Preparation and Structure−Activity Relationship of Novel P1/P1′-Substituted Cyclic Urea-Based Human Immunodeficiency Virus Type-1 Protease Inhibitors

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A series of novel P1/P1′-substituted cyclic urea-based HIV-1 protease inhibitors was prepared. Three different synthetic schemes were used to assemble these compounds. The first approach uses amino acid-based starting materials and was originally used to prepare DMP 323. The other two approaches use L-tartaric acid or L-mannitol as the starting material. The required four contiguous *R*,*S*,*S*,*R* centers of the cyclic urea scaffold are introduced using substrate control methodology. Each approach has specific advantages based on the desired P1/P1′ substituent. Designing analogs based on the enzyme's natural substrates provided compounds with reduced activity. Attempts at exploiting hydrogen bond sites in the S1/S1′ pocket, suggested by molecular modeling studies, were not fruitful. Several analogs had better binding affinity compared to our initial leads. Modulating the compound's physical properties led to a 10-fold improvement in translation resulting in better overall antiviral activity.

Introduction

Human immunodeficiency virus (HIV) has been identified as the probable causative agent of acquired immune deficiency syndrome (AIDS).[1] Several biological processes in the life cycle of the virus have been targeted for potential drug intervention.[2] An attractive target is the HIV-encoded protease (HIV-1 PR) which has been shown to be essential for viral maturation and infectivity. Site-directed mutagenisis of the catalytic aspartyl residues rendered the viron particles noninfectious.[3] The enzyme's crystal structure has been determined,[4] and several structural-based approaches to enzyme inhibition have been reported.

Highly potent transition-state mimetics of HIV-1 PR substrates have been reported, and many have potent antiviral activity in cell culture. Many of these protease inhibitors suffer from poor oral bioavailability due to their peptide-like nature. Several labs have made excellent progress in increasing oral bioavailability by modulating physical properties and retaining good potency.[5] Advanced clinical trials are currently ongoing with three promising candidates. The most advanced compound to date is Saquinavir (Ro 31-8959) which was approved by the FDA for use in combination therapy with AZT and DDC. Two other promising candidates, MK-639 and ABT-538, reduced viral load by 2 orders of magnitude within 2 weeks of administration.[6] MK-639 (Crixivan) was recommended for accelerated approval, and ABT-538 (Norvir) was approved for the treatment of patients with advanced AIDS. Most of this work has concentrated on optimizing the P2/P2′ and P3/P3′ binding elements of the molecule. There are few studies that address the potential for increased potency and translation by manipulation of the P1/P1′ binding elements.[7]

One of the first studies to address variations at P1/P1′ was reported by Urban and co-workers.[8] They showed several examples of increased enzyme inhibition from P1/P1′ manipulations, but these compounds were peptide-like analogs. Two studies from Merck reported modifications to one P1′ side chain in their indan-based inhibitor (L-685,434).[9] Substitution of the P1′ phenyl ring with a 4-(3-hydroxypropyl) group provided a 8−15-fold increase in potency. Other tethered substituents at P1′ provide similar increases in binding affinity. A report by Getman et al. introduced a novel (hydroxyethyl)urea isostere-based protease inhibitor that allowed variation of the P1 substituent.[10] Alkylation of the urea nitrogen projects a substituent into the S1 pocket and allows for the introduction of a variety of groups. Several examples with nanomolar binding constants were reported. A recent account from Budt et al. presented seven P1/P1′ analogs from a C_2-symmetric diol series.[11] They determined that lipophilic P1/P1′ substituents are necessary for good activity.

Lam and co-workers disclosed a novel approach to HIV-1 PR inhibition based on a 7-membered cyclic urea scaffold.[12] These compounds have nanomolar binding affinities and are orally bioavailable. DMP 323 is a representative example of this class. The crystal structure of DMP 323 bound in the active site of HIV-1 PR was solved at 1.8 Å resolution (Figure 1).[13] The inhibitor is bound symmetrically in the active site with the urea oxygen accepting two hydrogen bonds from the flap residues Ile 50/50′. The *p*-hydroxymethyl substituent at P2 picks up an additional hydrogen bond from the backbone NH of Asp 29/29′ and Asp 30/30′. The diol oxygens interact with the catalytic aspartate region. The cyclic urea provides a rigid scaffold for accurate alignment of all the key structural elements with their corresponding binding motifs. This alignment results from the unique *R*,*S*,*S*,*R* configuration of the four contiguous chiral centers. This stereochemical arrangement is critical for optimal binding interactions. The inhibitor creates an efficient hydrogen bond network between the aspartate residues and the flap region of the enzyme without the intervention of a water molecule commonly found in linear inhibitors.[14]

Phase I clinical trials of DMP 323 were disappointing despite its good oral bioavailability in animals.[15] The

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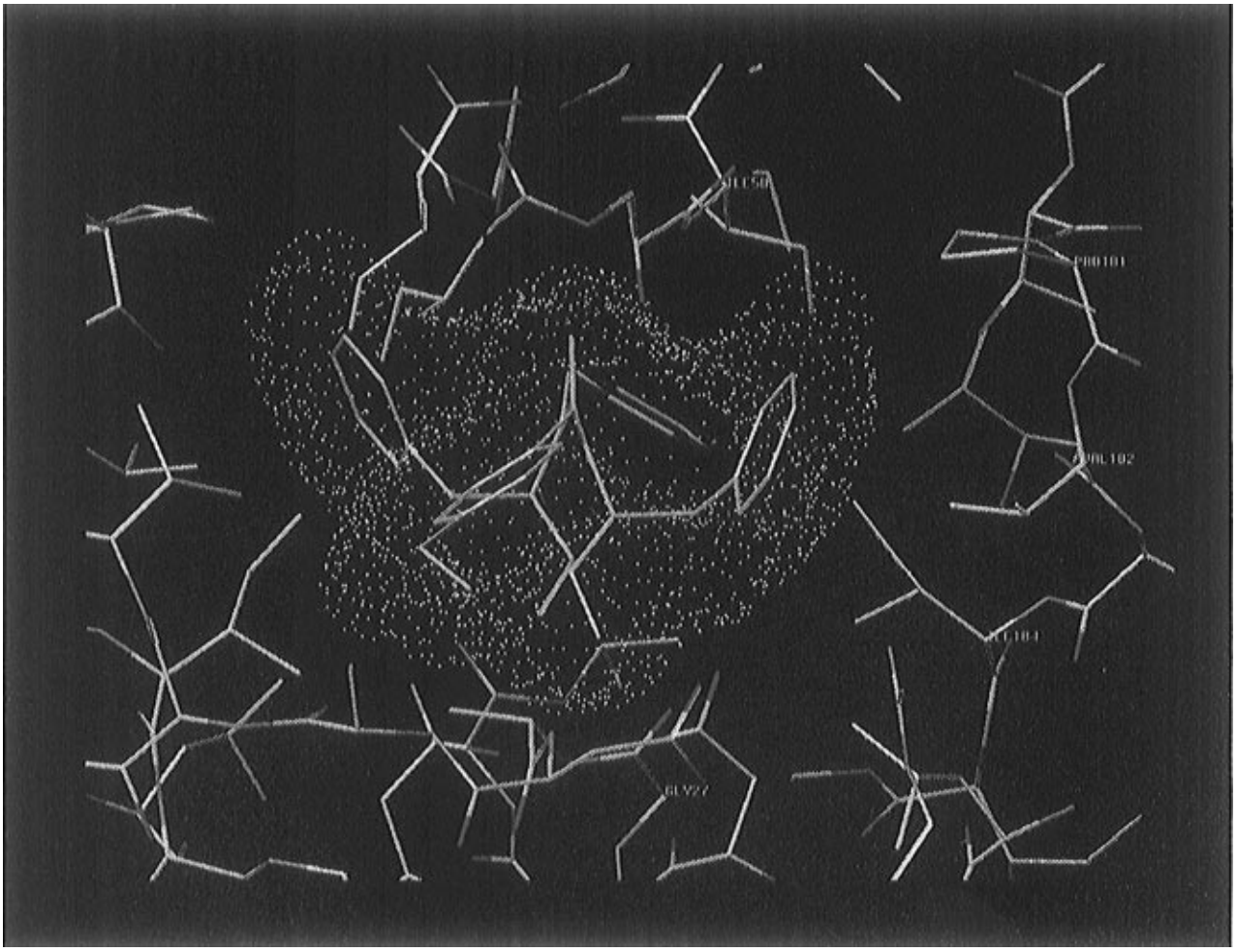
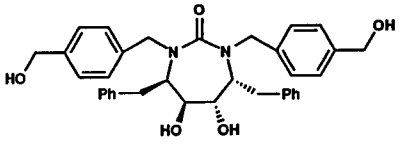
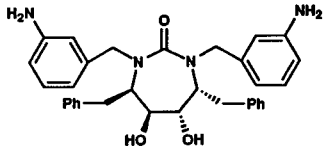


Figure 1. X-ray crystal structure of DMP 323 bound in the active site of HIV-1 PR. Key S1 residues are labeled, and the Connolly surface of DMP 323 is highlighted in yellow.

compound was withdrawn as a result of high blood level variability in humans. A second candidate, DMP 450, has recently completed phase I trials and was shown to have an improved pharmacokinetic profile in humans.[16]



DMP 323



DMP 450

We attempted to exploit this discovery and concentrate on new synthetic methodology to prepare novel P1/P1′-substituted cyclic ureas. P1/P1′ diversity would address two key issues: (1) increased binding affinity and (2) increased whole-cell antiviral efficacy through better translation (defined as the ratio between IC_{90} and K_i). Introducing novel functional groups at P1/P1′ would allow for additional interactions with the residues that line the S1/S1′ pocket of the enzyme. In addition, we could manipulate the physical properties of the molecule and improve its aqueous or lipid solubility thereby improving translation to whole-cell antiviral activity.

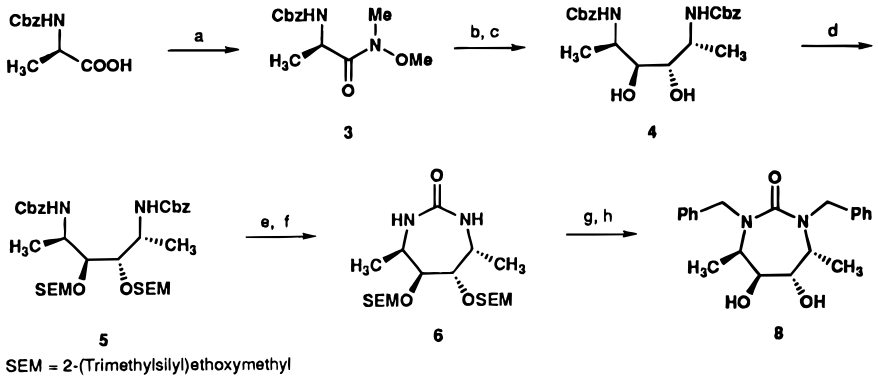
This paper describes three synthetic routes to P1/P1′-substituted cyclic ureas. We used the enzyme's natural substrate specificity as well as an X-ray crystallographic analysis of known inhibitors to target novel P1/P1′ substituents. The chemistry and structure−activity relationships are discussed below.

Chemistry

Three routes are used to construct P1/P1′-substituted cyclic ureas. The first approach uses amino acid starting materials and was originally used to prepare DMP 323.[17] This approach uses the diversity of amino acids to introduce novel P1/P1′ substituents. Scheme 1 shows the preparation of cyclic urea **8**.

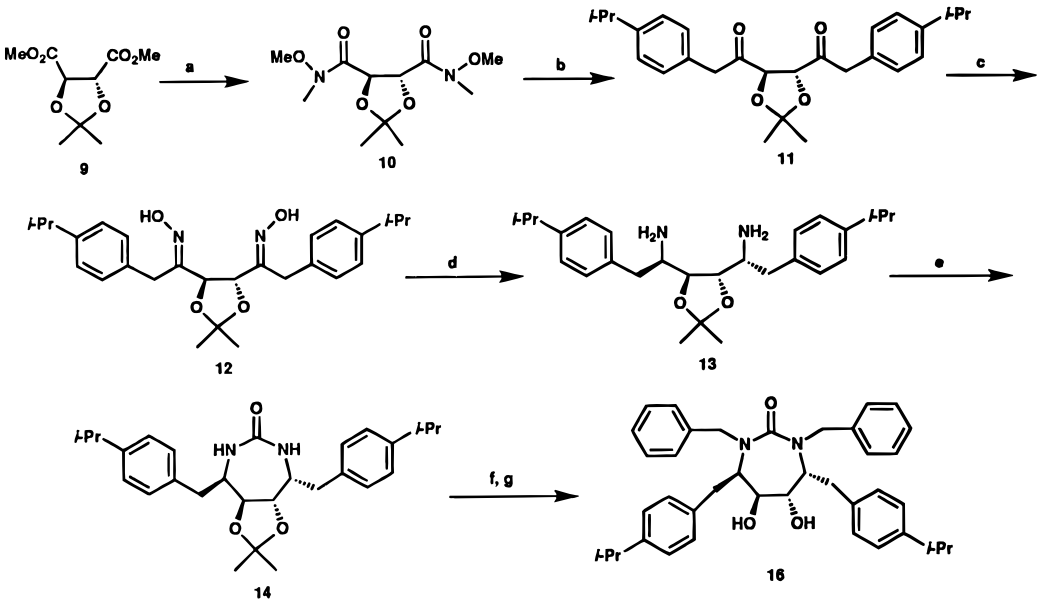
Commercially available *N*-Cbz-D-alanine was converted to the Weinreb amide via the *in situ* mixed anhydride methodology.[18] LAH reduction of the amide **3** provided the amino aldehyde cleanly in 96% yield. To avoid the possibility of racemization, the aldehyde is used without further purification. Addition of the aldehyde to a preformed slurry of $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ in CH_2Cl_2 provided the vanadium-mediated pinacol-coupling product **4** in 66% yield.[19] Column chromatography allows for the separation of the major *R*,*S*,*S*,*R* isomer from smaller amounts of the other isomers. The desired *R*,*S*,*S*,*R* configuration was confirmed by ^1H NMR data comparison with DMP 323.[20] Protection of

Scheme 1[a]



[a] Reagents and conditions: (a) *i*-BuOCOCl, NMM, *N*,*O*-dimethoxyhydroxylamine HCl, CH_2Cl_2, 0−25 °C, 3 h, 91%; (b) LAH, THF, 0−25 °C, 1 h, 96%; (c) $VCl_3(THF)_3$, Zn−Cu, CH_2Cl_2, 25 °C, 3 h, 66%; (d) SEMCl, DIPEA, CH_2Cl_2, 25 °C, 18 h, 87%; (e) catalytic $Pd(OH)_2$/C, cyclohexene, ethanol, reflux, 18 h; (f) CDI, CH_2Cl_2, reflux, 18 h, 81%; (g) $PhCH_2Br$, NaH, DMF, 25 °C, 18 h, 60%; (h) HCl in dioxane, CH_3OH, 25 °C, 18 h, 89%.

