Nonsymmetric P2/P2′ Cyclic Urea HIV Protease Inhibitors. Structure−Activity Relationship, Bioavailability, and Resistance Profile of Monoindazole-Substituted P2 Analogues

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Using the structural information gathered from the X-ray structures of various cyclic urea/HIVPR complexes, we designed and synthesized many nonsymmetrical P2/P2′-substituted cyclic urea analogues. Our efforts concentrated on using an indazole as one of the P2 substituents since this group imparted enzyme (K_i) potency as well as translation into excellent antiviral (IC_{90}) potency. The second P2 substituent was used to adjust the physical and chemical properties in order to maximize oral bioavailability. Using this approach several very potent (IC_{90} 11 nM) and orally bioavailable (F% 93−100%) compounds were discovered (**21**, **22**). However, the resistance profiles of these compounds were inadequate, especially against the double (I84V/V82F) and ritonavir-selected mutant viruses. Further modification of the second P2 substituent in order to increase H-bonding interactions with the backbone atoms of residues Asp 29, Asp 30, and Gly 48 led to analogues with much better resistance profiles. However, these larger analogues were incompatible with the apparent molecular weight requirements for good oral bioavailability of the cyclic urea class of HIVPR inhibitors (MW < 610).

Introduction

The identification of HIV as the causative agent of AIDS has prompted an intense international research effort to find effective therapies for this disease. One of the prime targets of research has been the effort to find inhibitors of the essential aspartic protease (PR) of HIV.[1] Several HIVPR inhibitors have been shown to reduce the viral load and increase the number of $CD4^+$ lymphocytes in HIV infected patients.[2] Saquinavir, ritonavir, indinavir, and nelfinavir have been approved by the FDA and are being used in AIDS therapy in combination with reverse transcriptase (RT) inhibitors. However, the ability of the virus to generate resistant mutants[3] suggests that there is an ongoing need for new, structurally diverse HIVPR inhibitors.

Lam and co-workers at Dupont Merck recently described the rational design of a novel class of cyclic urea HIVPR inhibitors.[4] This work resulted in the identification of two clinical candidates in this series, **DMP 323**[5] and **DMP 450**.[6] The first clinical candidate, **DMP 323**, was examined in seronegative male volunteers with single doses ranging from 60 to 1200 mg. Disappointingly, blood levels at each dose were low and showed a high degree of intersubject variation.[5]

At least two factors contributed to the variable and low plasma levels observed. First, the poor solubility (6 μg/mL) of **DMP 323** in aqueous media; second, metabolism of **DMP 323** was both rapid and extensive.[7] Thus, further development of **DMP 323** was discontinued.

The second clinical candidate, **DMP 450**, was taken to phase I clinical studies in HIV seronegative male volunteers and showed substantial blood levels. With a single dose of 11 mg/kg the C_{max} was 6.5 μM and the level at 6 h remained above 1 μM. The measured half-life in humans (5.7 h) is consistent with some degree of potential accumulation with multiple dosing every 6−8 h. A multiple dose study using 1000 mg QID showed an increase in trough level from 1.73 μM on day 2 to 3.2 μM by day 4. **DMP 450** was well tolerated with no adverse effects noted in these studies.[6]

Early clinical trial results of other protease inhibitors identified the potential for rebound in plasma RNA levels with concomitant emergence of HIV mutations,[3] probably due to inadequate blood levels at trough to cover wild-type or mutant virus strains. The importance of adequate blood levels and in particular free drug concentration was accentuated by the clinical failure of SC-52151,[8] which was ascribed to high plasma protein binding. These clinical results suggested that it was the relationship between the plasma level of free drug and the inherent drug potency against wild-type and mutant viruses that were the likely predictors of clinical efficacy.

To assess the binding of **DMP 450** to human plasma protein, equilibrium dialysis experiments using ^{14}C-labeled compound were conducted. These showed that

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DMP 450 was 90−93% protein bound. The effect of this plasma protein binding on the antiviral potency of **DMP 450** was examined by conducting antiviral assays in the presence of human serum proteins. In the presence of 45 mg/mL serum albumin plus 1 mg/mL α-1-acid glycoprotein, the apparent antiviral potency (IC_{90}) decreased 4.5−8.4-fold.[6]

The plasma levels obtained using the dosing regimen of 1000 mg QID would be sufficient to provide for 90% inhibition of wild-type HIV, but would not be high enough to provide for adequate inhibition of mutant variants (when adjusted for protein binding).[6] Further development of **DMP 450** was discontinued.

To discover superior inhibitors of HIVPR, we focused on the simultaneous optimization of multiple properties: potency, oral bioavailability, and resistance profile. Our goal was to design an inhibitor 10 times more potent than **DMP 450** which could provide sufficient free drug at trough to inhibit both wild-type and mutant variants of HIV with BID or TID dosing.

Potency

In order to increase the potency of cyclic ureas, we needed to design compounds with stronger interactions with HIVPR. Examination of the large amount of structural data obtained from the X-ray structures of various cyclic urea analogues complexed with HIVPR revealed several trends, which were useful in designing more potent compounds. First it became obvious that the cyclic urea is a very rigid scaffold, complementary to the enzyme, that always binds to HIVPR in the same mode. This makes the cyclic urea an ideal scaffold for structure-based design. Thus, it was possible to design P2 *N*-benzyl substituents and be confident that the resulting compound would interact with the enzyme with the same binding mode. For example, the X-ray structures of **DMP 323**,[5] **DMP 450**,[6] the naphthyl analogue **1**,[4] and the amide **7**[9a] were found to be superimposable in their common structural features (i.e., the four benzyl groups).

The X-ray structures of cyclic ureas complexed with HIVPR also revealed that the *N*-benzyl group serves two very important functions. First, it provides an important hydrophobic interaction with the lipophilic S2 enzyme pocket. Second, it serves as a scaffold for directing substituents from the meta or the para position toward the S2/S3 subsites where there are several H-bond donors/acceptors, primarily the side chains and/or backbone amides of residues Asp 29, Asp 30, and Gly 48.

Using the *N*-benzyl group as a scaffold for directing substituents toward the S2/S3 residues, inhibitors were designed to H-bond to these residues in order to increase potency. While compounds with P2/P2′ functional groups having multiple H-bond donor and acceptor possibilities were more potent enzyme inhibitors (K_i), many of them were polar and their translation to antiviral potency (IC_{90}) was poor. For example, the amide **2** and the amidoxime **10** were extremely potent inhibitors of the enzyme but showed only low to modest antiviral activity (Table 1).

However, adjusting the lipophilicity of some of these compounds resulted in better translation and more potent antiviral activity. Of particular note are the amides **2**−**8**,[9a,10] which show increasingly better translation as lipophilicity increases (Table 1). Several more lipophilic heterocyclic amides were synthesized and evaluated and showed exceptionally potent antiviral activity.[9a]

Table 1. Enzyme and Antiviral Potency of Selected Cyclic Urea Analogues

inhibitor	K_i[a] (nM)	IC_{90}[b] (nM)	reference
DMP 323	0.34	57	5
DMP 450	0.28	130	6
1	0.31	3900	4
2	0.039	709	10
3	0.066	81	10
4	0.21	138	10
5	0.043	2.8	10
6	0.027	4.2	9a
7	0.024	5.1	9a
8	0.014	60	9a
9	0.018	7	11
10	<0.010	300	this work
11	0.088	35	12a
12	0.023	6	this work
13	0.018	49	12a

[a] Values were measured by cleavage of a fluorescent substrate using HPLC as described previously.[5,13] [b] Values were measured by a sensitive viral RNA-based detection system described previously.[5,14]

An alternative approach to improving the translation of some of these more polar P2 substituents was the use of a more lipophilic scaffold. We recently described the discovery of tetrahydropyrimidinones as another class of very potent HIVPR inhibitors.[12a] The tetrahydropyrimidinones are more lipophilic than the seven-membered ring cyclic ureas (mono-ol vs diol). They have a better translation of protease inhibition (K_i) to antiviral potency (IC_{90}) for the more polar P2 groups that in general give more potent enzyme inhibitors. For example the amide **11** and amidoxime **13** analogues[12a] are more potent (IC_{90}) than the corresponding 7-membered cyclic ureas **2**[10] and **10** (Figure 1, Table 1).

Besides heterocyclic amides and tetrahydropyrimidinones, other compounds with the ability to translate enzyme potency into excellent antiviral potency were lipophilic heterocycles such as the indazole analogues **12** and **9**,[11] which had antiviral potencies of 6 and 7 nM (Table 1).

Bioavailability

Unfortunately, because of low solubility, the symmetrical amides (such as **7**) and indazole (**9**) analogues showed low oral bioavailability. While symmetric cyclic ureas provided synthetic and cost advantages, they also had significant limitations. The major disadvantage was their inherent crystallinity and subsequently low solubility.

On the other hand, nonsymmetric cyclic ureas offered the advantages of better solubility, flexibility in adjusting the physical and chemical properties, and greater versatility in designing enzyme interactions. These potential benefits prompted us to concentrate our synthesis efforts on nonsymmetrical analogues. In this way we could better address the often conflicting issues of solubility, potency, protein binding, resistance profile, and oral bioavailability.

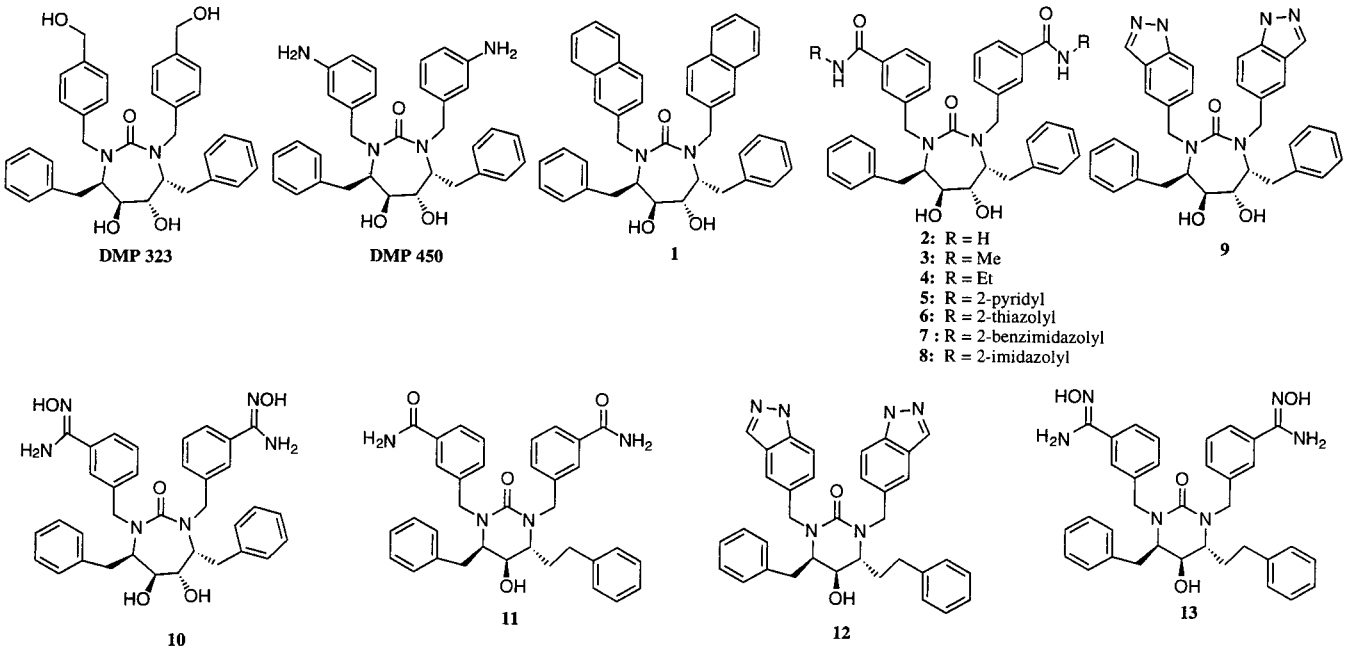


Figure 1. Structures of compounds discussed in the text.

