Structure-Based Design of Nonpeptidic HIV Protease Inhibitors from a Cyclooctylpyranone Lead Structure

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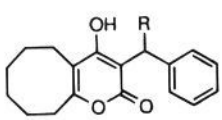
Received June 19, 1995®

Recently, the novel cyclooctylpyranone HIV protease inhibitor **1** was identified in our labs, and an X-ray structure of this inhibitor complexed with HIV-2 protease was obtained. This crystal structure was used to develop two strategies for creating derivatives of **1** with enhanced enzyme inhibitory activity. The first strategy, substitution on the cyclooctyl ring, met with limited success, but provided some interesting information about the conformationally-flexible cyclooctyl ring on the inhibitors. The second strategy, substitution at the *meta* position of the aryl ring, was far more successful and generated compounds, such as the carboxamide derivatives **41** ($K_i = 3.0 \pm 0.4$ nM) and **36** ($K_i = 4.0 \pm 0.8$ nM), which were significantly more active than the corresponding unsubstituted cyclooctylpyranone **2** ($K_i = 11.7 \pm 4.7$ nM). An X-ray crystal structure of **36** complexed with HIV-1 protease indicated the increase in binding affinity is most likely due to the additional interactions between the amide substituent and the S3 region of the protease.

Introduction

Inhibition of the HIV protease enzyme represents a promising therapeutic strategy for treatment of the escalating problem of HIV infection.[1] Although a number of HIV protease inhibitors have been identified to date, the majority of the more effective inhibitors are peptide-derived structures.[2] Such structures, however, often suffer from poor pharmacokinetic properties, such as low oral bioavailability and rapid excretion, thus limiting their usefulness as clinical agents.[3] The search for small, nonpeptidic protease inhibitors has focused on 4-hydroxypyrone and 4-hydroxycoumarin structures identified through screening efforts.[4] Using a 4-hydroxycoumarin structure as our lead, we recently discovered the cyclooctylpyranone inhibitors **1** and **2**.[5] The cyclooctylpyranone **2** showed good inhibitory activity of the HIV proteases ($K_i = 11.7 \pm 4.7$ nM against HIV-1, $K_i = 16$ nM against HIV-2) and excellent pharmacokinetic properties in rats ($F = 91–99\%$, $t_{1/2} = 4.9$ h). These factors, combined with the easy accessibility of the new inhibitor (synthesis in only three steps), made it an excellent template for further drug design.



1 R = Et
2 R = cPr
3 R = H

An X-ray crystal structure of **1** complexed with HIV-2 protease showed that the pyrone ring of this cyclooctylpyranone inhibitor binds into the active site and the substituents on the pyrone ring occupy three of the adjacent enzyme pockets.[5,6] The cyclooctyl ring folds into the S1′ pocket of the enzyme, while the two substituents α to the C-3 position of the pyrone ring, the ethyl group and the phenyl group, occupy the S1 and S2 regions, respectively (Figure 1). It is interesting to note that the cyclooctylpyranone analog with an unbranched substituent at the C-3 position (**3**), which is presumably only able to occupy two of the enzyme pockets adjacent to the active site, was far less active against the HIV protease (no enzyme inhibition at 30

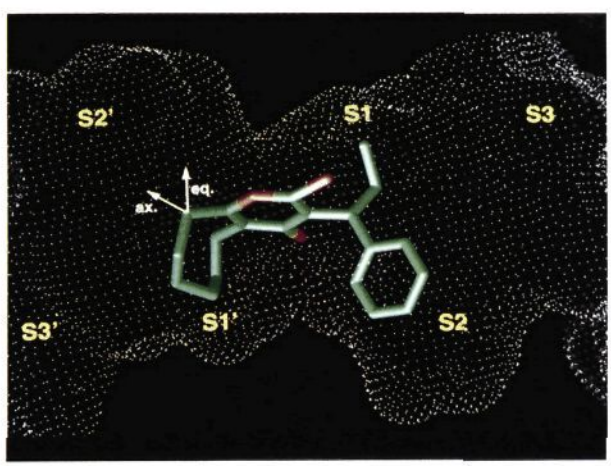


Figure 1. X-ray crystal structure of **1** (green with oxygen atoms shown in red) complexed with HIV-2 protease (represented by the white dot surface) showing the substituents of the pyrone ring occupying three of the enzyme pockets adjacent to the active site. The ethyl group is found in the S1 region, the phenyl group occupies the S2 region, and the cyclooctyl ring folds into the S1′ region. The arrows shown on the C-6 α position of the cyclooctyl ring indicate the two possible trajectories for a substituent at this position of the ring, provided the resulting inhibitor assumes the same binding conformation as that shown for **1**.

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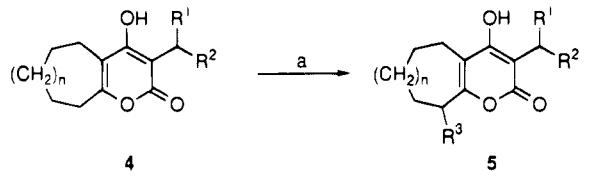
® Abstract published in *Advance ACS Abstracts,* October 1, 1995.

0022-2623/95/1838-4463$09.00/0

Scheme 1[a]



4 5

n = 1 or 2
R¹ = Et, R² = Ph; R¹ = cPr, R² = Ph; or R¹ = R² = cPr

[a] (a) 2 equiv of LDA, THF, −40 °C; then, R³X.

μM).[5] We became interested in exploring this relationship between the enzyme inhibitory activity of a compound and the number of pockets adjacent to the active site that the structure is able to occupy. If this straightforward relationship did exist, we surmised that we could design more potent enzyme inhibitors simply by substituting our lead structures, **1** and **2**, in a manner that would allow the new substituents to interact with previously-unoccupied regions of the protease near the active site.

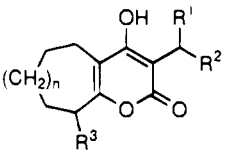
Substitution on the Cycloalkyl Ring. Study of the X-ray structure of **1** complexed with HIV-2 protease suggested two potential sites for substitution, one of which was on the cyclooctyl ring. It appeared to be possible to reach the S2′ region of the HIV protease by substituting on this alkyl ring at the carbon α to the C-6 position of the pyrone ring (see Figure **1**). We were cautioned, however, by the well-established flexibility of the cyclooctyl ring,[5] a factor which has the potential to introduce a number of variables into the predictive process and thus complicate inhibitor design. We also noted that two protons could be substituted at the C-6 α position. In the conformation shown in the X-ray structure, axial substitution (ax. arrow in Figure **1**) would vector the substituent in the desired direction, whereas equatorial substitution (eq. arrow in Figure 1) would be more likely to collide with the protein atoms.

Since alkylation at the C-6 α position of the cycloalkylpyranones is a straightforward process, we started our investigation by generating mixtures of diastereomers for evaluation in the enzyme inhibition assay. A dianionic intermediate can be formed from inhibitors with the structure of **4** using 2 equiv of LDA, and subsequent addition of an alkyl halide produces the desired products **5** (Scheme 1). This transformation works well for cycloalkylpyranones (**4**) with various substituents at the C-3 position of the pyrone ring and with various ring sizes.

Table 1 lists the substituted derivatives and their enzyme inhibitory activities; also listed are the unsubstituted compounds to allow for comparison.[7] Use of quite small (i.e. Me, **6**) and relatively large (i.e. benzyl, **7** and **9**) substituents resulted in decreases in enzyme inhibitory activity relative to the unsubstituted inhibitors **1** and **8**. Increasing the flexibility of the large substituent was also not beneficial, as is illustrated by **16**, which was considerably less active than its unsubstituted parent **2**. Substitution of smaller groups, however, on inhibitor **2** produced several derivatives which were good inhibitors (K_i < 35 nM), but even the best of these analogs (**14**, K_i = 24 nM) was, at best, comparable to the unsubstituted inhibitor **2**.

The possibility that the cyclooctyl ring on the compounds substituted above might be too large and

Table 1



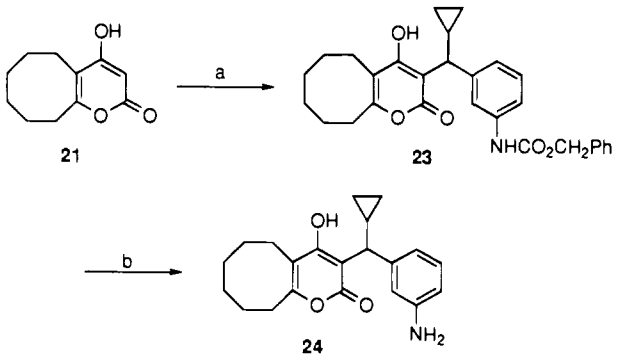
no.	n	R¹	R²	R³	K_i (nM)[a]
1	2	Et	Ph	H	58.3 ± 26.1
6	2	Et	Ph	Me	330
7	2	Et	Ph	CH_2Ph	266 ± 69
8	2	cPr	cPr	H	57
9	2	cPr	cPr	CH_2Ph	260
2	2	cPr	Ph	H	11.7 ± 4.7
10	2	cPr	Ph	Et	33
11	2	cPr	Ph	*n*-Pr	26
12	2	cPr	Ph	*n*-Bu	31
13	2	cPr	Ph	CH_2*i*-Pr	30
14	2	cPr	Ph	CH_2cPr	24
15	2	cPr	Ph	$(CH_2)_2$*i*-Pr	50
16	2	cPr	Ph		120
17	1	cPr	Ph	H	96
18	1	cPr	Ph	CH_2OCH_3	nd[b]
19	1	cPr	Ph	$(CH_2)_2OCH_3$	28
20	1	cPr	Ph	CH_2cPr	24

[a] K_i determinations were generally performed once except for the control compounds included to validate each experiment. The error determined in calculating the K_i value is derived from the fit of the data points to the theoretical curve for a competitive enzyme inhibitor (see ref 7). For those compounds which were tested more than once, the average K_i value with the standard error from the mean is given. For the control compounds tested, the values were 0.82 ± 0.11 μM (phenprocoumon,[7] n = 2), 45.3 ± 9.3 nM (U-96988,[7] n = 6), and 11.7 ± 4.7 nM (**2**, n = 8). [b] nd indicates K_i value was not determined due to relatively low protease inhibition.

substitution could therefore lead to steric crowding led us to investigate substitution of the somewhat smaller seven-membered ring analog **17**. In fact, two of the three substituted derivatives of **17** shown in Table 1 are significantly better protease inhibitors than unsubstituted parent compound. Substitution of a methylcyclopropyl group (**20**) or a methoxy ethyl ether (**19**) was quite favorable. Substitution of a methoxy methyl ether (**18**), however, resulted in a very poor inhibitor.

