Nonpeptide Cyclic Cyanoguanidines as HIV-1 Protease Inhibitors: Synthesis, Structure−Activity Relationships, and X-ray Crystal Structure Studies

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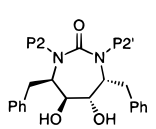
Comparison of the high-resolution X-ray structures of the native HIV-1 protease and its complexes with the inhibitors suggested that the enzyme flaps are flexible. The movement at the tip of the flaps could be as large as 7 Å. On the basis of this observation, cyclic cyanoguanidines have been designed, synthesized, and evaluated as HIV-1 protease (PR) inhibitors. Cyclic cyanoguanidines were found to be very potent inhibitors of HIV-1 protease. The choice of cyclic cyanoguanidines over cyclic guanidines was based on the reduced basicity of the former. X-ray structure studies of the HIV PR complex with cyclic cyanoguanidine demonstrated that in analogy to cyclic urea, cyclic cyanoguanidines also displace the unique structural water molecule. The structure−activity relationship of the cyclic cyanoguanidines is compared with that of the corresponding cyclic urea analogues. The differences in binding constants of the two series of compounds have been rationalized using high-resolution X-ray structure information.

Introduction

Human immunodeficiency virus type 1 (HIV-1), the virus that causes AIDS (acquired immune deficiency syndrome), is a member of the retrovirus family. The structural and replicative enzymes of the virus are encoded by the *gag* and *gag-pol* genes of HIV-1 as polyprotein precursors. HIV-1 protease (HIV PR) is a virally encoded protease enzyme involved in posttranslational processing of the *gag* and *gag-pol* gene products into the functional core proteins and other essential replicative viral enzymes. It is an essential component of the replicative cycle since inhibition of HIV PR leads to production of immature noninfectious viral progeny and hence prevention of further propagation of the virus. HIV PR inhibitors have been extensively investigated for the past several years.[3] Most recently HIV PR inhibitors such as indinavir, saquinavir, ritonavir, and nelfinavir have been approved as drugs for the treatment of HIV infection.

HIV PR is a member of the aspartyl protease family but structurally different from the human aspartic proteases such as renin, gastricin, and cathepsins D and E. Protein crystallographic studies have established that HIV PR is a C_2 symmetric dimer consisting of two identical 99-amino acid chains. The three-dimensional structure of the HIV PR complexes with acyclic inhibitors revealed a unique structural water molecule which connects the inhibitor to the flap through hydrogen-bonding interactions. The cyclic urea (**1**) class of inhibitors was designed to displace this unique structural water molecule. In further continuation of this work, we became interested in investigating structurally diverse classes of cyclic inhibitors which are capable of displacing the structural water molecule.[2] Guanidines of the structural type **2** appeared attractive synthetic targets as HIV PR inhibitors.



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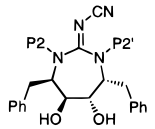

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Although guanidines are basic and ureas neutral, these two classes of compounds are isostructural.[3] In analogy to the oxygen of the cyclic urea carbonyl, the function of the exocyclic guanidine nitrogen was anticipated to be as a hydrogen bond acceptor for the backbone amides of flap residues Ile50/Ile50′. However, at the outset we recognized that the cyclic guanidine ($pK_a \sim 13$) would not be a good source of hydrogen bond acceptors since it 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.[3] 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 which can be utilized for substitution of the electron-withdrawing groups. Interactive modeling suggested that large electron-withdrawing 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. Comparison of the X-ray structures of the native enzyme with the enzyme−inhibitor com-

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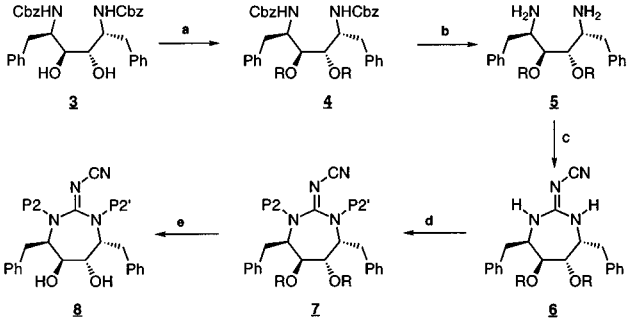
Scheme 1. Synthesis of Cyanoguanidines[a]



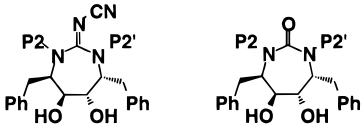
[a] (a) SEM-Cl/(iPr)$_2$EtN/DMF/25 °C/18 h; (b) 5% Pd on C/H_2/ethanol/1.5 h; (c) $CH_3S(C{=}N{-}CN)SCH_3$/pyridine/reflux/18 h; (d) NaH/DMF/2-bromomethylnaphthalene/25 °C/18 h; (e) 2 M HCl in 1:1 CH_3OH/dioxane/25 °C/18 h.

plex 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.[4] 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 such as cyano, nitro, and hydroxy.[5] The cyano group appeared more attractive because of its small size and electron-withdrawing property. Moreover, the cyanoguanidine moiety has been previously incorporated in a known therapeutic agent, cimetidine.[3]

Synthesis of Cyanoguanidines

Synthesis of diol **3** has been previously reported.[6] The diol moiety was protected with SEM [[(trimethylsilyl)-ethoxy]methoxy] groups under the standard protocol to provide the intermediate **4** in almost quantitative yield (Scheme 1). Alternatively, the diol group can be protected with MEM [(methoxyethoxy)methoxy] protecting groups. Protection of the diol moiety with acetonide can be readily achieved; however, it is not a suitable protecting group for later synthetic transformations. The cyclization of the acetonide-protected diamine to cyclic cyanoguanidines was difficult and proceeded only in poor yields. Removal of the CBZ (carbobenzyloxy) protecting group from **4** was readily achieved under catalytic hydrogenation conditions. Treatment of the resulting diamine intermediate **5** with dimethyl *N*-cyanodithioiminocarbonate provided the seven-membered cyclic cyanoguanidines **6** in 61% yield.[7] Alkylation of **6** with various alkyl halides furnished cyclic cyanoguanidines of the general formula **7**. The SEM group on the alkylated cyclic cyanoguanidines was readily removed under acidic conditions to provide the target compounds of the general formula **8**. In some cases the functional groups on the alkylating agents were protected with the appropriate protecting group prior to alkylation. For synthetic efficiency, whenever possible, the choice of a protecting group was such that all of the protecting groups could be removed under the acidic conditions. In cases (**8r,s**) where the phenolic groups on the P2/P2′ substituents were protected with benzyl protecting groups, additional deprotection steps (e.g., catalytic hydrogenolysis) were necessary to obtain the final product. Deprotection of **6** to obtain unalkylated cyanoguanidine with 4 M HCl in dioxane led to the deprotected diol with simultaneous hydrolysis of the cyano group to amide **8a**.

Table 1. Cyclic Cyanoguanidine HIV-1 Protease Inhibitors



8a-x **9a-x**

		8		**9**	
compd	P2/P2′	K_i (nM)	IC_{90} (μM)	K_i (nM)	IC_{90} (μM)
a	H (amidoguanidine)	>12,500	>142	267	
b	allyl	37	51.0	5.2	4.7
c	*n*-propyl	14	7.4	8.0	54
d	*n*-butyl	2.7	2.6	1.4	0.68
e	3,3-dimethylallyl	30	4.7	1.6	0.86
f	3-methylbutyl	3.8	1.1	12.0	4.3
g	cyclopropylmethyl	22	5.0	2.1	1.8
h	cyclobutylmethyl	2	0.84	1.3	1.0
i	cyclopentylmethyl	1.5	0.35	4.3	1.7
j	cyclohexylmethyl	5.7	1.1	37	96
k	benzyl	20	3.8	3.0	0.83
l	3-nitrobenzyl	89	17.7	2.8	0.97
m	4-nitrobenzyl	67	19.3	32	8.4
n	3-aminobenzyl	7.4	0.50	0.28	0.13
o	4-aminobenzyl	25	2.3	1.1	0.11
p	3-cyanobenzyl	27	3.1	3.0	2.2
q	4-cyanobenzyl	128	7.7	52	5.8
r	3-hydroxybenzyl	0.72	0.13	0.12	0.054
s	4-hydroxybenzyl	2.6	0.25	0.12	0.032
t	3-(benzyloxy)benzyl	1370	>67.3	340	>70
u	4-(benzyloxy)benzyl	900	67.3	542	>70
v	3-(hydroxymethyl)benzyl	1.7	0.59	0.14	0.038
w	4-(hydroxymethyl)benzyl	11	3.2	0.34	0.057
x	2-naphthylmethyl	22	>79	0.31	3.9

Results and Discussion

Structure−Activity Relationship of Cyanoguanidines. Many analogues of cyclic cyanoguanidines have been synthesized and their activities compared with those of the corresponding cyclic ureas.[6a] Cyclic cyanoguanidines (CNG) with allyl (**8b**), dimethylallyl (**8e**), and cyclopropylmethyl (**8g**) groups at P2/P2′ exhibited inhibition constants of 37, 30, and 22 nM, respectively, when measured in the HIV PR inhibition assay.[8] As compared to the corresponding cyclic ureas (CU) (Table 1), **8b**,**e**,**g** are ∼10 times less potent than **9b**,**e**,**g**. CNGs with *n*-propyl (**8c**), *n*-butyl (**8d**), 3-methyl-1-butyl (**8f**), or cyclobutylmethyl (**8h**) are as active as the corresponding CUs (**9c**, **9d**, **9f**, or **9h**). Interestingly, **9i** which contains cyclopentylmethyl groups at P2/P2′ is the most active cyanoguanidine in the aliphatic P2/P2′ series. Cyclohexyl derivative **8j** is ∼10 times more active than the corresponding CU derivative **9j**. The CNG derivative with benzyl at P2/P2′ is ∼7 times less potent than the corresponding cyclic urea. In appears that the affinity of the benzyl group at P2/P2′ on the CNG template is about 7−10 times lower than that of the corresponding cyclic urea analogues. Attachment of hydroxyl or hydroxymethyl (hydrogen bond/acceptor) groups on the meta or para position of the aromatic ring resulted in approximately a 10-fold improvement in activity.

