Nonsymmetrically Substituted Cyclic Urea HIV Protease Inhibitors

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A series of nonsymmetrically substituted cyclic ureacarboxamides was synthesized and evaluated for antiviral activity as a function of the inhibition of HIV-protease. Selected protease inhibitors were also evaluated for oral bioavailability. The synthesis, pharmacology, quantitative structure−activity relationship (QSAR), and pharmacokinetics for the series will be discussed.

Introduction

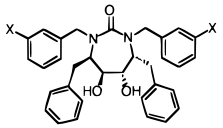
The viral encoded aspartyl protease of the human immunodeficiency virus (HIV) is responsible for the processing of the viral polyprotein precursor to the mature structural proteins and enzymes that comprise the virus particle. Since correct processing of the viral polypeptides is essential for the production of infectious virus, HIV protease inhibitors represent a potential target for therapeutic agents that may be effective in the treatment of autoimmune disease syndrome (AIDS).

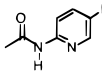
During our attempt to discover novel orally bioavailable HIV protease (HIV PR) inhibitors that might be useful in the treatment of AIDS, members of these laboratories synthesized the cyclic urea DMP450 (X = 3-NH_2 $MeSO_3H$). DMP450 was found to inhibit both HIV PR with a K_i = 0.31 nM and viral replication with an IC_{90} = 125.0 nM. Additionally, DMP450 was found to have a desirable bioavailability profile with a F% = 79.2 (see Table 1). Our objective was to synthesize more a potent cyclic urea (K_i < 0.030 nM and IC_{90} < 30 nM) than DMP450 but with comparable pharmacokinetic profile.

Chemistry

The syntheses of the symmetrically substituted cyclic ureas (**1a**−**c**) were accomplished using a modification of the method described by Basha et al.[1] where the ester **Ia**[2] was reacted with excess dimethylaluminum amide [$(CH_3)_2AlNHR$] prepared from equal molar amounts of trimethylaluminum [$(CH_3)_3Al$] and the amine (RNH_2) in dichloroethane, and refluxed until chromatographic methods indicated no **Ia**[2] remained. The method is illustrated in Scheme 1 and is referred to as the Weinreb Method. The nonsymmetrically substituted monocarboxamides were synthesized as shown in Scheme 2. Generally, the appropriate methylisourea (**Ib**) was alkylated with a substituted benzyl halide ($P2CH_2\dot{X}$) using NaH in anhydrous DMF. The resulting N-substituted benzylisourea (**II**) was treated with methyl 3-(bromomethyl)benzoate in acetonitrile to give the disubstituted cyclic urea (**III**). Intermediate **III** was treated with a dimethylaluminum amide[1] to give the corresponding amide (**IV**). Treating **IV** with dilute HCl produced the desired mixed pendent cyclic urea **V**. The ester **III** was saponified to give the benzoic acid derivative **IIIb** which was coupled with R^1NH_2 using *N*,*N*-dicyclohexylcarbodiimide-type reagents and conditions to give **IV**. The structural components of these compounds are shown in Table 2.

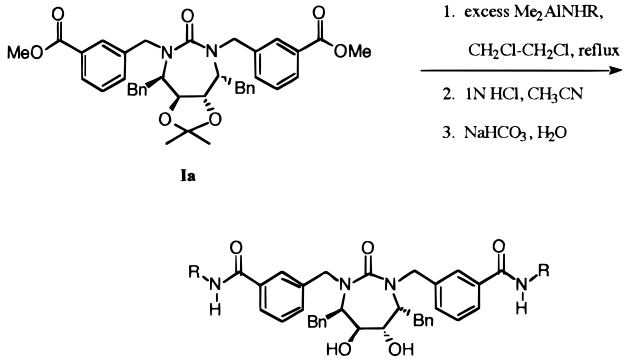
Table 1. Pharmacological and Pharmacokinetic Profile for Selected Anti-HIV *N*,*N*′-Bis-Substituted Cyclic Ureas[a]



	DMP450	1a	1b	1c
X	NH_2 $MeSO_3H$			
Parameter				
K_i, nM	0.310	0.043	0.011	0.018
IC_{90}, nM	125.0	2.8	3.1	3.5
CL, L/h/kg	0.2	4.2	4.0	2.8
Vss, L/kg	1.3	10.3	4.5	3.0
$t_{1/2}$, iv, h	3.6	1.1	1.0	0.8
C_{max}, μg/mL	6.0	<0.2	0.1	0.4
$t_{1/2}$, po, h	2.5	nd	nd	nd
%F	79.2	nd	nd	nd

[a] iv dosing was at 5.0 mg/kg and po dosing was at 10 mg/kg.

Scheme 1. Synthetic Approach to the Symmetrical Carboxamides **1a**−**c**



Pharmacology

The K_i values were determined with recombinant single-chain dimeric HIV protease and a fluorescent substrate (see Cheng et al.[3]) The use of single-chain dimeric protease allows enzyme concentrations as low

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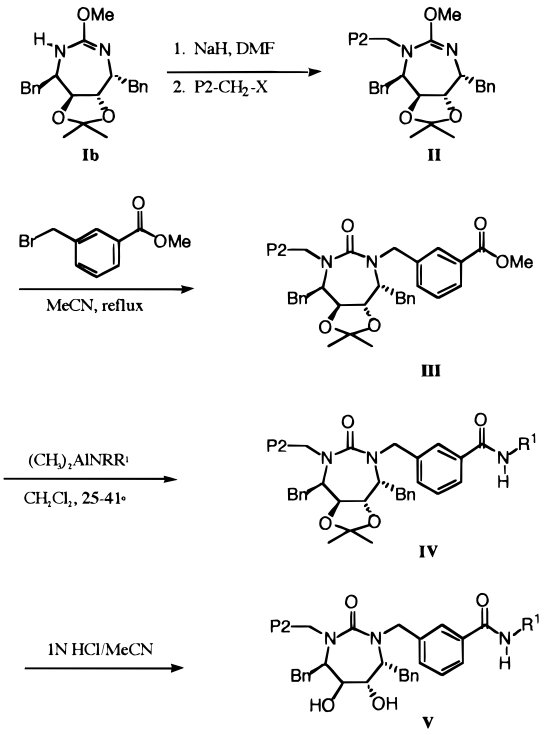
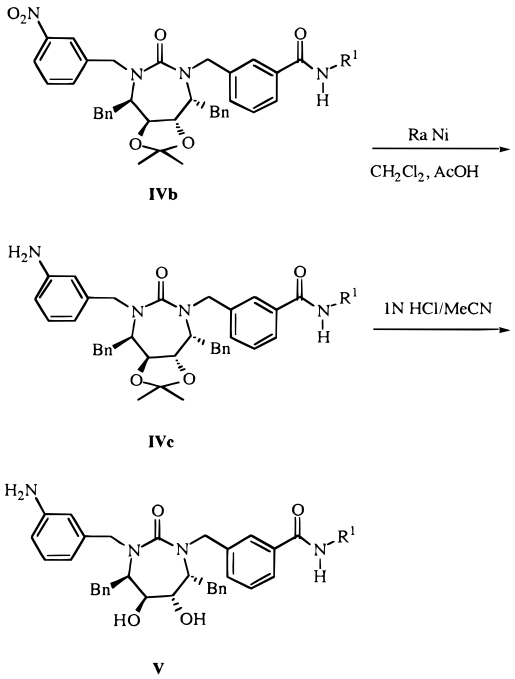
Scheme 2. Synthetic Approach to the Nonsymmetrical Carboxamides

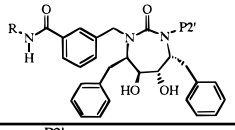


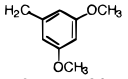
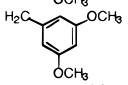
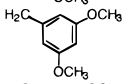
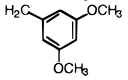
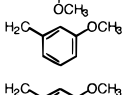
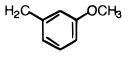
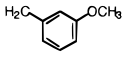
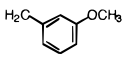
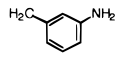
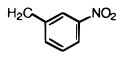
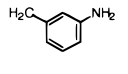
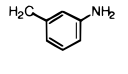
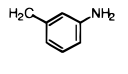
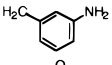
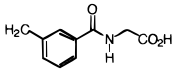
Scheme 3. Synthetic Approach to the Anilinecarboxamides



as 0.0625 nM to be used. Reaction products were separated by HPLC with a Pharmacia Mono Q anion-exchange column, and the product was quantified by fluorescence. The ability of test compounds to block cleavage of the HIV-1 gag polyprotein was assessed with [^{35}S]methionine-labeled *in vitro* translation product corresponding to gag p17 plus the first 78 amino acids of gag p24 and recombinant HIV PR as described by Erickson-Viitanen et al.[4] K_i values were measured with 62.5−250 pM HIV PR dimer and 1−10 nM inhibitor. Each compound was assayed at least twice, and the mean values for the experimental compounds are reported in Table 3. The standard deviation (sd) for the assay has been found to be $<\pm 40\%$. The K_i values for a series of reference compounds are also included in Table 3.

