HIV Protease Inhibitory Bis-benzamide Cyclic Ureas: A Quantitative Structure−Activity Relationship Analysis

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A series of N,N′-disubstituted cyclic urea 3-benzamides has been synthesized and evaluated for HIV protease inhibition and antiviral activity. Some of these benzamides have been shown to be potent inhibitors of HIV protease with $K_i < 0.050$ nM and $IC_{90} < 20$ nM for viral replication and, as such, may be useful in the treatment of AIDS. The synthesis and quantitative structure−activity relationship for this benzamide series will be discussed.

Introduction

The viral-encoded protease for human immunodeficiency virus (HIV) is responsible for the processing of viral polyprotein precursors to their mature polypeptides. Since correct processing of the viral polypeptides is essential for the production of infectious virus, HIV protease represents a potential target for therapeutic agents which may prove beneficial in the treatment of AIDS.[1]

We had previously determined (data not included) that for the cyclic ureas,[2−4] the best HIV protease inhibitors (Figure 1) resulted when P2 and P2′ were substituted benzyl (-CH_2-Ph-X), where the regiochemistry of X showed that the 3-isomer produced a better inhibitor than the 4-isomer that was far superior to the 2-isomer. We further determined that a hydrogen bond-donating (HBD) X produced a more potent HIV protease inhibitor than the corresponding hydrogen bond acceptor (HBA). The importance of the HBD was demonstrated early in the project as illustrated by the comparison between the highly potent secondary amide **6** (X = CONHMe, $K_i = 0.066$ nM) and the corresponding amide **31** (X = $CON(Me)_2$, $K_i = 1.900$ nM) (see Table 1). The implication was that a HBD was necessary but not sufficient for potent K_i. Examination of other physicochemical characteristics suggested that K_i is related to the lipophilicity of the inhibitor (ClogP), the electronic effect of the X-substituent (σ), and the hydrogen-bonding character [HB] of X. This relationship can be expressed by eq 1:

$$-\log(K_i) = a(\text{ClogP}) + b(\sigma_X) + c[\text{HB}] + C \quad (1)$$

where X = H, 3- and 4-alkyl, aryl, substituted aryl, CF_3, OR, OCF_3, CN, NO_2, F, Cl, Br, I, OH, CHO, COR′, CO_2Me, CO_2H, $CONH_2$, CONHR′, CH_2OH, NH_2, NHR′, NHAc, SR, SOnR′, and $B(OH)_2$.

One of the compounds discovered early in this work was **2** (X = $CONH_2$). The benzamide **2** was found to have excellent protease inhibitory activity ($K_i = 0.039$ nM) but was determined to have poor antiviral activity ($IC_{90} = 708.6$ nM). This study was initiated in an attempt to improve on both the protease inhibition and the antiviral activity of the benzamide series by applying classic quantitative structure−activity relationship (QSAR) techniques.

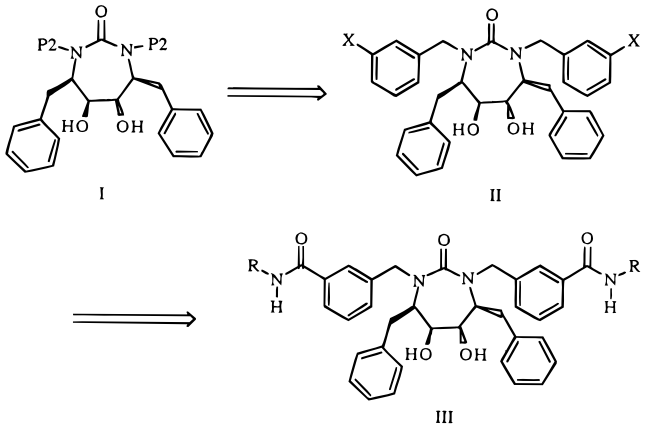

Figure 1. Lead progression to the carboxamides.

Chemistry

Structures, methods of amide bond formation, and corresponding physical data for the compounds in this study are shown in Table 1. For this study, **2** was synthesized from the corresponding nitrile using the method described by Noller[5] (see Scheme 1). Most of the other compounds in this study were synthesized by activating the carboxyl group of the cyclic ureas *bis*-benzoic acid (**1c**, see Scheme 2) followed by reaction with the appropriate amine (R-NH_2).

Carboxyl-activating conditions involved reaction with *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *N*-hydroxybenzotriazole (HOBt) (DCC−HOBt method), reaction with (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP, Castro's reagent),[6] or oxalyl chloride. The 'Acid Chloride Method', when conducted with oxalyl chloride under extremely anhydrous conditions, was able to effect some of the more difficult acylations. These approaches are illustrated in Scheme 3. Most of the syntheses, where R was aromatic, were accomplished with difficulty as evidenced by extremely long reaction times and poor yields (data not included). We believe that these results were caused by the poor nucleophilicity of the amine (R-NH_2). By chromatographic methods (TLC and HPLC), we were able to observe the rapid formation of HOBt active ester.

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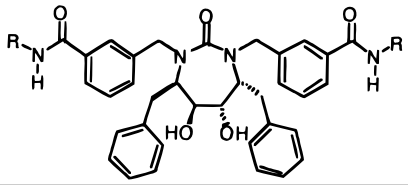
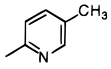
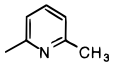
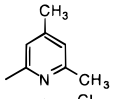
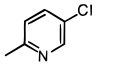
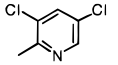
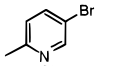
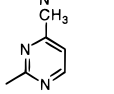
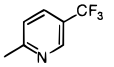
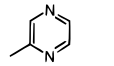
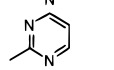
Table 1. Pharmacological, Structural, and Physical Chemical Data for Compounds **2**−**31**



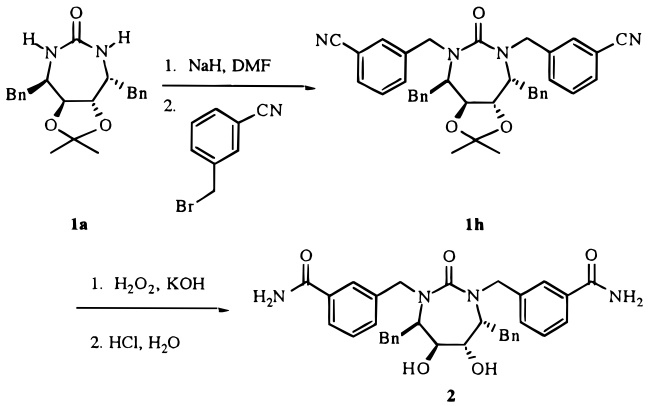
cmpd	K_i* nM	IC_{90}** nM	R	Coupling Method[a]	mp, °C	% yield	Analysis[b]
1b	na	na		na	101-102	66	$C_{40}H_{42}N_2O_7$
1c	na	na		na	218-220	82	$C_{38}H_{38}N_2O_7$
1h	na	na		na	155-156	35	$C_{38}H_{36}N_4O_3\ H_2O$
2[a]	0.039	708.6	H	Hydrolysis	143-145	92	$C_{35}H_{36}N_4O_5$
3	0.018	883.6	NH_2	Hydrazinolysis	161-163	91	$C_{35}H_{38}N_6O_5$
4	0.020	448.2	OH	BOP	139-142	74	$C_{35}H_{36}N_4O_7\ 0.5H_2O$
5	0.045	214.5	OCH_3	BOP	155 dec.	93	$C_{37}H_{40}N_4O_7$
6[a]	0.066	80.5	CH_3	BOP	163-165	99	$C_{37}H_{40}N_4O_5$
7[a]	0.210	138.7	CH_2CH_3	DCC-HOBt	160-162	92	$C_{39}H_{44}N_4O_5$
8[a]	0.579	265.9	$CH(CH_3)_2$	DCC-HOBt	131-135	82	$C_{41}H_{48}N_4O_5\ 2.5H_2O$
9[a]	0.359	259.0	$CH_2CH_2CH_3$	DCC-HOBt	166-168	90	$C_{41}H_{48}N_4O_5$
10	0.424	255.3	$CH_2CH_2CH_2CH_3$	BOP	132-134	98	$C_{43}H_{52}N_4O_5$
11	2.400	717.1	$C(CH_3)_3$	Weinreb, BOP	133 dec.	86	$C_{43}H_{52}N_4O_5$
12	0.741	485.1	CH_2-C_3H_5	Mixed anh.	116-118	27	$C_{43}H_{48}N_4O_5$
13	0.210	92.5	CH_2CF_3	WSC	116-120	15	$C_{39}H_{38}F_6N_4O_5$
14	0.063	596.3	CH_2CN	Acid chloride	141-143	41	$C_{39}H_{38}N_6O_5\ 1.5\ H_2O$
15	0.430	510.4		Weinreb, DCC-HOBt	157-160	94	$C_{47}H_{44}N_4O_5$
16	0.410	93.7		Weinreb	153-154	23	$C_{45}H_{42}N_6O_5$
17a	0.290	123.2		Weinreb	163-165	(50) 79	$C_{45}H_{42}N_6O_5$
18	0.043	2.8		Weinreb	131-133	91	$C_{45}H_{42}N_6O_5$
19	0.260	50.3		Weinreb	142-143	24	$C_{47}H_{46}N_6O_5\ H_2O$
20	0.027	7.7		Weinreb	139-140	18	$C_{47}H_{46}N_6O_5\ 1.5H_2O$
21	0.011	3.1		Weinreb	132-133	13	$C_{47}H_{46}N_6O_5\ 0.5H_2O$
22	0.020	3.2		Weinreb	135-136	17	$C_{47}H_{46}N_6O_5\ H_2O$
23	0.016	6.6		DCC-HOBt	166-170	66	$C_{49}H_{50}N_6O_5\ H_2O$
24	0.012	14.7		Weinreb	261-264	85	$C_{45}H_{40}N_6O_4Cl_2$
25	0.245	43.0		Weinreb	238-241	66	$C_{45}H_{38}N_6O_5Cl_4$
26	0.035	28.2		Weinreb	162-164	30	$C_{45}H_{40}N_6O_5Br_2\ H_2O$
27	0.115	124.4		Weinreb	154-159	24	$C_{45}H_{44}N_8O_5\ 1.5H_2O$
28	0.085	63.4		Acid chloride	261-262	22	$C_{47}H_{40}F_6N_6O_5$
29	0.018	3.5		Weinreb	146-148	58	$C_{43}H_{40}N_8O_5$
30	0.152	220.3		DCC-HOBt, Weinreb	149-151	81	$C_{43}H_{40}N_8O_5$
31[c]	1.900	3082.8	R = -CH_3 R' = -CH_3	BOP	glass	94	$C_{39}H_{44}N_4O_5$

Reference Compounds

cmpd	K_i* nM	IC_{90}** nM
DMP323	0.32	114.6
VX478	0.17	46.0
ABT538	0.37	76.0
Ro31-8959	0.25	10.4
MK-639	0.37	50.0

*K_i SD <±40%. **IC_{90} SD <±36%. [a] BOP, (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; DCC−HOBt, *N*,*N*′-dicyclohexylcarbodiimide and *N*-hydroxybenzotriazole; acid chloride with oxalyl chloride; WSC, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (water soluble carbodiimide); Weinreb, reaction of the amine with trimethylaluminum followed by reaction with **1b**. [b] All compounds except **28** were analyzed for C, H, and N, and analytical results were within ±0.4% of the theoretical values. [c] The only disubstituted amide in the data set and was not used in any of the regression models.

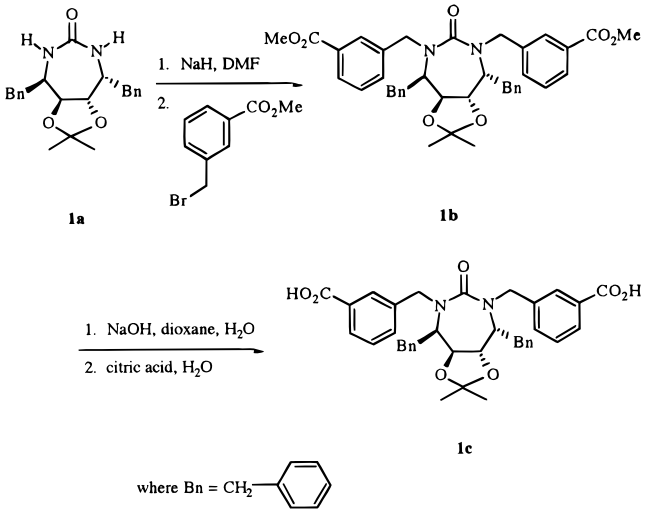
Scheme 1. Synthetic Approach to **2**



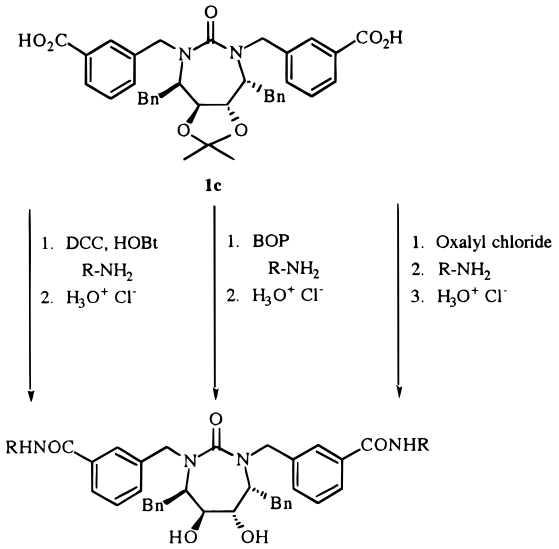
However, acylation of the amine was extremely slow and incomplete in some cases. We were able to isolate by column chromatography and fully characterize representative samples of the HOBt ester and the mixed HOBt ester−amide.

