Structure-Based Design of Nonpeptidic HIV Protease Inhibitors: The Sulfonamide-Substituted Cyclooctylpyranones

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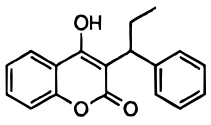
Recently, cyclooctylpyranone derivatives with *m*-carboxamide substituents (e.g. **2c**) were identified as potent, nonpeptidic HIV protease inhibitors, but these compounds lacked significant antiviral activity in cell culture. Substitution of a sulfonamide group at the *meta* position, however, produces compounds with excellent HIV protease binding affinity and antiviral activity. Guided by an iterative structure-based drug design process, we have prepared and evaluated a number of these derivatives, which are readily available via a seven-step synthesis. A few of the most potent compounds were further evaluated for such characteristics as pharmacokinetics and toxicity in rats and dogs. From this work, the *p*-cyanophenyl sulfonamide derivative **35k** emerged as a promising inhibitor, was selected for further development, and entered phase I clinical trials.

Introduction

The spread of human immunodeficiency virus (HIV) infection, which is generally considered to be the cause of AIDS, continues to grow at an alarming rate,[1] and the number of people infected worldwide is expected to exceed 30 million within the next 5 years.[2] One therapeutic approach which has garnered considerable attention over the past few years is inhibition of HIV protease, a homodimeric aspartyl protease which is essential for viral maturation.[3] A number of potent HIV protease inhibitors have been identified,[4] but these compounds are peptide-derived structures, and in many cases their clinical development is hindered by poor pharmacokinetics, including low oral bioavailability and rapid excretion.[5] Development may also be slowed by the complex and expensive syntheses[6] required to prepare these structures, which contain one or more stereocenters intimately associated with potency. Several nonpeptidic structures with some inhibitory activity have been identified, but the potency of these compounds is generally quite low, the structure is still quite complex, or both.[4]

Our search for a low molecular weight, nonpeptidic inhibitor began with a screening program. Within a short time, the 4-hydroxycoumarin **1** ($K_i = 0.8\ \mu$M) was identified as a lead structure, an X-ray of this inhibitor complexed with HIV protease was obtained, and a structure-based drug design program was initiated.[7,8] One of the classes of compounds developed from this lead was the cyclooctylpyranones (e.g. **2a**, $K_i = 75$ nM, and **2b**, $K_i = 15$ nM), which showed a dramatic increase in enzyme binding affinity relative to the 4-hydroxycoumarins.[9] An X-ray crystal structure of a representative compound demonstrated that the cyclooctyl ring folded into the S1′ region of the protease.[9,10] In the coumarin series, modeling based on X-ray crystal structures indicated that substitution at the *meta* position of the C-3α phenyl ring could allow the inhibitors to occupy the S3 region of the enzyme and form additional hydrogen bonds with enzyme residues.[11] When this substitution strategy was applied to the cyclooctylpyranones, compounds with better potency in the enzyme inhibition assay (e.g. **2c**, $K_i = 4$ nM) were obtained, but this increase in enzyme binding affinity was not accompanied by a significant increase in antiviral activity.[12] Use of a sulfonamide substituent, however, rather than a carboxamide substituent at the *meta* position produced analogs which were not only excellent HIV protease inhibitors but also showed significant antiviral activity.[13] This paper will discuss in detail the design and SAR of the cyclooctylpyranone sulfonamides and the selection of a clinical candidate from this promising new class of HIV protease inhibitors.



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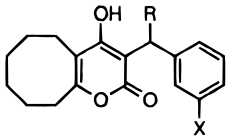

2a R = Et, X = H

2b R = cPr, X = H

2c R = cPr, X = $NHCO(CH_2)_2NHCO_2t$Bu

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[⊥] Medicinal Chemistry Research.
[∥] Chemical and Biological Screening.
[#] Infectious Diseases Research.
[@] Drug Metabolism Research.
[○] Toxicology.
[▽] Pharmaceutical Development.
[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1997.

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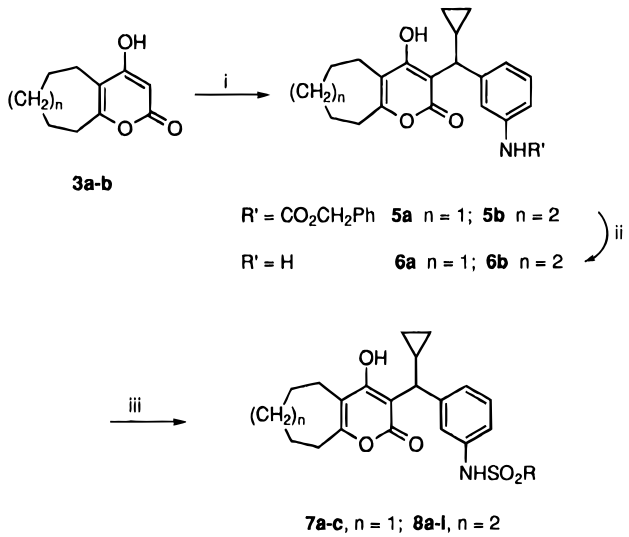
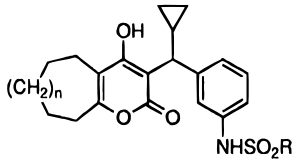
Scheme 1[a]



[a] (i) cPrCH(OH)-*m*-(NHCO$_2$CH$_2$Ph)C$_6$H$_4$ (**4**), *p*-TsOH, toluene; (ii) Pd/C, cyclohexene; (iii) RSO$_2$Cl, pyridine, CH$_2$Cl$_2$.

Table 1



no.	*n*	R	K_i (nM)[a]
7a	1	Me	120
7b	1	Et	63
7c	1	CH=CH$_2$	>200
8a	2	Me	11
8b	2	Et	10
8c	2	CH=CH$_2$	18
8d	2	*n*-Pr	4
8e	2	*i*-Pr	33
8f	2	*n*-Bu	4.6
8g	2	*n*-octyl	6
8h	2	Ph	3.2
8i	2	cyclohexyl	3.6

[a] Enzyme binding affinity (K_i values) determined as described in ref 7.

Discovery of the Cyclooctylpyranone Sulfonamides

The *m*-sulfonamide-substituted cycloalkylpyranone analogs were readily available from the cycloalkylpyranones **3a**,**b** and the secondary alcohol **4** (Scheme 1). The coupling and deprotection steps proceeded smoothly, and the resulting aniline intermediates **6a**,**b** readily reacted with various sulfonyl chlorides to produce the derivatives of interest. Since both cycloheptylpyranones and cyclooctylpyranones had previously demonstrated significant enzyme inhibitory activity, sulfonamide derivatives in both classes were prepared (Table 1). Since the cyclooctylpyranone derivatives **8a**−**c** were clearly more active than the corresponding cycloheptylpyranones **7a**−**c**, several more examples in the cyclooctyl series were prepared and evaluated (Table 1). Extension of the alkyl chain (**8d** and **8f**) was favorable, resulting in an approximately 2-fold improvement in activity relative to the methyl and ethyl cases. Extending the chain further (**8g**) or branching the chain (**8e**) attenuated activity. One of the best compounds in the initial series, however, was not an alkyl derivative but the phenyl sulfonamide **8h**, which had a K_i value of 3.2 nM in the enzyme inhibition assay. This activity is comparable to that of the most potent compounds prepared in the carboxamide-substituted series.[12] The saturated analog **8i** also had very good activity against the HIV protease (K_i = 3.6 nM).

Binding Mode of the Phenyl Sulfonamide Substituent

Modeling studies that led to the design of the phenyl sulfonamide series suggested that the sulfonamide group would be well positioned to form hydrogen bonds to the protein at the Gly 48 and Asp 29 residues and that attachments the size of a phenyl ring could be easily accommodated near the end of the enzyme's active site. Following the determination that **8h** bound to the protease more tightly than its alkyl precursors, a more thorough exploration of how this side chain might be orienting itself was undertaken using Monte Carlo conformational methods. Of the numerous binding modes that were shown to be possible, two were selected for further study—one placing the terminal phenyl ring in the S4′ site and the other placing it in the S3′ site (Figure 1). The two hydrogen bonds predicted earlier were present in both models, although each employed a different S=O bond for the acceptor. Interestingly, the two models suggested completely different strategies for synthetic elaboration of **8h**. For example, an inhibitor which bound with the phenyl group in the S4′ site would leave the S3′ site unfilled. It was noted that substitution of the sulfonamide NH hydrogen with groups the size of a benzyl or phenylethyl could be expected to fill the hydrophobic region, providing an inhibitor that occupied all of the binding pockets from S1 to S4′. The synthesis of these analogs from the aniline intermediate **6b** is shown in Scheme 2. Reductive alkylation of **6b** gave the N-alkylated intermediates **9a**,**b**, which were subsequently treated with a sulfonyl chloride to produce the analogs of interest. These derivatives, however, were uniformly less active than the parent compound **8h** (**10a** and **10b** showed <10% inhibition of protease at concentrations up to 10 and 3 μM, respectively). These results are more consistent with the model which places the sulfonamide aryl group in the S3′ region of the enzyme, not the S4′ region.

Compound **12** was a similar analog in which the sulfonamide hydrogen was replaced with a second benzenesulfonyl group (Scheme 3). Reaction of the aniline intermediate **6b** with 2 equiv of benzenesulfonyl chloride gave an intermediate which had undergone alkylation at both the nitrogen and oxygen atoms. Consequently, the desired compound **12** had to be prepared stepwise from this intermediate. The nitrogen atom was alkylated a second time, and the oxygen−sulfur bond was cleaved. Compound **12**, however, showed very little enzyme inhibitory activity (ca. 10% inhibition at 1 μM).

An X-ray crystal structure of **8h** complexed with HIV protease was subsequently obtained (Figure 2). As expected, the cycloalkylpyranone portion of the molecule shows the same binding features previously observed with the unsubstituted analog **2a**.[9] The crystal structure also clearly indicates that the aryl sulfonamide substituent curves into the S3′ region where the phenyl group of the sulfonamide participates in a stacking interaction with the Arg 8′ residue. It is interesting to note that the S3′ model discussed above, which con-

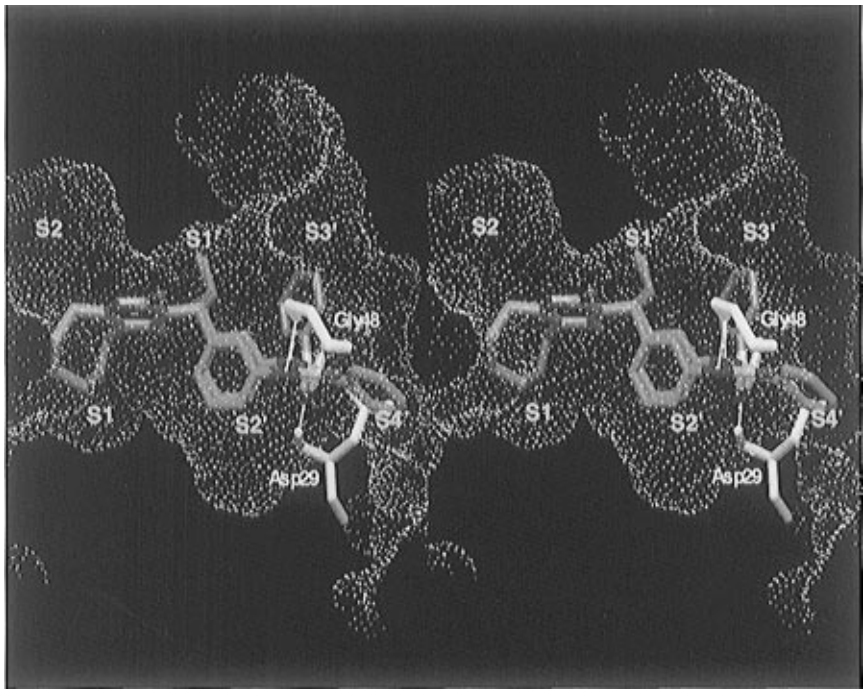
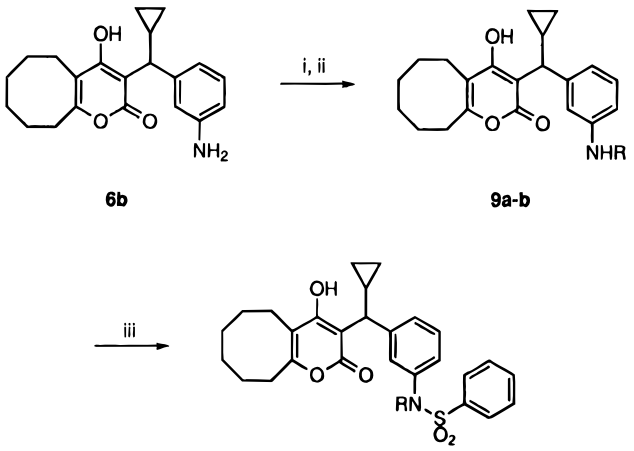


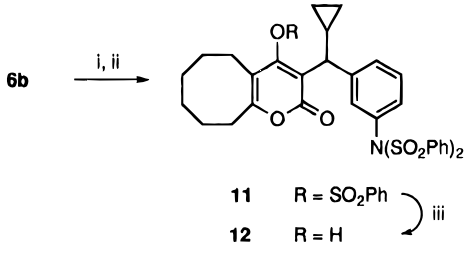
Figure 1. Stereodiagrams showing two working models of **8h**, developed from a Monte Carlo search of the inhibitor in the HIV protease binding site. The terminal phenyl ring was predicted to occupy either the S3′ (green) or S4′ (blue) site. Potential hydrogen bonds to two protein residues are highlighted. Shown in white is the surface of the HIV-2 protease substrate binding site, as determined in an X-ray crystal structure of a complex with 5,6,7,8,9,10-hexahydro-4-hydroxy-3-(1-phenylpropyl)-2*H*-cycloocta[*b*]-pyran-2-one that was used as the starting point for construction of the **8h** models.

Scheme 2[a]



[a] (i) RCHO, EtOH; (ii) $NaCNBH_3$, MeOH; (iii) $PhSO_2Cl$, pyr.