The results discussed above indicate this strategy of substitution on the cycloalkyl ring is a promising way to increase the enzyme inhibitory activity of the cycloheptylpyranones, but it is a less successful tactic for improving the potency of the cyclooctylpyranones. As was noted above, the conformational flexibility of medium-sized rings has been well-documented. It is very likely that the conformational preferences of these rings change as the rings are substituted and that the size of the ring influences those preferences. In the case of the substituted cyclooctylpyranones, for example, conformational analysis[8] of the unbound ligand with the *S*-configuration at the C-6 α position indicated that this inhibitor was 3.1 kcal less stable in the axial orientation, which would project toward the S2′ site, than in an equatorial orientation. Any productive interaction with the enzyme obtained by this substitution would be reduced by the amount of this conformational bias. On

Scheme 2[a]



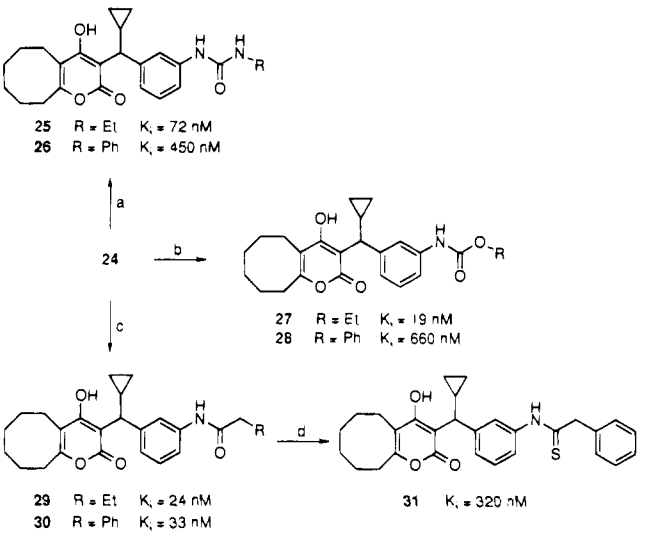
[a] Reagents: (a) c-PrCH(OH)-*m*-(NHCO$_2$CH$_2$Ph)Ph (**22**), *p*-TsOH, toluene, 62%; (b) Pd/C, cyclohexene, reflux, 68%.

the other hand, a similar analysis of the seven-membered analog revealed only a 0.95 kcal bias against the axial form. In this case, the same productive interaction of the substituent with the S2′ site would have less of a conformational bias to work against, providing a greater contribution toward potency relative to that of the eight-membered series.

As noted above, the new inhibitors shown in Table **1** are all diastereomeric mixtures. We chose to further investigate the potential of this substitution strategy by separating one of the more active mixtures, **11**, into its four-component diastereomers.[10] Two of these stereoisomers, **11c** (K_i = 15 ± 2.8 nM) and **11e** (K_i = 9 ± 1 nM), proved to be considerably more active than the other two isomers, **11b** (K_i = 210 ± 65 nM) and **11f** (K_i = 90 ± 30 nM). Presumably, the two more active stereoisomers are better able to achieve a favorable binding conformation than the other two stereoisomers, but the overall gain in binding affinity relative to the unsubstituted compounds **2** and **2b** is still negligible, indicating that the energy penalty to achieve this conformation is still significant. This is in contrast to the unsubstituted cyclooctylpyranone **2**, where the lowest energy conformation of the molecule in its unbound state is very similar to its conformation when bound.[5] Although this C-6 α substitution strategy did not provide a strategy for dramatic improvement of the enzyme inhibitory activity of the lead structure, it did allow us to make some interesting observations about the binding behavior of these conformationally-flexible, medium-sized rings, which are an unusual structural feature in enzyme inhibitors.

Substitution of the Aryl Ring. The second potential substitution site on the lead structure is found on the opposite side of our lead structure, away from the conformational complexities associated with the cyclooctyl ring. Study of the X-ray crystal structure of **1** and related compounds[11] complexed with HIV proteases indicated a substituent at the *meta* position of the phenyl ring could potentially reach the S3 region of the protease (see Figure 1). Molecular modeling, which included overlay of the related 4-hydroxypyrone template with a peptidic protease inhibitor, indicated a hypothetical *meta* substituent on the phenyl ring of the nonpeptidic inhibitor would overlap with an amide bond of the peptidic inhibitor.[11] This observation prompted us to explore the potential for hydrogen bonding by substituting polar functional groups, which were linked to nonpolar groups designed to interact with the hydrophobic S3 region of the enzyme, at the phenyl group's *meta* position.

Scheme 3[a]



[a] Reagents: (a) RN=C=O, CH_3CN, 63–74%; (b) $ClCO_2R$, pyridine, 0 °C, 60–78%; (c) RCH_2CO_2H, BOP·Cl, Et_3N, CH_2Cl_2, 53–61%; (d) Lawesson's reagent, $PhCH_3$, reflux 54%.

Our first step was to establish a chemical handle at the desired *meta* position of the phenyl ring of the lead cyclooctylpyranone structure **2**. Since a number of different polar functional groups could be derived from an amine intermediate (**24**), this was chosen as our initial target. Synthesis of **24** was accomplished in two steps from the known cyclooctylpyranone **21** (Scheme 2). Alkylation of this cyclooctylpyranone using the secondary alcohol **22** yielded the C-3-substituted cyclooctylpyranone **23**. The protecting group on the amine was then removed under transfer hydrogenation conditions. The resulting intermediate amine (**24**) showed moderate HIV protease inhibitory activity (K_i = 78 nM).

Compounds with four different functional groups were subsequently derived from the amine intermediate **24** (Scheme 3). Reaction of the amine **24** with isocyanates yielded the urea derivatives **25** and **26**,[12] and a similar reaction with chloroformates produced the desired carbamates **27** and **28**.[13] The amide analogs **29** and **30** were prepared from **24** and the appropriate carboxylic acid in the presence of bis(2-oxo-3-oxazolidinyl)phosphinic chloride.[14] The thioamide **31** was then generated by reaction of **30** with Lawesson's reagent.[15] Of this group of compounds, the best enzyme inhibition values were observed with the ethyl carbamate **27** (K_i = 19 nM) and the two amide derivatives, **29** (K_i = 24 nM) and **30** (K_i = 33 nM).

An X-ray crystal structure of **27** complexed with the HIV-1 protease was obtained (Figure 2), and this structure showed a binding pattern very similar to the unsubstituted cyclooctylpyranone **1**. As expected, the pyrone ring bound into the active site of the protease and formed hydrogen bonds with the Asp 25, Asp 25′, Ile 50, and Ile 50′ residues of the protease. The cyclooctyl ring then folded into the S1′ region, the cyclopropyl group occupied the S1 region, and the aryl ring filled the S2 region. The carbamate functional group, however, was able to form additional hydrogen bonds with the Gly 48′, Asp 29′, and Asp 30′ residues of the protease. These hydrogen-bonding interactions,

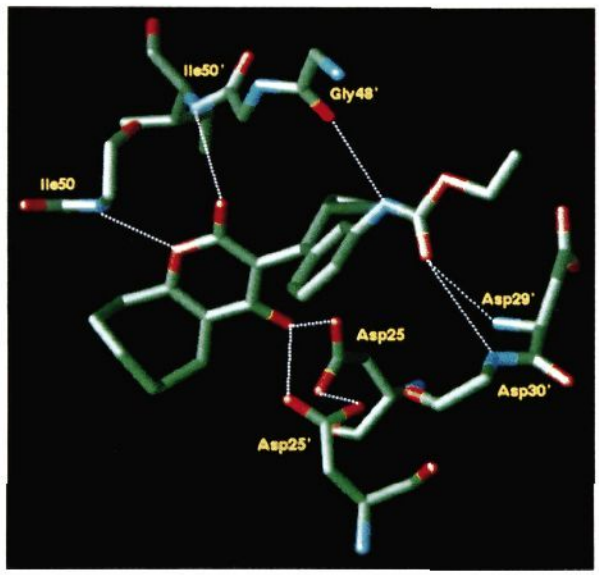
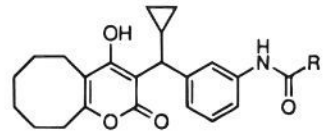
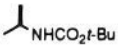


Figure 2. X-ray crystal structure of inhibitor **27** complexed with HIV-1 protease showing the hydrogen bonds formed between the inhibitor and enzyme residues (carbon atoms are shown in green, nitrogen atoms in blue, and oxygen atoms in red). The hydrogen bonds observed in the active site between the 4-hydroxyl group of the pyrone ring and the Asp 25 and Asp 25′ residues are very similar to those seen for other cyclooctylpyranone inhibitors, including **1**. Inhibitor **27** is able to form additional weak hydrogen bonds, however, between the carbonyl of the carbamate group and the Asp 29′ (3.67 Å) and Asp 30′ (3.57 Å) residues. A hydrogen bond is also formed between the NH of the carbamate group and the Gly 48′ residue (3.28 Å).