Carboxyl activation through the *N*-hydroxysuccinimide ester(s) has also been attempted to find the ester(s) even more resistant to amide formation. Amide bond formation with poorly nucleophilic amines was accomplished in moderate to good yields by activation of the amine using a modification of the method reported by Basha et al.[7] The ester **1b** was reacted with excess dimethylaluminum amide ($(CH_3)_2AlNHR$) prepared from equal molar amounts of trimethylaluminum ($(CH_3)_3Al$) and the amine ($R\text{-}NH_2$) in dichloroethane and refluxing until chromatographic methods indicated no **1b** remained. The method is illustrated in Scheme 4 and is referred to as the Weinreb method. However, this approach was unsuccessful in cases where the amine-complex was insoluble in dichloroethane. Compound **12**

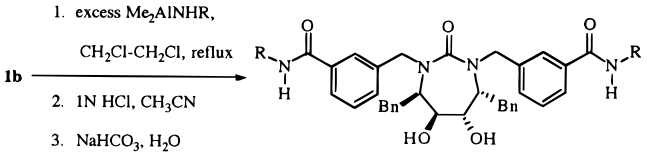
Scheme 2. Synthetic Approach to the Ester **1b** and the Carboxylic Acid **1c**



Scheme 3. Activated Carbonyl Approaches to the Benzamides



Scheme 4. Synthetic Approach to the Amides Using a Modification of the Weinreb Procedure



was synthesized by the mixed anhydride method utilizing ethyl chloroformate and **1c**.

Pharmacology

The K_i values were determined with recombinant single-chain dimeric HIV protease and a fluorescent substrate (see Cheng et al.[8]). The use of single-chain dimeric protease allows enzyme concentrations as low 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 protease (PR) as described by Erickson-Viitanen et al.[9] 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 1. 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 1.

HIV RNA Assay.[10] This 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 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 nanomolar (nM) for structure−activity relationship (SAR) studies (Table 1). 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 1.

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 study had $TC_{50} < 50$ μg/mL. A correct interpretation of the RNA assay requires that test molecules not be cytotoxic at RNA assay dose levels.

Statistical Methods and QSAR Parameters

Statistical analyses were conducted using JMP v3.0.2 by SAS Institute, Cary, NC. The statistical measures used are as follows: n, number of samples in the regression; r, correlation coefficient; s, root mean square error of the regression; and F-ratio.

Computer-generated lipophilicity of the molecule (ClogP) and bulk (CMR) were obtained using MedChem Software v3.0, Pomona College, Claremont, CA. Many of the parameters for the R-groups in Table 1 were not available from literature sources, which required us to derive other parameters that could be easily obtained and used in our attempt to derive QSAR expressions for protease inhibition (K_i) and viral replication (IC_{90}).

The hydrogen-bonding property of the R-group was indicated by hydrogen bond donor (HBD), (1, 1); hydrogen bond acceptor (HBA), (0, 1); and neither (0, 0). The parameters for ionization potential (IP), energy of the highest occupied orbital (ϵ_{HOMO}), energy of the lowest unoccupied orbital (ϵ_{LUMO}), and molecular volume (MV) were obtained using SYBYL v6.2 by Tripose Associates, Inc., St. Louis, MO, on a Silicon Graphics workstation. The molecules were minimized with Gasteiger Huckel

Table 2. Substituent Constants[21] Used in Deriving Regression Eq 2 for HIV Protease Inhibitors **2**−**15**[a]

compd	R	π	MR	σ_I	σ^*	F	R	L1	B1	B5	log(1/K_i)
2	H	0.00	0.10	0.00	0.49	0.00	0.00	2.06	1.00	1.00	1.409
3	NH_2	−1.23	0.54	0.12	0.62	0.08	−0.74	2.78	1.35	1.97	1.745
4	OH	−0.67	0.28	0.29	1.37	0.33	−0.70	2.74	1.35	1.93	1.699
5	OCH_3	−0.02	0.79	0.27	1.77	0.29	−0.56	3.98	1.35	3.07	1.347
6	CH_3	0.56	0.56	−0.04	0.00	0.01	−0.18	2.87	1.52	2.04	1.180
7	CH_2CH_3	1.02	1.03	−0.01	−0.10	0.00	−0.15	4.11	1.52	3.17	0.678
8	$CH(CH_3)_2$	1.53	1.50	0.01	−0.19	0.04	−0.19	4.11	1.90	3.17	0.237
9	$CH_2CH_2CH_3$	1.55	1.50	−0.01	−0.12	0.01	−0.14	4.92	1.52	3.49	0.445
10	$CH_2CH_2CH_2CH_3$	2.13	1.96	−0.04	−0.13	−0.01	−0.15	6.17	1.52	4.54	0.373
11	$C(CH_3)_3$	1.98	1.96	−0.07	−0.30	−0.02	−0.18	4.11	2.60	3.17	−0.380
12	CH_2-C_3H_5	(1.39)	1.82	nd	0.01	nd	nd	5.14	1.52	4.36	0.130
13	CH_2CF_3	(1.80)	0.97	0.16	0.92	0.15	−0.06	4.70	1.52	3.07	0.678
14	CH_2CN	−0.57	1.01	nd	1.25	0.17	0.01	3.99	1.52	4.12	1.201
15	Ph	1.96	2.54	0.12	0.60	0.12	−0.13	6.28	1.71	3.11	0.367
hypo-**1**	4-Pyr	0.46	2.30	0.24		0.21	0.23	5.92	1.71	3.11	
hypo-**2**	2-Pyr	0.50	2.30	0.40		0.40	−0.23	6.28	1.71	3.11	

[a] Parentheses indicate not in the regressions, calculated from ClogP: $\pi = 0.644\text{ClogP} - 2.609$; $n = 12$, $r^2 = 0.927$, SE = 0.332, $F = 126.618$.

Table 3. Cross-Correlation Matrix for the Parameters in Eq 2

variable	π	F	B1
π	1.000	−0.530	0.620
F		1.000	−0.300
B1			1.000

charge, and the minimized structures were given MOPAC v5.0[11] charges (AM1, mmok, parasok, Mulliken atomic charge population).[12,13]

Discussion

Because of the potent antiprotease activity of **2** (R = H, K_i = 0.039 nM), a small set of amides (**2**−**15**) was synthesized and evaluated for antiprotease (K_i) and antiviral (IC_{90}) activity. For protease inhibitory activity (log 1/K_i), the substituent constants (see Table 2) for lipophilicity (π and π^2), size, bulk, volume, or sterics (MR, MR^2, and STERIMOL parameters L1, B1, and B5), and electronic effects (σ_I, σ^*, Swain−Lupton's F and R[14]) were subjected to a stepwise 'multiple linear regression' (MLR) analysis. The result from this analysis was eq 2 which suggested that the π, F, and B1 for the R-group

$$\log(1/K_i)_{\mathbf{2-15}} = -0.337(\pm 0.044)\pi + 0.591(\pm 0.382)F - 0.739(\pm 0.125)\text{B1} + 2.210(\pm 0.192) \quad (2)$$

$$n = 13,\ r = 0.983,\ s = 0.134,\ F_{3,10} = 87.945_{(0.0001)}$$

were important to activity. The cross-correlation matrix for the parameters in eq 2 is shown in Table 3.

Equation 2 suggested that decreasing lipophilicity, increasing the inductive effects, and keeping the B1 as small as possible will result in increased activity. Subsequent analyses showed that σ_I and σ^* could replace F without a loss in the significance of eq 2. Note that Martin[15] has reported that σ^*, F, and R are related. The lack of a quadratic term for π and/or MR in eq 2 further suggested that this data set did not contain R-groups near the optima for these parameters.

Using these characteristics described by eq 2 as a guide, we prepared a data set of hypothetical compounds where the substituent parameters in Table 2 existed in the literature.[16−18] In this hypothetical data set were the isomeric pyridines hypo-**1** (where R = 4-Pyr) and hypo-**2** (where 2-Pyr) with predicted K_i values of 0.122 and 0.097 nM, respectively. The pyridines were of interest because of the possibility of influencing the lipophilicity, size, and/or electronic effects by making appropriate aromatic substitutions. Unfortunately, none of the analogues (**3**−**15**) of **2** met our antiviral criteria of an IC_{90} < 30.0 nM; only **6** (R = CH_3, IC_{90} = 80.5 nM) and **13** (R = CH_2CF_3, IC_{90} = 92.5 nM) came close.

In an attempt to determine the optimal regiochemistry of the aromatic nitrogen in the pyridine moiety, we synthesized the three isomeric pyridine derivatives hypo-**1** = 16 (where R = 4-Pyr), **17** (where R = 3-Pyr), and hypo-**2** = **18** (where R = 2-Pyr). The isomeric pyridine cyclic ureas had the same ClogP (6.70) and CMR (21.64). However, as protease inhibitors, **18** (K_i = 0.043 nM) was better than **17** (K_i = 0.290 nM) which was better than **16** (K_i = 0.410 nM). These results were very different from those predicted by eq 2. Unexpectedly, **18** had met our biological objectives. On the basis of these teachings, we concluded that the presence and regiochemistry of a potential hydrogen bond acceptor (pyridyl nitrogen) contributed to overall protease inhibition which in turn influenced viral replication inhibition. The best location for this HBA is *ortho* to the amide nitrogen as represented by **18** (2-Pyr) (see Figure 2). It is possible that the pyridyl nitrogen is acting as a base to form a salt bridge, influence the 'quality' of hydrogen-bonding properties of the amide proton, or influence the pK_a of the amide proton. Clearly the nitrogen is important as demonstrated by the contrast in activity of the phenylcarboxamide **15** (K_i = 0.370 nM, IC_{90} = 483.0 nM) and the 2-pyridinyl derivative **18** (K_i = 0.043 nM, IC_{90} = 2.8 nM). Since the only difference among the three isomers was the placement of the pyridinyl nitrogen, it is possible that the nitrogen of the 2-pyridine defined a new binding site with the enzyme as illustrated in Figure 2b. This potential HBA resulted in greater than predicted protease inhibition.

Having established that the 2-Pyr moiety produced the best anti-HIV activity, we next investigated the effect of substitutions on the 2-Pyr nucleus. A series of 2-picoline carboxamides (**19**, R = 2-(3-Me-Pyr); **20**, R = 2-(4-Me-Pyr); **21**, R = 2-(5-Me-Pyr); and **22**, R = 2-(6-Me-Pyr)) was synthesized and evaluated. As can be seen in the data in Table 1, moving the methyl group from the 3-position to the 6-position resulted in improvements in K_i and IC_{90}. All four isomers have the same CMR, and only **19** has a different ClogP (6.08) from the other picolines (ClogP = 7.70). Pharmacologi-

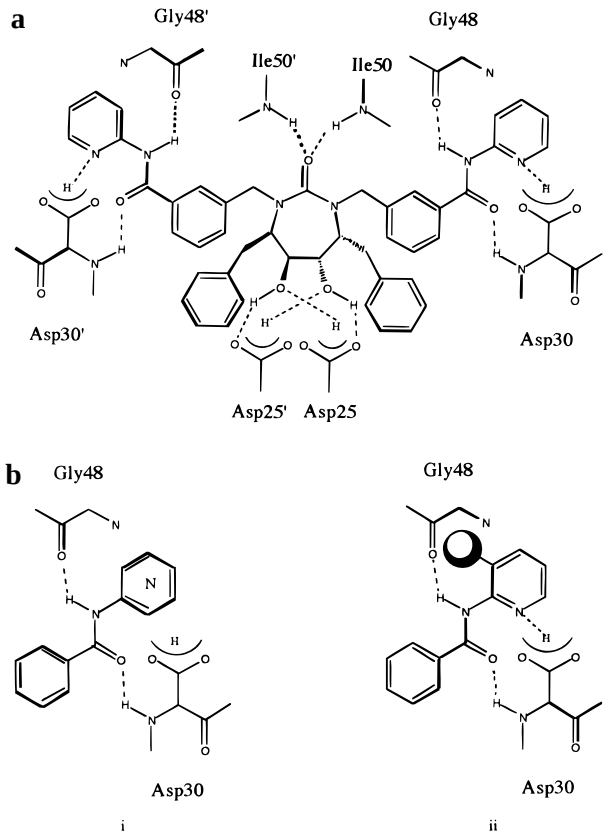


Figure 2. (a) Proposed interactions between **18** and HIV protease active site and (b) proposed interaction between the enzyme active site and (i) isomeric pyridine nitrogen and (ii) 3-substitution on the pyridine ring.

cally, **19** was determined to be different from the other three isomers. (Note that from this series and other carboxamides (not reported), the relationship between isomerism and potency is as follows: 6-Me ≥ 5-Me > 4-Me ≫ 3-Me.) The results from the picoline series suggested that a pocket existed (size and/or lipophilicity limiting) as defined by the 5-position on the pyridine ring (see Figure 2b). The less than anticipated activity of **25** (R = 3,5-di-Cl-Pyr) was further evidence for this conclusion. The importance of this structural property of the inhibitors was exemplified by the improvement in protease inhibition by **21** (R = 2-(5-Me-Pyr)) over **18** (R = 2-Pyr).