Scheme 3[a]



[a] (i) 2 equiv of $PhSO_2Cl$, pyr, $ClCH_2CH_2Cl$; (ii) *n*-BuLi, 1 equiv of $PhSO_2Cl$, THF; (iii) NH_3−MeOH.

tained this orientation of the phenyl ring, was not as favored as the S4′ model on an energetic basis. This is likely due to the fact that the stacking interaction between the phenyl group and the Arg 8′ residue

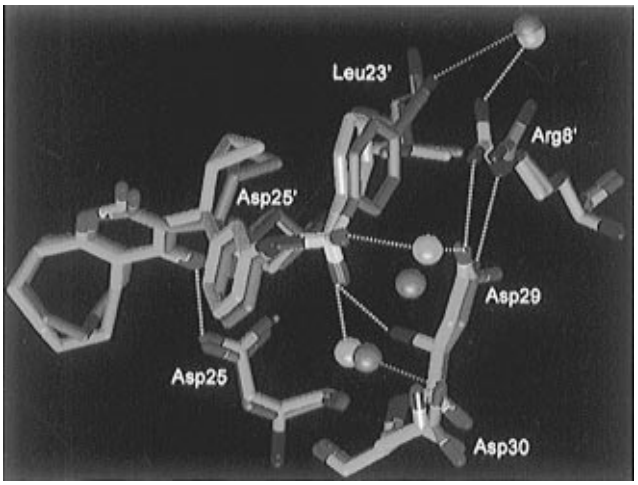
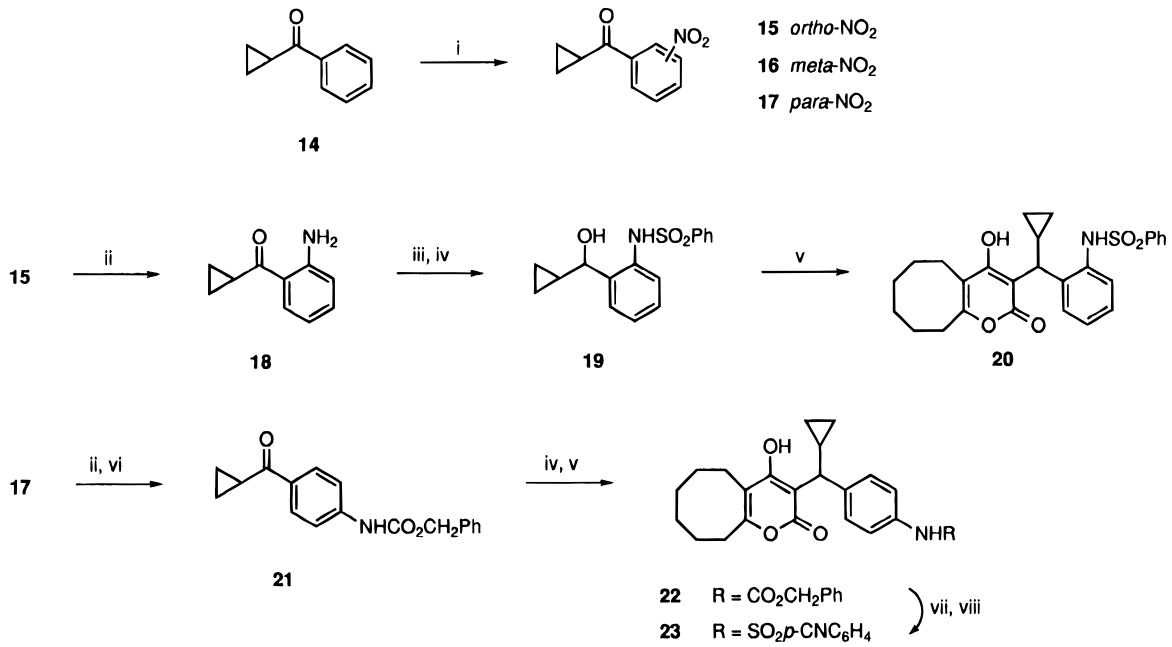


Figure 2. Overlay of the X-ray crystal structures of **8h** and **51a** complexed with HIV-1 protease. The **8h** and **51a** inhibitors with their neighboring protein regions are illustrated with cyan- and green-colored carbon atoms, respectively. The water molecules are represented by spheres of the corresponding colors.

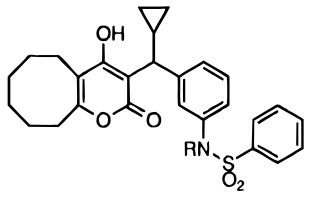
observed in the crystal structure was not accounted for in the molecular mechanics forcefield. The X-ray crystal structure of **8h** complexed with HIV protease also showed hydrogen-bonding interactions between the sulfonamide functional group and the enzyme. The NH forms a hydrogen bond with the carbonyl oxygen of the Gly 48 residue (3.0 Å). One of the sulfone oxygen atoms forms a hydrogen bond to the NH of the Asp 29 residue (3.1 Å) and to a water molecule (3.3 Å), which in turn forms hydrogen bonds with the Asp 30 residue (2.4 Å to the side-chain carboxylate oxygen and 3.3 Å to the main-chain NH). The second oxygen atom of the sulfone forms a hydrogen bond to a water molecule (3.0 Å) which has a hydrogen-bonding interaction with the side-chain carboxylate oxygen on Asp 29 (3.2 Å).

Scheme 4[a]



[a] (i) HNO_3; (ii) H_2, Pd/C, EtOAc; (iii) $PhSO_2Cl$, Et_3N, DMAP, THF; (iv) $NaBH_4$, THF, EtOH; (v) **3b**, *p*-TsOH, PhH; (vi) $ClCO_2CH_2Ph$, *i*-Pr_2NEt, CH_2Cl_2; (vii) 10% Pd/C, cyclohexene; (viii) *p*-$CNPhSO_2Cl$, pyr, CH_2Cl_2.

Study of this X-ray crystal structure suggested an unfilled region between the S2′ and S4′ pockets that might be able to accommodate moderately small groups attached to the sulfonamide nitrogen. Although the N-substitution strategy would result in the loss of an NH hydrogen bond to Gly 48 residue of the enzyme, this effect could potentially be offset by hydrophobic interaction of the appropriate group on the sulfonamide nitrogen with the Ile 47 residue of the HIV protease. Molecular mechanics-based calculations of approximate binding energies were carried out for a variety of *N*-alkyl- and *N*-aryl-substituted derivatives of **8h**. Of the compounds modeled, only the isopropyl and cyclopropylmethyl were predicted to be more active than their parent. The smallest substituent, methyl, was predicted to be somewhat less active than the parent compound, and the largest, benzyl, was predicted to be inactive. In fact, the *N*-Me compound **13a**,prepared in



13a R = Me

13b R = *i*-Pr

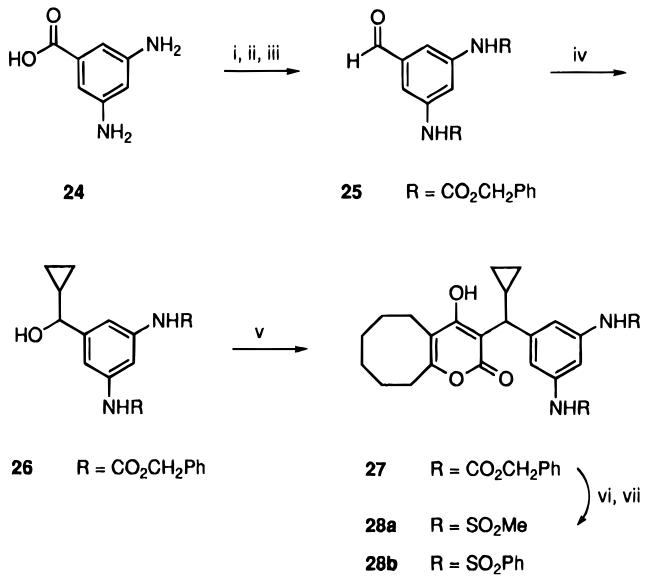
13c R = CH_2cPr

a manner analogous to that shown in Scheme 2, showed about a 10-fold reduction in activity (54% inhibition at 1.1 μM), and the *N*-benzyl derivative **10a**, prepared above, was indeed inactive against the HIV protease. However, the two derivatives that were predicted to have improved activity, **13b**,**c**, demonstrated no significant enzyme inhibitory activity (<10% inhibition at 1.1 μM). These results suggest that the hydrogen-bonding interaction between the sulfonamide NH and the Gly 48 residue of the protease contributes significantly to the binding affinity of this class of inhibitors. The predicted increase in hydrophobic interactions of certain *N*-alkyl groups with the Ile 47 residue did not offset the loss of the hydrogen-bonding interaction.

SAR: Optimization of the Sulfonamide Substituent

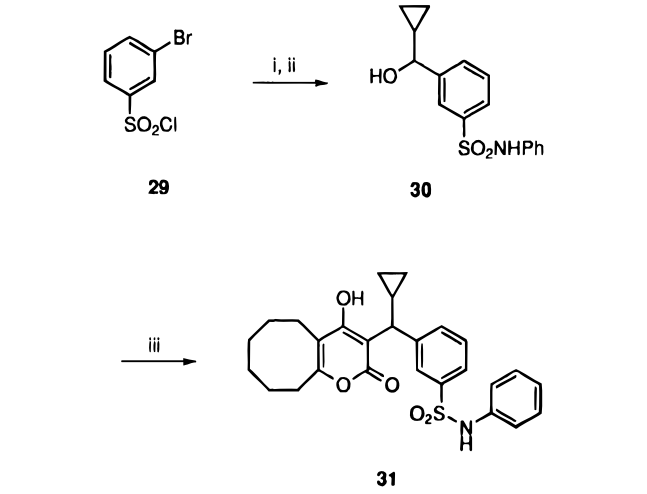
Once the potential of the *m*-sulfonamide-substituted cyclooctylpyranones became apparent, significant effort was devoted to optimization of the sulfonamide substituent. One item of interest was the position of attachment of this substituent to the C-3α phenyl ring. Examination of earlier X-ray crystal structures[11] had indicated that substitution at the *meta* position of the C-3α phenyl ring would allow the most favorable binding interactions, and examples of the *ortho*- and *para*-substituted derivatives were prepared to confirm this prediction. The requisite secondary alcohols for coupling with **3b** were synthesized from the minor products of the nitration of cyclopropyl phenyl ketone (**14**) (Scheme 4). In the case of the *ortho*-substituted analog **20**, the desired sulfonamide substituent was placed on the ketone intermediate **18** to avoid the potential cyclization of the *o*-aniline or protected *o*-aniline with the 4-hydroxypyrone ring of the cyclooctylpyranones. In the case of the *para*-substituted analog **23**, no interaction between the aniline group and the 4-hydroxypyrone group was anticipated, and the aniline was protected in a fashion analogous to that used in the synthesis of the *meta*-substituted analogs **8**. The *o*-sulfonamide derivative **20** showed no protease inhibition at concentrations up to 30 μM. The *p*-sulfonamide **23** showed weak protease inhibitory activity (15% inhibition at 3 μM), but its binding affinity was far less than that of the corresponding *m*-sulfonamide (see Table 4, **35k**). These results are consistent with modeling work which indicates the *ortho* and *para* isomers are unable to reach the S3′ pocket of the protease.

Scheme 5[a]



[a] (i) $ClCO_2CH_2Ph$, DMAP, pyr; (ii) BH_3-THF, THF; (iii) $(ClCO)_2$, DMSO, CH_2Cl_2; (iv) cPrBr, *t*-BuLi, THF; (v) **3b**, *p*-TsOH, sieves, CH_2Cl_2; (vi) H_2, 10% Pd/C; EtOH; (vii) RSO_2Cl, pyr, CH_2Cl_2.

Scheme 6[a]



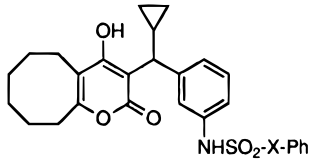
[a] (i) $PhNH_2$, pyr; (ii) *n*-BuLi, cPrCHO, THF; (iii) **3b**, *p*-TsOH, CH_2Cl_2.

We were also interested in the effect of substitution of a second *m*-sulfonamide group on the C-3α phenyl ring. Two examples of bis-*m*-sulfonamides are shown in Scheme 5. The protected secondary alcohol **26** was prepared in four steps from 3,5-diaminobenzoic acid. The C-3 alkylation, deprotection, and coupling with 2 equiv of the appropriate sulfonyl chloride then proceeded smoothly to give **28a**,**b**. Neither of these compounds, however, showed any enzyme inhibitory activity at concentrations up to 30 μM.

A final structural variation explored the effect of inversion of the sulfonamide functional group (Scheme 6). The secondary alcohol **30** required for this synthesis was formed in two steps from 3-bromobenzenesulfonyl chloride; a coupling reaction with **3b** generated the final product **31**. This analog did show significant enzyme binding affinity (K_i = 36 nM), but it was approximately 10-fold less active than the inverted sulfonamide **8h**.

Once the pattern of a single *m*-sulfonamide substituent on the C-3α phenyl ring was established, one question of interest was the optimal space between the sulfonamide and an aryl substituent. The phenyl sulfonamide **8h** is compared to the benzyl, phenethyl, and cinnamide derivatives in Table 2. The benzyl sulfonamide **32a** is significantly less potent than the phenyl sulfonamide **8h**, but binding affinity is regained with both the phenethyl (**32b**) and the cinnamide (**32c**) derivatives.

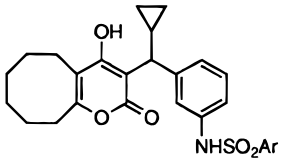
Table 2



no.	X	K_i (nM)[a]
8h		3.2
32a	CH_2	13
32b	CH_2CH_2	3.9
32c	CH=CH	3.0

[a] Enzyme binding affinity (K_i values) determined as described in ref 7.

Table 3



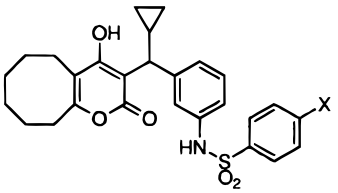
no.	Ar	K_i (nM)[a]	ED_{50} (μM)[b]
8h	Ph	3.2	5.5
33a	2-MePh	9.3	nd[c]
33b	2-FPh	11	5.9
33c	2-ClPh	9.3	nd[c]
33d	2-CF_3Ph	21	nd[c]
33e	2-CNPh	7.4	>10
34a	3-MePh	5.3	4.0
34b	3-ClPh	2.7	3.2
34c	3-BrPh	2.6	3.0
34d	3-CF_3Ph	3.0	3.8
34e	3-NO_2Ph	4.7	4.2
34f	3-CO_2HPh	4.5	>10
34g	3-CO_2MePh	1.4	2.6
34h	3-NH_2Ph	2.3	6.3
34i	3-CNPh	0.6[d]	>3

[a] Enzyme binding affinity (K_i values) determined as described in ref 7. [b] Antiviral activity in HIV-1-infected H9 cells. $CCTD_{50}$ values for all compounds were above 30 μM. [c] ED_{50} value not determined. [d] K_i values determined as described in ref 14. For comparison, under these conditions, the K_i values of **8h** and **35k** were 0.37 and 0.13 nM, respectively.