Scheme 2[a]



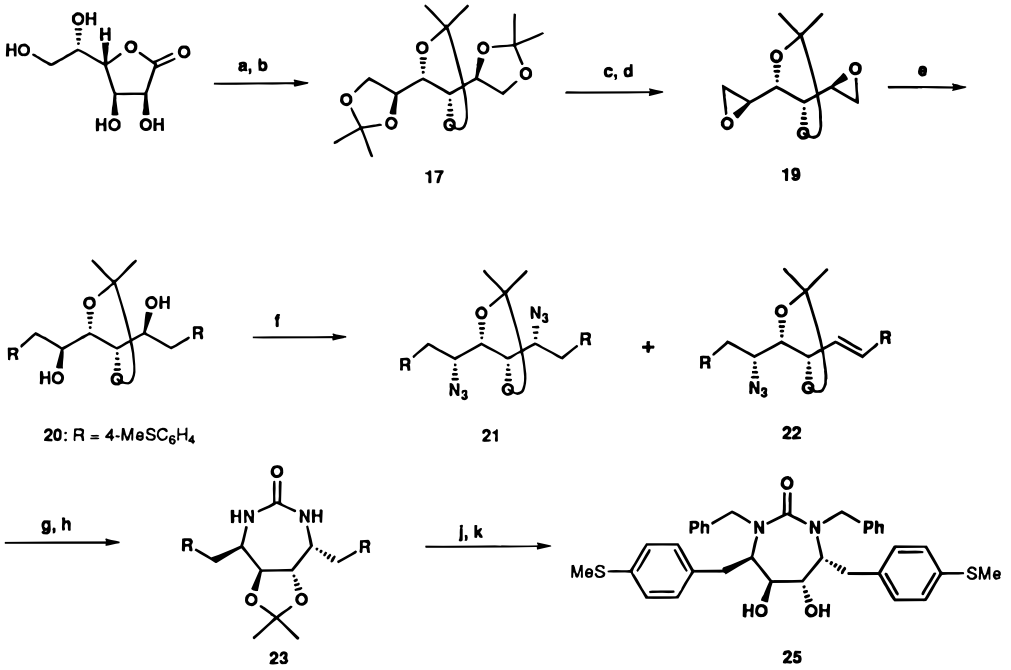
[a] Reagents and conditions: (a) HN(Me)OMe·HCl, $AlMe_3$, CH_2Cl_2, −10 °C, 83%; (b) 4-*i*-Pr-BnMgCl, THF, 95%; (c) H_2NOH·HCl, EtOH, H_2O, 82%; (d) DIBAL, toluene, 58%; (e) CDI, tetrachloroethane, reflux, 62%; (f) K^+t-BuO^-, BnBr, THF, 92%; (g) HCl, MeOH, H_2O, 73%.

the diol using 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) gave the ether **5** in 87% yield. Subsequent Cbz group removal using transfer hydrogenation and ring closure to the 7-membered cyclic urea using 1,1-carbonyldiimidazole gave urea **6** in 81% yield. Alkylation of the urea nitrogens with NaH and benzyl bromide introduced the P2/P2′ substituents. Diol deprotection under acidic conditions gave the target cyclic urea **8** in 54% yield for the two steps. Acidic proton-containing amino acids (Tyr, Trp) required additional protection of those elements for successful pinacol coupling. In the case of tryptophan, the indole nitrogen was protected with a benzyl group. The tyrosine phenol was protected as the methyl ether.

The amino acid-based approach is ideal for exemplifying the readily available *R*-configured amino acids. Heteroatom-containing substituents are not well tolerated in the vanadium-based coupling reaction. In addition, highly functionalized *R*-configured amino acids are tedious to prepare. To overcome these constraints, two other synthetic routes were designed. Our second approach uses L-tartaric acid as the chiral precursor for preparing P1/P1′-substituted cyclic ureas. This route allows for the introduction of the desired P1/P1′ substituent using substituted benzyl organometallic reagents. These substituents are introduced in a convergent manner exploiting the key Weinreb amide **10**. Since these organometallic species are easily prepared from the corresponding benzyl halides, a large diversity of P1/P1′ substituents could be made. Scheme 2 describes the preparation of cyclic urea **16** using this approach.

Commercially available (−)-dimethyl 2,3-*O*-isopropylidene-L-tartrate (**9**) was converted to the bis-Weinreb amide by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and trimethylaluminum.[21] The Weinreb amide **10** was treated with excess *p*-isopropylbenzylmagnesium chloride in THF to give the diketone **11** in 95% yield. Treatment with hydroxylamine hydrochloride under equilibrating conditions gave predominantly the *E*:*E* oxime isomer **12** along with smaller amounts of the *E*:*Z* isomer (4.5:1) that were not separated. Reduction of the oxime mixture with an excess of DIBAL (12 equiv) in toluene gave the diamine **13**, in moderate yield, exclusively as the *R*,*S*,*S*,*R* stereoisomer.[22]

Scheme 3[a]



[a] Reagents and conditions: (a) $LiBH_4$ MeOH, 0 °C, quantitative; (b) 2,2-dimethoxypropane, HCl, acetone, room temperature, 80%; (c) 70% AcOH, 45 °C, 80%; (d) Ph_3P, DEAD, toluene, reflux, 80%; (e) 4-$MeSC_6H_4Br$, BuLi, CuCN, THF, −78-0 °C, 90%; (f) Ph_3P, DEAD, $(PhO)_2P(O)N_3$, THF, 0-25 °C, 32%; (g) $LiAlH_4$, THF, room temperature, quantitative; (h) CDI, tetrachloroethane, room temperture-reflux, 84%; (j) K^+t-BuO^-, BnBr, THF, room temperature, 87%; (k) 20% concentrated HCl, CH_3CN, room temperature, 95%.

The choice of DIBAL in toluene is crucial to obtain the desired *R,S,S,R* stereoisomer. Other reducing agents (Raney nickel, LAH, borane) were tried, but none were as selective, giving significant amounts of the undesired stereoisomers. Noncoordinating solvents were also required to obtain the desired *R,S,S,R* stereoisomer. Addition of a coordinating solvent like THF changed the selectivity providing the *R,S,S,S* isomer as the major product.

The selectivity of DIBAL in a noncoordinating solvent may be due to complexation of DIBAL to the acetonide oxygens forming a bulky adduct which then undergoes a steric controlled attack by additional hydride to give the *R,S,S,R* stereoisomer. This rationale is consistent with the requirement of a large excess of DIBAL and is reminiscent of the mechanism proposed by Williams in the diastereoselective reduction of hydroxy oxime ethers.[23]

The diamine **13** was treated with 1,1′-carbonyldiimidazole at 25 °C to form an imidazolide intermediate which was cyclized by addition to refluxing tetrachloroethane under high-dilution conditions to give cyclic urea **14** in 62% yield. Forcing conditions were required for the cyclization due to the presence of the *trans*-fused acetonide. The cyclic urea was then alkylated with benzyl bromide in the presence of potassium *tert*-butoxide, and the acetonide was removed with aqueous HCl in methanol to give the target urea **16** in 67% yield for the two steps.

The third approach uses the diepoxide **19** as a key intermediate in the synthesis. The enantiomer of this intermediate was first described by Wiggins starting from (D)-mannitol.[24] Several other labs have used this intermediate to prepare HIV-1 protease inhibitors.[25] This diepoxide allows for the introduction of varied P1/P1′ substituents using substituted phenyl organometallic species. The numerous substituted benzenes, used to generate these organometallic species, allow for a large and unique P1/P1′ diversity compared to the other two routes.

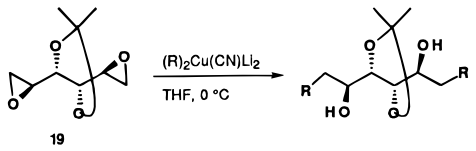
Since diepoxide **19** was prepared from L-mannitol, obtaining this starting material in a short, concise, and relatively inexpensive manner was crucial. Scheme 3 describes the preparation of cyclic urea **25** starting from commercially available L-mannonic γ-lactone. Lithium borohydride reduction of the lactone in methanol provided the crude L-mannitol. Treatment with 2,2-dimethoxypropane and HCl in acetone gave the desired triacetonide **17** in 80% overall yield for the two steps. Standard deprotection, using 70% aqueous acetic acid, gave the tetraol **18** in 80% yield.

Diepoxide **19** was generated in an improved manner using Mitsunobu methodology.[26] Treating the diol with triphenylphosphine and diethyl azodicarboxylate (DEAD) in toluene at 0 °C and then refluxing for 1 h provided the volatile diepoxide in 80% yield. This procedure is efficient and has been used to prepare multigram quantities of diepoxide **19**.

The desired P1/P1′ cyclic urea precursors can be prepared using cuprate chemistry. Table 1 shows several examples of this transformation. The yields are generally very good and allow for a wide range of substituted benzene or heterocyclic compounds as P1/P1′ substituents. The reaction's utility is highly dependent upon the stability of the organometallic reagent. Both electron-donating and electron-withdrawing substituents are tolerated. Heterocycles containing sulfur or oxygen can also be introduced in this manner.

Several attempts to introduce nitrogen-containing heterocycles using this methodology failed. The organometallic species of these nitrogen-containing heterocycles could be generated efficiently at −78 °C. Unfortunately, diepoxide **19** begins to react with the organometallic reagent only at temperatures approach-

Table 1



19

entry	R	yield (%)
1	2-methoxyphenyl	85
2	4-(methylthio)phenyl	90
3	2-naphthyl	75
4	4-(dimethylamino)phenyl	83
5	3-furanyl	70
6	2-thiazolyl	50
7	3-pyridyl	5−30

ing −10 °C. At that temperature, these nitrogen-containing organometallic reagents are unstable and do not provide the desired products. Boron trifluoride etherate-mediated epoxide openings,[27] which typically proceed at −78 °C, also failed to produce the desired heterocyclic P1/P1′ derivatives. This explains the low yields for entries 6 and 7 using thiazole and pyridine as the aromatic component. We were unable to introduce N-protected imidazoles, pyrazoles, or indoles using this methodology.

Displacement of the two hydroxyl groups with an azide source provides the desired urea nitrogen precursor with inversion of configuration. This reaction is the key yield limiting step of the entire sequence. Elimination of one hydroxyl group to give olefin **22** is a competing side reaction and has been observed previously.[25] Several attempts at improving this step were tried.[28] The benzylic hydrogens in **20** generate a system well situated for E2 elimination. Introduction of an additional methylene group between the phenyl ring and the activated alcohol, thereby generating a homobenzylic system, reduces the potential for elimination. This was observed in the preparation of **30** having a phenethyl group at P1. The formation of olefinic byproducts was not detected.

The best reaction conditions for preparing benzylic analogs again employ Mitsunobu-based methodology. Treatment of diol **20** with triphenylphosphine, DEAD, and diphenyl phosphorazidate provided the desired diazide **21** in 32% yield along with significant amounts of the monoazide **22** which could not be recycled back into the reaction sequence. Reduction of the diazide to the diamine using catalytic hydrogenation or lithium aluminum hydride provided the diamine in quantitative yield. This diamine was cyclized to the urea using the protocol described earlier. Introduction of the P2/P2′ residues and subsequent deprotection were performed as previously described.

X-ray Analysis

The substrate specificity of HIV-1 PR can provide insight in designing novel P1/P1′-substituted inhibitors. There is a general trend toward hydrophobic residues immediately adjacent to the scissile bond. These groups vary in size and shape (Phe, Pro, Leu, Met, Asn, Tyr) and help define the S1/S1′ pocket's dimensions and physical character. These considerations led us to focus on substituted phenyl rings as desirable P1 substituents. We also prepared the corresponding Leu, Met, Val, and Ala analogs to determine the cyclic urea scaffold's capability to accommodate nonaromatic P1 substituents.