The antiviral activity of CNGs was measured in a tissue culture assay by methods described earlier[9] (Table 1). Compounds with cyclopentylmethyl (**8i**) and cyclohexylmethyl (**8j**) have antiviral activity in the submicromolar range. Similarly CNGs (**8q**,**r**,**v**) with hydroxy- or (hydroxymethyl)benzyl groups at P2/P2′ also

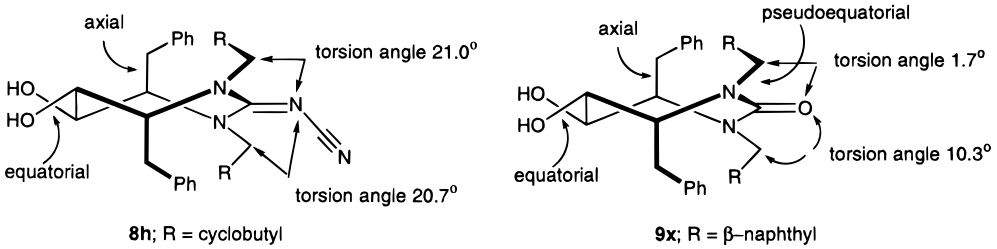


Figure 1. Schematic diagram showing the conformation of **8h** and **9x** as determined by small molecule X-ray crystal structure.

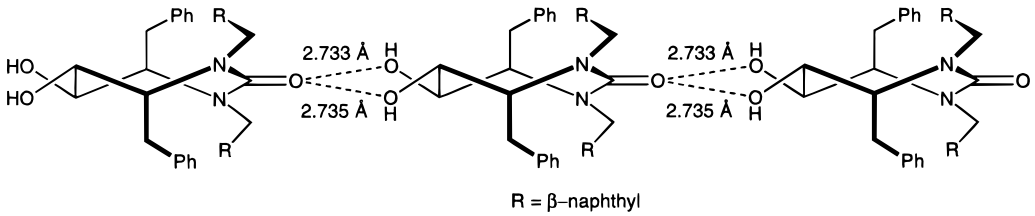


Figure 2. Schematic diagram showing the intermolecular hydrogen bonds between the cyclic urea carbonyl and the diol moiety in **9x** as observed by small molecule X-ray crystal structure.

have antiviral activity in the submicromolar range. The unalkylated guanidine (**8a**) in which there is a carboxamido group in place of cyano was inactive.

Small Molecule X-ray Structure of Cyclic Urea and Cyanoguanidine. Examination of the small molecule X-ray structures of cyclic urea[6a] and cyclic cyanoguanidines revealed very interesting structural similarities and differences. Cyclic urea (**9x**) structure was determined by using the crystals obtained from methanol. The seven-membered ring of the alkylated cyclic urea (**9x**) exists in a chairlike conformation (Figure 1) in which the P1/P1′ benzyl groups and the diol hydroxyl groups occupy axial and equatorial positions, respectively. The 2-naphthylmethyl groups occupy pseudoequatorial positions. Torsion angles around O═C−N−CH− of the urea and the methylene moieties of the P2 and P2′ are 1.7° and 10.3°, respectively. This arrangement results in placement of the carbonyl and the diol moieties as far away from each other as possible. Consequently, there are no intramolecular hydrogen bonds between the carbonyl of the cyclic urea and hydroxyl groups of the diol unit. However, there are strong intermolecular hydrogen bonds (2.733 and 2.735 Å) between the carbonyl of the cyclic urea and hydroxyl groups of the diol moiety on the neighboring molecule (Figure 2). In the crystal lattice, the cyclic urea molecules are aligned in the form of stacked rows with the neighboring stacks arranged in an antiparallel direction. This arrangement creates densely packed crystal structures which give cyclic ureas their high-crystalline characteristics.

Cyclic cyanoguanidine with cyclobutylmethyl groups at P2/P2′ (**8h**) was crystallized from an ethyl acetate−hexane mixture. Examination of the crystal structure of **8h** revealed that the seven-membered ring of CNG has a chairlike conformation (Figure 1) in which the P1/P1′ benzyl groups occupy axial conformations and the diol hydroxyl groups occupy equatorial positions. The P2/P2′ substituents are in pseudoequatorial positions. There is a perfect overlap between the seven-membered rings of CNG and CU. The exocyclic nitrogen of the CNG coincides with the carbonyl oxygen of the CU, and the cyano group is present on the exocyclic nitrogen of CNG. The P1/P1′ groups in CNG and CU have an almost identical trajectory of orientation from the seven-membered ring scaffold. Consequently, there is an almost perfect overlap of the P1/P1′ phenyl rings of CNG over the phenyl rings of CU. The torsion angles formed by −N═C−N−CH− atoms belonging to the cyanoguanidine and the methylene moieties of the P2 and P2′ are 21.0° and 20.7°, respectively (Figure 1). The trajectory of the orientation of the P2/P2′ groups from the seven-membered rings in CNG and CU is slightly different due to differences in the above-mentioned torsion angles. However, the P2/P2′ groups of the two different scaffolds overlap reasonably well. The cyano group is rotated out of the plane formed by the −N−C═N− atoms, away from the methylene of the cyclobutylmethyl (P2′) group, and toward the P1′ benzyl moiety. This is obviously due to steric interaction of the methylene moiety with the cyano group.

The arrangement of the CNGs in the crystal lattice is distinctly different from that of CU. Unlike CU, there are no intermolecular hydrogen bonds between the exocyclic nitrogen and the diol hydroxy groups. The intermolecular hydrogen bonds between the hydroxyl group and other hydrogen bond donors are more diverse. There are strong intermolecular hydrogen bonds (2.779 Å) between the hydroxyl groups. Similarly, the hydroxyl group also forms a strong hydrogen bond (2.802 Å) with the nitrogen of the cyano group (Figure 3). The network of hydrogen bonds between CNG and CU makes the packing arrangement of CNGs dramatically different from the CUs. This difference may have important implications on the physical properties of cyanoguanidines, their rate of desolution, and their oral bioavailability. Unfortunately, the potency of CNG in antiviral assay was not high enough for further evaluation of several members of this class for their oral bioavailability in dogs. Compound **8w**, the only cyanoguanidine examined for its oral bioavailability in dogs, was unsatisfactory.

X-ray Structure of HIV PR−Cyanoguanidine Complex. The three-dimensional structure of HIV-1 PR complexed with one of the cyanoguanidines (**8w**, whose P2/P2′ groups are 4-(hydroxmethyl)benzyl) was determined with 1.8-Å diffraction data. There were two orientations of the inhibitor (Figure 4) which are related

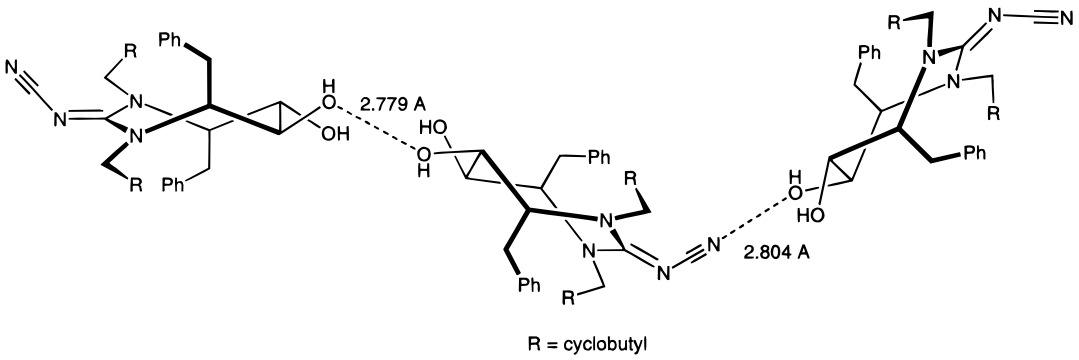


Figure 3. Schematic diagram showing the intermolecular hydrogen bonds between the hydroxyl groups and between the cyano and the hydroxyl group in **8h** as observed by small molecule X-ray crystal structure.