Thus, we focused our efforts on the synthesis of 7-membered cyclic urea analogues containing an indazole as one of the P2 groups, since this substituent showed excellent enzyme and antiviral potency (example **9** Table 1). We planned to use the second P2 group to adjust the physical and chemical properties of the compound in order to optimize oral bioavailability.

Many nonsymmetrical monoindazole-substituted analogues were prepared, and the results are summarized in Table 2. The *N*-monosubstituted cyclic urea **14** (R = H Table 2), while having a sub-nanomolar K_i, did not have adequate antiviral potency. Thus, nonsymmetrical analogues that have both P2/P2′ substituents were prepared. The second P2 groups contained H-bonding substituents to increase enzyme potency, but they were chosen from groups that were not too polar in order to maintain good translation into antiviral potency (IC_{90}). The penalty for disregarding this strategy was exemplified by the polar acid analogue **15**, which had an excellent K_i of 0.049 nM but had an IC_{90} of 750 nM. Several analogues with nonpolar H-bonding substituents were examined; all of them displayed potent enzyme inhibition activity (K_i) and several showed very good antiviral potency (Table 2; entries **14**−**28**).

Several of the more potent analogues were tested for oral bioavailability in dogs at a dose of 10 mg/kg. The anilines, **21** and **22**, showed potent antiviral activity (IC_{90} 11 nM) and excellent oral bioavailability in the dog (F% 93−100%). On the other hand the methyl ketone analogue **19** and the *N*-methyl-4-fluoroaniline **28** had lower oral bioavailability (F% 25−14%). This was probably due to poor solubility properties. While the anilines **21** and **22** had good water solubility (0.040 mg/mL) and excellent acid solubility (1 N HCl: 60 mg/mL), the ketone **19** had low aqueous (0.006 mg/mL) and acid (1 N HCl: 0.014 mg/mL) solubility. Likewise, **28** also had low aqueous (<0.001 mg/mL) and acid (1 N HCl: 0.446 mg/mL) solubility compared to **21** and **22**.

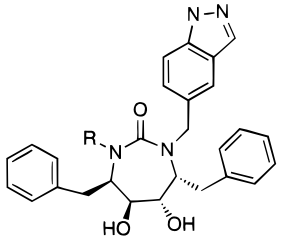
As previously noted, plasma protein binding of HIVPR inhibitors is an important parameter in determining clinical efficacy. To examine the effect of plasma protein binding on the antiviral potency of **21** and **22**, the antiviral assays were repeated in the presence of quantities of human serum albumin and α-1-acid glycoprotein that approximate those found in the blood of AIDS patients (45 mg/mL serum albumin plus 1 mg/mL α-1-acid glycoprotein). Under these conditions the apparent antiviral potency (IC_{90}) of **21** or **22** decreased 5-fold, similar to the decrease found for **DMP 450**.

Resistance Profile

Since our goal was to discover an inhibitor 10 times more potent than **DMP 450** which could provide sufficient free drug at trough to inhibit not only wild-type but also mutant variants of HIV, we next examined **21** and **22** against a panel of mutant viruses as previously described.[6,9a] This included mutant strains with single amino acid substitutions (I84V),[6] double amino acid substitutions (I84V/V82F),[6,23] and multiple amino acid changes (corresponding to mutations observed in clinical isolates of patients treated with ritonavir and indinavir).[9a] The results are summarized in Table 3. Unfortunately, both **21** and **22** had very poor resistance profiles, especially against the double mutant (I84V/V82F) and the related ritonavir-selected virus mutants (Table 3).

There is a very strong correlation between the number of H-bonds to the backbone atoms of residues Asp 29, Asp 30, and Gly 48 and the resistance profile of cyclic urea HIVPR inhibitors.[9a] For example, the heterocyclic benzamides **7** and **8**, which have H-bonding interactions[9b] with the backbone of residues Gly 48 and Asp 30, retain their antiviral potency against the double mutant (I84V/V82F) and the ritonavir- and indinavir-selected viruses which also contain amino acid substitutions at positions 82 and 84 of the protease (Table 3). The amidoximes **10** and **13**, which have the same H-bonding interactions[12b] as the heterocyclic benzamides **7** and **8**, also have an excellent resistance profile as shown in Table 3.

Table 2. P2/P2′ SAR of Nonsymmetric Cyclic Urea Inhibitors of HIV Protease



compd no.	R	K_i[a] (nM)	IC_{90}[b] (nM)	po bioavailability[c] C_{max} (μM) (F%)
14	H	0.32	550	
15	3-carboxybenzyl	0.049	750	
16	3-hydroxybenzyl	0.045	36	
17	3-(2-hydroxyethyl)benzyl	0.05	17	
18	3-(carbomethoxymethyl)benzyl	0.11	32	
19	3-acetylbenzyl	0.036	15	1.3 (25)
20	4-fluoro-3-carboxamidobenzyl	0.018	14	
21	3-aminobenzyl	0.03	11	7.2 (93)
22	4-aminobenzyl	0.03	11	10.6 (100)
23	3-amino-4-fluorobenzyl	0.018	14	
24	4-amino-3-fluorobenzyl	0.036	7	
25	3-amino-4-methylbenzyl	0.05	15	
26	3-(*N*,*N*-dimethylamino)benzyl	0.23	39	
27	3-(*N*-methylamino)benzyl	0.039	8	8.0 (92)
28	3-(*N*-methylamino)-4-fluorobenzyl	0.027	7	0.67 (14)
29	3-((pyrazol-1-yl)methyl)benzyl	0.17	46	
30	3-(1,2,4-triazol-1-yl)methyl)benzyl	0.054	35	
31	3-(1,2,3-triazol-1-yl)methyl)benzyl	0.11	30	
32	3-(1,2,3-triazol-2-yl)methyl)benzyl	0.081	32	
33	3-(pyrazol-1-yl)-4-aminobenzyl	0.045	6	
34	3-(1,2,4-triazol-1-yl)-4-aminobenzyl	0.029	35	0.5
35	3-(1,2,3-triazol-2-yl)-4-aminobenzyl	0.059	12	
36	3-(1,2,3-triazol-1-yl)-4-aminobenzyl	0.034	38	
37	3-(1,2,4-triazol-3-yl)benzyl	0.041	24	
38	3-(pyrazol-3-yl)-4-aminobenzyl	0.025	22	
39	3-(*N*-(5-methylpyrid-2-yl)carboxamido)benzyl	0.048	4	<0.05
40	3-(*N*-pyrid-2-ylcarboxamido)benzyl	0.051	5	
41	3-(*N*-(6-methylpyrid-2-yl)carboxamido)benzyl	0.04	3	
42	3-(*N*-thiazol-2-ylcarboxamido)benzyl	0.016	8	
43	3-(pyrid-2-ylacetyl)benzyl	0.073	15	0.7
44	3-(thien-2-ylacetyl)benzyl	0.23	18	
45	3-(pyrazol-1-ylacetyl)benzyl	0.063	15	
46	3-(1,2,3-triazol-1-ylacetyl)benzyl	0.021	30	
47	3-(1,2,3-triazol-2-ylacetyl)benzyl	0.046	15	
48	3-(1,2,4-triazol-1-ylacetyl)benzyl	0.022	51	0.15
49	3-(*N*-(benzimidazol-2-ylmethyl)amino)benzyl	0.016	63	
50	3-(*N*-(benzimidazol-2-ylmethyl)amino)-4-fluorobenzyl	0.028	30	
51	3-(*N*-(benzthiazol-2-ylmethyl)amino)benzyl	0.059	5	

[a] Values were measured by cleavage of a fluorescent substrate using HPLC as described previously.[5,13] [b] Values were measured by a sensitive viral RNA-based detection system described previously.[5,14] [c] Bioavailability was determined in dogs ($n = 3$ per group), dosed with compound in formulations containing propylene glycol, polyethylene glycol 400, water at 10 mg/kg. The maximum plasma concentration (C_{max}) is the observed peak plasma concentration after an oral dose. Oral bioavailability (F%) was determined by the ratio AUC po/AUC iv, where AUC is the area under the plasma concentration−time curve from time zero to infinity for oral and intravenous administration of compound and is normalized for dose.

In order to improve the resistance profiles of 7-membered cyclic ureas containing an indazole as one of the P2 groups, we synthesized analogues in which the second P2 substituent was designed to maximize H-bonding interaction with the backbone of residues Gly 48 and Asp 30. We chose to explore heterocycle-containing substituents since these had a better probability of having the right combination of H-bonding ability and lipophilicity needed to improve the resistance profile while maintaining antiviral potency. The results are summarized in Tables 2 and 3 (entries **29**−**51**).

We examined a variety of methods to connect heterocyclic substituents to the 3-position of the second P2 *N*-benzyl group. This included attaching the heterocycle to the benzyl group directly (**33**−**38**) and via a methylene (**29**−**32**), an amide (**39**−**42**), or a ketone (**43**−**48**) linkage. We also alkylated the aniline of **21** with a heterocyclic-alkyl group (**49**−**51**). Several compounds gave good to excellent antiviral potency and were examined against the panel of mutant viruses. Many showed an improvement, and a few gave significantly better resistance profiles when compared to **21** (Table 3). For example, the ketone **43** had only a 5-fold loss against the double mutant (I84V/V82F), compared to the 200-fold loss in potency for **21**.

However, while some of the more lipophilic heterocycles assisted in the translation to antiviral potency, they had a detrimental effect on protein binding. For example, in the presence of 45 mg/mL serum albumin plus 1 mg/mL α-1-acid glycoprotein, the potent pyridine-containing analogues **40** and **43**, and the potent benz-

Table 3. Resistance of Mutant Viruses to Cyclic Urea Analogues

			resistance of mutant viruses (IC_{90} mutant/IC_{90} WT)			
inhibitor	K_i (nM)[a]	IC_{90} (nM)[b]	84V[c]	84V/82F[c]	ritonavir[d] virus	indinavir[d] virus
DMP 323	0.34	57	28	97	93	18
DMP 450	0.28	130	10	100	49	27
7	0.024	5.1	0.6	1.0	1.2	0.7
8	0.014	60	0.7	0.7	0.2	0.4
10	<0.01	300	1.0	0.7		
13	0.018	49	1.0	0.4		
21	0.030	11	6.8	200	75	20
22	0.030	11	31	240	170	
33	0.081	32	3.3	50	70	
34	0.029	35	1.0	20	9.0	
37	0.041	24	3.3	18	3.8	
38	0.025	22	2.2	20	2.1	
42	0.016	8	2.0	22	9.0	7.3
43	0.073	15	1.0	5.0	10	
49	0.016	63	1.0	3.0		
51	0.059	5	3.3	20	25	

[a] Values were measured by cleavage of a fluorescent substrate using HPLC as described previously.[5,13] [b] Values were measured by a sensitive viral RNA-based detection system described previously.[5,14] [c] Values were measured using the yield reduction assay described previously.[6,22,23] [d] The viruses were constructed and the IC_{90} values were measured using the viral p24 readout as described previously.[6,9a] The ritonavir virus contains five mutations, 46I/63P/71V/82F/84V, and is named for its significant resistance to ritonavir. The indinavir virus also contains five mutations, 10R/63P/71V/82T/84V, and is named for its resistance to indinavir.

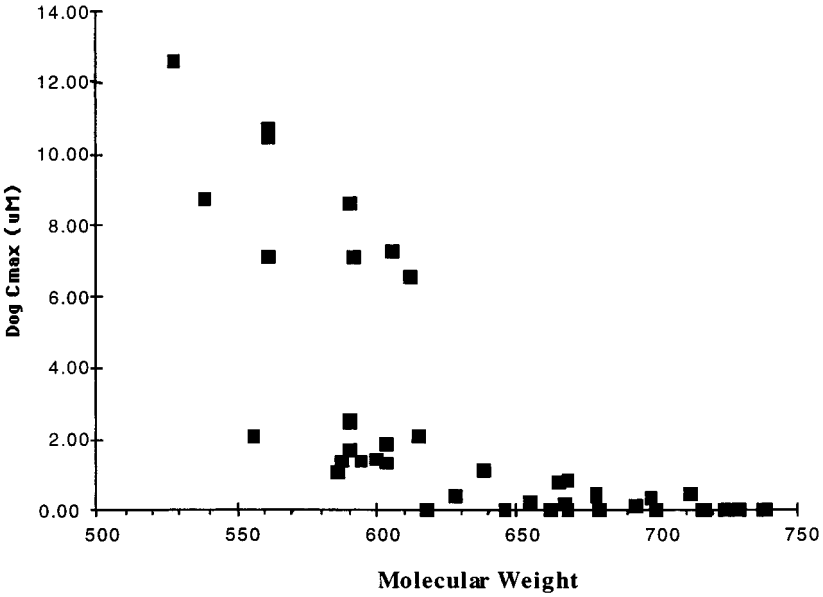


Figure 2. Oral bioavailability of indazole containing P2 substituents in dog at a dose of 10 mg/kg.

thiazole-containing analogue **51**, had 19-, 28-, and 25-fold losses, respectively, in their antiviral potency.

