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TRICYCLIC UREAS: A NEW CLASS OF HIV-1 PROTEASE INHIBITORS

Wei Han,* Jeffrey C. Pelletier[§] and C. Nicholas Hodge[#]

Department of Chemical and Physical Sciences
DuPont Pharmaceuticals Company
Experimental Station, P.O. Box 80500
Wilmington, Delaware 19880-0500, U. S. A.

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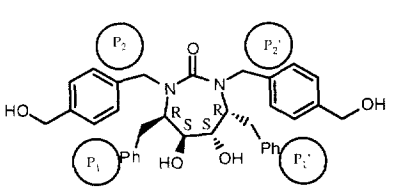
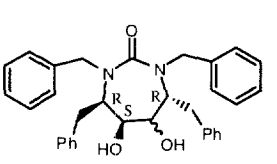
Abstract: A new class of tricyclic ureas containing a conformationally constrained proline was designed with the aid of molecular modeling. Efficient stereoselective intermolecular pinacol coupling represented the highlight of the synthesis. These rigid cyclic ureas are active towards HIV-1 protease, with **9** being the most potent compound (Ki = 9 nM) despite interacting with only three side chain binding pockets of HIV protease.

The human immunodeficiency virus type-1 (HIV-1), a member of the Lentivirinae subfamily, is the etiologic agent of the acquired immunodeficiency syndrome (AIDS).[1] As the rapid spread of the worldwide AIDS epidemic continues, there has been an intensive search for new therapies to combat this disease. One of the most extensively investigated targets is HIV protease, since this enzyme was shown to be essential for the production of infectious virus.[2] In the past decade or so, there have been many reports addressing the design and synthesis of HIV protease inhibitors,[3] as well as the introduction of effective treatments for AIDS based on protease inhibition.[4]

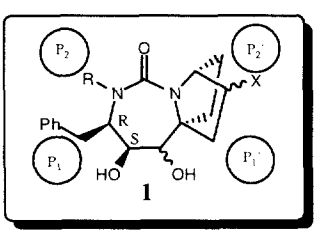
Our organization has been focused primarily upon the hexahydro-1,3-diazepin-2-one, a.k.a. cyclic urea, scaffold (e.g. **A**) that places a diol moiety within hydrogen bond distance of the enzyme's aspartic acid dyad, and projects benzyl-derived substituents into the S1/S1' and S2/S2' pockets.[5] A unique feature of this class of compounds is that the urea carbonyl oxygen displaces a water molecule bonded to both the native substrate and residues 50 and 150 of the enzyme. The cyclic ureas are pre-organized for highly complementary binding to HIV protease, and thus avoid paying the conformational entropic penalties during binding typically associated with binding of linear flexible inhibitors.[5] Previous studies of cyclic ureas indicated that (1) it is essential to install all four substituents (P1, P1', P2 and P2') on the cyclic urea core structure to maintain picomolar level inhibitory potency necessary for adequate suppression of viral replication in vivo;[4] (2) the stereochemistry of one of the two hydroxyl groups is crucial in terms of potency: the RSSR (*anti*-diol in **B**) and RSRR (*syn*-diol in **B**) isomers give similar results (Ki of 3.6 nM vs 6.0 nM), while the potency for RRRR isomer drops dramatically (Ki of 1350 nM).[5c]



A



B



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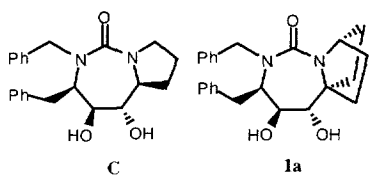
Like most other HIV protease inhibitors, the cyclic ureas rely on lipophilic interactions with two prime (S1', S2') and two non-prime (S1, S2) sites to achieve desired enzyme affinity. As a result, these inhibitors often have high molecular weight, which adversely affects oral bioavailability. In an effort to modify the cyclic urea core structure, we looked to enhance the degree of pre-organization and hope to optimize the interactions between inhibitor side chain and enzyme binding pockets. Cyclic ureas such as **A** can be regarded as symmetrical dimers of phenylalanine. We initially investigated target **C** (results to be reported elsewhere), by replacing one of the phenylalanine units with a proline. To achieve the similar binding mode as **A**, the cyclic urea ring of **C** needs to adopt a chair conformation directing both hydroxy groups to the equatorial orientation. Conformation analysis using quenched dynamics conformational searching[6] revealed that the lowest energy conformer was a twist boat. Further rigidification led to tricyclic urea **1a**. Conformational analysis showed that this modification was effective. As shown in figure 1, the lowest energy conformation of **1a** from modeling effectively directs the side chains into enzyme binding pockets.



