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SYNTHESIS OF 7-MEMBERED CYCLIC HYDROXYGUANIDINES: NOVEL HIV-1 PROTEASE INHIBITORS

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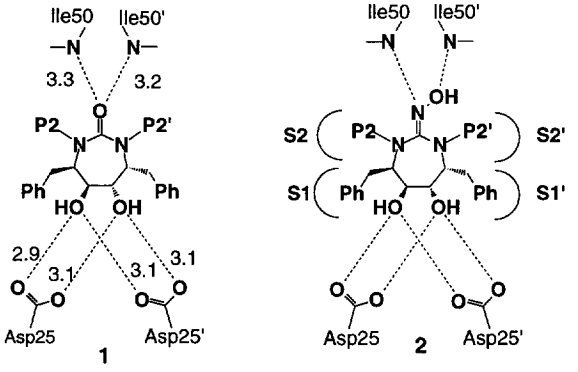
Abstract: Novel cyclic 7-membered hydroxyguanidine based HIV-1 protease inhibitors have been synthesized from 7-membered cyclic thiourea.

HIV-1 protease (HIV PR) has been intensely investigated as a target for effective therapies for the treatment of AIDS.[1-4] HIV PR is an ideal target since functional protease is essential for the maturation of fully infectious virus particles. The enzyme is virally encoded and structurally differs from mammalian aspartyl proteases. It consists of a symmetrical dimer in which each monomer is composed of 99 amino acid residues. The active site consists of two aspartic acid residues contributed by each monomer unit.[1-4] HIV PR inhibitors such as indinavir, saquinavir, and ritonavir have been approved for the treatment of HIV infection.[5]

Protein X-ray crystallography studies of the substrate based inhibitor and HIV PR complex revealed the presence of a unique water molecule that is hydrogen bonded to the two carbonyls of the inhibitor and the flap residues of the enzyme.[6] The cyclic urea (**1**) class of inhibitors was designed to displace this unique structural water molecule.[7] X-ray crystal structural studies of DMP323 (**1**; P2 = P2' = *p*-hydroxymethylbenzyl) complexed with HIV PR revealed that the carbonyl oxygen of the cyclic urea moiety displaced the structural water molecule and accepted hydrogen bonds from the two flap residues (Ile50 and Ile50') of the enzyme while the diol moiety is hydrogen bonded to the two catalytic aspartic acid residues (Asp25 and Asp25').[7] In further continuation of this work we became interested in investigating structurally diverse classes of cyclic inhibitors that are capable of displacing the structural water molecule.[8] Guanidines of the structural type **2** appeared an attractive target as HIV PR inhibitors.

Although guanidines are basic and ureas neutral, these two classes of compounds are isostructural.[9] In analogy to the oxygen of the cyclic urea carbonyl, the function of the exocyclic guanidine nitrogen was anticipated to be as a hydrogen bond acceptor for the backbone amides of flap the residues Ile50/Ile50'. However, at the outset we recognized that the cyclic guanidines (pKa ~13) would not be a good source of hydrogen bond acceptors since they will be protonated either at the physiological pH or under the enzyme inhibition assay conditions. The basicity of guanidine can be reduced dramatically by substitution of the nitrogen with electron

withdrawing groups.[9] In the case of cyclic guanidines of type (**2**) the ring nitrogens are needed for the substitution of the P2/P2' groups. Therefore, the exocyclic nitrogen is the only place that can be utilized for substitution of electron withdrawing groups. Interactive modeling suggested that large electron withdrawing

