Cyclic HIV Protease Inhibitors: Design and Synthesis of Orally Bioavailable, Pyrazole P2/P2′ Cyclic Ureas with Improved Potency

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Highly potent HIV-1 protease (HIVPR) inhibitors have been designed and synthesized by introducing bidentate hydrogen-bonding oxime and pyrazole groups at the meta-position of the phenyl ring on the P2/P2′ substituents of cyclic ureas. Nonsymmetrical cyclic ureas incorporating 3(1*H*)-pyrazolylbenzyl as P2 and hydrophilic functionalities as P2′ show potent protease inhibition and antiviral activities against HIV and have good oral bioavailabilities. The X-ray structure of HIVPR·**10A** complex confirms that the two pyrazole rings of **10A** form bidentate hydrogen bonds with the side-chain oxygen (C=O) and backbone nitrogen (N−H) of Asp30/30′ of HIVPR.

Introduction

The RNA genome of the human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), encodes an essential aspartic protease (PR)[1] that processes the viral *gag* and *gag-pol* polyproteins into structural and functional proteins. Inhibition of HIVPR in vitro results in the production of progeny virions which are immature and noninfectious.[2] In clinical settings, four HIVPR inhibitors, recently approved by the FDA for AIDS therapy in combination with reverse transcriptase inhibitors, have been shown to reduce the viral load and increase the number of CD4$^+$ lymphocytes in HIV-infected individuals.[3] In addition, the large abundance of structural information on HIVPR has made the enzyme an attractive target for computer-aided drug design strategies.[4] Consequently, HIVPR inhibitors have become a prime focus for the development of HIV therapeutics.[5] However, the daunting ability of the virus to rapidly generate resistant mutants[3e−f,6] suggests that there is an ongoing need for new HIVPR inhibitors with superior pharmacokinetic and efficacy profiles.

We have recently reported the rational design and discovery of a novel class of orally bioavailable, nonpeptidal cyclic ureas as potent HIVPR inhibitors.[7] The design strategy incorporates the unique structural water, commonly found in the X-ray complexes of linear peptidal mimetic inhibitors and HIVPR, in a preorganized cyclic urea scaffold. Structure-based optimization rapidly led to the first clinical candidate, DMP323[7] (Figure 1). However, the clinical trial was terminated due to highly variable oral bioavailability as a result of low aqueous solubility (6 μg/mL) and metabolic instability of the benzylic hydroxymethylene groups in DMP323. The second clinical candidate, DMP450[8] (Figure 1), which has excellent water solubility (>130 mg/mL), exhibited high oral bioavailability in humans with a C_{max} of 6.5 μM when dosed at 750 mg as a neat powder. In our continuing search for the second generation of cyclic inhibitors using structure-based design techniques, we have synthesized cyclic ureas containing ketones, oximes, pyrazoles, imidazoles, triazoles, and tetrazoles substituted at the meta-position of the phenyl ring on P2/P2′. These compounds have improved potency and oral bioavailability.

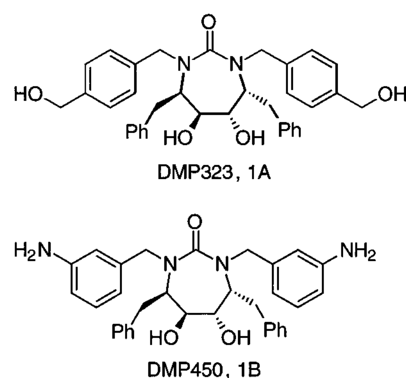

Figure 1. Structures of first clinical candidate DMP323 and second clinical candidate DMP450

Results and Discussion

Synthesis. Synthesis of cyclic ureas has been reported recently.[9] The synthesis of aldehyde, ketone, and oxime derivatives of the cyclic ureas is illustrated in Scheme 1. Alkylation of the parent cyclic urea **2** with *m*-cyanobenzyl bromide (**3A**) and *m*-iodobenzyl bromide (**3B**) in the presence of NaH in DMF gave **4A**,**B**, respectively. Reduction of **4A** with DIBAL-H (diisobutylaluminum hydride), followed by deprotection of the methoxyethoxymethyl (MEM) groups with HCl, provided aldehyde **5A**. Treatment of **4A** with Grignard reagents gave ketone derivatives **5B**−**D** after hydrolysis and deprotection of the MEM groups. Metalation of **4B** with *t*-BuLi followed by quenching of the organolithium with *N,N*-dimethyltrifluoroacetamide and then deprotection of the MEM groups provided **5E**. Metalation of **4A** with *t*-BuLi followed by hydrolysis and deprotection of the MEM groups provided **5F**. Reactions of **5A**−**E** with excess hydroxylamine in refluxing pyridine afforded the corresponding aldoxime and ketoximes **6A**−**E** in high yields.

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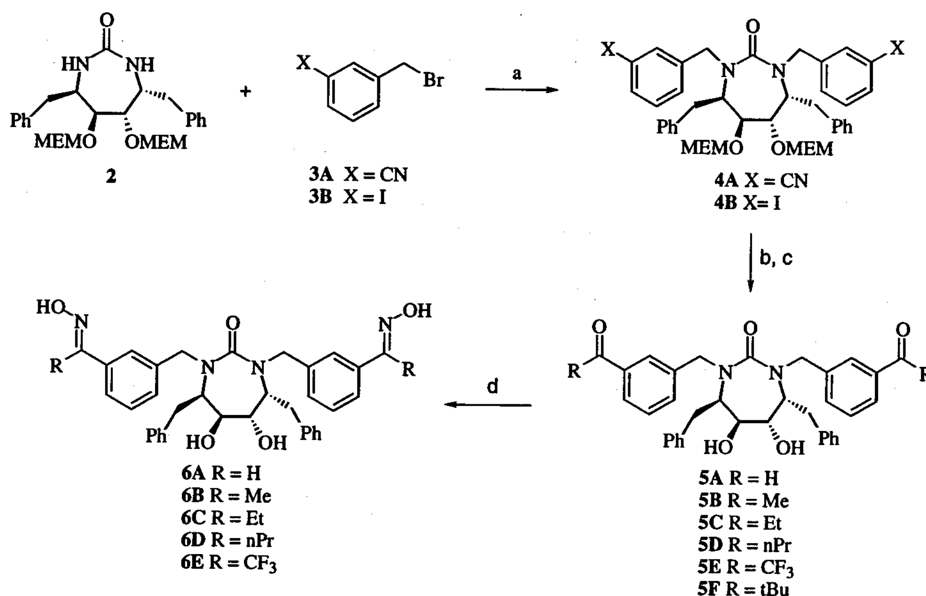
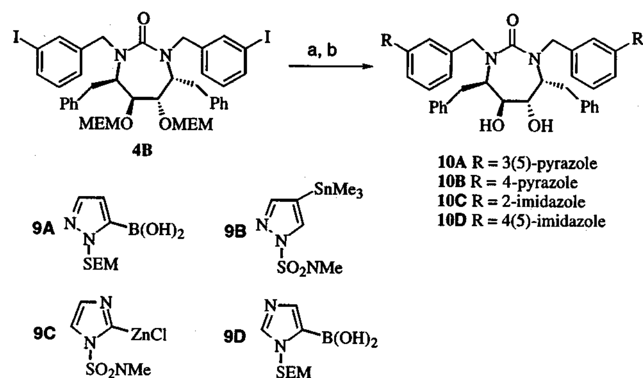
Scheme 1. Synthetic Sequence for Making Ketones and Oximes[a]



[a] Reagents: (a) 6 equiv of NaH, DMF; (b) for **5A**, DIBAL-H; for **5E**, *n*-BuLi, *N,N*-dimethyltrifluoroacetamide; for **5F**, *t*-BuLi; for the rest, RMgBr; (c) 4 M HCl in dioxane and MeOH; (d) NH_2OH, pyridine.