SAR: Use of Aryl Sulfonamide Substituents

The use of substituted phenyl groups on the sulfonamides was explored extensively (Tables 3−5). Analogs with *ortho* substituents on the terminal phenyl ring (**33a**−**e**) are less active than the parent compound **8h**, regardless of the electronic nature of the substituent (Table 3). This could be explained either by unfavorable stereoelectronic interactions between the *ortho* substituent and the nearby wall of the protease or by the *ortho* substituent forcing a rotation of the sulfur−phenyl bond, reducing the π-stacking interaction of the phenyl ring with the Arg 8 residue of the protease. Small *meta* substituents on the terminal phenyl ring are well tolerated, but do not offer a significant advantage over the unsubstituted parent compound (Table 3, **34a**−**i**). Bulkyl groups at the para position on the terminal phenyl ring, such as *tert*-butyl (**35e**), led to a decrease in enzyme binding affinity, but there appears to be space

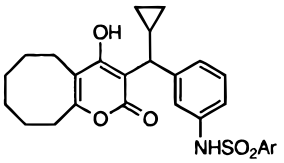
Table 4



no.	X	K_i (nM)[a]	ED_{50} (μM)[b]
35a	Me	3.3	3.6
35b	Et	5.0	nd[c]
35c	*n*-Pr	11	nd[c]
35d	*i*-Pr	13	nd[c]
35e	*t*-Bu	32	>10
35f	F	3.1	2.0
35g	Cl	2.5	2.0
35h	Br	2.1	3.2
35i	I	3.1	5.3
35j	CF_3	6.2	6.4
35k	CN	0.8	1.3
35l	NO_2	2.7	3.1
35m	CO_2H	11	>10
35n	$CONH_2$	1.9	5.8
35o	OMe	3.9	4.5
35p	O-*n*-Bu	18	nd[c]
35q	OCF_3	4.0	3.4
35r	NH_2	6.9	nd[c]
35s	NMe_2	2.8	8.7
35t	N_3	2.6	1.7

[a] Enzyme binding affinity (K_i values) determined as described in ref 7. [b] Antiviral activity in HIV-1-infected H9 cells. $CCTD_{50}$ values for all compounds were above 30 μM. [c] ED_{50} value not determined.

Table 5



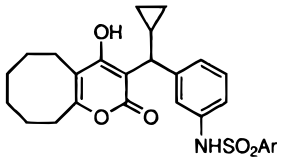
no.	Ar	K_i (nM)[a]	ED_{50} (μM)[b]
36a	2,6-di-MePh	>200	nd[c]
36b	2,6-di-ClPh	>200	nd[c]
36c	2,5-di-ClPh	74	nd[c]
36d	2,4-di-ClPh	6.2	nd[c]
36e	2,4-di-FPh	4.1	4.2
36f	2,3-di-ClPh	7.6	>3
36g	3,5-di-ClPh	6.9	>10
36h	3,4-di-CF_3Ph	47	nd[c]
36i	3,4-di-ClPh	4.1	3.4
36j	3,4-di-OMePh	6.8	4.1
36k	2,3,4-tri-ClPh	8.8	4.1

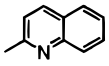
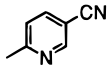
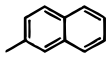
[a] Enzyme binding affinity (K_i values) determined as described in ref 7. [b] Antiviral activity in HIV-1-infected H9 cells. $CCTD_{50}$ values for all compounds were above 30 μM. [c] ED_{50} value not determined.

for nonbulky substituents (Table 4). For example, the *p*-fluoro (**35f**) and chloro (**35g**) analogs were as active as the unsubstituted parent compound. One of the most promising analogs was the *p*-cyano derivative **35k**, which had a K_i value of only 0.8 nM. A number of multisubstituted phenyl analogs were also prepared and evaluated (Table 5). The binding affinities of these compounds were consistent with the trends observed with the singly-substituted analogs: *ortho* substitution is disfavored, but *meta* and *para* substitution are well tolerated.

An X-ray crystal structure of an enantiomer of **35k** (**51a**, see Table 8) complexed with HIV protease was obtained (Figure 2), and it showed that the binding

Table 6



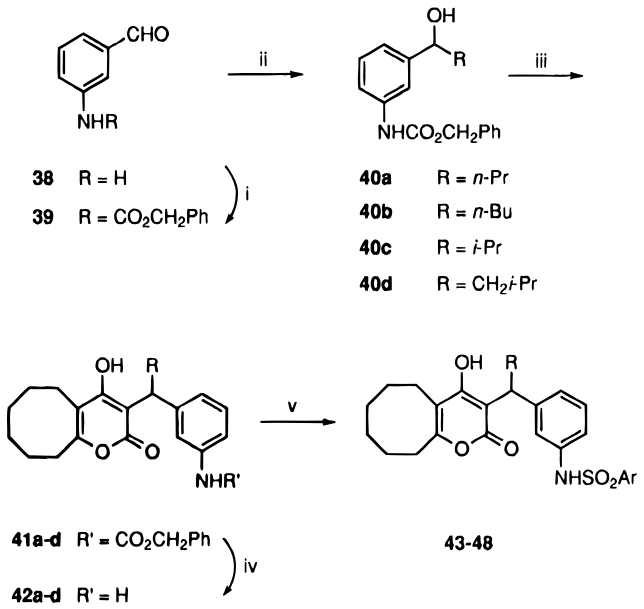
no.	Ar	K_i (nM)[a]	ED_{50} (μM)[b]
37a		1.6	2.7
37b		1.9	1.4
37c		0.4	5.4
37d		2.2	4.6
37e		1.0	0.9
37f		0.2	2.0
37g		0.8	1.7
37h		5.5	3.6
37i		4.1	3.4
37j		6.3	>10
37k		1.6	>3

[a] Enzyme binding affinity (K_i values) determined as described in ref 7. [b] Antiviral activity in HIV-1-infected H9 cells. $CCTD_{50}$ values for all compounds were above 30 μM.

patterns of **51a** and the phenyl sulfonamide derivative **8h** are very similar.[15] The crystal structure of the **51a** complex confirmed that there is space for nonbulky substituents, such as the linear cyano moiety, at the *para* position of the phenyl group. In fact, a water molecule forms an interaction between the nitrogen of the cyano group and the Arg 8′ residue. This additional interaction, in combination with the favorable hydrophobic interaction of the cyano group with the P3 pocket residues Leu 23′ and Val 82′, could help explain the 5-fold improved binding of **51a** relative to **8h**.

A variety of heterocyclic aryl sulfonamide derivatives are also potent HIV protease inhibitors, as illustrated in Table 6. Several analogs with excellent binding affinity were identified in the heterocyclic series, including the *N*-methylimidazole (**37a**), the quinolines (**37b**,**c**), the 2-pyridyl (**37d**,**e**), the pyrazine (**37f**), and the pyrimidine (**37g**) derivatives. An exception was the thiophene derivative **37j**; this benzene isostere is somewhat less potent than the parent compound **8h**. On the basis

Scheme 7[a]



[a] (i) $ClCO_2CH_2Ph$, *i*-Pr_2NEt, THF, H_2O; (ii) RMgX, THF; (iii) **3b**, *p*-TsOH, sieves, CH_2Cl_2; (iv) Pd/C, cyclohexene; (v) $ArSO_2Cl$, pyr, CH_2Cl_2.

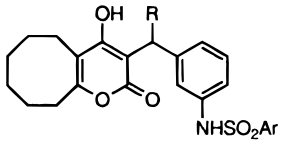
of X-ray crystal structures of related sulfonamides,[16] we postulated that a heterocyclic nitrogen atom *ortho* to the sulfonamide could form hydrogen-bonding interactions with the NH of the Asp 29 residue. This may account for the increased binding affinity observed with some heterocycles in Table 6, such as **37c** and **37f**.

SAR: Optimization of the C-3α Substituent

In addition to optimizing the aryl sulfonamide substituent, which resides in the S3′ region, we were interested in probing the S1′ region where the cyclopropyl group of **8h** is located. To explore this binding site, we synthesized a series of analogs in which the cyclopropyl group was replaced by alkyl groups of various sizes (Scheme 7). A synthesis was developed for the secondary alcohol intermediates **40a**−**d** from *m*-aminobenzaldehyde in two steps. The aniline **38** was protected and then reacted with the appropriate alkyl Grignard reagent to give the desired secondary alcohols **40a**−**d**, which were in turn coupled to the cyclooctylpyranone **3b**. For this work, we selected several aryl sulfonamides already associated with good enzyme binding affinity in the cyclopropyl series discussed above.

The enzyme binding affinities for the C-3α alkyl analogs are listed in Table 7; the corresponding C-3α cyclopropyl analogs are included for comparison. The SAR which emerges from this work is quite intriguing. Previously, an analogous series of cyclooctylpyranones without the *m*-sulfonamide substituent had been prepared, and the binding affinity of these compounds was related to the size of the alkyl substituent, with the three carbon analogs having the best enzyme inhibitory activity.[9] In the sulfonamide series, there is some size preference; the three-carbon cyclopropyl and *n*-propyl derivatives are somewhat more active than the two-carbon ethyl and four-carbon *n*-butyl and CH_2(*i*-Pr) derivatives. However, the isopropyl analogs are consistently significantly less active than any of the other derivatives, regardless of size. Examination of the X-ray crystal structures of cyclopropyl analogs complexed with

Table 7



no.	Ar	R	K_i (nM)[a]	ED_{50} (μM)[b]
35g	*p*-ClPh	cPr	2.5	1.8
43a		Et	3.5	4.7
43b		*n*-Pr	4.0	>10
43c		*i*-Pr	18	>10
35k	*p*-CNPh	cPr	0.8	1.3
44a		Et	3.1	3.3
44b		*n*-Pr	1.4	3.9
44c		*n*-Bu	2.1	7.6
44d		*i*-Pr	5.9	>10
44e		CH_2-*i*-Pr	1.5	6.1
35f	*p*-FPh	cPr	3.1	2.0
45a		*n*-Pr	2.1	6.3
45b		*n*-Bu	6.1	>10
45c		*i*-Pr	11	>10
45d		CH_2-*i*-Pr	2.8	>10
37a	*N*-Me-imidazole	cPr	0.112[c]	2.7
46a		*n*-Pr	0.1[c]	2.5
45b		*i*-Pr	0.5[c]	2.5
45c		CH_2-*i*-Pr	0.086[c]	1.3
37b	8-quinoline	cPr	1.9	1.4
47a		*n*-Pr	2.1	>3
47b		*i*-Pr	4.2	>10
47c		CH_2-*i*-Pr	3.3	>10
37d	3-pyridyl	cPr	2.2	4.6
48a		*n*-Pr	2.2	>10
48b		*i*-Pr	20	>10
48c		CH_2-*i*-Pr	9.3	>10

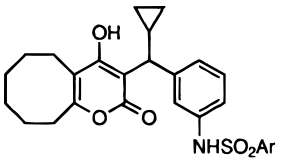
[a] Enzyme binding affinity (K_i values) determined as described in ref 7. [b] Antiviral activity in HIV-1-infected H9 cells. $CCTD_{50}$ values for all compounds were above 30 μM. [c] K_i values determined as described in ref 14.

HIV protease indicates the C-3α substituents which reside in the S1′ region of the binding site are actually in contact with the sulfonamide substituent residing in the S3′ region. Presumably, the relative bulk of the "β-branched" isopropyl group, in such a highly congested region of the binding site, causes a reduction in overall binding affinity.

Antiviral Activity

As noted above, one of the main advantages of the cyclooctylpyranone sulfonamides over closely related compounds is their antiviral activity. For example, the amide derivative **2c** (K_i = 4 nM) and the phenyl sulfonamide derivative **8h** (K_i = 3.2 nM) have similar enzyme binding affinities, but dramatically different levels of activity in the antiviral assay.[17] For **2c**, the ED_{50} value in HIV-1 infected H-9 cells was 33 μM,[12] but for **8h**, the ED_{50} value was only 5.5 μM. In addition, no cytotoxicity for **8h** was observed at concentrations up to 30 μM in cell culture. All of the analogs in the sulfonamide series which demonstrated good enzyme inhibitory activity were evaluated in the cell culture assay for antiviral activity, and these results are included in Tables 3−7. Four of the most promising compounds were the *p*-fluorophenyl sulfonamide **35f** (ED_{50} = 2.0 μM, $CCTD_{50}$ = 68 μM), the *p*-cyanophenyl sulfonamide **35k** (ED_{50} = 1.3 μM, $CCTD_{50}$ = 90 μM), the *N*-methylimidazole sulfonamide **37a** (ED_{50} = 2.7 μM, $CCTD_{50}$ > 100 μM), and the 8-quinoline sulfonamide **37b** (ED_{50} = 1.4 μM, $CCTD_{50}$ = 82 μM). All four of these compounds were originally prepared in racemic form, but we were also interested in evaluating the

Table 8



no.	Ar	stereochemistry	K_i (nM)[a]	ED_{50} (μM)[b]
8h	Ph	racemic	3.2	5.5
49a		*S*	3.2	2.6
49b		*R*	7.6	>10
35f	*p*-FPh	racemic	3.1	2.0
50a		*S*	1.4	0.8
50b		*R*	2.1	>10
35k	*p*-CNPh	racemic	0.8	1.3
51a		*S*	0.6	1.2
51b		*R*	0.7	8.3
37a	N-Me-imidazole	racemic	0.112[c]	2.7
52a		*S*	0.045[c]	2.1
52b		*R*	0.08[c]	nd[d]
37b	8-quinoline	racemic	1.9	1.4
53a		*S*	0.4	1.3
53b		*R*	0.9	7.2

[a] Enzyme binding affinity (K_i values) determined as described in ref 7. [b] Antiviral activity in HIV-1-infected H9 cells. $CCTD_{50}$ values for all compounds were above 30 μM. [c] K_i values determined as described in ref 14. [d] ED_{50} value not determined.

enantiomers separately. To obtain these enantiomers, the N-protected intermediate **5b** was separated into its component enantiomers using preparative chiral HPLC techniques. These enantiomers were then converted in two steps to the desired analogs using the same route illustrated in Scheme 1. The biological activities for both racemates and their component enantiomers are given in Table 8. In all the cases where both enantiomers were evaluated, the (*S*)-enantiomer was more potent in the antiviral assay than the (*R*)-enantiomer.[18]

Selection of a Clinical Candidate

The pharmacokinetics of four compounds with good antiviral activity were evaluated in male Sprague–Dawley rats. For **35f** and **35k**, both the racemates and the individual enantiomers were tested. The chief criteria for acceptable pharmacokinetic performance were persistence of the test compound in the body, indicated by total plasma clearance (CL) and the apparent terminal disposition half-life ($t_{1/2}$), and oral delivery, indicated by the maximum concentration observed after an oral solution dose (C_{max}) and the absolute oral bioavailability (F). Results from experiments in rats are summarized in Table 9. The heteroaryl sulfonamides **52a** and **53a** were eliminated from further consideration because of their relatively higher total plasma clearance and low oral C_{max} values, but the pharmacokinetics of **35k** and **35f** compared favorably with other HIV protease inhibitors approved for use in humans or in development.[19] The racemic compounds **35f** and **35k** were further evaluated in male beagle dogs, and results for these studies are presented in Table 10. The apparent terminal half-life of **35k** was much greater than that of **35f**, but other pharmacokinetic parameters of these two compounds were comparable. Plasma–time profiles of **35k** in rats and dogs are shown in Figure 3.