Analysis of several crystal structures of other potent inhibitors bound in the active site of HIV-1 PR also provides insight in designing new P1 variants. The S1 pocket is defined by a few key residues: Arg 8, Gly 27, Pro 81, Val 82, and Ile 84. Most of these residues have <4 Å contact distances with the inhibitor's P1 substituents. These interactions are generally hydrophobic in nature. There are several hydrogen bond-donating/accepting relationships that could also be exploited providing additional opportunity for increased binding affinity.

We used the X-ray crystal structure of the enzyme−inhibitor complex of DMP 323 as a good reference point for designing favorable binding elements into our P1 substituents (Figure 1). Analyzing the enzyme residues lining the S1 pocket suggested the carbonyl of Gly 27 might accept a hydrogen bond from an *ortho* substituent placed on the P1 phenyl ring. This is a key interaction found in many linear HIV-1 PR inhibitors.[14] The *meta* position of the phenyl ring projects toward the side chains of Arg 8 and Pro 81 allowing for additional sites of hydrogen bonding or hydrophobic interaction. The *para* position projects out into the enzyme's channel allowing various substituents. The lack of interactions at this position makes this a useful site to modulate solubility without significant negative consequences.

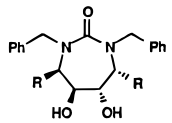
Results and Discussion

Table 2 presents a series of analogs in which we have generated diversity at P1/P1′ while keeping the P2/P2′ substituent constant, in this case benzyl. The compounds in Table 3 attempt to exploit the good bioavailability characteristics of the cyclopropylmethyl P2/P2′ substituent.

The best substituent that mimics the natural substrate is the benzyl group (Phe). Other P1 substituents derived from the enzyme's natural substrate (**26**−**28**, **51**, **53**, **62**) provided less potent inhibitors relative to the parent **1**. The urea scaffold provides potent compounds with the correct P1 substituent. Dramatically changing these substituents can lead to problems. The cyclic urea framework seems less flexible and cannot readily accommodate structural changes tolerated in the enzyme's substrates. These inhibitors are symmetrical, projecting the same side chain into both S1 and S1′ pockets simultaneously. The natural substrates are not symmetrical making direct comparisons difficult.

Further insight into the P1 pocket's dimensions is obtained from compounds **29** and **30**. Hydrogenation of the phenyl ring provides the cyclohexyl analog **29**. The more sterically demanding cyclohexane ring gives a 10-fold decrease in binding affinity due to the intolerant, narrow dimensions of the S1 pocket. Compound **30** shows how an incorrect orientation of the phenyl group in the S1 pocket can dramatically alter the binding affinity. Examining the X-ray crystal structure of the enzyme−inhibitor complex shows the 7-membered ring in a pseudochair conformation. The P1/P1′ substituents are forced into an axial orientation by allylic strain and are aligned nicely to interact with the S1/S1′ binding pockets. Introduction of an additional carbon atom produces a phenethyl derivative at P1. Now

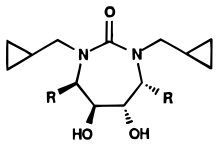
Table 2



compd	R	K_i (nM)[a]	IC_{90} (nM)[a]	translation factor,[b] IC_{90}/K_i	preparation method[c]
1	benzyl	3.4	790	230	A
8	methyl	5000	>10 000	ND	A
16	4-isopropylbenzyl	1.1	>10 000	ND	B
25	4-(methylthio)benzyl	3.4	1300	380	C
26	isobutyl	1700	>10 000	ND	A
27	2-(methylthio)ethyl	1100	>10 000	ND	A
28	3-indolylmethyl	580	>10 000	ND	A
29	cyclohexylmethyl	28	>10 000	ND	A
30	phenethyl	320	>10 000	ND	C
31	2-naphthylmethyl	9.8	3300	340	C
32	3-furanylmethyl	8.4	7800	920	C
33	3-(methylthio)benzyl	2.5	4170	1700	C
34	4-(methylsulfonyl)benzyl	2.5	470	190	C
35	2-methoxybenzyl	60	8800	150	C
36	2-hydroxybenzyl	35	6500	185	C
37	3-methoxybenzyl	4.7	350	75	C
38	4-methoxybenzyl	8.6	600	70	C
39	4-hydroxybenzyl	1.1	185	170	C
40	3-aminobenzyl	2.8	1300	460	C
41	3-(dimethylamino)benzyl	4.3	1200	280	C
42	4-aminobenzyl	8.5	1400	165	C
43	4-aminobenzyl 2HCl	7.1	1300	180	C
44	4-(dimethylamino)benzyl	46	2700	60	C
45	4-pyridylmethyl	22	5700	10	B
46	3-(2,5-dimethylpyrolyl)benzyl	160	>10 000	ND	C
47	3,4-(methylenedioxy)benzyl	1.3	500	385	C

[a] Values determined using methods described in the Experimental Section for $n = 2$. [b] ND = not determined. [c] A = amino acid route (Scheme 1); B = tartrate route (Scheme 2); C = mannitol route (Scheme 3).

Table 3



compd	R	K_i (nM)[a]	IC_{90} (nM)[a]	translation factor,[b] IC_{90}/K_i	preparation method[c]
2	benzyl	1.9	1840	970	A
51	isobutyl	86	>10 000	ND	A
52	isopropyl	250	>10 000	ND	A
53	2-(methylthio)ethyl	2500	>10 000	ND	A
54	4-fluorobenzyl	5.8	3200	550	A
55	2-methoxybenzyl	65	>10 000	ND	C
56	3-methoxybenzyl	0.87	650	750	C
57	3-hydroxybenzyl	13	2570	200	C
58	4-methoxybenzyl	2.9	320	110	A
59	2-naphthylmethyl	4.3	3400	790	C
60	3,5-dimethoxybenzyl	2.7	380	140	A
61	2-thienylmethyl	9.1	7800	860	A

[a] Values determined using methods described in the Experimental Section for $n = 2$. [b] ND = not determined. [c] A = amino acid route (Scheme 1); B = tartrate route (Scheme 2); C = mannitol route (Scheme 3).

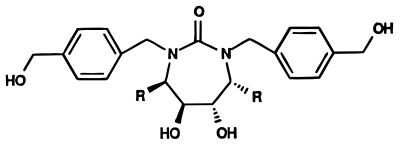
the phenyl group cannot obtain the desired orientation and is not optimally aligned for good binding interactions with the S1 pocket.

Compound **31** has a similar P1 substituent compared to **28** but is substituted at the 2-position so that the naphthyl ring sits in a preferred orientation along the S1 pocket. Although the compound is a potent inhibitor (K_i = 9.8 nM), the IC_{90} is 5-fold less than that of the parent **1**. The compound is very lipophilic (clog P = 9.2) and does not translate well into the whole-cell assay. This effect is less pronounced with the compounds in Table 3. Here the P2 substituent is relatively small (cyclopropylmethyl), and the clog P drops to 7.8. The large lipophilic naphthyl ring is now more balanced, and indeed **59** translates as well as the parent **2**.

In general, heterocyclic substituents at P1 are not well tolerated. Furan, pyridine, and thiophene analogs (**32**, **45**, **61**, **67**) gave less potent compounds. This is somewhat surprising especially in the case of thiophene which is generally a good bioisostere for a phenyl ring.[29]

Attempts at picking up a favorable hydrogen bond interaction between an *o*-hydroxy-substituted P1 derivative (**36**) and Gly 27 were unsuccessful. The phenol oxygen might project too far out into the S1 pocket and not provide the optimal geometry for this interaction. In addition, there may be a binding energy liability due

Table 4



compd	R	K_i (nM)[a]	IC_{90} (nM)[a]	translation factor,[b] IC_{90}/K_i	preparation method[c]
DMP 323	benzyl	0.27	136[d]	500	A
62	2-(methylthio)ethyl	3900	>10 000	ND	A
63	cyclohexylmethyl	32	>10 000	ND	A
64	4-fluorobenzyl	0.44	100	230	A
65	3-methoxybenzyl	0.11	37	340	C
66	3,4-difluorobenzyl	0.47	36	76	A
67	4-pyridylmethyl	4.8	>10 000	ND	B
68	4-methoxybenzyl	0.24	56	230	A
69	isobutyl	38	>10 000	ND	A

[a] Values determined using methods described in the Experimental Section for $n = 2$. [b] ND = not determined. [c] A = amino acid route (Scheme 1); B = tartrate route (Scheme 2); C = mannitol route (Scheme 3). [d] For $n = 181$ (SD ± 55).

to desolvation of the highly hydrophilic OH group in a highly hydrophobic pocket.

The *meta* and *para* positions of the P1 phenyl ring seem to be less restrictive and allow a variety of substituents without major binding affinity loss. Small branched substituents at the *meta* position are tolerated (**41**), but there is a size limitation (**46**). Branching at the *para* position (**44**) reduces binding affinity. Both lipophilic (**25**, **33**, **48**, **54**, **66**) and hydrophilic (**34**, **39**, **40**, **42**) substituents are tolerated. By introducing polar groups or basic amine functions, we hoped to improve water solubility and translation. Compounds **34**, **37**−**39**, and **42** all contain polar substituents and have good binding constants. In addition, they all have better translation properties compared to the parent **1**.

Table 4 presents analogs of our lead DMP 323. Since the parent already has a relatively polar group at P2, our strategy was to modulate this polarity by adding lipophilic substituents to the phenyl groups at P1. Methoxy substituents did not effect the K_i values substantially (**65**, **68**) and slightly decreased the translation factor. The addition of fluorine atoms had a similar effect on the binding constant but a more positive, additive effect on the translation factor as shown by compound **66**. The addition of two fluorine atoms provided a 7-fold increase in translation as well as a 4-fold increase in antiviral activity.

Conclusion

We presented three synthetic approaches to P1/P1′-substituted cyclic urea-based HIV-1 protease inhibitors. The required four contiguous *R*,*S*,*S*,*R* centers are introduced using chiral starting materials and substrate control methodology. Each approach has specific advantages based on the desired P1 substituent. Several analogs had better binding affinity compared to our initial leads. We were also able to modulate the compound's physical properties and improve translation resulting in better overall antiviral activity. Designing analogs based on the enzyme's natural substrates provided compounds with reduced activity. Attempts at exploiting hydrogen bonding sites in the S1/S1′ pocket were not fruitful. Further studies are in progress to determine P1/P1′ substituents with improved antiviral properties. The preparation and evaluation of such compounds will be reported in due course.

Experimental Section

All reactions were carried out with continuous stirring under an atmosphere of dry nitrogen. Commercial reagents were used as received without additional purification. THF was distilled from sodium benzophenone ketyl. ^{1}H NMR (300 MHz) spectra were recorded using tetramethylsilane as an internal standard. Melting points are uncorrected. TLC was performed on E. Merck 15719 silica gel plates. Flash chromatography was carried out using EM Science silica gel 60 (230−400 mesh). All final targets were obtained as noncrystalline amorphous solids unless specified otherwise. Elemental analysis was performed by Quantitative Technologies, Inc., Bound Brook, NJ. For compounds where analysis was not obtained, HPLC analysis was used, and purity was determined to be >98%.

(*R*)-*N*-(Benzyloxycarbonyl)alanine *N*-Methyl-*N*-methoxyamide (3). To a solution of *N*-Cbz-D-alanine (10.0 g, 44.8 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added *N*-methylmorpholine (12.4 mL, 112 mmol) followed by isobutyl chloroformate (7.4 mL, 56 mmol), and the resulting solution was allowed to stir at 0 °C for 15 min. Thereafter *N*,*O*-dimethylhydroxylamine HCl (5.3 g, 53.8 mmol) was added portionwise, and the resulting reaction mixture was allowed to stir at room temperature for 3 h. The reaction mixture was poured into 10% HCl (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Chromatography (silica gel, 50% ether/hexane) provided amide **3** as a white solid (11.92 g, 91%). **3**: mp 78−80 °C; NMR ($CDCl_3$) δ 7.35 (m, 5 H), 5.52 (bd, 1 H), 5.11 (m, 2 H), 4.74 (bt, 1 H), 3.75 (s, 3 H), 3.21 (s, 3 H), 1.35 (d, $J = 7$ Hz, 3 H); CIMS (NH_3) m/z 267 ($M + H^+$, 100); HRMS calcd for $C_{13}H_{19}N_2O_4$ ($M + H^+$) 267.1345, found 267.1340.

(2*R*,3*S*,4*S*,5*R*)-2,5-Bis[*N*-(benzyloxycarbonyl)amino]-3,4-hexanediol (4). To a solution of amide **3** (2.64 g, 9.9 mmol) in THF (15 mL) at 0 °C was added LAH (0.47 g, 12.4 mmol), and the resulting reaction mixture was allowed to stir at room temperature for 1 h. The reaction was quenched with 10% $KHSO_4$ and the mixture extracted with ether (4 × 100 mL). The combined ether extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure to provide a clear oil (1.98 g, 96%). The crude amino aldehyde was used without further purification to avoid possible

racemization. To a slurry of $VCl_3(THF)_3$[30] (2 g, 5.4 mmol) in CH_2Cl_2 (10 mL) at room temperature was added Zn−Cu[31] (0.4 g, 2.9 mmol), and the resulting solution was allowed to stir at room temperature for 15 min. A solution of the aldehyde (1.0 g, 4.9 mmol) in CH_2Cl_2 (6 mL) was added, and the resulting reaction mixture was allowed to stir at room temperature for 3 h. The reaction was quenched with 15% HCl and the mixture stirred at room temperature until two clear layers (blue/green aqueous and pale yellow organic) were observed. The CH_2Cl_2 layer was separated and dried (Na_2SO_4) and the solvent removed under reduced pressure. Chromatography (silica gel, EtOAc) provided diol **4** (0.67g, 66%). **4**: NMR (DMSO-d_6) δ 7.35 (bs, 10 H), 6.83 (bd, 2 H), 5.02 (m, 4 H), 4.36 (bd, 2 H), 3.77 (m, 2 H), 3.2 (m, 2 H), 1.0 (d, J = 7 Hz, 6 H); CIMS (NH_3) m/z 417 (M + H^+, 100); HRMS calcd for $C_{22}H_{29}N_2O_6$ (M + H^+) 417.2026, found 417.2022.