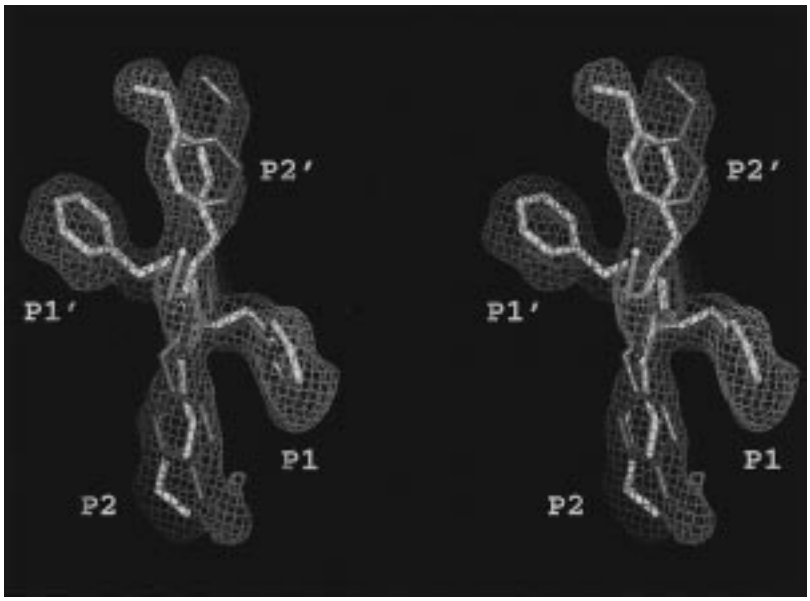


Figure 4. Electron density shown was calculated from a model containing only the protein atoms. One orientation of the inhibitor is shown in blue, the other in yellow. Two separate electron densities of the P2/P2′ groups of both orientations support our interpretation of two orientations, although the corresponding density of the cyano group in the yellow molecule is weak. The electron density map used in contoured at 2.5σ.

to each other by the pseudo-2-fold axis of symmetry that relates one monomer of the protease to the other. Since the interactions between protein and inhibitor are basically the same in the two orientations, details of the structure are described using only one orientation. The exocyclic nitrogen of the CNG occupies the same position of the bound water molecule located between the linear inhibitor and flaps of the protein. The cyano group extending from the nitrogen forced one of the flaps to move away from the inhibitor. The exocyclic nitrogen is located at a distance of 3.6 Å from the amide nitrogen of Ile50′, and the cyano nitrogen atom is located at a hydrogen-bonding distance of 3.2 Å from the amide nitrogen of Ile50. Interestingly, there is a hydrogen bond between Ile50′ amide nitrogen and carbonyl oxygen of the Ile50. The hydroxyl groups of the diol are located to form three hydrogen bonds with the catalytic aspartates, Asp25 and Asp25′. Details of the inhibitor binding mode are shown in Figure 5, where only one orientation is depicted. The electrostatic and van der Waals interactions are extensive between the inhibitor and the protein. The S1 pocket consists of residues Arg8, Pro81, Ile84, Gly27′, Asp29′, and the corresponding residues of the S1′ pocket are Gly27, Ile50, Arg8′, Asp25′, Pro81′, Val82′, and Ile84′. The S2 pocket consists of Ile50, Ala28′, Asp29′, Asp30′, Ile32′, and Ile47′, while Asp29, Asp30, and Ile32 form the S2′ pocket. The schematic diagram showing the hydrogen bond interactions between the HIV PR and the inhibitors **8w** and **9w** is depicted in Figure 6.

As found in the small molecule crystal structure, the CNG ring and the P1/P1′ groups retained a symmetric conformation. P2/P2′ groups are unsymmetrical due mainly to the presence of the cyano group. The torsion angle formed by the −N═C−N−CH of the P2 was 68.0°, while that of the P2′ was −10.2°. Carbon and the nitrogen atoms of the cyano group presumably exert steric pressure and push the methylene group away from the cyano group. As a result of the unique torsional angle at the P2 side, the hydroxymethyl group of the P2 did not form a hydrogen bond with the protein. The equivalent torsion angles in CU are 16.2° and 17.6°. Meanwhile, the P2′ side maintains the hydrogen bond with the backbone amide of Asp30′ as found on both P2 and P2′ in the CU[6a] (Figure 7).

The flaps of the HIV PR which contain two β-hairpins act as clamps on bound inhibitors and substrates.[1] They are flexible as found in the comparison of the native and inhibitor-bound structures.[4] The tip of the flaps also experiences a conformational switch when a symmetric

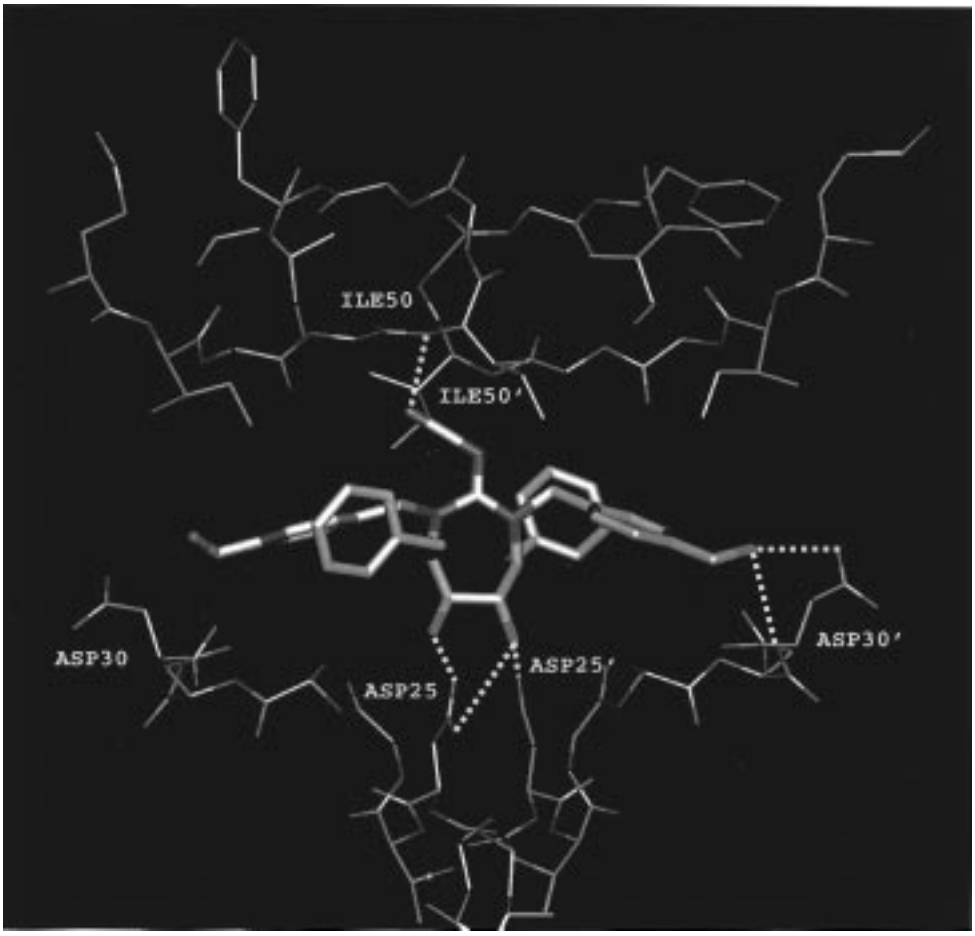
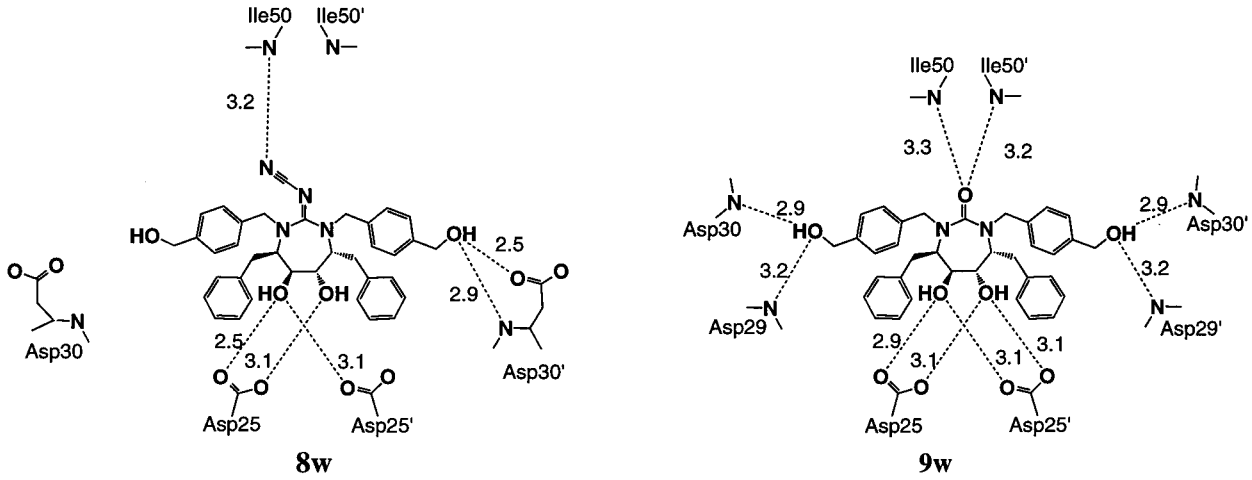


Figure 5. Hydrogen bonds between CNG and the protein. Residues of 24-30 at the active site and 46-54 at the flap are shown. The diagram represents the orientation of the blue molecule in Figure 4.