Several of these analogues (**34**, **39**, **43**, **48**) were tested for oral bioavailability in dogs at a dose of 10 mg/kg. Unfortunately, none of these compounds had good oral bioavailability. A major factor contributing to the low oral bioavailability of these compounds appeared to be their high molecular weights. The dog oral bioavailability of cyclic urea analogues have been examined, and the results are summarized as a scatter plot of C_{max} as a function of molecular weight (Figure 2). The use of the C_{max} as an approximate surrogate for oral bioavailability is used for convenience since the determination of F% is not always possible for many poorly bioavailable compounds due to detection difficulties. Our experience with cyclic ureas has shown that C_{max} is an adequate surrogate for F%. The data shows an apparent cutoff of oral bioavailability at a molecular weight (MW) of about 610. Most of the compounds with low bioavailability, that have a MW below 610, are either symmetrical or have low aqueous solubility. To improve the resistance profile, analogues need to be larger in order to have the multiple H-bonding interactions with residues Asp 29, Asp 30, and Gly 48. However, in doing so, the molecular weight of the resulting analogues often exceeds the 610 MW limit that seems to be important for oral bioavailability of HIVPR inhibitors in the cyclic urea class.

Conclusions

Using the structural information gathered from the X-ray structures of various cyclic urea/HIVPR complexes, we designed and synthesized many nonsymmetrical P2/P2′-substituted cyclic urea analogues. Our efforts concentrated on using an indazole as one of the P2 substituents since this group imparted enzyme (K_i) potency as well as translation into excellent antiviral (IC_{90}) potency. The second P2 substituent was used to adjust physical−chemical properties in order to maximize oral bioavailability. Through this approach several

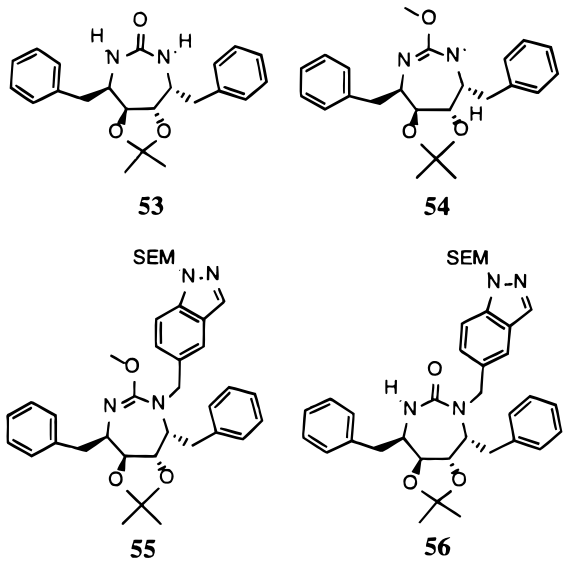
very potent (IC_{90} 11 nM) and orally bioavailable (F% 93−100%) compounds were discovered (**21**, **22**). However, the resistance profiles of these compounds were inadequate, especially against the double (I84V/V82F) and ritonavir-selected mutant viruses. Further modification of the second P2 substituent in order to increase H-bonding interactions with the backbone atoms of residues Asp 29, Asp 30, and Gly 48 led to analogues with much better resistance profiles. However, these larger analogues were incompatible with the apparent molecular weight requirements for good oral bioavailability in the cyclic urea class of HIVPR inhibitors (MW < 610). Thus we were not able to overcome the conflicting requirements needed for good oral bioavailability (low MW, aqueous solubility) and potency/resistance profile (large size, H-bonding, lipophilicity), using nonsymmetrical monoindazole-substituted P2/P2′ cyclic urea analogues.

Experimental Section

Biological Methods. Inhibition of HIVPR (K_i) was measured by the assay of the cleavage of a fluorescent substrate using HPLC as described previously.[5,13] The antiviral activity potency of compounds was assessed by measuring their effect on the accumulation of viral RNA transcripts 3 days after infection of MT-2 cells with HIV-1 RF as described previously.[5,14] The concentration of test compound which reduced the concentration of HIV viral RNA by 90% from the level measured in an untreated infected culture was designated IC_{90}. The cellular toxicity of compounds was assessed by measuring the extent of MTT dye reduction in uninfected MT-2 cell cultures grown for 3 days in the presence of various concentrations of test compound as previously described. The compound concentration which decreased the level of MTT dye reduction by 50% was designated the TC_{50}. Only compounds which displayed an antiviral IC_{90} concentration which was at least 3-fold less than the TC_{50} concentration were considered to have a specific antiviral effect. The single (I84V) and double (I84V/V82F) mutant virus were obtained from in vitro selection experiments in the presence of cyclic urea analogue **DMP 323** as previously described.[6,23] The IC_{90} of the single (I84V) and double (I84V/V82F) mutant virus were measured using the yield reduction assay as previously described.[6,22] The construction of the ritonavir and indinavir mutant viruses and the measurement of the IC_{90} values using the viral p24 readout was accomplished as previously described.[6,9a,21] The ritonavir virus contains five mutations, 46I/63P/71V/82F/84V, and is named for its significant resistance to ritonavir. The indinavir virus also contains five mutations, 10R/63P/71V/82T/84V, and is named for its resistance to indinavir. Oral bioavailability of compounds were determined as previously reported.[5,15]

General. All reactions were carried out under an atmosphere of dry nitrogen. Commercial reagents were used without further purification. ^{1}H NMR (300 MHz) spectra were recorded using tetramethylsilane as an internal standard. TLC was performed on E. Merck 15710 silica gel plates. Medium-pressure liquid chromatography (MPLC) was carried out using EM Science silica gel 60 (230−400 mesh). HPLC chromatography was carried out using Jasco PV-987 pumps, Jasco UV-975 detectors, and Dupont Zorbax Sil or Zorbax NH_2 1-in. preparative columns. All final targets were obtained as noncrystalline amorphous solids unless specified otherwise. Mass spectra were measured with a HP5988A mass spectrometer with particle beam interface using NH_3 for chemical ionization or a Finnigan MAT 8230 mass spectrometer with NH_3-DCI or VG TRIO 2000 for ESI. High-resolution mass spectra were measured on a VG 70-VSE instrument with NH_3 chemical ionization. Elemental analysis was performed by Quantitative Technologies, Inc., Bound Brook, NJ. For compounds where analysis was not obtained, HPLC analysis was used, and purity was determined to be >98%.

Synthesis of nonsymmetrical monoindazole-containing P2/P2′ cyclic ureas was accomplished by using the monoalkylation methods previously described,[5,9a] starting with the N,N-unsubstituted cyclic urea acetonide **53**.[16] Alternatively, the isourea **54**[17] was alkylated with 5-(bromomethyl)-1-SEM-indazole[11] to give the isourea **55** which was alkylated directly a second time as previously described[17] or converted to urea **56**, which was then alkylated a second time using the standard alkylating procedures.[5] The synthesis of the tetrahydropyrimidinone analogue was accomplished, starting with the 7-membered ring cyclic urea analogue **9**,[11] by the rearrangement, ring-contraction reaction previously reported.[12a]



53 **54** **55** **56**

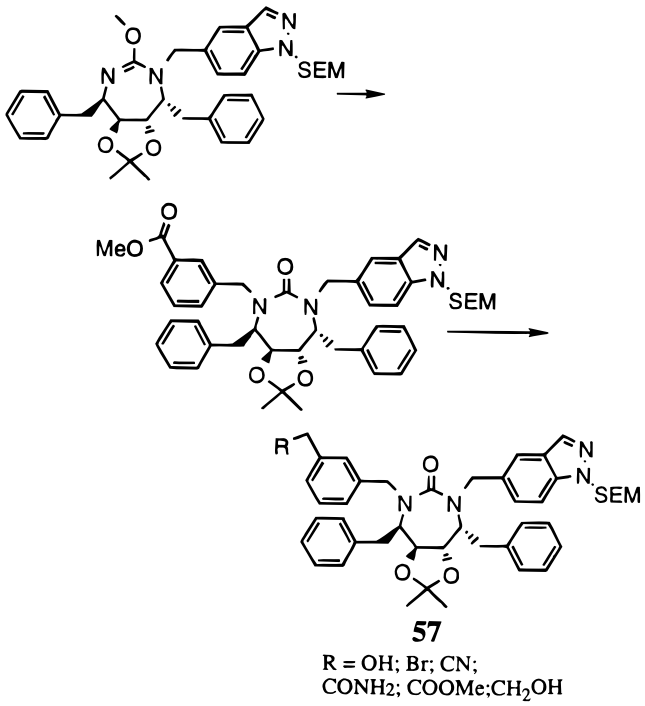
[4*R*-(4α,5*β*,6*β*)]-Tetrahydro-5-hydroxy-1,3-bis(1*H*-indazol-5-ylmethyl)-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (12). From 7-membered cyclic urea: To a solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis[1-SEM-indazol-5-ylmethyl]-4,7-bis-[phenylmethyl]-2*H*-1,3-diazapin-2-one[11] (0.38 g, 0.45 mmol) in CH_2Cl_2 (20 mL) at room temperature was added 2-acetoxyisobutyryl bromide (0.40 g, 1.9 mmol), and the solution was stirred at room temperature for 3 h at which time TLC showed complete conversion. The solution was quenched with saturated $NaHCO_3$, and the organic layer was separated and washed with water and brine, dried, and concentrated. The residue was chromatographed (MPLC silica gel 25−50% EtOAc/hexane) to give 0.25 g of the rearranged bromo acetate as a foam. The bromo acetate was dissolved in 50 mL of acetic acid, treated with 5 g of Zn (dust), and vigorously stirred at room temperature until TLC analysis showed complete conversion. The mixture was filtered, and the solid was washed thoroughly with EtOAc. The filtrate was washed with water, saturated $NaHCO_3$, and brine, dried, and evaporated to give the acetate. The crude acetate was chromatographed (MPLC silica gel 40−60% EtOAc/hexane) to give 125 mg of pure acetate as an oil. The acetate (125 mg, 0.68 mol) was dissolved in MeOH, treated with concentrated HCl (1 mL), and heated at reflux for 2 h. The mixture was concentrated, and the residue was partitioned between 1 N NaOH and EtOAc. The organic extract was washed with water and brine, dried, and concentrated. The resulting residue was chromatographed (MPLC, silica gel, EtOAc) to give 40 mg of **12** as a foam: mp 130−134 °C; ^{1}H NMR ($CDCl_3$) δ 10.95 (bs, 1H), 10.87 (bs, 1 H), 7.84 (s, 1 H), 7.72 (s, 1 H), 7.50 (s, 1 H), 7.47 (s, 1 H), 7.35−7.15 (m, 10 H), 7.07 (2 overlapping d, J = 7 Hz, 2 H), 6.95 (2 overlapping d, J = 7 Hz, 2 H), 5.51 (d, J = 15 Hz, 1 H), 5.48 (d, J = 15 Hz, 1 H), 4.10 (d, J = 16 Hz, 1 H), 3.94 (d, J = 15 Hz, 1 H), 3.53 (m, 1 H), 3.42 (m, 1 H), 3.32 (m, 1 H), 2.94 (m, 2 H), 2.42 (m, 2 H),

1.90 (m, 1 H), 1.76 (m, 1 H), 1.62 (bs, H); CIMS (NH_3) *m/z* 571 (M + H^+, 100). Anal. ($C_{35}H_{34}N_6O_2$) C, H, N.