Since both **35f** and **35k** showed favorable pharmacokinetic profiles, they were evaluated in a single dose safety study using male rats. The fasted male Sprague–Dawley rats were orally administered a single dose of 90, 180, 360, or 720 mg/kg of **35f** or **35k**. The *p*-cyano sulfonamide **35k** showed severe toxic signs (including death) at the 720 mg/kg dose, whereas the *p*-fluoro sulfonamide **35f** showed these signs (including death) at the 360 and 720 mg/kg doses. An analysis of the toxicokinetics indicated that AUC values for the compounds were proportional to the prescribed doses given and that the rats were exposed to high blood concentrations of drug at all dose levels. Subsequent safety studies with **35k** were very promising. For example, average steady-state concentrations above 100 μM of **35k** could be safely achieved in both rats (63 mg/kg/day) and dogs (125 mg/kg/day) after oral administration of **35k** in a solution formulation, twice daily, for 28 days.

Further evaluation of **35k** indicated this compound inhibits HIV-2 protease (K_i = 3.2 nM) as well as HIV-1 protease, and it has antiviral activity against a panel of 12 clinical isolates (median IC_{50} = 5 μM, range = 1–8 μM).[20] In addition, **35k** shows excellent selectivity; no significant activity against the human aspartyl proteases renin, pepsin, gastricsin, cathepsin D, and cathepsin E was observed.[21]

Summary

Guided by an iterative structure-based drug design process, we have prepared and evaluated a number of cyclooctylpyranones with *m*-sulfonamide substitution on the phenyl ring. These compounds are readily available via a seven-step synthesis, and they generally demonstrate both excellent enzyme inhibitory activity against HIV protease and potent antiviral activity. A few of the more potent compounds were further evaluated for such characteristics as pharmacokinetics and safety. From this work, the *p*-cyanophenyl sulfonamide derivative **35k** emerged as a promising inhibitor, was selected for further development, and entered into phase I clinical testing.

Experimental Section

Modeling and Computational Methods. Modeling and energy-based studies were carried out with the Mosaic molecular modeling system,[22] BatchMin v. 3.5,[22] the Amber* united atom forcefield (as implemented in BatchMin), and the PRCG minimizer. Monte Carlo searching was carried out with BatchMin's MCMM (Monte Carlo multiple minimum) facility which employs torsional variation followed by energy minimization and duplicate conformation elimination. In the studies reported here, the protein was held fixed while the ligand was allowed to vary within the field of protein atoms up to 8 Å from the inhibitor's starting position.

Derivation of Binding Models of 8h. An initial model was constructed by substituting a phenyl sulfonamide group at the appropriate position in an X-ray crystal structure of **2a** bound to HIV-2 protease.[9] This was followed by energy minimization of the ligand in the binding site. The model was then subjected to 1000 steps of MCMM search in which the three phenylsulfonamide acyclic bonds were varied, and the resulting ligand conformations were minimized to a convergence of 0.01 kcal/A^2. Two conformations were selected from the energy-ordered list of ligand orientations, one of which positioned the terminal phenyl ring in the S4′ site, and which was favored energetically, while the other placed the phenyl in the S3′ region, an orientation which was consistent with experimentally determined binding modes of earlier inhibitors in the coumarin series.[11] The selected conformations were used as working models for further synthesis decisions, pending the availability of an X-ray crystal structure.

Approximate Binding Energy Calculations for N-Substituted Inhibitors. Models of a variety of *N*-alkyl- and *N*-aryl-substituted derivatives of **8h** were constructed as follows. Starting from an energy minimized crystal structure of **8h**, the substituents were attached to the N atom using the

Table 9. Pharmacokinetic Parameters[a] in Male Sprague−Dawley Rats

no.	dose (mg/kg)	route	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	C_{max} (μM)	t_{max} (h)[b]	F (%)[c]	AUC
35f	2.7	iv	0.043 ± 0.009	0.16 ± 0.04	6.2 ± 2.6				130 ± 30
	5.2	po				31 ± 15	0.25−6	50 ± 6	124 ± 15
50a	2.8	iv	0.115 ± 0.031	0.13 ± 0.009	2.2 ± 0.6				52 ± 14
	5.1	po				10 ± 2	0.25	58 ± 4	46 ± 16
50b	2.8	iv	0.004 ± 0.003	0.15 ± 0.03	6.0 ± 1.4				140 ± 18
	5.2	po				24 ± 18	0.25−6	53 ± 7	135 ± 16
35k	2.5	iv	0.075 ± 0.014	0.11 ± 0.014	3.0 ± 0.2				71 ± 11
	5.1	po				24 ± 10	0.25−1	42 ± 3	58 ± 15
51a	5.1	iv	0.049 ± 0.016	0.12 ± 0.01	6.2 ± 0.4				223 ± 66
	5.0	po				19 ± 12	0.5−8	42 ± 1	91 ± 26
51b	2.6	iv	0.056 ± 0.014	0.15 ± 0.02	7.5 ± 0.6				96 ± 21
	5.0	po				13 ± 1	0.25−1	31 ± 12	6 ± 2
52a	2.5	iv	0.28 ± 0.03	0.20 ± 0.02	2.4 ± 0.6				19 ± 2
	5.0	po				0.64 ± 0.28	0.25−0.5	15 ± 5	6 ± 2
53a	2.5	iv	0.17 ± 0.06	0.15 ± 0.05	1.8 ± 0.9				32 ± 14
	5.0	po				6.2 ± 3.3	0.25−0.5	34 ± 11	23 ± 17

[a] Mean ± standard deviation; $n = 3$. Values for CL and V_{ss} are given per body weight in kilograms. [b] t_{max} values given as a range. [c] $\%F = (AUC_{po}/AUC_{iv}) \times (dose_{iv}/dose_{po})$.

Table 10. Pharmacokinetic Parameters[a] in Male Beagle Dogs

no.	dose (mg/kg)	route	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)	C_{max} (μM)	t_{max} (h)[b]	F (%)[c]	AUC
35f	1.8	iv	0.19 ± 0.03	0.08 ± 0.003	0.57 ± 0.19				19 ± 3.1
	10	po				61 ± 28	0.5−1	107 ± 56	115 ± 60
35k	4.9	iv	0.044 ± 0.008	0.085 ± 0.018	6.3 ± 1.8				224 ± 39
	10	po				156 ± 28	0.5−1	77 ± 4	358 ± 49

[a] Mean ± standard deviation; $n = 3$. Values for CL and V_{ss} are given per body weight in kilograms. [b] t_{max} values given as a range. [c] $\%F = (AUC_{po}/AUC_{iv}) \times (dose_{iv}/dose_{po})$.

molecule editor of Mosaic. The ligands were energy minimized in the binding site of the **8h** complex, with the catalytic aspartates protonated. Each ligand structure was reminimized with inclusion of the BatchMin surface area solvation approximation, to better account for hydrophobic interactions. The ligand model was then moved away from the protein and the procedure was repeated. The non-moving shell of protein atoms contributed a solvation component to the overall "unbound" energy (since the binding site was exposed to continuum "solvent"), even though it did not contribute an interaction energy with the ligand. The difference in energies of the bound and unbound systems became the approximate binding energy for that compound. Binding energies were computed for each of the proposed N-substituted inhibitors, plus the parent compound, **8h**, and were used to select compounds for synthesis.

X-ray Crystallography. Crystallization. The preparation and purification of the recombinant HIV-1 protease[17] and a triple mutant of HIV-1 protease (Q7K/L33I/L63I, referred to as HIV-1-2A protease)[23] have been described previously. The crystals of the protease complexed with inhibitors **8h** (complex A) and the mutant complexed with **51a** (complex B) were obtained by cocrystallization experiments in which 2 μL of the inhibitor solution (0.1 mg/μL in DMSO) were added to 130 μL of the corresponding freshly thawed ice-cold protease solution (ca. 6 mg/mL), the mixture was equilibrated on ice for 30 min, and undissolved inhibitor was then removed by centrifugation. Crystals were grown at room temperature in 10 μL hanging drops of equal volumes of protein/inhibitor complex and the precipitant from the well. Precipitants used were 0.1 M acetate (pH 4.8−5.2), 0.1 M citrate (pH 5.4−5.8), and 0.75, 1.0, 1.5, and 2.0 M sodium chloride solutions.

Data Collection. For each of the two complexes A and B, one single crystal was used for diffraction data collection using a Siemens area detector, with X-rays generated by a Siemens rotating anode source operating at 45 kV, 96 mA. Measurements were made as a series of 0.25° frames, with exposure times of 120 and 240 s/frame for A and B, respectively. Data sets were processed using XENGEN data reduction software,[24] and the statistics are summarized in Table 11. The effective resolution of each crystal was taken as the maximum resolution for which the mean I/σ was greater than 2.0, and data beyond this maximum were not used in the crystallographic refinement.

Structure Refinement. Since the space groups of the protease/inhibitor complexes A and B were the same as ones previously refined in our laboratory, refinement of these protease models was initiated without resolving the position of the molecule in the cell. The crystallographic refinement was carried out using CEDAR,[25] with periodic manual rebuilding using the interactive graphics programs FRODO[26] (for complex A) and CHAIN[27] (for complex B), based on $|2F_o| - |F_c|$ and $|F_o| - |F_c|$ electron density maps. Electron density maps were calculated using the XTAL package of crystallographic programs.[28] The inhibitors and solvent molecules were added during later stages of the refinements. For refinement statistics, see Table 11. The atomic coordinates of these structures have been deposited in the Protein Data Bank.[29]

Cell-Culture Antiviral Assay. H9 cells were infected with HIV-1_{IIIB} at an MOI of approximately 0.005. Following low-speed centrifugation (200*g*, 10 min), infected cells were resuspended to a concentration of 8×10^5 cells/mL in RPMI Complete medium. In appropriate wells of 24-well tissue culture plates (Corning no. 25820), 0.5 mL of infected cells were then combined with 0.5 mL of 2× test compound dissolved in RPMI Complete containing 0.2% DMSO. Each drug concentration was tested in triplicate. Virus control wells received RPMI Complete plus 0.2% DMSO without compound. The final DMSO concentration in each culture was 0.1%. After 5 days of incubation at 37 °C in 5% CO_2, 100 μL of supernatant was removed from each test well and live virus inactivated by the addition of lysis buffer containing 5% Triton X-100. The amount of HIV p24 core antigen was quantified with an ELISA procedure by following the manufacturer's direction (Coulter Diagnostics, Hialeah, FL). The ED_{50}, the amount of drug necessary to reduce the concentration of p24 in drug-containing cultures by 50% when compared to drug-free controls, was calculated by comparing the quantity of p24 produced in drug-containing with that of DMSO-containing drug-free supernatants.

Pharmacokinetic Evaluation. Rats were administered intravenous solutions of test compounds dissolved in 10% propylene glycol with 25% hydroxypropylcyclodextran in 0.1 N aqueous sodium hydroxide via a surgically implanted cannula. The cannula was thoroughly flushed with saline prior to its use as a sampling route for sequential blood samples. Oral dosing was performed with solutions of test compounds in 80% propylene glycol and 20% 0.1 N aqueous sodium hydroxide, pH range 8−10. Blood samples were obtained in heparinized vials for up to 24 h after dosing and centrifuged to provide clear plasma which was stored frozen

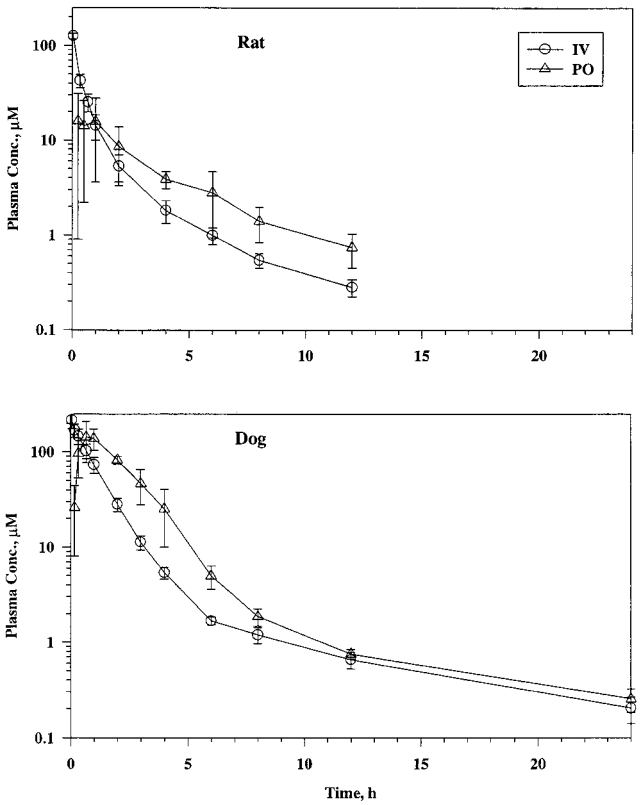


Figure 3. Plasma−time profiles of inhibitor **35k** in two species. The mean plasma concentrations for iv doses (circles) and po doses (triangles) are plotted as a function of time. Pharmacokinetic parameters from these studies are listed in Tables 9 (rats) and 10 (dogs).