Table 2. Structural and Physicochemical Data for the Nonsymmetrically Substituted Cyclic Ureas



cmpd	R	P2'	mp, °C	% yield	Analysis
2			133-136	99	$C_{51}H_{52}N_4O_9$ 1.5H_2O
3			151-153	40	$C_{40}H_{41}N_5O_6$
4			236-238	42	$C_{42}H_{44}N_4O_6$ 0.5H_2O
5			207-209	43	$C_{42}H_{44}N_4O_6$ 0.5H_2O
6			215-218	31	$C_{41}H_{42}N_4O_6$ 0.5H_2O
7			112 dec	32	$C_{39}H_{39}N_5O_5$
8			238-240	35	$C_{41}H_{42}N_4O_5$ 1.5H_2O
9			243-245	28	$C_{41}H_{42}N_4O_5$ 0.5H_2O
10			223-225	59	$C_{40}H_{40}N_4O_5$ 0.5H_2O
11			230-232	17	$C_{40}H_{41}N_5O_4$ 0.5 H_2O
12			235-238	<20	$C_{39}H_{37}N_5O_6$ 2H_2O
13			154-157	13	$C_{39}H_{39}N_5O_7$
14			135 dec	39	$C_{41}H_{40}N_6O_4$
15			166 dec	26	$C_{37}H_{38}N_6O_4$
16	CH_2-CN		102-105	82	$C_{38}H_{44}N_4O_4$

HIV RNA Assay.[5] The assay determines cell associated viral RNA levels 3 days after infection of susceptible T-cell lines grown in individual microtiter wells. Viral RNA was quantified by a sandwich hybridization assay, the first step of which was performed directly in crude infected cell lysates prepared in quinaldinium isothiocyanate. Levels of cell-associated viral RNA were shown to correlate with the yield of infectious virus and this correlation formed the basis of the test. Antiviral potencies of a large series of compounds tested in this RNA hybridization assay correlated closely with potency values determined by a sensitive but slower and more labor-intensive yield reduction assay. Both laboratory strains and selected clinical isolates of HIV can be

Table 3. Pharmacological, Chemical Characteristics, and Physiochemical Data for the Cyclic Ureas and Reference Compounds

compd	K_i (nM)	IC_{90} (nM)	log P HPLC	CLOGP	CMR	MW, anhydrous	ϑ_{NH}
2	2.511	743.1	4.84	6.10	19.49	687.80	11.14
3	1.900	281.7	5.59	7.27	20.16	700.84	10.76
4	0.700	281.7	5.69	7.27	20.16	700.84	10.78
5	0.860	129.3	5.20	6.77	19.70	686.82	10.77
6	0.038	91.2	4.75	6.01	18.87	657.77	11.15
7	0.069	41.6	5.51	7.18	19.55	670.82	10.98
8	0.053	42.7	5.54	7.18	19.55	670.82	10.67
9	0.047	30.0	5.06	6.68	19.08	656.79	10.76
10	0.075	16.5	4.47	6.03	19.30	655.80	10.66
11	0.096	97.5	5.05	6.50	19.19	671.75	10.75
12	0.410	114.4	5.28	6.74	20.75	620.80	6.45
13	0.016	20.2	3.77	4.86	18.62	642.76	11.12
14	0.023	13.2	4.95	6.42	19.23	680.81	10.22
15	0.012	26.2	3.39	4.82	18.27	630.75	11.75
16	0.024	741.0	2.44	3.40	19.09	689.77	8.93
						ref	**9.21**
DMP323	0.32	114.6	3.56	4.75	16.53		na
DMP450	0.31	125.0	3.17	4.37	16.04		na
VX478	0.17	46.0		3.19	13.53		
ABT538	0.37	76.0		3.77	20.12		
Ro31-8959	0.25	10.4		4.57	19.05		
MK-639	0.37	50.0		2.63	17.81		

detected in this RNA hybridization assay. Results are reported as IC_{90} (the concentration of antiviral compound required to inhibit HIV RNA synthesis by 90%). Initial results are reported in microgram per milliliter (μg/mL) and converted to nanomolar (nM) for structure−activity relationship studies (Table 3). The assay provides a rapid, high-capacity assay for evaluating the potency of anti-HIV compounds. The standard deviation (sd) for the assay has been found to be $<\pm 37\%$. The data obtained on reference compounds are listed in Table 3.

Cytotoxicity TC_{50}. Compound cytotoxicity was designated as TC_{50}, which is defined as the concentration of compound that produced a 50% reduction in the number of viable cells as determined by the metabolism of a tetrazolium dye. None of the compounds in this report had $TC_{50} < 50$ μg/mL. A correct interpretation of the RNA assay requires that test molecules not be cytotoxicity at RNA assay dose levels.

Pharmacokinetic Studies (PK). Pharmacokinetic methodologies in these laboratories have previously been reported.[2,6,7] The study was conducted in the female Beagle dog. The oral study (po) at 10.0 mg/kg was conducted in three dogs, and the intravenous study (iv) was conducted at 5.0 mg/kg. The vehicle used was PEG400, water, and EtOH (60/30/10). In the current study, the concentration was 10.0 mg/mL, and the dosing volume was 1.0 mL/kg. The iv formulation was the same as the oral: 10.0 mg/mL with dosing volume of 0.5 mL/kg. The method was validated in dog plasma at a concentration range 0.10−50.0 μg/mL.

Statistical Methods and QSAR Parameters. Statistical analyses were conducted using JMP v3.0.2 by SAS Institute, Cary, NC. The following statistical measures were used: *n*, the number of samples in the regression; *r*, correlation coefficient; *s*, root mean square error of the regression; *F*-ratio; and the probability of finding a greater *F*-ratio.

Hansch and Leo[8] have stated that "...the structural changes that affect the biological activities of a set of congeners are of three major types: electronic, steric, and hydrophobic". In accordance with this philosophy, we chose the computer-calculated lipophilicity (CLOGP) to represent the hydrophobic component, computer-calculated molar refractivity (CMR) or the molecular weight of the anhydrous compound (MW/100)[9] to represent the steric component, and the proton nuclear resonance chemical shift (ϑ_{NH}) of the amide proton (CONHR, ppm) to represent the electronic component.

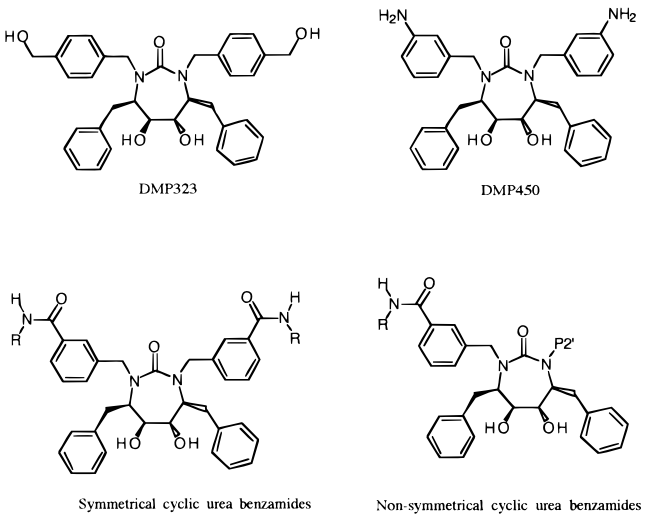


Figure 1. Anti-HIV cyclic ureas.

The CLOGP and CMR values were obtained using MedChem Software v3.0, Pomona College, Claremont, CA. It has been suggested that the CLOGP values for some of the compounds in this series were "unrealistically high". Consequently, a comparison was made between CLOGP and HPLC measured log *P* (see Experimental Section) and found to be in excellent agreement ($r^2 = 0.99$) where $\log P_{HPLC} = 0.83\text{CLOGP} - 0.39$ (see ref 10).

The proton nuclear resonance chemical shift (ϑ_{NH}) of the amide proton (CONHR, ppm) was used to represent potential electronic effects that might be associated with the R group. The chemical shift of the amide proton was used as a parameter because previous findings and molecular modeling studies on the symmetrical CUs[11] demonstrated the importance of the presence and nature of the amide proton for protease inhibition. Method and values are listed in the Experimental Section. This parameter has also been calculated by computer and found to be in excellent agreement with the observed values (data not included).

Discussion

Previous efforts in this laboratory resulted in the synthesis of a series of bisbenzamides cyclic ureas as exemplified by **1a**−**c**.[11] These bisamides were found to be some of the most potent inhibitors of HIV PR and viral replication (see Table 1). Unfortunately, the bisamides did not have the desired oral bioavailability profile as shown in Table 1. The previous study suggested that the "larger" symmetrically substituted cyclic ureas had poor gastrointestinal dissolution which resulted in poor absorption which resulted in less than desirable oral bioavailability. Dissolution and GI absorption were not problems with the smaller cyclic ureas such as DMP323[6,7,12−15] (X = 4-CH_2OH) or DMP450 (X = 3-NH_2) (see Figure 1). One attempt to enhance the solubility of the compounds was to synthesize nonsymmetrical cyclic ureas (increase the entropy, increase solubility).

Table 4. Cross-Correlations for the Components of Eq 1a

variable	log(1/K_i)	CLOGP	CMR	ϑ_{NH}
log(1/K_i)	1.000	−0.636	−0.801	0.209
CLOGP		1.000	0.712	−0.087
CMR			1.000	−0.608
ϑ_{NH}				1.000

Our first attempt to prepare nonsymmetrical cyclic ureas involved the substitution of one of the benzamides of **1c** with 5-(1,3-dimethoxyphenyl) (DMP) to produce **2** resulted in a loss of both protease inhibitory activity and antiviral replication activity. Similarly, the "half amide" **3** (R = 2-(5-Me-Pyr) and R′ = DMP) and 5 (R = 2-Pyr and R′ = DMP) were also less active than the corresponding bisamides **1b** and **1a**, respectively. These data clearly indicated that the attempt to alter the symmetry of the cyclic ureas with the DMP moiety resulted in loss of protease inhibition and that antiviral activity, and regardless of bioavailability, would not be of further interest. Substituting 3-methoxyphenyl (MMP) for DMP resulted in **6**, **7**, **8**, and **9**, respectively. Clearly the mixed amides of MMP were superior antiviral agents to the corresponding DMP derivatives and, in most cases, were superior to the reference compounds shown in Table 3. However, they did not meet our pharmacological objective of having a K_i < 0.030 nM and an IC_{90} < 30 nM.