[4*R*-(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*-hydroxybenzenecarboximidamide] (10). A solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis[3-cyanophenylmethyl]-4,7-bis[phenylmethyl]-2*H*-1,3-diazapin-2-one[5] in ethanol was treated with excess NH_2OH·HCl and Et_3N and heated to reflux for 4 h. The solution was concentrated to dryness and the residue partitioned between ethyl acetate and water. The ethyl acetate solution was washed with water and brine and dried over $MgSO_4$. The solution was filtered and concentrated to give a white solid. The solid was recrystallized from EtOAc/MeOH to give the amidoxime **10**: mp 142−145 °C; ^{1}H NMR (DMSO-d_6) δ 9.65 (s, 1 H), 7.57 (m, 4 H), 7.37−7.14 (m, 10 H), 6.98 (d, J = 7 Hz, 4 H), 5.78 (bs, 4 H), 5.10 (bs, 2 H), 4.51 (d, J = 15 Hz, 2 H), 3.45 (m, 4 H), 2.85 (d, J = 15 Hz, 1 H), 2.80 (m, 4 H, abx); ESIMS *m/z* 623 (M + $H)^+$, 100; HRMS calcd for $C_{35}H_{39}N_6O_5$ (M + H^+) 623.2982, found 623.2954. Anal. ($C_{35}H_{38}N_6O_5$·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (14). A solution of **53**[16] (0.26 g, 0.7 mmol) in DMF was treated with NaH (0.12 g; 60% oil dispersion) and stirred at room temperature for 30 min. Then the alkylating agent 5-(bromomethyl)-1-BOC-indazole[11] was added and stirred overnight. The reaction mixture was diluted with water and extracted into ethyl acetate. The organic extract was washed with water and brine, dried, and concentrated. The resulting residue was chromatographed (MPLC silica gel, 25−50% EtOAc/hexane) to give 170 mg of the monoalkylated product. This was dissolved in a saturated solution of $HCl_{(g)}$/MeOH and stirred at room temperature for 1 h. The solution was concentrated to dryness on a rotary evaporator, and the residue was partitioned between aqueous Na_2CO_3 and ethyl acetate. The organic layer was then washed with water and brine, dried, and concentrated. The residue was chromatographed (MPLC silica gel 5% MeOH/CH_2Cl_2) to give 45 mg of **14**: mp 143−145 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.91 (s, 1 H), 7.43−7.15 (m, 13 H), 5.91 (d, J = 7 Hz, 1 H), 4.97 (d, J = 15 Hz, 1 H), 3.85 (m, 1 H), 3.61−3.39 (m, 3 H), 3.10 (m, 4 H), 2.77 (m, 1 H); CI-MS *m/z* 457 (M + $H)^+$, 100. Anal. ($C_{27}H_{28}N_4O_3$·0.25H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-[(3-hydroxyphenyl)methyl]-3-(1*H*-indazol-5-ylmethyl)-4,7-bis-(phenylmethyl)-2*H*-1,3-diazepin-2-one (16). A solution of urea **56** (0.40 g, 0.6 mmol) and 3-(benzyloxy)benzyl bromide (0.23 g, 0.8 mmol) in THF was treated with KO-t-Bu (1.2 mL; 1 M THF solution) and stirred at room temperature overnight. The solution was poured into water and extracted into ethyl acetate. The organic layer was washed with water and brine and then concentrated on a rotary evaporator. The residue was chromatographed (MPLC silica gel 20% EtOAc/hexane) to give the dialkylated urea product. The dialkylated urea (300 mg, 0.36 mmol) was dissolved in THF and was treated with 10% Pd/C (100 mg) and hydrogenated at 50 psi for 3 days. The mixture was filtered (Celite) and the filtrate concentrated. The residue was chromatographed (MPLC silica gel EtOAc) to give 200 mg of the phenol as an oil. The protecting groups (acetonide and SEM) were removed by dissolving the oil in MeOH (10 mL), treating with concentrated HCl (5 mL), and heating at reflux for 2 h. The solution was concentrated to dryness on a rotary evaporator and the residue partitioned was between aqueous Na_2CO_3 and ethyl acetate. The organic layer was washed with water and brine, dried, and concentrated to give **16** as a white solid: mp 152−155 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.92 (s, 1 H), 7.39−7.20 (m, 10 H), 7.12−7.08 (m, 4 H), 6.71−6.61 (m, 3 H), 4.91 (d, J = 16 Hz, 1 H), 4.79 (d, J = 16 Hz, 1 H), 3.59−3.46 (m, 4 H), 3.09 (d, J = 16 Hz, 1 H), 3.00 (m, 4 H), 2.90 (d, J = 16 Hz, 1 H); ESIMS *m/z* 563 (M + $H)^+$, 100. Anal. ($C_{34}H_{34}N_4O_4$·H_2O) C, H, N.



57

R = OH; Br; CN;
$CONH_2$; COOMe;CH_2OH

[4*R*-(4α,5α,6*β*,7*β*)]-Methyl 3-[[Hexahydro-5,6-dihyroxy-3-(1*H*-indazol-5-ylmethyl)-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]benzeneacetate (18). A solution of isourea **55** (2.0 g, 3.0 mmol) and 3-(carbomethoxy)-benzyl bromide (1.4 g, 6.0 mmol) in acetonitrile was treated with KI (1.0 g, 6.0 mmol) and heated at reflux for 6 h. The mixture was diluted with water and extracted into ethyl acetate. The organic extract was washed with water, sodium bisulfite, and brine. The solution was concentrated, and the resulting residue was chromatographed (MPLC silica gel, 20% EtOAc/hexane) to give 1.2 g of the ester product.

The ester was dissolved in ether, cooled to 0 °C, treated with LAH (0.17 g, 4.5 mmol), and stirred at room temperature for 2 h. The solution was cooled at 0 °C and quenched with saturated aqueous NH_4Cl. The organic layer was washed with water and brine, dried, filtered, and concentrated to give 1.1 g of the benzyl alcohol **57** (R = OH) as a white foam. The benzyl alcohol **57** (1.1 g, 1.4 mmol) was then dissolved in CH_2Cl_2, cooled to 0 °C, and treated with CBr_4 (0.6 g, 1.8 mmol). To the resulting solution was added a solution of triphenylphosphine (0.47 g, 1.8 mmol) in CH_2Cl_2, dropwise via an addition funnel. After the addition was complete, the mixture was allowed to warm to room temperature (4 h). The reaction mixture was evaporated to dryness, and the residue was chromatographed (MPLC silica gel, 20% EtOAc/hexane) to give 0.6 g of the corresponding benzyl bromide **57** (R = Br). A solution of the benzyl bromide **57** (0.6 g, 0.7 mmol) in aqueous dioxane was treated with KCN (0.24 g, 3.6 mmol) and warmed to 60 °C overnight. The solution was diluted with water and extracted into ethyl acetate. The organic layer was washed with water and brine, dried, filtered, and concentrated to give 0.55 g of the benzyl cyanide **57** (R = CN) as a white foam. Using Katritzky's procedure[18] a solution of the benzyl cyanide **57** (0.55 g, 0.7 mmol) and K_2CO_3 in DMSO was treated with 2 mL of 30% H_2O_2 at 0 °C and then allowed to warm to room temperature (2 h). The solution was dilluted with water and extracted into ethyl acetate. The organic layer was washed with water and brine, dried, filtered, and concentrated to give 0.55 g of the corresponding carboxamide **57** (R = $CONH_2$) as a white foam. A solution of the carboxamide **57** (0.3 g, 0.38 mmol) in methanol (15 mL) was treated with 1 mL of H_2SO_4 and heated at reflux overnight. The solution was made basic with 1 N NaOH and was extracted into ethyl acetate. The organic layer was washed with water and brine, dried, filtered, and concentrated to give 0.2 g of a white foam. This was chromatographed (HPLC silica gel, 6% MeOH/EtOAc) to give

