DOCKING STUDIES ON BIFUNCTIONAL QUINOLINYL DIKETO ACIDS AS HIV-1 INTEGRASE IHNHIBITORS

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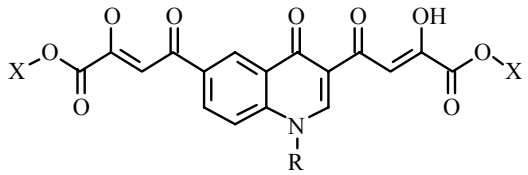
Combination therapy using RT and PR inhibitors is nowadays the best clinical approach in the acquired immunodeficiency syndrome (AIDS), caused by infection with the human immunodeficiency virus type-1 (HIV-1). However, the emergence of resistant strains calls urgently for researches on inhibitors of further viral targets such as integrase (IN), the enzyme that catalyzes the integration of the proviral DNA into the host chromosomes. In the past several years, numerous compounds with diverse structural features have been reported as IN inhibitors, of which the most promising are compounds characterized by β-diketo acid moiety (DKAs). Several reported DKAs selectively inhibit the strand transfer reaction of IN and exhibit potent antiviral effects against HIV-infected cells [1]. It is believed that DKAs function by competing with substrate DNA in binding to the in active site.

Recently, we were engaged in studies on quinolinyl-2,4-dioxobutanoic acids as potent IN inhibitors [2], endowed with selective activity against strand transfer step. Surprisingly, bifunctional compounds such as derivatives **1** showed lower selective activity if compared with the monofunctional counterparts. Docking studies are in progress to elucidate the binding mode of compounds **1** to IN in the presence of DNA substrate.



R = H, $CH_2C_6H_4F$
X = H, CH_2CH_3

[1] R. Costi, R. Di Santo, M. Artico, A. Roux, et al. *Bioorg. Med. Chem. Lett.* **2004,** *14*, 1745.
[2] R. Di Santo, R. Costi, M. Artico, Y. Pommier, C. Marchand, US Patent 2004, 60,552,423.