Since DMP450 (P2 = CH_2(3-NH_2Ph)) was a moderate inhibitor of viral protease and replication with the desired PK profile, we synthesized a series of "aniline−amides" (**10**, **12**, **13**, **14**, and **15**). The aniline-amide **10** met our requirements for viral replication inhibition (IC_{90} = 16.5 nM) but failed as a protease inhibitor (K_i = 0.075 nM), and **12** failed in both respects. We were successful in meeting our pharmacological objectives with the synthesis of the more polar aniline−amides **13** (K_i = 0.016 nM, IC_{90} = 20.2 nM), 14 (K_i = 0.023 nM, IC_{90} = 13.2 nM), and 15 (K_i = 0.012 nM, IC_{90} = 26.2 nM).

Anti-Protease and Antiviral QSAR. In an attempt to understand the physicochemical requirements for HIV protease inhibition (log(1/K_i)), a stepwise multiple regression was conducted on compounds **2**−**15** (Table 2) using the molecular parameters $(CLOGP)^2$, CLOGP, $(CMR)^2$, CMR, and ϑ_{NH} (see Table 3). The proton NMR chemical shift (ϑ_{NH}) of the amide proton was used as an electronic parameter.[16−20] This study then resulted in eq 1a and the corresponding correlation matrix in Table 4. Unfortunately, CLOGP and CMR were highly cross-correlated (r^2 = 0.71) as was CMR and ϑ_{NH} (r^2 = 0.61). The quadratic term for CLOGP in eq 1a would suggest that for this series of compounds, the optimum molecular lipophilicity occurred at $CLOGP_0$ = 4.442. The lack of such a term for size or volume (CMR) would suggest that the size of the molecules was not near optimum. The implication of eq 1a was that smaller more lipophilic carboxamides with less of a chemical shift of the amide proton produce the better protease inhibitor. The outliers to eq 1a were 2 (K_i obs = 2.511 nM vs K_i pred = 0.948 nM) and **10** (K_i obs = 0.075 nM, sd = ±0.010, n = 3; K_i pred = 0.197 nM). The reasons for the differences for **10** are not known. Within the framework of the error in the assay and the standard error of the regression, the differences between the observed versus the predicted K_i values for **2** are not significant; qualitatively, they are the same. The observed versus predicted K_i values using eq 1a are shown in Table 5 and 6. Compound **16** is a nonsymmetrical diamide that was synthesized and added to the regression analysis as a "bridge" between the bisamides (**1a**−**c**) and the monoamides (**2**−**15**).

Table 5. Cross-Correlations for the Components of Eq 2a

variable	log(1/IC_{90})	logK_i	CLOGP
log(1/IC_{90})	1.000	−0.646	0.087
log K_i		1.000	0.547
CLOGP			1.000

$$\log(1/K_i) = 0.221(\pm0.076)CLOGP^2 - 1.963(\pm0.789)CLOGP - 2.344(\pm0.337)CMR - 0.592(\pm0.118)\vartheta_{NH} + 56.052(\pm8.195) \quad (1a)$$

$n = 15$ $r = 0.941$ $s = 0.306$
$F = 19.406$ prob > $F = 0.000$
$CLOGP_0 = 4.44$

When $(MW/100)^2$ and (MW/100) replaced CMR^2 and CMR in a stepwise multiple regression, respectively, eq 1b resulted which was statistically less robust than eq 1a. However, (MW/100) was not highly correlated with CLOGP (r^2 = 0.36) as was observed with CMR, and eq 1b did not contain a term for ϑ_{NH}. The only outlier to eq 1b was **14** (K_i obs = 0.023 nM vs K_i pred = 0.198 nM). The reason for this difference is not known, but when **14** was removed from the regression model, the correlation was improved (r = 0.92).

$$\log(1/K_i) = 0.190(\pm0.123)CLOGP^2 - 2.377(\pm1.346)CLOGP - 7.398(\pm2.308)(MW/100)^2 + 96.294(\pm30.473)(MW/100) - 304.541(\pm99.365) \quad (1b)$$

$n = 15$ $r = 0.852$ $s = 0.474$
$F = 6.599$ prob > $F = 0.007$

A similar approach was applied to viral replication inhibition (log(1/IC_{90})) using the parameters $(CLOGP)^2$, CLOGP, $(CMR)^2$, CMR, and log K_i obs to produce eq 2a which was a modest descriptor of viral replication inhibition for this data set. The correlation matrix for eq 2a is shown in Table 5. The equation was of limited predictive value since it relied on measured protease inhibition activity (log K_i obs).

$$\log(1/IC_{90}) = -0.217(\pm0.080)CLOGP^2 + 2.778(\pm0.873)CLOGP + 0.329(\pm0.262)CMR - 0.813(\pm0.191)\log K_i\text{obs} - 16.440(\pm0.6.479) \quad (2a)$$

$n = 15$ $r = 0.867$ $s = 0.336$
$F = 7.589$ prob > $F = 0.004$
$CLOGP_0 = 6.40$

In an attempt to expand the utility of the relationship expressed in eq 2a, we conducted a stepwise multiple regression using $(CLOGP)^2$, CLOGP, $(CMR)^2$, CMR, and the logarithm of the predicted K_i (log K_i pred) from eq 1a. This study resulted in eq 2b which was statistically less satisfying than eq 2a. The principle outlier to eq 2b was **10** (R = 2-(5-MePyr)) which was predicted to be less active (IC_{90} = 77.6 nM) than observed (IC_{90} = 16.5 nM, sd = ±1.06, n = 3). The reason for the failure of

Table 6. Found Versus Predicted Anti-Protease (K_i) and -Viral (IC_{90}) Activity

IN no.	obs K_i (nM)	pred K_i (eq 1a)	pred K_i (eq 1b)	obs IC_{90} (nM)	pred IC_{90} (eq 2a)	pred IC_{90} (eq 2b)	pred IC_{90} (eq 2c)
2	2.511	0.948	0.440	743.1	503.4	198.9	297.2
3	1.900	1.493	1.964	281.7	574.3	349.9	348.0
4	0.700	1.534	1.964	281.7	255.0	355.7	354.5
5	0.860	0.458	0.351	129.3	250.1	132.7	151.5
6	0.038	0.040	0.046	91.2	26.3	29.5	35.3
7	0.069	0.093	0.059	41.6	55.2	60.9	51.2
8	0.053	0.061	0.059	42.7	44.5	47.1	38.3
9	0.047	0.020	0.042	30.0	35.0	19.2	17.8
10	**0.075**	**0.197**	0.044	16.5	33.2	**77.6**	
11	0.096	0.052	0.089	97.5	51.4	33.4	35.5
12	0.410	0.394	0.181	114.4	60.3	120.0	137.0
13	0.016	0.032	0.021	20.2	28.0	58.2	74.8
14	**0.023**	0.038	**0.198**	13.2	14.9	27.2	29.1
15	0.012	0.011	0.035	26.2	30.4	32.0	37.8
16	0.024	0.019	0.016	741.0	384.4	510.0	447.7

eq 2b to correctly predict the IC_{90} for **10** is believed to be the result of the poorly predicted K_i value from eq 1a (K_i obs = 0.075 nM, sd = ±0.010, n = 3; K_i pred = 0.197 nM).

$$\log(1/IC_{90}) = -0.166(\pm 0.080)\text{CLOGP}^2 + 2.112(\pm 0.885)\text{CLOGP} - 0.608(\pm 0.180)\log K_i \text{ pred} - 9.019(\pm 2.375) \quad (2b)$$

$n = 15$ $r = 0.797$ $s = 0.389$
$F = 6.372$ prob > $F = 0.009$
$\text{CLOGP}_0 = 6.36$

When **10** was removed from the regression, eq 2c resulted which was a marginal improvement over eq 2b. Equations 2a−c would suggest that the optimum CLOGP for this class of compounds would lie in the range 6.4−6.9. The observed versus predicted IC_{90} values for eqs 2a−c are listed in Table 6.

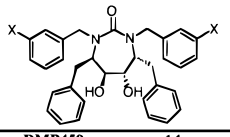
$$\log(1/IC_{90}) = -0.114(\pm 0.073)\text{CLOGP}^2 + 1.581(\pm 0.799)\text{CLOGP} - 0.685(\pm 0.159)\log K_i \text{ pred} - 7.891(\pm 2.107) \quad (2c)$$

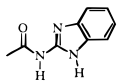
$n = 14$ $r = 0.851$ $s = 0.335$
$F = 8.727$ prob > $F = 0.004$
$\text{CLOGP}_0 = 6.93$

Pharmacokinetics

Two compounds (**15** and **14**) met our pharmacological objectives and were subjected to pharmacokinetic studies in the female Beagle dog. The results are shown in Table 7. The clearance for **15** was between that determined for **14** and DMP450. The volume of distribution was ~4 L/kg which was 3−4 times higher than that determined for **14** and DMP450. This result indicated that **15** distributed into tissues much more than the other two compounds. However, the site of increased distribution remains to be determined. One beneficial consequence was the prolongation of half-life. The observed a half-life for **15** was 5.6 h after iv and 10 after po dosing. At the same time, due to greater distribution to tissues, we had expected lower plasma concentrations. The C_{max} for **15** , after 10 mg/kg dose, was 0.9 μg/mL. Although it was lower than that for **14** and DMP450, and considering the longer half-life, the overall PK profile represented an improvement over the bisamides and DMP450.