Table 11

parameter	complex A	complex B
protease	HIV-1	HIV-1-2A
inhibitor	**8h**	**51a**
space group	$P2_12_12$	$P2_12_12$
unit cell		
a (Å)	60.37	60.54
b (Å)	89.61	88.42
c (Å)	47.34	46.48
resolution (Å)	2.0	2.5
no. of observations	51370	63195
unique reflections	13817	9119
completeness (%)	76.0	98.9
R merge (%)	7.8	13.2
reflns in refinement	13636	7560
R factor (%)	17.7	17.9
rms deviation		
distance (Å)	0.018	0.016
angle (deg)	3.321	2.618
fixed dihedrals (deg)	7.164	7.643
flexible dihedrals (deg)	15.375	15.392

until analysis by HPLC with UV detection. Similar formulations were administered to male beagle dogs, both intravenously and orally. Sequential blood samples were obtained by jugular venipuncture for 24 h after dosing.

Chemical Synthesis. Melting points are uncorrected. ^{1}H NMR spectra were measured on a Bruker AM 300 (300 MHz) instrument using tetramethylsilane as an internal standard. All other physical data were measured by the Analytical Chemistry group of Pharmacia and Upjohn. Flash chromatography was performed on 230−400 mesh silica gel 60.

Preparation of *m*-Sulfonamide-Substituted Cycloalkylpyranones. All of the *m*-sulfonamide-substituted cycloalkylpyranones listed in Tables 1−8 were prepared via the route shown in Scheme 1. Intermediates **3a**,[30] **3b**,[30] **4**,[11] **5b**,[12] and **6b**[12] were prepared as previously described in the literature; the syntheses of other intermediates are given below. Most of the sulfonyl chlorides used were commercially available. 4-Azidobenzene sulfonyl chloride was prepared as described in the literature;[31] the preparations for the other exceptions are given below. Compound **34g** was prepared by esterification (H_2SO_4, MeOH) of **34f**. Compounds **32b**, **34h**, and **35r** were prepared by catalytic hydrogenation (10% Pd/C, EtOAc) of **32c**, **34e**, and **35l**, respectively. Compound **35n** was prepared from **35k** using K_2CO_3 and H_2O_2 in DMSO, and compound **35s** was prepared from **35r** using paraformaldehyde and sodium cyanoborohydride in MeOH. The remaining *meta*-substituted sulfonamide cycloalkylpyranones were prepared using **6b** and the appropriate sulfonyl chloride unless otherwise noted.

***N*-(Benzyloxycarbonyl)benzaldehyde (39).** A mixture of $NaHCO_3$ (10.4 g, 123.8 mmol), *m*-aminobenzaldehyde (10.0 g, 82.5 mmol), and benzyl chloroformate (13.6 mL, 90.8 mmol) in 200 mL of THF and 200 mL of water was stirred at room temperature for 40 min. Ether was added, and the organic layer was separated, washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a brown oil. Column chromatography on 300 g of silica gel (elution with 5−50% ethyl acetate−hexane) yielded 16.3 g (77%) of **39** as a pale yellow solid: mp 100−104 °C; ^{1}H NMR ($CDCl_3$) δ 9.98 (s, H), 7.91 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.43−7.35 (m, 5H), 6.83 (br s, 1H), 5.23 (s, 2H) ppm; MS (EI) *m*/*z* 255 (M^+). Anal. ($C_{15}H_{13}NO_3$) C, H, N.

Representative Procedure for the Synthesis of 30a−d. 3-[*N*-(Benzyloxycarbonyl)amino]-α-propylbenzyl Alcohol (40a). Propylmagnesium chloride (2.2 mL, 2.0 mmol) was added to a solution of **39** (0.51 g, 2.0 mmol) in THF (15 mL), and the resulting mixture was stirred at room temperature for 18 h. Saturated NH_4Cl was then added, and the mixture was partitioned between ether, water, and saturated NH_4Cl. The organic layer was separated and washed with 4 N NaOH. The basic aqueous layer was back-extracted with EtOAc, and this organic layer was washed with 4 N HCl. The combined organic layers were then concentrated *in vacuo* to give 1.2 g of an oil which was purified via column chromatography (50 g of silica gel, elution with 20% ethyl acetate−hexane) to give 0.47 g (79%) of a pale yellow oil. The oil was crystallized from ethyl acetate−hexane to give 0.35 g of **40a** as a white crystalline solid: mp 103−106 °C; ^{1}H NMR ($CDCl_3$) δ 7.42−7.26 (m, 8H), 7.07−7.03 (m, 1H), 6.69 (br s, 1H), 5.20 (s, 2H), 4.68−4.63 (m, 1H), 1.79−1.62 (m, 3H), 1.44−1.29 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H) ppm; MS (EI) *m*/*z* 299 (M^+). Anal. ($C_{18}H_{21}NO_3$) C, H, N.

Representative Procedure for the Synthesis of 5a and 41a−d. [3-[1-(4-Hydroxy-6,7,8,9-tetrahydro-2-oxo-2(5*H*)-cyclohepta[*b*]pyran-3-yl)butyl]phenyl]carbamic Acid, Phenylmethyl Ester (5a). Toluene (5 mL) and *p*-toluenesulfonic acid (0.175 g) were heated to reflux, and water was removed from the solution via azeotrope. The mixture was cooled to 20 °C, and **3a** (0.75 g, 4.16 mmoL) and **4** (1.065 g, 3.58 mmoL) were added. After being stirred at 20 °C for 72 h, the reaction mixture was diluted with 100 mL of ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, and concentrated *in vacuo* to give 1.48 g of crude material. Column chromatography (elution with 50% EtOAc/hexane with 0.5% HOAc) yielded 1.13 g (68%) of **5a** as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.45−7.26 (m, 7H), 7.19 (d, J = 7.5 Hz, 1H), 6.73 (s, 1H), 6.30 (br s, 1H), 5.19 (s, 2H), 4.12 (d, J = 9 Hz, 1H), 2.69−2.59 (m, 2H), 2.42−2.39 (m, 2H), 1.76−1.50 (m, 7H), 1.30−1.25 (m, 1H), 0.74−0.65 (m, 1H), 0.60−0.54 (m, 2H), 0.29−0.22 (m, 1H) ppm; MS (EI) *m*/*z* 459 (M^+); HRMS (EI) calcd for $C_{28}H_{29}NO_5$ 459.2046, found 459.2041.

[3-[1-(5,6,7,8,9,10-Hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)butyl]phenyl]carbamic acid, phenylmethyl ester (41a): Prepared from **40a**; beige solid (18%); mp 64−67 °C; ^{1}H NMR ($CDCl_3$) δ 7.40−7.26 (m, 8H), 7.12 (d, J = 7.3 Hz, 1H), 6.71 (s, 1H), 5.92 (br s, 1H), 5.20 (s, 2H), 4.39 (t, J = 7.8 Hz, 1H), 2.62−2.57 (m, 2H), 2.43−2.39 (m, 2H), 2.09−1.94 (m, 2H), 1.74−1.67 (m, 2H), 1.61−1.26 (m, 8H), 0.96 (t, J = 7.3 Hz, 3H) ppm; MS (EI) *m*/*z* 475 (M^+); HRMS (EI) calcd for $C_{18}H_{21}NO_3$ 475.2359, found 475.2368.

[(3-Aminophenyl)cyclopropylmethyl]-4-hydroxy-6,7,8,9-tetrahydrocyclohepta[*b*]pyran-2(5*H*)-one (6a). Compound

5a (0.97 g, 2.1 mmoL), 10% Pd/C (0.24 g), and 100 mL of methanol were shaken under 48 psi of H_2 for 18 h. The reaction mixture was then filtered, washed with EtOAc, and concentrated *in vacuo* to give 0.652 g of crude material. This was dissolved in 5 mL of CH_2Cl_2, filtered through Celite, and concentrated *in vacuo* to give 0.56 g (82%) of **6a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.26 (s, 1H), 7.17 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.79 (s, 1H), 6.62−6.60 (m, 1H), 4.20 (br s, 1H), 3.85 (d, J = 9 Hz, 1H), 2.71−2.67 (m, 2H), 2.45−2.41 (m, 2H), 1.77−1.50 (m, 7H), 1.35−1.26 (m, 1H), 0.72−0.56 (m, 3H), 0.27−0.23 (m, 1H) ppm; MS (EI) m/z 325 (M^+); HRMS (EI) calcd for $C_{28}H_{29}NO_5$ 325.1678, found 325.1675.

Representative Procedure for the Synthesis of 42a−d. 3-[1-(3-Aminophenyl)butyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2*H*-cycloocta[*b*]pyran-2-one (42a). A mixture of **41a** (0.75 g, 1.58 mmol) and 10% Pd/C (0.40 g) in cyclohexene (12 mL) and absolute ethanol (12 mL) was warmed to reflux for 1.5 h. The mixture was then filtered through Celite (rinsing with EtOH) and concentrated *in vacuo* to give 0.51 g (95%) of **42a** as a beige solid. An analytical sample was purified by column chromatography: mp 86−91 °C; ^{1}H NMR ($CDCl_3$) δ 7.17 (t, J = 7.8 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.71 (s, 1H), 6.59 (br d, J = 7.8 Hz, 1H), 6.15 (br s, 1H), 4.37 (t, J = 7.7 Hz, 1H), 3.73 (br s, 2H), 2.64−2.56 (m, 2H), 2.45−2.33 (m, 2H), 2.10−1.97 (m, 1H), 1.96−1.83 (m, 1H), 1.82−1.70 (m, 2H), 1.60−1.33 (m, 8H), 0.97 (t, J = 7.3 Hz, 3H) ppm; MS (EI) m/z 341 (M^+). Anal. ($C_{21}H_{27}NO_3$) C, H, N.

5-Thiazolesulfonyl Chloride. A mixture of 5-thiazolesulfonic acid,[32] PCl_5, and $POCl_3$ was warmed to reflux for 5 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$(aq). The organic layer was separated, washed twice with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo* to give the title compound as a colorless oil which was used without further purification.

2-Pyridinesulfonyl Chloride. Chlorine gas was bubbled into a mixture of 2-mercaptopyridine (5.0 g, 45 mmol) and concentrated HCl (40 mL) at 0 °C for 1.5 h. The reaction mixture was then poured into ice water (100 mL), and a low-melting solid formed. The solid was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 6.1 g (76%) of 2-pyridinesulfonyl chloride as a colorless oil which was used without further purification. 4-Cyano-2-pyridinesulfonyl chloride, 2-pyrimidinesulfonyl chloride, and 2-pyrazinesulfonyl chloride were prepared in an analogous fashion.

Synthesis of *m*-Sulfonamide-Substituted Cycloalkylpyranones: Representative Procedure for the Synthesis of 7, 8, 32−37, and 43−48. *N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]benzenesulfonamide (8h). A solution of **6b** (0.100 g, 0.29 mmol), benzenesulfonyl chloride (0.053 g, 0.3 mmol), pyridine (0.05 mL), and 5 mL of CH_2Cl_2 was stirred at room temperature for 18 h. Column chromatography of the reaction mixture (elution with 50% EtOAc/hexane) gave 0.127 g (90%) of **8h** as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.76−7.35 (m, 2H), 7.52−7.41 (m, 3H), 7.26−7.17 (m, 4H), 7.04−6.98 (m, 1H), 3.81 (d, J = 8.4 Hz, 1H), 2.61 (m, 2H), 2.46 (m, 2H), 1.71−1.42 (m, 10H), 0.72−0.52 (m, 2H), 0.52−0.40 (m, 1H), 0.20−0.08 (m, 1H) ppm; ^{13}C NMR (CD_3OD) δ 169.8, 168.6, 165.2, 147.8, 143.2, 140.7, 136.6, 132.9, 132.7, 130.9, 128.4, 124.8, 123.4, 114.8, 110.1, 48.6, 34.8, 33.0, 32.8, 30.1, 29.6, 26.1, 16.3, 9.6, 7.9 ppm; IR (mineral oil) 3211, 1665, 1652, 1609, 1593, 1555, 1533, 1438, 1420, 1345, 1252, 1199, 1168, 1156 cm^{-1}; MS (EI) m/z 479 (M^+). Anal. ($C_{27}H_{29}NO_5S$) C, H, N.

