

Introduction to HIV Integrase Inhibitors for SAMPL

Background:

HIV integrase is one of the viral targets for which small molecule therapeutics have now been approved to treat AIDS. Integrase is a critical enzyme in the HIV life cycle as it is required for the integration of viral DNA into the host chromatin and performs both the 3' viral processing step as well as the strand transfer step to insert viral genome into the host DNA. The structure of HIV integrase has been thoroughly investigated [Jenkins, Godgur, Chen, Cherepanov 2005, Wang], and consists of three domains (N-terminal DNA binding, catalytic core (CCD) and C-terminal DNA binding). The CCD has several pockets to which small molecules have been shown to bind and inhibit the enzymatic activity [Christ, Wielens, Rhodes, Schrijvers, Kessl]. Integrase forms a complex with viral DNA and several host cellular factors that has been termed the pre-integration complex (PIC) [Cherepanov 2003]. One component of this complex is lens epithelium derived growth factor (LEDGF/p75), which has a conserved integrase binding domain (IBD, residues 347-429) that mediates binding [Cherepanov 2005]. Within the IBD is a loop (residues 362 to 369) that binds in a pocket formed by a dimer of the HIV integrase CCD. Small peptides composed of the residues in this IBD loop can bind to the integrase CCD with micromolar affinity and can compete with the IBD for this binding site [Tsiang 2009]. Several crystal structures with various peptide sequences have been solved showing the interactions between these peptides and integrase [Rhodes 2011]. Several groups have also found small molecule inhibitors of HIV integrase that bind in the LEDGF pocket [Schrijvers, Christ, De Luca, Fan, De Luca, Tsantrizos, Peat].

The challenge in this case is based on the intermediate level compounds that were developed to bind to HIV integrase during the med chem program conducted by CSIRO and Avexa Ltd. Various aspects of this program have been published previously (Peat PONE 2012, Wielens J.Bio.Screen. 2013, Rhodes ChemBiochem 2011, Rhodes AVCC 2011) but the compounds selected for this challenge are not incorporated in these previous publications. The compounds were developed from a fragment screen run against the Maybridge fragment library and compounds were found in multiple sites on HIV integrase noted in the references above, including the LEDGF pocket, an allosteric site, and a so-called fragment site.

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