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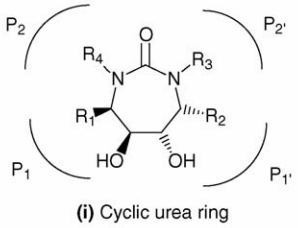
Nonsymmetrical cyclic urea inhibitors of HIV-1 aspartic protease

The HIV-1 aspartic protease cleaves the viral Gag–Pol fusion precursor polypeptide, generating active viral structural proteins and replicative enzymes such as reverse transcriptase, endonuclease and integrase. Because it plays an essential role in the maturation of HIV-1 particles and viral replication, this protease is seen as an important target for the design of specific antiviral agents. The rapidity and frequency of viral RNA mutations and the ability of HIV-1 to rapidly generate drug-resistant protease mutants necessitates continual discovery of new, more-potent protease inhibitors. These compounds need to have improved pharmacokinetic properties and activity against a wider spectrum of aspartic protease mutant forms. Cyclic ureas have been reported to constitute a new class of potent and perspective non-peptidic inhibitors of aspartic protease, see general structure **(i)** [1]. A fundamental feature of these cyclic urea inhibitors is the carbonyl oxygen that mimics the hydrogen-bonding features of the key structural water molecule present in the active site of the aspartic protease. The presence of this structural water distinguishes the retroviral aspartic protease from the human aspartic proteases pepsin and rennin.

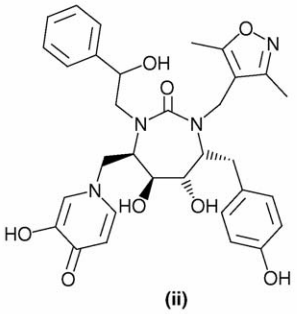
Recent work in this area has employed computer-assisted combinatorial chemistry methods to design, focus and screen, *in silico*, a virtual library of nonsymmetrically $P_1 - P_{1'}$ and $P_2 - P_{2'}$ substituted cyclic urea inhibitors [2]. This work centered around deriving a small, highly focused library subset containing analogues with substituted aryl side chains that had been predicted by computational techniques, providing inhibition constants (K_i) in the low pM range, a wide-range of lipophilicity and water solubility. All of these properties predicted that the virtual compounds had the potential to be developed into an antiviral agent. A set of structural filters and penalties were introduced to reduce the number of commercially available monomers employed in the virtual library generation. Specifically, 11 different descriptors related to shape, size, polarity, hydrogen bonding, lipophilicity, solubility and conformational flexibility, relevant to the match between the monomers and the characteristics of the S_3 to $S_{3'}$ specificity pockets of the aspartic protease binding site, were computed.

Further reduction in the virtual library size was affected by subjecting all of the virtually generated cyclic urea analogues to docking into a model of the aspartic protease receptor – derived from the crystal structure of the PR–XV-638 complex (Protein Data Bank entry 1QBR) [3]. This analysis provided 90 cyclic urea analogues with the highest predicted aspartic protease inhibition potencies: $K_i^* < 10$ pM. This work has yielded a small, highly focused virtual combinatorial subset of fully nonsymmetrical cyclic ureas that contains potential lead compounds with high predicted inhibitory potencies against the wild-type form of HIV-1 aspartic protease. The predicted inhibition constants of the new leads are up to two orders of magnitude lower than the K_is of the training set.

One of the most potent compounds predicted from this analysis was **(ii)** with a predicted K_i of 0.5 pM. The subset contained potent cyclic urea aspartic protease inhibitors – predicted to be endowed with a wide-range of properties such as aqueous solubility, lipophilicity, number of hydrogen-bonding groups and a cell membrane permeability rate that might allow discovery of a potent orally administrable antiviral drug with favourable pharmacokinetic properties. This work is important because it helps to attract the attention of synthetic chemists working on the preparation of the next generation of nonsymmetrical cyclic ureas to a particular subset of chemical space that is predicted to contain compounds with high HIV-1 aspartic protease inhibition potencies and favourable pharmacokinetic properties.



(i) Cyclic urea ring



(ii)

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2 Frecer, V. *et al.* (2005) Combinatorial design of nonsymmetrical cyclic urea inhibitors of aspartic protease of HIV-1. *Bioorg. Med. Chem.* 13, 5492–5501

3 Jadhav, P.K. *et al.* (1997) Cyclic urea amides: HIV-1 protease inhibitors with low nanomolar potency against both wild type and protease inhibitor resistant mutants of HIV. *J. Med. Chem.* 40, 181–191

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