Table 7. Pharmacological and Pharmacokinetic Profile for Selected Anti-HIV Nonsymmetrically Substituted Cyclic Ureas



		DMP450	14	15
	X	NH_2	NH_2	NH_2
		$MeSO_3H$		
	X'	NH_2		
		$MeSO_3H$		
Parameter				
K_i, nM		0.310	0.023	0.012
IC_{90}, nM		125.0	13.2	26.2
Dose, mg/kg, iv		10.0	5.0	5.0
CL, L/h/kg		0.2	0.8	0.5
Vss, L/kg		1.3	1.0	4.0
$t_{1/2}$, iv, h		3.6	0.9	5.6
Dose, mg/kg, po		10.0	10.0	10.0
C_{max}, μg/mL		6.0	5.5	0.9
$t_{1/2}$, po, h		2.5	1.5	10.3
%F		79.2	109.0	68.0

Conclusion

By incorporating the P2 substituent of DMP450 (CH_2(3-NH_2Ph)) and the P2′ substituent of selected biscarboxamides (CH_2(3-RNHCOPh)), we have been successful in synthesizing cyclic urea "aniline−amides" with the desired biochemical properties of both "parents": excellent inhibitory activity against the protease (K_i < 0.030 nM) and viral (IC_{90} < 30.0 nM) and good to excellent oral bioavailability (see Tables 1 and 5).

Limited QSAR studies on this series of cyclic ureas suggest that protease inhibition is related to electronic property of the amide proton as determined by NMR chemical shift and the size and lipophilicity of the molecule (eq 1a). A large portion of the antiviral activity could be explained by the inhibition of the protease; and the size and, possibly more importantly, the lipophilicity of the molecule. However, the QSAR studies demonstrated that the optimum lipophilicity for protease inhibition (CLOGP_0 = 4.44) was different from that

required to inhibit viral replication ($CLOGP_0 = 6.36$). These differences make it more difficult to optimize both pharmacological activities for the same molecule. Similar differences and difficulties may exist for other properties considered in selecting a compound for further development.

The selection of **14** or **15** as possible development candidates will also depend on other characteristics such as protein binding, toxicity, and activity against selected HIV mutants. All such studies are presently under investigation

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were recorded with a Varian-300S spectrometer, IR spectra were recorded with a Perkin-Elmer 1650 FTIR spectrophotometer, UV spectra were obtained with a Cary 2415 spectrophotometer, optical rotations (OR) were determined on a Perkin-Elmer 241 polarimeter, and mass spectra (MS) were obtained using the Hewlett-Packard HP5988A GC−MS system. Analytical HPLC determinations were obtained with a system composed of two Varian 2510 pumps and a Varian 2550 variable-wavelength detector using a 4.6 × 250 mm Zorbax ODS column and CH_3CN−water mobile phase, HPLC log *P* determinations were obtained with a Varian STAR-9000 system using a YMC C18 column and 55% MeOH and 45% pH 7.0 phosphate buffer as mobile phase. Thin layer chromatography (TLC) was performed on silica gel plates.

Synthesis of Intermediate Methylisourea (Ib). A solution of [3a*S*-(3aα,4*β*,8α,8a*β*)]-hexahydro-2,2-dimethyl-4,8-bis-(phenylmethyl)-6*H*-1,3-dioxolo[4,5-*e*][1,3]diazepin-6-one (**I**[2]) (3.00 g, 8.19 mmol) in dichloroethane (20 mL) was treated with methyl trifluoromethanesulfonate (1.02 mL, 9.01 mmol) and refluxed for 16 h under anhydrous conditions. The solution was cooled to room temperature, diluted with CH_2Cl_2 (100 mL), and washed with saturated $NaHCO_3$. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the desired isourea as a foam (3.10 g, 99% yield). The foam was inspected by TLC ($CHCl_3$−EtOAc, 3:2) and found to be homogeneous, and used without further purification: IR (Nujol) no C=O; MS (NH_3-DCI) *m/e* 381 (M + 1); $C_{23}H_{28}N_2O_3$, MW 380.49.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-*1H*-1,3-diazepine-1,3(*2H*)-diyl]bis-(methylene)]bis[*N*-2-pyridinylbenzamide] (1a). The compound was synthesized using a modification of the Weinreb method.[1] A solution of 2-aminopyridine (100 mmol) in dichloroethane (50 mL) was treated with 2 M trimethylaluminum (TMA) (50.0 mL, 100 mmol), stirred at room temperature for 10 min, and added to a solution of **Ia**[2] (5.00 g, 7.54 mmol) in dichloroethane (150 mL). The mixture was refluxed under dry nitrogen for 25 h and inspected by TLC ($CHCl_3$−EtOAc, 3:2) which showed no **Ia**. The mixture was diluted with 500 mL of CH_2Cl_2 and 500 mL of water, stirred for 1 h, and filtered through a bed of Celite. The organic phase was washed with water (50 mL), 5% $NaHCO_3$ (2 × 25 mL), water, and brine; dried over $MgSO_4$; filtered; and concentrated to give the bisamide acetonide as an off-white solid.

The acetonide (1.93 g, 2.45 mmol) in 20 mL CH_3CN was treated with 10 mL of 1 N HCl and stirred at room temperature until no starting material remained as demonstrated by TLC ($CHCl_3$−MeOH, 9:1). The mixture was concentrated *in vacuo* at 60 °C to give a white solid which was triturated with 10 mL of water and placed in the cold for 16 h. The resulting crystals were collected by filtration, washed with a small amount of cold water, and air-dried to give the desired product in 77% (1.415 g) yield: mp 158−161 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.77 (dd, 2H, Ar′CH), 2.99 (d, J = 12.4 Hz, 2H, Ar′CH), 3.07 (d, J = 14.3 Hz, 2H, NCH), 3.55 (s, 2H, OCH), 3.60 (d, J = 11.7 Hz, 2H, Ar′CCH), 4.68 (d, J = 14.3 Hz, 2H, NCH), [6.95 (d, 2H), 7.22 (m, 6H), 7.4 (m, 4H), 7.52 (dd, 2H), 7.92 (s, 2H), 8.04 (d, 2H), 8.16 (m, 4H), 8.45 (d, 2H), Ar], 11.59 (s, 2H, NH); IR (Nujol) 3334 (OH), 1676 (C=O), 1640 (C=O) cm^{-1}; MS (NH_3-DCI) *m/e* 747 (M + 1); $[\alpha]^{20}_D$ +57.14° (*c* = 0.098, DMSO). Anal. Calcd for $C_{45}H_{42}N_6O_5$·2HCl, MW 819.80: C, 65.93; H, 5.41; N, 10.25. Found: C, 65.72; H, 5.64; N, 10.10.

A solution of the dihydrochloride salt (0.240 g, 0.030 mmol) in 10 mL of acetonitrile was made alkaline with 5% $NaHCO_3$ and stirred at room temperature for an additional 3 h. The resulting white solid was collected by filtration, washed with water, and air-dried to give the desired product as the free base in 91% (0.2046 g) yield: ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.78 (dd, 2H, Ar′CH), 3.0 (m, 4H, Ar′CHCNCH), 3.5 (m, 4H, OCHCH), 4.64 (d, J = 13.9 Hz, 2H, NCH), 5.16 (s, 2H, OH), [6.95 (d, 4H), 7.2 (m, 8H), 7.37 (d, 2H), 7.44 (dd, 2H), 7.85 (m, 4H), 7.95 (d, 2H), 8.18 (d, 2H), 8.40 (d, 2H), Ar], 10.77 (s, 2H, NH); IR (Nujol) 3397 (OH), 1678 (C=O), 1635 (C=O) cm^{-1}; UV−vis (c = 0.0149 mg/mL, MeOH) λ_{max} 281 (29 686), 246 (25 352), 214 (57 591) nm; MS (NH_3-DCI) *m/e* 747 (M + 1). Anal. Calcd for $C_{45}H_{42}N_6O_5$, MW 746.78: C, 72.37; H, 5.67; N, 11.25. Found: C, 71.98; H, 5.98; N, 11.06.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-*1H*-1,3-diazepine-1,3(*2H*)-diyl]bis-(methylene)]bis[*N*-(5-methyl-2-pyridinyl)benzamide] (1b). By substituting 2-amino-5-picoline in the Weinreb method, the desired product was obtained in 13% (0.157 g) yield: mp 132−133 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.28 (s, 6H, $ArCH_3$), 2.78 (dd, 2H, Ar′CH), 3.0 (m, 4H, Ar′CHCNCH), 3.45 (2, OH), 3.5 (m, 4H, Ar′CCHCHO), 4.68 (d, J = 14.3 Hz, 2H, NCH), [6.96 (d, 4H), 7.22 (m, 6H), 7.37 (d, 2H), 7.46 (dd, 2H), 7.68 (m, 2H), 7.87 (s, 2H), 7.95 (d, 2H), 8.08 (d, 2H), 8.22 (s, 2H), Ar], 10.72 (s, 2H, NH); IR (Nujol) 3392 (OH), 1676 (C=O), 1646 (C=O) cm^{-1}; UV−vis (c = 0.0170 mg/mL, MeOH) λ_{max} 287 (28 399), 258 (24 980), 215 (50 962) nm; MS (NH_3-DCI) *m/e* 775 (M + 1), 388 (M + 2H)$^{2+}$; $[\alpha]^{20}_D$ +82.93° (c = 0.082, MeOH). Anal. Calcd for $C_{47}H_{46}N_6O_5$·0.5H_2O, MW 783.93: C, 72.01; H, 6.04; N, 10.72. Found: C, 71.84; H, 6.08; N, 10.47.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-*1H*-1,3-diazepine-1,3(*2H*)-diyl]bis-(methylene)]bis[*N*-2-pyrazinylbenzamide] (1c). By substituting 2-aminopyrazine in the Weinreb method for **1a**, the desired product was obtained in 58% (0.659 g) yield from **Ia**: mp 146−148 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.77 (dd, 2H, Ar′CH), 2.99 (d, J = 13.18 Hz, 2H, Ar′CH), 3.07 (d, J = 14.28 Hz, 2H, NCH), 3.55 (m, 4H, OCHCH), 4.69 (d, J = 14.28 Hz, 2H, NCH), 5.17 (s, 2H, OH), [6.95 (d, 4H), 7.22 (m, 6H), 7.42 (d, 2H), 7.50 (dd, 2H), 7.90 (s, 2H), 7.98 (d, 2H), 8.42 (d, 2H), 8.48 (d, 2H), 9.41 (s, 2H), Ar], 11.13 (s, 2H, NH); IR (KBr) 4312 (OH, 1686 (C=O), 1642 (C=O) cm^{-1}; UV−vis (c = 0.0210 mg/mL, MeOH) λ_{max} 298 (20 076), 284 (25 140), 245 (25 140), 217 (42 898) nm; MS (NH_3-DCI) *m/e* 749 (M + 1), 375 (M + 2)$^{2+}$; $[\alpha]^{20}_D$ +78.57° (c = 0.084, MeOH). Anal. Calcd for $C_{43}H_{40}N_8O_5$, MW 748.84: C, 68.97; H, 5.38; N, 14.96. Found: C, 68.70; H, 5.38; N, 14.72.