Replacing the $-CH_3$ of **20** with $-CF_3$ of **28** resulted in a loss of protease (K_i = 0.027 vs 0.085 nM) and antiviral (IC_{90} = 7.70 vs 63.4 nM) potencies. The change resulted in an increase in ClogP (18%), a smaller increase in CMR (5%), and an upfield chemical shift of 0.51 ppm for the amide proton. All individually or in combination could be responsible for the reduction in potencies. The replacement of -H on **30** (K_i = 0.152 nM, IC_{90} = 220.3 nM) with $-CH_3$ produced **27** (K_i = 0.085 nM, IC_{90} = 124.4 nM), which was a better anti-HIV compound. Increasing the size and lipophilicity of **18** with two methyl groups to give **23** or by adding one methyl to **20** or **21** to give **23** did not significantly change K_i or IC_{90} values. These results would suggest that for a given K_i, increasing lipophilicity while decreasing or maintaining the size of the R-group should improve translation (viral replication inhibition).

Compounds **19**−**23** are less electron deficient than **24** (R = 2-(5-Cl-Pyr), **26** [R = 2-(5-Br-Pyr)], and **25** (R = 2-(3,5-di-Cl-Pyr)) because of the electron-withdrawing substituents. In terms of protease inhibition, **24** (K_i = 0.012 nM) < **26** (K_i = 0.035 nM) ≪ **25** (K_i = 0.245 nM), and similarly for viral replication, **24** (IC_{90} = 14.7 nM) < **26** (IC_{90} = 28.2 nM) < **25** (IC_{90} = 43.0 nM). The large drop-off in K_i for **25** may be associated with the 'steric hindrance' caused by the 3-Cl substituent. For this small data set, we concluded that the introduction of an electron-withdrawing group on the azine did not enhance activity.

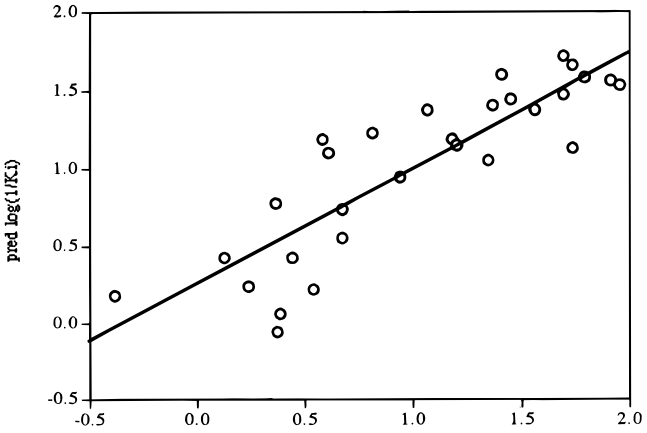
A comparison between **15** (R = Ph, K_i = 0.370 nM, IC_{90} = 483.0 nM), **29** (R = Prz, K_i = 0.034 nM, IC_{90} = 3.5 nM), **30** (R = 2-Pym, K_i = 0.152 nM, IC_{90} = 220.3 nM), and **18** (R = 2-Pyr, K_i = 0.043 nM, IC_{90} = 2.8 nM) further demonstrated that the nitrogen in the R-group was important for activity. The pharmacological difference between **29** and **30** was the first indication that ClogP and CMR may not be the main contributors to activity since both compounds had ClogP = 5.36 and CMR = 21.21. These two diazines differed only in the placement of the nitrogens in the aromatic nucleus which may contribute to different degrees of binding to the enzyme which resulted in different K_is. The Prz derivative was a better protease inhibitor than the Pym derivative, and **29** was a significantly better inhibitor of replication than **30**. These results were added evidence that the placement of the nitrogen(s) in R was important for both enzyme inhibition and viral replication inhibition.

QSAR for log(1/K_i). One of the major problems encountered in this study was the lack of published substituent constants for the R-groups which could be used in a classical (traditional) QSAR. What was needed was a set of parameters such as ClogP and CMR that could be calculated (semiempirical) and used in a multiple linear regression (MLR) analysis.[21−23] By using geometry-optimized structures, we were able to generate a set of quantum mechanical constants for ionization potential (IP), energy of the highest occupied orbital (ϵ_{HOMO}), energy of the lowest unoccupied orbital (ϵ_{LUMO}), dipole moment (DM), and molecular volume (MV/100 and $(MV/100)^2$), where $\epsilon_{HOMO} = -IP$ and ϵ_{LUMO} = electron affinity (EA). Because we believed that the regiochemistry of the 2-Pyr nitrogen was important for activity, an indicator variable (I) was added to regression models for all compounds containing a nitrogen approximating that of the 2-Pyr nitrogen. These parameters along with the molecular parameters $ClogP^2$, ClogP, CMR^2, and CMR were used in a stepwise MLR to derive regression equations for K_i and IC_{90} for the carboxamides **2**−**30**. This analysis produced eq 3 (see Chart 1) which contained the parameters for lipophilicity ($ClogP^2$ and ClogP), volume (MV/100), electronic (IP), and the indicator variable (I). The cross-correlation matrix for eq 3 is shown in Table 5. The comparison of the predicted K_i values from eqs 3 and 2 was in good to excellent agreement (n = 13, r^2 = 0.797, s = 0.278).

$$\log(1/K_i)_{2-30} = -1.273(\pm 0.512)\mathrm{IP} + 0.076(\pm 0.021)\mathrm{ClogP}^2 - 0.866(\pm 0.270)\mathrm{ClogP} - 1.006(\pm 0.330)\mathrm{MV}/100 + 0.990(\pm 0.184)I + 20.770(\pm 5.267) \quad (3)$$

$$\mathrm{ClogP}_0 = 5.697,\ n = 29,\ r = 0.864,\ s = 0.349,\ F_{5,23} = 13.495_{(0.0001)}$$

Chart 1. Found vs Predicted Protease Inhibition Using Eq 3



In an attempt to develop a QSAR for viral replication inhibition (IC_{90}), we conducted a stepwise MLR on log(K_i), ClogP^2, ClogP, CMR^2, CMR, MV/100, (MV/100)^2, and the hydrogen-bonding property of the R-group where hydrogen bond donor, to produce eq 4 (see Table 7 and Chart 2). Equation 4 suggests that larger less hydrogen bond-donating protease inhibitors will produce a better antiviral agent. However, the quadratic term for CMR indicates that the relationship between molecular size and activity is not linear.

$$\log(1/IC_{90})_{2-30} = -0.863(\pm 0.135)\log(K_i) + .004(\pm 0.001)CMR^2 - 1.062(\pm 0.337)HBD - 4.226(\pm 0.539) \quad (4)$$

$$n = 29,\ r = 0.878,\ s = 0.403,\ F_{3,25} = 28.081_{(0.0001)}$$

Predictability of Eqs 3 and 4. In an attempt to determine the utility of eqs 3 and 4 as predictors of protease inhibition and viral replication inhibition, respectively, a series of heteroaromatic carboxamides (test-**1**−test-**8**) was examined. Compounds test-**1**−test-**8** were synthesized contemporaneously with this QSAR study.[24] Using the parameters in Table 4 and eq 3 and the parameters in Table 6 and eq 4, we were able to calculate and compare the K_i and IC_{90} values. Within the error of the assay (±40%), we found the predicted K_i values to be in good agreement with those observed. All predicted IC_{90} values from eq 4 were in good agreement with those found. In an attempt to extend the utility of the QSAR, we also applied the predicted K_i from eq 3 to eq 4 and found a good to excellent agreement between the observed antiviral activity and the predicted activity. These results buttressed our confidence in eqs 3 and 4.

Conclusion

A series of N,N′-disubstituted cyclic urea bis(3-benzamides) was synthesized and evaluated for anti-HIV activity. The objective was to find benzamides with HIV protease activity with K_i < 0.050 nM that translated into antiviral replication activity with IC_{90} < 20 nM. The objective was met with the discovery of **18**, **20**−**22**, **24**, and **29**. These bis-carboxamide cyclic ureas are more potent than the 'reference compounds' DMP323,[4] VX-478,[25] ABT-538,[26] Ro31-8959,[27] and MK639 (L-735,-524)[28] (also see De Clercq[29]). A retrospective analysis of the data showed that viral replication inhibition was related to the ability of the compound to inhibit HIV protease (K_i) and the volume (CMR) and lipophilicity (ClogP) of the amide substituent (R). Increasing inhibitor lipophilicity while decreasing molecular size improved IC_{90}. The SAR also showed that the amide substituent should contain a hydrogen bond acceptor whose position was best represented by the nitrogen in 2-pyridine. This represented one of the more important findings from this study: the identification of an additional binding site (hydrogen bond acceptor) as defined by the location of the nitrogen in the 2-pyridyl series. This inhibitor property was represented in the QSAR equations by an indicator variable, *I*. The finding has been extended to other heteroaromatic series with a hydrogen bond acceptor *ortho* to the amide nitrogen.

The ability to develop a robust traditional QSAR for protease inhibition was limited because of the lack of available substituent constants for the R-group. Because of this limitation, the predictive value of the QSAR was limited. Because of this limitation, we chose to investigate the use of semiempirical constants to develop the QSARs. Because the biological evaluation of the compounds was faster than the synthesis of the compounds, we were in need of structure−activity information to facilitate our choices for synthetic targets. The results from these studies have been instrumental in our understandings of the enzyme-inhibitor interactions and have been applied successfully to the discovery of even more potent cyclic ureas. This study has also been used to better understand the pharmacokinetics, toxicity, and drug resistance profile of the anti-HIV cyclic ureas and in the selection of other potential drug development candidates.

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. Thin layer chromatography (TLC) was performed on silica gel plates.

Chemical Synthesis. Dimethyl (3aα,4*β*,8α,8a*β*)-3,3′-[[Dihydro-2,2-dimethyl-6-oxo-4,8-bis(phenylmethyl)-4*H*-1,3-dioxolo-[4,5-*e*][1,3]diazepine-5,7(6*H*,8*H*)-diyl]bis(methylene)]bis[benzoate] (**1b**). A suspension of NaH (5.46 g, 136.4 mmol) in 250 mL of dry DMF was cooled in an ice bath and treated with the cyclic urea **1a** (10.00 g, 27.28 mmol). The mixture was stirred in the ice bath for 30 min under dry nitrogen and treated with methyl 3-(bromomethyl)benzoate (17.18 g, 75.02 mmol). The mixture was stirred at room temperature for 72 h and poured into a mixture of 500 g of cracked ice and saturated NH_4Cl. The mixture was stirred until the ice had melted, and the resulting solid was collected by filtration, washed with water, and dissolved in 200 mL of EtOAc. The EtOAc solution was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a thick oil. The crude product was purified by column chromatography over silica gel using EtOAc−hexane (10:90). Appropriate fractions were combined and concentrated. The desired product was collected after recrystallization from hexanes in 66% (11.9 g) yield: mp 101−102 °C; ^{1}H NMR (DMSO-d_6 TMS, 300 MHz) δ 1.33 (s, 6H, CH_3CCH_3), 2.70 (dd, 2H, Ar′CH), 2.84 (m, 2H, Ar′CH), 3.35 (d, J = 13.9 Hz, 2H, NCH), 3.81 (s, 6H, OCH_3),

Table 4. Found vs Predicted K_i Values for **2**−**30** Using Eq 3

compd	R	IP or $-\epsilon_{HOMO}$	MV	ClogP	CMR	*I*	K_i (nM) found	K_i (nM) pred (eq 3)
2	H	9.416	494.20	3.850	17.035	0	0.060	0.028
3	NH_2	9.303	532.05	2.990	17.770	0	0.018	0.024
4	OH	9.318	521.74	3.050	17.341	0	0.020	0.021
5	OCH_3	9.314	544.04	4.630	18.269	0	0.080	0.098
6	CH_3	9.391	527.90	4.262	17.962	0	0.060	0.072
7	CH_2CH_3	9.379	560.40	5.320	18.890	0	0.210	0.207
8	$CH(CH_3)_2$	9.373	610.05	5.938	19.818	0	0.580	0.652
9	$CH_2CH_2CH_3$	9.376	593.80	6.378	19.818	0	0.280	0.421
10	$CH_2CH_2CH_2CH_3$	9.378	660.70	7.436	20.745	0	0.424	1.278
11	$C(CH_3)_3$	9.360	625.00	6.736	20.745	0	2.600	0.744
12	CH_2-C_3H_5	9.379	592.30	6.208	20.470	0	0.710	0.425
13	CH_2CF_3	9.469	575.70	6.838	18.983	0	0.210	0.315
14	CH_2CN	9.498	557.70	2.999	18.918	0	0.063	0.079
15	Ph	9.110	623.60	7.840	22.057	0	0.370	0.187
16	4-Pyr	9.520	616.30	6.700	21.635	0	0.410	0.986
17	3-Pyr	9.394	616.70	6.700	21.635	0	0.290	0.687
18b	2-Pyr	9.233	616.30	6.700	21.635	1	0.010	0.043
19	2-(3-CH_3-Pyr)	9.105	648.10	6.078	22.563	1	0.260	0.072
20	2-(4-CH_3-Pyr)	9.183	649.10	7.698	22.563	1	0.030	0.047
21	2-(5-CH_3-Pyr)	9.057	648.40	7.698	22.563	1	0.010	0.032
22	2-(6-CH_3-Pyr)	9.106	648.70	7.698	22.563	1	0.020	0.037
23	2-(4,6-di-CH_3-Pyr)	9.059	681.30	8.696	23.490	1	0.020	0.029
24	2-(5-Cl-Pyr)	9.332	639.60	8.487	22.618	1	0.010	0.031
25	2-(3,5-di-Cl-Pyr)	9.448	663.30	8.294	23.601	1	0.240	0.089
26	2-(5-Br-Pyr)	9.443	650.50	8.787	23.189	1	0.040	0.040
27	2-(4-CH_3-Pym)	9.375	640.10	6.357	22.140	1	0.120	0.126
28	2-(5-CF_3-Pyr)	9.526	662.40	9.098	22.656	1	0.090	0.047
29	2-Prz	9.468	608.10	5.359	21.213	1	0.020	0.083
30	2-Pym	9.390	607.50	5.359	21.213	1	0.150	0.065

Table 5. Correlation Matrix for the Parameters in Eq 3

variable	IP	ClogP^2	ClogP	MV/100	*I*
IP	1.000	−0.221	−0.229	−0.304	−0.321
ClogP^2		1.000	0.988	0.865	0.564
ClogP			1.000	0.883	0.550
MV/100				1.000	0.667
I					1.000

4.00 (m, 4H, OCHCH), 4.54 (d, J = 13.8 Hz, 2H, NCH), [6.86 (m, 4H), 7.21 (m, 6H), 7.51 (m, 4H), 7.84 (m, 4H), Ar]; IR (KBr) 1724 (C═O), 1634 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 680 (M + NH_4); $[\alpha]^{20}_D$ +113.88° (*c* = 0.49, MeOH). Anal. Calcd for $C_{40}H_{42}N_2O_7$, MW 662.78: C, 72.49; H, 6.40; N, 4.24. Found: C, 72.42; H, 6.26; N, 4.19.