150 mg of **18** as a white foam: mp 99−101 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1 H), 7.39−7.02 (m, 17 H), 4.98 (d, J = 14 Hz, 1 H), 4.79 (d, J = 16 Hz, 1 H), 3.59−3.46 (m, 4 H), 3.09 (d, J = 16 Hz, 1 H), 3.00 (m, 4 H), 2.90 (d, J = 16 Hz, 1 H); ESIMS (M + H^+, 100) 619; HRMS calcd for $C_{37}H_{39}N_4O_5$ (M + H^+) 619.2920, found 619.2943. Anal. ($C_{37}H_{38}N_4O_5$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-[[3-(2-hydroxyethyl)phenyl]methyl]-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (17). A solution of the ester **18** in THF was reduced with LAH. This was chromatographed (MPLC silica gel, 6% MeOH/$CHCl_3$) to give the ethyl alcohol **17** as a white solid: mp 102−105 °C; ESIMS (M + H^+, 100) 591; HRMS calcd for $C_{36}H_{39}N_4O_4$ (M + H^+) 619.2920, found 619.2943. Anal. ($C_{36}H_{38}N_4O_4$·0.66$CHCl_3$·0.33CH_3OH) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[(3-Acetylphenyl)methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (19). The urea **56** was alkylated with 3-(2-methyl-1,3-dioxolan-2-yl)benzyl bromide in THF using 1 M KO-t-Bu/THF, and the protecting groups were removed using HCl/MeOH as described above for **16**: mp 120−122 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1 H), 7.82 (d, J = 7 Hz, 1 H), 7.72 (s, 1 H), 7.45−7.24 (m, 11 H), 7.13−7.07 (m, 4 H), 4.95 (d, J = 14 Hz, 1 H), 4.91 (d, J = 14 Hz, 1 H), 3.65−3.40 (m, 6 H), 3.19−2.93 (m, 6 H); CIMS (M + NH_4^+, 100) 606; HRMS calcd for $C_{36}H_{37}N_4O_4$ (M + H^+) 589.2815, found 589.2811. Anal. ($C_{36}H_{36}N_4O_4$·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-2-Fluoro-5-[[hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]benzamide (20). The urea **56** was alkylated with 4-fluoro-3-cyanobenzyl bromide in THF using 1 M KO-t-Bu/THF, and the protecting groups were removed using HCl/MeOH as described above for **16**. Finally the cyano group was then converted to the amide using 30% H_2O_2 in DMSO as described for **18** to give **20** as a white solid: mp 143−146 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.92 (s, 1 H), 7.76 (dd, J = 2 Hz, 7 Hz, 1 H), 7.46−7.20 (m, 11 H), 7.12−7.08 (m, 4 H), 4.88 (d, J = 14 Hz, 1 H), 4.72 (d, J = 14 Hz, 1 H), 3.69−3.46 (m, 3 H), 3.59 (d, J = 14 Hz, 1 H), 3.35 (m, 1 H), 3.18 (d, J = 14 Hz, 1 H), 3.06 (m, 2 H), 3.05−2.75 (m, 2 H); ESIMS m/z 608 (M + H^+, 100). Anal. ($C_{35}H_{34}N_5O_4F$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[(3-Amino-4-fluorophenyl)methyl]-hexahydro-5,6-dihydroxy-3-[(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (23). The urea **56** was alkylated with 4-fluoro-3-nitrobenzyl bromide in THF using 1 M KO-t-Bu/THF. The nitro group was hydrogenated (10% Pd/C, THF, 30 psi) to give the aniline, and the protecting groups were removed using HCl/MeOH to give a white solid. This was chromatographed (MPLC silica gel, EtOAc) to give **23**. This was recrystallized from chloroform: mp 183−184 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.87 (s, 1 H), 7.39−7.14 (m, 13 H), 6.84 (dd, J = 11 Hz, 8 Hz, 1 H), 6.64−6.36 (m, 2 H), 4.93 (d, J = 14 Hz, 1 H), 4.72 (d, J = 14 Hz, 1 H), 3.65−3.40 (m, 4 H), 3.19−2.93 (m, 6 H); ESIMS m/z 580 (M + H^+, 100). Anal. ($C_{34}H_{34}N_5O_3F$·0.20$CHCl_3$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[(4-amino-3-fluorophenyl)methyl]-hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (24). The urea **56** was alkylated with 4-azido-3-fluorobenzyl bromide in THF using 1 M KO-t-Bu/THF. The azido was reduced to the aniline with LAH in THF at room temperature, and the protecting groups were removed using HCl/MeOH to give a white solid. This was chromatographed (HPLC Zorbax Sil, 6% MeOH/$CHCl_3$) to give **24**: mp 125−130 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1 H), 7.39−7.24 (m, 9 H), 7.18 (d, J = 7 Hz, 2 H), 7.12 (d, J = 7 Hz, 2 H), 6.77−6.61 (m, 3 H), 4.98 (d, J = 14 Hz, 1 H), 4.77 (d, J = 14 Hz, 1 H), 3.65−3.40 (m, H), 3.19−2.93 (m, 6 H); ESIMS m/z 580 (M + H^+, 100). Anal. ($C_{34}H_{34}N_5O_3F$·0.25$CHCl_3$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[(3-Aminophenyl)methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (21). Procedure detailed for **23** was used except alkylating with 3-nitrobenzyl bromide: mp 134−136 °C; ^{1}H NMR (DMSO-d_6) δ 13.03 (bs, 1 H), 8.05 (s, 1 H), 7.51 (d, J = 8 Hz, 2 H), 7.36−7.19 (m, 8 H), 7.13 (d, J = 8 Hz, 2 H), 7.01 (d, J = 8 Hz, 2 H), 6.94 (t, J = 8 Hz, 1 H), 6.42 (d, J = 8 Hz, 1 H), 6.33 (s, 1 H), 6.23 (d, J = 8 Hz, 1 H), 5.07 (bs, 2 H), 5.00 (bs, 2 H), 4.79 (d, J = 14 Hz, 1 H), 4.61 (d, J = 14 Hz, 1 H), 3.55−3.35 (m, 4 H), 3.00−2.80 (m, 5 H), 2.59 (d, J = 14 Hz, 1 H); ESIMS m/z 562 (M + H^+, 100); HRMS calcd for $C_{34}H_{36}N_5O_3$ (M + H^+) 562.2818, found 562.2807. Anal. ($C_{34}H_{35}N_5O_3$·H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[(4-Aminophenyl)methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (22). Similar procedure as detailed for **23** was used except alkylating with 4-azidobenzyl or 4-nitrobenzyl bromide: mp 137−140 °C; ^{1}H NMR (DMSO-d_6) δ 13.02 (bs, 1 H), 8.04 (s, 1 H), 7.49 (d, J = 8 Hz, 1 H), 7.36−7.19 (m, 8 H), 7.11 (d, J = 7 Hz, 2 H), 7.01 (d, J = 7 Hz, 2 H), 6.75 (d, J = 8 Hz, 2 H), 6.49 (d, J = 8 Hz, 2 H), 5.00 (bs, 2 H), 4.95 (bs, 2 H), 4.79 (d, J = 14 Hz, 1 H), 4.59 (d, J = 14 Hz, 1 H), 3.55−3.21 (m, 4 H), 3.00−2.80 (m, 5 H), 2.62 (d, J = 14 Hz, 1 H); ESIMS m/z 562 (M + H^+, 100); HRMS calcd for $C_{34}H_{36}N_5O_3$ (M + H^+) 562.2818, found 562.2834. Anal. ($C_{34}H_{35}N_5O_3$·0.75H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[(3-Amino-4-methylphenyl)methyl]-hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (25). Similar procedure as detailed for **23** was used except alkylating with 3-nitro-4-methylbenzyl bromide: mp 151−153 °C; ^{1}H NMR (DMSO-d_6) δ 13.03 (bs, 1 H), 8.05 (s, 1 H), 7.49 (d, J = 8 Hz, 1 H), 7.36−7.19 (m, 8 H), 7.16 (d, J = 8 Hz, 2 H), 7.05 (d, J = 8 Hz, 2 H), 6.82 (d, J = 8 Hz, 1 H), 6.36 (s, 1 H), 6.17 (d, J = 8 Hz, 1 H), 5.07 (bs, 2 H), 5.00 (bs, 2 H), 4.79 (d, J = 14 Hz, 1 H), 4.58 (d, J = 14 Hz, 1 H), 3.55−3.35 (m, 4 H), 3.00−2.80 (m, 5 H), 2.59 (d, J = 14 Hz, 1 H); ESIMS m/z 576 (M + H^+, 100); HRMS calcd for $C_{35}H_{38}N_5O_3$ (M + H^+) 576.2975, found 576.2982.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-3-[[3-(methylamino)phenyl]methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (27). The urea **56** was alkylated with 3-nitrobenzyl bromide in THF using 1 M KO-t-Bu/THF. The nitro group was hydrogenated (10% Pd/C, THF, 30 psi) to give the aniline. The aniline was converted to the trifluoroacetamide (trifluoroacetic anhydride/CH_2Cl_2/Et_3N/room temp) and then alkylated with MeI (NaH/DMF/rt) to give the *N*-methyltrifluoroacetamide intermediate. All the protecting groups were then removed (concentrated HCl/MeOH/reflux) to give **27**: mp 210 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.92 (s, 1 H), 7.46−7.08 (m, 14 H), 6.51 (m, 2 H), 6.37 (bs, 1 H), 4.95 (d, J = 14 Hz, 1 H), 4.82 (d, J = 14 Hz, 1 H), 3.62−3.33 (m, 4 H), 3.12 (d, J = 14 Hz, 1 H), 3.05 (m, 4 H), 2.85 (d, J = 14 Hz, 1 H), 2.75 (s, 3 H); ESIMS m/z 288.8 (M + $2H^{2+}$, 100). Anal. ($C_{35}H_{37}N_5O_3$·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[[3-(Dimethylamino)phenyl]methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (26). The urea **56** was alkylated with 3-nitrobenzyl bromide in THF using 1 M KO-t-Bu/THF. The nitro group was hydrogenated (10% Pd/C, THF, 30 psi) to give the aniline. The aniline was converted to the trifluoroacetamide (trifluoroacetic anhydride/CH_2Cl_2 Et_3N/room temperature) and then alkylated with MeI (NaH/DMF/room temperature) to give the *N*-methyltrifluoroacetamide intermediate. The trifluoroacetamide was hydrolyzed (1 N NaOH/DMF) and was alkylated with MeI (NaH/DMF/room temperature to give the *N*,*N*-dimethyl analogue. All the protecting groups were then removed (concentrated HCl/MeOH/reflux) to give **26**: mp 190−191 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1 H), 7.46−7.12 (m, 14 H), 6.62 (d, J = 8 Hz, 1 H), 6.50 (d, J = 8 Hz, 1 H), 6.46 (bs, 1 H), 4.95 (d, J = 14 Hz, 1 H), 4.87 (d, J = 14 Hz, 1 H), 3.62−3.33 (m, 6 H), 3.12 (d, J = 14 Hz, 1 H), 3.10−2.90 (m, 4 H), 2.93 (d, J = 14 Hz, 1 H), 2.87 (s, 6 H); ESIMS m/z 590 (M + H^+, 100). Anal. ($C_{36}H_{39}N_5O_3$·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[[4-Fluoro-3-(methylamino)phenyl]-methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (28). The urea **56** was alkylated with 3-(*N*-methyl-*N*-trifluoroacetyl)-

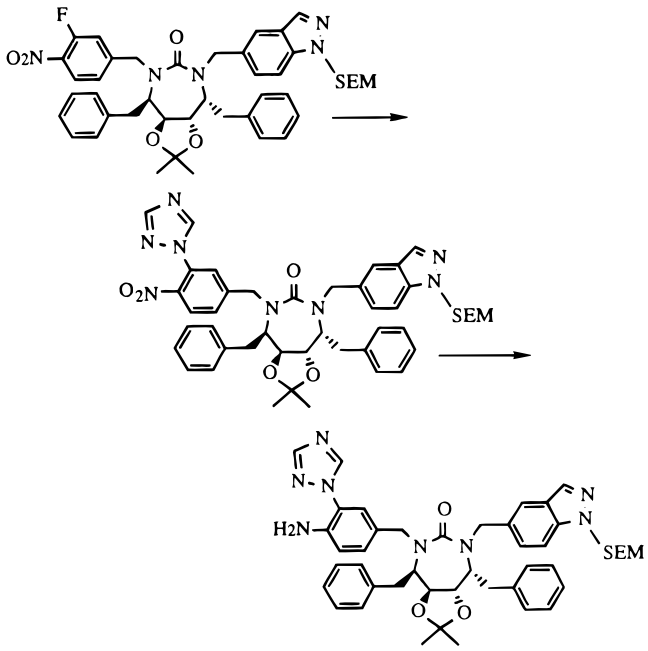
4-fluorobenzyl bromide in THF using 1 M KO-t-Bu/THF. All the protecting groups were then removed (concentrated HCl/MeOH/reflux) to give **28**. Recrystallized from chloroform: mp 191−193 °C; ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.87 (s, 1 H), 7.32 (d, J = 8 Hz, 1 H), 7.29−7.15 (m, 8 H), 7.10 (d, J = 7 Hz, 2 H), 7.05 (d, J = 7 Hz, 2 H), 6.77 (dd, J = 11 Hz, 8 Hz, 1 H), 6.36 (dd, J = 8 Hz, 2 Hz, 1 H), 6.24 (m, 1 H), 4.84 (d, J = 14 Hz, 1 H), 4.70 (d, J = 14 Hz, 1 H), 3.55−3.25 (m, 4 H), 3.00 (d, J = 14 Hz, 1 H), 2.96−2.84 (m, 4 H), 2.78 (d, J = 14 Hz, 1 H), 2.66 (s, 3 H); ESIMS m/z 297.8 (M + 2H^{+2}, 100). Anal. ($C_{35}H_{36}N_5O_3F\cdot0.5H_2O$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(1*H*-pyrazol-1-ylmethyl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (29). A solution of pyrazole (0.16 g, 2.4 mmol) in DMF was treated with NaH (0.1 g, 2.4 mmol, 60% oil dispersion), and the mixture is stirred at room temperature for 30 min. Then a solution of the benzyl bromide **57** (R = Br) (0.2 g, 0.24 mmol) in DMF was added, and the mixture was stirred at room temperature for 30 min. The solution was diluted with water, made acidic with 1 N HCl, and extracted into ethyl acetate. The organic layer is washed with water and brine, dried over $MgSO_4$, filtered, and then concentrated on a rotary evaporator. The residue was dissolved in MeOH (10 mL), treated with concentrated HCl (5 mL), and heated at reflux for 2 h. The solution was concentrated on a rotary evaporator and the residue partitioned between aqueous Na_2CO_3 and ethyl acetate. The organic layer was washed with water and brine, dried, and concentrated. The residue was chromatographed (MPLC silica gel EtOAc) to give **29** as a white solid: mp 118−122 °C; ^{1}H NMR ($CDCl_3$) δ 11.0 (bs, 1 H), 7.77 (s, 1 H), 7.39−6.9 (m, 18 H), 6.71 (bs, 1 H), 6.16 (dd, J = 2 Hz, 2 Hz, 1 H), 5.07 (dd, J = 15 Hz, 2 Hz, 2 H), 4.96 (d, J = 14 Hz, 1 H), 4.83 (d, J = 14 Hz, 1 H), 4.40 (bs, 1 H), 3.90 (bs, 1 H), 3.59−3.13 (m, 4 H), 3.10 (d, J = 14 Hz, 1 H), 3.09−2.76 (m, 4 H), 2.95 (d, J = 14 Hz, 1 H); ESIMS m/z 314 (M + 2H^{+2}, 100); HRMS calcd for $C_{38}H_{39}N_6O_3$ (M + H$^+$) 627.3084, found 627.3108. Anal. ($C_{38}H_{38}N_6O_3\cdot0.75H_2O$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(1*H*-1,2,4-triazol-1-ylmethyl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (30). The procedure detailed for **29** was used except starting with 1,2,4-triazole: mp 120−124 °C; ^{1}H NMR ($CDCl_3$) δ 11.3 (bs, 1 H), 7.77 (s, 1 H), 7.73 (s, 1 H), 7.68 (s, 1 H), 7.60 (s, 1 H), 7.31−7.03 (m, 16 H), 6.96 (bs, 1 H), 5.13 (dd, J = 15 Hz, 22 Hz, 2 H), 4.96 (d, J = 14 Hz, 1 H), 4.85 (d, J = 14 Hz, 1 H), 4.45 (bs, 2 H), 3.59−3.43 (m, 4 H), 3.07 (d, J = 14 Hz, 1 H), 3.08−3.02 (m, 4 H), 3.02 (d, J = 14 Hz, 1 H), 2.80 (m, 1 H); ESIMS m/z 314.8 (M + 2H^{+2}, 100); HRMS calcd for $C_{37}H_{38}N_7O_3$ (M + H$^+$) 628.3036, found 628.3030. Anal. ($C_{37}H_{37}N_7O_3\cdot0.75H_2O$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (31). The procedure detailed for **29** was used except starting with 1,2,3-triazole. Two isomers were obtained. The more polar isomer is **31**: mp 114−118 °C; ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.77 (s, 1 H), 7.73 (s, 1 H), 7.56 (s, 1 H), 7.48 (s, 1 H), 7.38−6.99 (m, 17 H), 5.46 (dd, J = 15 Hz, 22 Hz, 2 H), 4.91 (d, J = 15 Hz, 1 H), 4.80 (d, J = 15 Hz, 1 H), 3.59−3.43 (m, 4 H), 3.05 (d, J = 15 Hz, 1 H), 3.07−2.90 (m, 3 H), 3.01 (d, J = 15 Hz, 1 H), 2.66 (m, 1 H); ESIMS m/z 314.9 (M + 2H^{+2}, 100); HRMS calcd for $C_{37}H_{38}N_7O_3$ (M + H$^+$) 628.3036, found 628.3017. Anal. ($C_{37}H_{37}N_7O_3\cdot0.66H_2O$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(2*H*-1,2,3-triazol-2-ylmethyl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (32). The procedure detailed for **29** was used except starting with 1,2,3-triazole. Two isomers were obtained. The less polar isomer is **32**: mp 112−116 °C; ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.77 (s, 1 H), 7.45 (s, 2 H), 7.38−6.99 (m, 17 H), 5.43 (s, 2 H), 4.98 (d, J = 14 Hz, 1 H), 4.84 (d, J = 14 Hz, 1 H), 3.59−3.33 (m, 4 H), 3.07−2.80 (m, 6 H); ESIMS m/z 628.5 (M + H$^+$, 100). Anal. ($C_{37}H_{37}N_7O_3\cdot0.66H_2O$) C, H, N.