(2*R*,3*S*,4*S*,5*R*)-2,5-Bis[*N*-(benzyloxycarbonyl)amino]-3,4-bis-*O*-[[2-(trimethylsilyl)ethoxy]methyl]hexanediol (5). To a solution of diol **4** (90 mg, 0.22 mmol) in DMF (1 mL) at room temperature was added *N*,*N*-diisopropylethylamine (0.14 mL, 0.77 mmol) followed by SEM-Cl (0.12 mL, 0.66 mmol), and the resulting reaction mixture was stirred at room temperature for 18 h. The reaction mixture was poured into water and extracted with ether (3 × 50 mL). The combined ether extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Chromatography (silica gel, 50% ether/hexane) gave **5** as an oil (130 mg, 87%). **5**: NMR ($CDCl_3$) δ 7.35 (m, 10 H), 5.06 (m, 6 H), 4.70 (d, J = 7.7 Hz, 4 H), 4.03 (m, 2 H), 3.75 (m, 2 H), 3.50 (m, 4 H), 1.2 (d, J = 7.0 Hz, 6 H), 0.92 (m, 4 H), 0.01 (s, 18 H); CIMS (NH_3) m/z 694 (M + NH_4^+, 100); HRMS calcd for $C_{34}H_{57}N_2O_8Si_2$ (M + H^+) 677.3653, found 677.3663.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-bis-*O*-[[2-(trimethylsilyl)ethoxy]methyl]-4,7-dimethyl-2*H*-1,3-diazapin-2-one (6). To a solution of **5** (810 mg, 1.20 mmol) in ethanol (20 mL) was added 20% $Pd(OH)_2$/C (80 mg) followed by cyclohexene (20 mL), and the resulting reaction mixture was allowed to stir at reflux for 18 h. The reaction mixture was cooled to room temperature and filtered (Celite) and the filtrate concentrated under reduced pressure. The diamine was used without further purification. To a solution of diamine in CH_2Cl_2 (25 mL) was added 1,1-carbonyldiimidazole (238 mg, 1.44 mmol), and the resulting reaction mixture was stirred at reflux for 18 h. The reaction mixture was cooled and concentrated under reduced pressure. Chromatography (silica gel, ether) gave cyclic urea **6** as an oil (420 mg, 81%). **6**: NMR ($CDCl_3$) δ 4.7 (d, J = 7.7 Hz, 4 H), 3.97 (bs, 2 H), 3.75 (m, 2 H), 3.63 (m, 4 H), 3.51 (bs, 2 H), 1.24 (d, J = 7 Hz, 6 H), 0.91 (m, 4 H), 0.02 (s, 18 H); CIMS (NH_3) m/z 435 (M + H^+, 100); HRMS calcd for $C_{19}H_{43}N_2O_5Si_2$ (M + H^+) 435.2711, found 435.2722.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-bis-*O*-[[2-(trimethylsilyl)ethoxy]methyl]-1,3-bis(phenylmethyl)-4,7-dimethyl-2*H*-1,3-diazapin-2-one (7). To a solution of cyclic urea **6** (0.19 g, 0.44 mmol) in DMF (4 mL) at room temperature was added NaH (70 mg, 1.76 mmol, 60% in oil) followed by benzyl bromide (0.3 mL, 2.63 mmol), and the resulting reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture was poured into water and extracted with ether (3 × 100 mL). The combined ether extracts were dried (Na_2SO_4), and the solvent was removed at reduced pressure. Chromatography (silica gel, 30% ether/hexane) provided alkylated urea **7** as an oil (160 mg, 60%). **7**: NMR ($CDCl_3$) δ 7.35 (m, 10 H), 4.70 (d, J = 14.0 Hz, 2 H), 4.55 (d, J = 7.7 Hz, 4 H), 4.28 (d, J = 14.0 Hz, 2 H), 3.56 (m, 2 H), 3.42 (m, 6 H), 1.16 (d, J = 7.0 Hz, 6 H), 0.84 (m, 4 H), 0.0 (s, 18 H); CIMS (NH_3) m/z 615 (M + H^+, 100); HRMS calcd for $C_{33}H_{55}N_2O_5Si_2$ (M + H^+) 615.3650, found 615.3635.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(phenylmethyl)-4,7-dimethyl-2*H*-1,3-diazapin-2-one (8). To a solution of urea **7** (90 mg, 0.15 mmol) in methanol (2 mL) was added 4 N HCl in dioxane (2 mL), and the resulting reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*. Chromatography (silica gel, EtOAc) gave urea **8** (47 mg, 89%). **8**: NMR ($CDCl_3$) δ 7.35 (m, 10 H), 4.78 (d, J = 14.0 Hz, 2 H), 4.14 (d, J = 14.0 Hz, 2 H), 3.58 (m, 2 H), 3.34 (m, 2 H), 2.22 (bs, 2 H), 1.16 (d, J = 7.0 Hz, 6 H); CIMS (NH_3) m/z 355 (M + H^+, 100); HRMS calcd for $C_{21}H_{27}N_2O_3$ (M + H^+) 355.2022, found 355.2013. Anal. ($C_{21}H_{26}N_2O_3$) C, H, N.

2,3-*O*-Isopropylidene-L-tartaric Acid *N*-Methyl-*N*-methoxyamide (10). To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (14.6 g, 150 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added trimethylaluminum (75 mL, 150 mmol, 2 M in hexane) over 30 min. The solution was allowed to warm to room temperature. After stirring for 15 min, the solution was cooled to −10 °C, and (−)-dimethyl 2,3-*O*-isopropylidene-L-tartrate (7.27 g, 33 mmol) in CH_2Cl_2 (20 mL) was added over 30 min. After the mixture had stirred for 2 h, the reaction was carefully quenched with dilute aqueous hydrochloric acid and the mixture extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was chromatographed (silica gel, 5% methanol/CH_2Cl_2) to give **10** as a white solid (7.66 g, 83%). **10**: mp 78−80 °C; NMR ($CDCl_3$) δ 5.17 (s, 2 H), 3.69 (s, 6 H), 3.23 (s, 6 H), 1.52 (s, 6 H); IR (KBr) ν 2990, 2940, 1680, 1380 cm^{-1}; CIMS (NH_3) m/z 277 (M + H^+, 100); HRMS calcd for $C_{11}H_{21}N_2O_6$ (M + H^+) 277.1399, found 277.1385.

(3*R*,4*R*)-1,6-Bis(4-isopropylphenyl)-2,5-dioxo-3,4-*O*-isopropylidenehexanediol (11). To a solution of Weinreb amide **10** (4.5 g, 16.3 mmol) in THF (150 mL) at 0 °C was added *p*-isopropylbenzylmagnesium chloride (133 mL, 100 mmol, 0.75 M in ether) dropwise. After 3 h, the reaction was quenched with saturated NH_4Cl and the mixture acidified with 1 N HCl and extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, 10% EtOAc/hexane) to give bisketone **11** as an oil (6.53 g, 95%). **11**: NMR ($CDCl_3$) δ 7.16 (ab, J = 8.4 Hz, $\Delta\nu$ = 16.5 Hz, 8 H), 4.70 (s, 2 H), 3.90 (ab, J = 15.8 Hz, $\Delta\nu$ = 17.6 Hz, 4 H), 2.88 (m, 2 H), 1.45 (s, 6 H), 1.23 (d, J = 7.0 Hz, 12 H); IR (KBr) ν 2960, 1730, 1510, 1380, 1080 cm^{-1}; CIMS (NH_3) m/z 423 (M + H^+, 100); HRMS calcd for $C_{27}H_{35}O_4$ (M + H^+) 423.2535, found 423.2533.

(3*R*,4*R*)-1,6-Bis(4-isopropylphenyl)-2,5-bis(hydroxyimino)-3,4-*O*-isopropylidenehexanediol (12). To a solution of bis-ketone **11** (6.5 g, 15.4 mmol) in ethanol (150 mL) and water (45 mL) was added hydroxylamine hydrochloride (2.81 g, 40.5 mmol). After stirring overnight, the solvent was partially removed under reduced pressure, and the residue was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, 25% EtOAc/hexane) to give bis-oxime **12** as predominantly the *E*:*E* oxime isomer (5.68 g, 82%). **12** (*E*:*E* isomer): NMR ($CDCl_3$) δ 8.41 (s, 2 H), 7.13 (ab, $J = 8.1$ Hz, $\Delta\nu = 21.7$ Hz, 8 H), 4.55 (s, 2 H), 3.72 (ab, $J = 13.9$ Hz, $\Delta\nu = 41.4$ Hz, 4 H), 2.85 (m, 2 H), 1.41 (s, 6 H), 1.21 (d, $J = 7.0$ Hz, 12 H); IR (KBr) ν 3340, 2960, 1510, 1380 cm^{-1}; CIMS (NH_3) m/z 453 ($M + H^+$, 100); HRMS calcd for $C_{27}H_{37}N_2O_4$ ($M + H^+$) 453.2753, found 453.2766.

(2*R*,3*S*,4*S*,5*R*)-1,6-Bis(4-isopropylphenyl)-2,5-diamino-3,4-*O*-isopropylidenehexanediol (13). To a solution of bis-oxime **12** (3.30 g, 7.3 mmol) in toluene (55 mL) at 0 °C was added diisobutylaluminum hydride (59 mL, 88 mmol, 1.5 M in toluene) over 30 min, and the solution was allowed to warm to room temperature. After stirring overnight, the solution was warmed to 50 °C for 2 h. The solution was cooled, the reaction was quenched with saturated Rochelle's salt (600 mL), and the mixture was gently stirred at room temperature. After stirring for 3 h, the solution was extracted with EtOAc and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, 10% MeOH/CH_2Cl_2) to give the diamine **13** as the *R*,*S*,*S*,*R* isomer as an oil (1.79 g, 58%). **13**: NMR ($CDCl_3$) δ 7.15 (ab, $J = 8.1$ Hz, $\Delta\nu = 21.9$ Hz, 8 H), 4.02 (s, 2 H), 2.92 (m, 2 H), 2.88 (m, 2 H), 2.76 (m, 2 H), 2.51 (m, 2 H), 1.46 (s, 6 H), 1.23 (d, $J = 6.6$ Hz, 12 H); IR (KBr) ν 2960, 1510, 1380, 1050 cm^{-1}; CIMS (NH_3) m/z 425 ($M + H^+$, 100); HRMS calcd for $C_{27}H_{41}N_2O_2$ ($M + H^+$) 425.3170, found 425.3178.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-*O*-isopropylidene-4,7-bis[(4-isopropylphenyl)methyl]-2*H*-1,3-diazapin-2-one (14). To a solution of diamine **13** (1.88 g, 4.4 mmol) in 1,1,2,2-tetrachloroethane (30 mL) was added 1,1′-carbonyldiimidazole (0.79 g, 4.8 mmol). After 10 min, the solution was added dropwise over 40 min to 1,1,2,2-tetrachloroethane (125 mL) at reflux. The solution was cooled, washed with dilute HCl, water, and brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, 33% EtOAc/hexane) to give cyclic urea **14** (1.25 g, 62%). **14**: NMR ($CDCl_3$) δ 7.17 (ab, $J = 8.1$ Hz, $\Delta\nu = 13.5$ Hz, 8 H), 4.93 (d, $J = 6.2$ Hz, 2 H), 4.26 (s, 2 H), 3.52 (m, 2 H), 2.84 (m, 6 H), 1.54 (s, 6 H), 1.24 (d, $J = 7.0$ Hz, 12 H); IR (KBr) ν 3260, 2960, 1680, 1100 cm^{-1}; CIMS (NH_3) m/z 451 ($M + H^+$, 100); HRMS calcd for $C_{28}H_{39}N_2O_3$ ($M + H^+$) 451.2961, found 451.2957.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-*O*-isopropylidene-1,3-bis(phenylmethyl)-4,7-bis[(4-isopropylphenyl)-methyl]-2*H*-1,3-diazapin-2-one (15). To a solution of cyclic urea **14** (62 mg, 0.14 mmol) and benzyl bromide (55 mg, 0.32 mmol) in THF (3 mL) was added potassium *tert*-butoxide (0.3 mL, 0.3 mmol, 1.0 M in THF). After stirring 30 min at room temperature, the solvent was removed under reduced pressure and the residue was chromatographed (silica gel, 7.5% EtOAc/hexane) to give cyclic urea **15** (80 mg, 92%). **15**: NMR ($CDCl_3$) δ 7.17 (m, 18 H), 4.96 (d, $J = 14.3$ Hz, 2 H), 3.80 (s, 2 H), 3.76 (m, 2 H), 3.09 (d, $J = 14.3$ Hz, 2 H), 2.91 (m, 6 H), 1.32 (s, 6 H), 1.26 (d, $J = 7.0$ Hz, 12 H); IR (KBr) ν 2960, 2930, 1630, 1230 cm^{-1}; CIMS (NH_3) m/z 631 ($M + H^+$, 100); HRMS calcd for $C_{42}H_{51}N_2O_3$ ($M + H^+$) 631.3899, found 631.3881.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(phenylmethyl)-4,7-bis[(4-isopropylphenyl)methyl]-2*H*-1,3-diazapin-2-one (16). Cyclic urea **15** (78 mg, 0.12 mmol) was dissolved in 6.7% concentrated HCl in methanol (3 mL). After 2 h, water was added and the suspension was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was recrystallized from EtOAc/hexanes to give urea **16** as a white solid (53 mg, 73%). **16**: mp >250 °C; NMR ($CDCl_3$) δ 7.20 (m, 18 H), 4.92 (d, $J = 14.3$ Hz, 2 H), 3.59 (s, 2 H), 3.53 (m, 2 H), 3.09 (d, $J = 14.3$ Hz, 2 H), 2.94 (m, 6 H), 2.14 (s, 2 H), 1.26 (d, $J = 7.0$ Hz, 12 H); IR (KBr) ν 3450, 2960, 1590, 1230 cm^{-1}; CIMS (NH_3) m/z 591 ($M + H^+$, 100); HRMS calcd for $C_{39}H_{47}N_2O_3$ ($M + H^+$) 591.3587, found 591.3579. Anal. ($C_{39}H_{46}N_2O_3$) C, H, N.