(3aα,4*β*,8α,8a*β*)-3,3′-[[Dihydro-2,2-dimethyl-6-oxo-4,8-bis(phenylmethyl)-4*H*-1,3-dioxolo[4,5-*e*][1,3]diazepine-5,7(6*H*,8*H*)-diyl]bis(methylene)]bis[benzoic acid] (1c). A suspension of 60% NaH in mineral oil (4.36 g, 109.12 mmol) in 250 mL of dry DMF was treated with **1a** (10.0 g, 27.28 mmol) and stirred at room temperature for 30 min, cooled in an ice bath, treated with methyl 3-(bromomethyl)benzoate (18.74 g, 81.84 mmol) in 20 mL of DMF, and stirred in the ice bath for 1 h and at room temperature for 16 h. The mixture was poured into 1 kg of ice containing 100 mL of saturated NH_4Cl and stirred until the ice had melted. The resulting precipitate was collected by decanting the aqueous phase, dissolved in 250 mL of CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to a thick dark oil. The crude product was column chromatographed on silica gel (100 g/1 g crude product) using hexanes−EtOAc (4:1) as mobile phase. Appropriate fractions were combined and concentrated *in vacuo* to give the desired intermediate **1b** as a thin amber oil in 82% (14.77 g) yield: ^{1}H NMR (300 MHz, $CDCl_3$ TMS) δ 1.36 (s, 6H, CH_3CCH_3), 2.9 (m, 4H, Ar′CH_2), 3.15 (d, J = 14.6 Hz, 2H, NCH), 3.77 (d, J = 11.0 Hz, 2H, Ar′CCH), 3.84 (s, 6H, OCH_3), 3.91 (s, 2H, OCH), 4.95 (d, J = 14.6 Hz, 2H, NCH), [7.08 (d, 4H), 7.3 (m, 10H), 7.87 (s, 2H), 7.92 (m, 2H), Ar]; IR (neat) 1724 (C═O), 1632 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 663 (M + 1) for $C_{40}H_{42}N_2O_7$ MW 662.30.

The ester **1b** (12.23 g, 18.47 mmol) in 100 mL of dioxane was treated with 1 N NaOH (40 mL) and stirred at room temperature until TLC ($CHCl_3$-EtOAc, 3:2) indicated that no starting material remained. The mixture was made acidic with citric acid, and the resulting gum was collected by decanting the liquid phase. The gum was dissolved in 200 mL of CH_2Cl_2, washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the desired product **1c** as a white crystalline solid in 95% (12.1 g) yield: mp 218−220 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$ TMS) δ 1.36 (s, 6H, CH_3CCH_3), 2.86 (dd, 2H, Ar′CH), 3.00 (d, 2H, Ar′CH), 3.21 (d, J = 14.6 Hz, 2H, NCH), 3.82 (d, J = 11.0 Hz, 2H, Ar′CCH), 3.95 (s, 2H, OCH), 4.93 (d, J = 14.6 Hz, 2H, NCH), 7.05−8.07 (m, 18H, Ar); IR (KBr) 1694 (C═O), 1644 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 635 (M + 1). Anal. Calcd for $C_{38}H_{38}N_2O_7$, MW 634.74: C, 71.91; H, 6.03, 6.12; N, 4.41. Found: C, 71.69; H, 6.12; N, 4.44.

(3aα,4*β*,8α,8a*β*)-3,3′-[[Dihydro-2,2-dimethyl-6-oxo-4,8-bis(phenylmethyl)-4*H*-1,3-dioxolo[4,5-*e*][1,3]diazepine-5,7(6*H*,8*H*)-diyl]bis(methylene)]bis[benzonitrile] (1h). A suspension of NaH (0.53 g, 22.2 mmol) in 30 mL of dry THF was treated in small portions with **1a** (3.7 g, 10.1 mmol). The mixture was stirred at room temperature for 30 min and treated with α-bromo-*m*-tolunitrile (4.3 g, 21.9 mmol). The mixture was stirred at room temperature for 16 h under dry nitrogen and inspected by MS that showed *m/e* 482 (M + 1) for monosubstituted cyclic urea and *m/e* 597 (M + 1) for disubstituted cyclic urea. An additional 1 equiv of NaH was added, and the mixture was stirred for 30 min, treated with an additional 1 equiv of α-bromo-*m*-tolunitrile, and refluxed for 16 h. The mixture was cooled to room temperature and poured onto 250 g of cracked ice. The mixture was stirred until the ice had melted and extracted with 2 × 100 mL of EtOAc. The EtOAc solution was washed with water and brine, dried over $MgSO_4$, filtered, and inspected by TLC ($CHCl_3$−EtOAc, 3:2). The mixture contained two components (R_f = 0.75 and 0.65), neither of which was the starting cyclic urea (R_f = 0.55) nor starting α-bromo-*m*-tolunitrile. The mixture was concentrated to a solid which was recrystallized from 50 mL of 2-propanol to give the desired product in 35% (2.10 g) yield: mp 155−156 °C; R_f 0.65 ($CHCl_3$−EtOAc, 3:2); ^{1}H NMR (300 MHz, $CDCl_3$ TMS) δ 1.44 (s, 6H, CH_3), 2.75 and 3.0 (2m, 4, $PhCH_2$) 3.26 (d, J = 14.6 Hz, 2H, NCH_2), 3.77 (d, J = 11.0 Hz, 2H, NCH), 3.96 (s, 2H, OCH), 4.73 (d, J = 14.7 Hz, 2H, NCH_2), [6.97 (m, 4H), 7.26 (m, 6H), 7.4 (m, 6H), 7.54 (m, 2H), Ar]; IR (Nujol) 2228 (CN), 1638 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 597

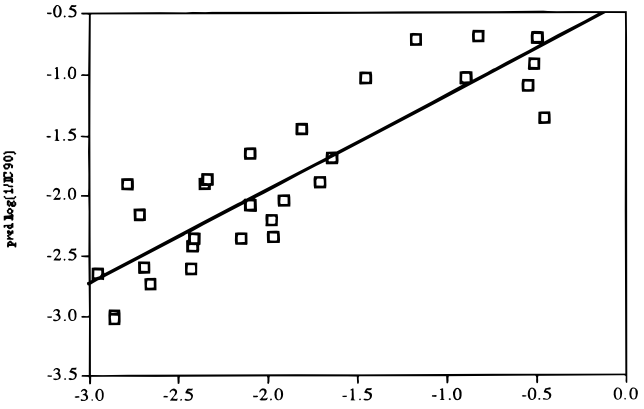
Table 6. Found vs Predicted IC_{90} Using Eq 4, Predicted IC_{90} Using Eq 4, and Predicted K_i from Eq 3

compd	R	found IC_{90} (nM, SD <±36%)	log K_i	ClogP	CMR	HBD	HBA	IC_{90} (nM) SD <±36%	IC_{90} (nM) pred (eq 4)	pred IC_{90} (eq 4) and pred K_i (eq 3)
2	H	708.6	−1.409	3.85	17.04	1	0	708.6	1065.1	728.1
3	NH_2	883.6	−1.745	2.99	17.77	1	1	883.6	442.1	521.1
4	OH	448.2	−1.699	3.05	17.34	1	1	448.2	548.6	523.9
5	OCH_3	214.5	−1.347	4.63	18.27	0	1	214.5	72.8	130.0
6	CH_3	80.5	−1.180	4.26	17.96	0	0	80.5	111.1	109.0
7	CH_2CH_3	138.7	−0.678	5.32	18.89	0	0	138.7	227.2	204.2
8	$CH(CH_3)_2$	265.9	−0.237	5.94	19.82	0	0	265.9	404.8	408.7
9	$CH_2CH_2CH_3$	259.0	−0.445	6.38	19.82	0	0	259.0	268.0	280.2
10	$CH_2CH_2CH_2CH_3$	255.3	−0.373	7.44	20.75	0	0	255.3	226.5	534.6
11	$C(CH_3)_3$	717.1	0.380	6.74	20.75	0	0	717.1	1011.2	335.2
12	CH_2-C_3H_5	485.1	−0.130	6.21	20.47	0	0	485.1	402.9	227.1
13	CH_2CF_3	92.5	−0.678	6.84	18.98	0	0	92.5	220.7	284.8
14	CH_2CN	596.3	−1.201	3.00	18.92	0	1	596.3	79.7	87.8
15	Ph	510.4	−0.367	7.84	22.06	0	1	510.4	144.0	64.1
16	4-Pyr	93.7	−0.387	6.70	21.64	0	1	93.7	161.0	312.3
17a	3-Pyr	123.2	−0.538	6.70	21.64	0	1	123.2	119.4	228.9
18	2-Pyr	2.8	−1.367	6.70	21.64	0	1	2.8	23.0	21.1
19	2-(3-Me-Pyr)	50.3	−0.585	6.08	22.56	0	1	50.3	77.3	23.4
20	2-(4-Me-Pyr)	7.7	−1.569	7.70	22.56	0	1	7.7	11.0	16.3
21	2-(5-Me-Pyr)	3.1	−1.959	7.70	22.56	0	1	3.1	5.0	11.7
22	2-(6-Me-Pyr)	3.2	−1.699	7.70	22.56	0	1	3.2	8.5	13.3
23	2-(4,6-di-Me-Pyr)	6.6	−1.796	8.70	23.49	0	1	6.6	4.9	7.5
24	2-(5-Cl-Pyr)	14.7	−1.921	8.49	22.62	0	1	14.7	5.3	10.9
25	2-(3,5-di-Cl-Pyr)	43.0	−0.611	8.29	23.60	0	1	43.0	49.4	18.8
26	2-(5-Br-Pyr)	28.2	−1.456	8.79	23.19	0	1	28.2	10.8	11.0
27	2-(4-Me-Pym)	124.4	−0.939	6.36	22.14	0	1	124.4	44.7	44.2
28	2-(5-CF_3-Pyr)	63.4	−1.071	9.10	22.66	0	1	63.4	28.5	15.6
29	2-Prz	3.5	−1.745	5.36	21.21	0	1	3.5	12.6	43.1
30	2-Pym	220.3	−0.818	5.36	21.21	0	1	220.3	79.4	34.9

Table 7. Cross-Correlation Matrix for the Parameter in Eq 4

variable	log K_i	CMR^2	HBD
log K_i	1.000	−0.047	−0.330
CMR^2		1.000	−0.584
HBD			1.000