[4*R*-(4α,5α,6*β*,7*β*)]-1-[[4-Amino-3-(1*H*-1,2,4-triazol-1-yl)-phenyl]methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (34). The urea **56** was alkylated with 4-nitro-3-fluorobenzyl bromide in THF using 1 M KO-t-Bu/THF to give the dialkylated urea. A solution of triazole (0.16 g, 2.3 mmol) in DMF was treated with NaH (0.1 g, 2.4 mmol, 60% oil dispersion), and the mixture is stirred at room temperature for 30 min. This solution was cooled to 0 °C, and the dialkylated urea (containing the 4-nitro-3-fluorobenzyl group) (0.2 g, 0.26 mmol) was added. The resulting dark mixture stirred at 0 °C for 30 min and then warmed to room temperature and stirred for 2 h. The solution was diluted with water, acidified with 1 N HCl, and extracted into ethyl acetate. The organic layer was washed with water and brine, dried, filtered, and concentrated. The residue was chromatographed (MPLC silica gel, 50% EtOAc/hexane) to give 0.1 g of the corresponding 3-(1,2,4-triazol-1-yl)-4-nitrobenzyl compound. This was dissolved in THF, treated with 100 mg of 10% Pd/C, and hydrogenated at 50 psi for 5 h. The mixture was filtered (Celite), and the residue was chromatographed (MPLC silica gel, 60% EtOAc/hexane) to give 70 mg of the corresponding 3-(1,2,4-triazol-1-yl)-4-aminobenzyl compound. Finally the protecting groups were removed by dissolving in MeOH (20 mL), treating with concentrated HCl (5 mL), and heating at reflux for 2 h. The mixture was concentrated, and the residue was partitioned between 1 N NaOH and EtOAc. The organic extract was washed with water and brine and dried over $MgSO_4$. Solution was filtered and concentrated and the residue was triturated with ethyl acetate/hexane to give 40 mg of **34** as a white solid: mp 144−148 °C; ^{1}H NMR ($CDCl_3$) δ 12.13 (bs, 1 H), 8.31 (s, 1 H), 8.15 (s, 1 H), 7.82 (s, 1 H), 7.31−6.33 (m, 16 H), 4.96 (d, J = 14 Hz, 1 H), 4.75 (d, J = 14 Hz, 1 H), 4.75 (bs, 2 H), 4.12 (bs, 2 H), 3.59−3.33 (m, 4 H), 3.05−2.80 (m, 6 H); ESIMS m/z 315.3 (M + 2H^{+2}, 100); HRMS calcd for $C_{36}H_{37}N_8O_3$ (M + H$^+$) 629.2989, found 629.2971. Anal. ($C_{36}H_{36}N_8O_3\cdot0.5EtOAc\cdot0.1hexane\cdot0.75H_2O$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[[4-Amino-3-(1*H*-pyrazol-1-yl)-phenyl]methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (33). The procedure detailed for **34** was used except starting with pyrazole: recrystallized from ethyl acetate; mp 139−141 °C; ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.95 (s, 1 H), 7.74 (d, J = 2 Hz, 1 H), 7.64 (d, J = 2 Hz, 1 H), 7.42−6.47 (m, 17 H), 4.96 (d, J = 14 Hz, 1 H), 4.83 (d, J = 14 Hz, 1 H), 3.59−3.33 (m, 4 H), 3.19−2.80 (m, 6 H); ESIMS m/z 628.5 (M + H$^+$, 100); HRMS calcd for $C_{37}H_{38}N_7O_3$ (M + H$^+$) 628.3036, found 628.3031. Anal. ($C_{37}H_{37}N_7O_3\cdot0.66EtOAc\cdot0.66H_2O$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[[4-Amino-3-(2*H*-1,2,3-triazol-2-yl)-phenyl]methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (35). The procedure detailed for **34** was used except starting with 1,2,3-triazole to give 2 isomers. The less polar isomer is **35**: recrystallized from ethyl acetate; mp 139−142 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 12.41 (bs, 1 H), 7.95 (s, 1 H), 7.79 (s, 2 H), 7.62−6.77 (m, 16 H), 5.50 (bs, 2 H), 4.96 (d, J = 14 Hz, 1 H), 4.77 (d, J = 14 Hz, 1 H), 4.31 (bs, 1 H), 4.25 (bs, 1 H), 3.59−3.33 (m, 4 H), 3.19−2.80 (m, 6 H); ESIMS m/z 315.3 (M + 2H^{+2}, 100); HRMS calcd for $C_{36}H_{37}N_8O_3$ (M + H$^+$) 629.2989, found 629.2979. Anal. ($C_{36}H_{36}N_8O_3$·0.5EtOAc·0.25H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[[4-Amino-3-(1*H*-1,2,3-triazol-1-yl)-phenyl]methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (36). The procedure detailed for **34** was used except starting with 1,2,3-triazole to give two isomers. The more polar isomer is **36**: recrystallized from ethyl acetate; mp 142−148 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 12.41 (bs, 1 H), 7.95 (s, 1 H), 7.84 (s, 1 H), 7.80 (s, 1 H), 7.47−6.87 (m, 16 H), 4.96 (d, J = 14 Hz, 1 H), 4.86 (bs, 2 H), 4.77 (d, J = 14 Hz, 1 H), 4.31 (bs, 1 H), 4.25 (bs, 1 H), 3.59−3.33 (m, 4 H), 3.19−2.80 (m, 6 H); ESIMS m/z 315.3 (M + 2H^{+2}, 100); HRMS calcd for $C_{36}H_{37}N_8O_3$ (M + H$^+$) 629.2989, found 629.2983. Anal. ($C_{36}H_{36}N_8O_3$·0.25EtOAc·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(4*H*-1,2,4-triazol-3-yl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (37). The urea **56** was alkylated with 3-cyanobenzyl bromide in THF using 1 M KO-t-Bu/THF. The 3-cyanobenzyl group was converted to the corresponding carboxamide (30% H_2O_2 and K_2CO_3 in DMSO).[18] The 1,2,4-triazole group was obtained from the carboxamide using the literature[24] procedure by first heating with *N*,*N*-dimethylformamide dimethyl acetal (90 °C) for 2 h to obtain the corresponding *N*′-acyl-*N*,*N*-dimethylamidine. The *N*′-acyl-*N*,*N*-dimethylamidine intermediate is cyclized by heating with hydrazine in AcOH (90 °C) for 2 h to give the triazole ring. Finally the protecting groups were removed using HCl/MeOH, and the product was chromatographed (MPLC silica gel, 5% MeOH/$CHCl_3$) to give **37**: mp 166−168 °C; ^{1}H NMR (DMSO-d_6) δ 13.04 (s, 1 H), 8.05 (s, 1 H), 7.93 (br s, 1 H), 7.53−7.01 (m, 16 H), 5.05 (dd, J = 16 Hz, 4 Hz, 2 H), 4.76 (t, J = 14 Hz, 2 H), 3.52−3.35 (m, 4 H), 2.99−2.73 (m, 6 H); ESIMS m/z 614 (M + H$^+$, 100); HRMS calcd for $C_{36}H_{36}N_7O_3$ (M + H$^+$) 614.2879, found 614.2852. Anal. ($C_{36}H_{35}N_7O_3$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[[4-Amino-3-(1*H*-pyrazol-3-yl)-phenyl]methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (38). Isourea **55** was alkylated with 3-carbomethoxy-4-fluorobenzyl bromide using the procedure detailed for **18**. This was converted to the Weinreb amide using the procedure detailed for **43**. The amide was treated with methylmagnesium bromide to give the 3-acetyl-4-fluorobenzyl group. A suspension of the 3-acetyl-4-fluorobenzyl analogue (0.3 g, 0.39 mmol) and NaN_3 (1.0 g, 15.3 mmol) in DMF was stirred at 90 °C for 3 days. After being cooled to room temperature, the suspension was diluted with H_2O and extracted into EtOAc. The organic layer was washed with water and brine, dried, filtered, and concentrated in vacuo. The residue was chromatographed (MPLC silica gel, 30% EtOAc/hexane) to give 0.1 g of the corresponding 3-acetyl-4-azidobenzyl group. The 3-acetyl group was treated with *N*,*N*-dimethylformamide dimethyl acetal (90 °C) for 4 h. After being cooled to room temperature, the suspension was diluted with H_2O and extracted into EtOAc. The residue was then heated with hydrazine in refluxing EtOH for 2 h to give the 3-(pyrazol-3-yl)-4-aminophenylmethyl analogue. Finally the protecting groups were removed using the HCl/MeOH procedure, and the product was chromatographed (MPLC silica gel, 9:95:1 MeOH:$CHCl_3$:aqueous NH_3) to give **38**: mp 147−151 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.94 (s, 1 H), 7.60−7.07 (m, 17 H), 6.53 (br s, 1 H), 4.93 (d, J = 14 Hz, 2 H), 3.64−3.53 (m, 4 H), 3.39 (br s, 2 H), 3.18−2.97 (m, 4 H); ESIMS m/z 628 (M + H$^+$, 100); HRMS calcd for $C_{37}H_{38}N_7O_3$ (M + H$^+$) 628.3036, found 628.3034.