1,2:3,4:5,6-Tri-*O*-isopropylidene-L-mannitol (17). Lithium borohydride (1.2 g, 56.2 mmol) was added in four portions to a suspension of L-mannonic γ-lactone (5.0 g, 28.1 mmol) in methanol (250 mL) at 0 °C over 10 min. The ice bath was removed, and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched at 0 °C with 2 N HCl. The solvent was evaporated, and the residue was suspended in acetone (75 mL) to which 2,2-dimethoxypropane (20 mL, 168.6 mmol) and 4 N HCl in dioxane (21.1 mL, 84.3 mmol) were added. The reaction mixture was stirred at room temperature for 14 h. The solvent volume was reduced by two-thirds at reduced pressure and poured into saturated $NaHCO_3$ (100 mL). The solid was filtered off and recrystallized from ethanol to give the desired triacetonide **17** as a white solid (7.1 g, 80%). **17**: mp 72−74 °C; NMR ($CDCl_3$) δ 4.25 (m, 2 H), 4.15 (m, 2 H), 4.05 (m, 4 H), 1.5 (s, 6 H), 1.45 (s, 6 H), 1.4 (s, 6 H); CIMS (NH_3) m/z 303 ($M + H^+$, 100).

3,4-*O*-Isopropylidene-L-mannitol (18). A solution of **17** (14.0 g) in 70% AcOH (200 mL) was stirred at 45 °C for 2 h. The solvent was removed at reduced pressure with a bath temperature of 45 °C. The residue was dissolved in acetone, and a precipitate was filtered off. Evaporating the solvent and recrystallization from ether gave the desired monoacetonide **18** as a white solid (8.2 g, 80%). **18**: mp 83−86 °C; $[\alpha]_D = -26.40°$ ($c = 3$, H_2O); NMR ($CDCl_3$) δ 5.1 (d, $J = 6.3$ Hz, 2 H), 4.45 (t, $J = 8.4$ Hz, 2 H), 3.85 (m, 2 H), 3.5 (m, 4 H), 3.35 (m, 2 H), 1.25 (s, 6 H); CIMS (NH_3) m/z 240 ($M + NH_4^+$, 100). Anal. ($C_9H_{18}O_6$) C, H.

1,2:5,6-Dianhydro-3,4-*O*-isopropylidene-L-mannitol (19). To a suspension of tetraol **18** (7.0 g, 31.5 mmol) in toluene (70 mL) was added triphenylphosphine (20.7 g, 78.8 mmol) in one portion. The reaction mixture was cooled to 0 °C and treated with diethyl azodicarboxylate (12.5 mL, 78.8 mmol) via syringe over 1 min. The cooling bath was removed, and the reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and directly chromato-

graphed (silica gel, 30−50% ether/hexane) to give **19** as a volatile oil (4.4 g, 80%). **19**: $[\alpha]_D = +0.38$ ($c = 0.8$, $CHCl_3$); NMR ($CDCl_3$) δ 3.81 (m, 2 H), 3.10 (m, 2 H), 2.80 (t, $J = 9.5$ Hz, 2 H), 2.68 (m, 2 H), 1.40 (s, 6 H); CIMS (NH_3) m/z 204 ($M + NH_4^+$, 100). Anal. ($C_9H_{14}O_4$) C, H.

1,6-Dideoxy-1,6-bis[4-(methylthio)phenyl]-3,4-*O*-isopropylidene-L-mannitol (20). To a solution of *p*-bromothioanisole (1.3 g, 6.45 mmol) in THF (20 mL) at −78 °C was added *n*-butyllithium (2.6 mL, 6.45 mmol, 2.5 M in hexane). After 10 min, the reaction mixture was allowed to reach −20 °C to which copper cyanide (0.285 g, 3.2 mmol) was added in one portion. After complete dissolution of the solid, the reaction mixture was warmed to 0 °C to which diepoxide **19** (0.20 g, 1.08 mmol) in THF (4 mL) was added via cannula. The reaction mixture was allowed to reach room temperature, and stirring was continued for 30 min. The reaction was quenched with saturated NH_4Cl solution (1 mL), and the mixture was diluted with ether (50 mL) and washed with saturated NH_4Cl solution (2 × 30 mL). The organic layer was separated and dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (silica gel, 30−70% ether/hexane) gave diol **20** (0.41 g, 90%). **20**: NMR ($CDCl_3$) δ 7.2 (s, 8 H), 3.75 (m, 4 H), 3.1 (dd, $J = 15.0$, 3.0 Hz, 2 H), 3.0 (s, 2 H), 2.7 (q, $J = 8.0$ Hz, 2 H), 2.45 (s, 6 H), 1.45 (s, 6 H); CIMS (NH_3) m/z 452 ($M + NH_4^+$, 20), 435 ($M + H^+$, 100).

(2*R*,3*S*,4*S*,5*R*)-1,6-Bis[4-(methylthio)phenyl]-2,5-diazido-3,4-*O*-isopropylidenehexanediol (21). To a solution of diol **20** (0.35 g, 0.81 mmol) and triphenylphosphine (0.53 g, 2.0 mmol) in THF (5 mL) at 0 °C was added slowly diethyl azodicarboxylate (0.32 mL, 2.0 mmol). After 10 min, diphenyl phosphorazidate (0.44 mL, 2.0 mmol) was added to the reaction mixture slowly. The reaction mixture was allowed to reach room temperature and stirred for 1 h. The reaction was quenched with methanol (0.5 mL) at 0 °C. The mixture was then stirred at room temperature for 30 min and the solvent removed at reduced pressure. Chromatography (silica gel, 50−100% benzene/hexane) gave the diazide **21** (0.125 g, 32%) as an oil. **21**: NMR ($CDCl_3$) δ 7.15 (dd, $J = 22.5$, 7.5 Hz, 8 H), 4.1 (s, 2 H), 3.2 (m, 2 H), 3.0 (m, 4 H), 2.5 (s, 6 H), 1.55 (s, 6 H); CIMS (NH_3) m/z 502 ($M + NH_4^+$, 100).

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-*O*-isopropylidene-4,7-bis[[4-(methyl thio)phenyl]methyl]-2*H*-1,3-diazapin-2-one (23). A solution of **21** (0.12 g, 0.25 mmol) in THF (2 mL) was cooled to 0 °C and treated with a solution of LAH (0.5 mL, 0.5 mmol, 1 M in ether). The cooling bath was removed, and the reaction reached room temperature. After 20 min, the reaction mixture was recooled to 0 °C and the reaction quenched with 1 N NaOH. The mixture was diluted with EtOAc (5 mL), dried (Na_2SO_4), and filtered (Celite). The solvent was removed at reduced pressure, and the diamine was used without further purification. A solution of the diamine in tetrachloroethane (3 mL) was treated with 1,1-carbonyldiimidazole (46 mg, 0.29 mmol) in one portion. After 15 min, the reaction mixture was added via cannula to tetrachloroethane (2 mL) at reflux. After 15 min, the reaction mixture was cooled and chromatographed directly (silica gel, 2:1 to 1:1 EtOAc/hexane) to give urea **23** as a white solid (65 mg, 84%). **23**: mp 242−243 °C; NMR ($CDCl_3$) δ 7.2 (dd, $J = 22.5$, 7.5 Hz, 8 H), 4.95 (bs, 2 H), 4.25 (s, 2 H), 3.5 (bs, 2 H), 3.0 (d, $J = 15.0$ Hz, 4 H), 2.8 (t, $J = 17.0$ Hz, 2 H), 2.45 (s, 6 H), 1.55 (s, 6 H); CIMS (NH_3) m/z 459 ($M + H^+$, 100).

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-*O*-isopropylidene-1,3-bis(phenylmethyl)-4,7-bis[[4-(methylthio)phenyl]methyl]-2*H*-1,3-diazapin-2-one (24). To a solution of **23** (40 mg, 0.09 mmol) in dry DMF (2 mL) at room temperature was added NaH (15.0 mg, 0.35 mmol, 60% suspension in oil). After 5 min, benzyl bromide (0.03 mL, 0.26 mmol) was added and the reaction mixture stirred at room temperature for 2 h. The reaction was quenched with methanol, and the mixture was diluted with ether (15 mL), washed with water (10 mL), dried ($MgSO_4$), and concentrated. Chromatography (silica gel, 30% ether/hexane) gave the alkylated urea **24** (50 mg, 87%). **24**: NMR ($CDCl_3$) δ 7.2 (m, 14 H), 7.0 (d, $J = 7.5$ Hz, 4 H), 4.9 (d, $J = 13.0$ Hz, 2 H), 3.8 (m, 4 H), 3.15 (d, $J = 13.0$ Hz, 2 H), 2.85 (m, 4 H), 2.5 (s, 6 H), 1.3 (s, 6 H); CIMS (NH_3) m/z 639 ($M + H^+$, 100).

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[[4-(methylthio)phenyl]methyl]-2*H*-1,3-diazapin-2-one (25). To a solution of urea **24** (45 mg, 0.07 mmol) in CH_3CN (2 mL) at room temperature was added 20% concentrated HCl in methanol (0.5 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then poured into saturated $NaHCO_3$ (4 mL) and extracted with EtOAc (10 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was crystallized from ether to give **25** as a white solid (40 mg, 95%). **25**: mp 214−215 °C; NMR ($CDCl_3$) δ 7.2 (m, 14 H), 7.0 (d, $J = 7.5$ Hz, 4 H), 4.9 (d, $J = 13.0$ Hz, 2 H), 3.6 (m, 5 H), 3.1 (d, $J = 13.0$ Hz, 2 H), 2.9 (m, 5 H), 2.5 (s, 6 H); CIMS (NH_3) m/z 599 ($M + H^+$, 100). Anal. ($C_{35}H_{38}N_2O_3S_2$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-diisobutyl-2*H*-1,3-diazapin-2-one (26): NMR ($CDCl_3$) δ 7.32 (m, 10 H), 5.16 (d, $J = 14.0$ Hz, 2 H), 3.87 (d, $J = 14.0$ Hz, 2 H), 3.49 (s, 2 H), 3.36 (m, 2 H), 1.95 (s, 2 H), 1.74 (m, 4 H), 1.34 (m, 2 H), 0.93 (d, $J = 7.0$ Hz, 6 H), 0.85 (d, $J = 7.0$ Hz, 6 H); CIMS (NH_3) m/z 439 ($M + H^+$, 100); HRMS calcd for $C_{27}H_{39}N_2O_3$ ($M + H^+$) 439.2961, found 439.2970.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[2-(methylthio)ethyl]-2*H*-1,3-diazapin-2-one (27): NMR ($CDCl_3$) δ 7.20−7.41 (m, 10 H), 5.02 (d, $J = 14.0$ Hz, 2 H), 4.01 (d, $J = 14.0$ Hz, 2 H), 3.40−2.59 (m, 4 H), 2.31−2.59 (m, 6 H), 2.04 (s, 6 H), 1.95 (m, 2 H), 1.27 (m, 2 H); CIMS (NH_3) m/z 475 ($M + H^+$, 100); HRMS calcd for $C_{25}H_{35}N_2O_3S_2$ ($M + H^+$) 475.2089, found 475.2091.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis(3-indolylmethyl)-2*H*-1,3-diazapin-2-one (28):[32] NMR ($CDCl_3$) δ 8.05−6.79 (m, 22 H), 4.86 (d, $J = 14.0$ Hz, 2 H), 3.78 (s, 4 H), 3.13−3.34 (m, 4 H), 3.05 (d, $J = 14.0$ Hz, 2 H); CIMS (NH_3) m/z 585 ($M + H^+$, 100); HRMS calcd for $C_{37}H_{37}N_4O_3$ ($M + H^+$) 585.2866, found 585.2859.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis(cyclohexylmethyl)-2*H*-1,3-diazapin-2-one (29):[33] NMR ($CDCl_3$) δ 7.3 (m, 10 H), 5.04 (d, $J = 14.0$ Hz, 2 H), 3.86 (d, $J = 14.0$ Hz, 2 H), 3.67 (s, 2 H), 3.46 (bs, 2 H), 3.37 (bd, 2 H), 2.27 (bs, 2 H), 1.8−1.0 (m, 20 H), 0.83 (m, 2 H); ESIMS m/z 519