Chart 2. Found vs Predicted Viral Replication Inhibition Using Eq 4



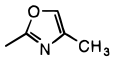
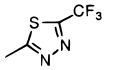
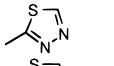
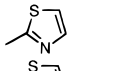
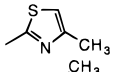
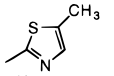
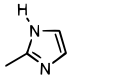
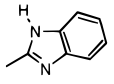
(M + 1); $[\alpha]^{20}_D$ +124.56° (c = 0.228, MeOH). Anal. Calcd for $C_{38}H_{36}N_4O_3 \cdot H_2O$, MW 614.75: C, 74.24; H, 6.23; N, 9.11. Found: C, 74.36; H, 6.47; N, 8.82.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[benzamide] (2). A solution of **1h** (0.33 g, 0.56 mmol) in EtOH (10 mL) and KOH (0.325 g, 5.6 mmol) was stirred at room temperature in a water bath for 30 min and treated with 5 mL of 30% H_2O_2. The mixture was stirred at room temperature for 24 h and inspected by TLC ($CHCl_3$−MeOH, 9:1) (R_f R-CN = 0.85 and R_f R-$CONH_2$ = 0.33) and IR and found to contain no starting nitrile at 2228 cm^{-1}. The mixture was concentrated *in vacuo*, and the residue was triturated with 100 mL of 10% citric acid. The resulting white solid was collected by filtration, washed with additional water, and dried. The "benzamide−acetonide" was dissolved in acetonitrile (10 mL), treated with 1 N HCl (10 mL), and stirred at 50 °C until no starting acetonide remained as evidenced by TLC ($CHCl_3$−MeOH, 9:1). The mixture was concentrated *in vacuo*, and the residue was triturated with water at 70 °C and placed in the cold for 3 h. The resulting white crystals were collected by filtration, washed with cold water, and dried *in vacuo* to give the desired product in 92% (0.305 g) yield: mp 143−145 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.75 (dd, 2H, Ar′CH), 3.03 (m, 4H, Ar′CH, NCH), 3.49 (s, 2H, OCH), 3.51 (d, J = 11.9 Hz, 2H, OCCH), 4.65 (d, J = 14.3 Hz, 2H, NCH), 4.6 (br s, 2H, OH), [6.94 (d, 4H), 7.23 (m, 10H), 7.40 (dd, 2H), 7.7 (m, 2H, Ar)], 7.76 and 7.95 (2s, $CONH_2$); IR (KBr) 3348 (OH), 1662 (C═O), 1616 (C═O) cm^{-1}; UV−vis (c = 0.016 mg/mL, MeOH) λ_{max} 274 (1852), 222 (38 673) nm; MS (NH_3-DCI) m/e 610 (M + NH_4); $[\alpha]^{20}_D$ +121.00° (c = 0.100, MeOH). Anal. Calcd for $C_{35}H_{36}N_4O_5$, MW 592.70: C, 70.93; H, 6.12; N, 9.45. Found: C, 70.84; H, 5.91; N, 9.23.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[benzoic acid] Dihydrazide (3). A solution of **1b** (0.500 g, 0.75 mmol) in 25 mL of MeOH was treated with anhydrous hydrazine (0.5 mL, 15.3 mmol) and stirred at room temperature for 16 h. The mixture was diluted to the cloud point with water, allowed to stand for 2 h, and further diluted to 250 mL with water. The resulting white crystals were collected by filtration, washed with water, and dried *in vacuo* to give the intermediate hydrazide−acetonide in 99% (0.493 g) yield: mp 76−78 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 1.33 (d, 6H, CH_3CCH_3), 2.74 (dd, 2H, Ar′CH), 2.85 (d, 2H, Ar′CH), 3.32 (d, 2H, NCH), 3.81 (s, 4H, NH_2), 4.0 (m, 4H, CHCHCHCH), 4.57 (d, 2H, NCH), [6.88 (m, 4H), 7.20 (m, 6H), 7.37 (m, 1H), 7.5 (m, 3H), 7.75 (m, 1H), 7.86 (m, 3H), Ar], 9.75 (s, 2H, NH); MS (NH_3-DCI) m/e 663 (M + 1), 685 (M + NH_4).

A solution of the acetonide (0.450 g, 0.679 mmol) in 10 mL of acetonitrile was treated with 10 mL of 1 N HCl and stirred at room temperature until no acetonide was evidenced by TLC ($CHCl_3$−MeOH, 9:1). Fine white needles formed (HCl salt?). The mixture was treated with 100 mL of 5% $NaHCO_3$, stirred for 1 h, and filtered to collect the white solid. The solid was washed with water and dried *in vacuo* to give the desired product in 92% (0.401 g) yield from the acetonide or 91% from **1b**: mp 161−163 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.72 (dd, 2H, Ar′CH), 2.97 (d, 2H, Ar′CH), 3.07 (d, J = 13.9

Table 8. Found vs Predicted Activity Using Eqs 3 and 4 for a Set of Compounds (test-**1**−test-**8**) Not Used To Generate the Regression Equations

cmpd	R	IP	ClogP	CMR	MV	I	HBD	fnd K_i sd < ± 40%	pred K_i eq 3	fnd IC_{90} sd < ± 36%	pred IC_{90} eq 4
Test-1		9.271	5.590	20.990	611.60	1	0	0.064	0.046	59.6	40.7
Test-2		9.666	7.002	21.852	637.70	1	0	0.180	0.204	74.8	73.2
Test-3		9.557	4.673	20.831	590.80	1	0	0.110	0.056	51.3	68.7
Test-4		9.475	6.244	21.253	599.00	1	0	0.027	0.061	1.7	17.6
Test-5		9.346	6.782	22.181	632.00	1	0	0.025	0.077	4.1	11.8
Test-6		9.351	6.782	22.181	631.50	1	0	0.014	0.076	17.8	7.2
Test-7		9.003	5.276	20.494	585.70	1	1	0.014	0.011	45.5	150.2
Test-8		8.652	8.464	23.870	664.70	1	1	0.024	0.007	3.9	69.0

Hz, 2H, NCH), 3.49 (m, 4H, CHCHCHCH), 3.82 (s, 4H, NH_2), 4.62 (d, 14.2H), 5.15 (s, 2H, OH), [6.92 (m, 4H), 7.23 (m, 6H), 7.44 (m, 4H), 7.6 (m, 1H), 7.8 (m, 3H), Ar], 7.24 (s, 2H, NH); IR (KBr) 3440 (OH), 1724 (C═O), 1642 (C═O) cm^{-1}; MS (ESI) *m/e* 623 (M + 1); $[\alpha]^{20}_D$ +106.73° (*c* = 0.208, MeOH). Anal. Calcd for $C_{35}H_{38}N_6O_5$, MW 622.72: C, 67.51; H, 6.15; N, 13.50. Found: C, 67.83; H, 6.31; N, 13.82.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-hydroxybenzamide] (4). A solution of **1c** (0.635 g, 1.000 mmol) in 20 mL of THF was treated with (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP, Castro's reagent) (1.33 g, 3.0 mmol), stirred for 15 min, and treated with hydroxylamine hydrochloride (0.5 g, 7.2 mmol) and triethylamine (0.25 g, 2.5 mmol). The reaction mixture was stirred for 48 h and concentrated *in vacuo*. The residue was partitioned between 100 mL of water and 100 mL of EtOAc. The organic phase was washed with 3 × 100 mL of 5% $NaHCO_3$, water, and brine, dried over $MgSO_4$, filtered, concentrated to a foam (0.518 g, 78% yield), and found to be homogenous by TLC ($CHCl_3$−MeOH, 4:1): ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 1.27 (s, 6H, CH_3CCH_3), 2.7−2.9 (m, 4H, Ar′CH_2), 3.22 (d, *J* = 13.9 Hz, 2H, NCH), 4.0 (m, 4H, CHCHCHCH), 4.56 (d, *J* = 13.9 Hz, 2H, NCH), 6.9−7.7 (m, 18H, Ar), 9.04 (d, 4H, CONH), 11.24 (s, 2H, NOH); IR (CH_2Cl_2 film) 3240 (OH and NH), 1636 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 665 (M + 1).

The acetonide (0.450 g, 0.68 mmol) was dissolved in 10 mL of MeOH and treated with 10 mL of 1 N HCl. The mixture was stirred at room temperature until no acetonide remained as evidenced by TLC ($CHCl_3$−MeOH, 4:1). The organic solvent was removed *in vacuo*, and the resulting solid was collected by filtration and dried *in vacuo* to give the desired product in 95% (0.404 g) yield from the acetonide or 74% from **1c**: mp 139−142 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.77 (dd, 2H, Ar′CH), 3.97 (m, 4H, Ar′CH, NCH), 3.49 (m, 4H, CHCH-CHCH), 4.64 (d, *J* = 14.3 Hz, 2H, Ar′CH), 5.13 (s, 2H, OH), [6.9 (m, 4H), 7.24 (m, 8H), 7.40 (dd, 2H), 7.64 (m, 3H), 7.80 (m, 1H), Ar], 9.03 (s, 2H, CONH), 11.22 (s, 2H, NOH); IR (KBr) 3242 (broad), 1644 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 625 (M + 1); $[\alpha]^{20}_D$ +109.13° (*c* = 0.21, MeOH). Anal. Calcd for $C_{35}H_{36}N_4O_7 \cdot 0.5H_2O$, MW 633.71: C, 66.34; H, 5.89: N, 8.84. Found: C, 66.60; H, 5.96; N, 8.90.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-(methyloxy)benzamide] (5). By substituting methoxylamine hydrochloride in the procedure used to synthesize **4**, the desired product was obtained in 93% (0.606 g) yield: mp 155° dec; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.7 (m, 2H, Ar′CH), 2.96 (m, 4H, Ar′CH, NCH), 3.5 (m, 4H, CHCHCHCH), 3.66 (s, 6H, OCH_3), 4.64 (d, *J* = 14.3 Hz, 2H, NCH), 5.15 (br s, 2H, OH), [6.95 (d, 4H), 7.24 (m, 6H), 7.32 (d, 2H), 7.42 (dd, 2H), 7.61 (m, 4H), Ar], 11.74 (s, 2H, NH); IR (KBr) 3406 (OH), 3218 (NH), 1650 (C═O), 1628 (C═O) cm^{-1}; UV−vis (*c* = 0.017 mg/mL, MeOH) λ_{max} 275 (2342) nm; MS (NH_3-DCI) *m/e* 653 (M + 1); $[\alpha]^{20}_D$ +73.05° (*c* = 0.204, MeOH). Anal. Calcd for $C_{37}H_{40}N_4O_7$, MW 652.75: C, 68.08; H, 6.18; N, 8.58. Found: C, 68.42; H, 6.17; N, 8.69.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-methylbenzamide] (6). By substituting methylamine hydrochloride in the procedure for **4**, the desired product was obtained in 99% (0.612 g) yield: mp 163−165 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.75 (m, 8H, Ar′CH, NCH_3), 2.96 (m, 4H, Ar′CH, NCH), 3.49 (m, 4H, CHCHCHCH), 4.66 (d, *J* = 14.0 Hz, 2H, NCH), 5.10 (br s, 2H, OH), [6.93 (d, 4H), 7.23 (m, 8H), 7.40 (dd, 2H), 7.7 (m, 4H), Ar], 8.41 (m, 2H, NH); IR (KBr) 3352 (OH, NH), 1640 (C═O) cm^{-1}; UV−vis (*c* = 0.014 mg/mL, MeOH) λ_{max} 275 (2017) nm; MS (NH_3-DCI) *m/e* 621 (M + 1); $[\alpha]^{20}_D$ +105.19° (*c* = 0.212, MeOH). Anal. Calcd for $C_{37}H_{40}N_4O_5$, MW 620.76: C, 71.59; H, 6.50; N, 9.03; Found: C, 71.27; H, 6.64; N, 8.81.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-(1-methylethyl)benzamide] (8). A mixture of **1c** (0.500 g, 0.787 mmol), HOBt (0.212 g, 1.57 mmol), and isopropylamine (0.139 g, 2.36 mmol) in EtOAc (20 mL) was stirred at room temperature and treated with DCC (0.357 g, 1.73 mmol). The mixture was purged with dry nitrogen, capped, and stirred at room temperature for 48 h. The mixture was treated with water (50 mL), stirred an additional 1 h, and filtered to remove the DCU. The mixture was filtered, and the organic layer was separated, washed with water, 5% $NaHCO_3$, water, and brine, dried over $MgSO_4$, stored at −20 °C for 4 h, and filtered to remove additional DCU. The filtrate was concentrated to a foam of constant weight (0.560 g): ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 1.12 (d, *J* = 6.6 Hz, 6H, CH_3CCH_3), 1.30 (s, 6H, CH_3CCH_3), 2.8 (m, 4H, Ar′CH_2), 3.23 (d, *J* = 14.3 Hz, 2H, NCH), 3.96 (d, *J* = 13.2 Hz, 2H, Ar′CCH), 4.01 (s, 2H, OCH), 4.07 (m, 2H, CCHC), 4.61 (d, *J* = 14.3 Hz, 2H, NCH), [6.92 (m, 4H), 7.22 (m, 6H), 7.39 (m, 4H), 7.74 (m, 4H), Ar], 8.21 (s, 2H, NH); MS (NH_3-DCI) *m/e* 734 (M + NH_4) for $C_{44}H_{52}N_4O_5$, MW 716.92.

The above intermediate acetonide was dissolved acetonitrile (10 mL), treated with 1 N HCl (10 mL), stirred for 16 h, diluted with 50 mL of water, and stirred for 1 h. The resulting white solid was collected by filtration, washed with water, and dried *in vacuo* to give the desired product in 77% (0.428 g) yield from

1c: mp 131−135 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 1.11 (2d, 12H, CH_3CCH_3), 2.77 (dd, 2H, Ar′CH), 2.96 (m, 4H, Ar′CH, NCH), 3.44 (s, 2H, OCH), 3.51 (d, J = 11.3 Hz, 2H, OCCH), 4.70 (d, J = 13.9 Hz, 2H, NCH), 5.14 (broad s, 2H, OH), [6.98 (d, 4H), 7.24 (m, 8H), 7.40 (dd, 2H), 7.69 (s, 2H), 7.73 (d, 2H), Ar], 8.20 (d, J = 7.7 Hz, 2H, NH); IR (KBr) 3346 (OH, NH), 1640 (C=O) cm^{-1}; UV−vis (c = 0.0290 mg/mL, MeOH) λ_{max} 267 (35 663), 218 (2264) nm; MS (NH_3-DCI) m/e 694 (M + NH_4); $[\alpha]^{20}_D$ +90.23° (c = 0.174, MeOH). Anal. Calcd for $C_{41}H_{48}N_4O_5 \cdot 2.5H_2O$, MW 721.90: C, 68.23; H, 7.40; N, 7.76. Found: C, 68.35; H, 7.08; N, 7.63.