Scheme 2. Synthetic Sequence for Making Pyrazoles and Imidazoles[a]

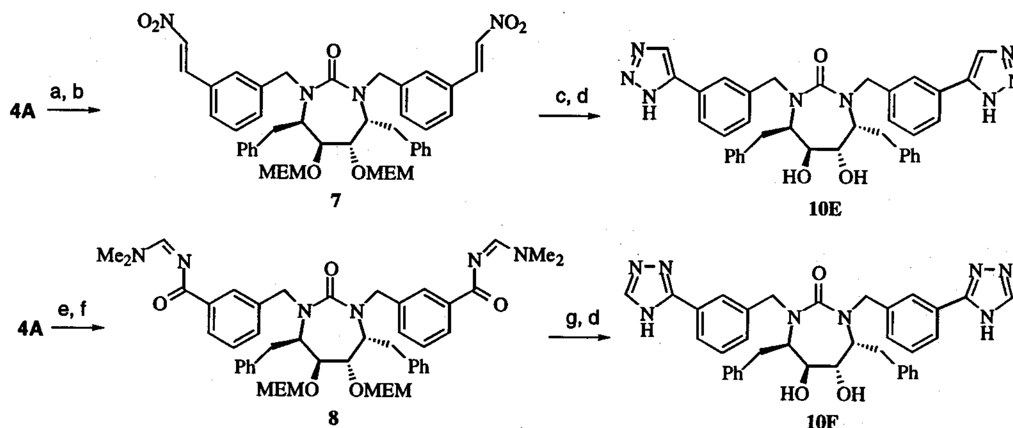


[a] Reagents: (a) **9**, $Pd(PPh_3)_4$; (b) 4 M HCl in dioxane and MeOH.

The synthesis of cyclic urea derivatives with *m*-pyrazolylbenzyl and *m*-imidazolylbenzyl as P2/P2′ substituents is described in Scheme 2. The pyrazole and imidazole derivatives **10A–D** were obtained respectively from coupling reactions of **4B** with 1-[[(2-(trimethylsilyl)ethoxy]methyl]pyrazolyl-5-boronic acid (**9A**), 1-[(dimethylamino)sulfonyl]pyrazolyl-4-trimethyltin (**9B**), 1-[(dimethylamino)sulfonyl]imidazolyl-2-zinc chloride (**9C**), and 1-[[(2-(trimethylsilyl)ethoxy]methyl]imidazolyl-5-boronic acid (**9D**), followed by treatment with HCl. The structure of **10A** was further confirmed by X-ray diffraction as illustrated in Figure 2.

The preparation of cyclic urea derivatives with *m*-triazolylbenzyl and *m*-tetrazolylbenzyl as P2/P2′ substituents is described in Schemes 3 and 4. Aldol condensation of MEM-protected **5A** with nitromethane afforded intermediate **7**. Treatment of **7** with NaN_3 in DMSO, followed by deprotection of the MEM groups, provided 1,2,3-triazole derivative **10E**. Oxidation of **4A** with H_2O_2 in basic DMSO gave an amide, which reacted with *N,N*-dimethylformamide diethyl acetal to form **8**. Cyclization of **8** with hydrazine followed by deprotection of MEM groups provided 1,2,4-triazole derivative **10F**. 5-Tetrazolylbenzyl-substituted derivative **10G** was prepared by the reaction of **4A** with NaN_3 and then treatment with HCl.

Scheme 3. Synthetic Sequence for Making Triazoles[a]



[a] Reagents: (a) DIBAL-H; (b) CH_3NO_2, NH_4OAc, HOAc; (c) NaN_3, DMSO; (d) 4 M HCl in dioxane and MeOH; (e) H_2O_2, K_2CO_3; (f) $Me_2NCH(OEt)_2$; (g) NH_2NH_2, HOAc.

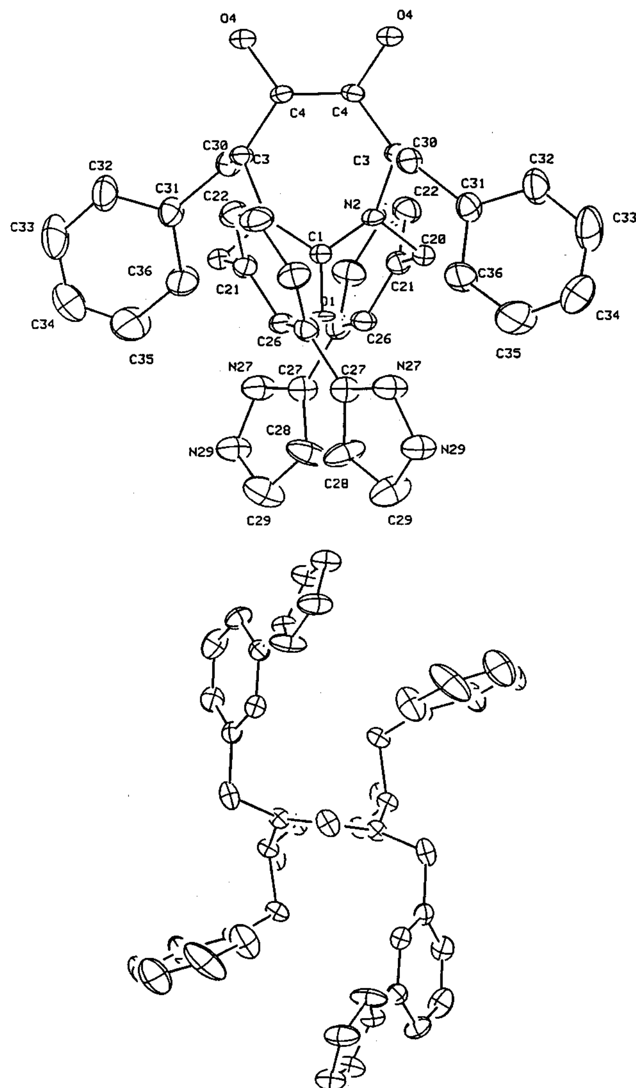
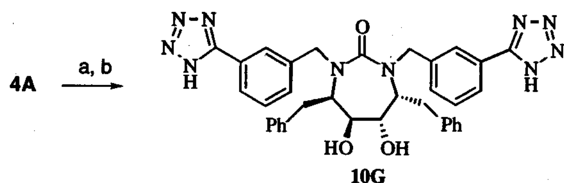


Figure 2. Crystal structure of pyrazole **10A**.

Scheme 4. Synthetic Sequence for Making Tetrazole[a]



[a] Reagents: (a) NH_4Cl, NaN_3, DMF; (b) 4 M HCl in dioxane and MeOH.

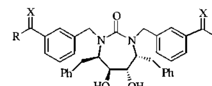
The nonsymmetrical cyclic ureas **12A**–**G** were prepared as shown in Scheme 5. Monoalkylation of **2** with 3 equiv of KOH and 2 equiv of *m*-iodobenzyl bromide (**3B**) in toluene in the presence of 10% PEG gave monoalkylated intermediate. Suzuki coupling reaction of the intermediate with boronic acid **9A** in the presence of palladium catalyst afforded **11**. Deprotection of **11** with HCl provided mono-3(1*H*)-pyrazolylbenzyl alkylated cyclic urea **12A**. Further alkylation of **11** with substituted benzyl bromides in the presence of NaH in DMF, followed by deprotection of MEM groups, formed nonsymmetrical cyclic ureas **12B**–**G**.

Structure-Based Design and Optimization of Cyclic Ureas. To design more potent HIVPR inhibitors than DMP450, we decided to increase the hydrogen-bonding network of the inhibitors with the protease at the S2/S2′ subsites. Molecular modeling suggests that the S2/S2′ subsites are essentially lipophilic except toward the edge of the pockets near the entrance to the active site where there are numerous hydrogen-bonding donors and acceptors comprised of the side chains and backbone amides of Asp29/29′, Asp30/30′, and Gly48/48′. In addition, there is sufficient space available around the meta-positions of the phenyl ring on P2/P2′ benzyl for attachment of functional groups.

Our initial objective was to introduce ketone groups at the meta-positions of the phenyl ring on P2/P2′ substituents since oxygen of the carbonyl group of ketone can be a good hydrogen bond acceptor. In addition, ketones can be readily elaborated into other derivatives. All ketone derivatives exhibit very potent activities against HIVPR (Table 1). The methyl ketone **5B** and trifluoromethyl ketone **5E** are more potent than DMP450. The affinity of the ketone derivatives is decreased as the size of the R-group increases from methyl (**5B**) to ethyl (**5C**), *n*-propyl (**5D**), and *tert*-butyl (**5F**). Interestingly, although a trifluoromethyl group is bulkier than a methyl group, **5E** has a lower K_i than **5B**. That is probably due to the existence of a hydrated form of trifluoromethyl ketone, which is capable of forming more hydrogen bonds. To further increase the number of potential hydrogen bond donors/acceptors, we introduced oxime functional groups. The oximes **6A**–**D** have lower K_i's than DMP450 (Table 1). Methyl ketoxime **6B** has the lowest K_i (0.018 nM) and IC_{90} (2 nM). The trifluoromethyl ketoxime **6E** is a weak binder probably because of steric reasons. The methyl ketoxime derivative **6B** is stable in weak acid solutions but decomposes under strong acidic conditions. Although the chemical instability of **6B** may limit its usefulness as a drug candidate, the extremely potent K_i and IC_{90} provide a very important lead for further design.

