

SAR STUDIES ON QUINOLINYL-2,4-DIOXOBUTANOIC ACIDS, HIV-1 INTEGRASE INHIBITORS THAT BLOCK HIV-1 REPLICATION IN INFECTED CELLS

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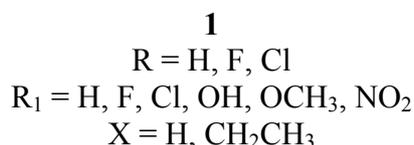
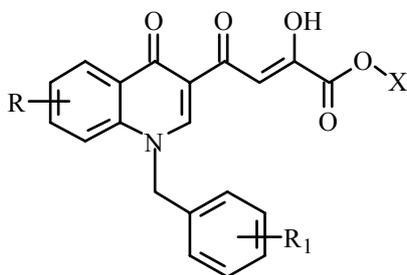
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Acquired immunodeficiency syndrome (AIDS), caused by infection with the human immunodeficiency virus type-1 (HIV-1), remains a serious global health problem. Drugs approved so far include nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PRIs). Due to failure of monotherapy with the above inhibitors, combination protocols were designed with both RTIs and PRIs in order to increase the clinical efficacy and reduce the emergence of resistant variant. 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.

Aryl diketo acids (DKAs) containing a distinct dioxobutanoic acid moiety (i.e. L-731,988) have been identified as potent and specific inhibitors of HIV-1 IN, which block HIV-1 replication in infected cells. Pursuing our studies on HIV-1 IN inhibitors [1,2] we recently reported the potent anti-IN activity of pyrrolyl diketo hexenoic acids (PDKHAs) characterized by elongated diketo acid chain [3]. More recently, we designed and synthesized quinolinyl diketo acids **1** as conformation ally restrained analogues of PDKHAs [4]. SAR and MM studies on these novel HIV-1 IN inhibitors will be shown.



[1] M. Artico, R. Di Santo, R. Costi, et al. *J. Med. Chem.* **1998**, *41*, 3948.

[2] R. Costi, R. Di Santo, M. Artico, et al. *Bioorg. Med. Chem.* **2004**, *12*, 199.

[3] R. Costi, R. Di Santo, M. Artico, A. Roux, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1745.

[4] R. Di Santo, R. Costi, M. Artico, Y. Pommier, US Patent 2004, 60,552,423.