[4*R*-(4α,5α,6*β*,7*β*)]-3-[[Hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]benzoic Acid (15). The urea **56** (0.20 g, 0.3 mmol) was alkylated with 3-carbomethoxybenzyl bromide (0.27 g, 1.2 mmol) under the standard conditions[5] (DMF/NaH (0.06 g, 1.5 mmol, 60% oil dispersion). The protecting groups (acetonide and SEM) were removed by dissolving in MeOH (10 mL) and 4 N HCl/dioxane (5 mL) and heating at reflux for 3 h. The solution was evaporated to dryness, and the residue was redissolved in dioxane, treated with 50% aqueous NaOH (0.34 g), and stirred at room temperature for 24 h. The solution was acidified with 1 N HCl and extracted into ethyl acetate. The organic layer was washed with water and brine, dried, and concentrated on a rotary evaporator. The residue was triturated with hot water and then with hot methylene chloride to give 80 mg of **15** as a white solid: mp 151−153 °C; ^{1}H NMR (DMSO-d_6) δ 13.07 (bs, 1 H), 8.04 (s, 1 H), 7.84 (bs, 1 H), 7.50 (d, J = 7 Hz, 1 H), 7.37−6.99 (m, 16 H), 5.22 (bs, 2 H), 4.76 (d, J = 14 Hz, 1 H), 4.72 (bs, 2 H), 4.77 (d, J = 14 Hz, 1 H), 3.59−3.30 (m, 4 H), 2.95−2.49 (m, 6 H); ESIMS m/z 591 (M + H$^+$, 100); HRMS calcd for $C_{35}H_{35}N_4O_5$ (M + H$^+$) 591.2607, found 591.2612. Anal. ($C_{35}H_{34}N_4O_5$·0.75CH_2Cl_2·0.25H_2O) C, H, N.

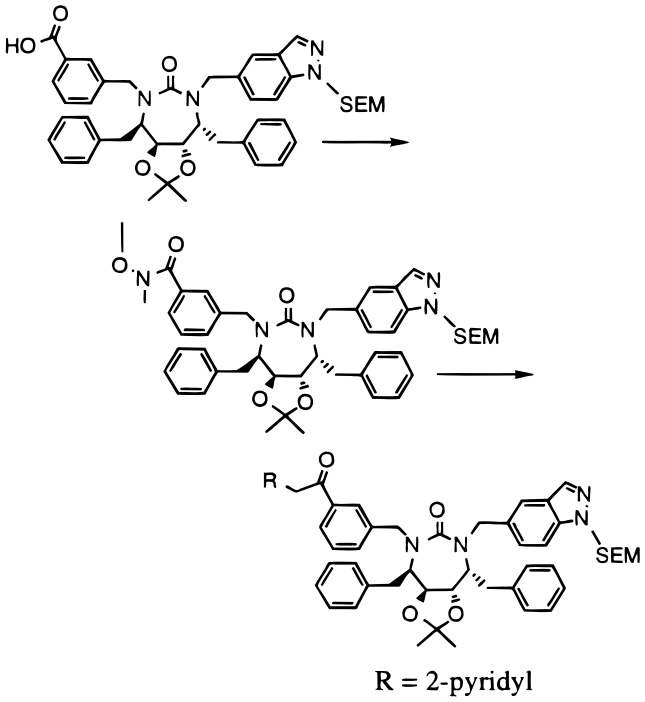
[4*R*-(4α,5α,6*β*,7*β*)]-3-[[Hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-(2-thiazolyl)benzamide (42). A solution of the acid **15** (60 mg, 0.1 mmol) in CH_2Cl_2/CH_3CN was treated with 2-aminothiazole (300 mg, 3.0 mmol) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (58 mg, 0.3 mmol) and stirred at room temperature for 24 h. The solution was diluted with water and extracted into ethyl acetate. The organic layer was washed with water and brine, dried, and concentrated on a rotary evaporator. The residue was chromatographed (HPLC Zorbax Sil, 10% MeOH/CH_2Cl_2) to give 30 mg of **42**: mp 167−169 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.95 (s, 1 H), 7.87 (d, J = 7 Hz, 1 H), 7.76 (s, 1 H), 7.50 (d, J = 3.6 Hz, 1 H), 7.47−7.22 (m, 12 H), 7.11 (d, J = 7 Hz, 2 H), 7.04 (d, J = 3.6 Hz, 1 H), 6.91 (d, J = 7 Hz, 2 H), 4.90 (d, J = 14 Hz, 1 H), 4.77 (d, J = 14 Hz, 1 H), 3.59−3.33 (m, 4 H), 3.25 (d, J = 14 Hz, 1 H), 3.19−2.80 (m, 5 H); CIMS m/z 673 (M + H$^+$, 100); HRMS calcd for $C_{38}H_{37}N_6O_4S$ (M + H$^+$) 673.2597, found 673.2615. Anal. ($C_{38}H_{36}N_6O_4S$·1.25H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-3-[[Hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-(5-methyl-2-pyridinyl)benzamide (39). The procedure detailed for **42** was used except using 2-amino-5-methylpyridine: mp 141−143 °; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 8.23 (d, J = 8 Hz, 1 H), 8.13 (d, J = 2 Hz, 1 H), 7.95 (s, 1 H), 7.85−7.04 (m, 19 H), 4.90 (m, 2 H), 3.62−3.38 (m, 4 H), 3.19−2.80 (m, 6 H); CIMS m/z 681 (M + H$^+$, 100); HRMS calcd for $C_{41}H_{41}N_6O_4$ (M + H$^+$) 681.3189, found 681.3192. Anal. $C_{41}H_{40}N_6O_4$·H_2O C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-3-[[Hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-(2-pyridinyl)benzamide (40). The procedure detailed for **42** was used except using 2-aminopyridine: mp 150−152 °C; ^{1}H NMR (DMSO-d_6) δ 13.07 (bs, 1 H), 10.77 (s, 1 H), 8.39 (dd, J = 2 Hz, 2 Hz, 1 H), 8.17 (d, J = 8 Hz, 1 H), 8.04 (s, 1 H), 7.94 (d, J = 7 Hz, 1 H), 7.87−7.80 (m, 3 H), 7.50−6.99 (m, 11 H), 7.02 (d, J = 8 Hz, 2 H), 6.97 (d, J = 8 Hz, 2 H), 5.09 (bs, 1 H), 5.03 (bs, 1 H), 4.76 (d, J = 14 Hz, 1 H), 4.71 (d, J = 14 Hz, 1 H), 3.59−3.30 (m, 4 H), 3.05−2.59 (m, 6 H); ESIMS m/z 667 (M + H$^+$, 100); HRMS calcd for $C_{40}H_{39}N_6O_4$ (M + H$^+$) 667.3033, found 667.3045.

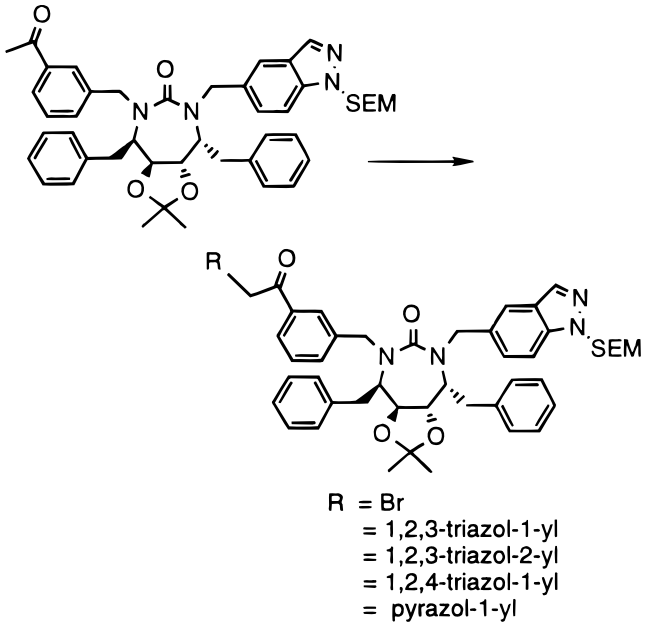
[4*R*-(4α,5α,6*β*,7*β*)]-3-[[Hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-2-oxo-4,7-bis(phenylmethyl)-1*H*-1,3-diazepin-1-yl]methyl]-*N*-(6-methyl-2-pyridinyl)benzamide (41). A similar procedure as detailed for **42** was used except using 2-amino-6-methylpyridine: mp 147−149 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 8.13 (d, 8 Hz, 1 H), 7.80 (s, 1 H), 7.71

(d, J = 7 Hz, 1 H), 7.63−7.56 (m, 2 H), 7.39−7.20 (m, 11 H), 7.11 (d, J = 7 Hz, 2 H), 7.04 (d, J = 7 Hz, 2 H), 6.88 (d, J = 7 Hz, 1 H), 4.95 (d, J = 16 Hz, 1 H), 4.81 (d, J = 16 Hz, 1 H), 3.69−3.48 (m, 4 H), 3.19−2.80 (m, 6 H), 2.32 (s, 3 H); CIMS m/z 681 (M + H^+, 100); HRMS calcd for $C_{41}H_{41}N_6O_4$ (M + H^+) 681.3189, found 681.3174. Anal. ($C_{41}H_{40}N_6O_4 \cdot H_2O$) C, H, N.



[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(2-pyridinylacetyl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (43). The urea **56** was alkylated with 3-carbomethoxybenzyl bromide under the standard conditions[5] (DMF/NaH (60% oil dispersion). The ester (1.7 g, 2.2 mmol) was dissolved in dioxane (30 mL), treated with 1 N NaOH (7 mL), and stirred at room temperature for 24 h. The solution was acidified with 1 N HCl and extracted into ethyl acetate. The organic layer was washed with water and brine, dried, and concentrated on a rotary evaporator. The acid formed was converted to the Weinreb[19] amide using the Ph_3P/CBr_4 procedure.[20] A suspension of acid (0.83 g, 1.1 mmol), CBr_4 (1.42 g, 1.3 mmol), *N*-methoxy-*N*-methylamine hydrochloride (0.14 g, 1.3 mmol), and pyridine (0.12 g, 1.4 mmol) in methylene chloride was treated portionwise with Ph_3P (0.37 g, 1.4 mmol) and was stirred at room temperature for 1 h until homogeneous. The solution was concentrated to dryness and the residue triturated with 50% EtOAc/hexane (100 mL). The solid was removed by filtration and the filtrate concentrated on a rotary evaporator. The residue is chromatographed (MPLC silica gel, 3% MeOH/CH_2Cl_2) to give 0.70 g of the *N*-methoxy-*N*-methylamide. A solution of 2-picoline (46 mg, 0.49 mmol) in THF was treated with phenyllithium (0.25 mL, 0.45 mmol, 1.8 M solution) and stirred for 1 h at room temperature. The solution was cooled to −78 °C, and the above *N*-methoxy-*N*-methylamide (0.18 g, 0.22 mmol) was added. The mixture was allowed to warm to room temperature, and the reaction was quenched with saturated NH_4Cl. The mixture was extracted into ethyl acetate, and the organic layer was washed with water and brine, dried, and concentrated on a rotary evaporator. The residue was chromatographed (MPLC silica gel, 50% ETOAc/hexane) to give 0.16 g of ketone as a yellow solid. The protecting groups (acetonide and SEM) were removed by dissolving in MeOH (10 mL) and 4 N HCl/dioxane (5 mL) and heating at reflux for 8 h. The solution was evaporated to dryness, and the residue was chromatographed (MPLC silica gel, 7% MeOH/CH_2Cl_2) to give 80 mg of **43** as a mixture of keto−enol forms: mp 119−121 °C; ^{1}H NMR (DMSO-d_6) δ 13.07 (bs, 1 H), 8.39 (m, 1 H), 8.04 (s, 1 H), 7.95−6.80 (m, 20 H), 6.02 (s, 1 H, enol), 5.09 (vbs, 3 H), 4.86 (d, J = 14 Hz, 1 H), 4.61 (d, J = 14 Hz, 1 H), 4.42 (s, 1 H, keto form), 3.59−3.30 (m, 4 H), 3.05−2.59 (m, 6 H); ESIMS m/z 666 (M + H^+, 100); HRMS calcd for $C_{41}H_{40}N_5O_4$ (M + H^+) 666.3080, found 666.3098. Anal. ($C_{41}H_{39}N_5O_4 \cdot H_2O$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(2-thienylacetyl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (44). A solution of isourea **55** (0.2 g, 0.3 mmol) and 3-(thien-2-ylacetyl)-benzyl bromide (0.28 g, 0.94 mmol) in acetonitrile was heated at reflux for 20 h. The mixture was concentrated, and the resulting residue was chromatographed (MPLC silica gel, 10−30% EtOAc/hexane) to give the dialkylated urea (0.10 g). The protecting groups were removed by dissolving in MeOH (20 mL), treating with concentrated HCl (5 mL), and heating at reflux for 2 h. The mixture was concentrated, and the residue was partitioned between 1 N NaOH and EtOAc. The organic extract was washed with water and brine, and dried over $MgSO_4$. Solution was filtered and concentrated and the residue was chromatographed (MPLC silica gel, 5% MeOH/CH_2Cl_2) to give 40 mg of **44**: mp 121−123 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.96 (s, 1 H), 7.90 (d, J = 7 Hz, 1 H), 7.78 (s, 1 H), 7.45−7.21 (m, 12 H), 7.12 (d, J = 7 Hz, 2 H), 7.07 (d, J = 7 Hz, 2 H), 6.94 (m, 1 H), 6.88 (m, 1 H), 4.93 (d, J = 14 Hz, 1 H), 4.82 (d, J = 14 Hz, 1 H), 4.45 (s, 2 H), 3.63−3.30 (m, 4 H), 3.15−2.81 (m, 6 H); ESIMS m/z 671 (M + H^+, 100); HRMS calcd for $C_{40}H_{39}N_4O_4S$ (M + H^+) 671.2692, found 671.2684. Anal. ($C_{40}H_{38}N_4O_4S \cdot 0.33H_2O$) C, H, N.