To understand the nature of the increased binding of oxime analogues, we have obtained the low-resolution X-ray structure[10] of **6A**/HIV-1 PR. Each oxime hydroxyl group donates a hydrogen bond to the carboxylate of Asp30/30′, identical to the amino group of DMP450. In addition, each oxime nitrogen accepts a hydrogen bond from the backbone amide N–H of Asp30/30′. The two additional hydrogen bonds as part of the new bidentate interactions provide 1 order of magnitude increase in

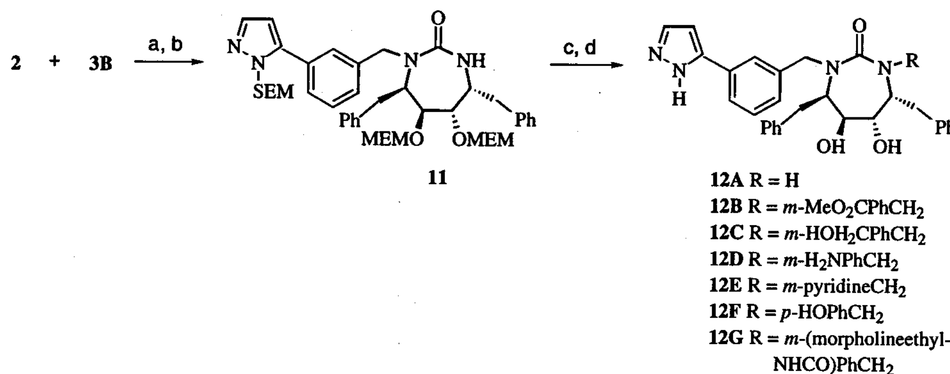
Table 1. SAR of Ketones and Oximes



#	R	X	HIVPR Ki (nM)	Cell RNA assay IC_{90} (nM)	TC_{50} (µM)	Rat P.O. @ 10 mg/kg Cmax (µM)
5A	H	O	0.44	36	19	0.26
5B	Me	O	0.06	39	20	0.5
5C	Et	O	0.21	142	≥ 80	
5D	nPr	O	1.4	1439	> 77	
5E	CF_3	O	0.037	33	5.4	
5F	tBu	O	3.6	-	-	
6A	H	N(OH)	0.010	5	16	0.30
6B	Me	N(OH)	0.018	2	81	0.06 *
6C	Et	N(OH)	0.031	7	5	
6D	nPr	N(OH)	0.031	64	3.7	
6E	CF_3	N(OH)	3.9	714	14	
DMP450	-	-	0.28	130		2.25

*0.51 μM in gelucire.

Scheme 5. Synthetic Sequence for Making Nonsymmetric Cyclic Ureas[a]



[a] Reagents: (a) 3 equiv of KOH, toluene; (b) **9A**, $Pd(PPh_3)_4$; (c) NaH, $ArCH_2Br$, DMF; (d) 4 M HCl in dioxane and MeOH.

Table 2. SAR of Heterocyclic Ring Compounds

#	R	HIVPR K_i (nM)	Cell RNA assay IC_{90} (nM)	TC_{50} (μM)	Rat P.O. @ 10 mg/kg Cmax (μM)
10A		0.027	20	4.2	0.068*
10B		0.62	32	1.4	0.075
10C		0.16	234	78	
10D		0.19	84	8.8	< 0.042
10E		0.17	94	47	
10F		0.052	128	53	
10G		6.6	> 70,000	78	

*For po in rat: Cl is 5.3 L/kg/h, $t_{1/2}$ is 0.2 h. For iv in dog: Cl is 1.2 L/kg/h, $t_{1/2}$ is 1.7 h, V_{ss} is 1.1 L/kg.

binding of the oximes **6A–D** over DMP450. To utilize this new bidentate hydrogen-bonding feature and stabilize the oxime functional group, we replaced the oximes with heterocycles which mimic the hydrogen bond donor/acceptor arrays of the extremely potent oxime. Table 2 shows a series of heterocycles capable of donating and accepting hydrogen bonds. Pyrazole (**10A**,**B**)-, imidazole (**10C**,**D**)-, and triazole (**10E**,**F**)-substituted cyclic urea derivatives are all tight binders of HIVPR except tetrazole (**10G**). The reason **10G** is not active is not clear. The tightest binder is 3-pyrazole **10A** with a similar K_i as oximes **6A**,**B**.

The three-dimensional structure of the complex of HIV-1 PR and **10A** with 2.0-Å diffraction data has been determined. The overall conformation of the structure is similar to the previously reported one for DMP323[9] and DMP450.[8] The urea oxygen atom interacts with the backbone nitrogen atom of Ile50/50′ at the flap. The diols in the seven-membered ring participate in an extensive hydrogen-bonding network with the catalytic Asp 25/25′ at the base of the pocket. Two benzyl groups attached at the 4*R*,7*R* positions of the cyclic urea ring occupy S1/S1′ pockets. The pyrazolylbenzyl groups attached to the urea nitrogens are located within the S2/S2′ pockets. The pyrazole ring forms bidentate hydrogen bonds with the side-chain oxygen and backbone nitrogen of Asp30/30′. The bonding distances are between 3.3 and 3.5 Å. The benzyl and pyrazole rings are nearly coplanar with the angle between two rings

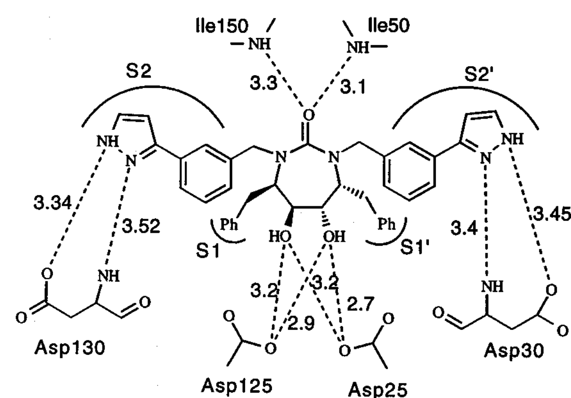


Figure 3. Hydrogen-bonding interactions of pyrazole **10A** with HIV-1 PR based on X-ray.

of P2 being 6° and P2′ being 15°. The inhibitor molecule binds symmetrically to the active site of the enzyme with two symmetric portions being related to each other by the pseudo-2-fold axis of symmetry that relates one monomer of the protease to the other. Details of the inhibitor binding model are shown in Figures 3 and 4.

Unfortunately, all these heterocycle-substituted compounds, despite the excellent chemical stability, have low oral bioavailablity probably due to low aqueous solubilities. For example, pyrazole **10A** has an aqueous solubility at pH 7.4 of less than 0.0001 mg/mL, compared with DMP450 (bis-myslate salt) which is >130 mg/mL. Nonsymmetric cyclic ureas should have the advantage of better solubility due to lower crystal-packing energy. This can result in improvement of oral bioavailability. We therefore decided to synthesize nonsymmetric cyclic urea derivatives (Table 3). Since 3-pyrazole derivative **10A** has the best K_i and IC_{90} among the heterocycles **10A–G**, it was chosen for nonsymmetric cyclic ureas. Three of the nonsymmetric cyclic ureas (**12D**,**F**,**G**) have similar low K_i values as the symmetric **10A**, and **12D** has the lowest IC_{90} of 27 nM. The nonsymmetric cyclic ureas in general have better oral bioavailability than the symmetric cyclic ureas. The dog oral bioavailability of **12D** is 0.85 μM in C_{max} at a dose of 2.5 mg/kg. This is quite good considering the low dose. Monopyrazole **12A** shows a relatively good C_{max} of 0.78 μM in rats at 10 mg/kg po, probably due to its relatively small size. In general, smaller size compounds tend to show better pharmacokinetics.[11]