Table 2



no.	R	K_i (nM)
32	Ph	42
33	*p*-FPh	55
34		470
35		5.5 ± 1.8[a]
36		4.0 ± 0.8[a]
37		14
38		6.9
39		32
40		43
41		3.0 ± 0.4[a]
42		11

[a] K_i values were determined three times.

however, are relatively weak and are not likely to enhance the binding affinity of this analog. This observation is consistent with the similar K_i values measured for **27** and the unsubstituted analog **2**.

Encouraged by the new hydrogen-bonding interactions shown in the X-ray crystal structure of **27** complexed with HIV protease and the reasonably good enzyme inhibitory activity of **29** and **30**, we chose to further explore the amide derivatives of **2**. First, a few additional amide derivatives with aryl substitution were synthesized and evaluated (Table 2). Although the phenyl (**32**) and *p*-fluorophenyl (**33**) analogs both showed fairly good enzyme inhibitory activity, these derivatives were clearly not more potent than the unsubstituted lead structure **2**. Coupling of the amide **24** with several *N*-BOC-protected amino acids, however, produced a number of potent amide derivatives (Table 2). In fact, two of these compounds, **36** and **41**, were significantly more active against the HIV-1 protease than the unsubstituted cyclooctylpyranone **2**.

Several interesting structure–activity relationships emerged from amide derivatives formed by coupling of various amino acids to **24**. The analogs with one- and two-carbon chains, **35** and **36**, both had K_i values lower than the derivative with a three-carbon chain, **37**. There is some space for substitution on the carbon chain at the position α to the amide. Both the L-alanine (**38**) and the L-histidine (**41**) derivatives were very good enzyme inhibitors with K_i values of 6.9 and 3.0 nM, respectively. On the other hand, the cyclic analog **40**, which was derived from L-proline, had a much higher K_i value (43 nM). Control of the chiral center α to the amide also appears to be important. The D and L amino acids of alanine and histidine were coupled to the aniline **24** to form **38**, **39**, **41**, and **42**. In both cases, the L amino acid produced the more potent enzyme inhibitor.

An X-ray crystal structure of **36** complexed with HIV-1 protease was also obtained (Figure 3). Once again, the pyrone ring formed hydrogen-bonding interactions with the Asp 25, Asp 25′, Ile 50, and Ile 50′ residues of the active site, and the cyclooctyl, cyclopropyl, and aryl substituents occupied the S1′, S1, and S2 regions of the protease, respectively, as in the case of the unsubstituted cyclooctylpyranone **1**. Also, as in the case of the ethyl carbamate derivative **27**, the amide functional group was able to form weak hydrogen bonds with the Gly 48′, Asp 29′, and Asp 30′ residues of the protease. The superior binding affinity of the amide **36** appears to be related to its ability to occupy the S3 region of the protease. The NH of the *tert*-butyl carbamate appears to be forming a hydrogen bond with a water molecule (2.79 Å), which is in turn hydrogen bonding with the Asp 29′ residue (3.76 Å). The X-ray crystal structure also indicates that the *tert*-butyl group fits into the hydrophobic pocket of the S3 region. Presumably, these hydrophobic interactions are making an important contribution to the increased binding affinity of **36** relative to the unsubstituted parent compound **2**.

Several of the more active derivatives of **2** synthesized above were evaluated in an antiviral assay (Table 3).[16] Inhibitor **11e**, which had an IC_{50} value of 5.3 μM in this assay, was more than 10-fold more active than the unsubstituted analog **2** (IC_{50} = 60 μM). Several of the *m*-carboxamide derivatives, including **36** (IC_{50} = 33 μM),

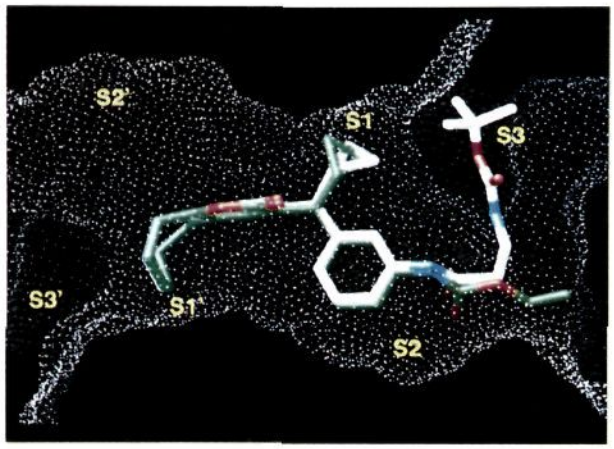


Figure 3. X-ray crystal structure of **36** (white) complexed with HIV-1 protease (represented by the white dot surface) compared to the X-ray crystal structure of **27** (green). Inhibitor **36** is able to form the same hydrogen-bonding interactions as **27**, and the cyclooctyl ring, cyclopropyl group, and the aryl ring occupy the same regions of the enzyme (S1′, S1, and S2, respectively). The *N*-BOC-protected amine substituent, however, is able to fold into the S3 region, which cannot be reached by the ethyl substituent of **27**. Presumably, the additional binding interactions in the S3 region account for much of the enhanced enzyme inhibitory activity of **36** relative to **27**.

Table 3

no.	enzyme inhibitory activity, K_i (nM)[a]	antiviral activity, IC_{50} (μM)[b]
2	11.7 ± 4.7	57.3
11e	9 ± 1	5.3
25	72	>60
26	450	21.7
29	240	35.1
30	33	17.3
32	420	23.5
33	55	21.9
34	470	17.1
35	5.5 ± 1.8	29.8
36	4.0 ± 0.8	33.4
37	14	49.5
38	6.9	31.8
39	32	>60
40	43	29.2
41	3.0 ± 0.4	45.3

[a] HIV protease inhibition was measured against HIV-1 protease and K_i values were determined as described in ref 7. [b] Antiviral activity was measured in HIV-1-infected H9 cells as described in ref 16.

showed an approximately 2-fold increase in antiviral activity. There is, however, a poor correlation between the enzyme inhibitory activity and the antiviral activity of these protease inhibitors. The X-ray crystal structures and modeling techniques are excellent tools for designing structures with enhanced enzyme inhibitory activity, but there are a number of other factors, including protein binding, cell permeability, and intracellular distribution, just to name a few, which can ultimately influence the antiviral activity of an inhibitor.[17]

Conclusions

In summary, the X-ray crystal structure of **1** bound to HIV-protease provided the basis for two strategies with the potential to generate derivatives of the cyclooctylpyranone lead structures with enhanced protease inhibitory activity. The second strategy, substitution at the *meta* position of the phenyl ring, was quite successful and generated compounds which were significantly more active than the lead cyclooctylpyranone **2**. An X-ray crystal structure of the carboxamide derivative **36** complexed with HIV protease indicates this dramatic increase is most likely due to additional interactions between the *tert*-butyl carbamate substituent and the S3 region of the protease. This result, obtained through structure-based drug design, represents an important step forward in our continuing development of potent, nonpeptidic protease inhibitors.

Table 4. Summary of Selected Diffraction Data Collection and Refinement Statistics for the Three HIV Protease Inhibitor Complexes

	complex A	complex B	complex C
protease	HIV-2	HIV-1	HIV-1[a]
inhibitor	**1**	**36**	**27**
space group	$P2_12_12_1$	$P6_122$	$P2_12_12_1$
unit cell			
a (Å)	33.38	63.36	60.28
b (Å)	45.28	63.36	88.52
c (Å)	133.36	84.19	46.46
resolution (Å)	2.3	2.6	2.5
no. of observations	33887	45388	38538
unique reflections	8579	5940	9067
% complete	90	100	99.7
R merge	0.064	0.118	0.92
R factor (refinement)	0.187	0.156	0.167
rms deviations			
distance (Å)	0.034	0.020	0.017
angle (deg)	4.021	2.897	2.662
fixed dihedrals (deg)	10.581	10.004	8.162
flexible dihedrals (deg)	16.111	15.214	15.099

[a] In this complex, the protease employed was the triple mutant W7K/L331/L631.

Experimental Section

X-ray Crystallography: (A) Crystallization. The preparation and purification of the recombinant HIV-1 protease, HIV-2 protease, and a triple mutant of HIV-1 protease (Q7K/L33I/L63I) have been described elsewhere.[16,18,19] The protein preparation of HIV-2 protease contains a Lys^{57}/Leu mutation, but has been found to be indistinguishable in activity and specificity from the wild-type enzyme. The crystals of the proteases complexed with the selected inhibitors were obtained by cocrystallization experiments in which 2 μL of the inhibitor solution (0.1 mg/μL concentration) in DMSO was added to 130 μL of the freshly thawed ice-cold protease solution (ca. 6 mg/mL concentration) and the mixture equilibrated on ice for 30 min. The undissolved inhibitor that precipitates upon mixing was removed by centrifugation. In the case of HIV-1 proteases, crystals were grown at room temperature in 4−7 μL hanging drops by vapor diffusion against a precipitant of 0.75−2.0 M NaCl at pH 4.8−5.2 (0.1 M acetate buffer), 5.4−5.8 (0.1 M citrate buffer). In the case of HIV-2 protease, they were grown against a precipitant of 30−35% (w/v) PEG 4000 at pH 6.8−7.6 (0.1 M HEPES buffer). Larger single crystals could occasionally be grown by addition of 1−3% 1-butanol to the well solution.