(M + H^+, 100); HRMS calcd for $C_{33}H_{47}N_2O_3$ (M + H^+) 519.3587, found 519.3567. Anal. ($C_{33}H_{46}N_2O_3$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis(phenylethyl)-2*H*-1,3-diazapin-2-one (30): NMR ($CDCl_3$) δ 7.4−7.1 (m, 20 H), 5.15 (d, J = 14.0 Hz, 2 H), 3.9 (d, J = 14.0 Hz, 2 H), 3.5 (bs, 2 H), 3.35 (m, 3 H), 2.8 (m, 3 H), 2.6 (m, 2 H), 2.0 (m, 4 H); CIMS (NH_3) m/z 535 (M + H^+, 100); HRMS calcd for $C_{35}H_{39}N_2O_3$ (M + H^+) 535.2961, found 535.2964.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis(β-naphthylmethyl)-2*H*-1,3-diazapin-2-one (31): mp 214−217 °C; NMR ($CDCl_3$) δ 7.8 (m, 6 H), 7.5 (m, 6 H), 7.2 (m, 12 H), 4.9 (d, J = 13.0 Hz, 2 H), 3.75 (m, 4 H), 3.2 (m, 4 H), 3.1 (d, J = 13.0 Hz, 2 H), 2.25 (s, 2 H); CIMS (NH_3) m/z 607 (M + H^+, 100). Anal. ($C_{41}H_{38}N_2O_3$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis(4-furanylmethyl)-2*H*-1,3-diazapin-2-one (32): mp 188−190 °C; NMR ($CDCl_3$) δ 7.45 (s, 2 H), 7.3 (m, 10 H), 7.1 (s, 2 H), 6.3 (s, 2 H), 5.0 (d, J = 13.0 Hz, 2 H), 3.6 (s, 2 H), 3.5 (m, 2 H), 3.4 (d, J = 13.0 Hz, 2 H), 2.8 (m, 4 H), 2.15 (s, 2 H); CIMS (NH_3) m/z 487 (M + H^+, 100). Anal. ($C_{29}H_{30}N_2O_5$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[[3-(methylthio)phenyl]methyl]-2*H*-1,3-diazapin-2-one (33): mp 173−174 °C; NMR ($CDCl_3$) δ 7.3 (m, 10 H), 7.2 (m, 4 H), 7.0 (s, 2 H), 6.9 (d, J = 8.0 Hz, 2 H), 4.9 (d, J = 13.0 Hz, 2 H), 3.6 (bs, 2 H), 3.55 (m, 2 H), 3.1 (d, J = 13.0 Hz, 2 H), 3.0 (m, 2 H), 2.5 (s, 6 H), 2.2 (bs, 2 H); CIMS (NH_3) m/z 599 (M + H^+, 100); HRMS calcd for $C_{35}H_{39}N_2O_3S_2$ (M + H^+) 599.2402, found 599.2402. Anal. ($C_{35}H_{38}N_2O_3S_2$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[[4-(methylsulfonyl)phenyl]methyl]-2*H*-1,3-diazapin-2-one (34): mp 244−246 °C; NMR (acetone-d_6) δ 7.8 (d, J = 7.0 Hz, 4 H), 7.3 (m, 14 H), 4.75 (d, J = 13.0 Hz, 2 H), 3.7 (m, 4 H), 3.2−2.9 (m, 8 H), 3.15 (s, 6 H); CIMS (NH_3) m/z 663 (M + H^+, 100). Anal. ($C_{35}H_{38}N_2O_7S_2$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[(2-methoxyphenyl)methyl]-2*H*-1,3-diazapin-2-one (35): mp 194−195 °C; NMR ($CDCl_3$) δ 7.25 (m, 12 H), 7.0 (d, J = 8.0 Hz, 2 H), 6.9 (m, 4 H), 4.9 (d, J = 14.0 Hz, 2 H), 3.8 (s, 6 H), 3.65 (s, 4 H), 3.1 (m, 6 H), 2.05 (s, 2 H); CIMS (NH_3) m/z 567 (M + H^+, 100). Anal. ($C_{35}H_{38}N_2O_5$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[(2-hydroxyphenyl)methyl]-2*H*-1,3-diazapin-2-one (36): NMR (methanol-d_4) δ 7.35 (m, 10 H), 7.2 (t, J = 7.0 Hz, 2 H), 7.0 (d, J = 9.0 Hz, 2 H), 6.85 (m, 2 H), 4.85 (d, J = 13.0 Hz, 2 H), 3.9 (m, 2 H), 3.4 (s, 4 H), 3.15 (m, 4 H); CIMS (NH_3) m/z 539 (M + H^+, 100); HRMS calcd for $C_{33}H_{35}N_2O_5$ (M + H^+) 539.2546, found 539.2534.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[(3-methoxyphenyl)methyl]-2*H*-1,3-diazapin-2-one (37): NMR ($CDCl_3$) δ 7.3 (m, 12 H), 6.8 (m, 2 H), 6.75 (m, 2 H), 6.65 (s, 2 H), 4.9 (d, J = 13.0 Hz, 2 H), 3.8 (s, 6 H), 3.6 (m, 4 H), 3.1 (d, J = 13.0 Hz, 2 H), 3.0 (m, 4 H); CIMS (NH_3) m/z 567 (M + H^+, 100); HRMS calcd for $C_{35}H_{39}N_2O_5$ (M + H^+) 567.2859, found 567.2862.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[(4-methoxyphenyl)methyl]-2*H*-1,3-diazapin-2-one (38): NMR ($CDCl_3$) δ 7.3 (m, 10 H), 7.0 (d, J = 7.0 Hz, 4 H), 6.9 (d, J = 7.0 Hz, 4 H), 4.9 (d, J = 14.0 Hz, 2 H), 3.8 (s, 6 H), 3.75−3.4 (m, 4 H), 3.1 (d, J = 14.0 Hz, 2 H), 2.95 (m, 2 H); CIMS (NH_3) m/z 567 (M + H^+, 100); HRMS calcd for $C_{35}H_{39}N_2O_5$ (M + H^+) 567.2859, found 567.2858.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[(4-hydroxyphenyl)methyl]-2*H*-1,3-diazapin-2-one (39): NMR ($CDCl_3$) δ 7.3 (m, 10 H), 6.98 (d, J = 7.0 Hz, 4 H), 6.86 (d, J = 7.0 Hz, 4 H), 4.9 (d, J = 14.0 Hz, 2 H), 3.05 (d, J = 14.0 Hz, 2 H), 2.95 (m, 4 H), 2.2 (bs, 2 H); CIMS (NH_3) m/z 539 (M + H^+, 100); HRMS calcd for $C_{33}H_{35}N_2O_5$ (M + H^+) 539.2546, found 539.3348.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[(3-aminophenyl)methyl]-2*H*-1,3-diazapin-2-one (40): mp 177−178 °C; NMR ($CDCl_3$) δ 7.4−7.2 (m, 10 H), 7.0 (t, J = 5.5 Hz, 2 H), 6.6−6.3 (m, 6 H), 4.95 (d, J = 13.0 Hz, 2 H), 4.55 (bs, 4 H), 4.15 (s, 2 H), 3.55 (m, 2 H), 3.1 (d, J = 13.0 Hz, 2 H), 2.9 (m, 4 H); CIMS (NH_3) m/z 537 (M + H^+, 100). Anal. ($C_{33}H_{36}N_4O_3$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[[3-(*N*,*N*-dimethylamino)phenyl]methyl]-2*H*-1,3-diazapin-2-one (41): NMR ($CDCl_3$) δ 7.6 (m, 4 H), 7.35 (m, 12 H), 7.2 (bs, 2 H), 4.7 (d, J = 13.0 Hz, 2 H), 3.8 (m, 4 H), 3.35 (s, 12 H), 3.2 (m, 6 H); CIMS (NH_3) m/z 593 (M + H^+, 100); HRMS calcd for $C_{37}H_{45}N_4O_3$ (M + H^+) 593.3492, found 593.3480.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[(4-aminophenyl)methyl]-2*H*-1,3-diazapin-2-one (42): mp 125−130 °C; NMR ($CDCl_3$) δ 7.2 (m, 10 H), 6.9 (d, J = 8.0 Hz, 4 H), 6.6 (d, J = 8.0 Hz, 4 H), 4.9 (d, J = 13.0 Hz, 2 H), 3.5 (m, 6 H), 3.1 (d, J = 8.0 Hz, 4 H), 2.9 (m, 4 H); CIMS (NH_3) m/z 537 (M + H^+, 100). Anal. ($C_{33}H_{36}N_4O_3$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[[4-(*N*,*N*-dimethylamino)phenyl]methyl]-2*H*-1,3-diazapin-2-one (44): mp 185 °C dec; NMR (methanol-d_4) δ 7.55 (d, J = 7.0 Hz, 4 H), 7.3 (m, 10 H), 7.15 (d, J = 7.0 Hz, 4 H), 4.6 (d, J = 13.0 Hz, 2 H), 3.7 (s, 4 H), 3.3 (s, 12 H), 3.1 (d, J = 13.0 Hz, 2 H), 3.05 (d, J = 10.0 Hz, 2 H), 2.9 (m, 2 H); CIMS (NH_3) m/z 593 (M + H^+, 100); HRMS calcd for $C_{37}H_{45}N_4O_3$ (M + H^+) 593.3492, found 593.3506.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis(4-pyridylmethyl)-2*H*-1,3-diazapin-2-one (45): mp 88−92 °C; NMR ($CDCl_3$) δ 8.40 (d, J = 6.2 Hz, 4 H), 7.27 (m, 4 H), 7.14 (m, 4 H), 7.00 (d, J = 5.9 Hz, 4 H), 4.84 (d, J = 14.3 Hz, 2 H), 3.66 (bs, 4 H), 3.60 (m, 4 H), 3.14 (d, J = 14.3 Hz, 2 H), 3.00 (m, 4 H); IR (KBr) ν 3400, 3030, 1640, 1600, 1230, 1070 cm^{-1}; CIMS (NH_3) m/z 509 (M + H^+, 100); HRMS calcd for $C_{31}H_{32}N_4O_3$ (M + H^+) 509.2553, found 509.2554.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[3-(2,5-dimethylpyrolyl)methyl]-2*H*-1,3-diazapin-2-one (46): mp 190−191 °C; NMR ($CDCl_3$) δ 7.5 (t, J = 8.0 Hz, 2 H), 7.3 (m, 14 H), 6.9 (s, 2 H), 6.0 (s, 4 H), 5.0 (d, J = 13.0 Hz, 2 H), 3.7 (m, 4 H), 3.2−3.0 (m, 6 H), 2.05 (s, 12 H); CIMS (NH_3) m/z 693 (M + H^+, 100). Anal. ($C_{33}H_{36}N_4O_3$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis(phenylmethyl)-4,7-bis[[3,4-(methylenedioxy)phe-