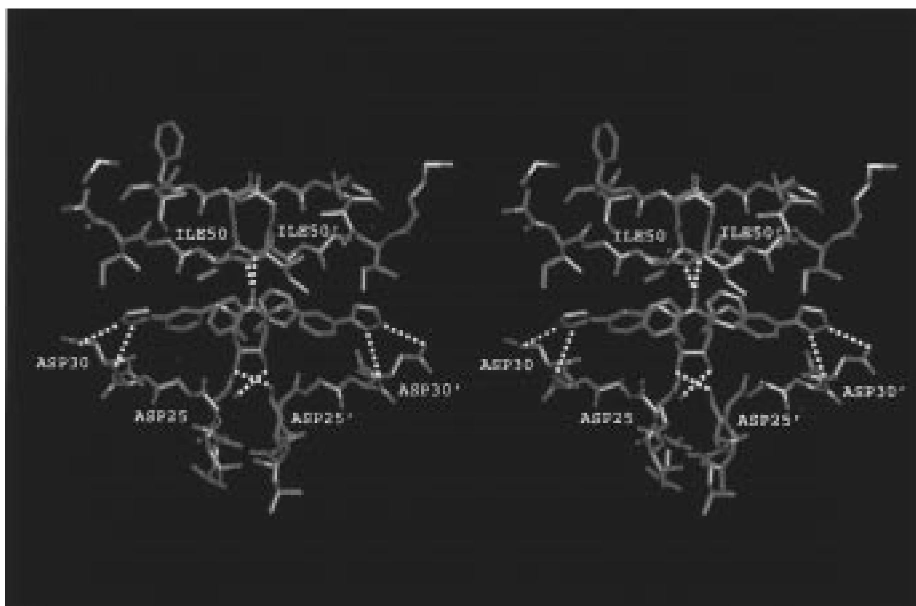


Figure 4. Stereoview of X-ray of the **10A** and HIVPR complex. Residues 24−30 at the active site and 46−54 at the flap are shown. The hydrogen bond is the yellow dotted line. Two of the eight possible hydrogen bonds between the hydroxyls of CU and catalytic aspartates (Asp25/25′) are shown. The two pyrazole rings of **10A** form bidentate hydrogen bonds with the side-chain oxygen (C=O) and backbone nitrogen (N−H) of Asp30/30′ of HIVPR.

Table 3. SAR of Nonsymmetric Cyclic Ureas

#	R	HIVPR Ki (nM)	Cell RNA assay IC_{90} (nM)	TC_{50} (μM)	Rat P.O. @ 10 mg/kg Cmax (μM)
12A	H	0.26	67	21	0.78
12B	CO_2Me	0.14	32	5.7	0.32
12C	CH_2OH	0.16	234	20	0.11
12D	NH_2	0.035	27	6.8	0.85*
12E	N	0.17	94	6.3	
12F	OH	0.021	30	4.8	
12G		0.052	128	43	

*@2.5 mg/kg in dog.

Conclusion

In conclusion, with the help of X-ray structures, we have designed and synthesized more potent HIVPR inhibitors relative to our first-generation candidates DMP323 and DMP450 by introducing bidentate hydrogen-bonding groups on the P2/P2′ benzyl of cyclic urea. The best inhibitor combining potent antiviral activity and metabolic stability is **10A** (K_i = 0.027 nM; IC_{90} = 20 nM). Nonsymmetric cyclic urea **12D**, hybrid of **10A** and DMP450, also combines good potency and stability. The IC_{90} of **12D** is 5-fold better than that of DMP450 (IC_{90} = 130 nM). Importantly, **12D** has good dog oral bioavailability with a plasma C_{max} of 0.85 μM at a low dose of 2.5 mg/kg. These inhibitors have potential for further development in the search of a second-generation drug candidate. Further work awaits to be done in this *m*-heterocyclic benzyl P2/P2′ CU area.

Experimental Section

Biological Methods. Inhibition of HIV protease was measured by assaying the cleavage of a fluorescent peptide substrate using HPLC.[12] The antiviral potency of compounds was assessed by measuring their effect on the accumulation of viral RNA transcripts 3 days after infection of MT-2 cells with HIV-1 RF.[13] Uninfected cells were incubated in microtiter plate wells with serial dilutions of test compound in cell culture medium for 30 min; then virus was added. After 3 days of culture at 37 °C and 5% CO_2, infected cell cultures were lysed and the levels of HIV RNA determined using a microtiter plate-based hybridization assay. The concentration of test compound which reduced the concentration of HIV viral RNA by 90% from the level measured in an untreated infected culture was designated the IC_{90}. The cytotoxity of the compounds (TC_{50}) as determined by a 50% reduction in the number of viable cells as determined by the metabolism of a tetrazolium dye was at least 20-fold greater than the antiviral RNA IC_{90}. Oral bioavailability was measured as previously described.[7−9]

Chemical Methods. All procedures were carried out under inert gas in oven-dried glassware unless otherwise indicated. Proton and carbon NMR spectra were obtained on VXR or Unity 300- or 400-MHz instruments (Varian Instruments, Palo Alto) with TMS as an internal reference standard. Mass spectra were measured with a HP5988A mass spectrometer with particle beam interface using NH_3 for chemical ionization or a Finnigan MAT 8230 mass spectrometer with NH_3-DCI or VG TRIO 2000 for ESI. High-resolution mass spectra were measured on a VG 70-VSE instrument with NH_3 chemical ionization. Melting points were determined on a Mettler SP61 apparatus and are uncorrected. Separation of isomers was performed using supercritical fluid chromatography with a Chiracel OD (Diacel Chemical Ind. Ltd.) and 20% methanol-modified CO_2 mobile phase. Solvents and reagents were obtained from commercial vendors in the appropriate grade and used without further purification unless otherwise indicated. All compounds were determined to be homogeneous by TLC, elemental analysis, and/or HPLC. Elemental analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ. Purity values were obtained by reverse-phase analytic HPLC using a Jasco system equipped with a UV detector. Combustion analyses are within ±0.4% of the calculated value. Compounds for elemental analysis are further purified by HPLC with a reverse-phase preparative

column by using gradient solvents ($H_2O-CH_3CN-0.05\%$ TFA) as a mobile phase.

Representative Procedures for Ketone Derivatives: (4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[(3-acetylphenyl)methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (5B). To a solution of **4A** (750 mg, 1.02 mmol) in THF (20 mL) was added methylmagnesium bromide (3 M in Et_2O, 3 mL), and the resulting mixture was allowed to reflux for 2 h. After all solvents were removed on a rotary evaporator, the resulting residue was dissolved in MeOH (15 mL), followed by carefully treating with 4 M HCl in dioxane (15 mL) and stirring for 16 h. The reaction mixture was concentrated and then partitioned in ethyl acetate and water (200 mL, 4:1). The organic layer was washed with 10% $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting crude residue was purified by thin-layer chromatography (TLC) with 40% EtOAc in CH_2Cl_2 to give **5B** (600 mg, 90%) as a white solid: mp 158−159 °C; DCIMS *m*/*z* 608 ($M + NH_4$)$^+$; HRMS $(M + H)^+$ 591.2849 (calcd 591.2859); ^{1}H NMR ($CDCl_3$) δ 7.82 (dd, $J = 6.6$ Hz, $J = 3.8$ Hz, 2H), 7.78 (s, 2H), 7.72 (bs, 4H), 7.43−7.23 (m, 6H), 7.06 (d, $J = 6.6$ Hz, 4H), 4.87 (d, $J = 14.3$ Hz, 2H), 3.70 (s, 2H), 3.57 (d, $J = 11.0$ Hz, 2H), 3.18 (d, $J = 14.3$ Hz, 2H), 3.09 (dd, $J = 13.2$ Hz, $J = 2.1$ Hz, 2H), 2.91 (dd, $J = 11.4$ Hz, $J = 1.8$ Hz, 2H), 2.58 (b, 2H), 2.53 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 198.03, 161.83, 139.40, 138.78, 137.12, 133.87, 129.29, 129.04, 128.74, 128.52, 127.36, 126.46, 71.25, 65.32, 55.82, 30.73, 26.51. Anal. ($C_{37}H_{38}N_2O_5\cdot0.5H_2O$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[3-(trifluoroacetyl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (5E). To a solution of **4B** (980 mg, 1.07 mmol) in THF (10 mL) at −78 °C was added *t*-BuLi (2.64 mL of 1.7 M in hexane, 4.5 mmol), and the resulting solution was stirred for an additional 30 min. Then *N*,*N*-dimethyltrifluoroacetamide (560 mg, 4 mmol) was added, and the resulting mixture was warmed to room temperature over 2.5 h. The mixture was diluted with ether and acidified to pH 6 with 2 N HCl. The ether layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography with gradient solvents (0−20% ethyl acetate in CH_2Cl_2) to give an oil (350 mg). The oil was dissolved in $CHCl_3$ (5 mL) and treated with 4 M HCl in dioxane (5 mL) for 16 h. General workup and purification by TLC with 40% EtOAc in CH_2Cl_2 gave **5E** (300 mg, 40.2% for two steps): CIMS *m*/*z* 699.4 $(M + H)^+$; HRMS $(M + H)^+$ 699.2286 (calcd 699.2294); ^{1}H NMR (CD_3COCD_3) δ 7.97 (bs, 4H), 7.73 (s, 2H), 7.70−7.59 (m, 2H), 7.30−7.21 (m, 6H), 7.98−6.96 (m, 4H), 4.75 (d, $J = 13.9$ Hz, 2H), 4.41 (s, 2H), 3.72−3.63 (m, 4H), 3.32 (d, $J = 14.3$ Hz, 2H), 3.18−3.13 (m, 2H), 2.95−2.79 (m, 2H); ^{19}F NMR (CD_3COCD_3) δ −72.54; ^{13}C NMR (CD_3COCD_3) δ 180.83 (q, $J = 34.3$ Hz), 162.39, 141.27, 141.06, 137.90, 131.60, 130.43, 130.35, 130.23, 129.73, 129.16, 127.05, 117.62 (q, $J = 291.4$ Hz), 71.83, 67.40, 56.55, 33.59.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[(3-pivaloylphenyl)methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (5F). To a solution of **4A** (366 mg, 0.5 mmol) in THF (15 mL) at −78 °C was added dropwise *t*-BuLi (2.59 mL of 1.7 M in hexane, 4.4 mmol), and the resulting solution was allowed to warm to room temperature. The mixture was diluted with ether, washed with saturated NH_4Cl and water, and dried over $MgSO_4$. A concentrated residue was deprotected by general de-MEM procedure and was then purified by TLC with 10% EtOAc in CH_2Cl_2 to give **5F** (287 mg, 85%): CIMS *m*/*z* 675.5 $(M + H)^+$; HRMS $(M + H)^+$ 675.3805 (calcd 675.3798); ^{1}H NMR ($CDCl_3$) δ 7.56−7.54 (m, 2H), 7.05 (s, 2H), 7.43−7.25 (m, 12H), 7.08−7.06 (m, 2H), 4.88 (d, $J = 14.3$ Hz, 2H), 3.64 (s, 2H), 3.53 (d, $J = 11.0$, Hz, 2H), 3.09−2.87 (m, 6H), 2.58 (b, 2H), 1.29 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 209.24, 161.87, 139.35, 139.05, 138.23, 131.66, 129.43, 128.70, 128.36, 126.96, 126.62, 71.58, 64.76, 55.80, 44.21, 32.89, 27.94. Anal. ($C_{43}H_{50}N_2O_5\cdot0.29TFA\cdot0.4H_2O$) C, H, N, F.

