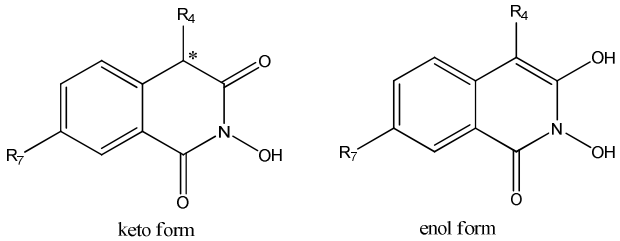
Subject proposal for Erasmus student in Chemistry

Synthesis of 2-hydroxyisoquinoline-1,3-diones
as second generation HIV-1 integrase inhibitors

Acquired immunodeficiency syndrome (AIDS) is the most challenging pandemic of the 21st century. Highly Active Antiretroviral Treatment (HAART), consists of a cocktail of drugs which includes reverse transcriptase (RT) inhibitors, protease innibitors (PI), and/or a fusion inhibitor. This regimen can achieve a significant reduction of the viral load in HIV-infected patients. However, its success is often limited by drug-related toxicities, drug-drug/food interactions, and by the emergence of multidrug resistant viral strains.
In 2007, the Food and Drug Administration approved raltegravir (Isentress™, Merck & Co., Inc.), the first drug targeting the integration step in the viral life cycle (i.e. inhibiting the integrase enzyme). The clinical outcomes with its addition into HAART have been encouraging during its two first years of use. In treatment-experienced and multidrug resistant HIV-1 patients, treatment with raltegravir resulted in significant and sustained suppression of viral RNA levels. However resistant viral strains were recently observed, limiting the efficiency of raltegravir. Thus, the addition of integrase inhibitors to the repertoire of antiretroviral drugs provides an important therapeutic alternative for the treatment of HIV-1 infection, which must already be developed and improved... There is already a need for a second generation of HIV-1 integrase inhibitors.

During the last three years, we synthesized a series of heterocyclic compounds containing the 2-hydroxyisoquinoline-1,3-dione scaffold variously substituted on positions 4 or 7. A series of compounds substituted on position 4 showed promising anti-integrase activities (nanomolar range) together with average antiviral activities (micromolar range). These have been patented, since biomolecular studies highlighted them as new integrase inhibitors.

The student will be in charge with the synthesis of further structurally-related derivatives. The pharmacomodulation will be aimed at obtaining analogues with improved antiviral activities and pharmacokinetic profile.



Structure of the second generation HIV-1 integrase inhibiting scaffold

The candidate will be learnt in organic synthesis in liquid phase and practical multinuclear 1 and 2D NMR to be able to realize his own experiments.

Keywords: 2-Hydroxyisoquinoline-1,3-diones, HIV-1 integrase inhibitors

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