nyl]methyl]-2*H*-1,3-diazapin-2-one (47): mp 189−191 °C; NMR ($CDCl_3$) δ 7.3 (m, 6 H), 7.2 (m, 4 H), 6.8 (d, J = 7.5 Hz, 4 H), 6.6 (m, 2 H), 6.5 (d, J = 7.5 Hz, 2 H), 6.0 (m, 4 H), 4.9 (d, J = 13.0 Hz, 2 H), 3.6 (bs, 2 H), 3.5 (m, 2 H), 3.2 (d, J = 13.0 Hz, 2 H), 2.9 (m, 4 H); CIMS (NH_3) m/z 595 (M + H^+, 100); HRMS calcd for $C_{35}H_{35}N_2O_7$ (M + H^+) 595.2444, found 595.2443. Anal. ($C_{35}H_{34}N_2O_7$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-diisobutyl-2*H*-1,3-diazapin-2-one (51): mp 137−139 °C; NMR ($CDCl_3$) 3.94 (s, 2 H), 3.80 (dd, J = 7.0, 7.0 Hz, 2 H), 3.47 (d, J = 11.0 Hz, 2 H), 2.91 (bs, 2 H), 2.64 (dd, J = 7.0, 7.0 Hz, 2 H), 1.98 (m, 2 H), 1.84 (m, 2 H), 1.42 (m, 2 H), 1.24 (s, 4 H), 1.20 (m, 2 H), 0.92 (d, J = 7.0 Hz, 6 H), 0.88 (d, J = 7.0 Hz, 6 H), 0.52 (m, 4 H), 0.21 (m, 4 H); CIMS (NH_3) m/z 367 (M + H^+, 100); HRMS calcd for $C_{21}H_{39}N_2O_3$ (M + H^+) 367.2961, found 367.2954.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-diisopropyl-2*H*-1,3-diazapin-2-one (52): NMR ($CDCl_3$) δ 4.2 (bs, 2 H), 3.72 (m, 2 H), 3.2 (m, 4 H), 2.66 (m, 4 H), 1.10 (d, J = 7.0 Hz, 6 H), 0.91 (d, J = 7.0 Hz, 6 H), 0.49 (m, 4 H), 0.18 (m, 4 H); CIMS (NH_3) m/z 339 (M + H^+, 100); HRMS calcd for $C_{19}H_{35}N_2O_3$ (M + H^+) 339.2648, found 339.2653.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-bis[2-(methylthio)ethyl]-2*H*-1,3-diazapin-2-one (53): NMR ($CDCl_3$) δ 3.87 (s, 2 H), 3.65−3.79 (m, 4 H), 2.40−2.79 (m, 8 H), 2.26 (m, 2 H), 2.07 (s, 6 H), 1.01 (m, 2 H), 0.52 (m, 4 H), 0.13−0.35 (m, 4 H); CIMS (NH_3) m/z 403 (M + H^+, 100); HRMS calcd for $C_{19}H_{35}N_2O_3S_2$ (M + H^+) 403.2089, found 403.2085.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-bis[(4-fluorophenyl)methyl]-2*H*-1,3-diazapin-2-one (54): mp 193−194 °C; NMR ($CDCl_3$) δ 7.12 (m, 4 H), 6.97 (m, 4 H), 4.00 (bs, 2 H), 3.54 (dd, J = 14.3, 6.6 Hz, 2 H), 3.08 (m, 4 H), 2.28 (bs, 2 H), 1.97 (dd, J = 14.3, 6.6 Hz, 2 H), 0.88 (m, 2 H), 0.42 (m, 4 H), 0.06 (m, 4 H); CIMS (NH_3) m/z 471 (M + H^+, 100); HRMS calcd for $C_{27}H_{33}N_2O_3F_2$ (M + H^+) 471.2459, found 471.2441.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-bis[(2-methoxyphenyl)-methyl]-2*H*-1,3-diazapin-2-one (55): mp 155−156 °C; NMR ($CDCl_3$) δ 7.2 (t, J = 6.0 Hz, 2 H), 7.1 (d, J = 6.0 Hz, 2 H), 6.85 (m, 4 H), 4.1 (bs, 2 H), 3.85 (s, 6 H), 3.5 (dd, J = 7.0, 7.0 Hz, 2 H), 3.25 (dd, J = 9.0, 2.0 Hz, 2 H), 3.0 (m, 2 H), 2.75 (bs, 2 H), 2.15 (dd, J = 7.0, 7.0 Hz, 2 H), 0.9 (m, 2 H), 0.4 (m, 4 H), 0.1 (m, 4 H); CIMS (NH_3) m/z 495 (M + H^+, 100). Anal. ($C_{29}H_{38}N_2O_5$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-bis[(3-methoxyphenyl)-methyl]-2*H*-1,3-diazapin-2-one (56): NMR ($CDCl_3$) δ 7.2 (t, J = 8.0 Hz, 2 H), 6.8 (m, 6 H), 4.1 (bs, 2 H), 3.8 (s, 6 H), 3.65 (m, 2 H), 3.6 (dd, J = 7.0, 7.0 Hz, 2 H), 3.1 (m, 4 H), 2.75 (s, 2 H), 2.1 (dd, J = 7.0, 7.0 Hz, 2 H), 0.9 (m, 2 H), 0.4 (m, 4 H), 0.1 (m, 4 H); CIMS (NH_3) m/z 495 (M + H^+, 100); HRMS calcd for $C_{29}H_{39}N_2O_5$ (M + H^+) 495.2859, found 495.2867.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-bis[(3-hydroxyphenyl)-methyl]-2*H*-1,3-diazapin-2-one (57): NMR (methanol-d_4) δ 7.2 (m, 2 H), 6.75 (m, 6 H), 4.0 (m, 2 H), 3.6 (m, 2 H), 3.5 (dd, J = 7.0, 7.0 Hz, 2 H), 3.1 (m, 4 H), 2.75 (s, 2 H), 2.4 (dd, J = 7.0, 7.0 Hz, 2 H), 0.9 (m, 2 H), 0.4 (m, 4 H), 0.1 (m, 4 H); CIMS (NH_3) m/z 467 (M + H^+, 100); HRMS calcd for $C_{27}H_{35}N_2O_5$ (M + H^+) 467.2546, found 467.2532.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-bis[(4-methoxyphenyl)-methyl]-2*H*-1,3-diazapin-2-one (58): mp 145−147 °C; NMR ($CDCl_3$) δ 7.11 (d, J = 7.0 Hz, 4 H), 6.82 (d, J = 7.0 Hz, 4 H), 4.07 (bs, 2 H), 3.78 (s, 6 H), 3.66 (m, 4 H), 3.07 (m, 4 H), 2.08 (m, 2 H), 0.92 (m, 2 H), 0.43 (m, 4 H), 0.09 (m, 4 H); CIMS (NH_3) m/z 495 (M + H^+, 100); HRMS calcd for $C_{29}H_{39}N_2O_5$ (M + H^+) 495.2859, found 495.2858.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-bis(*β*-naphthylmethyl)-2*H*-1,3-diazapin-2-one (59): mp 118−121 °C; NMR ($CDCl_3$) δ 7.8 (m, 6 H), 7.7 (s, 2 H), 7.4 (s, 6 H), 4.2 (s, 2 H), 3.8 (m, 2 H), 3.6 (m, 2 H), 3.3 (m, 4 H), 2.05 (m, 4 H), 0.95 (m, 2 H), 0.4 (m, 4 H), 0.05 (m, 4 H); CIMS (NH_3) m/z 535 (M + H^+, 100). Anal. ($C_{35}H_{38}N_2O_3$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-bis[(3,5-dimethoxyphenyl)-methyl]-2*H*-1,3-diazapin-2-one (60): NMR ($CDCl_3$) δ 6.3 (s, 4 H), 6.2 (s, 2 H), 3.9 (bs, 2 H), 3.7 (bs, 2 H), 3.63 (s, 12 H), 3.58 (m, 2 H), 3.5 (dd, J = 7.0, 7.0 Hz, 2 H), 3.0 (m, 4 H), 2.0 (dd, J = 7.0, 7.0 Hz, 2 H), 0.9 (m, 2 H), 0.4 (m, 4 H), 0.1 (m, 4 H); CIMS (NH_3) m/z 555 (M + H^+, 100); HRMS calcd for $C_{31}H_{43}N_2O_7$ (M + H^+) 555.3070, found 555.3068.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-(cyclopropylmethyl)-4,7-bis(2-thienylmethyl)-2*H*-1,3-diazapin-2-one (61): NMR ($CDCl_3$) δ 7.15 (m, 2 H), 6.9 (m, 2 H), 6.8 (m, 2 H), 4.05 (bs, 2 H), 3.7 (m, 2 H), 3.7 (dd, J = 7.0, 7.0 Hz, 2 H), 3.4 (m, 2 H), 3.35 (m, 2 H), 2.9 (s, 2 H), 2.2 (dd, J = 7.0, 7.0 Hz, 2 H), 0.9 (m, 2 H), 0.4 (m, 4 H), 0.1 (m, 4 H); CIMS (NH_3) m/z 447 (M + H^+, 100); HRMS calcd for $C_{23}H_{31}N_2O_3S_2$ (M + H^+) 447.1776, found 447.1770.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-[[4-(hydroxymethyl)phenyl]methyl]-4,7-bis[2-(methylthio)ethyl]-2*H*-1,3-diazapin-2-one (62): NMR ($CDCl_3$) 5.1 (d, J = 14.0 Hz, 2 H), 4.7 (s, 4 H), 4.0 (d, J = 14.0 Hz, 2 H), 3.6 (s, 2 H), 3.6 (m, 2 H), 3.4 (s, 2 H), 2.6 (m, 2 H), 2.4 (m, 2 H), 2.1 (s, 6 H), 1.9 (m, 4 H), 0.9 (m, 4 H); CIMS (NH_3) m/z 552 (M + NH_4^+, 100); HRMS calcd for $C_{27}H_{39}N_2O_5S_2$ (M + H^+) 535.2300, found 535.2302.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[4-(hydroxymethyl)phenyl]methyl]-4,7-bis(cyclohexylmethyl)-2*H*-1,3-diazapin-2-one (63): NMR (CD_3OD) δ 7.4 (bs, 8 H), 5.1 (d, J = 14.0 Hz, 2 H), 4.95 (s, 4 H), 4.7 (s, 2 H), 4.1 (d, J = 14.0 Hz, 2 H), 3.5 (m, 4 H), 2.0−1.2 (m, 20 H), 0.9 (m, 2 H); ESIMS m/z 579 (M + H^+, 100); HRMS calcd for $C_{35}H_{51}N_2O_5$ (M + H^+) 579.3798, found 579.3811.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-[[4-(hydroxymethyl)phenyl]methyl]-4,7-bis[(4-fluorophenyl)methyl]-2*H*-1,3-diazapin-2-one (64): mp 174−175 °C; NMR ($CDCl_3$) δ 7.28 (m, 4 H), 7.07 (m, 12 H), 4.82 (d, J = 14.3 Hz, 2 H), 4.61 (bs, 4 H), 3.48 (m, 2 H), 3.41 (m, 2 H), 3.03 (d, J = 14.3 Hz, 2 H), 2.92 (m, 4 H), 2.67 (bs, 1 H), 2.05 (bs, 1 H), 1.60 (bs, 2 H); CIMS (NH_3) m/z 620 (M + NH_4^+, 100); HRMS calcd for $C_{35}H_{37}N_2O_5F_2$ (M + H^+) 603.2671, found 603.2676.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-[[4-(hydroxymethyl)phenyl]methyl]-4,7-bis[(3-methoxyphenyl)methyl]-2*H*-1,3-diazapin-2-one (65): NMR ($CDCl_3$) δ 7.2 (m, 8 H), 7.1 (d, J = 7.0 Hz, 2 H), 6.75 (dd, J = 19.0, 7.0 Hz, 4 H), 6.55 (s, 2 H), 4.8 (d, J = 13.0 Hz, 2 H), 4.55 (d, J = 4.0 Hz, 4 H), 3.8 (s, 6 H), 3.5 (m, 4 H), 3.1 (d, J = 13.0 Hz, 2 H), 2.9 (m, 6 H), 2.3 (m, 2 H); CIMS (NH_3) m/z 627 (M + H^+, 100); HRMS calcd for $C_{37}H_{43}N_2O_7$ (M + H^+) 627.3070, found 627.3055.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-[[4-(hydroxymethyl)phenyl]methyl]-4,7-bis[(3,4-difluorophenyl)methyl]-2*H*-1,3-diazapin-2-one (66): mp 97−102 °C; NMR ($CDCl_3$/CD_3OD) δ 7.30 (m, 4 H), 7.05 (m, 6 H), 6.8 (m, 4 H), 4.75 (d, J = 14.3 Hz, 2 H), 4.6 (bs, 4 H), 3.45 (m, 4 H), 3.1 (d, J = 14.3 Hz, 2 H), 3.05 (bs, 4 H), 2.95 (m, 4 H); CIMS (NH_3) m/z 639 (M + H^+, 100); HRMS calcd for $C_{35}H_{35}N_2O_5F_4$ (M + H^+) 639.2482, found 639.2503. Anal. ($C_{35}H_{34}N_2O_5F_4$) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis[[4-(hydroxymethyl)phenyl]methyl]-4,7-bis(4-pyridylmethyl)-2*H*-1,3-diazapin-2-one (67): NMR (CD_3OD) δ 8.38 (bs, 4 H), 7.26 (ab, J_{ab} = 8.1 Hz, $\Delta\nu$ = 27.1 Hz, 8 H), 7.03 (d, J = 5.1 Hz, 4 H), 4.62 (d, J = 14.3 Hz, 2 H), 4.57 (s, 4 H), 3.70 (m, 4 H), 3.26 (d, J = 14.3 Hz, 2 H), 3.01 (m, 4 H); IR (KBr) ν 3380, 2920, 1610, 1380 cm^{-1}; CIMS (NH_3) m/z 569 (M + H^+, 100); HRMS calcd for $C_{33}H_{37}N_4O_5$ (M + H^+) 569.2764, found 569.2744.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-[[4-(hydroxymethyl)phenyl]methyl]-4,7-bis[(4-methoxyphenyl)methyl]-2*H*-1,3-diazapin-2-one (68): NMR ($CDCl_3$) δ 7.3 (d, J = 8.0 Hz, 4 H), 7.15 (d, J = 8.0 Hz, 4 H), 7.0 (d, J = 8.0 Hz, 4 H), 6.85 (d, J = 8.0 Hz, 4 H), 5.3 (s, 2 H), 4.8 (d, J = 13.0 Hz, 2 H), 4.6 (m, 4 H), 3.8 (s, 6 H), 3.45 (m, 4 H), 3.1 (d, J = 13.0 Hz, 2 H), 2.9 (m, 4 H), 2.65 (bs, 2 H); CIMS (NH_3) m/z 627 (M + H^+, 100); HRMS calcd for $C_{37}H_{43}N_2O_7$ (M + H^+) 627.3070, found 627.3058.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-1,3-bis-[[4-(hydroxymethyl)phenyl]methyl]-4,7-diisobutyl-2*H*-1,3-diazapin-2-one (69): NMR (CD_3OD) δ 7.36 (bs, 8 H), 5.02 (d, J = 14.0 Hz, 2 H), 4.89 (s, 4 H), 3.90 (d, J = 14.0 Hz, 2 H), 3.41 (m, 4 H), 1.65 (m, 4 H), 1.41 (m, 4 H), 0.90 (d, J = 7.0 Hz, 6 H), 0.93 (d, J = 7.0 Hz, 6 H); CIMS (NH_3) m/z 516 (M + NH_4^+, 100); HRMS calcd for $C_{29}H_{43}N_2O_5$ (M + H^+) 499.3172, found 499.3174. Anal. ($C_{29}H_{42}N_2O_5$) C, H, N.