(4α,5α,6β,7β)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-ethylbenzamide] (7). By substituting ethylamine hydrochloride in the method for **8**, the desired product was obtained in 92% yield: mp 160−162 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 1.09 (t, 6H, CH_3), 2.76 (m, 2H, Ar′CH), 2.97 (m, 4H, Ar′CH, NCH), 3.26 (m, 4H, NCH_2), 3.49 (m, 4H, CHCHCHCH), 4.69 (d, J = 14.3 Hz, 2H, NCH), 6.9−7.9 (m, 18H, Ar), 8.47 (m, 2H, NH); IR (KBr) 3348 (OH, NH), 1642 (C=O) cm^{-1}; UV−vis (c = 0.0180 mg/mL, MeOH) λ_{max} 275 (1968) nm; MS (NH_3-DCI) m/e 649 (M + 1); $[\alpha]^{20}_D$ +100.47° (c = 0.214, MeOH). Anal. Calcd for $C_{39}H_{44}N_4O_5$, MW 648.81: C, 72.20; H, 6.84; N, 8.64. Found: C, 72.33; H, 6.80; N, 8.53.

(4α,5α,6β,7β)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-propylbenzamide] (9). By substituting propylamine hydrochloride in the method for **8**, the desired product was obtained in 90% yield: mp 166−168°; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 0.85 (t, 6H, CH_3), 1.48 (m, 4H, CH_2), 2.51 (m, 2H, Ar′CH), 2.96 (m, 4H, Ar′CH, NCH), 3.18 (m, 4H, NCH_2), 3.47 (m, 4H, CHCHCHCH), 4.48 (d, J = 14.3 Hz, 2H, NCH), 6.9−7.9 (m, 18H, Ar), 8.45 (m, 2H, NH); IR (KBr) 3348 (OH, NH), 1640 (C=O) cm^{-1}; UV−vis (c = 0.0190 mg/mL, MeOH) λ_{max} 275 (2230) nm; MS (NH_3-DCI) m/e 677 (M + 1); $[\alpha]^{20}_D$ +88.61° (c = 0.202, MeOH). Anal. Calcd for $C_{41}H_{48}N_4O_5$, MW 676.86: C, 72.76; H, 7.15; N, 8.28. Found: C, 72.49; H, 7.16; N, 8.29.

(4α,5α,6β,7β)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-butylbenzamide] (10). By substituting *n*-butylamine in the procedure used to synthesize **4**, the desired product was obtained in 98% yield from **1c**: mp 132−134 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 0.84 (t, 6H, CH_3), 1.27 (m, 4H, CH_2), 1.45 (m, 4H, CH_2), 2.77 (dd, 2H, Ar′CH), 2.95 (m, 4H, Ar′CH, NCH), 3.21 (m, 4H, NCH_2), 3.45 (s, 2H, OCH), 3.50 (d, J = 11.1 Hz, 2H, Ar′CCH), 4.68 (d, J = 13.9 Hz, 2H, NCH), 5.12 (s, 2H, OH), [6.96 (d, 4H), 7.23 (m, 8H), 7.40 (dd, 2H), 7.68 (s, 2H), 7.70 (d, 2H), Ar], 8.40 (t, 2H, NH); IR (KBr) 3340 (OH, NH), 1640 (C=O) cm^{-1}; MS (NH_3-DCI) m/e 705 (M + 1); $[\alpha]^{20}_D$ +80.88° (c = 0.0204, MeOH). Anal. Calcd for $C_{43}H_{52}N_4O_5$, MW 704.92: C, 73.27; H, 7.45; N, 7.96. Found: C, 73.20; H, 7.66; N, 8.11.

(4α,5α,6β,7β)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-(1,1-dimethylethyl)benzamide] (11). By substituting *tert*-butylamine in the procedure used to synthesize **4**, the desired product was obtained in 97% yield from **1c**: mp 131−133 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 1.32 (s, 9H, ^{t}Bu), 2.79 (dd, 2H, Ar′CH), 2.95 (m, 4H, Ar′CH, NCH), 3.41 (s, 2H, OCH), 3.50 (d, J = 10.7 Hz, 2H, Ar′CCH), 4.73 (d, J = 14.0 Hz, 2H, NCH), 5.13 (s, 2H, OH), [7.03 (d, 4H), 7.26 (m, 8H), 7.35 (dd, 2H), 7.61 (s, 2H), 7.68 (d, 2H), Ar], 7.71 (s, 2H, NH); IR (KBr) 3384 (OH, NH), 1646 (C=O) cm^{-1}; MS (NH_3-DCI) m/e 705 (M + 1); $[\alpha]^{20}_D$ +74.50° (c = 0.20, MeOH). Anal. Calcd for $C_{43}H_{52}N_4O_5$, MW 704.92: C, 73.27; H, 7.44; N, 7.96, 7.84. Found: C, 73.23; H, 7.08; N, 7.84.

Alternatively, by substituting *tert*-butylamine in the modification of the Weinreb method, the desired product was obtained in an overall yield of 86% (0.43 g) from **1b**: mp 133 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 1.32 (s, 18H, ^{t}Bu), 2.80 (dd, 2H, Ar′CH), 2.96 (m, 4H, Ar′CH, NCH), 3.40 (s, 2H, OCH), 3.50 (d, J = 10.2 Hz, 2H, Ar′CCH), 4.68 (d, J = 14.3 Hz, 2H, NCH), 5.11 (s, 2H, OH), [7.03 (d, 4H), 7.26 (m, 8H), 7.38 (dd, 2H), 7.62 (s, 2H), 7.67 (d, 2H), Ar], 7.71 (s, 2H, NH); ^{1}H NMR (300 MHz, $CDCl_3$ TMS) δ 1.40 (s, 18H, ^{t}Bu), 2.84 (m, 2H, Ar′CH), 3.05 (m, 4H, Ar′CH, NCH), 3.57 (d, J = 11.4 Hz, 2H, Ar′CCH), 3.64 (s, 2H, OCH), 3.75 (br s, 2, OH), 4.85 (d, J = 13.6 Hz, 2H, NCH), 5.98 (s, 2H, NH), [7.21 (d, 4H), 7.3 (m, 10H), 7.43 (s, 2H), 7.54 (dd, 2H), Ar, Ar′]; IR (KBr) 3420 (OH, NH), 1646 (C=O) cm^{-1}; UV−vis (c = 0.019 mg/mL, MeOH) no clearly defined λ_{max}; MS (NH_3-DCI) m/e 703 (M + 1), 720 (M + NH_4); $[\alpha]^{20}_D$ +73.33° (c = 0.15, MeOH). Anal. Calcd for $C_{43}H_{52}N_4O_5$, MW 704.92: C, 73.27; H, 7.44; N, 7.95. Found: C, 72.88; H, 7.46; N, 7.90.

(4α,5α,6β,7β)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-(cyclopropylmethyl)benzamide] (12). To a solution of **1c** (0.54 g, 0.85 mmol) in dry THF (50 mL) was added *N*-methylmorpholine (0.51 g, 5.0 mmol) and isobutyl chloroformate (0.23 g, 1.68 mmol). The mixture was stirred at room temperature for 1 h, cooled in an ice bath, and treated with cyclopropylmethylamine hydrochloride (0.42 g, 3.9 mmol). The reaction mixture was stirred at room temperature for 6 h, concentrated *in vacuo*, triturated with water, and extracted with EtOAc. The EtOAc solution was dried over Na_2SO_4 and concentrated to dryness. The crude product was column chromatographed on silica gel using hexane−EtOAc (4:1). Appropriate fractions were combined and concentrated to give the intermediate as a foam: MS (NH_3-DCI) m/e 758 (M + NH_4). The 'amide−acetonide' (0.17 g, 0.230 mmol) was dissolved in MeOH (20 mL), treated with pTsOH·H_2O (0.24 g, 0.94 mmol), stirred at room temperature for 4 h, and poured into water (10 mL). The mixture was extracted with EtOAc, and the EtOAc extract was washed with water, 5% $NaHCO_3$, water, and brine, dried over Na_2SO_4, filtered, and concentrated to give the product as a white solid in 27% (0.160 g) yield: mp 116−118 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 0.18 (m, 4H, CH_2), 0.37 (m, 4H, CH_2), 0.99 (m, 2H, CH), 2.78 (dd, 2H, Ar′CH), 2.96 (d, J = 14.3 Hz, 2H, NCH), 3.11 (dd, 2H, Ar′CH), 3.33 (d, 4H, NCH_2), 3.5 (m, 4H, OCHCH), 4.66 (d, J = 14.3 Hz, 2H, NCH), 5.13 (s, 2H, OH), [6.96 (d, 4H), 7.23 (m, 8H), 7.41 (dd, 2H), 7.69 (s, 2H), 7.73 (d, 2H), Ar], 8.82 (dd, 2H, NH); MS (NH_3-DCI) m/e calcd for $C_{43}H_{49}N_4O_5$ (M + 1) 701.368 959, found 701.370 296, 718 (M + NH_4). Anal. Calcd for $C_{43}H_{48}N_4O_5$, MW 700.89: C, 73.69; H, 6.90; N, 7.99. Found: C, 73.32; H, 6.91; N, 8.02.

(4α,5α,6β,7β)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-(2,2,2-trifluoroethyl)benzamide] (13). A mixture of **1c** (0.635 g, 1.00 mmol), triethylamine (0.22 g, 2.2 mmol), and 2,2,2-trifluoroethylamine hydrochloride (0.30 g, 2.2 mmol) in 25 mL of DMF was stirred for 10 min and treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (water soluble carbodiimide, WSC). The mixture was stirred at room temperature for 16 h and diluted with 150 mL of water. The resulting gum was collected by decanting the aqueous phase, dissolved in 100 mL of EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude bis-amide acetonide. The crude acetonide was dissolved in 10 mL of $CHCl_3$, treated with 40 mL of 1 N HCl/Et_2O, and stirred at room temperature until TLC ($CHCl_3$−MeOH, 8:2) indicated no starting acetonide. The mixture was concentrated *in vacuo* and purified by preparative TLC on silica gel plates using $CHCl_3$−MeOH (8:2) as mobile phase. The desired product was isolated in 15% (0.114 g) yield: mp 116−120 °C; R_f 0.66 ($CHCl_3$−MeOH, 8:2); ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.74 (dd, 2H, Ar′CH), 2.98 (dd, 4H, Ar′CHCH), 3.51 (s, 2H, OCH), 3.55 (d, 2H, NCH), 4.09 (m, 4H, NCH_2CF_3), 4.63 (d, J = 14.2 Hz, 2H, NCH), 5.20 (s, 2H, OH), [6.91 (m, 4H), 7.21 (m, 6H), 7.38 (m, 2H), 7.45 (dd, 2H), 7.72 (s, 2H), 7.78 (d, 2H), Ar], 9.10 (s, 2H, NH); ^{19}F NMR (282 MHz, DMSO-d_6 TMS) δ −70.979; MS (NH_3-DCI) m/e 774 (M + NH_4), 757 (M + 1). Anal. Calcd for $C_{39}H_{38}F_6N_4O_5$, MW 756.75: C, 61.90; H, 5.06; N, 7.40. Found: C, 61.83; H, 5.11; N, 7.44.

(4α,5α,6β,7β)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis-(methylene)]bis[*N*-(cyanomethyl)benzamide] (14). A solution of **1c** (1.27 g, 2.0 mmol) in 50 mL of CH_2Cl_2 was treated with oxalyl chloride (0.76 g, 3.0 mmol) and 1 drop of DMF.

The mixture was stirred for 30 min and treated with aminoacetonitrile hydrochloride (0.556 g, 6.0 mmol). The mixture was stirred for an additional 10 min and treated with diisopropylethylamine (1.56 g, 12.0 mmol). The mixture was stirred at room temperature for 16 h and concentrated *in vacuo*. The residue was diluted with 100 mL of water, triturated, and filtered to collect the tan solid. The solid was washed with water, dried, and chromatographed on silica gel using EtOAc−$CHCl_3$ (3:2) as mobile phase. Appropriate fractions were combined and concentrated to an off-white solid of constant weight (0.780 g): ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 1.34 (s, 6H, CH_3CCH_3), 2.70 (dd, 2H, Ar′CH), 2.83 (m, 2H, Ar′CH), 3.31 (d, J = 14.0 Hz, 2H, NCH), 4.0 (m, 4H, CHCHCHCH), 4.31 (d, J = 5.5 Hz, 4H, CH_2CN), 4.52 (d, J = 14.0 Hz, 2H, NCH), 6.8−7.8 (m, 18H, Ar), 9.22 (t, 2H, NH).