8w **9w**

Figure 6. Schematic diagram showing the hydrogen bond interactions between the HIV PR and the inhibitors CNG **8w** (one of two orientations) and CU **9w**.

inhibitor is bound to the homodimer as found in the solution structure.[10] One of the flaps in the structure reported here moved away from the active site as the cyano group points to the flap. A comparison of the flaps of the two complexes shows that the largest shift is 2.1 Å at the Gly51′ Cα atom. There are seven residues, viz., Gly48′, Gly49′, Ile50′, Gly51′, Gly52′, Phe53′, and Ile54′, involved where the movement of the backbone atom is larger than 0.5 Å. The other flap maintains a closed conformation as in the CU complex. Identical movement of the equivalent flap in the other binding orientation has been observed (Figure 8). Comparison of the bound conformation of **8w** with that of **9w** indicates that the P1, P1′, and P2 groups in **8w** nearly overlap with the corresponding groups in **9w**. However, there is a significant difference between the conformation of the P2′ group in **8w** and the P2′ group in **9w** (Figure 9).

The X-ray structure of HIV PR complexed with **8w** was helpful in analysis and comparison of the structure–activity relationship of cyclic cyanoguanidines with the cyclic ureas. The presence of the cyano group in CNGs causes movement of one of the flaps away from the

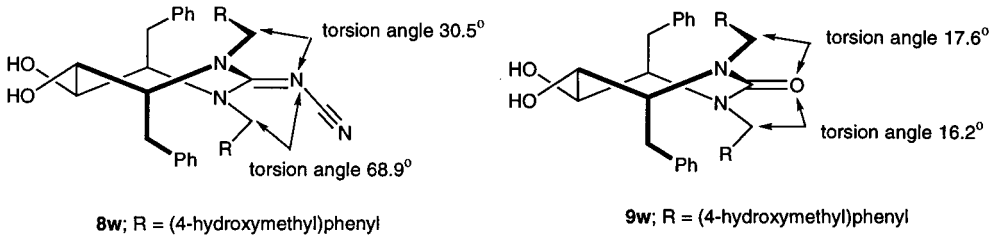


Figure 7. Schematic diagram showing the conformation of CNG **8w** and CU **9w** as determined by X-ray crystal structure of their respective complexes with HIV PR. Compare the torsion angles in **8h** (Figure 1) with **8w**.

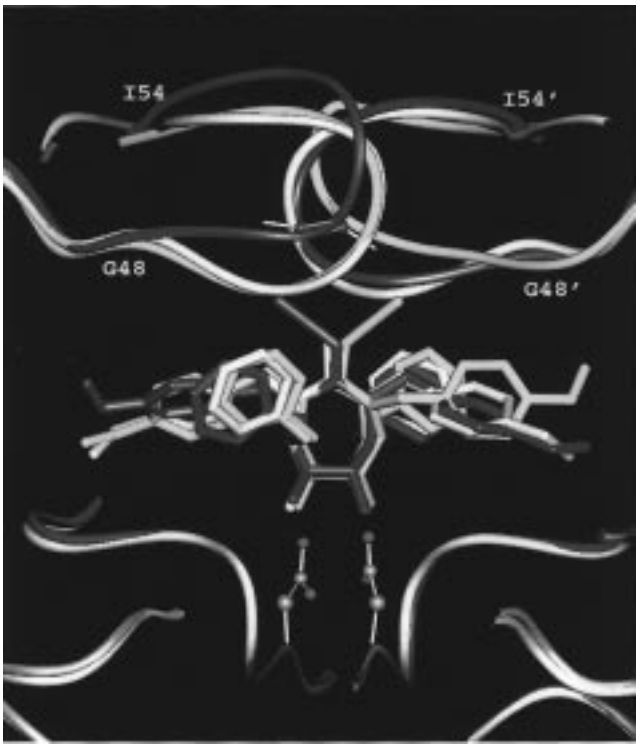


Figure 8. Comparison between the CNG (blue/yellow) and CU (gray) complex structures. The catalytic aspartate residues and amide nitrogen atoms at Ile50 and Ile50′ are shown as found in CNG. Notice the movement of one of the flaps due to the presence of a cyano group of each orientation, while the other flap maintains the same orientation as found in CU. The first and last residues of the flap involved in the movement are labeled. The colors used in the aspartate are gray, carbon; blue, nitrogen; and red, oxygen.

active site which presumably results in enlargement of the S2 pocket of the enzyme. Consequently, CNGs with large P2 groups such as cyclopentylmethyl (**8i**) and cyclohexylmethyl (**8j**) are ~10 times more active than the corresponding CUs since these groups presumably can be more readily accommodated in the active site as compared to the corresponding CU analogues. The CNG **8w** is ~10 times less potent than **9w**. This is obviously due to the movement of 4-(hydroxymethyl)-benzyl from its optimum position caused by the change in the torsional angle of the −N=C−N−CH− moiety after binding to the enzyme. It is interesting to note the differences (compare Figures 1 and 7) observed in the torsional angles of the cyclic urea and the cyclic cyanoguanidine before and after complex formation with HIV-1.

In conclusion we have demonstrated that potent inhibitors of HIV PR can be synthesized based on a cyclic cyanoguanidine scaffold. The X-ray crystal structure study of the cyanoguanidine complex with the

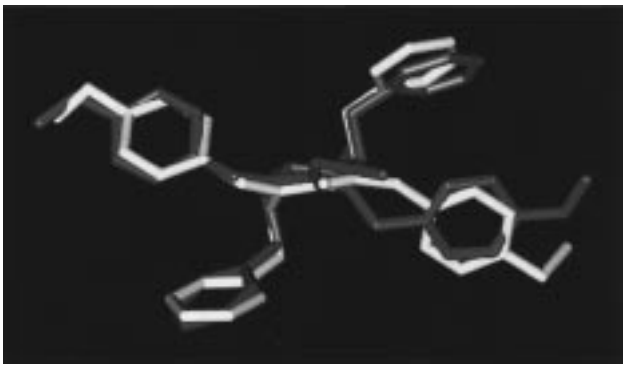


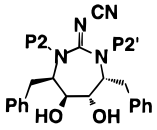
Figure 9. Comparison between the CNG and CU as bound in the HIV PR. The view represents a rotation of 90° about the parallel axis of the view of Figure 7. One dihedral angle around N−C−N−C is the same as that of CU, but the other side is substantially different due to the presence of a cyano group.

enzyme indicated that in analogy to the cyclic urea, the structural water molecule is displaced by the exocyclic nitrogen of the cyclic cyanoguanidine. The binding conformation of the seven-membered ring of the cyclic cyanoguanidine is identical to the binding conformation of the seven-membered ring of the cyclic urea. The cyano group present on the exocyclic nitrogen causes movement of one of the flaps of the enzyme away from the active site. The cyano group also causes entropically adverse movement of the P2′ substituent which also results in loss of hydrogen bond interaction between Asp30 and the hydroxymethyl group in **8w** (Figure 6). The conformational change observed in the P2′ substituent in **8w** and the movement of one of the flaps of the enzyme may account for most of the differences observed in the binding constants of the cyclic ureas and cyclic guanidines.

