SEARCHING FOR NOVEL HIV-1 INTEGRASE INHIBITORS BY 3D-DATABASE VIRTUAL SCREENING

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Despite significant advances in antiretroviral therapy, the search for new anti-AIDS drugs continues in the attempt to develop drugs capable of overcoming toxicity and resistence. HIV-1 integrase (IN) has emerged as an attractive and validated target for antiretroviral agents because of its crucial role in the viral replication processes [1]. The addition of an IN inhibitor to existing components of combination regimen is expected to improve the therapeutic outcome. Substantial progress has been made in understanding the structure and function of HIV-1 IN and application of that information to the rational design of IN inhibitors [2]. In particular, IN is a testable target because rapid and sensitive assays exist for ascertaining enzymatic activity and, even if there is currently no solved structure for the full-length enzyme, several crystal and NMR structures are available for use in rational structure-based drug design.

As more IN inhibitors are entering clinical trials [3], it is important to develop diverse chemical classes of selective inhibitors. In this context, together with other traditional strategies, several computational approaches have been performed and the large number of successful applications demonstrates their utility in the modern drug discovery paradigm [4]. Among them, virtual screening is one of the most interesting computational tools for rapid discovery of putative lead structures containing different chemical scaffolds. This method is used with the goal to detect molecules in compound libraries in order to increase the hit rate in subsequent biological assays [5].

Aim of this study was to develop a new virtual screening strategy to be used for the discovery of new potential pharmacophores for further chemical developments. In this context, starting from the available crystal structures of the HIV-1 IN catalytic core domain (PDB codes 1QS4 and 1BIS), we first selected a pool of known inhibitors in order to define putative pharmacophore criteria. Then we screened a database of commercially available compounds in a hierarchical fashion, using fast 2D filters, 3D pharmacophore searches, and protein-ligand docking. So far, a preliminary study has been performed and work is in progress to extend this virtual screening method in terms of scoring functions, databases, and target structures. Also, enzyme assays for a first set of selected compounds are under investigation and preliminary results will be presented.

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