The above acetonide was dissolved in 10 mL of acetonitrile, treated with 10 mL of 1 N HCl, and stirred at room temperature for 4 h. The mixture was diluted with 100 mL of water and triturated. The resulting solid was collected by filtration, washed with additional water, and dried *in vacuo* to give the desired product in 41% (0.544 g) yield from **1c**: mp 141−143 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.72 (dd, 2H, Ar′CH), 2.96 (m, 2H, Ar′CH), 3.04 (d, J = 14.0 Hz, 2H, NCH), 3.53 (m, 4H, CHCHCHCH), 4.61 (d, J = 13.9 Hz, 2H, NCH), 5.16 (s, 2H, OH), [6.89 (d, 4H), 7.21 (m, 6H), 7.39 (d, 2H), 7.46 (dd, 2H), 7.72 (m, 4H), Ar], 9.21 (t, 2H, NH); IR (KBr) 3388 (OH, NH), 1654 (C=O) cm^{-1}; MS (NH_3-DCI) *m/e* 671 (M + 1); $[\alpha]^{20}_D$ +98.72° (c = 0.16, MeOH). Anal. Calcd for $C_{39}H_{38}N_6O_5 \cdot 1.5H_2O$, MW 697.80: C, 67.13; H, 5.92; N, 12.04. Found: C, 67.23; H, 5.59; N, 12.16.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[phenylbenzamide] (15). The compound was synthesized using a modification of the Weinreb method.[7] A solution of aniline (0.93 g, 9.98 mmol) in dichloroethane (5 mL) was treated with 2 M trimethylaluminum (TMA) (5.0 mL, 10 mmol), stirred at room temperature for 10 min, and added to a solution of **1b** (0.500 g, 0.754 mmol) in dichloroethane (15 mL). The mixture was refluxed under dry nitrogen for 25 h and inspected by TLC ($CHCl_3$−EtOAc, 3:2) which showed no **1b**. Mass spectral analysis showed *m/e* 802 (M + NH_4). The mixture was diluted with 100 mL of CH_2Cl_2 and 50 mL of water, stirred for 1 h, and filtered through a bed of Celite. The filtrate was washed with water (50 mL), 5% $NaHCO_3$ (2 × 25 mL), water, and brine, dried over $MgSO_4$, filtered, and concentrated to a brown solid (0.300 g) whose mass spec. showed 745 (M + 1) and NMR (DMSO-d_6 TMS) showed no acetonide group. (*Note: Most preps do not show the loss of the acetonide protecting group.)* The crude product was triturated with 25 mL of 1 N HCl for 1 h, collected by filtration, washed with water, dried *in vacuo*, and recrystallized from warm acetonitrile to give the desired product in 43% (0.2401 g) yield as fine slightly yellow crystals: mp 156−159 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.79 (dd, 2H, Ar′CH), 3.00 (m, 4H, Ar′CH, NCH), 3.51 (s, 2H, OCH), 3.56 (d, J = 12.4 Hz, 2H, Ar′CCH), 4.73 (d, J = 14.3 Hz, 2H, NCH), 5.17 (s, 2H, OH), [6.98 (d, 4H), 7.09 (dd, 2H), 7.2−7.45 (m, 12H), 7.50 (dd, 2H), 7.77 (m, 6H), 7.87 (d, 2H), Ar], 10.25 (s, 2H, NH); MS (NH_3-DCI) *m/e* 762 (M + NH_4).

Alternatively, by substituting aniline in the method for **8**, the desired amide was obtained in 94% (0.550 g) yield as a pure amorphous white solid. A small amount was recrystallized from warm acetonitrile to give white opaque plates: mp 157−160 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.79 (dd, 2H, Ar′CH), 3.01 (m, 4H, Ar′CH, NCH), 3.5 (m, 4H, OCHCH), 4.73 (d, J = 13.9 Hz, 2H, NCH), 5.17 (s, 2H, OH), [6.98 (d, 4H), 7.09 (dd, 2H), 7.15−7.40 (m, 12H), 7.50 (dd, 2H), 7.8 (m, 6H), 7.87 (d, 2H), Ar], 10.25 (s, 2H, NH); IR (KBr) 3420 (OH, NH), 1660 (C=O), 1600 (C=O) cm^{-1}; MS (NH_3-DCI) *m/e* 762 (M + NH_4); $[\alpha]^{20}_D$ +85.83° (c = 0.12, MeOH). Anal. Calcd for $C_{47}H_{44}N_4O_5 \cdot 0.5H_2O$, MW 753.90: C, 74.88; H, 6.02; N, 7.43. Found: C, 75.24; H, 5.91; N, 7.41.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-4-pyridinylbenzamide] (16). By substituting 4-aminopyridine in the Weinreb method for **15**, the desired product was obtained in 23% (0.348 g) yield from **1c**: mp 153−154 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.76 (dd, 2H, Ar′CH), 2.98 (d, J = 12.8 Hz, 2H, Ar′CH), 3.06 (d, J = 14.0 Hz, 2H, NCHAr′), 3.51 (s, 2H, OCH), 3.56 (d, J = 11.0 Hz, 2H, NCHC), 4.71 (d, J = 14.0 Hz, 2H, NCHAr′), 5.17 (s, 2H, OH), [6.97 (m, 4H), 7.22 (m, 6H), 7.42 (d, 2H), 7.52 (dd, 2H), 7.85 (m, 2H), 7.88 (d, 2H), Ar, Ar″], [7.77 (d, 4H), 8.47 (d, 4H), 4-Pyr], 10.59 (s, 2H, NH); IR (KBr) 3414 (broad OH), 1686 (C=O) cm^{-1}; MS (NH_3-DCI) *m/e* 728 (M − H_2O); $[\alpha]^{20}_D$ 75.00° (c = 0.300, MeOH). Anal. Calcd for $C_{45}H_{42}N_6O_5$, MW 746.87: C, 72.37; H, 5.67; N, 11.25. Found: C, 72.33; H, 5.67; N, 11.19.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-3-pyridinylbenzamide] (17). By substituting 3-aminopyridine in the Weinreb method for **15**, the desired product was obtained in 50% (0.585 g) yield from the acid: mp 163−165 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.78 (dd, 2H, Ar′CH), 2.99 (d, J = 12.8 Hz, 2H, Ar′CH), 3.05 (d, J = 13.9 Hz, 2H, NCH), 3.45−3.65 (m, 4H, OCHCH), 4.72 (d, J = 13.9 Hz, 2H, NCH), 5.18 (s, 2H, OH), [6.97 (d, 4H), 7.23 (m, 6H), 7.40 (m, 4H), 7.52 (dd, 2H), 7.81 (s, 2H), 7.90 (d, 2H), 8.18 (d, 2H), 8.31 (s, 2H), 8.91 (s, 2H), Ar], 10.47 (s, 2H, NH); IR (KBr) 3320 (OH), 1654 (C=O) cm^{-1}; MS (NH_3-DCI) *m/e* 747 (M + 1); $[\alpha]^{20}_D$ +80.70° (c = 0.228, MeOH). Anal. Calcd for $C_{45}H_{42}N_6O_5$, MW 746.87: C, 72.37; H, 5.68; N, 11.25. Found: C, 72.56; H, 5.28; N, 11.16.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-2-pyridinylbenzamide] Dihydrochloride (18a). A solution of **1c** (2.0 g, 3.15 mmol) in 75 mL of EtOAc, HOBt (0.98 g, 7.24 mmol), and DCC (1.49 g, 7.24 mmol) was stirred for 30 min, treated with 2-aminopyridine (1.48 g, 15.75 mmol), and stirred for 24 h. TLC (hexanes−EtOAc, 3:7) showed a mixture of bis-OBt ester {^{1}H NMR (300 MHz, $CDCl_3$ TMS) δ 1.43 (s, 6H, CH_3CCH_3), 2.90 (m, 2H, Ar′CH), 3.05 (m, 2H, Ar′CH), 3.38 (d, J = 14.6 Hz, 2H, NCH), 3.86 (d, J = 10.2 Hz, 2H, Ar′CCH), 4.06 (s, 2H, OCH), 4.88 (d, J = 14.6 Hz, 2H, NCH), [7.0 (m, 4H), 7.26 (m, 8H), 7.4−7.65 (m, 8H), 8.06 (m, 4H), 8.16 (d, 2H), Ar]; MS (NH_3-DCI) *m/e* 869 (M + 1), 886 (M + NH_4) for $C_{50}H_{44}N_8O_7$, MW 868.96}, OBt ester/2-aminopyridine benzamide {^{1}H NMR (300 MHz, $CDCl_3$ TMS) δ 1.41 (s, 6H, CH_3CCH_3), 2.85−3.1 (m, 4H, Ar′CH_2), 3.25−3.43 (m, 2H, NCH), 3.84 (m, 2H, Ar′CCH), 4.03 (m, 2H, OCH), 4.85 (m, 2H, NCH), [6.9 (d, 1H), 7.03 (d, 4H), 7.26 (m, 7H), 7.35−7.6 (m, 5H), 7.62 (s, 2H), 7.79 (m, 1H), 8.03−8.2 (m, 6H), Ar], 8.52 (s, 1H, NH); MS (NH_3-DCI) *m/e* 828(M + 1) for $C_{49}H_{45}N_7O_6$, MW 827.95}, and the desired bis-2-aminopyridine benzamide acetonide. The mixture was filtered to remove the DCU, the filtrate was treated with triethylamine (1 g), and stirring was continued until all of the bis-OBt ester and the OBt ester/2-aminopyridine benzamide had been converted to the desired bis-benzamide (1−4 days) as indicated by TLC (hexanes−EtOAc, 3:7). The mixture was diluted with 100 mL of water, and the organic phase was washed with water, 5% $NaHCO_3$, water, and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to an impure solid. The crude product was column chromatographed on silica gel (100 g/1 g crude material) using $CHCl_3$-EtOAc (7:3) as mobile phase. Appropriate fractions were collected, combined, and concentrated to give the desired intermediate as a white foam in 88% (2.17 g) yield: ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 1.30 (s, 6H, CH_3CCH_3), 2.74 (dd, 2H, Ar′CH), 2.86 (m, 2H, Ar′CH), 3.32 (d, J = 14.0 Hz, 2H, NCH), 4.03 (d, J = 11.0 Hz, 2H, Ar′CCH), 4.06 (s, 2H, OCH), 4.60 (d, J = 14.0 Hz, 2H, NCH), [6.91 (m, 4H), 7.19 (m, 8H), 7.48 (m, 4H), 8.83 (m, 2H), 7.92 (m, 2H), 7.95 (s, 2H), 8.17 (d, 2H), 8.40 (d, 2H), Ar], 10.79 (s, 2H, NH); IR (Nujol) 3246 (NH), 1680 (C=O), 1631 (C=O) cm^{-1}; MS (NH_3-DCI) *m/e* 787 (M + 1) for $C_{48}H_{46}N_6O_5$, MW 786.35.