Experimental Section

Chemical Methods. All procedures were carried out under inert gas in oven-dried glassware unless otherwise indicated. Proton NMR spectra were obtained on VXR or Unity 300- or 400-MHz instruments (Varian Instruments, Palo Alto, CA) with chemical shifts δ in ppm downfield from TMS as an internal reference standard. Melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. Elemental analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ 08805. Mass spectra were measured with a HP 5988A 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. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter at 25 °C. Solvents and reagents were obtained from commercial vendors in the appropriate grade and used

Table 2. Physical Data for Cyclic Cyanoguanidines



8a-x

compd	P2/ P2′	mp (°C)	formula	anal.
a	H (amidoguanidine)	141.5	$C_{20}H_{22}N_4O_2 \cdot 0.5H_2O$	ND
b	allyl	70.2	$C_{26}H_{30}N_4O_2 \cdot 0.5H_2O$	C, H, N
c	*n*-propyl	216.6	$C_{26}H_{34}N_4O_2 \cdot 0.5H_2O$	C, H, N
d	*n*-butyl	58.3	$C_{28}H_{38}N_4O_2 \cdot 1.2H_2O$	C, H, N
e	3,3-dimethylallyl	72.9	$C_{30}H_{38}N_4O_2 \cdot 0.5H_2O$	C, H, N
f	3-methylbutyl	76.1	$C_{30}H_{42}N_4O_2$	C, H, N
g	cyclopropylmethyl	211.2	$C_{28}H_{34}N_4O_2 \cdot 0.5H_2O$	C, H, N
h	cyclobutylmethyl	235.5	$C_{30}H_{38}N_4O_2$	C, H, N
i	cyclopentylmethyl	99.7	$C_{32}H_{42}N_4O_2 \cdot 0.75H_2O$	C, H, N
j	cyclohexylmethyl	96.4	$C_{34}H_{46}N_4O_2 \cdot H_2O$	C, H, N
k	benzyl	94	$C_{34}H_{34}N_4O_2 \cdot 0.5H_2O$	C, H, N
l	3-nitrobenzyl	114	$C_{34}H_{32}N_6O_6$	C, H, N
m	4-nitrobenzyl	130.3	$C_{34}H_{32}N_6O_6 \cdot 1.7H_2O$	C, H, N
n	3-aminobenzyl	114.4	$C_{34}H_{36}N_6O_2 \cdot H_2O$	C, H, N
o	4-aminobenzyl	226.3	$C_{34}H_{36}N_6O_2 \cdot H_2O$	C, H, N
p	3-cyanobenzyl	108.5	$C_{36}H_{32}N_6O_2 \cdot H_2O$	C, H, N
q	4-cyanobenzyl	ND	$C_{36}H_{32}N_6O_2 \cdot 0.6H_2O$	C, H, N
r	3-hydroxybenzyl	124	$C_{34}H_{34}N_4O_4$	C, H, N
s	4-hydroxybenzyl	103.3	$C_{34}H_{34}N_4O_4 \cdot 0.6H_2O$	C, H, N
t	3-(benzyloxy)benzyl	75.2	$C_{48}H_{46}N_4O_4 \cdot 0.7H_2O$	C, H, N
u	4-(benzyloxy)benzyl	90.1	$C_{48}H_{46}N_4O_4$	C, H, N
v	3-(hydroxymethyl)benzyl	193.8	$C_{36}H_{38}N_4O_4 \cdot 0.5H_2O$	C, H, N
w	4-(hydroxymethyl)benzyl	114.4	$C_{36}H_{38}N_4O_4 \cdot H_2O$	C, H, N
x	2-naphthylmethyl	111.1	$C_{42}H_{38}N_4O_2$	C, H, N

without further purification unless otherwise indicated. Physical data for cyclic cyanoguanidines **8a**−**x** are listed in Table 2.

1,2,5,6-Tetradeoxy-1,6-diphenyl-2,5-bis[[(phenylmethoxy)carbonyl]amino]-3,4-bis-*O*-[[2-(trimethylsilyl)ethoxy]methyl]-D-iditol (4). To a solution of 1,2,5,6-tetradeoxy-1,6-diphenyl-2,5-bis[[(phenylmethoxy)carbonyl]amino]-D-iditol (**3**) (60 g, 105 mmol) in dry DMF (600 mL) were added diisopropylethylamine (75 mL) and SEM-Cl (66.8 g, 400 mmol). The mixture was stirred for 16 h at room temperature under N_2. The solution was diluted with water (1 L) and extracted with hexane (400 mL). The organic layer was separated and washed with water (2 × 100 mL). The aqueous layers were combined and extracted with hexane (2 × 300 mL). The organic layers were combined, washed with water (2 × 100 mL), dried over $MgSO_4$, filtered, and evaporated. Chromatography (silica gel, 10−30% ethyl acetate/hexane) provided **4** as a white solid (91 g, 100%, yield): ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 18H, SiCH_3), 0.8−1.0 (m, 4H, SiCH_2), 2.76 (br d, 4H, PhCH_2), 3.5 (s, 4H, OCH_2CH$_2$), 3.6−4.25 (m, 4H, CHOCH_2, HNCH), 4.5−4.95 (m, 6H, NH, OCH_2O), 5.01 (br s, 4H, PhCH_2-OCO), 7.0−7.4 (m, 20H, Ar); ^{13}C NMR ($CDCl_3$) δ 1.21, 18.27, 39.56, 52.46, 66.43, 66.70, 79.24, 96.75, 126.47, 128.17, 128.54, 128.65, 129.73, 136.87, 138.13, 155.79; MS 846 (M + NH_4), 695 (M − SEM).

2,5-Diamino-1,2,5,6-tetradeoxy-1,6-diphenyl-3,4-bis-*O*-[[2-(trimethylsilyl)ethoxy]methyl]-D-iditol (5). To a solution of **4** (90 g, 108.5 mmol) in absolute ethanol (2.5 L) was added 5% Pd/C (6.5 g). The solution was stirred under hydrogen for 1.5 h until hydrogen uptake ceased. The solution was filtered through Celite and evaporated to give **5** as a colorless gum (60 g, 99%, yield): ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 18H, SiCH_3), 0.95 (m, 4H, SiCH_2), 2.55−2.95 (m, 4H, PhCH_2), 3.15 (m, 2H, CHNH$_2$), 3.5−3.9 (m, 6H, NH_2, CH$_2$OCH), 4.72 (m, 4H, OCH_2O), 7.1−7.35 (m, 10H, Ar).

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]-2*H*-1,3-diazepin-2-ylidene]cyanamide (6). To a solution of **5** (561 mg, 1 mmol) in pyridine (2 mL) was added dimethyl *N*-cyanodithioiminocarbonate (175 mg, 1.2 mmol). The mixture was refluxed in a 125 °C oil bath for 2 h. (**Caution:** Methyl mercaptan is a byproduct, and the reaction should be vented to a Clorox scrubber.) TLC indicated a complete reaction. The reaction mixture was diluted with dichloromethane (100 mL). The organic layer was washed with 1 N HCl (2 × 25 mL) and saturated sodium bicarbonate solution (25 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated. Chromatography (silica gel, 1:3 followed by 1:2 EtOAc/hexane) provided **6** as a colorless oil (372 mg, 60.9%, yield): ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 18H, SiCH_3), 0.95 (m, 4, SiCH_2), 2.95 (d, J = 6.8 Hz, PhCH_2), 3.49−3.71 (m, 6H, NH, OCH, CH$_2$OCH), 3.88 (br t, J = 6.8 Hz, 2H, NCH), 4.66 (d, J = 7.1 Hz, 2H, OCHHO), 4.73 (d, J = 7.1 Hz, 2H, OCHHO), 7.25−7.40 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$) δ −1.01, 18.36, 38.56, 54.35, 66.39, 75.82, 95.76, 116.65, 127.75, 129.22, 136.21, 166.21; HRMS-CI calcd for $C_{32}H_{51}N_4O_4Si_2$ $[M]^+$ 611.3448, found 611.3434.

General Procedure A: Alkylation and Deprotection of Cyanoguanidine. To a solution of **6** (305 mg, 0.5 mmol) in dimethylformamide (2 mL) cooled in an ice bath was added NaH (60% in oil, 80 mg, 2 mmol). The mixture was stirred at room temperature for 30 min. It was then cooled in a 0 °C ice bath, the alkylating agent (2 mmol) was added, and the mixture was stirred at room temperature for 18 h. The reaction was monitored by TLC. The reaction was quenched with MeOH, and the solvents were pumped off. The residue was stirred with HCl (3 mL, 4 M in dioxane) and stirred at room temperature for 0.25−18 h. The reaction was monitored by TLC. The mixture was poured into saturated sodium bicarbonate and extracted with dichloromethane (3 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel provided the desired product.

General Procedure B: Hydrogenation, Reduction, or Deprotection. To a solution of the compound in ethanol (1 g/15 mL) was added 5% palladium on carbon (1 g). The suspension was stirred for 18 h under hydrogen (1 atm). The reaction was monitored by TLC. The suspension was filtered through a Celite pad and the filtrate taken to dryness. Purification of the residue by flash chromatography on silica