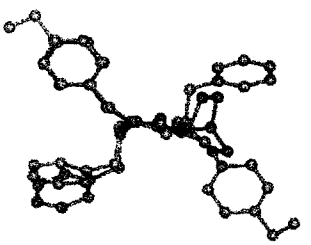
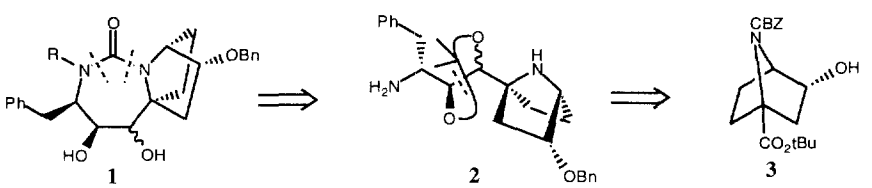


Figure 1. **1a** superimposed onto X-ray structure of **A** (top view)

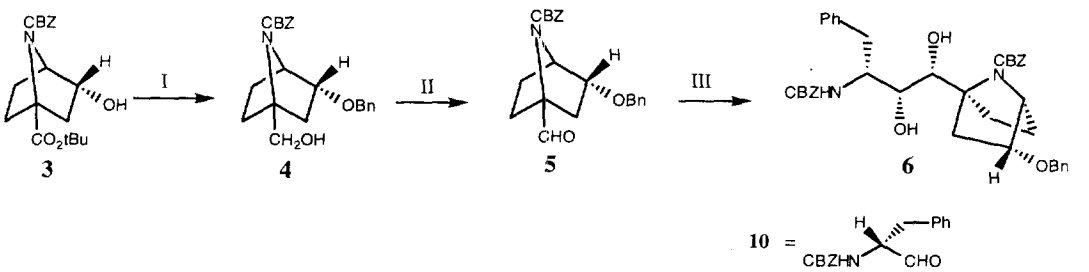
The retrosynthetic analysis of the proposed target is shown in Scheme 1. Disconnection at two C-N bonds of the cyclic urea ring leads to **2**. Diamine **2**, in turn, is envisioned to derive from the aldehyde derivative of **3**[7] and (D)-phenylalaninal via pinacol coupling.[8]

Scheme 1



Scheme 2 outlines the synthesis of intermediate **6**. Protection of the hydroxyl group in **3** followed by reduction yielded **4**. Swern oxidation provided the aldehyde **5** for the key pinacol coupling. Attempts using $TiCl_4/Zn$[9] and $TiCl_3(DME)/Zn\text{-}Cu$[10] conditions gave low yields of the coupled products, while no desired product was observed with SmI_2.[11] In contrast, the coupling proceeded efficiently when a mixture of aldehyde **5** and 1.5 eq. of (D)-phenylalaninal **10** was treated with 1.3 eq. $VCl_3\cdot(THF)_3/Zn$ at room temperature for 2.5 hours. Under these conditions, the desired coupling product **6** was obtained in 84% yield and 85% diastereoselectivity.

Scheme 2



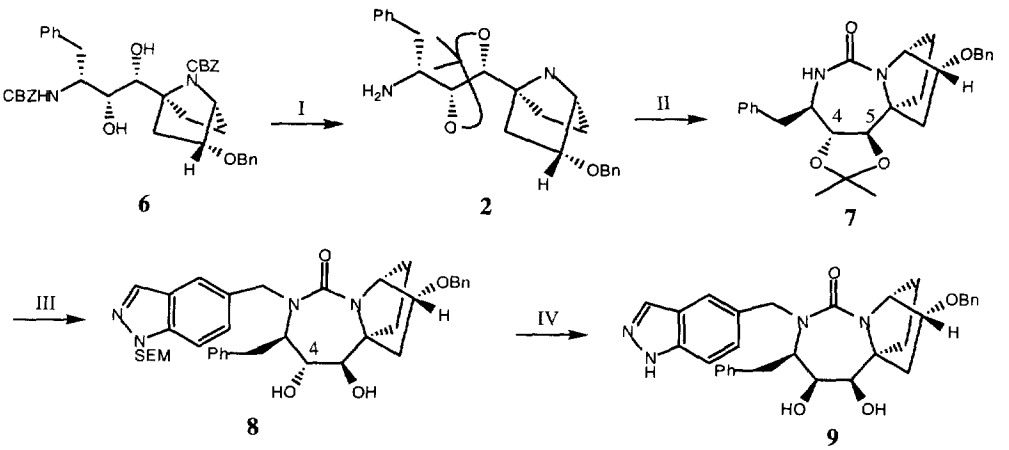
Reagents and Conditions **I**: (a) BnBr, NaH, DMF, rt, 2.5 h; (b) $LiBH_4$, Et_2O, rt, 15 h, (84% for 2 steps). **II**: $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C - rt, 2 h, (81%). **III**: **10**, $VCl_3(THF)_3$, Zn, CH_2Cl_2, rt, 2.5 h, (84%).

