Structure-based Design of HIV-1 Protease Inhibitors based on a Pyrrolidine scaffold

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The HIV-1 protease is an aspartic protease, composed of two identical 11kDa subunits. It cleaves viral polyproteins into their functional units that are essential for viral assembly and subsequent infectivity [1]. Nine approved drugs targeting the HIV protease have been launched to market, improving the quality of life and life expectancy for an increasing number of HIV infected patients. But the high mutation rate of the virus caused by the error-prone viral reverse transcriptase, and the fast replication lead to HIV strains which are resistant to approved drugs [2].

In our group novel HIV protease inhibitors addressing the catalytic aspartic acid side chains via an endocyclic amino function have been developed [3]. In this project 3,4-disubstituted-C$_2$-symmetric pyrrolidines have been investigated as new lead structure for HIV protease inhibition. Initial SAR-studies were followed by the crystal structure determination of the most potent derivative ($K_i = 2.2\mu M$). The analysis of the co-crystal structure revealed three possible strategies for optimization via symmetric introduction of substituents. All pursued strategies led to an increase in affinity towards the target. At least one representative of each optimization strategy was crystallized in complex with the HIV protease and the crystal structures were determined using in-house and synchrotron radiation sources. The structures were precisely analyzed and two strategies were identified for the consecutive combination. The combination of the two most promising substitution patterns led to the final inhibitor, showing with 74 nM a noticeable improvement in affinity.

Figure 1: Crystal structure of the combination inhibitor in complex with the HIV-1 protease (resolution 1.48 Å)

References