Representative Procedures for Oxime Derivatives: (4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[3-[1-(hydroxyimino)ethyl]phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (6B). A solution of **5B** (84 mg, 0.142 mmol) and hydroxylamine hydrochloride (59.4 mg, 0.854 mmol) in pyridine and ethanol (6 mL, 1:1) was refluxed for 16 h. Evaporation of all solvents under full vacuum gave a residue, which was purified by TLC with ethyl acetate, methylene chloride, and methanol (50:50:2) to give **6B** (71 mg, 83%) as a solid: mp 200−202 °C; DCIMS *m*/*z* 621 $(M + H)^+$; HRMS $(M + H)^+$ 621.3070 (calcd 621.3077); ^{1}H NMR (CD_3OD) δ 7.47 (d, $J = 7.8$ Hz, 2H), 7.39 (s, 2H), 7.27−7.17 (m, 8H), 7.09 (d, $J = 7.6$ Hz, 2H), 7.06 (d, $J = 6.8$ Hz, 4H), 4.74 (d, $J = 13.9$ Hz, 2H), 3.64−3.62 (m, 4H), 3.09−2.89 (m, 6H), 2.17 (s, 6H); ^{13}C NMR (CD_3OD) δ 163.94, 155.43, 141.23, 139.46, 138.97, 130.77, 130.65, 129.69, 129.37, 128.10, 127.47, 126.32, 72.02, 67.16, 57.08, 33.62, 11.96. Anal. ($C_{37}H_{40}N_4O_5\cdot H_2O$) C, H, N.

1-*N*-[[2-(Trimethylsilyl)ethoxy]methyl]pyrazolyl-5-boronic Acid (9A). To a solution of 1-*N*-SEM-protected pyrazole (1.98 g, 10 mmol) in THF (40 mL) at −78 °C was added dropwise *n*-BuLi (1.6 M, 7.5 mL, 12 mmol), and the resulting solution was stirred for an additional 30 min. After triisopropyl borate (9.4 g, 50 mmol) was added, the mixture was allowed to warm to room temperature over 2 h. The reaction mixture was acidified to pH 6 with 2 N HCl, extracted with ethyl acetate, washed with water and brine, and dried over $MgSO_4$. After filtration, concentration, and purification by column chromatography with gradient solvents (CH_2Cl_2−EtOAc−MeOH), **9A** was obtained in almost quantitative yield: ^{1}H NMR (CD_3OD) δ 7.57 (s, 1H), 6.80 (s, 1H), 5.70 (s, 2H), 3.57 (t, $J = 7.8.0$ Hz, 2H), 0.89 (t, $J = 8.0$ Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (CD_3OD) δ 138.54, 115.65, 78.98, 65.98, 17.31, −2.30.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[3-(1*H*-pyrazol-3-yl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (10A). To a solution of **4B** (932 mg, 1 mmol) in THF (5 mL) were added **9A** (968 mg, 4 mmol), Pd(PPh_3)$_4$ (57.8 mg, 0.05 mmol), and Na_2CO_3 (1.7 g in 4 mL of H_2O), and the resultant mixture was allowed to reflux under nitrogen over 48 h. General workup gave a residue, which was purified by column chromatography with gradient solvents (CH_2Cl_2−EtOAc) to give a MEM-protected intermediate. A solution of the intermediate in MeOH (15 mL) was treated with 4 M HCl in dioxane (15 mL) and stirred for 16 h. General workup followed by purification by thin-layer chromatography with 20% EtOH in hexane gave **10A** (560 mg, 87.8%) as a solid: CIMS *m*/*z* 639 $(M + H)^+$; HRMS $(M + H)^+$ 639.3081 (calcd 639.3083); ^{1}H NMR (CD_3OD) δ 8.32 (d, $J = 1.6$ Hz, 2H), 7.74 (d, $J = 6.9$ Hz, 2H), 7.66 (s, 2H), 7.49 (d, $J = 6.9$ Hz, 4H), 7.15−7.09 (m, 8H), 6.89−6.87 (m, 4H), 4.68 (d, $J = 13.9$ Hz, 2H), 3.87 (b, 2H), 3.80 (d, $J = 11.3$ Hz, 2H), 3.33 (dd, $J = 10.2$ Hz, $J = 1.1$ Hz, 2H), 3.06 (d, $J = 12.8$ Hz, 2H), 2.78−2.69 (m, 2H); ^{13}C NMR (CD_3OD) δ 162.82, 140.19, 139.01, 129.67, 129.22, 128.96, 128.59, 127.06, 126.49, 125.03, 102.41, 71.02, 66.69, 56.37, 32.65. Anal. ($C_{39}H_{38}N_6O_3\cdot2.0TFA\cdot0.12HCl\cdot1.0H_2O$) C, H, N, F, Cl. The single crystal of **10A** was obtained from recrystallization in CD_3OD.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[3-(1*H*-prazol-4-yl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (10B). A solution of 4-iodopyrazole (1.54 g, 8 mmol) in THF (20 mL) was treated with NaH (0.43 g, 10.6 mmol) at room temperature, followed by slowly quenching with dimethylsulfamoyl chloride (1.38 g, 9.6 mmol). General workup provided *N*-[(dimethylamino)sulfonyl]pyrazole (2.4 g, 92%). The N-protected intermediate (1.5 g, 5 mmol) in THF (25 mL) was reacted with hexamethylditin (1.8 g, 5.5 mmol) in the presence of Pd(Ph_3P)$_4$ (0.115 g, 0.1 mmol) under nitrogen at 78 °C for 16 h and then cooled to room temperature. To the solution (**9B**) were added **4B** (0.932 g, 1.0 mmol) and another portion of Pd(Ph_3P)$_4$ (0.18 g, 0.16 mmol) under nitrogen, and the resulting mixture was stirred under nitrogen at 80 °C for 18 h. General workup followed by deprotection by general de-MEM procedure gave a residue, which was purified by reverse-phase thin-layer chromatography with 85% MeOH in water to give **10B** (516 mg, 81%) as a solid: DCIMS *m*/*z* 639 $(M + H)^+$; HRMS $(M + H)^+$ 639.3100 (calcd 639.3083); ^{1}H NMR (CD_3OD) δ 7.77−7.12 (m, 4H), 7.38−6.95 (m, 18H),