Following the protection of diol **6** as the acetonide, the two CBZ groups were selectively removed to provide diamine **2** (scheme 3). Treatment of **2** with carbonyldiimidazole in the presence of pyridine effected cyclization to give urea **7**. NOE studies of **7**[12] confirmed the 4R and 5S configuration as shown, thus the stereochemistry from the pinacol coupling. Alkylation of **7** with bromomethylindazole **11**[13] was followed by acidic removal of acetonide to provide free diol **8**. The undesired C4 configuration in **8** was inverted by an oxidation-reduction sequence. Swern oxidation occurred exclusively at the less hindered C4 position to produce the corresponding α-hydroxyl ketone, and subsequent reduction with $NaBH_4$ gave a 3:1 mixture of the *syn*- and *anti*-diols. Due to the steric hindrance, attempts to invert the C5 configuration proved unsuccessful.

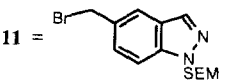
Following analogous sequence, compounds **12-16** were synthesized. Table 1 lists the inhibition constants of these compounds against HIV protease. Inhibitors lacking P1' & P2' groups gave only micromolar Ki values in both trans and cis diols (**13** & **14**). As expected, removal of P2 group further reduced the potency (**12**). Improvement in potency was achieved with addition of P2' groups (**15**). With indazole as P2 group, the P2' addition led to an inhibitor with Ki of 9 nM. Noteworthy here is the absence of P1' group in **9**.

In general, the newly designed derivatives are not as potent as the best cyclic ureas, although they are competitive with inhibitors that project only 3 residues into the enzyme side chain pockets. Examination of the models revealed that the bridgehead proton of the bicyclic moiety could be too close to the side chain of Ile 50 (or 150). Although the active site is moderately flexible, one explanation for limited affinity of **1** is that the enzyme can only accommodate this proton at the expense of other beneficial interactions, such as hydrogen bonding to carbonyl from the flaps.

Scheme 3



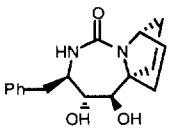
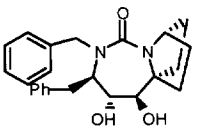
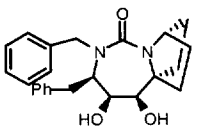
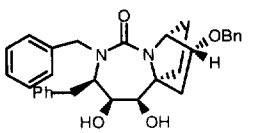
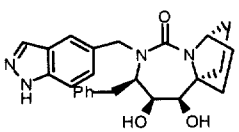
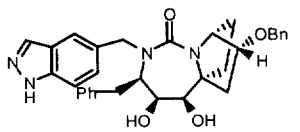
Reagents and Conditions: **I**: (a) 2,2-dimethoxypropane, camphorsulfonic acid, CH_2Cl_2, rt, 6 h (95%); (b) H_2, Pd/C, MeOH/NH_3, rt, 1 atm, 2 h (95%). **II**: carbonyldiimidazole, Pyr., CH_2Cl_2, rt, overnight (67%). **III**: (a) **11**, KO^tBu, THF, rt, 4 h; (b) 1N HCl, CH_3CN, rt, 6 h (45% for 2 steps). **IV**: (a) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C - rt, 2 h; (b) $NaBH_4$, EtOH, 0 °C - rt, 1 h; (c) tetrabutylammonium fluoride, THF, 45 °C, 18 h (51% for 3 steps).

11 = 

In summary, we have designed and synthesized a novel class of HIV-1 protease inhibitors. These compounds contain a tricyclic urea core structure. A low nanomolar (9 nM) inhibitor has been identified (**9**). A noteworthy structure feature of **9** is the absence of P1' group. Although any potential potency gains due to increased rigidity were likely offset by unfavorable interactions introduced by the structure modification, the tricyclic urea nonetheless represents a new scaffold that can be stereo- and regio-specifically varied for interactions with HIV protease in ways that are not available with other templates. Further studies on the applications of the conformationally constrained proline to HIV protease inhibitors and other novel protease inhibitors have also been completed, and these data will be reported in detail in the near future.

Acknowledgments: We would like to thank Professor Henry Rapoport and Dr. Jeffrey A. Campbell for developing the synthetic route to 7-azabicycloteptane carboxylic acid *tert*-butyl ester (**3**) through our joint program; Dr. Gregory Nemeth and Mr. Ernest M. Schubert in NMR lab for the NOE studies , and Dr. James L. Meek and Mr. Ronald M. Klabe for the Ki measurements.