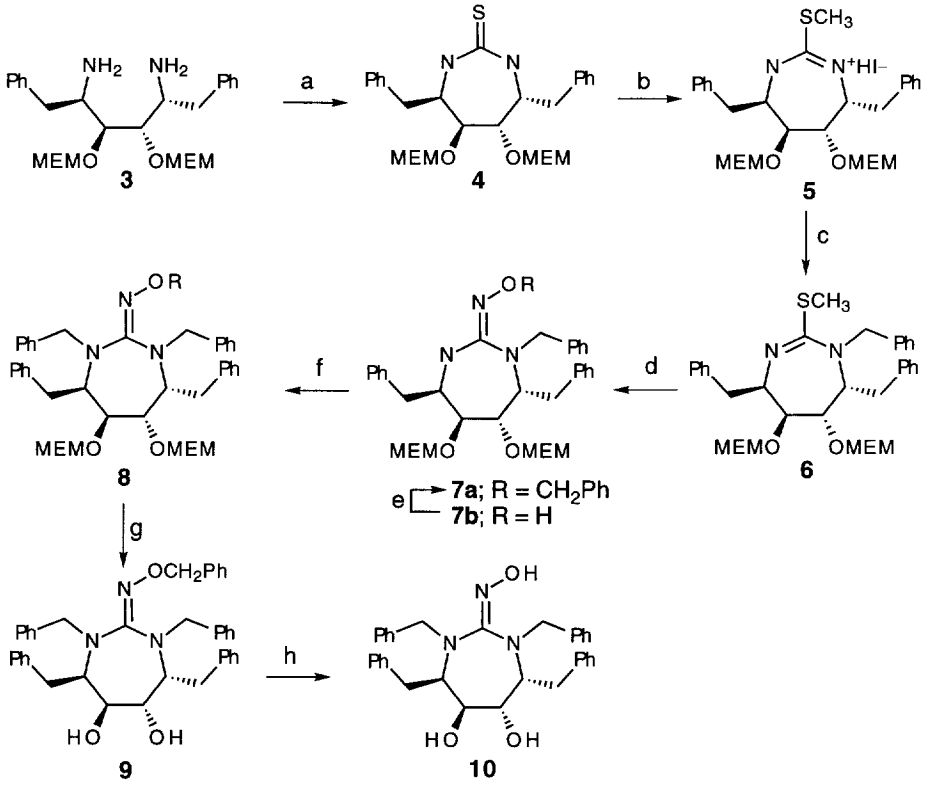


1; Observed binding mode of DMP323 (1; P2 = P2' = hydroxymethylbenzyl) with HIV-1 protease
2; Proposed binding mode of hydroxyguanidine with HIV-1 protease

groups would sterically interact with the flaps of HIV PR and may prevent them from closing on the inhibitor upon binding. On the contrary, we envisioned that small groups could be accommodated on the exocyclic nitrogen. Comparision of the X-ray structures of the native enzyme with the enzyme-inhibitor complex suggested that the enzyme flaps are flexible. It has been observed that the flap movement at the tip of the flaps could be as large as 7 Å.[10] Consequently, the steric and electronic requirements of the group that can be used as a substituent on the exocyclic nitrogen of the cyclic guanidine template became limited to a few groups viz cyano, nitro and hydroxy. The hydroxy group appeared more attractive because of its small size and electron withdrawing property. The proposed binding mode of guanidine to HIV PR is shown in (**2**; P2=P2'= benzyl) where the four benzyl groups occupy the S1/S1' and S2/S2' binding pockets.[11] The diol hydroxyl groups would form hydrogen bonds with Asp25/Asp25'. The exocyclic nitrogen and the oxygen of the hydroxy guanidine moiety would form hydrogen bonds to the flap residues Ile50/Ile50'.

The 7-membered thiourea (**4**) was obtained in 73% yield from the diamine[12] (**3**) by cyclization with 1,1'-thiocarbonyldiimidazole. It was readily activated to methylthioisouronium salt (**5**) upon treatment with methyl iodide. Alkylation of the intermediate (**5**) with benzyl bromide in the presence of sodium hydride in dimethyl formamide (DMF) provided monobenzylated thioisourea (**6**) in 56% yield based on **4**. Excess sodium hydride was needed to free base methylthioisouronium salt (**5**) in situ prior to the alkylation. Conversion of methylthioisourea (**6**) to benzyloxyguanidine[13a] (**7a**) was achieved in only 22% yield by heating **6** with benzylhydroxylamine hydrochloride in refluxing pyridine. Alternatively, benzyloxyguanidine (**7a**) was obtained in two steps from **6** in higher overall (79%) yield. Thus, treatment of **6** with hydroxyl amine[13b] hydrochloride in refluxing pyridine furnished **7b** (81%), which was then subjected to alkylation with benzyl bromide in the presence of sodium hydride and tetrabutylammonium iodide (TBAI) in THF to provide **7a** in 98% yield. The alkylation of **7a** with benzyl bromide in the presence of sodium hydride and DMF readily provided cyclic