gel provided the desired hydrogenated, reduced, or hydrogenolysis product.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]urea, Q8188 (8a). To a solution of **6** was added 4 M HCl in dioxane, and the mixture stirred at room temperature for 15 min. TLC indicated a complete reaction. The mixture was poured into saturated sodium bicarbonate and extracted with dichloromethane (3 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered, concentrated, and purified by chromatography to provide **8a** in 35% yield as a white solid: ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 2.91 (dd, J = 6, 12 Hz, 2H), 2.97 (dd, J = 6, 12 Hz, 2H), 3.38 (br s, 2H), 3.81 (t, J = 6 Hz, 2H), 4.85 (br s, 4H), 7.12−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 37.66, 54.18, 68.96, 126.32, 128.11, 128.28, 128.49, 129.19, 137.81, 161.65, 161.72, 161.74, 162.01, 162.03; HRMS-CI calcd for $C_{20}H_{25}N_4O_3$ $[M]^+$ 369.1926, found 369.1914. Anal. ($C_{20}H_{24}N_4O_3$·HCl) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-1,3-di-2-propenyl-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8244 (8b). The compound **8b** was obtained from **6** by using the general procedure A in 43.4% yield as a white solid: mp 70.2 °C; $[\alpha]_D$ +163.4°(*c* 1.16, DMSO); ^{1}H NMR ($CDCl_3$) δ 1.59 (br s, 2H), 2.71 (dd, J = 11.4, 13.6 Hz, 2H), 3.17 (dd, J = 2.6, 13.9 Hz, 2H), 3.38 (dd, J = 7.7, 14.6 Hz, 2H), 3.67−3.77 (m, 2H), 3.88 (br s, 2H), 4.18 (dd, J = 6.2, 14.3 Hz, 2H), 5.11 (dd, J = 1.1, 8.4 Hz, 2H), 5.15 (d, J = 0.7 Hz, 2H), 5.53−5.65 (m, 2H), 7.13−7.16 and 7.26−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 32.68, 56.98, 65.17, 69.96, 116.24, 121.15, 127.04, 128.96, 129.53, 132.68, 138.32, 163.11; HRMS-CI calcd for $C_{26}H_{31}N_4O_2$ $[M + H]^+$ 431.2447, found 431.2432. Anal. ($C_{26}H_{30}N_4O_2$·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-1,3-dipropyl-2*H*-1,3-diazepin-2-ylidene]-cyanamide, Q8259 (8c). The compound **8c** was obtained from **6** by using the general procedure A in 33.1% yield as a white solid: mp 216.6 °C; $[\alpha]_D$ −120.2°(*c* 0.96, DMSO); ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7 Hz, 6H), 1.15−1.35 (m, 4H), 2.53−2.65 (m, 4H), 3.04 (dd, J = 1.5, 13.5 Hz, 2H), 3.36−3.52 (m, 4H), 3.68 (s, 4H), 3.77 (br, 2H), 7.03−7.30 (m, 10H); HRMS-CI calcd for $C_{26}H_{35}N_4O_2$ $[M + H]^+$ 435.2751, found 435.2751. Anal. ($C_{26}H_{34}N_4O_2$·H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[1,3-Dibutylhexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8245 (8d). The compound **8d** was obtained from **6** by using the general procedure A in 41.8% yield as a white solid: mp 58.3 °C; $[\alpha]_D$ −80.5°(*c* 1.04, DMSO); ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7 Hz, 6H), 1.15−1.25 (m, 2H), 1.38−1.42 (m, 4H), 1.59 (br s, 2H), 2.76 (dd, J = 10.9, 13.5 Hz, 2H), 2.78−2.85 (m, 2H), 3.16 (dd, J = 2.2, 13.5 Hz, 2H), 3.54−3.62 (m, 4H), 3.96 (br s, 2H), 7.16−7.19 and 7.26−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 13.96, 20.38, 30.64, 32.81, 54.42, 67.11, 70.14, 116.60, 126.92, 128.95, 129.55, 138.86, 163.00; HRMS-CI calcd for $C_{28}H_{39}N_4O_2$ $[M + H]^+$ 463.3073, found 463.3054. Anal. ($C_{28}H_{38}N_4O_2$·1.2H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis(3-methyl-2-butenyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8256 (8e). The compound **8e** was obtained from **6** by using the general procedure A in 55.7% yield as a white solid: mp 72.9 °C; $[\alpha]_D$ −165.7°(*c* 0.95, DMSO); ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 6H), 1.66 (br s, 8H), 2.73 (dd, J = 11.7, 13.5 Hz, 2H), 3.14 (dd, J = 1.83, 13.6 Hz, 2H), 3.40 (dd, J = 8.4, 14.6 Hz, 2H), 3.56−3.9 (m, 2H), 3.85 (br, 2H), 4.15 (dd, J = 6.6, 14.65 Hz, 2H), 4.99−5.04 (m, 2H), 7.15−7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 17.99, 26.18, 32.65, 51.63, 65.52, 70.34, 116.69, 118.80, 126.85, 128.91, 129.51, 138.73, 138.91, 163.07. Anal. ($C_{30}H_{38}N_4O_2$·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis(3-methylbutyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8260 (8f). The compound **8f** was obtained from **8e** by using the general procedure B in 54.0% yield as a white solid: mp 76.1 °C; $[\alpha]_D$ −108.4°(*c* 0.98, DMSO); ^{1}H NMR ($CDCl_3$) δ 0.78−0.82 (m, 12H), 1.10−1.14 (m, 2H), 1.26−1.49 (m, 4H), 1.61 (s, 2H), 2.68−2.84 (m, 4H), 3.18 (dd, J = 1.8, 13.6 Hz, 2H), 3.40 (br s, 2H), 3.55−3.65 (m, 4H), 3.94 (br, 2H), 7.16−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 22.44, 26.18, 32.56, 36.92, 52.83, 66.59, 70.12, 126.83, 128.82, 129.31, 138.42, 162.81; HRMS-CI calcd for $C_{30}H_{43}N_4O_2$ $[M + H]^+$ 491.3386, found 491.3377. Anal. ($C_{30}H_{42}N_4O_2$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[1,3-Bis(cyclopropylmethyl)hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8239 (8g). The compound **8g** was obtained from **6** by using the general procedure A in 45.9% yield as a white solid: mp 211.2 °C; $[\alpha]_D$ −104.4° (*c* 1.06, DMSO); ^{1}H NMR ($CDCl_3$) δ 0.13−0.17 (m, 4H), 0.40−0.60 (m, 4H), 2.65 (dd, J = 6.6, 14.1 Hz, 2H), 2.89−2.98 (m, 2H), 3.19 (dd, J = 2.1, 13.5 Hz, 2H), 3.53 (dd, J = 4.2, 14.1 Hz, 2H), 3.85−3.92 (m, 2H), 4.06 (br, 2H), 7.18−7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 4.31, 4.52, 4.52, 10.30, 32.51, 59.24, 66.76, 70.30, 116.78, 126.95, 129.02, 129.50, 138.92, 162.89; HRMS-CI calcd for $C_{28}H_{35}N_4O_2$ $[M + H]^+$ 459.2760, found 459.2751. Anal. ($C_{28}H_{34}N_4O_2$·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[1,3-Bis(cyclobutylmethyl)hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8258 (8h). The compound **8h** was obtained from **6** by using the general procedure A in 27.1% yield as a white solid: mp 235.5 °C; $[\alpha]_D$ −114.7°(*c* 0.98, DMSO); ^{1}H NMR (CD_3OD) δ 1.55−1.95 (m, 12H), 2.35−2.70 (m, 6H), 3.02 (dd, J = 1.8, 13.5 Hz, 2H), 3.41−3.72 (m, 6H), 7.10−7.33 (m, 10H); ^{13}C NMR (MeOD + $CDCl_3$) δ 18.08, 27.90, 31.73, 34.54, 60.24, 67.20, 69.58, 116.24, 126.45, 128.55, 129.00, 138.54, 162.44; HRMS-CI calcd for $C_{30}H_{39}N_4O_2$ $[M + H]^+$ 487.3073, found 487.3053. Anal. ($C_{30}H_{38}N_4O_2$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[1,3-Bis(cyclopentylmethyl)hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8243 (8i). The compound **8i** was obtained from **6** by using the general procedure A in 24.7% yield as a white solid: mp 99.7 °C; $[\alpha]_D$ −59.7°(*c* 0.88, DMSO); ^{1}H NMR ($CDCl_3$) δ 1.08−1.17 (m, 4H), 1.43−1.80 (m, 14H), 2.04−2.08 (m, 2H), 2.53 (dd, J = 5.9, 13.9 Hz, 2H), 2.90 (dd, J = 11, 13.9 Hz, 2H), 3.11−3.17 (m, 2H), 3.82 (dd, J = 8.1, 13.9 Hz, 2H), 3.98 (br s, 2H), 7.18−7.21 and 7.24−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 25.47, 25.68, 32.01, 32.53, 39.34, 61.16, 67.69, 70.42, 116.53, 126.96, 129.06, 129.44, 138.94, 162.74; HRMS-CI calcd for $C_{32}H_{43}N_4O_2$ $[M + H]^+$ 515.3386, found 515.3370. Anal. ($C_{32}H_{42}N_4O_2$·0.75H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[1,3-Bis(cyclohexylmethyl)hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8257 (8j). The compound **8j** was obtained from **6** by using the general procedure A in 37.6% yield as a white solid: mp 96.4 °C; $[\alpha]_D$ −37.0°(*c* 0.95, DMSO); ^{1}H NMR ($CDCl_3$) δ 0.85−1.95 (m, 22H), 2.35 (dd, J = 4, 13 Hz, 2H), 2.83 (d, J = 11.6, 13.5 Hz, 2H), 3.12−3.40 (m, 4H), 3.62−3.70 (m, 4H), 3.95 (br s, 2H), 7.10−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.11, 26.11, 26.32, 32.33, 32.47, 32.65, 37.39, 62.72, 68.20, 70.45, 116.25, 126.98, 129.08, 129.22, 129.43, 129.81, 138.99, 162.55; HRMS-CI calcd for $C_{34}H_{47}N_4O_2$ $[M + H]^+$ 543.3699, found 543.3696. Anal. ($C_{34}H_{46}N_6O_2$·H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3,4,7-tetrakis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8247 (8k). The compound **8k** was obtained from **6** by using the general procedure A in 50.5% yield as a white solid: mp 94 °C; $[\alpha]_D$ −28.0°(*c* 1.03, DMSO); ^{1}H NMR ($CDCl_3$) δ 1.58 (br s, 2H), 2.81 (dd, J = 11.4, 13.9 Hz, 2H), 3.04 (dd, J = 2.6, 13.9 Hz, 2H), 3.33 (br s, 2H), 3.56 (d, J = 13.9 Hz, 2H), 3.68−3.72 (m, 2H), 5.02 (d, J = 14 Hz, 2H), 7.15−7.43 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 32.67, 58.77, 66.14, 70.15, 116.07, 127.12, 128.63, 129.10, 129.38, 130.17, 135.85, 138.64, 162.49; HRMS-CI calcd for $C_{34}H_{35}N_4O_2$ $[M + H]^+$ 531.2760, found 531.2774. Anal. ($C_{34}H_{34}N_4O_2$·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis[(3-nitrophenyl)methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8250 (8l). The compound **8l** was obtained from **6** by using the general procedure A in 71.5% yield as a white solid: mp 114 °C; $[\alpha]_D$ +40.0° (*c* 0.52, DMSO); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 2H), 2.60 (dd, J = 11.5, 13.2 Hz, 2H), 3.09−3.13 (m, 2H), 3.43−3.62 (m, 4H), 3.99 (d, J = 15