***N*-[3-[Cyclopropyl(2,5,6,7,8,9-hexahydro-4-hydroxy-2-oxocyclohepta[*b*]pyran-3-yl)methyl]phenyl]methanesulfonamide (7a)**: prepared from **6a**; white foam (15%); ^{1}H NMR ($CDCl_3$) δ 7.31−7.15 (m, 5H), 3.85 (d, J = 9 Hz, 1H), 3.01 (s, 3H), 2.73−2.68 (m, 2H), 2.53−2.48 (m, 2H), 1.80−1.25 (m, 7H), 0.92−0.86 (m, 1H), 0.82−0.45 (m, 3H), 0.35−0.25 (m, 1H) ppm; MS (EI) m/z 403 (M^+); HRMS (EI) calcd for $C_{21}H_{25}NO_5S$ 403.1453, found 403.1463.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]methanesulfonamide (8a)**: white foam (59%); ^{1}H NMR ($CDCl_3$) δ 7.31−7.24 (m, 4H), 7.16−7.13 (m, 1H), 7.06 (br s, 1H), 3.81 (d, J = 8.8 Hz, 1H), 2.97 (s, 3H), 2.62−2.58 (m, 2H), 2.51−2.47 (m, 2H), 1.73−1.40 (m, 9H), 0.74−0.72 (m, 1H), 0.61−0.57 (m, 1H), 0.48−0.43 (m, 1H), 0.27−0.23 (m, 1H) ppm; MS (EI) m/z 417 (M^+); HRMS (EI) calcd for $C_{22}H_{27}NO_5S$ 417.1610, found 417.1619.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]benzenemethanesulfonamide (32a)**: white foam (49%); ^{1}H NMR ($CDCl_3$) δ 7.34−7.24 (m, 8H), 7.11−7.08 (m, 1H), 6.46 (br s, 1H), 4.30 (s, 2H), 3.87 (d, J = 8.7 Hz, 1H), 2.64−2.60 (m, 2H), 2.50−2.46 (m, 2H), 1.75 (m, 2H), 1.59−1.42 (m, 8H), 0.75−0.71 (m, 1H), 0.62−0.56 (m, 1H), 0.54−0.49 (m, 1H), 0.31−0.28 (m, 1H) ppm; MS (EI) m/z 493 (M^+). Anal. ($C_{28}H_{31}NO_5S$) C, H, N.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-2-methylbenzenesulfonamide (33a)**: white foam (76%); ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.90 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.42−7.38 (m, 1H), 7.26−7.08 (m, 5H), 6.87 (m, 1H), 3.43−3.55 (m, 2H), 2.63−2.59 (m, 5H), 2.55−2.51 (m, 2H), 1.74−1.26 (m, 9H), 0.62−0.58 (m, 1H), 0.47−0.42 (m, 1H), 0.23−0.18 (m, 1H), 0.13−0.08 (m, 1H) ppm; MS (EI) m/z 493 (M^+). Anal. ($C_{28}H_{31}NO_5S$) C, H, N, S.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-3-methylbenzenesulfonamide (34a)**: white foam (79%); ^{1}H NMR ($CDCl_3$) δ 7.58−7.53 (m, 2H), 7.30−7.13 (m, 6H), 6.98−6.96 (m, 1H), 3.80 (d, J = 8.7 Hz, 1H), 2.61−2.57 (m, 2H), 2.47−2.43 (m, 2H), 2.32 (s, 3H), 1.57−1.25 (m, 9H), 0.90−0.85 (m, 1H), 0.65−0.52 (m, 2H), 0.44−0.40 (m, 1H), 0.14−0.09 (m, 1H) ppm; MS (EI) m/z 493 (M^+); HRMS (EI) calcd for $C_{28}H_{31}NO_5S$ 493.1923, found 493.1931.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-4-methylbenzenesulfonamide (35a)**: white foam (45%); ^{1}H NMR ($CDCl_3$) δ 7.65−7.62 (m, 2H), 7.26−7.12 (m, 6H), 6.98−6.94 (m, 1H), 3.80 (d, J = 8.7 Hz, 1H), 2.61−2.57 (m, 2H), 2.48−2.44 (m, 2H), 2.35 (s, 3H), 1.73−1.33 (m, 9H), 0.65−0.52 (m, 2H), 0.44−0.40 (m, 1H), 0.15−0.10 (m, 1H) ppm; MS (EI) m/z 493 (M^+). Anal. ($C_{28}H_{31}NO_5S$) C, H, N, S.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-4-fluorobenzenesulfonamide (35f)**: white solid (32%); mp 227−228 °C; ^{1}H NMR ($CDCl_3$) δ 7.69−7.65 (m, 2H), 7.29−7.00 (m, 6H), 6.55 (s, 1H), 6.25 (s, 1H), 3.35 (d, J = 10 Hz, 1H), 2.55 (m, 2H), 2.44 (m, 2H), 1.80−1.25 (m, 9H), 0.68−0.75 (m, 1H), 0.70−0.60 (m, 1H), 0.60−0.50 (m, 1H), 0.22−0.12 (m, 1H) ppm; MS (EI) m/z 497 (M^+). Anal. ($C_{27}H_{28}FNO_5S$) C, H, N, F.

4-Cyano-*N*-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]benzenesulfonamide (35k): white solid (51%); mp 183−183.5 °C; ^{1}H NMR (DMSO-d_6) δ 10.39 (s, 1H), 8.01 (d, J = 8.5 Hz, 2H), 7.85−7.82 (m, 2H), 7.85 (d, J = 8.5 Hz, 2H), 7.13−7.04 (m, 3H), 6.84 (d, J = 7.9 Hz, 1H), 3.30 (d, J = 10.7 Hz, 1H), 1.75−1.38 (m, 9H), 0.62−0.59 (m, 1H), 0.38−0.34 (m, 1H), 0.11−0.01 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 169.7, 168.6, 165.3, 148.4, 147.7, 140.0, 136.6, 132.9, 131.7, 129.0, 125.2, 123.6, 114.7, 110.2, 48.7, 34.8, 33.0, 32.8, 30.1, 29.6, 26.2, 16.2, 9.7, 7.9 ppm; IR (mineral oil) 3234, 2234, 1666, 1652, 1608, 1587, 1550, 1497, 1441, 1414, 1349, 1248, 1168, 1157 cm^{-1}; MS (EI) m/z 504 (M^+). Anal. ($C_{28}H_{28}N_2O_5S$) C, H, N, S.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-2,6-dimethylbenzenesulfonamide (36a)**: white foam (69%); ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.75 (s, 1H), 7.72−7.19 (m, 2H), 7.14−7.07 (m, 3H), 6.89−6.86 (m, 1H), 3.40−3.27 (m, 2H), 2.62−2.55 (m, 7H), 2.31 (s, 3H), 1.74−1.26 (m, 9H), 0.62−0.56 (m, 1H), 0.47−0.41 (m, 1H), 0.23−0.18 (m, 1H), 0.13−0.09 (m, 1H) ppm; MS (EI) m/z 507 (M^+); HRMS (EI) calcd for $C_{29}H_{33}NO_5S$ 507.2079, found 507.2082.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-1-methyl-1*H*-imidazole-4-sulfonamide (37a)**: white foam (72%); ^{1}H NMR (DMF-d_7) δ 10.50 (s, 1H), 9.90 (s, 1H), 7.70 (s, 2H), 7.57 (s, 1H), 6.90 (s, 3H), 3.58 (s, 3H), 3.38 (br s, 1H), 3.25 (d, J = 11.3 Hz, 1H), 2.73−2.42 (m, 4H), 1.80−1.70 (m, 1H), 1.60−

1.20 (m, 8H), 0.60−0.51 (m, 1H), 0.30−0.20 (m, 1H), 0.10−0.01 (m, 2H) ppm; MS (EI) 483 *m/z* (M^+). Anal. ($C_{25}H_{29}N_3O_5S$) C, H, N.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-8-quinolinesulfonamide (37b)**: white foam (60%); ^{1}H NMR ($CDCl_3$) δ 8.31 (br s, 1H), 8.30−8.25 (m, 2H), 8.00 (d, J = 8.4 Hz, 1H), 7.62−7.52 (m, 2H), 7.10−6.95 (m, 4H), 3.70 (d, J = 8.4 Hz, 1H), 2.61−2.57 (m, 2H), 2.42−2.38 (m, 2H), 1.73−1.68 (m, 2H), 1.54−1.12 (m, 7H), 0.97−0.93 (m, 1H), 0.88−0.85 (m, 1H), 0.47−0.44 (m, 2H), 0.32−0.29 (m, 1H), −0.09 to −0.11 (m, 1H) ppm; MS (EI) *m/z* 530 (M^+). Anal. ($C_{30}H_{30}N_2O_5S$) C, H, N.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-3-pyridinesulfonamide (37d)**: white foam (60%); ^{1}H NMR ($CDCl_3$) δ 8.93 (s, 1H), 8.78 (d, J = 4.2 Hz, 1H), 8.03−7.96 (m, 1H), 7.45−7.35 (m, 1H), 7.30−7.17 (m, 5H), 7.05−7.00 (m, 1H), 3.79 (d, J = 8.7 Hz, 1H), 2.61−2.57 (m, 2H), 2.49−2.43 (m, 2H), 1.80−1.30 (m, 9H), 0.90−0.83 (m, 1H), 0.70−0.50 (m, 2H), 0.45−0.35 (m, 1H), 0.20−0.10 (m, 1H) ppm; MS (EI) *m/z* 480 (M^+); HRMS (EI) calcd for $C_{26}H_{28}N_2O_5S$ 480.1719, found 480.1725.

4-Cyano-*N*-[3-[1-(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)propyl]phenyl]benzenesulfonamide (44a): prepared from 3-[(3-aminophenyl)propyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2*H*-cycloocta[*b*]pyran-2-one;[33] white solid (68%); mp 108−111 °C; ^{1}H NMR ($CDCl_3$) δ 10.46 (br s, 1H), 10.39 (s, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H), 7.13−7.08 (m, 2H), 7.01 (d, J = 7.9 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 4.05−4.00 (m, 1H), 2.56−2.54 (m, 2H), 2.11−2.04 (m, 1H), 1.99−1.86 (m, 1H), 1.63−1.53 (m, 5H), 1.43−1.28 (m, 5H), 0.74 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6) δ 164.7, 162.9, 160.5, 145.4, 143.6, 136.5, 133.4, 128.6, 127.5, 124.2, 120.1, 118.3, 117.7, 115.3, 110.0, 104.1, 40.9, 30.4, 29.2, 28.8, 25.9, 25.5, 23.2, 21.8, 12.5 ppm; IR (mineral oil) 3252, 2235, 1667, 1633, 1607, 1558, 1464, 1405, 1377, 1341, 1228, 1198, 1167, 1091 cm^{-1}; MS (EI) *m/z* 492 (M^+). Anal. ($C_{27}H_{28}N_2O_5S$) C, H, N.

4-Cyano-*N*-[3-[1-(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)propyl]butyl]benzenesulfonamide (44b): prepared from **42a**; white crystals (77%); mp 130−135 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.22 (m, 2H), 7.12 (s, 1H), 7.05 (d, J = 7.3 Hz, 1H), 7.00 (s, 1H), 5.75 (s, 1H), 4.25 (t, J = 7.8 Hz, 1H), 2.64−2.59 (m, 2H), 2.49−2.43 (m, 2H), 2.06−1.95 (m, 2H), 1.80−1.67 (m, 2H), 1.65−1.24 (m, 8H), 0.93 (t, J = 7.3 Hz, 3H) ppm; MS (EI) *m/z* 506 (M^+). Anal. ($C_{28}H_{30}N_2O_5S$) C, H, N, S.

4-Cyano-*N*-[3-[1-(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)propyl]pentyl]benzenesulfonamide (44c): prepared from **42b**; white solid (63%); mp 107−112 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.24−7.19 (m, 2H), 7.03−6.99 (m, 2H), 5.82 (br s, 1H), 4.24 (t, J = 7.7 Hz, 1H), 2.64−2.60 (m, 2H), 2.49−2.45 (m, 2H), 2.05−1.97 (m, 2H), 1.74−1.69 (m, 2H), 1.59−1.21 (m, 10H), 0.87 (t, J = 7.2 Hz, 3H) ppm; MS (EI) *m/z* 520 (M^+). Anal. ($C_{29}H_{32}N_2O_5S$) C, H, N, S.

4-Cyano-*N*-[3-[1-(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)propyl]-2-methylpropyl]-benzenesulfonamide (44d): prepared from **42c**; white solid (80%); mp 158−163 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.23−7.16 (m, 2H), 7.09 (s, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.07 (br s, 1H), 3.68 (d, J = 11.1 Hz, 1H), 2.82−2.75 (m, 1H), 2.61−2.57 (m, 2H), 2.51−2.47 (m, 2H), 1.80−1.62 (m, 5H), 1.47−1.40 (m, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.75 (d, J = 6.5 Hz, 3H) ppm; MS (EI) *m/z* 506 (M^+). Anal. ($C_{28}H_{30}N_2O_5S$) C, H, N, S.

4-Cyano-*N*-[3-[1-(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)propyl]-3-methylbutyl]-benzenesulfonamide (44e): prepared from **42d**; white solid (65%); mp 109−114 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2 H), 7.23−7.18 (m, 1H), 7.13 (s, 1H), 7.02−6.97 (m, 2H), 5.83 (br s, 1H), 4.37−4.32 (m, 1H), 2.63−2.59 (m, 2H), 2.49−2.45 (m, 2H), 1.99−1.80 (m, 2H), 1.74−1.66 (m, 2H), 1.65−1.59 (m, 2H), 1.47−1.33 (m, 5H), 0.92 (d, J = 4.5 Hz, 3H), 0.90 (d, J = 4.5 Hz, 3H) ppm; MS (EI) *m/z* 520 (M^+). Anal. ($C_{29}H_{32}N_2O_5S$) C, H, N, S.

Separation of 5b into Component Enantiomers. A solution of **5b** in 35% 2-propanol/hexane was chromatographed on a 1.0 × 25 cm (R,R) Whelk-O 1 (Regis Technologies, Inc., Morton Grov, IL 60053) column at 5 mL per injection using an automated chromatographic system. The eluant was monitored at 310 nm, and appropriate fractions from multiple injections were combined and concentrated *in vacuo*. Fractions from multiple injections were analyzed on a 0.46 × 25 cm (R,R) Whelk-O column with the same solvent at 1.0 mL/min, and enantiomeric purity was greater than 95%.

(−)-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]carbamic acid, phenylmethyl ester: white foam; [α] (MeOH) = −49°.

(+)-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]carbamic acid, phenylmethyl ester: white foam; [α] (MeOH) = +53°.

(−)-4-Cyano-*N*-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]benzenesulfonamide (51a) was prepared in two steps using procedures analogous to those above for **42a** and **8h** from (−)-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]carbamic acid, phenylmethyl ester: white solid (74%); mp 162−163 °C; [α] (MeOH) = −87°; ^{1}H NMR ($CDCl_3$) δ 7.84−7.81 (m, 2H), 7.73−7.70 (m, 2H), 7.26−7.23 (m, 4H), 7.13 (s, 1H), 7.00−6.90 (m, 1H), 6.79 (s, 1H), 6.34 (s, 1H), 3.84 (d, J = 8.4 Hz, 1H), 2.68−2.61 (m, 2H), 2.52−2.47 (m, 2H), 1.80−1.70 (m, 2H), 1.65−1.30 (m, 5H), 1.75−1.55 (m, 2H), 0.45−0.40 (m, 1H), 0.25−0.15 (m, 1H) ppm; MS (EI) *m/z* 504 (M^+). Anal. ($C_{28}H_{28}N_2O_5S$) C, H, N.

(+)-4-Cyano-*N*-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]benzenesulfonamide (51b) was prepared in two steps using procedures analogous to those above for **42a** and **8h** from (+)-[3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]carbamic acid, phenylmethyl ester: white foam (70%); [α] (MeOH) = +87°; ^{1}H NMR ($CDCl_3$) δ 7.84−7.81 (m, 2H), 7.73−7.70 (m, 2H), 7.26−7.23 (m, 4H), 7.13 (s, 1H), 7.00−6.90 (m, 1H), 6.79 (s, 1H), 6.34 (s, 1H), 3.84 (d, J = 8.4 Hz, 1H), 2.68−2.61 (m, 2H), 2.52−2.47 (m, 2H), 1.80−1.70 (m, 2H), 1.65−1.30 (m, 5H), 1.75−1.55 (m, 2H), 0.45−0.40 (m, 1H), 0.25−0.15 (m, 1H) ppm; MS (EI) *m/z* 504 (M^+); HRMS (EI) calcd for $C_{28}H_{28}N_2O_5S$ 504.1790, found 504.1700.

