HIV-1 INTEGRASE INHIBITORS: PHARMACOPHORE MODELING AND RATIONAL DRUG DESIGN

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Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase (IN).

HIV-1 IN has emerged as an attractive target for antiviral therapy, because it plays a key role in stable infection and a known functional analog is lacking in the human host [1]. The integration reaction is carried out in two steps (3'-end processing and strand transfer) and divalent cations such as Mn^{2+} or Mg^{2+} are required for the catalytic activity.

Although a wide variety of compounds have been reported as IN inhibitors, drugs active against this enzyme have not as yet been approved by the FDA.

To date, β-diketo acid (DKA) analogues represent the major leads in the development of anti-HIV-1 IN drugs, seeing that the only two IN inhibitors undergoing clinical trials belong to this family.

For the above reasons and as a continuation of our work in this research field [2-4], our idea was to generate a simple 3D pharmacophore model that could correctly predict the activity of compounds belonging to the DKA class.

On the basis of the statistically most significant hypothesis, we designed and synthesized new potential DKA IN-inhibitors containing a benzylindole skeleton.

The biological results of the IN inhibitory activity confirmed the strength of our rational approach and suggested that our 3D QSAR model can be useful and predictive in designing new compounds.

In particular, our ongoing work is to use the quantitative pharmacophore as 3D query for the identification of new potential IN inhibitors in large 3D databases of molecules.

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