4.72 (d, J = 14.3 Hz, 2H), 3.59−3.55 (m, 4H), 3.02−2.88 (m, 6H); ^{13}C NMR (CD_3OD) δ 163.36, 140.63, 139.40, 133.75, 130.19, 129.83, 129.18, 127.87, 127.38, 127.12, 125.47, 122.79, 71.64, 66.46, 56.76, 33.23. Anal. ($C_{39}H_{38}N_6O_3$·1.2TFA·0.16HCl·2.0H_2O) C, H, N, F, Cl.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[3-(1*H*-imidazol-2-yl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (10C). *N*-(Dimethylsulfamoyl)imidazolyl-2-zinc chloride (**9C**) was made in situ by lithiation of *N*-(dimethylsulfamoyl)imidazole (0.97 g, 5.5 mmol) in THF (20 mL) with *t*-BuLi (1.7 M, 6.7 mL) at −78 °C for 20 min, followed by quenching with a solution of zinc chloride (1.87 g, 13.75 mmol) in THF (15 mL) at the same temperature and then warming to room temperature over 1 h. A coupling reaction of the crude **9C** and **4B** (0.932 g, 1.0 mmol) in the presence of Pd($Ph_3P)_4$ (0.12 g, 0.1 mmol) was carried out under nitrogen and refluxed for 16 h. After being cooled to room temperature, the reaction mixture was poured into EtOAc−H_2O (250 mL, 1:1). The organic layer was dried over $MgSO_4$ and concentrated to give a residue. The residue was dissolved in MeOH and treated with 4 M HCl in dioxane under reflux for 2 h. The resulting mixture was worked up and purified on reverse-phase TLC plate with 80% MeOH in water to give **10C** (370 mg, 50%) as a solid: mp 178−180 °C; CIMS *m*/*z* 639.4 (M + H)$^+$; HRMS (M+ H)$^+$ 639.3069 (calcd 639.3084); ^{1}H NMR (CD_3OD) δ 7.75−7.70 (m, 4H), 7.42−7.33 (m, 2H), 7.28−7.12 (m, 12H), 7.00−6.94 (m, 4H), 4.73 (d, J = 14.3 Hz, 2H), 3.71 (bs, 4H), 3.14 (d, J = 13.9 Hz, 2H), 3.04−2.99 (m, 2H), 2.85−2.77 (m, 2H); ^{13}C NMR (CD_3OD) δ 162.00, 146.27, 139.58, 138.87, 130.23, 129.36, 129.11, 128.80, 128.00, 126.20, 125.89, 124.36, 122.64, 70.39, 67.14, 56.29, 32.22. Anal. ($C_{39}H_{38}N_6O_3$·2.1TFA·0.23HCl·2.5H_2O) C, H, N, F, Cl.

1-[[2-(Trimethylsilyl)ethoxy]methyl]imidazolyl-5-boronic Acid (9D). To a solution of *N*-[[(trimethylsilyl)ethoxy]-methyl](SEM)-imidazole (2 g, 10 mmol) in THF (20 mL) was added *t*-BuLi (1.7 M, 6.9 mL) at −78 °C, and the mixture stirred for an additional 20 min. After TMSCl (1.25 g) was added, the mixture was allowed to warm to 0 °C over 2 h and then cooled to −78 °C again. The mixture was treated with *t*-BuLi (1.7 M, 6.9 mL) at the same temperature over 30 min, followed by quenching with B($OMe)_3$ (10.4 g, 100 mmol). After the resulting mixture was warmed to room temperature and stirred for 16 h, it was poured into EtOAc−H_2O (250 mL, 4:1), and the organic layer was acidified to pH 7 with 1 N HCl, dried over $MgSO_4$, and purified by column chromatography with gradient solvents (CH_2Cl_2−MeOH) to give pure **9D** (2.3 g, 95%) as a solid: ^{1}H NMR (CD_3OD) δ 7.63 (d, J = 0.74 Hz, 1H), 6.87 (d, J = 1.1 Hz, 1H), 5.47 (s, 2H), 3.55 (t, J = 8.4 Hz, 2H), 0.93 (t, J = 8.4 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (CD_3OD) δ 138.97, 134.54, 77.89, 68.00, 20.19, 0.00.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[3-(1*H*-imidazol-4-yl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (10D). A solution of **9D** (1.3 g, 5.37 mmol), **4B** (0.937 g, 1.01 mmol), Pd($Ph_3P)_4$ (0.18 g, 0.16 mmol), and K_2CO_3 (7.5 g) in THF (20 mL) and H_2O (20 mL) was degassed and then heated to reflux under nitrogen for 16 h. The reaction mixture was cooled to room temperature and partitioned in EtOAc−H_2O (250 mL, 4:1). The organic layer was dried over $MgSO_4$ and concentrated to give a residue, which was treated with 4 M HCl in dioxane under reflux for 16 h. The mixture was concentrated, and the resulting residue was purified on reverse-phase TLC plate with 80% MeOH in water to give **10D** (0.24 g, 37%) as a solid: mp 171−175 °C; CIMS *m*/*z* 639.4 (M + H)$^+$; HRMS (M + H)$^+$ 639.3089 (calcd 639.3084); ^{1}H NMR (CD_3OD) δ 7.71 (bs, 2H), 7.61 (d, J = 7.7 Hz, 2H), 7.52 (s, 2H), 7.35−7.19 (m, 10H), 7.10−7.08 (m, 6H), 4.78 (d, J = 13.9 Hz, 2H), 3.71−3.65 (m, 4H), 3.32−3.00 (m, 4H), 2.96−2.87 (m, 2H); ^{13}C NMR (CD_3OD) δ 163.80, 141.26, 139.94, 137.20, 134.78, 130.67, 130.11, 129.52, 128.88, 127.40, 127.08, 125.22, 72.00, 67.72, 57.38, 33.60. Anal. ($C_{39}H_{38}N_6O_3$·2.2TFA·0.13HCl·3.0H_2O) C, H, N, F, Cl.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[3-(1,2,3-triazolyl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (10E). To a solution of **4A** (10.0 g, 13.6 mmol) in toluene (150 mL) at −78 °C was added dropwise DIBAL-H (1.5 M in toluene, 27 mL, 40.9 mmol), and the mixture stirred for an additional 2.5 h. After slowly warming to room temperature and stirring for 16 h, the mixture was cooled to −20 °C, quenched with methanol, and then poured into 5% HCl (50 mL) and ether (200 mL). The organic layer was separated, washed with saturated sodium bicarbonate (100 mL), water (3 × 100 mL), and brine (80 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (50% ethyl acetate in hexane) purification of the residue gave an aldehyde intermediate (6.3 g, 63%). To a solution of the aldehyde (2.0 g, 2.7 mmol) in acetic acid (15 mL) was added ammonium acetate (0.17 g, 2.16 mmol) followed by addition of nitromethane (0.42 g, 7.04 mmol). After the mixture was refluxed for 3 h, another portion of nitromethane (0.33 g, 5.4 mmol) was added and the resulting mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL) and water (20 mL). The organic phase was separated, washed with saturated sodium bicarbonate (2 × 15 mL), water (15 mL), and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatographic (30% ethyl acetate in hexane) purification gave nitrostyrene **7** (0.6 g, 30%). To a solution of **7** (0.21 g, 0.25 mmol) in DMSO (5 mL) was added NaN_3 (0.10 g, 6 mmol), and the mixture stirred at room temperature for 16 h and then was poured into water (20 mL). A yellow precipitate was collected, washed with water, and air-dried to give a residue (0.2 g), which was treated with 4 M HCl (in dioxane, 1.5 mL) in methanol (10 mL) at room temperature for 16 h. After solvents and reagent were removed under reduced pressure, a residue was purified by flash column chromatograph (10% methanol in chloroform) to give **10E** (0.12 g, 78%) as yellow crystals: mp 224−226 °C; HRMS (M + H)$^+$ 641.2999 (calcd 641.2989); ^{1}H NMR (CD_3OD) δ 8.06 (bs, 2H), 7.90 (s, 2H), 7.74 (d, J = 7.7 Hz, 2H), 7.69 (s, 2H), 7.39−7.43 (m, 2H), 7.21−7.27 (m, 10H), 7.07 (d, J = 6.2 Hz, 2H), 4.78 (d, J = 14.3 Hz, 2H), 3.69−3.61 (m, 4H), 3.10−2.85 (m, 6H). Anal. ($C_{37}H_{36}N_8O_3$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[3-(1,2,4-triazolyl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (10F). To a slurry solution of **4A** (3.0 g, 4.09 mmol) and K_2CO_3 (4.5 g, 32.7 mmol) in DMSO (10 mL) at 0 °C was added dropwise H_2O_2 (30%, 18 mL), and the mixture stirred for 0.5 h. After slowly warming to room temperature and stirring for an additional 2 h, the reaction mixture was poured into water (80 mL) and extracted with ethyl acetate. The organic phase was separated, washed with water (3 × 40 mL) and brine (2 × 30 mL), dried over $MgSO_4$, filtered, and concentrated. A residue was purified by flash chromatography (40% ethyl acetate in hexane) to give an amide intermediate (1.6 g, 51%). A mixture of the amide (300 mg, 0.39 mmol) and *N*,*N*-dimethylformaldehyde diethyl acetal (500 mg, 3.4 mmol) was stirred at 100 °C for 2 h, followed by removing excess of *N*,*N*-dimethylformaldehyde diethyl acetal under reduced pressure, to give compound **8** (320 mg, 93%). A solution of **8** (320 mg, 0.36 mmol) in acetic acid (3 mL) was treated with anhydrous hydrazine (70 mg, 2 mmol) at 90 °C for 2.5 h. After excess hydrazine and acetic acid were removed under reduced pressure, a residue was partitioned between water (10 mL) and ethyl acetate (10 mL). The organic phase was separated, washed with water (2 × 5 mL) and saturated sodium bicarbonate (5 mL), dried over $MgSO_4$, and concentrated to leave the MEM-protected intermediate. The intermediate was deprotected by general de-MEM procedure and workup, followed by flash chromatographic (15% methanol in chloroform) purification to give **10F** (100 mg, 64%) as a pale-yellow solid: mp 190−192 °C; HRMS (M + H)$^+$ 641.2990 (calcd 641.2989); ^{1}H NMR (CD_3OD) δ 9.58 (s, 2H), 8.00 (s, 2H), 7.98 (d, J = 6.6 Mz, 2H), 7.70−7.60 (m, 4H), 7.30−7.20 (m, 8H), 7.06−7.01 (m, 4H), 4.75 (d, J = 14.3, 2H), 3.90 (s, 2H), 3.84 (d, J = 10.6, 2H), 3.44−3.40 (m, 4H), 3.18 (d, J = 12.8, 2H), 2.98−2.88 (m, 2H). Anal. ($C_{37}H_{36}N_8O_3$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[3-(5-tetrazolyl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-