(4α,5α,6*β*,7*β*)-3-[[3-[(3,5-Dimethoxyphenyl)methyl]-hexahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-2-pyrazinylbenzamide (2). A suspension of 60% NaH in mineral oil (0.82 g, 20.46 mmol) in dry THF (50 mL) was treated with the cyclic urea[2] (5.00 g, 13.64 mmol) and stirred under dry nitrogen in an ice bath for 30 min. The suspension was treated with 3,5-dimethoxybenzyl chloride (3.82 g, 20.46 mmol) in dry THF (10 mL). The mixture was stirred in the ice bath for 5 min and at room temperature for 48 h and diluted with EtOAc (150 mL) and saturated NH_4-Cl (50 mL). The organic layer was washed with water, 5% $NaHCO_3$, water, and brine; dried over $MgSO_4$; filtered; and concentrated *in vacuo* to give a crude product containing mono- and disubstituted cyclic urea and unreacted starting cyclic urea. The crude product was column chromatographed on silica gel using EtOAc−hexane (1:1) to remove the disubstituted urea followed by straight EtOAc to recover the desired product. Appropriate fractions were combined and concentrated *in vacuo* to give the desired monoalkylated cyclic urea (6.91 g, 98% yield) as a foam: ^{1}H NMR (300 MHz, $CDCl_3$−TMS) δ 1.45 (d, 6H, CH_3CCH_3), 2.8 (m, 2H, Ar′CH and NCH), 3.05 (m, 3H, Ar′CH_2 and Ar′CH), [3.55 (m, 1H), 3.8 (m, 1H), 3.88 (m, 1H), 4.25 (m, 1H, CHCH(O)CH(O)CH]), 3.71 (s, 6H, OCH_3), 4.92 (d, 1H, NH), 5.06 (d, J = 14.7 Hz, 1H, NCH), [6.20

(d, 2H), 6.33 (m, 1H), 7.2−7.4 (m, 10H), Ar]; MS (NH_3-DCI) *m/e* 534 (M + NH_4) for $C_{31}H_{36}N_2O_5$, MW 516.64.

A mixture of the above monoalkylated cyclic urea (2.5 g, 4.84 mmol) and 60% NaH (0.252 g, 6.29 mmol) in dry DMF (25 mL) was stirred at room temperature for 30 min and treated with methyl 3-(bromomethyl)benzoate (1.22 g, 5.32 mmol) in dry DMF (2 mL). The mixture was stirred at room temperature until TLC (EtOAc−hexane, 1:3) showed no starting material. The mixture was poured into a mixture of cracked ice (250 g) and saturated NH_4Cl (75 mL). The mixture was stirred until the ice had melted, and the resulting solid was collected by filtration. The solid was dissolved in EtOAc (50 mL); washed with water, 5% $NaHCO_3$, water, and brine; dried over $MgSO_4$; filtered; and concentrated to an impure solid (TLC, EtOAc−hexane, 1:3). The crude product was column chromatographed on silica gel using EtOAc−hexane (1:4) as mobile phase. Two sets of fractions were collected and concentrated to constant weight: half ester fractions A, pure product (1.050 g); and fraction B, impure product (1.95 g) (90+% product by analytical HPLC). Fraction A was collected as a white foam in 33% (1.05 g) yield: ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 1.31 (2s, 6H, CH_3CCH_3), 2.7 (m, 1H, Ar′CH), 2.85 (m, 3H, Ar′CH), 3.00 (d, J = 13.9 Hz, 1H, NCH), 3.32 (d, J = 7.3 Hz, 1H, Ar′CCH), 3.40 (d, J = 14.3 Hz, 1H, NCH), 3.69 (s, 6H, $ArOCH_3$), 3.81 (s, 3H, CO_2CH_3), 3.9 (m, 1H, Ar′CCH), 4.03 (d, J = 8.4 Hz, 2H, OCH), 4.58 (“d”, J = 13.9 Hz, 2H, NCH), [6.31 (m, 2H), 6.39 (s, 1H), 6.85 (m, 2H), 7.05 (d, 2H), 7.23 (m, 6H), 7.45 (dd, 1H), 7.48 (d, 1H), 7.84 (m, 2H), Ar]; IR (KBr) 1724 (C═O), 1632 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 682 (M + NH_4) for $C_{40}H_{44}N_2O_7$, MW 664.80. Analytical HPLC: Zorbax ODS column F44558, 4.6 × 25 cm, flow rate 1 mL/min, water−acetonitrile, wavelength 256. Fraction B was also used in subsequent syntheses.

The above half ester (0.500 g, 0.752 mmol) was dissolved in 10 mL of dichloroethane and treated with a mixture of 2-aminopyrazine (0.946 g, 9.95 mmol) and 2 M trimethylaluminum (4.97 mL) in 10 mL of dichloroethane. The mixture was refluxed under dry nitrogen for 24 h, cooled to room temperature, and diluted with 150 mL of methylene chloride and 50 mL of water. The mixture was stirred for 30 min and filtered through a bed of Celite. The aqueous phase was decanted, and the organic phase was evaporated *in vacuo*. The residue was dissolved in EtOAc (50 mL), and the solution was washed with water (2 × 25 mL), 5% $NaHCO_3$ (25 mL), water (25 mL), and brine (25 mL); dried over $MgSO_4$; filtered; and concentrated to a gum. The crude intermediate was column chromatographed on silica gel (50 g) using EtOAc−hexanes (3:1) as solvent. Appropriate fractions were combined and concentrated to constant weight to give the desired intermediate as a pure white foam (0.33 g, 60% yield): ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.39 (d, 6H, CH_3CCH_3), 2.88 (dd, 1H, Ar′CH), 3.0 (m, 4H), 3.36 (d, J = 14.3 Hz, 1H, NCH), 3.72 (s, 6H, OCH_3), 3.78−4.02 (m, 5H), 4.87 (d, J = 14.3 Hz, 1H, NCH), 4.90 (d, J = 14.3 Hz, 1H, NCH), [6.25 (d, 2H), 6.33 (d, 1H), 7.02 (d, 2H), 7.17 (d, 2H), 7.23−7.40 (m, 6H), 7.47 (m, 2H), 7.64 (s, 1H), 7.82 (d, 1H), 8.29 (s, 1H), 8.38 (d, 1H), 8.49 (s, 1H), Ar], 9.68 (s, 1H, NH); IR (KBr) 3420 (NH), 1684 (C═O), 1630 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 728 (M + 1) for $C_{43}H_{45}N_5O_6$, MW 727.86.

The above intermediate (0.30 g, 0.412 mmol) was dissolved in 10 mL of acetonitrile, treated with 10 mL of 1 N HCl, and stirred at room temperature for 16 h. The mixture was diluted with 150 mL of water, stirred for 1 h, and filtered. The resulting white solid was washed with water and dried *in vacuo* to give the desired product in 74% (0.209 g) yield or 40% yield from the half ester: mp 151−153 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.7 (m, 2H, Ar′CH), 2.9−3.15 (m, 4H, Ar′CH and NCH), 3.5 (m, 3H), 3.58 (m, 2H), 3.69 (s, 6H, OCH3), 4.60−4.74 (2d, 2H, NCH), 5.16 (2s, 2H, OH), [6.23 (d, 2H), 6.39 (m, 1H), 6.94 (d, 2H), 7.11 (d, 2H), 7.16−7.38 (m, 6H), 7.42 (d, 1H), 7.50 (dd, 1H), 7.89 (s, 1H), 7.97 (d, 1H), 8.40 (m, 1H), 8.47 (m, 1H), 9.40 (s, 1H), Ar], 11.14 (s, 1H, NH); IR (KBr) 3412 (OH and NH), 1684 (C═O), 1640 (C═O) cm^{-1}; UV−vis (*c* = 0.0120 mg/mL, MeOH) λ_{max} 302 (10 145), 292 (11 349), 283 (14 959), 251 (13 240) nm; MS (NH_3-DCI) *m/e* 705 (M + NH_4); $[\alpha]^{20}_D$ +75.46° (c = 0.33, MeOH). Anal. Calcd for $C_{40}H_{41}N_5O_6$, MW 687.80: C, 69.85; H, 6.02; N, 10.18. Found: C, 69.59; H, 5.88; N, 9.87. Analytical HPLC: Zorbax ODS 4.6 × 250 mm column; solvent H_2O−CH_3CN; flow rate of 1 mL/min; detector at 256 nm.