[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(1*H*-pyrazol-1-ylacetyl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (45). The urea **56** was alkylated with 3-cyanobenzyl bromide in THF using 1 M KO-t-Bu/THF. The 3-cyanobenzyl group was converted to the 3-acetylbenzyl group with methylmagnesium bromide (THF, reflux). The acetyl group was brominated by treating a solution of the methyl ketone (1.29 g, 1.7 mmol) in ether with a solution of 2,4,4,6-tetrabromocyclohexa-2,5-dienone (1.44 g, 3.44 mmol) in ether (containing 1 M HCl) and stirred at room temperature overnight. The mixture was concentrated to dryness, and the residue was chromatographed (MPLC silica gel, 30−50% EtOAc/hexane) to give 0.4 g of the bromoacetyl product as the free diol. The diol was then reprotected as the acetonide under standard conditions to give **58** (R = Br). A solution of pyrazole (13 mg, 0.19 mmol) in THF was treated with NaH (8 mg, 0.2 mmol, 60% oil dispersion), and the mixture was stirred at room temperature for 30 min.

Then a solution of the bromoacetylacetonide **58** (0.1 g, 0.13 mmol) in THF was added, and the mixture was stirred at room temperature for 30 min. The solution was diluted with aqueous NH_4Cl and extracted into ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was chromatographed (MPLC silica gel, 50% EtOAc/hexane) to give 80 mg of pyrazole-substituted product **58**. This was dissolved in MeOH (10 mL) and concentrated HCl (5 mL) and heated at reflux for 2 h. The solution was concentrated on a rotary evaporator, and the residue was partitioned between aqueous Na_2CO_3 and ethyl acetate. The organic layer was then washed with water and brine, dried, and concentrated. The residue was chromatographed (MPLC silica gel 9:1:90 MeOH:NH_3:$CHCl_3$) to give **45** as a white solid: mp 125−127 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.94 (s, 1 H), 7.85 (m, 1 H), 7.73 (s, 1 H), 7.58 (d, J = 2 Hz, 1 H), 7.49−7.21 (m, 8 H), 7.14−7.07 (m, 4 H), 6.39 (t, J = 2 Hz, 1 H), 5.55 (bs, 2 H), 4.94 (d, J = 14 Hz, 1 H), 4.86 (d, J = 14 Hz, 1 H), 3.63−3.30 (m, 4 H), 3.15−2.81 (m, 6 H); ESIMS m/z 328 (M + 2H^{+2}, 100); HRMS calcd for $C_{39}H_{39}N_6O_4$ (M + H$^+$) 655.3033, found 655.3014.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(1-1,2,3-triazol-1-ylacetyl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (46). A similar procedure as detailed for **45** was used except using 1,2,3-triazole to give two isomers. The more polar isomer is **46**: mp 140−142 °C; ^{1}H NMR (DMSO-d_6) δ 13.00 (s, 1 H), 8.09−8.00 (m, 3 H), 7.80 (m, 3 H), 7.57−7.50 (m, 3 H), 7.35−7.23 (m, 8H), 7.00 (m, 4 H), 6.16 (bs, 2 H), 5.05 (bs, 2 H), 4.77 (d, J = 14 Hz, 1 H), 4.69 (d, J = 14 Hz, 1 H), 3.51−3.44 (m, 3 H), 3.14−2.74 (m, 7 H); ESIMS m/z 328 (M + 2H^{+2}, 100); HRMS calcd for $C_{38}H_{38}N_7O_4$ (M + H$^+$) 656.2985, found 656.2985. Anal. ($C_{38}H_{37}N_7O_4$) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(2*H*-1,2,3-triazol-2-ylacetyl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (47). A similar procedure as detailed for **45** was used except using 1,2,3-triazole to give two isomers. The less polar isomer is **47**: mp 125−128 °C; ^{1}H NMR (DMSO-d_6) δ 13.00 (s, 1 H), 8.01 (d, J = 8 Hz, 1 H), 7.92 (m, 1 H), 7.83 (s, 2 H), 7.74 (s, 1H), 7.53−7.45 (m, 3 H), 7.31−7.18 (m, 8 H), 6.92 (bs, 4 H), 6.16 (s, 2 H), 5.05 (bs, 2 H), 4.72 (d, J = 14 Hz, 1 H), 4.62 (d, J = 14 Hz, 1 H), 3.56−3.48 (m, 3 H), 3.15−2.68 (m, 7 H); ESIMS m/z 656 (M + H$^+$, 100); HRMS calcd for $C_{38}H_{38}N_7O_4$ (M + H$^+$) 656.2985, found 656.2977. Anal. ($C_{38}H_{37}N_7O_4$·0.33EtOAc) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-Hexahydro-5,6-dihydroxy-1-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-3-[[3-(1*H*-1,2,4-triazol-1-ylacetyl)phenyl]methyl]-2*H*-1,3-diazepin-2-one (48). The procedure detailed for **45** was used except using 1,2,4-triazole to give **48**: mp 142−145 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 8.21 (s, 1 H), 7.99 (s, 1 H), 7.93 (s, 1 H), 7.85 (d, J = 7 Hz, 1 H), 7.76 (s, 1 H), 7.54−7.02 (m, 13 H), 5.65 (s, 2 H), 4.92 (d, J = 14 Hz, 1 H), 4.80 (d, J = 14 Hz, 1 H), 3.69−3.26 (m, 4 H), 3.11−2.79 (m, 6 H); ESIMS m/z 328 (M + 2H^{+2}, 100); HRMS calcd for $C_{38}H_{38}N_7O_4$ (M + H$^+$) 656.2985, found 656.2975. Anal. ($C_{38}H_{37}N_7O_4$·0.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[[3-[(1*H*-Benzimidazol-2-ylmethyl)-amino]phenyl]methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (49). The urea **56** was alkylated with 3-nitrobenzyl bromide in THF using 1 M KO-t-Bu/THF, and the nitro group was hydrogenated (10% Pd/C, THF, 40 psi). The resulting aniline (0.3 g, 0.44 mmol) was dissolved in MeCN, treated with 2-(chloromethyl)benzimidazole (0.12 g, 0.72 mmol) and *N*-diisopropylethylamine (0.08 mL, 0.44 mmol), and stirred at room temperature for 2 days. The solution was concentrated under vacuum and the residue extracted into EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, filtered, and concentrated in vacuo. The residue was chromatographed (MPLC silica gel, 60:35:5 EtOAc:hexane:MeOH) to give 0.04 g of the corresponding *N*-alkylaniline. This was dissolved in MeOH (10 mL) and HCl (5 mL) and heated at reflux for 2 h. The solution was concentrated on a rotary evaporator, and the residue was partitioned between aqueous Na_2CO_3 and ethyl acetate. The organic layer was then washed with water and brine, dried, and concentrated. The residue was chromatographed (HPLC Zorbax Sil, 10% MeOH/$CHCl_3$) to give **49**: mp 162−164 °C; ^{1}H NMR (DMSO-d_6) δ 13.02 (s, 1 H), 12.30 (s, 1 H), 8.04 (s, 1 H), 7.48−6.93 (m, 18 H), 6.52 (bs, 1 H), 6.41−6.35 (m, 2 H), 4.98 (bs, 2 H), 4.78 (d, J = 14 Hz, 1 H), 4.61 (d, J = 14 Hz, 1 H), 4.42 (s, 2 H), 3.53−3.30 (m, 4 H), 2.97−2.60 (m, 6 H); ESIMS m/z 692 (M + H$^+$, 100); HRMS calcd for $C_{42}H_{42}N_7O_3$ (M + H$^+$) 692.3349, found 692.3368. Anal. ($C_{42}H_{41}N_7O_3$·1.5H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[[3-[(1*H*-Benzimidazol-2-ylmethyl)-amino]-4-fluorophenyl]methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (50). The procedure detailed for **49** was used to give **50**: mp 175−177 °C; ^{1}H NMR (DMSO-d_6) δ 13.02 (s, 1 H), 12.20 (s, 1 H), 8.04 (s, 1 H), 7.54−7.00 (m, 15 H), 6.82 (bs, 2 H), 6.41−6.33 (m, 2 H), 6.17 (bs, 1 H), 5.04 (d, J = 3 Hz, 1 H), 4.95 (d, J = 3 Hz, 1 H), 4.75 (d, J = 14 Hz, 1 H), 4.55−4.42 (m, 3 H), 3.52−3.31 (m, 5 H), 2.97−2.72 (m, 5 H), 2.54 (d, J = 14 Hz, 1 H); ESIMS m/z 710 (M + H$^+$, 100); HRMS calcd for $C_{42}H_{41}N_7O_3F$ (M + H$^+$) 710.3254, found 710.3240. Anal. ($C_{42}H_{40}N_7O_3F$·H_2O) C, H, N.

[4*R*-(4α,5α,6*β*,7*β*)]-1-[[3-[(2-Benzothiazolylmethyl)amino]phenyl]methyl]hexahydro-5,6-dihydroxy-3-(1*H*-indazol-5-ylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (51). The procedure detailed for **49** was used in order to obtain the protected aniline. A solution of the aniline (0.3 g, 0.45 mmol) in MeOH was treated with benzothiazole-2-carboxaldehyde (0.33 g, 2.0 mmol), $NaBH_3CN$ (0.12 g, 1.9 mmol), and AcOH (0.1 mL, 1.74 mmol) and stirred at room temperature for 20 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted into EtOAc. The organic layer was washed with brine, dried, filtered, and concentrated in vacuo. The residue was chromatographed (MPLC silica gel, 50% EtOAc/hexane) to give 0.08 g of the corresponding *N*-alkylaniline. The protecting groups were removed using HCl/MeOH, and the product was chromatographed (MPLC silica gel, 7% MeOH/$CHCl_3$) to give **51**: mp 125−128 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.78 (s, 1 H), 7.69 (d, J = 7 Hz, 1 H), 7.61 (d, J = 7 Hz, 1 H), 7.30−6.86 (m, 16 H), 6.43−6.34 (m, 2 H), 6.28 (bs, 1 H), 4.71 (d, J = 14 Hz, 1 H), 4.58 (d, J = 14 Hz, 1 H), 4.53 (s, 2 H), 3.41−3.26 (m, 4 H), 3.19 (bs, 1 H), 2.90−2.66 (m, 6 H); ESIMS m/z 709 (M + H$^+$, 100); HRMS calcd for $C_{42}H_{41}N_6O_3S$ (M + H$^+$) 709.2961, found 709.2948. Anal. ($C_{42}H_{40}N_6O_3S$·0.5H_2O) C, H, N.

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