Table 1[14]

Compound	Structure	Ki[15] (μM)
12		21
13		6.3
14		2.4
15		0.75
16		2.3
9		0.009

References and Notes:

ζ. Present address: Wyeth Ayerst Research, 401 North Midletown Rd., Pearl River, NY 10965.

#. Present address: Caliper Technologies Corporation, 1275 California Ave., Palo Alto, CA 94304.

1. (a) Weiss, R. A. *Science* **1993**, *260*, 1273 and references cited therein. (b) Debouck, C. *AIDS Res. Human Retroviruses* **1992**, *8*, 153. (c) Katz, R. A.; Skalka, A. M. *Annu. Rev. Biochem.* **1994**, *63*, 133.
2. Kohl, N. E.; Emini, E. A.; Schleif, W. A.; Davis, L. J.; Heimbach, J. C.; Dixon, R. A. F.; Scolnick, E. M.; Sigal, I. S. *Proc. Natl. Acad. Sci.*. **1988**, *85*, 4686.
3. (a) Norbeck, D. W.; Kempf, D. J. *Annu. Rep. Med. Chem.* **1991**, *26*, 141. (b) Tomasselli, A. G.; Howe, W. J.; Sawyer, T. K.; Wlodawer, A.; Heinrikson, R. L. *Chim. Oggi* **1991**, 6. (c) Wlodawer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543. (d) Appelt, K. *Perspect. Drug Discovery Des.* **1993**, *1*, 23.

4. (a) Lin, J. H. *Adv. Drug Delivery Rev.* **1997**, *27*, 774. (b) Vacca, J. P.; Condra, J. H. *Drug Discovery Today* **1997**, *2*, 261.
5. (a) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, N.; Chang, C-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380. (b) Lam, P. Y. S.; Ru, Y.; Jadhav, P. K.; Aldrich, P. E.; DeLucca, G. V.; Eyermann, C. J.; Chang, C-H.; Emmett, G.; Holler, E. R.; Daneker, W. F.; Li, L.; Confalone, P. N.; McHugh, R. J.; Han, Q.; Markwalder, J. A.; Seitz, S. P.; Sharpe, T. R.; Bacheler, L. T.; Rayner, M. M.; Klabe, R. M.; Shum, L.; Winslow, D. L.; Kornhauser, D. M.; Jackson, D. A.; Erickson-Viitanen, S.; Hodge, C. N. *J. Med. Chem.* **1996**, *39*, 3514. (c) Kaltenbach, R. F.; Nugiel, D. A.; Lam, P. Y. S.; Klabe, R. M.; Seitz, S. P. *J. Med. Chem.* submitted.
6. (a) O'Connor, S. D.; Smith, P. E.; Al-Obeidi, F.; Pettitt, B. M. *J. Med. Chem.* **1992**, *35*, 2870. (b) Hodge, C. N.; Straatsma, T. P.; McCammon, J. A. *Structure Biology of Viruses* **1997**, 451.
7. The synthetic methodology of compound **4** was developed in Professor Henry Rapoport's laboratory based on the joint program between DuPont-Merck and U. C. Berkeley. Campbell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313.
8. (a) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1992**, *57*, 28. (b) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316. (c) Kraynack, E. A.; Pedersen, S. F. *J. Org. Chem.* **1993**, *58*, 6114.
9. Swindell, C. S.; Chander, M. C.; Heerding, J. M.; Klimko, P. G. *J. Org. Chem.* **1996**, *61*, 1101.
10. McMurry, J. E.; Lectka, T.; Rico, J. G . *J. Org. Chem.* **1989**, *54*, 3748.
11. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.
12. The experiment was done in $CDCl_3$. NOE effects were observed with the protons at 4 and 5 positions.
13. (a) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Greenberg, R. A.; Erickson-Viitanen, S.; Klabe, R. M.; Bacheler, L.; Cordova, B. C.; Rayner, M. M.; Lam, G. N.; Chang, C-H. *Bioog. Med. Chem. Lett.* **1996**, 2919. (b) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Erickson-Viitanen, S.; Klabe, R. M.; Bacheler, L.; Cordova, B. C.; Chang, C-H. *Bioog. Med. Chem. Lett.* **1998**, 715.
14. All compounds give satisfactory ^{1}H, ^{13}C and HRMS spectra.
15. Inhibition of HIV protease was measured by assaying the cleavage of a fluorescent peptide using HPLC. Erickson-Viitanen, S.; Klabe, R. M.; Cawood, P. G.; O'Neal, P. L.; Meek, J. L. *Antimicro. Agents Chemo.* **1994**, *38*, 1628.