(4α,5α,6*β*,7*β*)-3-[[3-[(3,5-Dimethoxyphenyl)methyl]-hexahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-(5-methyl-2-pyridinyl)-benzamide Hemihydrate (3). By substituting 2-amino-5-methylpyridine in the method for **2**, the desired product was obtained in 42% yield from the ester: mp 236−238 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.28 (s, $ArCH_3$), 2.71 (m, 2H, Ar′CH), 2.93−3.08 (m, 4H, Ar′CH and NCH), 3.37−3.60 (m, 4H, CHCHCHCH), 3.68 (s, 6H, OCH_3), 4.63 (d, J = 14.3 Hz, 1H, NCH), 4.70 (d, J = 13.9 Hz, 1H, NCH), 5.05 (broad s, 2H, OH), [6.23 (2, 2H), 6.39 (s, 1H), 6.94 (d, 2H), 7.1 (d, 2H), 7.2−7.46 (m, 8H), 7.68 (d, 1H), 7.86 (1, 1H), 7.94 (d, 1H), 8.06 (d, 1H), 8.22 (s, 1H), Ar], 10.76 (s, 1H, NH); IR (KBr) 3400 (OH), 3288 (NH), 1684 (C═O), 1616 (C═O) cm^{-1}; UV−vis (c = 0.0219 mg/mL, MeOH) λ_{max} 284 (14 465), 270 (12 481), 261 (11 969) nm; MS (NH_3-DCI) *m/e* 701 (M + 1); $[\alpha]^{20}_D$ +73.81° (c = 0.210, MeOH). Anal. Calcd for $C_{42}H_{44}N_4O_6$ $0.5H_2O$, MW 709.85: C, 71.07; H, 6.39; N, 7.89. Found: C, 71.27; H, 6.25; N, 7.79.

(4α,5α,6*β*,7*β*)-3-[[3-[(3,5-Dimethoxyphenyl)methyl]-hexahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-(6-methyl-2-pyridinyl)-benzamide Hemihydrate (4). By substituting 2-amino-6-methylpyridine in the method for **2**, the desired product was obtained in 43% yield from the half ester: mp 207−209 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.46 (s, 3H, $ArCH_3$), 2.72 (m, 2H, Ar′CH), 2.89−3.10 (m, 4H, Ar′CH and NCH), 3.43−3.62 (m, 4H, CHCHCHCH), 3.68 (s, 6H, OCH_3), 4.63 (d, J = 14.3 Hz, 1H, NCH), 4.71 (d, J = 14.3 Hz, 1H, NCH), 4.90 (broad s, 2H, OH), [6.23 (s, 2H), 6.39 (s, 1H), 6.93 (d, 2H), 7.06 (d, 2H), 7.1−7.48 (m, 7H), 7.75 (m, 1H), 7.89 (s, 1H), 7.97 (m, 2H), Ar], 10.78 (s, 1H, NH); IR (KBr) 3370 (OH), 3304(NH), 1670 (C═O), 1609 (C═O) cm^{-1}; UV−vis (c = 0.0150 mg/mL, MeOH) λ_{max} 284 (15 745), 278 (13 783) nm; MS (NH_3-DCI) *m/e* 701 (M + 1); $[\alpha]^{20}_D$ +72.53° (c = 0.142, MeOH). Anal. Calcd for $C_{42}H_{44}N_4O_6$ $0.5H_2O$, MW 709.85: C, 71.07; H, 6.39; N, 7.89. Found: C, 71.05; H, 6.39; N, 7.52.

(4α,5α,6*β*,7*β*)-3-[[3-[(3,5-Dimethoxyphenyl)methyl]-hexahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-2-pyridinylbenzamide Hemihydrate (5). By substituting 2-aminopyridine in the method for 2, the desired product was obtained in 31% yield from the half ester: mp 215−218 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.73 (m, 2H, Ar′CH), 2.87−3.09 (m, 4H, Ar′CH and NCH), 3.32−3.59 (m, 4H, CHCHCHCH), 3.68 (s, 6H, OCH3), 4.64 (d, J = 14.3 Hz, 1H, NCH), 4.72 (d, J = 14.0 Hz, 1H, NCH), 5.15 (2s, 2H, OH), [6.24 (d, 2H), 6.39 (s, 2H), 6.94 (d, 2H), 7.1−7.4 (m, 11H), 7.83 (m, 2H), 7.95 (d, 1H), 8.18 (d, 1H), 8.39 (d, 1H), Ar], 10.77 (s, 1H, NH); IR (KBr) 3410 (OH and NH), 1686 (C═O), 1600 (C═O) cm^{-1}; UV−vis (c = 0.021 mg/mL, MeOH) λ_{max} 282 (15 371), 277 (14 914) nm; MS (NH_3-DCI) *m/e* 704 (M + NH_4); $[\alpha]^{20}_D$ +75.00° (c = 0.144, MeOH). Anal. Calcd for $C_{41}H_{42}N_4O_6$·$0.5H_2O$, MW 695.82: C, 70.77; H, 6.23; N, 8.05. Found: C, 70.87; H, 6.18; N, 7.66.

(4α,5α,6*β*,7*β*)-3-[[Hexahydro-5,6-dihydroxy-3-[(3-methoxyphenyl)-methyl]-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-2-pyrazinylbenzamide (6). By substituting 3-methoxybenzyl chloride in the method used to synthesize **2**, the desired intermediate half ester was obtained. A solution of half ester (0.500 g, 0.788 mmol) in 10 mL of dichloroethane was treated with a mixture of 2-aminopyrazine (0.992 g, 10.43 mmol) and 2 M trimethylaluminum (5.23 mL) in 10 mL of dichloroethane. The mixture was refluxed under dry nitrogen for 48 h, cooled to room temperature, and diluted with 200 mL of CH_2Cl_2 and 75 mL of water. The resulting emulsion was filtered through Celite. The organic phase was separated from the aqueous phase; washed with water, 5% $NaHCO_3$, water, and brine; dried over $MgSO_4$; filtered; and concentrated to an impure foam (0.47 g). The crude material was column chromatographed on silica gel using EtOAc−hexane (3:2) as mobile phase. Appropriate fractions were combined and concentrated to give the desired pure intermediate a foam (0.190 g, 35%): ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1. 37 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 2.81−3.04 (m, 6H,

Ar′CH_2 and NCH), 3.32 (d, J = 14.6 Hz, 1H, NCH), 3.74 (s, 3H, OCH_3), 3.78−3.89 (m, 4H, CHCHCHCH), 4.84 (d, J = 14.3 Hz, 1H, NCH), 4.91 (d, J = 14.6 Hz, 1H, NCH), [6.64 (s, 1H), 6.71 (m, 2H), 7.02 (d, 2H), 7.2−7.37 (m, 10H), 7.45 (d, 1H), 7.64 (s, 1H), 7.81 (d, 1H), 8.27 (d, 1H), 8.38 (d, 1H), 8.47 (s, 1H), Ar], 9.69 (s, 1H, NH); MS (NH_3-DCI) *m/e* 698 (M + 1) for $C_{42}H_{43}N_5O_5$, MW 697.84.

A solution of the acetonide (0.170 g, 0.244 mmol) in 10 mL of acetonitrile was treated with 10 mL of 1 N HCl and stirred at room temperature for 24 h. The mixture was diluted with 50 mL of water and adjusted to pH 8 with 5% $NaHCO_3$. The mixture was stirred at 4 °C for 2 h, and the resulting white solid was collected by filtration, washed with cold water, and dried *in vacuo* at 80 °C for 16 h to give the desired product in 90% (0.145 g) yield, or 32% from the half ester: mp 112 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.65−3.1 (m, 6H, 2Ar′CH_2 + 2NCH)), 3.3−3.65 (m, 4H, NCHCHCHCHN), 3.59 (s, 3H, OCH_3), 4.66 (d, J = 14.3 Hz, 1H, NCH), 4.71 (d, J = 14.3 Hz, 1H, NCH), 5.15 (s, 2H, 2OH), [6.65 (s, 1H), 6.69 (d, 1H), 6.83 (m, 1H), 6.94 (d, 2H), 7.07 (d, 2H), 7.15−7.35 (m, 7H), 7.42 (d, 1H), 7.49 (dd, 1H), 7.89 (s, 1H), 7.97 (d, 1H), 8.42 (m, 1H), 8.48 (m, 1H), 9.40 (s, 1H), Ar], 11.15 (s, 1H, NH); IR (KBr) 3412 (OH and NH), 1686 (C═O), 1604 (C═O) cm^{-1}; UV−vis (c = 0.0270 mg/mL, MeOH) λ_{max} 303 (10 183), 287 (14 593), 252 (12 888) nm; MS (NH_3-DCI) *m/e* 675 (M + NH_4). Anal. Calcd for $C_{39}H_{39}N_5O_5$, MW 657.77: C, 71.21; H, 5.99; N, 10.65. Found: C, 70.98; H, 6.09; N, 10.34. Analytical HPLC: Zorbax ODS 4.6 × 250 mm column, solvent H_2O−CH_3CN, flow rate of 1 mL/min, detector at 256 nm.

(4α,5α,6*β*,7*β*)-3-[[Hexahydro-5,6-dihydroxy-3-[(3-methoxyphenyl)methyl]-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-(5-methyl-2-pyridinyl)benzamide Sesquihydrate (7). By substituting 5-methyl-2-aminopyridine in the method for **6**, the desired product was obtained in 74% (0.327 g) or 35% from the half ester: mp 238−240 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.30 (s, 3H, CH3), 2.7−3.09 (m, 6H, Ar′CH_2 and NCH), 3.40−3.58 (m, 4H, CHCHCHCH), 3.70 (s, 3H, OCH_3), 4.66 (d, J = 14.3 Hz, 1H, NCH), 4.71 (d, J = 14.3 Hz, 1H, NCH), 5.40 (broad s, 2H, OH), [6.65 (s, 1H), 6.68 (d, 1H), 6.81 (m, 1H), 6.93 (d, 1H), 7.06 (d, 2H), 7.18−7.33 (m, 7H), 7.38 (d, 1H), 7.45 (dd, 1H), 7.58 (d, 1H), 7.88 (s, 1H), 7.96 (d, 1H), 8.04 (d, 1H), 8.24 (s, 1H), Ar], 10.98 (s, 1H, NH); IR (KBr) 3364 (OH and NH), 1686 (C═O), 1612 (C═O) cm^{-1}; UV−vis (c = 0.0160 mg/mL, MeOH) λ_{max} 287 (16 603), 263 (14 003), 221 (42 597) nm; MS (NH_3-DCI) *m/e* 671 (M + 1), 688 (M + 14); $[\alpha]^{20}_D$ +80.77° (c = 0.16, MeOH). Anal. Calcd for $C_{41}H_{42}N_4O_5$·1.5H_2O, MW 697.84: C, 70.58; H, 6.48; N, 8.03. Found: C, 70.82; H, 6.17; N, 8.01.