(B) Data Collection. A single crystal of each complex was used for data collection in all three cases. Diffraction data were collected using a Siemens X-1000 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 an exposure time of 240 s per frame in the cases of complexes A and B and an exposure time of 180 s per frame for complex C. Data sets were processed using XENGEN data reduction software.[20] Table 4 summarizes the data collection statistics of the three data sets along with statistics from the refinement of the models. The effective resolution of each crystal was taken as the maximum resolution for which

the mean I/σ was greater than 2.0. Data beyond this maximum were discarded and not used in the crystallographic refinement.

Structure Refinement. Since the space groups of the protease/inhibitor complexes A, B, and C were the same as ones previously refined in our laboratory, refinement of these protease models could be initiated without resolving the position of the molecule in the cell. Whereas the crystallographic refinement on complex A was performed using the PROLSQ,[21] the structural refinement for the complexes B and C was carried out using CEDAR,[22] with periodic manual rebuilding using the interactive graphics programs FRODO (for complex A)[23] and CHAIN (for complexes B and C),[24] based on $2|F_o - F_c|$ and $|F_o - F_c|$ electron density maps. Electron density maps were calculated using the XTAL package of crystallographic programs.[25] The inhibitors and solvent molecules were added during later stages of the refinements. The atomic coordinates of these structures will be deposited with the Protein Data Bank.[26]

Chemistry. 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 Upjohn Laboratories. Flash chromatography was performed on 230–400 mesh silica gel 60.

Representative Procedure for the Preparation of 6–7, 9–16, and 18–20. 4-Hydroxy-10-methyl-3-(1-phenylpropyl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (6). A 50-mL, three-necked, round-bottomed flask fitted with a nitrogen inlet and a 10-mL, pressure-equalizing addition funnel was charged with diisopropylamine (0.15 mL, 1.08 mmol) and 2 mL of THF, and the addition funnel was charged with a solution of **2** (0.134 g, 0.43 mmol) in 6 mL of THF. The flask was placed in an ice bath, and *n*-butyllithium (0.68 mL of 1.6 M solution in hexanes, 1.08 mmol) was added dropwise. After stirring at 0 °C for 20 min, the reaction mixture was cooled to −40 °C, and the solution of **2** was added dropwise. The resulting bright yellow solution was stirred for 25 min at ca. −40 °C. Iodomethane (0.037 mL, 0.43 mmol) was added dropwise, and the reaction mixture was stirred another 1 h as it warmed to 0 °C. The pale yellow solution was quenched with 10 mL of 10% HCl, and a small amount of NaCl was added. The reaction mixture was then extracted with two 30-mL portions of CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.162 g of a yellow solid. Column chromatography on 25 g of silica gel (elution with 10–20% EtOAc/hexane) yielded 0.057 g (41%) of **6** as a white solid: mp 182–186 °C; ^{1}H NMR ($CDCl_3$) δ 7.44–7.35 (m, 4 H), 7.30–7.25 (m, 1 H), 5.89 (br s, 0.5 H), 5.82 (br s, 0.5 H), 4.43–4.33 (m, 1 H), 3.07–3.00 (m, 1 H), 2.71–2.61 (m, 1 H), 2.24–2.12 (m, 2 H), 2.09–1.98 (m, 1 H), 1.73–1.51 (m, 6 H), 1.39–1.15 (m, 2 H), 1.31–1.28 (m, 3 H), 1.05–0.99 (m, 3 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.4, 163.8, 162.9, 162.8, 141.7, 141.6, 129.4, 127.6, 127.3, 111.0, 110.9, 106.0, 105.9, 41.3, 41.1, 37.9, 33.5, 33.4, 30.2, 30.1, 26.9, 26.0, 24.0, 23.9, 22.8, 22.7, 16.9, 12.3, 12.2 ppm; IR (mineral oil) 3131, 3086, 3058, 3026, 1669, 1632, 1546, 1535 cm^{-1}; MS (EI) *m/z* 326 (M^+). Anal. ($C_{21}H_{26}O_3$) C, H.

10-Benzyl-4-hydroxy-3-(1-phenylpropyl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (7): 0.041 g (32%) of white solid; mp 76–80 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.40–7.30 (m, 4 H), 7.28–7.17 (m, 6 H), 5.77–5.75 (m, 1 H), 4.40–4.35 (m, 1 H), 3.30–3.19 (m, 2 H), 2.88–2.81 (m, 1 H), 2.78–2.59 (m, 1 H), 2.21–1.94 (m, 3 H), 1.70–1.60 (m, 6 H), 1.33–1.23 (m, 2 H), 1.05–0.90 (m, 3 H) ppm; IR (mineral oil) 3158, 3103, 3085, 3061, 1659, 1630, 1543 cm^{-1}; MS (EI) *m/z* 402 (M^+). Anal. ($C_{27}H_{30}O_3$) C, H.

10-Benzyl-3-(dicyclopropylmethyl)-4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (9): 0.085 g (43%) of white solid; mp 94–97 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (br s, 1 H), 7.29–7.14 (m, 5 H), 3.29–3.21 (m, 2 H), 2.89–2.75 (m, 3 H), 2.22–2.13 (m, 1 H), 1.84–1.81 (m, 2 H), 1.77–1.55 (m, 4 H), 1.43–1.31 (m, 2 H), 1.00–0.86 (m, 2 H), 0.53–0.43 (m, 8 H) ppm; ^{13}C NMR ($CDCl_3$) δ 194.4, 164.0, 160.9, 140.2, 128.9, 128.3, 125.9, 111.9, 105.0, 40.9, 39.2, 37.3, 35.2, 30.2, 27.1, 25.6, 23.0, 12.4, 12.2, 3.6, 3.4, 2.5, 2.2 ppm; IR (mineral oil) 3366, 3139, 3078, 3065, 3026, 3000, 1657, 1631, 1543 cm^{-1}; MS (EI) *m/z* 378 (M^+). Anal. ($C_{25}H_{30}O_3$) C, H.

3-(Cyclopropylphenylmethyl)-10-ethyl-4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (10): 0.103 g (44%) of white solid; mp 94–98 °C; ^{1}H NMR ($CDCl_3$) δ 7.54–7.50 (m, 2 H), 7.38 (dd, J = 7.9, 7.0 Hz, 2 H), 7.28 (d, J = 7.0 Hz, 1 H), 6.22 (s, 1 H), 4.05 (d, J = 8.5 Hz, 0.5 H), 3.99 (d, J = 8.8 Hz, 0.5 H), 2.84–2.70 (m, 2 H), 2.23–2.14 (m, 1 H), 2.01–1.97 (m, 1 H), 1.80–1.51 (m, 5 H), 1.39–1.31 (m, 4 H), 0.98–0.86 (m, 4 H), 0.76–0.71 (m, 1 H), 0.64–0.57 (m, 2 H), 0.32–0.27 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.7, 163.8, 162.3, 141.1, 129.2, 128.0, 127.9, 127.5, 112.5, 112.4, 106.0, 105.8, 43.8, 43.6, 41.0, 40.9, 35.7, 30.5, 30.4, 27.3, 25.8, 24.4, 23.1, 13.2, 13.1, 12.8, 5.0, 4.7, 3.8 ppm; IR (mineral oil) 3137, 3075, 3060, 3024, 1658, 1632, 1545 cm^{-1}; MS (EI) *m/z* 352 (M^+). Anal. ($C_{24}H_{28}O_3$) C, H.

3-(Cyclopropylphenylmethyl)-4-hydroxy-10-propyl-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (11): 0.093 g (34%) of white solid; mp 78–84 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (dd, J = 7.4, 2.6 Hz, 2 H), 7.38 (dd, J = 7.4, 7.2 Hz, 2 H), 7.29 (dd, J = 7.2, 2.6 Hz, 1 H), 6.24 (s, 0.5 H), 6.21 (s, 0.5 H), 4.04 (d, J = 8.3 Hz, 0.5 H), 3.98 (d, J = 8.8 Hz, 0.5 H), 2.97–2.91 (m, 1 H), 2.76–2.69 (m, 1 H), 2.18–2.14 (m, 1 H), 2.02–1.94 (m, 1 H), 1.78–1.56 (m, 5 H), 1.36–1.26 (m, 6 H), 1.22–1.07 (m, 1 H), 0.95–0.86 (m, 3 H), 0.77–0.71 (m, 1 H), 0.65–0.57 (m, 2 H), 0.31–0.25 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.7, 163.8, 162.4, 141.1, 129.2, 128.0, 127.9, 127.4, 112.3, 112.2, 106.0, 105.8, 43.8, 43.6, 38.6, 38.5, 35.9, 33.4, 30.5, 30.4, 27.3, 25.8, 25.7, 23.1, 21.2, 14.1, 13.2, 13.1, 5.1, 4.7, 3.8 ppm; IR (mineral oil) 3141, 3075, 3060, 3025, 1658, 1632, 1546 cm^{-1}; MS (EI) *m/z* 366 (M^+). Anal. ($C_{25}H_{30}O_3$) C, H.