diazepin-2-one (10G). A solution of **4A** in DMF (10 mL) was treated with ammonium chloride (214 mg, 4 mmol) and sodium azide (260 mg, 4 mmol) at 100 °C for 48 h. The mixture was diluted with water (50 mL) and extracted with ether (2 × 25 mL). The aqueous layer was acidified and extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford MEM-protected intermediate (808 mg), which was treated with 4 M HCl in dioxane and methanol (1:1, 8 mL) at room temperature for 18 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and purified by reverse-phase (C18) preparative HPLC using gradient solvents ($H_2O-CH_3CN-0.05\%$ TFA) as a mobile phase to afford **10G** (548 mg, 85.3% for the two steps) as a white solid: ^1H NMR (CD_3OD) δ 2.75−2.86 (m, 2H), 3.00−3.08 (m, 2H), 3.16−3.25 (d, 2H), 3.62−3.8 (m, 4H), 4.6−4.7 (d, 2H), 6.85−6.97 (m, 4H), 7.05−7.19 (m, 6H), 7.37−7.5 (m, 4H), 7.8−7.9 (m, 4H); ^{13}C NMR (CD_3OD) δ 33.93, 57.54, 68.53, 72.00, 127.46, 129.47, 129.54, 130.55, 130.78, 133.51, 141.06, 157.87, 163.69; HRMS (M^+ + H) 643.2898 (calcd for $C_{35}H_{35}N_{10}O_3$ 643.2893).

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1-[[3-[1-*N*-[[(trimethylsilyl)ethoxy]methyl]pyrazol-5-yl]phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (11). A mixture of **2** (5.2 g, 10.4 mmol), 85% KOH (2 g, 31 mmol), and PEG1000 (0.5 g) in toluene (80 mL) was refluxed for 3 h to remove water. After cooling to room temperature, to the formed potassium salt was added *m*-iodobenzyl bromide (6.1 g, 20.7 mmol), and the resulting mixture was stirred at 75 °C for 18 h. The mixture was then poured into ice-cold NH_4Cl (aq) and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a residue. The residue was purified by column chromatography with ethyl acetate and hexane (4:6) to give a monoalkylated cyclic urea (2.9 g, 40%). The mono-*m*-iodobenzyl cyclic urea (2.9 g, 4 mmol) in THF (15 mL) was coupled with **9A** (3.87 g, 16 mmol) by the same procedure to make and purify **10A** to provide pure coupled product **11** (2.4 g, 75%): ESMS *m*/*z* 6812.2 (M + Na)$^+$; ^1H NMR ($CDCl_3$) δ 7.62 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.45−7.18 (m, 13H), 6.43 (d, *J* = 1.8 Hz, 1H), 5.42 (s, 2H), 4.94−4.64 (m, 4H), 4.68 (dd, *J* = 18.3 Hz, *J* = 7.0 Hz, 2H), 4.02−3.98 (m, 1H), 3.92−3.80 (m, 1H), 3.74 (t, *J* = 8.3 Hz, 2H), 3.85−3.43 (m, 11H), 3.41 (s, 3H), 3.35 (s, 3H), 3.28 (d, *J* = 10.6 Hz, 1H), 3.09 (dd, *J* = 10.4 Hz, *J* = 2.5 Hz, 2H), 2.78 (t, *J* = 10.7 Hz, 1H), 0.93 (t, *J* = 8.4 Hz, 2H), 0.00 (s, 9H).

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1-[[3-(1*H*-pyrazol-3-yl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (12A). Compound **11** (0.45 g, 0.57 mmol) was treated with 4 M HCl in dioxane (5 mL) and methanol (5 mL) at room temperature for 18 h. The mixture was neutralized to pH 6 with saturated sodium bicarbonate and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a crude. The crude was purified on prepared TLC plate with EtOAc, followed by acidification with HCl (gas) in methanol and then concentration to afford **12A** (207 mg, 70%) as a white solid: mp 152−154 °C; aqueous solubility at pH 7.4 is 0.047 mg/mL; ^1H NMR (CD_3OD) δ 7.67−7.05 (M, 15H), 6.58 (d, *J* = 4.0 Hz, 1H), 4.80 (d, *J* = 14.7 Hz, 1H), 3.86−3.82 (m, 1H), 3.71−3.62 (m, 2H), 3.51−3.48 (m, 1H), 3.18−2.99 (m, 4H), 2.80−2.72 (m, 1H); ^{13}C NMR (CD_3OD) δ 163.90, 141.47, 140.89, 130.63, 130.49, 130.09, 130.01, 129.64, 129.49, 129.27, 127.52, 127.25, 125.85, 103.33, 72.99, 72.55, 66.50, 66.47, 55.27, 35.13, 34.32; CIMS *m*/*z* 483.2 (M + H)$^+$; HRMS (M + H)$^+$ 483.2401 (calcd for $C_{29}H_{31}N_4O_3$ 483.2400). Anal. ($C_{29}H_{30}N_4O_3$·1.25TFA·0.09HCl·1.0H_2O) C, H, N, F, Cl.