Binding Affinity Assay. Inhibition of HIV protease was measured by assay of the cleavage of a fluorescent peptide substrate using HPLC.[34]

Whole-Cell Antiviral Assay. 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.[35] 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 cellular toxicity of compounds was assessed by measuring the extent of MTT dye reduction in uninfected MT-2 cell cultures grown for 3 days in the presence of various concentrations of test compound. The compound concentration which decreased the level of MTT dye reduction by 50% was designated the TC_{50}. Only compounds which displayed an antiviral IC_{90} concentration which was at least 3-fold less than the TC_{50} concentration were considered to have a specific antiviral effect.

References

(1) Weiss, R. A. How Does HIV Cause AIDS? *Science* **1993**, *260*, 1273−79 and references cited therein.

(2) Johnston, M. I.; Hoth, D. F. Present Status and Future Prospects of HIV Therapies. *Science* **1993**, *260*, 1286−93 and references cited therein.

(3) Kohl, N. E.; Emini, E. A.; Schlief, W. A.; Davis, L. J.; Heimbach, J. C.; Dixson, R. A. F.; Scolnik, E. M.; Sigal, I. S. Active Human Immunodeficiency Virus Protease is Required for Viral Infectivity. *Proc. Natl. Acd. Sci. U.S.A.* **1988**, *85*, 4686−90.

(4) Wlodawer, A.; Miller, M.; Jaskolski, M.; Sathyanarayana, B. K.; Baldwin, E.; Weber, I. T.; Selk, L. M.; Clawson, L.; Schnieder, L.; Kent, S. B. H. Conserved Folding in Retroviral Proteases: Crystal Structure of a Synthetic HIV-1 Protease. *Science* **1989**, *245*, 616−21.

(5) (a) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A.C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. Studies Toward the Large-scale Synthesis of the HIV Proteinase Inhibitor Ro 31-8959. *J. Org. Chem.* **1994**, *59*, 3656−64 and references cited therein. (b) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. L-735,524: The Design of a Potent and Orally Bioavailable HIV Protease Inhibitor. *J. Med. Chem.* **1994**, *37*, 3443−51. (c) Kempf, D. J.; Marsh, K. C.; Denissen, J.; McDonald, E.; Vasavanonda, S.; Flentge, C.; Green, B. G.; Fino, L.; Park, C.; Kong, X.; Wideburg, N. E.; Saldivar, A.; Ruiz, L.; Kati, W. M.; Sham, H. L.; Robins, T.; Stewart, K. D.; Plattner, J. J.; Leonard, J.; Norbeck, D. ABT-538 is a Potent Inhibitor of Human Immunodeficiency Virus Protease with High Oral Bioavailability in Humans. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 2484−88.

(6) Ho, D. D.; Neumann, A. U.; Perelson, A. S.; Chen, W.; Leonard, J. M.; Markowitz, M. Rapid Turnover of Plasma Virons and CD4 Lymphocytes in HIV-1 Infection. *Nature* **1995**, *373*, 123−6.

(7) Thaisrivongs, S. HIV Protease Inhibitors. *Annu. Rep. Med. Chem.* **1994**, *29*, 133−44.

(8) Urban, J.; Konvalinka, J.; Stehlekova, J.; Gregorova, E.; Majer, P.; Soucek, M.; Andreansky, M.; Fabray, M.; Strop, P. Reduced-Bond Tight-Binding Inhibitors of HIV-1 Protease. *FEBS Lett.* **1992**, *298*, 9−13.

(9) (a) Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Schleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. J.; Schwering, J. E.; Homnick, C. F.; Nunberg, J.; Springer, J. P.; Huff, J. R. Synthesis and Antiviral Activity of a Series of HIV-1 Protease Inhibitors with Functionality Tethered to the P1 or P1′ Phenyl Substituents: X-ray Crystal Structure Assisted Design. *J. Med. Chem.* **1992**, *35*, 1685−701. (b) Young, S. D.; Payne, L. S.; Thompson, W. J.; Gaffin, N.; Lyle, T. A.; Britcher, S. F.; Grahm, S. L.; Schultz, T. H.; Deana, A. A.; Darke, P. L.; Zugay, J. A.; Schleif, W. A.; Quintero, J. C.; Emini, E. A.; Anderson, P. S.; Huff, J. R. HIV-1 Protease Inhibitors Based on Hydroxyethylene Dipeptide Isosteres: An Investigation into the Role of the P1′ Side Chain on Structure-Activity. *J. Med. Chem.* **1992**, *35*, 1702−9.

(10) Getman, D. P.; DeCrescenzo, G. A.; Heintz, R. M.; Reed, K. L.; Talley, J. J.; Bryant, M. L.; Clare, M.; Houseman, K. A.; Marr, J. J.; Mueller, R. A.; Vazquez, M. L.; Shieh, H.-S.; Stallings, W. C.; Stegeman, R. A. Discovery of a Novel Class of Potent HIV-1 Protease Inhibitors Containing the (R)-(Hydroxyethyl)urea Isostere. *J. Med. Chem.* **1993**, *36*, 288−91.

(11) Budt, K. H.; Peyman, A.; Hansen, J.; Knolle, J.; Meichsner, C.; Paessens, A.; Ruppert, D.; Stowasser, B. HIV Protease Inhibitor HOE/BAY 793, Structure-Activity Relationships in a Series of C2-Symmetric Diols. *BioMed. Chem.* **1995**, *3* (5), 559−71.

(12) Lam, P. Y. S.; Jadhav, P. K.; Eyerman, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. Rational Design of Potent, Bioavailable, Nonpeptide Cyclic Ureas as HIV Protease Inhibitors *Science* **1994**, *263*, 380−4.

(13) See: Chang, C.-H.; Schadt, M. C.; Lewandowski, F. A.; DeLoskey, R.; Duke, J.; Calabrese, J. C.; Lam, P. Y. S.; Jadhav, P. K.; Eyerman, C. J.; Hodge, C. N.; Weber, P.C. Three Dimensional Structures of the HIV-1 Protease Complexed with Novel Non-Peptide, Cyclic Urea-Containing Inhibitors. Submitted for publication.

(14) Wlodawer, A.; Erickson, J. W. Structure Based Inhibitors of HIV-1 Protease. *Annu. Rev. Biochem.* **1993**, *62*, 543−85.

(15) Wong, Y. N.; Burcham, D. L.; Saxton, P. L.; Erickson-Viitanen, S.; Grubb, M. F.; Quon, C. Y.; Huang, S.-M. A Pharmacokinetic Evaluation of HIV Protease Inhibitors, Cyclic Ureas, in Rats and Dogs. *Biopharm. Drug Dispos.* **1994**, *15*, 535−44.

(16) Hodge, C. N.; Aldrich, P. E.; Bacheler, L. T.; Chang, C.-H.; Eyerman, C. J.; Grubb, M.; Jackson, D. A.; Jadhav, P. K.; Korant, B.; Lam, P. Y. S.; Maurin, M. B.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Sharpe, T. R.; Shum, L.; Winslow, D. L.; Erickson-Viitanen, S. DMP 450: An Orally Bioavailable Cyclic Urea Inhibitor of the HIV Protease. Submitted for publication.

(17) Lam, P. Y. S.; Ru, Y.; Jadhav, P. K.; Aldrich, P. E.; De Lucca, G. V.; Eyermann, C. J.; Chang, C.-H.; Emmett, G.; Holler, E. R.; Daneker, W. F.; Li, L.; Confalone, P. N.; McHugh, R. J.; Han, Q.; Li, R.; Markwalder, J. A.; Seitz, S. P.; Sharpe, T. R.; Bacheler, L. T.; Rayner, M. M.; Klabe, R. M.; Shum, L.; Winslow, D. L.; Kornhauser, D. M.; Jackson, D. A.; Erickson-Viitanen, S.; Hodge, C. N. Cyclic HIV Protease Inhibitors: Synthesis, Conformational Analysis, P2/P2′ SAR and Molecular Recognition of Cyclic Ureas. Submitted for publication. The preparation of compounds **1** and **2** is also disclosed in this manuscript.

(18) (a) Nahm, S.; Weinreb, S. M. N-Methoxy-N-methylamides as Effective Acylating Agents. *Tetrahedron Lett.* **1981**, *22*, 3815−8. (b) Angelastro, M. R.; Peet, N. P.; Bey, P. An Efficient Synthesis of Novel α-Diketone and α-Keto Ester Derivatives of N-Protected Amino Acids and Peptides. *J. Org. Chem.* **1989**, *54*, 3913−6.

(19) Konradi, A. W.; Pederson, S. F. Pinacol Coupling of (S)-2-[N-(Benzyloxycarbonyl)amino]Aldehydes by $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$. Synthesis of C_2-Symmetric (1S,2R,3R,4S)-1,4-Diamino 2,3-Diols. *J. Org. Chem.* **1992**, *57*, 28−32.

(20) The absolute configuration of DMP 323 was established by the preparation of the intermediate diaminol diol from D-mannitol which contains this stereochemistry. See: Jadhav, P. K.; Woerner, F. J. Synthesis of C_2-Symmetric HIV-1 Protease Inhibitors from D-mannitol. *BioMed. Chem. Lett.* **1992**, *2*, 353−6.

(21) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. An Alternative Procedure for the Aluminum-Mediated Conversion of Esters to Amides. *Synth. Commun.* **1982**, *12*, 989−93. (b) Basha, A.; Lipton, M.; Weinreb, S. M. A Mild, General Method for Conversion of Esters to Amides. *Tetrahedron Lett.* **1977**, *48*, 4171−4.

(22) The major byproduct isolated is the secondary amine resulting from the Lewis acid-catalyzed Beckmann rearrangement. For example, see: Sasatani, S.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. Diisobutylaluminum Hydride. A Novel Reagent for the Reduction of Oximes. *Tetrahedron Lett.* **1983**, *24* (43), 4711−2.

(23) Williams, D. R.; Osterhaut, M. H.; Reddy, J. P. Diastereoselective Reduction of α-Hydroxy Oxime Ethers. Synthesis of syn-1,2-Amino Alcochols. *Tetrahedron Lett.* **1993**, *34* (20), 3271−4.

(24) Wiggins, L. F. The Anhydrides of Polyhydric Alcohols. Part II. Derivatives of 1:2-5:6-Dianhydro Mannitol. *J. Chem. Soc.* **1946**, 384−8.

(25) (a) Ghosh, A. K.; McKee, S. P.; Thompson, W. J. Stereocontrolled Synthesis of HIV-1 Protease Inhibitors with C_2-Axis of Symmetry. *Tetrahedron Lett.* **1991**, *32*, 5729−32. (b) Chenera, B.; Boehm, J. C.; Dreyer, G. B. Synthesis of C_2-Symmetric and Pseudosymmetric HIV-1 Protease Inhibitors from D-Mannitol and D-Arabitol. *BioMed. Chem. Lett.* **1991**, *1*, 219−22.

(26) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, 1−28.

(27) Yamaguchi, M.; Hirao, I. An Efficient Method for the Alkynylation of Oxiranes Using Alkynyl Boranes. *Tetrahedron Lett.* **1983**, *24* (4), 391−4.

(28) Converting the alcohol to a good leaving group using *p*-toluenesulfonyl chloride, methanesulfonyl chloride, or trifluoromethanesulfonic anhydride resulted in lower yields favoring the elimination product. Other nitrogen sources (tetramethylguanadinium azide, benzylamine, phthalimide) did not improve the yield.

(29) Lipinski, C. A. Bioisosterism in Drug Design. *Annu. Rep. Med. Chem.* **1986**, *21*, 283−91.

(30) For the preparation of the vanadium trichloride reagent, see: Manzer, L. E. Tetrahydrofuran Complexes of Selected Early Transition Metals. *Inorg. Synth.* **1982**, *21*, 135−40.

(31) For the preparation of the Zn−Cu couple, see: Smith, R. D.; Simmons, H. E. Norcarane (Bicyclo[4.1.0]heptane). *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. No. V, pp 855−858. Alternatively, Zn dust (Aldrich, −325 mesh/<10 μm) can also be used to achieve similar results.

(32) The indole nitrogen was protected with a benzyl group to facilitate proper pinacol coupling of (*R*)-*N*-Cbz-tryptophan aldehyde according to Scheme 1. Both the benzyl group and the acetonide were removed using 12 equiv of $AlCl_3$ at 50 °C for 5 h according to Tsuji, T.; Kataoka, T.; Yoshioka, M.; Sendo, Y.; Nishitani, Y.; Hirai, S.; Maeda, T.; Nagata, W. Synthetic Studies on β-Lactam Antibiotics. VII. Mild removal of the Benzyl Ester Protecting Group with Aluminum Trichloride. *Tetrahedron Lett.* **1979**, *30*, 2793−6.

(33) This compound was prepared by catalytic hydrogenation of the parent unsubstituted cyclic urea used to prepare DMP 323 according to Stocker, J. H. Rhodium-Catalyzed Nuclear Hydrogenation of α-Substituted Benzyl Alcohols and Esters. A Useful Procedure for Establishing Configurations. *J. Org. Chem.* **1962**, *27*, 2288−9.

(34) Erickson-Viitanen, S.; Klabe, R. M.; Cawood, P. G.; O'Neal, P. L.; Meek, J. L. Potency and Selectivity of Inhibition of the HIV Protease by a Small Nonpeptide Cyclic Urea, DMP 323. *Antimicrob. Agents Chemother.* **1994**, *38*, 1628−34.

(35) Bacheler, L. T.; Paul, M.; Jadhav, P. K.; Otto, M.; Stone, B.; Miller, J. An Assay for HIV RNA in Infected Cell Lysates, and Its Use for the Rapid Evaluation of Antiviral Efficacy. *Antiviral Chem. Chemother.* **1994**, *5* (2), 111−21.

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