10-Butyl-3-(cyclopropylphenylmethyl)-4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (12): 0.178 g (62%) of white solid; mp 78–82 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (dd, J = 2.6, 7.1 Hz, 2 H), 7.38 (dd, J = 7.1, 7.2 Hz, 2 H), 7.29 (dd, J = 2.6, 7.1 Hz, 1 H), 6.22 (br s, 1 H), 4.05 (d, J = 8.3 Hz, 0.5 H), 3.98 (d, J = 8.7 Hz, 0.5 H), 2.92–2.89 (m, 1 H), 2.76–2.69 (m, 1 H), 2.18–2.17 (m, 1 H), 1.98–1.96 (m, 1 H), 1.78–1.59 (m, 6 H), 1.56–1.46 (m, 1 H), 1.40–1.26 (m, 6 H), 1.23–1.09 (m, 1 H), 0.93–0.86 (m, 3 H), 0.76–0.72 (m, 1 H), 0.64–0.57 (m, 2 H), 0.32–0.27 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.6, 163.6, 162.4, 141.0, 129.1, 127.9, 127.8, 127.3, 112.1, 105.9, 43.7, 43.5, 38.8, 38.7, 35.7, 30.9, 30.4, 30.3, 30.2, 27.2, 25.6, 23.0, 22.6, 14.0, 13.1, 13.0, 4.9, 4.6, 3.7 ppm; IR (mineral oil) 3140, 3075, 3060, 3025, 1657, 1632, 1545 cm^{-1}; MS (EI) *m/z* 380 (M^+). Anal. ($C_{25}H_{32}O_3$) C, H.

3-(Cyclopropylphenylmethyl)-4-hydroxy-10-isobutyl-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (13): 0.073 g (26%) of white solid; mp 86–92 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 7.0 Hz, 2 H), 7.37 (dd, J = 7.0, 7.2 Hz, 2 H), 7.29 (d, J = 7.2 Hz, 1 H), 6.21 (s, 0.5 H), 6.20 (s, 0.5 H), 4.04 (d, J = 8.4 Hz, 0.5 H), 3.98 (d, J = 8.7 Hz, 0.5 H), 3.03–2.98 (m, 1 H), 2.74–2.67 (m, 1 H), 2.21–2.18 (m, 1 H), 1.99–1.92 (m, 1 H), 1.79–1.65 (m, 2 H), 1.61–1.57 (m, 4 H), 1.34–1.22 (m, 4 H), 1.19–0.96 (m, 1 H), 0.92–0.87 (m, 6 H), 0.75–0.73 (m, 1 H), 0.63–0.58 (m, 2 H), 0.29–0.28 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.5, 163.6, 162.3, 162.2, 141.0, 129.2, 129.1, 128.1, 128.0, 127.4, 112.0, 105.9, 105.7, 43.7, 43.5, 40.2, 40.1, 36.3, 36.0, 35.9, 30.5, 30.4, 27.3, 26.1, 26.0, 25.6, 23.2, 23.1, 22.4, 22.3, 13.1, 5.0, 4.6, 3.7 ppm; IR (mineral oil) 3134, 3076, 3060, 3025, 1658, 1633, 1545 cm^{-1}; MS (EI) *m/z* 380 (M^+). Anal. ($C_{25}H_{32}O_3$) C, H.

10-(Cyclopropylmethyl)-3-(cyclopropylphenylmethyl)-4-hydroxy-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (14): 0.132 g (49%) of white solid; mp 86–90 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 7.4 Hz, 2 H), 7.38 (dd, J = 7.4, 7.1 Hz, 2 H), 7.30 (d, J = 7.1 Hz, 1 H), 6.23 (br s, 1 H), 4.03 (d, J = 8.6 Hz, 0.5 H), 3.99 (d, J = 8.7 Hz, 0.5 H), 3.07–3.03 (m, 1 H), 2.78–2.73 (m, 1 H), 2.24–2.20 (m, 1 H), 2.02–1.94 (m, 1 H), 1.79–1.56 (m, 5 H), 1.39–1.24 (m, 4 H), 1.21–1.14 (m, 1 H), 0.86–0.64 (m, 2 H), 0.63–0.58 (m, 2 H), 0.43–0.39 (m, 2 H), 0.32–0.27 (m, 1 H), 0.09–0.07 (m, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.5, 163.7, 162.4, 162.3, 141.0, 129.1, 127.9, 127.8, 127.3, 112.0, 105.9, 105.7, 43.6, 43.5, 39.5, 39.4, 36.2, 35.5, 30.4, 30.3, 27.2, 25.7, 25.6, 23.0, 13.1, 13.0, 9.6, 9.5, 4.9, 4.6, 4.4, 3.7, 3.6

ppm; IR (mineral oil) 3141, 3075, 3061, 3024, 1657, 1631, 1545 cm^{-1}; MS (EI) m/z 378 (M^+). Anal. ($C_{25}H_{30}O_3$) C, H.

3-(Cyclopropylphenylmethyl)-4-hydroxy-10-(3-methylbutyl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (15): 0.235 g (76%) of white solid; mp 83–88 °C; ^1H NMR ($CDCl_3$) δ 7.50 (d, J = 8.7 Hz, 2 H), 7.37 (dd, J = 8.7, 7.4 Hz, 2 H), 7.27 (d, J = 7.4 Hz, 1 H), 6.22 (s, 0.5 H), 6.21 (s, 0.5 H), 4.04 (d, J = 8.5 Hz, 0.5 H), 3.98 (d, J = 8.7 Hz, 0.5 H), 2.86–2.80 (m, 1 H), 2.75–2.72 (m, 1 H), 2.21–2.15 (m, 1 H), 1.99–1.89 (m, 1 H), 1.77–1.47 (m, 8 H), 1.37–1.26 (m, 2 H), 1.21–1.11 (m, 3 H), 0.91–0.86 (m, 6 H), 0.77–0.72 (m, 1 H), 0.64–0.60 (m, 2 H), 0.29–0.28 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.7, 165.6, 163.8, 162.5, 162.4, 141.1, 129.3, 129.2, 128.0, 127.9, 127.5, 127.4, 112.2, 106.0, 105.8, 43.8, 43.7, 39.4, 39.3, 37.4, 35.9, 35.8, 30.5, 30.4, 29.2, 29.1, 28.2, 28.1, 27.4, 25.8, 23.2, 22.7, 22.6, 13.3, 13.2, 5.1, 4.7, 3.8 ppm; IR (mineral oil) 3145, 3076, 3060, 3024, 1658, 1632, 1546 cm^{-1}; MS (EI) m/z 394 (M^+). Anal. ($C_{26}H_{34}O_3$) C, H.

3-(Cyclopropylphenylmethyl)-4-hydroxy-10-(tetrahydropyran-2-ylmethyl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (16): 0.41 g (13%) of white solid; mp 88–93 °C; ^1H NMR ($CDCl_3$) δ 7.50 (d, J = 7.7 Hz, 2 H), 7.3 (dd, J = 7.3, 7.7 Hz, 2 H), 7.28 (d, J = 7.3 Hz, 1 H), 6.21 (s, 0.5 H), 6.19 (s, 0.5 H), 4.04–3.94 (m, 2 H), 3.42–3.34 (m, 2 H), 3.21–3.12 (m, 1 H), 2.70–2.68 (m, 1 H), 2.26–2.20 (m, 1 H), 2.04–1.96 (m, 1 H), 1.80–1.69 (m, 4 H), 1.61–1.43 (m, 8 H), 1.34–1.20 (m, 4 H), 0.74–0.73 (m, 1 H), 0.62–0.56 (m, 2 H), 0.29–0.25 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.7, 165.6, 163.9, 162.6, 162.5, 141.1, 129.3, 129.2, 128.1, 128.0, 127.4, 111.7, 111.6, 106.0, 105.9, 74.9, 68.5, 43.8, 43.7, 37.7, 34.9, 34.0, 32.3, 30.4, 27.3, 27.2, 26.2, 25.7, 23.6, 23.0, 13.3, 13.1, 5.1, 4.8, 3.8 ppm; MS (EI) m/z 422 (M^+). Anal. ($C_{27}H_{34}O_4$) C, H.

3-(Cyclopropylphenylmethyl)-6,7,8,9-tetrahydro-4-hydroxy-9-(methoxymethyl)cyclohepta[*b*]pyran-2(5*H*)-one (18): 0.075 g (24%) of white solid; mp 69–71 °C; ^1H NMR ($CDCl_3$) δ 7.54–7.49 (m, 2 H), 7.41–7.35 (m, 2 H), 7.32–7.29 (m, 1 H), 6.25 (br s, 1 H), 3.95 (d, J = 9.1 Hz, 1 H), 3.82–3.76 (m, 1 H), 3.59 (t, J = 9.0 Hz, 1 H), 3.40 (s, 3 H), 3.10–3.07 (m, 1 H), 2.63–2.55 (m, 1 H), 2.40–2.32 (m, 1 H), 1.93–1.84 (m, 2 H), 1.73–1.53 (m, 3 H), 1.47–1.42 (m, 1 H), 1.37–1.30 (m, 1 H), 0.77–0.71 (m, 1 H), 0.66–0.57 (m, 2 H), 0.31–0.26 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.0, 163.7, 162.9, 140.8, 129.1, 128.0, 127.4, 113.4, 106.0, 71.7, 58.8, 43.8, 43.7, 28.3, 28.1, 26.8, 25.9, 25.8, 21.0, 20.9, 13.0, 4.9, 4.0, 3.9 ppm; IR (mineral oil) 3144, 3075, 3060, 3024, 1657, 1544, 1495 cm^{-1}; MS (EI) m/z 354 (M^+). Anal. ($C_{22}H_{26}O_3$) C, H.