Hz, 2H), 4.78 (d, J = 15 Hz, 2H), 6.95−6.99 and 7.15−7.50 and 8.01−8.15 (m, 18H); HRMS-CI calcd for $C_{34}H_{33}N_6O_6$ [M + H]$^+$ 621.2461, found 621.2469. Anal. ($C_{34}H_{32}N_6O_6$) H, N; C: calcd, 65.8; found, 66.36.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis[(4-nitrophenyl)methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8249 (8m). The compound **8m** was obtained from **6** by using the general procedure A in 62.2% yield as a white solid: mp 130.3 °C; [α]$_D$ +4.7°(*c* 0.92, DMSO); ^{1}H NMR ($CDCl_3$) δ 2.65−2.76 (m, 2H), 2.86 (s, 2H), 3.15 (d, J = 13 Hz, 2H), 3.55−3.62 (m, 4H), 3.98 (d, J = 15 Hz, 2H), 4.85 (d, J = 14 Hz, 2H), 6.98−7.05 and 7.16−7.30 and 8.03−8.10 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 33.03, 57.60, 66.38, 69.48, 115.22, 124.20, 127.46, 129.23, 129.36, 130.95, 137.95, 142.48, 147.98, 162.94; HRMS-CI calcd for $C_{34}H_{33}N_6O_6$ [M + H]$^+$ 621.2461, found 621.2475. Anal. ($C_{34}H_{32}N_6O_6$·1.7H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[1,3-Bis[(3-aminophenyl)methyl]-hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8253 (8n). The compound **8n** was obtained from **8l** by using the general procedure B in 33.6% yield as a white solid: mp 114.4 °C; [α]$_D$ −85.7°(*c* 1.05, DMSO); ^{1}H NMR ($CDCl_3$) δ 2.74 (dd, J = 11.6, 13.7 Hz, 2H), 2.99 (dd, J = 2.1, 13.7 Hz, 2H), 3.27−3.28 (m, 2H), 3.34 (d, J = 13.7 Hz, 2H), 3.63−3.67 (m, 2H), 4.89 (d, J = 13.7 Hz, 2H), 6.5−6.7 (m, 2H), 7.0−7.45 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 32.55, 58.62, 65.96, 69.82, 115.28, 116.34, 116.88, 120.44, 126.96, 129.05, 129.41, 137.11, 138.90, 146.74, 162.53; HRMS-CI calcd for $C_{34}H_{37}N_6O_2$ [M + H]$^+$ 561.7129, found 561.2987. Anal. ($C_{34}H_{36}N_6O_2$·H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[1,3-Bis[(4-aminophenyl)methyl]-hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8252 (8o). The compound **8o** was obtained from **8m** by using the general procedure B in 52.2% yield as a white solid: mp 226.3 °C; [α]$_D$ −73.0°(*c* 0.97, DMSO); ^{1}H NMR ($CDCl_3$) δ 2.67 (dd, J = 11.2, 13.5 Hz, 2H), 2.92 (d, J = 14.1 Hz, 2H), 3.21−3.26 (m, 4H), 3.66 (d, J = 12 Hz, 2H), 4.70−4.78 (m, 8H), 6.52−6.58 (m, 4H), 6.80−6.83 (m, 4H), 7.03−7.08 (m, 4H), 7.10−7.30 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 32.03, 57.74, 65.50, 69.47, 115.26, 116.37, 125.10, 126.51, 128.66, 129.05, 130.86, 138.70, 146.69, 162.25; HRMS-CI calcd for $C_{34}H_{37}N_6O_2$ [M + H]$^+$ 561.2978, found 561.2985. Anal. ($C_{34}H_{36}N_6O_2$·H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[1,3-Bis[(3-cyanophenyl)methyl]-hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8255 (8p). The compound **8p** was obtained from **6** by using the general procedure A in 40.2% yield as a white solid: mp 108.5 °C; [α]$_D$ +20.0°(*c* 0.89, DMSO); ^{1}H NMR ($CDCl_3$) δ 1.57 (br s, 2H), 2.63 (dd, J = 11.9, 13.2 Hz, 2H), 3.12−3.16 (m, 2H), 3.56−3.65 (m, 4H), 3.95 (d, J = 13.9 Hz, 2H), 4.82 (d, J = 13.9 Hz, 2H), 7.02−7.06 (m, 4H), 7.25−7.61 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 32.97, 57.61, 66.47, 69.35, 113.07, 115.39, 118.51, 127.45, 129.19, 129.29, 129.93, 132.34, 133.63, 134.58, 136.97, 137.94, 162.81; HRMS-CI calcd for $C_{36}H_{33}N_6O_2$ [M + H]$^+$ 581.2665, found 581.2676. Anal. ($C_{36}H_{32}N_6O_2$·H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[1,3-Bis[(4-cyanophenyl)methyl]-hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8254 (8q). The compound **8q** was obtained from **6** by using the general procedure A in 30.0% yield as a white solid: [α]$_D$ −10.9°(*c* 0.87, DMSO); ^{1}H NMR ($CDCl_3$) δ 2.67 (dd, J = 11.5, 13.8 Hz, 2H), 2.89 (br s, 2H), 3.1 (dd, J = 1.5, 13.5 Hz, 2H), 3.489 (br, 2H), 3.57 (d, J = 10 Hz, 2H), 3.85 (d, J = 14 Hz, 2H), 4.86 (d, J = 14.2 Hz, 2H), 7.02−7.06 and 7.18−7.35 and 7.55−7.60 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 32.96, 58.03, 66.41, 69.42, 112.45, 115.29, 118.32, 127.43, 129.22, 129.35, 130.79, 132.81, 138.05, 140.71, 162.84; HRMS-CI calcd for $C_{36}H_{33}N_6O_2$ [M + H]$^+$ 581.2665, found 581.2652. Anal. ($C_{36}H_{32}N_6O_2$·0.6H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis[(3-hydroxyphenyl)methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8251 (8r). The compound **8r** was obtained from **8t** by using the general procedure B in 54.3% yield as a white solid: mp 124 °C; [α]$_D$ −55.3°(*c* 0.88, DMSO); ^{1}H NMR ($CDCl_3$) δ 2.66−2.80 (m, 2H), 2.95−3.02 (m, 2H), 3.20−3.35 (m, 2H), 3.42 (br, 2H), 3.65−3.73 (m, 2H), 4.75−4.82 (m, 4H), 6.52−6.62 and 7.10−7.35 (m, 18H); ^{13}C NMR (CD_3OD) δ 33.46, 59.72, 68.30, 71.01, 116.63, 117.45, 118.01, 122.32, 127.83, 129.98, 130.57, 131.11, 138.68, 140.40, 159.14, 164.00; HRMS-CI calcd for $C_{34}H_{35}N_4O_4$ [M + H]$^+$ 563.2658, found 563.2676. Anal. ($C_{34}H_{34}N_4O_4$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis[(4-hydroxyphenyl)methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8242 (8s). To the solution of **8u** (1.16 g, 1.56 mmol) in ethanol (15 mL) was added 5% palladium on carbon (1.1 g). The suspension was stirred for 18 h under hydrogen (1 atm). TLC indicated a complete reaction. The suspension was filtered through a Celite pad and the filtrate taken to dryness. Chromatography (silica gel, 10:1:10 followed by 10:2:10 EtOAc/EtOH/hexane) provided **8s** as a white solid (458 mg, 52.2%): mp 103.3 °C; [α]$_D$ −57.8°(*c* 0.97, DMSO); ^{1}H NMR (CD_3OD) δ 2.61−2.72 (m, 2H), 2.88−2.95 (m, 2H), 3.22−3.38 (m, 4H), 3.65−3.76 (m, 2H), 4.74−4.83 (m, 2H), 6.62−6.81 and 6.98−7.40 (m, 18H); ^{13}C NMR (CD_3OD) δ 33.46, 59.12, 68.03, 70.89, 116.75, 117.67, 127.78, 127.99, 129.96, 130.54, 132.57, 140.44, 158.90, 163.97; HRMS-CI calcd for $C_{34}H_{35}N_4O_4$ [M + H]$^+$ 563.2658, found 563.2647. Anal. ($C_{34}H_{34}N_4O_4$·0.6H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis[[3-(phenylmethoxy)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8248 (8t). The compound **8t** was obtained from **6** by using the general procedure A in 60.8% yield as a white solid: mp 75.2 °C; [α]$_D$ −27.9°(*c* 1.08, DMSO); ^{1}H NMR ($CDCl_3$) δ 1.57 (br s, 2H), 2.75 (dd, J = 11, 13.6 Hz, 2H), 2.98 (dd, J = 2.56, 13.6 Hz, 2H), 3.30 (br, 2H), 3.52 (d, J = 13.9 Hz, 2H), 3.63−3.67 (m, 2H), 4.95 (d, J = 15 Hz, 2H), 5.02 (s, 4H), 6.76−6.80 (m, 4H), 6.92−6.95 (m, 2H), 7.12−7.16 and 7.23−7.45 (m, 32H); ^{13}C NMR ($CDCl_3$) δ 32.68, 58.64, 65.80, 70.12, 70.25, 115.50, 116.01, 116.45, 122.70, 127.14, 127.45, 128.15, 128.78, 129.18, 129.37, 130.16, 136.92, 137.35, 138.50, 159.19, 162.42; HRMS-CI calcd for $C_{48}H_{47}N_4O_4$ [M + H]$^+$ 743.3597, found 743.3588. Anal. ($C_{48}H_{46}N_4O_4$·0.7H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis[[4-(phenylmethoxy)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8241 (8u). The compound **8u** was obtained from **6** by using the general procedure A in 74.7% yield as a white solid: mp 90.1 °C; [α]$_D$ −63.2° (*c* 0.97, DMSO); ^{1}H NMR ($CDCl_3$) δ 2.83 (dd, J = 11.4, 13.9 Hz, 2H), 3.05 (dd, J = 5.8, 13.9 Hz, 2H), 3.38 (s, 2H), 3.53 (d, J = 13.5 Hz, 2H), 3.61−3.63 (m, 2H), 4.93 (d, J = 13.4 Hz, 2H), 5.02 (s, 4H), 6.85−6.91 and 7.15−7.19 and 7.30−7.45 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 32.68, 57.99, 65.70, 70.19, 70.28, 115.40, 116.31, 127.09, 127.68, 128.22, 128.76, 129.17, 129.39, 131.44, 136.83, 138.65, 158.97, 162.46; HRMS-CI calcd for $C_{48}H_{47}N_4O_4$ [M + H]$^+$ 743.3597, found 743.3587. Anal. ($C_{48}H_{46}N_4O_4$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis[[3-(hydroxymethyl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8262 (8v). The compound **8v** was obtained from **6** by using the general procedure A in 11.2% yield as a white solid: mp 193.8 °C; [α]$_D$ −34.0°(*c* 0.76, DMSO); ^{1}H NMR (CD_3OD) δ 2.86 (dd, J = 11.9, 13.7 Hz, 2H), 3.15 (dd, J = 1.7, 13.7 Hz, 2H), 3.40−3.46 (m, 2H), 3.62 (d, J = 13.8 Hz, 2H), 3.83−3.87 (m, 2H), 4.68 (s, 4H), 5.05 (d, J = 13.8 Hz, 2H), 7.2−7.6 (m, 18H); ^{13}C NMR (CD_3OD) δ 33.40, 59.63, 64.87, 68.43, 70.68, 117.33, 127.84, 128.07, 129.76, 130.01, 130.09, 130.53, 137.36, 140.35, 143.70, 164.04; HRMS-CI calcd for $C_{36}H_{39}N_4O_4$ [M + H]$^+$ 591.2971, found 591.2973. Anal. ($C_{36}H_{38}N_4O_4$·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis[[4-(hydroxymethyl)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8261 (8w). The compound **8w** was obtained from **6** by using the general procedure A in 15% yield as a white solid: mp 100.9 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 2.76 (dd, J = 11, 13.6 Hz, 2H), 3.02 (dd, J = 1.5, 13.5 Hz, 2H), 3.16 (br, 2H), 3.49 (d, J = 14.3 Hz, 2H), 3.56−3.62 (m, 2H), 4.58 (s, 4H), 4.97 (d, J = 14 Hz, 2H),