benzyloxyguanidine (**8**) in 74% yield. Deprotection of the MEM ether in **8** with HCl yielded **9**[14] in 71% yield. Reductive debenzylation of **9** with palladium hydroxide and hydrogen in ethanol provided the target compound (**10**)[15] in 70% yield.



(a) 1,1'-Thiocarbonyldiimidazole/THF/25 °C/18 h/ 72.8%; (b) CH_3I/CH_3CN/25 °C/2 h; (c) NaH/ $PhCH_2Br$/DMF/25 °C/18 h/ 56.5% from **4**; (d) NH_2OH•HCl/pyridine/125 °C/1 h/80.8%; (e) $PhCH_2Br$/ NaH/TBAI/THF/25 °C/18 h/ 98 %; (f) $PhCH_2Br$/NaH/DMF/25 °C/18 h/74.2%; (g) HCl (4 M) dioxane/25 °C/ 18 h/70.5%; (h) $H_2/Pd(OH)_2$/EtOH/25 °C/18h/69.5%.

The target compound (**10**) has an inhibition constant of 42 nM for HIV PR which is about 10-fold higher than the corresponding cyclic urea. The potency of hydroxyguanidines may be further improved by attachment of optimum P2/P2' substituents.[7] Interestingly, hydroxyguanidine (**9**) is a weak inhibitor of HIV PR (K_i = 3 μM). The presence of a larger group such as benzyloxy on the guanidine moiety has a dramatic effect on its binding to the active site of HIV PR because of its unfavorable steric interactions with the flap region of the enzyme. In conclusion, small electron withdrawing groups can be accommodated on the cyclic guanidine moiety with only a 10-fold loss of potency against HIV PR as compared to the corresponding cyclic urea.

References and Notes

1. West, M. L.; Fairlie, D. P. *Trends Pharmacol Sciences* **1995**, *16*, 67.

2. Blundell, T. L. *Trends Biochem. Sci.* **1990**, *15*, 425.

3. Darke, P. L.; Huff, J. R. *Adv. Pharm.* **1994**, *25*, 399.

4. Tomasselli, A. G. *Chim. Oggi.* **1992**, *9*, 6.

5. Moyle, G.; Gazzard, B. *Drugs* **1996**, *51*, 701.

6. Wlodawer, A.; Erickson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543.

7. (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, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380. (b) Nugiel, D. A.; Jacobs, K.; Worley, T.; Patel, M.; Kaltenbach III, R. F.; Meyer, D. T.; Jadhav, P. K.; Delucca, G. V.; Smyser, T. E.; Klabe, R. M.; Bacheler, L. T.; Rayner, M. M.; Seitz, S. P. *J. Med. Chem.* **1996**, *39*, 2156. (c) 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.; Bacheler, L. T.; Rayner, M. M.; Klabe, R. M.; Shum, L.; Winslow, D. L.; Kornhauser, D. M.; Jackson, D. A.; Erickson-Viitanen, S.; Sharp, T. R.; Hodge, C. N. *J. Med. Chem.* **1996**, *39*, 3514.

8. (a) Cyclic oxamide: Jadhav, P. K.; Man, H. W. *Tetrahedron Letts.* **1996**, *37*, 1153. (b) Cyclic sulfamide: Jadhav, P. K.; Woerner, F. J. *Tetrahedron Letts.* **1995**, *36*, 6383. (c) cyclic cyanoguandine: Jadhav, P. K.; Woerner, F. J.; Lam, P. Y. S.; Hodge, C. N.; Eyermann, C. J.; Man, H. W.; Bacheler, L. T.; Rayner, M. M.; Meek, J. L.; Erickson-Viitanen, S.; Jackson, D. A.; Chang H.-C.: Nonpeptide cyclic cyanoguanidines as HIV PR inhibitors: synthesis, structure-activity relationship and X-Ray crystal structure studies; manuscript in preparation.