3-(Cyclopropylphenylmethyl)-6,7,8,9-tetrahydro-4-hydroxy-9-(methoxyethyl)cyclohepta[*b*]pyran-2(5*H*)-one (19): 0.098 g (31%) of white solid; mp 58–60 °C; ^1H NMR ($CDCl_3$) δ 7.51 (d, J = 7.3 Hz, 2 H), 7.38 (dd, J = 7.2, 7.3 Hz, 2 H), 7.29 (d, J = 7.2 Hz, 1 H), 6.26 (br s, 1 H), 3.96 (d, J = 9.0 Hz, 1 H), 3.46 (dd, J = 5.9, 6.7 Hz, 2 H), 3.33 (s, 3 H), 2.99–2.96 (m, 1 H), 2.50–2.45 (m, 2 H), 2.23–2.17 (m, 1 H), 1.87–1.50 (m, 7 H), 1.34–1.32 (m, 1 H), 0.77–0.72 (m, 1 H), 0.64–0.57 (m, 2 H), 0.31–0.26 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.1, 163.9, 140.9, 129.2, 128.0, 127.9, 127.4, 112.7, 105.7, 70.7, 70.6, 58.6, 43.8, 40.4, 30.7, 29.5, 29.4, 27.3, 27.1, 26.1, 20.9, 20.8, 13.0, 4.9, 3.9 ppm; IR (mineral oil) 3132, 3076, 3060, 3024, 1656, 1543, 1495 cm^{-1}; MS (EI) m/z 368 (M^-). Anal. ($C_{23}H_{28}O_4$) C, H.

9-(Cyclopropylmethyl)-3-(cyclopropylphenylmethyl)-4-hydroxy-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyran-2-one (20): 0.087 g (58%) of white solid; mp 77–83 °C; ^1H NMR ($CDCl_3$) δ 7.52 (dd, J = 7.5, 2.5 Hz, 2 H), 7.38 (dd, J = 7.5, 7.1 Hz, 2 H), 7.29 (dd, J = 7.1, 2.5 Hz, 1 H), 6.21–6.20 (m, 1 H), 4.00–3.96 (m, 1 H), 2.94–2.90 (m, 1 H), 2.60–2.50 (m, 1 H), 2.44–2.33 (m, 1 H), 1.83–1.69 (m, 4 H), 1.64–1.60 (m, 4 H), 1.37–1.26 (m, 2 H), 0.80–0.71 (m, 2 H), 0.65–0.53 (m, 2 H), 0.52–0.38 (m, 2 H), 0.32–0.24 (m, 1 H), 0.13–0.07 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.7, 165.3, 164.0, 140.9, 129.2, 127.9, 127.4, 112.4, 105.6, 44.5, 43.7, 35.4, 28.7, 28.6, 26.6, 26.5, 26.3, 20.7, 13.0, 9.2, 4.9, 4.1, 3.8, 3.7 ppm; IR (mineral oil) 3143, 3076, 3062, 3024, 1654, 1628, 1541 cm^{-1}; MS (EI) m/z 364 (M^+). Anal. ($C_{24}H_{28}O_3$) C, H.

3(*R* or *S*)-(Cyclopropylphenylmethyl)-4-hydroxy-10(*R* and *S*)-propyl-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (11a). (±)-3-(Cyclopropylphenylmethyl)-5,6,7,8,9,10-hexahydro-4-hydroxy-2*H*-cycloocta[*b*]pyran-2-one[5] was alkylated using iodopropane as described in the general procedure above: ^1H NMR ($CDCl_3$) δ 7.53–7.50 (m, 2 H), 7.38 (dd, J = 7.8, 7.2 Hz, 2 H), 7.30–7.28 (m, 1 H), 6.19 (s, 0.5 H), 6.16 (s, 0.5 H), 4.05 (d, J = 8.3 Hz, 0.5 H), 3.99 (d, J = 8.8 Hz, 0.5 H), 2.93–2.90 (m, 1 H), 2.76–2.65 (m, 1 H), 2.18–2.10 (m, 1 H), 2.01–1.94 (m, 1 H), 1.78–1.41 (m, 5 H), 1.37–1.27 (m, 6 H), 1.22–1.13 (m, 1 H), 0.97–0.83 (m, 3 H), 0.77–0.73 (m, 1 H), 0.63–0.58 (m, 2 H), 0.29–0.26 (m, 1 H) ppm; MS (EI) m/z 366 (M^+); HRMS calcd for $C_{24}H_{30}O_3$ 366.2195, found 366.2200.

Separation of 11a into Component Diastereomers 11b and 11c. Separation was carried out using a 2.1 × 25 cm Chiralcel OD column as the chiral stationary phase and 1.5% ethanol and 0.2% acetic acid in hexane (v/v) as the mobile phase (16 mL/min). A UV detector at 295 nm was used to monitor the separation of 2 mg of racemate/run.

3(*R* or *S*)-(Cyclopropylphenylmethyl)-4-hydroxy-10(*R* or *S*)-propyl-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (11b): t_R = 16 min.

3(*R* or *S*)-(Cyclopropylphenylmethyl)-4-hydroxy-10(*R* or *S*)-propyl-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (11c): t_R = 19 min.

3(*R* or *S*)-(Cyclopropylphenylmethyl)-4-hydroxy-10(*R* and *S*)-propyl-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (11d). (±)-3-(Cyclopropylphenylmethyl)-5,6,7,8,9,10-hexahydro-4-hydroxy-2*H*-cycloocta[*b*]pyran-2-one[5] was alkylated using iodopropane as described in the general procedure above: ^1H NMR ($CDCl_3$) δ 7.53–7.50 (m, 2 H), 7.37 (dd, J = 7.8, 7.3 Hz, 2 H), 7.30–7.28 (m, 1 H), 6.18 (s, 0.5 H), 6.16 (s, 0.5 H), 4.05 (d, J = 8.3 Hz, 0.5 H), 3.99 (d, J = 8.8 Hz, 0.5 H), 2.96–2.93 (m, 1 H), 2.78–2.73 (m, 1 H), 2.18–2.10 (m, 1 H), 2.01–1.94 (m, 1 H), 1.78–1.43 (m, 5 H), 1.38–1.22 (m, 6 H), 1.19–1.13 (m, 1 H), 0.97–0.86 (m, 3 H), 0.78–0.69 (m, 1 H), 0.63–0.58 (m, 2 H), 0.29–0.26 (m, 1 H) ppm; MS (EI) m/z 366 (M^+); HRMS calcd for $C_{24}H_{30}O_3$ 366.2195, found 366.2200.

Separation of 11d into Component Diasteromers 11e and 11f. Separation was carried out using a 2.1 × 25 cm Chiralcel OD column as the chiral stationary phase and 4.5% ethanol and 0.2% acetic acid in hexane (v/v) as the mobile phase (16 mL/min). A UV detector at 295 nm was used to monitor the separation of 2 mg of racemate/run.

3(*R* or *S*)-(Cyclopropylphenylmethyl)-4-hydroxy-10(*R* or *S*)-propyl-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (11e): t_R = 60 min.

3(*R* or *S*)-(Cyclopropylphenylmethyl)-4-hydroxy-10(*R* or *S*)-propyl-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyran-2-one (11f): t_R = 70 min.

[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 (23). A 500-mL, three-necked, round-bottomed flask with a Dean–Stark trap and nitrogen inlet was charged with *p*-toluenesulfonic acid (0.635 g) and 240 mL of toluene and warmed to reflux to remove ca. 40 mL of water. The solution was allowed to cool to room temperature, and cyclooctylpyranone **21**[27] (2.54 g, 13.1 mmol) and alcohol **22**[5] (3.83 g, 12.9 mmol) were added. The resulting mixture was then stirred at room temperature for ca. 16 h. The reaction mixture was diluted with 700 mL of EtOAc and washed with three 75-mL portions of water, two 75-mL portions of saturated $NaHCO_3$(aq), and another 75-mL portion of water. The organic layer was then concentrated *in vacuo* to give 6.5 g of a foam. Column chromatography on 150 g of silica gel (elution with 30–50% ethyl acetate/hexane) yielded 3.81 g (62%) of **23** as a white solid: mp 113–115 °C dec; ^1H NMR ($CDCl_3$) δ 7.48 (s, 1 H), 7.38–7.26 (m, 7 H), 7.17 (d, J = 7.3 Hz, 1 H), 6.70 (s, 1 H), 6.29 (br s, 1 H), 5.20 (s, 2 H), 3.95 (d, J = 8.7 Hz, 1 H), 2.64–2.60 (m, 2 H), 2.47–2.43 (m, 2 H), 1.76–1.72 (m, 2 H), 1.61–1.42 (m, 7 H), 0.73–0.72 (m, 1 H), 0.63–0.55 (m, 2 H), 0.29–0.26 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.6, 164.0, 161.3, 153.0, 142.2, 138.5, 135.8, 129.9, 128.5, 128.3, 128.2, 122.9, 117.9, 117.6, 110.7, 106.0, 67.0, 43.7, 30.7, 29.1, 28.8, 26.2, 25.8, 22.1, 13.0, 4.9, 3.8 ppm; IR (mineral oil) 3383, 3304, 3211, 3147, 3075, 3032, 1734, 1698, 1665, 1666, 1633, 1610, 1595, 1553, 1491, 1222 cm^{-1}; MS (EI) m/z 473 (M^+); HRMS calcd for $C_{29}H_{31}NO_5$ 473.2201, found 473.2202.