(4α,5α,6*β*,7*β*)-3-[[Hexahydro-5,6-dihydroxy-3-[(3-methoxyphenyl)methyl]-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-(6-methyl-2-pyridinyl)benzamide Hemihydrate (8). By substituting 6-methyl-2-aminopyridine in the method for **6**, the desired product was obtained in 82% (0.146 g) or 28% from the half ester: mp 243−245 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.45 (s, 3H, CH3), 2.7−3.08 (m, 6H, Ar′CH_2 and NCH), 3.35−3.58 (m, 4H, CHCHCHCH), 3.70 (s, 3H, OCH3), 4.66 (d, J = 14.3 Hz, 1H, NCH), 4.71 (d, J = 14.6 Hz, 1H, NCH), 5.13 (broad s, 2H, OH), [6.65 (1, 1H), 6.68 (d, 1H), 6.83 (m, 1H), 6.93 (d, 2H), 7.00 (d, 1H), 7.06 (d, 2H), 7.2−7.34 (m, 7H), 7.36 (d, 1H), 7.42 (dd, 1H), 7.68 (dd, 1H), 7.88 (s, 1H), 7.94 (d, 1H), 7.98 (d, 1H), Ar], 10.67 (s, 1H, NH); IR (KBr) 3448 (OH), 3310 (NH), 1690 (C═O), 1608 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 671 (M + 1), 688 (M + NH_4); $[\alpha]^{20}_D$ +97.37° (c = 0.08, MeOH). Anal. Calcd for $C_{41}H_{42}N_4O_5$·0.5H_2O, MW 679.83: C, 72.44; H, 6.38; N, 8.24. Found: C, 72.76; H, 6.31; N, 8.14.

(4α,5α,6*β*,7*β*)-3-[[Hexahydro-5,6-dihydroxy-3-[(3-methoxyphenyl)methyl]-2-oxo-4,7-bis(phenylmethyl)-*1H*-1,3-diazepin-1-yl]methyl]-*N*-2-pyridinylbenzamide Hemihydrate (9). By substituting 2-aminopyridine in the method for **6**, the desired product was obtained in 59% yield from the half ester: mp 223−225 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.7−3.1 (m, 6H, Ar′CH_2 and NCH), 3.4−3.65 (m, 4H, CHCHCHCH), 3.70 (s, 3H, OCH3), 4.67 (d, J = 14.7 Hz, 1H, NCH), 4.72 (d, J = 14.6 Hz, 1H, NCH), 5.12 (m, 2H, OH), [6.65 (s, 1H), 6.69 (d, 1H), 6.83 (m, 1H), 6.96 (d, 2H), 7.08 (d, 2H), 7.1−7.35 (m, 8H), 7.39 (d, 1H), 7.44 (dd, 1H), 7.82 (m, 1H), 7.88 (s, 1H), 7.95 (d, 1H), 8.18 (d, 1H), 8.39 (d, 1H), Ar], 10.76 (s, 1H, NH); IR (KBr) 3452 (OH), 3304 (NH), 1692 (C═O), 1612 (C═O) cm^{-1}; UV−vis (c = 0.12 mg/mL, MeOH) λ_{max} 286 (17 022), 261 (12 588), 221 (40 611) nm; MS (NH_3-DCI) *m/e* 657 (M + 1), 674 (M + NH_4); $[\alpha]^{20}_D$ +91.25° (c = 0.080, MeOH). Anal. Calcd for $C_{40}H_{49}N_4O_5$·0.5H_2O: C, 72.18; H, 6.21; N, 8.42. Found: C, 71.78; H, 5.88; N, 8.15.

(4α,5α,6*β*,7*β*)-3-[[3-[(3-Aminophenyl)methyl]hexahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-(5-methyl-2-pyridinyl)benzamide Hemihydrate (10). The methylisourea **Ib** (13.14 mmol) was alkylated with methyl 3-bromobenzoate using NaH in dry DMF to give (methyl 3-methylbenzoate)−methylisourea in 86% (5.96 g) yield as an oil after column chromatography on silica gel (EtOAc−hexane, 1:4): ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 1.46 (s, 6H, CH_3CCH_3), 2.7−2.86 (m, 2H, Ar′CH), 2.99−3.10 (m, 2H, Ar′CH), 3.18 (d, J = 14.3 Hz, 1H, NCH), 3.38 (s, 3H, OCH_3), 3.71 (m, 1H, CH), 3.86 (s, 3H, OCH_3), 4.18 (m, 3H, CHCHCH), 4.38 (d, J = 14.65, 1H, NCH), 6.98−7.92 (m, 14H, Ar); MS (NH_3-DCI) *m/e* 529 (M + NH_4). The methyl benzoate−methylisourea (11.22 mmol) was alkylated by refluxing with 3-nitrobenzyl bromide in acetonitrile for 3 days. After the usual workup, the crude material was column chromatographed of silica gel (EtOAc−hexane, 9:1) to give desired product in 54% yield: MS (NH_3-DCI) *m/e* 667 (M + NH_4). The nitrobenzyl methyl benzoate (1.38 mmol) was reacted with 2-amino-5-methylpyridine under Weinreb conditions to give the corresponding amide in 35% yield as a foam: MS (NH_3-DCI) *m/e* 726 (M + NH_4). The nitrobenzyl amide acetonide (0.45 mmol) was reduced with 10% Pd/C in CH_2Cl_2 to give the desired anilino amide acetonide in 100% yield.

The acetonide protecting group was removed in the usual manner to give the desired product in 62% yield (overall yield = 10% for five steps): mp 230−232 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.27 (s, 3H, CH_3), 2.59 (d, J = 14.3 Hz, 1H, NCH), 2.76 (dd, 1H, Ar′CH), 2.96 (m, 3H, Ar′CH), 3.05 (d, J = 14.3 Hz, 1H, NCH), 3.50 (m, 4H, CHCHCHCH), 4.58 (d, J = 14.3 Hz, 1H, NCH), 4.71 (d, J = 14.3 Hz, 1H, NCH), 5.07 (m, 4H, OH and NH2), [6.24 (d, 1H), 6.34 (s, 1H), 6.43 (d, 1H), 6.94 (m, 3H), 7.12 (d, 2H), 7.26 (m, 7H), 7.45 (dd, 1H), 7.64 (dd, 1H), 7.86 (s, 1H), 7.94 (d, 1H), 8.07 (d, 1H), 8.21 (s, 1H,) Ar], 10.66 (s, 1H, NH); IR (KBr) 3366 (OH and NH), 1678 (C═O), 1606 (C═O) cm^{-1}; UV−vis (c = 0.014 mg/mL, MeOH) λ_{max} 310 (19 130), 254 (16 095) nm; MS (NH_3-DCI) *m/e* 656 (M + 1); $[\alpha]^{20}_D$ +78.75° (c = 0.08, MeOH). Anal. Calcd for $C_{40}H_{41}N_5O_4$·0.5H_2O, MW 664.81: C, 72.27; H, 6.37; N, 10.53. Found: C, 72.57; H, 6.33; N, 10.35.

(4α,5α,6*β*,7*β*)-3-[[Hexahydro-5,6-dihydroxy-3-[(3-nitrophenyl)methyl]-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-2-pyridinylbenzamide dihydrate (11). By substituting 2-aminopyridine in the method for **10**, the desired product was obtained in 42% yield after chromatography on silica using $CHCl_3$−MeOH (99:1): mp 235−238 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.65−2.79 (m, 2H, Ar′CH), 2.98 (m, 3H, Ar′CH and NCH), 3.51−3.64 (m, 4H, CHCHCHCH), 4.50 (d, J = 13.9 Hz, 1H, NCH), 4.67 (d, J = 13.9 Hz, 1H, NCH), 5.18 (s, 2H, OH), 6.85−8.38 (m, 22H, Ar), 10.75 (s, 1H, NH); IR (KBr) 3332 (OH), 1678 (C═O), 1640 (C═O) cm^{-1}; UV−vis (c = 0.017 mg/mL, MeOH) λ_{max} 284 (16 122), 264 (15 647) nm; MS (NH_3-DCI) *m/e* 672 (M + 1); $[\alpha]^{20}_D$ +77.21° (c = 0.136, MeOH). Anal. Calcd for $C_{39}H_{37}N_5O_6$·2H_2O, MW 707.79: C, 66.18; H, 5.84; N, 9.89. Found: C, 66.51; H, 5.56; N, 9.61.

(4α,5α,6*β*,7*β*)-3-[[3-[(3-Aminophenyl)methyl]hexahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-(1,1-dimethylethyl)benzamide (12). By substituting *tert*-butylamine in the method used to obtain **10**, the desired intermediate nitro amide acetonide was obtained in 103% (1.10 g) yield: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.41 (m, 15H, ^{t}Bu and iPr), 2.75−3.1 (m, 4H, ArCH_2), 3.16 (d, J = 14.3 Hz, 1H, NCH), 3.40 (d, J = 14.6 Hz, 1H, NCH), 3.8 (m, 2H, ArCCH), 3.09−4.05 (m, 2H, OCH), 4.80 (d, J = 14.6 Hz, 1H, NCH), 4.89 (d, J = 14.3 Hz, 1H, NCH), 5.85 (s, 1H, NH), 6.95−8.1 (m, 18H, Ar); MS (NH_3-DCI) *m/e* 708 (M + NH_4) for $C_{41}H_{46}N_4O_6$, MW 690.85.