Representative Procedures for Nonsymmetric Cyclic Urea Derivatives: Method C, (4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1-[[3-(1*H*-pyrazol-3-yl)phenyl]methyl]-3-[(3-aminophenyl)methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (12D). A solution of **11** (560 mg, 0.71 mmol) in DMF (10 mL) at 0 °C was treated with NaH (0.114 g, 2.84 mmol, 60% in mineral oil), followed by quenching with *m*-nitrobenzyl chloride (0.360 g, 2.13 mmol). After the resulting mixture was stirred at room temperature for 18 h, it was partitioned in EtOAc and water. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a residue. The residue was purified by column chromatography with a gradient solvent system (ethyl acetate and hexane) to give the desired nonsymmetric cyclic urea. The urea was deprotected by general de-MEM and de-SEM procedures with 4 M HCl, followed by purification on TLC plates with EtOAc to give the pure nitro intermediate (230 mg, 52.5% for the two steps). Hydrogenation of the nitro intermediate (210 mg, 0.34 mmol) in MeOH (5 mL) and 1 N HCl (1 mL) in the presence of 10% Pd on C (10% w/w) was carried out at room temperature for 16 h. After the reaction mixture was filtered, the filtrate was concentrated to give a residue, which was purified on TLC plates with EtOAc to give **12D** (140 mg, 61%) as a solid: mp 136−138 °C; ^1H NMR (CD_3-OD) δ 8.31 (s, 1H), 7.81−6.88 (m, 19H), 4.60 (d, *J* = 13.6 Hz, 2H), 3.80−3.57 (m, 4H), 3.16−2.68 (m, 6H); ^{13}C NMR (CD_3-OD) δ 163.99, 149.09, 141.38, 141.23, 140.01, 130.73, 130.65, 130.35, 130.15, 129.93, 129.55, 129.46, 128.04, 127.42, 127.35, 125.97, 120.06, 117.33, 115.81, 103.32, 72.11, 71.99, 66.39, 57.28, 56.97, 33.66, 33.53; MS 605 (M^+ + NH_4, 100%); HRMS (M + H)$^+$ 588.2983 (calcd for $C_{36}H_{38}N_5O_3$ 588.2975).

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1-[[3-(1*H*-pyrazol-3-yl)phenyl]methyl]-3-[[3-(methoxycarbonyl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (12B): mp 127−130 °C; CIMS *m*/*z* 631.4 (M + H)$^+$; HRMS (M + H)$^+$ 631.2916 (calcd 631.2920); ^1H NMR (CD_3OD) δ 7.85−7.82 (m, 2H), 7.66−7.57 (m, 4H), 7.35−7.01 (m, 13H), 6.56 (s, 1H), 4.76 (d, *J* = 14.3 Hz, 1H), 4.69 (d, *J* = 14.3 Hz, 1H), 3.77 (s, 3H), 3.72−3.58 (m, 4H), 3.11−3.02 (m, 4H), 2.94−2.84 (m, 2H); ^{13}C NMR (CD_3OD) δ 166.79, 162.24, 139.69, 139.59, 138.56, 138.50, 133.63, 130.09, 129.16, 128.78, 128.61, 128.46, 128.29, 128.16, 126.59, 126.08, 124.60, 102.00, 70.50, 66.36, 66.31, 55.99, 55.63, 51.32, 32.23, 32.15. Anal. ($C_{38}H_{38}N_4O_5$·1.5TFA·0.18HCl·0.8H_2O) C, H, N, F, Cl.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1-[[3-(1*H*-pyrazol-3-yl)phenyl]methyl]-3-[[3-(hydroxymethylene)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (12C). To a solution of compound **12B** (63 mg, 0.1 mmol) in THF (1 mL) were added $LiBH_4$ (2 M in THF, 0.3 mL) and MeOH (57.6 mg, 1.8 mmol), and the resulting mixture was stirred at room temperature for 16 h. The mixture was acidified to pH 1 with 2 N HCl and extracted with EtOAc. The organic layer was washed with H_2O brine, dried over $MgSO_4$, and concentrated to give a residue. The residue was purified on TLC plate with EtOAc to give compound **12C** (46 mg, 76.3%): ^1H NMR (CD_3OD) δ 7.78−7.60 (m, 4H), 7.50−7.07 (m, 15H), 6.68 (d, *J* = 2.2 Hz, 1H), 4.90−4.81 (m, 2H), 4.66 (bs, 2H), 3.79−3.63 (m, 4H), 3.18−3.00 (m, 6H); ^{13}C NMR (CD_3-OD) δ 163.92, 143.24, 141.32, 141.23, 139.41, 130.67, 130.17, 129.93, 129.69, 129.57, 129.53, 129.30, 129.04, 128.04, 127.45, 127.41, 127.25, 126.01, 103.33, 72.02, 71.96, 67.04, 64.97, 57.30, 57.07, 33.63, 33.57; MS *m*/*z* 603.2 (M + H)$^+$; HRMS (M + H)$^+$ 603.2968 (calcd for $C_{37}H_{39}N_4O_4$ 603.2971).

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1-[[3-(1*H*-pyrazol-3-yl)phenyl]methyl]-3-[(4-hydroxyphenyl)methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (12F). A solution of **11** (220 mg, 0.28 mmol) in DMF (3 mL) was treated with NaH (0.045 g, 1.12 mmol, 60% in mineral oil), followed by quenching with *p*-(benzyloxy)benzyl chloride (0.13 g, 0.56 mmol). After the mixture stirred at room temperature for over 18 h, general workup and purification gave the desired asymmetric cyclic urea, which was deprotected by general de-MEM procedure to give a benzyl-protected intermediate. The intermediate was hydrogenated in MeOH in the presence of 10% (w/w) Pd on C, followed by purification by thin-layer chromatography with EtOAc−CH_2Cl_2 (3:1) to produce **12F** (109 mg, 66% for the two steps): mp 150−153 °C; ^1H NMR (CD_3-OD) δ 7.68−7.58 (m, 3H), 7.39−7.05 (m, 12H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 2.2 Hz, 1H), 4.78 (d, *J* = 14.3 Hz, 1H), 4.66 (d, *J* = 13.9 Hz, 1H), 3.68−3.50 (m, 4H), 3.08−2.83 (m, 6H); ^{13}C NMR (CD_3OD) δ 163.94,

158.15, 141.31, 140.11, 131.73, 130.69, 130.65, 130.16, 129.96, 129.56, 129.48, 128.04, 127.46, 127.35, 125.98, 116.39, 103.32, 72.10, 72.02, 66.42, 57.22, 56.37, 33.56; LRMS 589.3 (M + H)$^+$; HRMS (M + H)$^+$ 589.2811 (calcd for $C_{36}H_{37}N_4O_4$ 589.2815). Anal. ($C_{36}H_{36}N_4O_4 \cdot 1.5H_2O$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1-[[3-(1*H*-pyrazol-3-yl)phenyl]methyl]-3-[[3-[[2-(4-morpholinyl)ethylamino]carbonyl]phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (12G). To compound **12B** (63 mg, 0.1 mmol) was added 4-(2-aminoethyl)morpholine (0.13 g, 1 mmol), and the resulting mixture was stirred at 110 °C for 16 h. The mixture was evaporated under full vacuum to remove excess of 4-(2-aminoethyl)morpholine, and the residue was purified on TLC plate with 10% MeOH in EtOAc to give pure **12G** (44 mg, 60.4%): ^{1}H NMR (CD_3OD) δ 8.04 (s, 1H), 7.73–6.99 (m, 18H), 6.59 (d, J = 2.2 Hz, 1H), 4.72 (d, J = 14.4 Hz, 2H), 3.69–3.64 (m, 8H), 3.36 (t, J = 6.6 Hz, 2H), 3.14 (J = 14.2 Hz, 2H), 3.08–2.85 (m, 4H), 2.54 (t, J = 6.6 Hz, 2H), 2.51–2.45 (m, 4H); ^{13}C NMR (CD_3OD) δ 169.84, 163.68, 141.25, 141.12, 140.09, 136.07, 133.65, 130.63, 129.87, 129.56, 129.51, 128.02, 127.44, 103.31, 71.98, 71.91, 68.26, 67.75, 58.62, 58.37, 58.45, 54.68, 37.76, 35.76, 33.69, 33.62; CIMS *m/z* 729.5 (M + H)$^+$; HRMS (M + H)$^+$ 729.3753 (calcd for $C_{43}H_{49}N_6O_5$ 729.3764).

Crystallography. The complex of **10A** and HIV protease was crystallized as described previously.[14] The unit cell dimensions of the complex are $a = b = 63.3$ Å and $c = 83.6$ Å. The diffraction data were collected with an R-AXIS II imaging plate mounted on a RU200 Rigaku rotating anode generator operating at 50 kV and 100 mA. The crystal diffracts up to 2.0 Å with a total of 50 870 reflections of which 10 694 were unique reflections; the completeness of data was 82% and the R_{sym} was 10.5%. Difference maps calculated with the protein coordinate of XK263[7] revealed the corresponding inhibitor position. The structure was refined using the simulated annealing method XPLOR.[15] The final R-factor[16] was 0.186 without addition of any water molecules. No constraints were applied to maintain an identity between two monomers of the protease. Standard geometry of the inhibitor was based on the single-crystal structure of a cyclic urea.

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