3-[(3-**Aminophenyl)cyclopropylmethyl]-5,6,7,8,9,10-hexahydro-4-hydroxy-2*H*-cycloocta[*b*]pyran-2-one (24).** In a 100-mL, three-necked, round-bottomed flask with a reflux condenser and nitrogen inlet, 10% palladium on carbon (1.0 g) was added to a mixture of **23** (1.95 g, 4.12 mmol) in cyclohexene (50 mL), and the mixture was refluxed for 4 h. The mixture was then filtered through Celite, washed with CH_2Cl_2, and concentrated to give 1.25 g (90%) of **24** as a white solid. An analytical sample was purified by column chromatography on silica gel (elution with 30–75% ethyl acetate/hexane): mp 75–79 °C; ^{1}H NMR ($CDCl_3$) δ 7.16 (dd, J = 7.8 Hz, 1 H), 6.96 (d, J = 7.8 Hz, 1 H), 6.84 (s, 1 H), 6.63 (d, J = 7.8 Hz, 1 H), 5.67 (s, 1 H), 3.88 (d, J = 8.8 Hz, 1 H), 2.63–2.59 (m, 2 H), 2.48–2.37 (m, 2 H), 2.00–1.97 (m, 1 H), 1.79–1.71 (m, 2 H), 1.63–1.41 (m, 5 H), 1.36–1.26 (m, 1 H), 0.74–0.65 (m, 1 H), 0.61–0.53 (m, 2 H), 0.28–0.22 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.8, 164.2, 161.1, 142.8, 130.2, 117.7, 117.6, 114.7, 114.5, 110.9, 106.2, 43.5, 30.6, 29.1, 28.8, 26.2, 25.8, 22.1, 12.8, 4.7, 3.7 ppm; IR (mineral oil) 3359, 3209, 3074, 1660, 1619, 1605, 1590, 1551, 1491, 1447, 1404 cm^{-1}; MS (EI) m/z 339 (M^+); HRMS calcd for $C_{21}H_{25}NO_3$ 339.1834, found 339.1845.

***N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]-*N'*-ethylurea (25).** In a flame-dried, 10-mL, two-necked flask under nitrogen, ethyl isocyanate (0.021 g, 0.29 mmol) was added dropwise to a solution of **24** (0.100 g, 0.29 mmol) in 1 mL of CH_3CN. The reaction mixture was stirred at room temperature for 24 h, and then the white precipitate was collected by filtration to yield 0.075 g (63%) of **25**. An analytical sample was recrystallized from $CHCl_3$: mp 215 °C dec; ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.40 (s, 1 H), 7.18 (d, J = 5.3 Hz, 2 H), 7.10 (m, 1 H), 3.48 (d, J = 9.68 Hz, 1 H), 3.23 (q, J = 7.2 Hz, 2 H), 2.62 (t, J = 6.1 Hz, 2 H), 2.53 (t, J = 6.2 Hz, 2 H), 1.74 (m, 3 H), 1.63 (m, 2 H), 1.47 (m, 4 H), 1.15 (t, J = 7.2 Hz, 3 H), 0.72 (m, 1 H), 0.52 (m, 1 H), 0.29 (m, 2 H) ppm; ^{13}C NMR (DMSO-d_6) δ 163.9, 163.4, 160.2, 155.2, 144.3, 140.1, 128.0, 120.3, 116.9, 115.2, 110.1, 106.1, 44.7, 34.0, 30.3, 29.2, 28.7, 26.0, 25.4, 21.9, 15.6, 12.6, 6.6, 3.8 ppm; IR (mineral oil) 1682, 1660, 1631, 1595, 1562, 1535, 1448, 1408 cm^{-1}; HRMS (FAB, M + 1) calculated 411.2284, found 411.2293. Anal. ($C_{24}H_{30}N_2O_3$) 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]-*N'*-phenylurea (26)** was prepared as described above for **25**: 0.197 g (74%) of white solid; mp 214–215 °C; ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.43 (m, 3 H), 7.31–7.13 (m, 5 H), 7.03 (t, J = 7.1 Hz, 1 H), 3.47 (d, J = 9.6 Hz, 1 H), 2.62 (m, 2 H), 2.55 (m, 2 H), 1.75 (m, 3 H), 1.64 (m, 2 H), 1.48 (m, 4 H), 0.73 (m, 1 H), 0.52 (m, 1 H), 0.29 (m, 2 H) ppm; ^{13}C NMR (DMSO-d_6) δ 163.9, 163.3, 160.2, 152.5, 144.6, 139.8, 139.3, 128.8, 128.1, 121.8, 121.2, 118.1, 117.4, 115.6, 110.1, 106.0, 44.7, 30.3, 29.2, 28.7, 26.0, 25.5, 22.0, 12.6, 6.6, 3.8 ppm; IR (mineral oil) 1660, 1630, 1596, 1562, 1548, 1446, 1409 cm^{-1}; MS (EI) m/z 459 (M^+). Anal. ($C_{28}H_{30}N_2O_3$) C, H, N.

[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]ethyl Ester of Carbamic Acid (27). In a flame-dried, 10-mL, two-necked flask under nitrogen at 0 °C, ethyl chloroformate (0.062 g, 0.58 mmol) was added dropwise to **24** (0.200 g, 0.58 mmol) in 2.3 mL of pyridine. The resulting mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and then concentrated *in vacuo*. The residue was dissolved in 5 mL of toluene and then concentrated *in vacuo* three times to produce 0.329 g of crude material. Column chromatography on ca. 25 g of silica gel (elution with 30% EtOAc/hexane) yielded 0.186 g (78%) of **27** as a white solid: mp 162 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 (s, 1 H), 7.38 (d, J = 8.1 Hz, 1 H), 7.28 (m, 1 H), 7.15 (d, J = 7.5 Hz, 1 H), 6.71 (s, 1 H), 6.50 (br s, 1 H), 4.21 (q, J = 7.2 Hz, 2 H), 3.91 (d, J = 8.8 Hz, 1 H), 2.61 (t, J = 6.2 Hz, 2 H), 2.44 (m, 2 H), 1.73 (m, 2 H), 1.57–1.35 (m, 7 H), 1.30 (t, J = 7.1 Hz, 3 H), 0.74 (m, 1 H), 0.58 (m, 2 H), 0.27 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.6, 164.1, 161.2, 153.4, 142.3, 138.6, 129.7, 122.7, 117.9, 117.4, 110.7, 106.0, 61.1, 43.8, 30.6, 29.1, 28.8, 26.1, 25.7, 22.0, 14.4, 13.0, 4.9, 3.8 ppm; IR (mineral oil) 3293, 3258, 1679, 1647, 1614, 1598, 1558, 1447, 1440, 1405 cm^{-1}; MS (EI) m/z 411 (M^+). Anal. ($C_{21}H_{29}NO_5$) C, H, N.

[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]phenyl ester of carbamic acid (28) was prepared as described above for **27**: 0.161 g (60%) of white solid; mp 208–209 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1 H), 7.43–7.30 (m, 5 H), 7.28 (m, 4 H), 6.54 (br s, 1 H), 3.93 (d, J = 8.6 Hz, 1 H), 2.60 (m, 2 H), 2.44 (m, 2 H), 1.73 (s, 2 H), 1.58–1.41 (m, 7 H), 0.78–0.69 (m, 1 H), 0.64–0.52 (m, 2 H), 0.31–0.24 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.6, 164.1, 161.3, 151.5, 150.4, 142.4, 138.0, 129.8, 129.3, 125.6, 123.3, 121.5, 118.1, 117.5, 110.7, 105.9, 43.8, 30.6, 29.1, 28.7, 26.1, 25.7, 22.1, 13.0, 5.0, 3.8 ppm; IR (mineral oil) 3325, 1742, 1668, 1654, 1614, 1596, 1559, 1538, 1492, 1439 cm^{-1}; MS (EI) m/z 459 (M^+). Anal. ($C_{28}H_{29}NO_5$) C, H, N.