9. Ganellin, C. R. In *Chron. Drug Discovery*; Bindra, J. S.; Lednicer, D., Eds., Wiley: New York, 1982,Vol. 1; pp 1-38.

10. Miller, M.; Schneider, J.; Sathyanarayana, B. K.; Toth, M. V.; Marshall, G. R.; Clawson, L.; Seik, L.; Kent, S. B. H.; Wlodawer, A. *Science* **1989**, 1149.

11. Schecter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157.

12 Pierce, M. E.; Harris, G. D.; Islam, Q.; Radesca, L. A.; Storace, L.; Waltermire, R. E.; Wat, E.; Jadhav, P. K.; Emmett, G. C. *J. Org. Chem.* **1996**, *61*, 444.

13 (a) Moynihan, H. A.; Roberts, S. M.; Weldon, H.; Allcock, G. H.; Anggard, E. E.; Warner, T. D. *J. Chem. Soc., Perkin Trans. 1* **1994**, *7*, 769. (b) Feldman, P. L. *Tetrahedron Lett.* **1991**, *32*, 875.

14 Compound (**9**): 1H NMR (300 MHz, $CDCl_3$) δ 1.59 (br.s, 1H, O*H*), 2.10 (br.s, 1H, O*H*), 2.64 (dd, *J* = 9.9, 13.5 Hz, 1, CHCH*H*), 2.97-3.26 (m, 4H, CHCH*H*, CHCH_2, NC*H*), 3.35-3.3.47 (m, 2H, PhCH*H*, NC*H*), 3.55 (dd, *J* = 5.1, 9.9 Hz, 1, HOC*H*), 3.77 (dd, *J* = 3.6, 9.9 Hz, 1, OHC*H*), 4.16 (d, *J* = 15 Hz, 1, PhCH*H*), 4.65 (d, *J* = 15 Hz, PhCH*H*), 4.80 (d, *J* = 15 Hz, PhCH*H*), 4.87 (d, *J* = 12 Hz, 1, OCH*H*), 4.92(d, *J* = 12 Hz, 1, OCH*H*), 6.90-7.31 (m, 25H, Ar); 13C NMR (75 MHz, $CDCl_3$) 33.02, 33.74, 55.49, 55.87, 61.22, 62.36, 69.51, 72.82, 75.35, 126.02, 126.32, 126.71, 127.25, 127.32, 127.81, 127.89, 128.21, 128.41, 128.56, 128.89, 129.65, 129.75, 129.89, 137.44, 138.72, 138.95, 139.45, 140.23, 154.38; HRMS-CI calcd for $C_{40}H_{42}N_3O_3$ $(M+H)^+$ 612.3226, found 612.3218.

15 Compound (**10**) 1H NMR (300 MHz, $CDCl_3$) δ 2.65 (d, *J* = 10.5, 13.5 Hz, 1, CHCH*H*), 3.1-3.3 (m, 5H, O*H*, CHCH*H*, CHCH_2, NC*H*, PhCH*H*) 3.47-3.70 (m, 3H, O*H*, OC*H*, NC*H*), 3.83 (dd, *J* = 3.9, 9.9 Hz, 1, HOC*H*), 4.25 (d, *J* = 15 Hz, 1, PhCH*H*), 4.76 (d, *J* = 15 Hz, PhCH*H*), 4.81 (d, *J* = 15 Hz, PhCH*H*), 6.98-7.37 (m, 20H, Ar); 13C NMR (75 MHz, $CDCl_3$) 33.03, 33.79, 55.31, 55.72, 61.30, 62.21, 69.31, 72.51, 126.19, 126.47, 126.91, 127.54, 127.99, 128.15, 128.37, 128.53, 128.37, 128.84, 129.19, 129.49, 129.68, 129.89, 137.22, 138.18, 139.19, 140.06, 155.78; HRMS-CI calcd for $C_{33}H_{36}N_3O_3$ $(M+H)^+$ 522.2757, found 522.2741.

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