Representative Procedure for the Synthesis of 9a−e. Note **9c** (R = Me), **9d** (R = *i*-Pr), and **9e** (R = CH_2cPr) were used to prepared **11a−c**, respectively. **3-[Cyclopropyl[3-[(phenylmethyl)amino]phenyl]methyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2*H*-cycloocta[*b*]pyran-2-one (9a).** A solution of **6b** (0.100 g, 0.29 mmol) and benzaldehyde (0.035 mL, 0.34 mmol) in EtOH (6 mL) was refluxed for 30 min, cooled, and concentrated *in vacuo*. The resulting oil was dissolved in MeOH (6 mL), treated with sodium cyanoborohydride (0.015 g, 0.24 mmol), and stirred at room temperature for 18 h. The reaction mixture was then quenched with water and diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography (elution with 30% EtOAc/hexane) gave 0.093 g (73%) of **9a** as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.40−7.14 (m, 6H), 6.88 (d, J = 8.7 Hz, 1H), 6.75 (s, 1H), 6.55 (d, J = 9.0 Hz, 1H), 6.37 (s, 1H), 4.29 (s, 2H), 3.98 (d, J = 9.7 Hz, 1H), 2.60 (m, 2H), 2.41 (m, 2H), 1.4 (m, 2H), 1.60−1.20 (m, 7H), 0.70−0.50 (m, 3H), 0.25−0.18 (m, 1H) ppm; MS (EI) *m/z* 429 (M^+).

***N*-Methyl-3-[(3-aminophenyl)cyclopropylmethyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2*H*-cycloocta[*b*]pyran-2-one (9c)**: white foam (16%); ^{1}H NMR ($CDCl_3$) δ 7.22 (t, J = 7.8 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.71 (s, 1H), 6.54−6.52 (m, 1H), 3.89 (d, J = 9.0 Hz, 1H), 2.80 (s, 3H), 2.63−2.59 (m, 2H), 2.43−2.39 (m, 2H), 1.75−1.26 (m, 9H), 0.70−0.53 (m, 3H), 0.28−0.22 (m, 1H) ppm.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-*N*-(phenylmethyl)benzenesulfonamide (10a)** was prepared from **9a** according to the procedure for **8h**: white foam (80%); ^{1}H NMR ($CDCl_3$) δ 7.65−7.45 (m, 5H), 7.26−7.14 (m, 7H), 7.04

(s, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.17 (s, 1H), 4.72 (s, 2H), 3.79 (d, J = 9.3 Hz, 1H), 2.61 (m, 2H), 2.45 (m, 2H), 1.74 (m, 2H), 1.80−1.15 (m, 9H), 0.55−0.38 (m, 3H), 0.04−0.02 (m, 1H) ppm; MS (EI) m/z 569 (M^+); HRMS (EI) calcd for $C_{34}H_{35}NO_5S$ 569.2236, found 569.2227.

***N*-[3-[Cyclopropyl[5,6,7,8,9,10-hexahydro-4-[(phenylsulfonyl)oxy]-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl]methyl]phenyl]-*N*-(phenylsulfonyl)benzenesulfonamide (11).** A solution of **6b** (0.185 g, 0.545 mmol), pyridine (0.22 mL, 2.72 mmol), and benzenesulfonyl chloride (0.155 mL, 1.21 mmol) in 1,2-dichloroethane (11 mL) was stirred at room temperature for 16 h and then concentrated *in vacuo* to a pink solid. Column chromatography on 7 g of silica gel (elution with 20% EtOAc/CH_2Cl_2) gave 0.131 g (39%) of *N*-[3-[cyclopropyl[5,6,7,8,9,10-hexahydro-4-[(phenylsulfonyl)oxy]-2-oxo-2*H*-cycloocta[*b*]-pyran-3-yl]methyl]phenyl]benzenesulfonamide as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 7.85−7.62 (m, 5H), 7.50−7.26 (m, 5H), 7.12 (m, 2H), 7.02−6.93 (m, 2H), 6.48 (s, 1H), 2.81 (m, 1H), 2.65−2.58 (m, 3H), 1.80−1.60 (m, 5H), 1.57−1.30 (m, 4H), 0.60 (m, 1H), 0.48 (m, 1H), 0.19 (m, 1H), −0.22 (m, 1H) ppm; MS (FAB) m/z 620 ($[M + H]^+$). *n*-BuLi (0.0375 mL, 0.06 mmol) was added to a solution of the above intermediate (0.036 g, 0.058 mmol) in THF (3 mL) at −78 °C. The reaction mixture was stirred for 15 min, and then benzenesulfonyl chloride (0.012 mL, 0.09 mmol) was added. The reaction mixture was allowed to warm to room temperature and then heated to reflux for 1.75 h. The sequence was then repeated using 0.050 mL (0.08 mmol) of *n*-BuLi and 0.010 mL (0.078 mmol) of benzenesulfonyl chloride. The reaction mixture was then concentrated *in vacuo* and purified via prep TLC (500 μm plate, Analtech, elution with 2% EtOAc/CH_2Cl_2) to give 0.024 g (54%) of **11** as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 7.93−7.83 (m, 7H), 7.64−7.45 (m, 9H), 7.28 (m, 1H), 6.94 (m, 2H), 2.71 (m, 3H), 1.85−1.31 (m, 10H), 0.86 (m, 2H), 0.51 (m, 1H), 0.39 (m, 1H), 0.02 (m, 1H) ppm; MS (FAB) m/z 760 ($[M + H]^+$).

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl]methyl]phenyl]-*N*-(phenylsulfonyl)benzenesulfonamide (12).** A solution of **11** (0.022 g, 0.029 mmol) in NH_3−MeOH (5 mL) was stirred at room temperature for 4.5 h and then concentrated *in vacuo*. Column chromatography on 6 g of silica gel (elution with 5% acetone/$CHCl_3$) gave 0.0099 g (55%) of **12** as a colorless solid: mp 97−100 °C; ^{1}H NMR ($CDCl_3$) δ 7.96−7.92 (m, 4H), 7.70−7.64 (m, 2H), 7.57−7.51 (m, 4H), 7.48 (d, J = 7 Hz, 1H), 7.35 (dd, J = 7, 7 Hz, 1H), 7.10 (s, 1H), 7.02 (d, J = 7 Hz, 1H), 6.17 (s, 1H), 3.92 (d, J = 9 Hz, 1H), 2.68−2.62 (m, 2H), 2.50−2.43 (m, 2H), 1.80−1.72 (m, 2H), 1.65−1.37 (m, 6H), 1.28−1.20 (m, 1H), 0.60−0.50 (m, 3H), 0.20−0.15 (m, 1H) ppm; MS (EI) m/z 619 (M^+); HRMS (EI) calcd for $C_{33}H_{33}NO_7S_2$ 619.1698, found 619.1687.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl]methyl]phenyl]-*N*-methylbenzenesulfonamide (13a)** was prepared from **9c** according to the procedure for **8h**: white foam (43%); ^{1}H NMR ($CDCl_3$) δ 7.59−7.41 (m, 5H), 7.33−7.23 (m, 3H), 6.98−6.96 (d, J = 7.5 Hz, 1H), 6.44 (s, 1H), 3.90 (d, J = 8.4 Hz, 1H), 3.16 (s, 3H), 2.64−2.60 (m, 2H), 2.50−2.48 (m, 2H), 1.75−1.20 (m, 9H), 0.67−0.40 (m, 3H), 0.23−0.20 (m, 1H) ppm; MS (EI) m/z 493 (M^+); HRMS (EI) calcd for $C_{28}H_{31}NO_5S$ 494.2001, found 494.2009.

2-Nitrophenyl Cyclopropyl Ketone (15) and 4-Nitrophenyl Cyclopropyl Ketone (17). Phenyl cyclopropyl ketone (**14**) was treated with nitric acid, and the major product, 3-nitrophenyl cyclopropyl ketone (**16**) was separated by recrystallization as previously reported.[11] The two minor isomers were then isolated from the mother liquor by medium-pressure liquid chromatography on 500 g of silica gel (40−60 μm), eluting with 0−20% EtOAc in hexanes.

2-Nitrophenyl cyclopropyl ketone (15): yellow oil; ^{1}H NMR ($CDCl_3$) δ 8.10−8.02 (m, 1H), 7.77−7.66 (m, 1H), 7.66−7.56 (m, 1H), 7.54−7.47 (m, 1H), 2.26−2.15 (m, 1H), 1.37−1.30 (m, 2H), 1.18−1.07 (m, 2H) ppm; MS (EI) m/z 192 (M^+). Anal. ($C_{10}H_9NO_3$) C, H, N.

4-Nitrophenyl cyclopropyl ketone (17): yellow crystals; mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 8.30−8.38 (m, 2H), 8.20−8.10 (m, 2H), 2.74−2.61 (m, 1H), 1.37−1.28 (m, 2H), 1.22−1.10 (m, 2H) ppm; MS (EI) m/z 191 (M^+). Anal. ($C_{10}H_9NO_3$) C, H, N.

2-Aminophenyl Cyclopropyl Ketone (18). A mixture of **15** (1.0 g, 5.24 mmol) and 10% Pd/C (0.20 g) in EtOAc (25 mL) was hydrogenated at 35 psi for 3 h. The reaction mixture was then filtered and concentrated *in vacuo* to give 0.88 g (104%) of **18** as a amber gum which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 1H), 7.30−7.21 (m, 1H), 6.74−6.49 (m, 2H), 6.13 (m, 2H), 2.70−2.58 (m, 1H), 1.21−1.13 (m, 2H), 1.00−0.90 (m, 2H) ppm; MS (EI) m/z 163 (M^+).

***N*-[2-(Cyclopropylhydroxymethyl)phenyl]benzenesulfonamide (19).** Benzenesulfonyl chloride (0.95 g, 5.38 mmol) was added to a solution of **18** (0.85 g, 5.28 mmol) and triethylamine (0.55 g, 5.44 mmol) in THF (15 mL) at 0 °C, and the resulting mixture was stirred for 4 h. Additional triethylamine (0.73 g, 7.23 mmol) was added, and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was then heated to reflux for 3 h, cooled to room temperature, and filtered. The filtrate was concentrated *in vacuo*, suspended in EtOAc, and filtered and concentrated a second time. Chromatography via MPLC (150 g silica gel, 40−60 μm, elution with 10−20% EtOAc/hexane) gave 0.60 g (38%) of cyclopropyl[2-(aminosulfonyl)phenyl]methanone as yellow crystals: mp 115 °C; ^{1}H NMR ($CDCl_3$) δ 11.23 (s, 1H), 7.99 (dd, J = 1.6, 7.9 Hz, 1H), 7.84−7.76 (m, 2H), 7.69 (dd, J = 1.1, 8.3 Hz, 1H), 7.56−7.37 (m, 4H), 7.18−7.08 (m, 1H), 2.57−2.45 (m, 1H), 1.24−1.16 (m, 2H), 1.08−0.98 (m, 2H) ppm; MS (EI) m/z 301 (M^+). Anal. ($C_{16}H_{15}NO_3S$) C, H, N, S. Sodium borohydride (0.060 g, 1.59 mmol) was added to a mixture of the above ketone (0.412 g, 1.37 mmol) in THF (10 mL) and EtOH (10 mL), and the resulting mixture was stirred for 1 h. The reaction mixture was then concentrated, and the residue was partitioned between EtOAc and 1 N HCl. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. Recrystallization from acetone/hexane gave 0.338 g (82%) of **19** as a yellow solid: mp 155−156 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 7.79 (d, J = 8.6 Hz, 2H), 7.58−7.47 (m, 2H), 7.47−7.37 (m, 2H), 7.30−7.17 (m, 2H), 7.12−7.02 (m, 1H), 3.52 (dd, J = 3.1, 9.2 Hz, 1H), 2.27 (d, J = 3.1 Hz, 1H), 1.15−1.00 (m, 1H), 0.68−0.56 (m, 1H), 0.56−0.42 (m, 1H), 0.37−0.23 (m, 1H), 0.10 to −0.03 (m, 1H) ppm; MS (EI) m/z 303 (M^+). Anal. ($C_{16}H_{17}NO_3S$) C, H, N, S.

***N*-[2-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]benzenesulfonamide (20).** A mixture of **3b** (0.187 g, 0.96 mmol), **19** (0.292 g, 0.96 mmol), and *p*-toluenesulfonic acid (0.046 g, 0.242 mmol) in benzene (25 mL) was warmed to reflux for 3 h in a flask equipped with a Dean-Stark trap. The reaction mixture was then allowed to cool, and the resultant precipitate was filtered. Recrystallization from acetone/hexane gave 0.305 g (66%) of **20** as white crystals: mp 220−221 °C; ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1H), 7.77−7.58 (m, 4H), 7.58−7.46 (m, 2H), 7.18−7.05 (m, 3H), 3.08 (d, J = 10.1 Hz, 1H), 2.67−2.44 (m, 4H), 1.95−1.80 (m, 1H), 1.73−1.19 (m, 9H), 0.42−0.18 (m, 2H), −0.72 to −0.85 (m, 1H) ppm; MS (EI) m/z 479 (M^+). Anal. ($C_{27}H_{29}NO_5S$) C, H, N, S.

Cyclopropyl[4-[(benzyloxycarbonyl)amino]phenyl]methanone (21). A mixture of **17** (1.1 g, 5.7 mmol) and 10% Pd/C (0.110 g) in EtOAc (25 mL) was hydrogenated at 10 psi for 45 min. The reaction mixture was filtered through Celite and concentrated *in vacuo* to give 0.940 g (quantitative) of 4-aminophenyl cyclopropyl ketone as a solid which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.93 (dd, J = 1.9, 6.7 Hz, 2H), 6.68 (dd, J = 1.9, 6.7 Hz, 2H), 2.64−2.56 (m, 1H), 1.24−1.13 (m, 2H), 1.20−0.90 (m, 2H) ppm.

Benzyl chloroformate (1.07 g, 6.3 mmol) was added to a solution of the above amine (0.92 g, 5.7 mmol) and diisopropylethylamine (0.89 g, 6.9 mmol) in CH_2Cl_2 (20 mL) at 0 °C, and the resulting mixture was allowed to warm to room temperature over 2 h. The reaction mixture was then washed with 1 N HCl, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Recrystallization from $CHCl_3$/hexane gave 1.15 g (68%) of **21**: mp 166−168 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.43−7.32 (m, 5H), 6.96

(s, 1H), 5.22 (s, 2H), 2.68−2.59 (m, 1H), 1.25−1.20 (m, 2H), 1.07−1.01 (m, 2H) ppm; MS (EI) *m*/*z* 295 (M^+).

