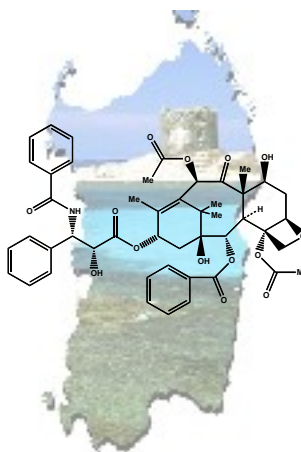




SardiniaChem2008

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

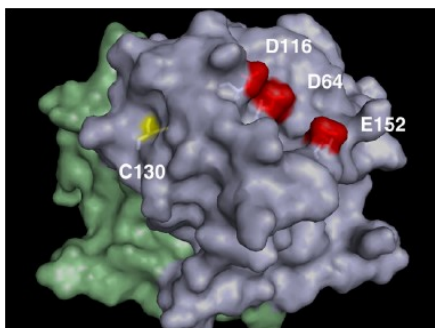
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HIV-1 integrase (IN) mediates the insertion of viral cDNA into the cell genome, a vital process for replication. This step is catalyzed by two separate DNA reaction events, termed 3'-processing (3'-P) and strand transfer (ST). The second step, ST, 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.



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- 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.