7.13−7.45 (m, 18H); ^{13}C NMR (CD_3OD + $CDCl_3$) δ 32.67, 58.26, 64.53, 65.85, 69.73, 116.11, 127.07, 127.66, 129.14, 129.35, 130.34, 135.09, 138.78, 141.40, 162.61; HRMS-CI calcd for $C_{36}H_{39}N_4O_4$ $[M + H]^+$ 591.2971, found 591.2973. Anal. ($C_{36}H_{38}N_4O_4 \cdot H_2O$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-[Hexahydro-5,6-dihydroxy-1,3-bis(2-naphthalenylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-ylidene]cyanamide, Q8246 (8x). To a solution of **6** (305 mg, 0.5 mmol) in dimethylformamide (2 mL) cooled in an ice bath was added NaH (60% in oil, 80 mg, 2 mmol) slowly. The mixture was stirred at room temperature for 30 min. The mixture was cooled in a 0 °C ice bath, 2-(bromomethyl)-naphthalene (442 mg, 2 mmol) was added, and the mixture was stirred at room temperature for 18 h. TLC indicated a complete reaction. The reaction was quenched with MeOH, and the solvents were pumped off. The residue was stirred with HCl (3 mL, 4 M in dioxane) at room temperature for 15 min. TLC indicated a complete reaction. The mixture was poured into saturated sodium bicarbonate and extracted with dichloromethane (3 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Chromatography (silica gel, 1:1 EtOAc/hexane) provided **8x** as a white solid (170 mg, 53.9%): mp 111.1 °C; $[\alpha]_D$ −25.1° (*c* 1.09, DMSO); ^{1}H NMR ($CDCl_3$) δ 2.27 (m, 2H, O*H*), 2.88 (dd, J = 13.6, 11.3 Hz, 2H, PhCH*H*), 3.05 (dd, J = 2.5, 13.6 Hz, 2H, PhCH*H*)), 3.32 (s, 2H, OC*H*), 3.75−3.76 (m, 2H, NC*H*), 3.76 (d, J = 13.8 Hz, 2H, NCH*H*), 5.17 (d, J = 13.8 Hz, 2H, NCH*H*), 7.1−7.9 (m, 24H, Ar); ^{13}C NMR ($CDCl_3$) δ 32.68, 58.84, 65.78, 70.10, 116.11, 127.14, 127.19, 127.88, 128.18, 129.02, 129.18, 129.39, 129.80, 133.13, 133.21, 133.40, 138.58, 162.61; HRMS-CI calcd for $C_{42}H_{39}N_4O_2$ $[M + H]^+$ 631.3073, found 631.3079. Anal. ($C_{42}H_{38}N_4O_2$) C, H, N.

Biological Methods. Inhibition of HIV protease was measured by assaying the cleavage of a fluorescent peptide substrate using HPLC.[8] The lower limit of the detection for the reported[8] assay has been improved by lowering the enzyme concentration from 62 to 50 pM. 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.[9]

X-ray Methods. The complex of **8w** and HIV protease was crystallized as described previously.[11] Briefly, the crystal was obtained at 18 °C using the hanging drops method with vapor diffusion in the presence of inhibitor at concentrations of a 5000-fold molar excess over the K_i value of the inhibitor. Hexagonal rods (0.06 × 0.06 × 0.3 mm) appeared in 5 days from 5-μL drops containing 1 mg/mL protease, 250 mM acetate buffer, and 100 mM ammonium sulfate. The unit cell dimensions of the complex are $a = b = 63.2$ Å and $c = 83.7$ Å, and the space group is $P6_1$. The diffraction data were collected with an R-AXIS II imaging plate mounted on an RU200 Rigaku rotating anode generator operating at 50 kV and 100 mA. The crystal diffracts up to 1.8 Å with a total of 69 844 reflections, of which 16 515 were unique reflections; the completeness of data was 90%, and the R_{sym} was 8.0%. Difference maps calculated with the protein coordinate of XK263[108] revealed the corresponding inhibitor position. The structure was refined using the simulated annealing method, XPLOR.[12] The final R-factor was 0.188 with 115 water molecules. (R-factor = $\sum||F_o| - |F_c||/\sum|F_o|$, where $|F_o|$ and $|F_c|$ are the observed and calculated structure factor amplitudes, respectively.) 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. rms deviations from ideal geometry for bond lengths, angles, and dihedral are 0.013 Å, 2.6°, and 22°, respectively. The coordinates for the complex have been deposited in the Brookhaven Data Bank (ID code 1hvh).

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