[4-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]carbamic Acid, Phenylmethyl Ester (22). A mixture of **21** (1.1 g, 3.7 mmol) and $NaBH_4$ (0.567 g, 15 mmol) in THF (7 mL) and EtOH (7 mL) was stirred at room temperature overnight and then concentrated. The residue was partitioned between 1 N HCl and $CHCl_3$. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo* to give 1.12 g (quantitative) of cyclopropyl[4-(aminocarbobenzoxy)phenyl]methanol, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.45−7.34 (m, 9H), 6.72 (s, 1H), 5.21 (s, 2H), 4.00 (d, J = 8.34 Hz, 1H), 1.94 (s, 1H), 1.25−1.15 (m, 1H), 0.52−0.30 (m, 4H) ppm; MS (EI) *m*/*z* 297 (M^+). A mixture of **3b** (1.25 g, 3.7 mmol), the above alcohol (1.1g, 3.7 mmol), and *p*-toluenesulfonic acid (0.175 g, 0.9 mmol) in CH_2Cl_2 (25 mL) was heated to reflux in a flask equipped with a Dean-Stark trap. The reaction mixture was then washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography (elution with 30% EtOAc/hexane) afforded 1.2 g (69%) of **22** as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.45−7.34 (m, 9H), 6.72 (s, 1H), 6.30 (s, 1H), 5.28 (s, 1H), 3.94 (d, J = 8.7 Hz, 1H), 2.62−2.58 (m, 2H), 2.48−2.40 (m, 2H), 1.62−1.50 (m, 9H), 0.76−0.68 (m, 1H), 0.65−0.50 (m, 2H), 0.31−0.22 (m, 1H) ppm; MS (EI) *m*/*z* 473 (M^+).

4-Cyano-*N*-[4-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-benzenesulfonamide (23). A mixture of **22** (1.0 g, 2.1 mmol) and 10%Pd/C (0.50 g) in cyclohexene (50 mL) was heated to reflux for 5 h. The reaction mixture was then filtered through Celite, washed with EtOAc and $CHCl_3$, and concentrated *in vacuo* to give 0.720 g (quantitative) of 3-[(4-aminophenyl)-cyclopropylmethyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2*H*-cycloocta[*b*]pyran-2-one: ^{1}H NMR ($CDCl_3$) δ 7.30 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 3.86 (d, J = 7.2 Hz, 1H), 2.65−2.60 (m, 2H), 2.45−2.38 (m, 2H), 1.80−1.22 (m, 8H), 0.97−0.82 (m, 1H), 0.75−0.65 (m, 1H), 0.62−0.52 (m, 2H), 0.30−0.20 (m, 1H) ppm; MS (EI) *m*/*z* 339 (M^+). A mixture of the above amine (0.100 g, 0.294 mmol), pyridine (0.07 mL, 0.882 mmol), and *p*-cyanobenzenesulfonyl chloride (0.059 g, 0.294 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature overnight. The reaction mixture was then washed with 1 N HCl, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a pink solid. Column chromatography (elution with 33% EtOAc/hexane) gave 0.11 g (74%) of **23** as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.66 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.28 (s, 1H), 6.98 (d, J = 8.5 Hz, 2H), 6.53 (s, 1H), 2.65−2.56 (m, 2H), 2.52−2.45 (m, 2H), 1.80−1.22 (m, 8H), 0.90−0.84 (m, 1H), 0.77−0.65 (m, 1H), 0.65−0.55 (m, 1H), 0.50−0.40 (m, 1H), 0.27−0.17 (m, 1H) ppm; MS (EI) *m*/*z* 504 (M^+).

3,5-Bis[*N*-(benzyloxycarbonyl)amino]benzaldehyde (25). Benzyl chloroformate (55 mL, 385 mmol) was added dropwise to a solution of 3,5-diaminobenzoic acid (26.8 g, 176 mmol) and (dimethylamino)pyridine (4.05 g, 33 mmol) in pyridine (220 mL) at 0 °C, and the mixture was then allowed to warm to room temperature overnight. Additional DMAP (2.2 g, 18 mmol) and benzyl chloroformate (25 mL, 175 mmol) were added at 0 °C, and the reaction mixture was stirred for another 45 min. The reaction was quenched with 1 N HCl and then extracted with EtOAc. The organic layer was separated and washed with 1 N HCl until the aqueous phase pH was 1−2. The aqueous layers were then combined, acidified (to pH 1−2), and extracted with three 300-mL portions of EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a mauve solid. Column chromatography followed by recrystallization gave 31.56 g (43%) of 3,5-bis[*N*-(benzyloxycarbonyl)amino]-benzoic acid as a lavender solid: ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 1H), 7.72 (m, 1H), 7.37 (m, 10H), 5.14 (s, 4H) ppm; MS (FAB) *m*/*z* 421 ($[M + H]^+$). A solution of the above acid (16.38 g, 39 mmol) in THF (400 mL) was cooled to −10 °C, and BH_3−THF complex (90 mL, 90 mmol) was slowly added in two portions. After 5.5 h, the reaction was slowly quenched with 10 mL of 1 N HCl, and the mixture was then concentrated *in vacuo*. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were then washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 22.85 g of crude product. Column chromatography on 1 kg of silica gel (elution with 25% EtOAc/CH_2Cl_2) gave 10.26 g (65%) of 3,5-bis[*N*-(benzyloxycarbonyl)-amino]benzyl alcohol as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 11H), 7.08 (s, 2H), 5.17 (s, 4H), 4.55 (s, 2H) ppm; MS (EI) *m*/*z* 406 (M^+). A solution of DMSO (1.85 mL, 26.1 mmol) in CH_2Cl_2 (4 mL) was added slowly to a solution of oxalyl chloride (1.4 mL, 16.1 mmol) in CH_2Cl_2 (20 mL) at −30 °C. The reaction mixture was stirred an additional 30 min, and then a solution of the above benzyl alcohol (5.072 g, 12.5 mmol) in CH_2Cl_2 (60 mL) was added slowly. The resulting mixture was stirred for 1 h, and then a solution of diisopropylethylamine (6.55 mL, 37.6 mmol) in CH_2Cl_2 (16 mL) was added. The reaction mixture was kept below −25 °C during these operations and then allowed to warm to room temperature over 1 h. The reaction was quenched with 20% aqueous citric acid, and the aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 7.126 g of yellow solid. Column chromatography on 740 g of silica gel (elution with 5% EtOAc/CH_2Cl_2) gave 4.529 g (90%) of **25** as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.91 (s, 1H), 7.89 (s, 1H), 7.62 (m, 2H), 7.40−7.35 (m, 10H), 7.17 (s, 2H), 5.21 (s, 4H) ppm; MS (EI) *m*/*z* 404 (M^+).

3,5-Bis[*N*-(benzyloxycarbonyl)amino]-α-cyclopropylbenzyl Alcohol (26) *tert*-Butyllithium (19.5 mL, 33.15 mmol) was added dropwise to a solution of cyclopropyl bromide (2.65 mL, 33.08 mmol) in THF (200 mL) at −78 °C. The reaction mixture was stirred for 15 min, and then a solution of **25** (4.44 g, 10.98 mmol) in THF (20 mL) was added. The reaction mixture was allowed to warm to room temperature over 1.5 h and was then concentrated *in vacuo*. The residue was partitioned between water and EtOAc. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Column chromatography on 720 g of silica gel (elution with 15% EtOAc/CH_2Cl_2) afforded 2.117 g (43%) of **26** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.48 (br s, 1H), 7.39−7.32 (m, 10H), 7.16 (m, 2H), 6.76 (br s, 2H), 5.18 (s, 4H), 3.94 (d, 2H), 1.14 (m, 1H), 0.66−0.32 (m, 4H) ppm; MS (EI) *m*/*z* 446 (M^+).

3-[Cyclopropyl[3,5-bis[*N*-(benzyloxycarbonyl)amino]-phenyl]methyl]-4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (27). A mixture of **3b** (0.877 g, 4.52 mmol), **26** (2.016 g, 4.51 mmol), *p*-toluenesulfonic acid (0.200 g, 1.05 mmol), and molecular sieves in CH_2Cl_2 (200 mL) was stirred at room temperature for 1.5 h and then heated to reflux for 1.5 h. The reaction mixture was then filtered and concentrated *in vacuo*. The residue was partitioned between 100 mL of 1 N HCl and 200 mL of EtOAc, and the aqueous layer was separated and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 3.2 g of an orange oil. Column chromatography on 190 g of silica gel (elution with 10% acetone/$CHCl_3$) afforded 2.15 g (76%) of **27** as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 7.56 (br s, 1H), 7.33 (m, 10H), 7.17 (s, 2H), 6.83 (s, 2H), 6.59 (br s, 1H), 5.14 (s, 4H), 3.81 (d, 1H), 2.57 (m, 2H), 2.41 (m, 2H), 1.71−1.43 (m, 9H), 0.69 (m, 1H), 0.52 (m, 2H), 0.22 (m, 1H) ppm; MS (EI) *m*/*z* 622 (M^+).

***N,N′*-[5-Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]-1,3-phenylene]-bisbenzenesulfonamide (28a).** A solution of **27** (2.068 g, 3.32 mmol) and 10% Pd/C (2.07 g) in EtOH (150 mL) was hydrogenated at 40 psi for 1.25 h. The reaction mixture was then filtered through Celite, rinsing with EtOH, and concentrated *in vacuo* to 1.2 g of solid. Column chromatography on 190 g of silica gel (elution with 5% MeOH/$CHCl_3$) gave 0.744 g (63%) of 3-[cyclopropyl(3,5-diaminophenyl)methyl]-4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one as a brown solid: mp 87 °C dec; ^{1}H NMR ($CDCl_3$) δ 6.28 (s, 2H), 5.93 (s, 1H), 3.79 (d, 1H), 3.63−3.49 (m, 3H), 2.61 (m, 2H), 2.41 (m, 2H), 1.75 (m, 2H), 1.56−1.41 (m, 7H), 1.20 (m, 1H), 0.67−0.54 (m, 3H), 0.22 (m, 1H) ppm; MS (EI) *m*/*z* 354 (M^+). A solution

of the above amine (0.077 g, 0.217 mmol), pyridine (0.052 mL, 0.643 mmol), and benzenesulfonyl chloride (0.060 mL, 0.47 mmol) in CH_2Cl_2 (5.5 mL) was stirred at room temperature for 2 h and then concentrated *in vacuo* to a pink foam. Column chromatography on 20 g of silica gel (elution with 25% EtOAc/CH_2Cl_2) gave 0.090 g (65%) of **28a** as a white solid: mp 99 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.89 (br s, 1H), 7.16 (s, 2H), 7.03 (s, 1H), 3.63 (d, J = 9. Hz, 1H), 3.00 (s, 6H), 2.66−2.61 (m, 2H), 2.59−2.55 (m, 2H), 1.76−1.60 (m, 5H), 1.57−1.44 (m, 4H), 0.78−0.70 (m, 1H), 0.60−0.52 (m, 1H), 0.42−0.37 (m, 1H), 0.32−0.28 (m, 1H) ppm; MS (EI) m/z 510 (M^+); HRMS (EI) calcd for [$C_{23}H_{30}N_2O_7S_2$] 510.1494, found 510.1505.

***N*-Phenyl-3-(cyclopropylhydroxymethyl)benzenesulfonamide (30).** Compound **29** (1.04 g, 4.07 mmol) was added to a solution of aniline (0.39 mL, 4.28 mmol) in pyridine (4 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight and then concentrated *in vacuo*. The residue was diluted with CH_2Cl_2, washed twice with 5% HCl(aq), dried over Na_2SO_4 and activated charcoal, filtered, and concentrated *in vacuo* to afford a yellow oil. Column chromatography on 80 g of silica gel (elution with 25% EtOAc/hexane) gave 1.15 g (90%) of *N*-phenyl-3-bromobenzenesulfonamide as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.93 (t, J = 1.8 Hz, 1H), 7.69−7.64 (m, 2H), 7.33−7.24 (m, 3H), 7.15−7.07 (m, 3H), 6.92 (s, 1H) ppm; MS (EI) m/z 311 (M^+). *n*-BuLi (1.9 mL, 3.04 mmol) was added to a solution of the above aryl bromide (0.970 g, 3.10 mmol) in THF (55 mL) at −78 °C, and the resulting mixture was stirred for 10 min. Cyclopropanecarboxaldehyde (0.35 mL, 4.68 mmol) was added, and the reaction mixture was stirred another 1.5 h. The mixture was diluted with water and EtOAc and then treated with 5% HCl and brine. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography (elution with 5% MeOH/CH_2Cl_2) gave 0.517 g (55%) of **30** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.26−7.20 (m, 2H), 7.12−7.06 (m, 3H), 6.99 (s, 1H), 3.98 (d, J = 8.4 Hz, 1H), 1.08−1.03 (m, 1H), 0.62−0.28 (m, 4H) ppm; MS (EI) m/z 303 (M^+); HRMS (EI) calcd for $C_{16}H_{17}NO_3S$ 303.0929, found 303.0917.

***N*-Phenyl-3-[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cyclooct[*b*]pyran-3-yl)methyl]benzenesulfonamide (31).** A mixture of **30** (0.437 g, 1.44 mmol), **3b** (0.283 g, 1.45 mmol), *p*-toluenesulfonic acid (0.052 g, 0.27 mmol), and molecular sieves in CH_2Cl_2 (100 mL) was heated to reflux for 1.5 h and then concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with water, and washed twice with 1 N NaOH. The combined aqueous layers were treated with 5% HCl and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Column chromatography on 80 g of silica gel (elution with 50% EtOAc/hexane) gave 0.067 g (10%) of **31** as a white solid: mp 200−203 °C; ^{1}H NMR (CD_3OD) δ 7.82 (s, 1H), 7.60 (d, J = 7.4 Hz, 1H), 7.54 (d, J = 7.3 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.19−7.14 (m, 2H), 7.06−7.03 (m, 3H), 3.37 (d, J = 10.2 Hz, 1H), 2.73−2.50 (m, 4H), 1.90−1.37 (m, 9H), 0.76−0.61 (m, 1H), 0.53−0.40 (m, 1H), 0.29−0.09 (m, 2H) ppm; MS (FAB) m/z 480 ([M + H]$^+$); HRMS (FAB) calcd for [$C_{27}H_{29}NO_5S$ + H] 480.1845, found 480.1850.

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(15) In our previous communication (ref 13) we reported that the presence of the *p*-cyano substituent causes a shift of the sulfonamide which weakens the hydrogen-bonding interaction between the NH of the inhibitor and the Gly 48 residue. Further refinement of the HIV protease complexes with **8h** and **51a** indicates that this is not the case.

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