The acetonide (1.93 g, 2.45 mmol) in 20 mL of 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 (68% yield from **1c**): 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.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-2-pyridinylbenzamide] (18b). A solution of **18a** (0.240 g, 0.030 mmol) in 10 mL of acetonitrile was treated with 10 mL of 1 N HCl and stirred at room temperature until no starting material remained (2.5 h) as evidenced by TLC ($CHCl_3$-MeOH, 9:1). The mixture 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 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)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-(3-methyl-2-pyridinyl)benzamide] (19). By substituting 2-amino-3-picoline in the Weinreb method described for **15**, the desired product was obtained in 24% (0.296 g) yield: mp 142−143 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.13 (s, 6H, $ArCH_3$), 2.81 (dd, 2H, Ar′CH), 3.0 (m, 4H, Ar′CH, NCH), 3.5 (m, 6H, Ar′CCHCH(OH)), 4.68 (d, J = 14.3 Hz, 2H, NCH), [6.95 (d, 4H), 7.22 (m, 8H), 7.35 (m, 2H), 7.48 (dd, 2H), 7.72 (d, 2H), 7.86 (s, 2H), 7.92 (d, 2H), 8.31 (d, 2H), Ar], 10.56 (s, 2H, NH); IR (Nujol) 3420 (OH), 1674 (C=O), 1630 (C=O) cm^{-1}; MS (NH_3-DCI) m/e 775 (M + 1), 388 (M + 2H)$^{2+}$; $[\alpha]^{20}_D$ +86.49° (c = 0.074, MeOH). Anal. Calcd for $C_{47}H_{46}N_6O_5$·H_2O, MW 792.94, 774.93: C, 71.19; H, 6.10; N, 10.60. Found: C, 71.27; H, 6.05; N, 10.49.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-(4-methyl-2-pyridinyl)benzamide] (20). By substituting 2-amino-4-picoline in the Weinreb method for **15**, the desired product was obtained in 18% (0.221 g) yield: mp 139−140 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.37 (s, 6H, $ArCH_3$), 2.79 (m, 2H, Ar′CH), 3.0 (m, 4H, Ar′CHCNCH), 3.5 (m, 4H, Ar′CCHCHO), 4.68 (d, J = 14.3 Hz, 2H, NCH), [6.97 (m, 4H), 7.05 (d, 2H), 7.23 (m, 6H), 7.39 (d, 2H), 7.47 (dd, 2H), 7.88 (s, 2H), 7.96 (d, 2H), 8.00 (s, 2H), 8.25 (d, 2H), Ar], 10.85 (s, 2H, NH); IR (Nujol) 3385 (OH), 1678 (C=O), 1650 (C=O) cm^{-1}; UV−vis (c = 0.0190 mg/mL, MeOH) λ_{max} 280 (28 631), 256 (24 226), 216 (50 778) nm; MS (NH_3-DCI) m/e 775 (M + 1), 388 (M + 2H)$^{2+}$; $[\alpha]^{20}_D$ +80.00° (c = 0.080, MeOH). Anal. Calcd for $C_{47}H_{46}N_6O_5$·1.5H_2O, MW 791.94: C, 70.39; H, 6.16; N, 10.48. Found: C, 70.56; H, 6.08; N, 10.36.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-(5-methyl-2-pyridinyl)benzamide] (21). By substituting 2-amino-5-picoline in the Weinreb method for **15**, 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)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-(6-methyl-2-pyridinyl)benzamide] (22). By substituting 2-amino-6-picoline in the Weinreb method for **15**, the desired product was obtained in 17% (0.219 g) yield: mp 135−136 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.47 (s, 6H, $ArCH_3$), 2.76 (dd, 2H, Ar′CH), 3.0 (m, 4H, Ar′CHCNCH), 3.55 (m, 4H, Ar′CCHCHO), 4.6 (br s, 2H, OH), 4.68 (d, J = 14.3 Hz, 2H, NCH), [6.95 (d, 4H), 7.08 (d, 2H), 7.2 (m, 6H), 7.40 (d, 2H), 7.46 (dd, 2H), 7.79 (dd, 2H), 7.89 (s, 2H), 8.0 (m, 4H), Ar], 10.80 (s, 2H, NH); IR (Nujol) 3385 (OH), ∼1660 (C=O) cm^{-1}; UV−vis (c = 0.0200 mg/mL, MeOH) λ_{max} 285 (29 408), 251 (19 412), 216 (45 178) nm; MS (NH_3-DCI) m/e 775 (M + 1), 388 (M + 2H)$^{2+}$; $[\alpha]^{20}_D$ +81.69° (c = 0.142, MeOH). Anal. Calcd for $C_{47}H_{46}N_6O_5$·H_2O, MW 792.94: C, 71.19; H, 6.10; N, 10.60. Found: C, 71.02; H, 6.04; N, 10.39.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-(4,6-dimethyl-2-pyridinyl)benzamide] (23). By substituting 2-amino-4,6-dimethylpyridine in the DCC−HOBt method for **8**, the desired product was obtained in 66% yield from **1c**: mp 166−170 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.40 (s, 6H, $ArCH_3$), 2.51 (s, 6H, $ArCH_3$), 2.78 (dd, 2H, Ar′CH), 3.00 (d, J = 13.2 Hz, 2H, Ar′CH), 3.07 (d, J = 14.3 Hz, 2H, NCH), 3.6 (m, 4H, OCHCH), 4.67 (d, J = 14.3 Hz, 2H, NCH), [6.94 (d, 4H), 7.10 (s, 2H), 7.2 (m, 6H), 7.42 (d, 2H), 7.51 (dd, 2H), 7.92 (s, 2H), 7.96 (s, 2H), 8.05 (d, 2H), Ar], 11.27 (s, 2H, NH); IR (KBr) 3418 (OH, 1680 (C=O), 1644(C=O) cm^{-1}; MS (NH_3-DCI) m/e 803 (M + 1); $[\alpha]^{20}_D$ +74.66° (c = 0.446, MeOH). Anal. Calcd for $C_{49}H_{50}N_6O_5$·3.5H_2O, MW 866.00: C, 67.95; H, 6.64; N, 9.71. Found: C, 67.72; H, 6.26; N, 9.66.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-(5-chloro-2-pyridinyl)benzamide] (24). By substituting 2-amino-5-chloropyridine in the Weinreb method for **15**, the desired product was isolated in 85% (1.042 g) yield: mp 261−264 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.77 (dd, 2H, Ar′CH), 2.98 (d, J = 12.4 Hz, 2H, Ar′CH), 3.04 (d, J = 14.28 Hz, 2H, NCH), 3.52 (2d, 4H, OCHCH), 4.68 (d, J = 14.28 Hz, 2H, NCH), 5.15 (s, 2H, OH), [6.95 (d, 4H), 7.22 (m, 6H), 7.39 (d, 2H), 7.47 (dd, 2H), 7.87 (s, 2H), 7.95 (d, 4H), 8.223 (d, 2H), 8.44 (d, 2H), Ar], 10.99 (s, 2H, NH); IR (KBr) 3420 (OH, NH), 1680 (C=O) cm^{-1}; MS (NH_3-DCI) m/e 832 (M + NH_4); $[\alpha]^{20}_D$ +59.13° (c = 0.504, DMSO). Anal. Calcd for $C_{45}H_{40}N_6O_5Cl_2$·0.5H_2O: C, 65.53; H, 5.01; N, 10.19. Found: C, 65.34; H, 4.82; N, 10.00.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-(3,5-dichloro-2-pyridinyl)benzamide] (25). By substituting 2-amino-3,5-dichloropyridine in the Weinreb method for **15**, the desired product was isolated in 66% yield from **1b**: mp 238−241 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.79 (dd, 2H, Ar′CH), 3.01 (m, 4H, Ar′CHCNCH), 3.53 (m, 4H, OCHCH), 4.65 (d, J = 13.92 Hz, 2H, NCH), 5.16 (s, 2H, OH), [6.94 (d, 4H), 7.21 (m, 6H), 7.39 (d, 2H), 7.49 (dd, 2H), 7.83 (s, 2H), 7.89 (d, 2H), 8.34 (d, 2H), 8.54 (d, 2H), Ar], 10.83 (s, 2H, NH); IR (KBr) 3420 (OH, NH), 1680 (C=O), 1644 (C=O) cm^{-1}; MS (NH_3-DCI) m/e 885 (M + 1), 902 (M + NH_4); $[\alpha]^{20}_D$ +53.87° (c = 0.698, DMSO). Anal. Calcd for $C_{45}H_{38}N_6O_5Cl_4$, MW 884.65: C, 61.10; H, 4.33; N, 9.50; Cl, 16.03. Found: C, 61.41; H, 4.35; N, 9.31; Cl, 16.04.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-(5-bromo-2-pyridinyl)benzamide] Monohydrate (26). By substituting 2-amino-5-bromopyridine in the modified Weinreb method for **15**, the desired product was obtained in 30% (0.406 g) yield: mp 162−164 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.77 (dd, 2H, Ar′CH), 3.00 (m, 4H, Ar′CH, NCH), 3.5 (m, 4H, OCHCH), 4.68 (d, J = 13.9 Hz, 2H, NCH), [6.95 (d, 4H), 7.2 (m, 6H), 7.38 (d, 2H), 7.47 (dd, 2H), 7.87 (s, 2H), 7.93 (m, 2H), 8.19 (d, 2H), 8.51 (m, 2H), Ar], 10.98 (s, 2H, NH); IR (KBr) 3422 (OH, NH), 1688

(C═O), 1642 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 922 (M + NH_4); $[\alpha]^{20}_D$ +51.30° (*c* = 0.31, DMSO). Anal. Calcd for $C_{45}H_{40}N_6O_5Br_2 \cdot H_2O$, MW 922.68: C, 58.58; H, 4.59; N, 9.11; Br, 17.32. Found: C, 58.51; H, 4.22; N, 8.99; Br, 17.43.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-(4-methyl-2-pyrimidinyl)benzamide] Sesquihydrate (27). By substituting 2-amino-4-methylpyrimidine in the modified Weinreb method for **15**, the desired product was obtained in 24% (0.245 g) yield: mp 154−159 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.47 (s, 6H, CH_3), 2.79 (dd, 2H, Ar′CH), 3.0 (m, 4H, Ar′CH, NCH), 3.35 (s, HOD), 3.5 (m, 4H, OCHCH), 4.68 (d, *J* = 13.9 Hz, 2H, NCH), 5.17 (s, 2H, OH), [6.95 (m, 4H), 7.12 (d, 2H), 7.25 (m, 6H), 7.35 (d, 2H), 7.46 (dd, 2H), 7.83 (s, 2H), 7.88 (d, 2H), 8.55 (d, 2H), Ar], 10.90 (s, 2H, NH); IR (KBr) 3420(OH and NH), 1694 (C═O), 1640 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 777 (M + 1); $[\alpha]^{20}_D$ +68.22° (*c* = 0.26, MeOH). Anal. Calcd for $C_{45}H_{44}N_8O_5 \cdot 1.5H_2O$, MW 803.89: C, 67.24; H, 5.89; N, 13.94. Found: C, 67.05; H, 5.58; N, 13.72.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-[5-(trifluoromethyl)-2-pyridinyl]benzamide] (28). By substituting 2-amino-5-(trifluoromethyl)-pyridine in the acid chloride method for **14**, the desired product was obtained in 22% overall yield: mp 251−252 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.75 (dd, 2H, Ar′CH), 2.98 (m, 2H, Ar′CH), 3.05 (d, *J* = 14.3 Hz, 2H, NCH), 3.56 (m, 4H, CHCHCHCH), 4.68 (d, *J* = 14.3 Hz, 2H, NCH), 5.15 (s, 2H, OH), [6.95 (d, 4H), 7.21 (m, 6H), 7.40 (d, 2H), 7.48 (dd, 2H), 7.88 (s, 2H), 7.96 (d, 2H), 8.23 (m, 2H), 8.39 (d, 2H), 8.78 (s, 2H), Ar], 11.27 (s, 2H, NH); UV−vis (*c* = 0.0190 mg/mL, MeOH) λ_{max} 282 (36 476), 254 (32 387) nm; MS (NH_3-DCI) *m/e* calcd for $C_{47}H_{41}F_6N_6O_5^+$ 883.306 949, found 883.305 332.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-2-pyrazinylbenzamide] (29). By substituting 2-aminopyrazine in the Weinreb method for **15**, the desired product was obtained in 58% (0.659 g) yield from **1b**: 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′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-2-pyrimidinylbenzamide] (30). Alternate Method. By substituting 2-aminopyrimidine in the Weinreb method for **15**, the desired product was obtained in 81% yield from **1b**: mp 149−151 °C; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.80 (dd, 2H, Ar′CH), 2.99 (m, 4H, Ar′CH-CNCH), 3.52 (m, 4H, OCHCH), 4.69 (d, *J* = 13.92 Hz, 2H, NCH), 5.17 (s, 2H, OH), [6.95 (d, 4H), 7.23 (m, 8H), 7.37 (d, 2H), 7.47 (dd, 2H), 7.83 (s, 2H), 7.94 (d, 2H), 8.73 (d, 4H), Ar], 11.01 (s, 2H, NH); IR (KBr) 3410 (OH, NH), 1694 (C═O), 1638 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 749 (M + 1), 375 $(M + 2)^{2+}$; $[\alpha]^{20}_D$ +80.75° (*c* = 0.40, MeOH). Anal. Calcd for $C_{43}H_{40}N_8O_5$, MW 748.85: C, 68.97; H, 5.38; N, 14.96. Found: C, 68.98; H, 5.53; N, 14.75.

Alternatively, by substituting 2-aminopyrimidine in the method for **8**, the desired product was obtained in 7% (0.055 g) yield: mp 147 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$ TMS) δ 2.93 (m, 2H), 3.17 (m, 2H, Ar′CH_2), 3.31 (d, *J* = 14.5 Hz, 2H, NCH), 3.68 (d, *J* = 10.3 Hz, 2H, Ar′CCH), 3.94 (s, 2H, OCH), 4.76 (d, *J* = 14.5 Hz, 2H, NCH), 6.95−8.2 (m, 26H, Ar, NH); IR (Nujol) 3410 (OH), 1798 (C═O), 1640 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 749 (M + 1). Anal. Calcd for $C_{43}H_{40}N_8O_5$, MW 748.85: C, 68.97; H, 5.38; N, 14.96. Found: C, 69.01; H, 5.43; N, 14.88.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*,*N*′-dimethylbenzamide] (31). By substituting dimethylamine in the BOP method, the desired product was obtained in 94% yield as a glass: ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.69 (m, 2H, Ar′CH), 2.9−3.03 (m, 4H, Ar′CH, NCH), 3.38 (s, 12H, $N(CH_3)_2$), 3.47 (m, 4H, CHCH-CHCH), 4.56 (d, *J* = 14.0 Hz, 2H, NCH), 5.16 (s, 2H, OH), 6.8−7.7 (m, 18H, Ar); MS (NH_3-DCI) *m/e* 649 (M + 1). Anal. Calcd for $C_{39}H_{44}N_4O_5$, MW 648.81: C, 72.20; H, 6.84; N, 8.64. Found: C, 71.89; H, 7.02; N, 8.57.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-(4-methyl-2-oxazolyl)benzamide] (Test-1). By substituting 2-amino-4-methyloxazole in the DCC−HOBt method, the desired product was obtained in 8% yield: mp 155−157 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.08 (s, 6H, CH_3), 2.76 (dd, 2H, Ar′CH), 3.0 (m, 4H, Ar′CH, NCH), 3.53 (m, 4H, OCHCH), 4.65 (d, *J* = 13.9 Hz, 2H, NCH), 5.16 (s, 2H, OH), 6.9−7.95 (m, 20H, Ar), 11.44 (s, 2H, NH); IR (KBr) 3420 (OH, NH), 1694 (C═O), 1602 (C═O) cm^{-1}; UV−vis (*c* = 0.0160 mg/mL, MeOH) λ_{max} 267 (19 862), 218 (41 187) nm; MS (NH_3-DCI) *m/e* 755 (M + 1); $[\alpha]^{20}_D$ +78.75° (*c* = 0.08, MeOH). Anal. Calcd for $C_{43}H_{42}N_6O_7 \cdot 0.5H_2O$, MW 763.82: C, 67.61; H, 5.67; N, 11.00. Found: C, 67.30; H, 5.60; N, 10.76.

(4α,5α,6*β*,7*β*)-3,3′-[[Tetrahydro-5,6-dihydroxy-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepine-1,3(2*H*)-diyl]bis(methylene)]bis[*N*-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]benzamide] (Test-2). By substituting 2-amino-5-(trifluoromethyl)-1,3,4-thiadiazole in the DCC−HOBt method, the desired product was obtained in 91% yield: mp 196 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6 TMS) δ 2.79 (m, 2H, Ar′CH), 3.04 (m, 2H, Ar′CH), 3.36 (d, *J* = 14.3 Hz, 2H, NCH), 3.45−3.75 (m, 4H, CHCHCHCH), 4.62 (d, *J* = 14.3 Hz, 2H, NCH), 5.23 (s, 2H, OH), 6.9−8.3 (m, 18H, Ar), 8.05 (s, 2H, NH); ^{19}F NMR (282 MHz, DMSO-d_6 TMS) δ −58.739; IR (Nujol) 3464 (OH, NH), 1648 (C═O) cm^{-1}; MS (NH_3-DCI) *m/e* 897 (M + 1). Anal. Calcd for $C_{41}H_{34}F_6N_8O_5S_2$, MW 896.89: C, 54.91; H, 3.82; N, 12.49. Found: C, 54.86; H, 4.01; N, 12.38.

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