The above intermediate (1.00 g, 1.54 mmol) in 25 mL of tBuOH and ammonium formate (2 g, mmol) and 10% Pd/c (0.2 g) was stirred at room temperature until no starting material remained as evidenced by TLC ($CHCl_3$−EtOAc, 3:2). The reaction mixture was filtered through Celite to remove the catalyst. The Celite bed was washed with 3 × 50 mL of EtOAc, and the filtrate and washings were combined, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to a foam. The foam was dissolved in 20 mL of acetonitrile, treated with 10 mL of 1 N HCl, stirred for 16 h, and concentrated to a foam. The foam was dissolved in 25 mL of EtOH and precipitated with 100 mL of 5% $NaHCO_3$. The resulting precipitate was collected by filtration, washed with water, and dried *in vacuo* at 80 °C to give the desired product in 82% (0.780 g) yield from the nitro ester acetonide: mp 102−105 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 1.32 (s, 9H, ^{t}Bu), 2.63 (d, J = 14.3 Hz, 2H, NCH), 2.8 (m, 2H, Ar′CH), 2.95 (m, 4H, Ar′CH and NCH), 3.4 (m, 4H, CHCCHCHCH), 4.61 (d, J = 14.3 Hz, 1H, NCH), 4.75 (d, J = 13.9 Hz, 1H, NCH), 5.08 (broad s, 2H, OH), 6.24 (d, 1H, NH), 6.36 (s, 1H, CONH), 6.45 (d, 1H, NH), 6.9−7.71 (m, 18H, Ar); IR (KBr) 3362 (OH and NH), 1642 (C═O) cm^{-1}; UV−vis (c = 0.014 mg/mL, MeOH) λ_{max} 284 (3059) nm; MS (NH_3-DCI) *m/e* 621 (M + 1), 638 (M + NH_4); $[\alpha]^{20}_D$ +76.06° (c = 0.14, MeOH). Anal. Calcd for $C_{38}H_{44}N_4O_4$, MW 620.80: C, 73.52; H, 7.14; N, 9.02. Found: C, 73.39; H, 7.16; N, 8.99.

[4*R*-(4α,5α,6*β*,7*β*)]-3-[[3-[(3-Aminophenyl)methyl]hexahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-2-pyrazinylbenzamide (13). By substituting 2-aminopyrazine in the procedure used to synthesize 10, the desired product was obtained in an overall yield of 13% from the isourea: mp 154−157 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.58 (d, 2H, Ar′CH), 2.73 (dd, 2H, Ar′CH), 2.93 (d, J = 13.9 Hz, 1H, NCH), 3.05 (d, J = 14.3 Hz, 1H, NCH), 3.4−3.6 (m, 4H, CHCHCHCH), 4.56 (d, J = 13.9 Hz, 1H, NCH), 4.69 (d, J = 14.3 Hz, 1H, NCH), 5.09 (d, 2H, OH), 6.4−8.5 (m, 21H, Ar), 9.38 (s, 2H, NH2), 11.12 (s, 1H, NH); IR (KBr) 3360 (NH and OH), 1682 (C═O), 1606 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* calcd for $C_{38}H_{39}N_6O_4$: 643.303 279 (M + 1), found 643.303 224, 690 (M + 1). Anal. Calcd for $C_{38}H_{38}N_6O_4$, MW 642.76: C, 71.01; H, 5.96; N, 13.07. Found: C, 70.92; H, 6.00; N, 12.98.

[4*R*-(4α,5α,6*β*,7*β*)]-3-[[3-[(3-Aminophenyl)methyl]hexahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-1*H*-benzimidazol-2-ylbenzamide (14). By substituting 2-aminobenzimidazole in the procedure for **10**, the desired product was obtained in an overall yield of 39%: mp 134−135 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.59 (d, 1H, Ar′CH), 2.82 (dd, 1H, Ar′CH), 2.9−3.1 (m, 4H, Ar′CH and NCH), 3.5 (m, 4H, CHCHCHCH), 4.58 (d, J = 13.9 Hz, 1H, NCH), 4.72 (d, J = 1, 14.3 Hz, 1H, NCH), 5.03 (m, 4H, OH and NH2), [6.22 (d, 1H), 6.34 (s, 1H), 6.42 (d, 1H), 6.9 (m, 3H), 7.13 (m, 3H), 7.20 (m, 2H), 7.23 (m, 4H), 7.35 (m, 3H), 7.44 (m, 3H), 8.05 (d, 1H), Ar], 8.00 (s, 1H, NH), 12.23 (broad s, 1 NH); IR (KBr) 3368(NH and OH), 1630 (C═O), 1606 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* calcd for $C_{41}H_{41}N_6O_4$: high-resolution MS 681.317 592, found 681.317 126, 681 (M + 1). Anal. Calcd for $C_{41}H_{40}N_6O_4$, MW 680.81: C, 72.33; H, 5.92; N, 12.34. Found: C, 71.27; H, 6.01; N, 12.29.

[4*R*-(4α,5α,6*β*,7*β*)]-3-[[3-[(3-Aminophenyl)methyl]hexahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-1*H*-imidazol-2-ylbenzamide (15). By substituting 2-aminoimidazole in the method for 10, the desired product was obtained in 26% overall yield: mp 166 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.58 (d, J = 14.3 Hz, 2H, Ar′CH), 2.8−3.03 (m, 4H, Ar′CH and NCH), 3.44−3.55 (m, 4H, Ar′CCHCH), 4.58 (d, J = 13.9 Hz, 1H, NCH), 4.70 (d, J = 13.9 Hz, 1H, NCH), 5.06 (s, 2H, OH), [6.24 (m, 1H), 6.33 (s, 1H), 6.43 (d, 1H), 6.79 (s, 2H), 6.86−6.96 (m, 4H), 7.10−7.35 (m, 10H), 7.43 (dd, 1H), 7.92 (s, 1H), 7.97 (d, 1H), Ar], 11.75 (s, 2H, NH); IR (KBr) 3376 (OH and NH), 1604 (C═O) cm^{-1}; UV−vis (MeOH) λ_{max} 285 (13 862) nm; MS (NH_3-DCI) *m/e* 631 (M + 1); $[\alpha]^{20}_D$ +79.81° (c = 0.104, MeOH). Anal. Calcd for $C_{37}H_{38}N_6O_4$, MW 630.75: C, 70.46; H, 6.07; N, 13.32. Found: C, 70.39; H, 6.33; N, 13.28.

(4α,5α,6*β*,7*β*)-N-[3-[[3-[[3-[[(Cyanomethyl)amino]carbonyl]phenyl]methyl]hexahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]benzoyl]-glycine (16). The ester **Ia** was saponified to give the bisacid acetonide (0.635 g, 1.0 mmol) which was dissolved in 25 mL of CH_2Cl_2 and treated with oxalyl chloride (0.38 g, 3.0 mmol) and 1 drop of DMF. The mixture was stirred for 30 min. The mixture was treated with aminoacetonitrile hydrochloride (0.278 g, 3.0 mmol), stirred for an additional 10 min, and treated with diisopropylethylamine (0.78 g, 6.0 mmol). The mixture was stirred at room temperature for 16 h and diluted with 100 mL of water and 50 mL of CH_2Cl_2. The organic layer was washed with additional water, 5% citric acid, water, and brine; dried over $MgSO_4$; filtered; and concentrated to a foam of constant weight: ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.70 (dd, 2H, Ar′CH), 2.84 (m, 2H, Ar′CH), 3.25 (d, J = 14.0 Hz, 2H, NCH), 4.02 (d, J = 11.0, 2H, Ar′CCH), 4.07 (s, 2H, OCH), 4.31 (d, J = 5.5 Hz, 4H, CH_2-CN), 4.52 (d, J = 14.0 Hz, 2H, NCH), [6.93 (m, 4H), 7.2 (m, 6H), 7.44 (m, 4H), 7.77 (m, 4H), Ar and Ar′], 9.20 (dd, 2H, NH).

The acetonide was dissolved in 10 mL of acetonitrile and treated with 10 mL of 10.0 N HCl (accidentally used instead of 1.0 N). The mixture was stirred at room temperature until no starting acetonide remained. The mixture was diluted with 100 mL of water and triturated. The resulting solid was collected by filtration, washed with water, and dried *in vacuo*. Recrystallization from EtOAc produced 0.201 g of white solid which was identified by analytical methods to be the "half-acid, half-nitrile, diol": mp 154−157 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ 2.7 (m, 2H, Ar′CH), 2.9 (m, 4H, Ar′CH and NCH), 3.5 (m, 4H, CHCHCHCH), 3.80 (d, J = 5.9 Hz, 2H, $CHCO_2$), 4.30 (d, J = 5.2 Hz, 2H, CHCN), 4.6 (m, 2H, NCH), 5.15 (s, 2H, OH), [6.9 (m, 4H), 7.2 (m, 6H), 7.4 (m, 4H), 7.75 (m, 4H), Ar], 8.63 (t, 1H, $HNCCO_2$), 9.21 (t, 1H, HN-C-CN); IR (KBr) 3390 (OH and NH), 2254 (CN), 1650 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 690 (M + 1), 707 (M + NH_4). Anal. Calcd for $C_{39}H_{39}N_5O_7$, MW 689.77: C, 67.91; H, 5.70; N, 10.15. Found: C, 67.74; H, 5.85; N, 10.52.

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$$\text{CLOGP} = 1.236(\pm 0.034) \log P_{\text{HPLC}} + 0.294(\pm 0.168)$$

$$n = 15 \qquad r^2 = 0.990 \qquad s = 0.114$$

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