Representative Procedure for the Preparation of 29–30, 32–40, and 42. *N*-[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]-phenyl]butanamide (29). In a flame-dried, 25-mL, two-necked flask under nitrogen, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.150 g, 0.59 mmol) was added to a mixture of **24** (0.200 g, 0.59 mmol), triethylamine (0.119 g, 1.2 mmol), and butyric acid (0.052 g, 0.59 mmol) in 5.8 mL of CH_2Cl_2. The reaction mixture was stirred for 24 h at room temperature and then diluted with 10 mL of H_2O and 10 drops 4 N HCl. The aqueous layer was separated, and the organic layer was washed with an additional two 5-mL portions of water and 10 mL of brine. The organic layer was then washed with H_2O, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Recrystallization from CH_2Cl_2 yielded 0.148 g (61%) of 31 as a white solid: mp 222–224 °C; ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.52 (s, 1 H), 7.41 (d, J = 7.4 Hz, 1 H), 7.22 (m, 2 H), 3.56 (d, J = 9.4 Hz, 1 H), 2.62 (t, J = 6.1 Hz, 2 H), 2.52 (t, J = 6.1 Hz, 2 H), 2.33 (t, J = 7.5 Hz, 2 H), 1.78–1.44 (m, 11 H), 1.00 (t, J = 7.4 Hz, 3 H), 0.73 (m, 1 H), 0.54 (m, 1 H), 0.35 (m, 1 H), 0.27 (m, 1 H) ppm; ^{13}C NMR (DMSO-d_6) δ 171.3, 164.7, 163.9, 160.1, 143.7, 138.0, 127.8, 122.5, 118.7, 117.4, 110.1, 106.0, 44.4, 38.6, 30.4, 28.8, 28.3, 25.8, 25.2, 21.8, 18.5, 13.3, 12.2, 5.8, 3.3 ppm; IR (mineral oil) 3103, 1677, 1654, 1616, 1595, 1561, 1448, 1405 cm^{-1}; MS (EI) m/z 409 (M^+). Anal. ($C_{25}H_{31}NO_4$) 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]benzacetamide (30):** 0.144 g (53%) of white solid; mp 211–212 °C; ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.53 (s, 1 H), 7.37 (m, 5 H), 7.30 (m, 1 H), 7.20 (d, J = 5.4 Hz, 2 H), 3.67 (s, 2 H), 3.43 (d, J = 9.7 Hz, 1 H), 2.61 (t, J = 6.2 Hz, 2 H), 2.53 (t, J = 6.2 Hz, 2 H), 1.75 (m, 3 H), 1.62 (m, 2 H), 1.45 (m, 4 H), 0.71 (m, 1 H), 0.51 (m, 1 H), 0.28 (m, 2 H) ppm; ^{13}C NMR (DMSO-d_6) δ 169.0, 163.9, 163.4, 160.3, 144.5, 138.8, 136.2, 129.2, 128.3, 128.0, 126.5, 122.5, 118.4, 116.6, 110.2, 106.0, 44.6, 43.4, 30.3, 29.2, 28.7, 26.0, 25.4, 21.9, 12.5, 6.6, 3.8 ppm; IR (mineral oil) 3104, 1676, 1654, 1640, 1618, 1594, 1560, 1404, 1216 cm^{-1}; MS (EI) m/z 457 (M^+). Anal. ($C_{29}H_{31}NO_4$) 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]benzeneethanethioamide (31).** In a flame-dried flask under nitrogen, 1.9 mL toluene was added to a mixture of **30** (0.200 g, 0.437 mmol) and Lawesson's reagent (0.177 g, 0.437 mmol). The reaction mixture was brought to reflux for 1.5 h and then cooled in an ice bath to induce precipitation. The solid was collected by filtration and dried under vacuum at 60 °C to afford 0.111 g (54%) of **31**. An analytical sample was obtained using preparative thin layer chromatography (elution with 15% $CH_3CN/CHCl_3$): mp 163 °C; ^{1}H NMR ($CDCl_3$) δ 8.67 (br s, 1 H), 7.89 (br s, 1 H), 7.44–7.29 (m, 8 H), 6.54 (br s, 1 H), 4.26 (s, 2 H), 3.93 (d, J = 8.5 Hz, 1 H), 2.60 (t, J = 6.1 Hz, 2 H), 2.47 (t, J = 6.1 Hz, 2 H), 1.72 (m, 2 H), 1.59–1.34 (m, 7 H), 0.71 (m, 1 H), 0.64–0.50 (m, 2 H), 0.25 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 201.3, 165.6, 164.2, 161.3, 141.9, 138.8, 134.8, 129.5, 129.32, 129.28, 128.0, 126.5, 123.3, 122.0, 110.8, 105.7, 54.8, 43.7, 30.7, 29.1, 28.8, 26.1, 25.8, 22.1, 13.0, 4.9, 3.8 ppm; IR (mineral oil) 1660, 1646, 1593, 1559, 1552, 1437, 1393 cm^{-1}; MS (EI) m/z 473 (M^+); Anal. ($C_{29}H_{31}NO_3S$) 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]benzamide (32):** 0.136 g (21%) of solid; mp 217 °C; ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.93, (d, J = 7.4 Hz, 2 H), 7.68 (br s, 1 H), 7.54

(m, 4 H), 7.29 (m, 2 H), 3.50 (d, J = 8.9 Hz, 1 H), 2.64 (t, J = 6.7 Hz, 2 H), 2.58 (t, J = 6.7 Hz, 2 H), 1.91–1.70 (m, 3 H), 1.65 (m, 2 H), 1.59–1.39 (m, 4 H), 0.77 (m, 1 H), 0.54 (m, 1 H), 0.32 (m, 2 H) ppm; ^{13}C NMR (DMSO-d_6) δ 165.5, 164.2, 163.4, 160.2, 144.5, 138.8, 135.2, 131.5, 128.4, 127.7, 122.9, 119.8, 117.9, 110.3, 106.0, 44.7, 30.4, 29.2, 28.7, 26.0, 25.5, 21.9, 12.6, 6.7, 3.8 ppm; **IR** (mineral oil) 1679, 1640, 1614, 1595, 1578, 1551, 1432, 1404 cm^{-1}; MS (EI) m/z 443 (M^+). Anal. ($C_{28}H_{29}NO_4$) 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]-4-fluorobenzamide (33):** 0.172 g (64%) of white solid; mp 239–240 °C; ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.96 (dd, J = 5.3, 8.8 Hz, 2 H), 7.63 (s, 1 H), 7.55 (d, J = 7.6 Hz, 1 H), 7.29 (t, J = 7.5 Hz, 1 H), 7.24 (s, 1 H), 7.19 (s, 1 H), 7.17 (t, J = 8.7 Hz, 1 H), 3.49 (d, J = 9.9 Hz, 1 H), 2.63 (t, J = 6.1 Hz, 2 H), 2.56 (t, J = 6.2 Hz, 2 H), 1.75 (m, 3 H), 1.64 (m, 2 H), 1.48 (m, 4 H), 0.75 (m, 1 H), 0.53 (m, 1 H), 0.30 (m, 2 H) ppm; ^{13}C NMR (DMSO) δ 165.7, 164.4, 164.1, 163.4, 160.2, 144.5, 138.6, 131.6, 130.5, 130.4, 127.8, 123.0, 119.8, 118.0, 115.4, 115.2, 110.2, 106.0, 44.7, 30.4, 29.2, 28.8, 26.0, 25.4, 21.9, 12.6, 6.6, 3.8 ppm; IR (mineral oil) 1675, 1640, 1616, 1603, 1589, 1554, 1508, 1445, 1436, 1402 cm^{-1}; MS (EI) m/z 461 (M^+). Anal. ($C_{28}H_{28}NO_4F$) 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-phenyl-2-propenamide (34):** 0.093 g (33%) of white solid; mp 253–254 °C; ^{1}H NMR ($CDCl_3$ and CD_3OD) δ 7.64 (d, J = 15.7 Hz, 1 H), 7.57 (s, 1 H), 7.49 (m, 3 H), 7.31 (m, 3 H), 7.21 (m, 2 H), 6.60 (d, J = 15.7 Hz, 1 H), 3.49 (d, J = 9.6 Hz, 1 H), 2.55 (t, J = 6.1 Hz, 2 H), 2.46 (t, J = 6.1 Hz, 2 H), 1.68 (m, 3 H), 1.56 (m, 2 H), 1.40 (m, 4 H), 0.68 (m, 1 H), 0.48 (m, 1 H), 0.25 (m, 2 H) ppm; ^{13}C NMR (DMSO-d_6) δ 164.1, 163.4, 160.2, 144.7, 139.9, 138.9, 134.9, 129.8, 129.1, 128.1, 127.7, 122.7, 122.6, 118.5, 116.8, 110.2, 105.9, 44.6, 30.4, 29.2, 28.7, 26.0, 25.5, 21.9, 12.6, 6.6, 3.8 ppm; IR (mineral oil) 1680, 1661, 1629, 1611, 1591, 1560, 1434, 1401, 1216 cm^{-1}; MS (EI) m/z 469 (M^+). Anal. ($C_{30}H_{31}NO_4$) C, H, N.

[2-[[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]amino]-2-oxoethyl]carbamic acid, 1,1-dimethylethyl ester (35): 0.115 g (33%) of off-white solid; mp 114–124 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.30 (br s, 1 H), 7.55 (s, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.31–7.21 (m, 2 H), 5.30 (br s, 1 H), 3.90–3.86 (m, 3 H), 2.60 (m, 2 H), 2.46 (m, 2 H), 1.74 (m, 2 H), 1.57–1.48 (m, 7 H), 1.47 (s, 9 H), 0.75 (m, 1 H), 0.60–0.51 (m, 2 H), 0.28 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 167.8, 165.7, 164.1, 161.3, 156.2, 142.4, 137.9, 129.6, 123.8, 119.3, 118.7, 110.7, 106.0, 45.4, 43.9, 30.7, 30.2, 29.1, 28.8, 28.2, 26.2, 25.7, 22.1, 12.9, 5.0, 3.8 ppm; IR (mineral oil) 3299, 1670, 1661, 1612, 1594, 1557, 1516, 1489, 1445, 1405, 1394 cm^{-1}; MS (EI) m/z 497 (M^+). Anal. ($C_{28}H_{36}N_2O_6$) C, H, N.

[2-[[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]amino]-3-oxopropyl]carbamic acid, 1,1-dimethylethyl ester (36): 0.055 g (73%) of off-white solid; mp 197–199 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1 H), 7.60 (s, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.31 (dd, J = 8.0, 7.7 Hz, 1 H), 7.20 (d, J = 7.7 Hz, 1 H), 3.90 (d, J = 8.6 Hz, 1 H), 3.46 (t, J = 5.7 Hz, 2 H), 2.63–2.52 (m, 4 H), 2.47 (m, 2 H), 1.73 (m, 2 H), 1.64–1.56 (m, 7 H), 1.43 (s, 9 H), 0.77–0.73 (m, 1 H), 0.63–0.51 (m, 2 H), 0.29–0.25 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$, DMSO) δ 169.0, 163.8, 163.3, 159.4, 154.9, 143.5, 137.4, 127.0, 122.0, 118.1, 116.4, 109.5, 105.4, 77.6, 44.0, 39.0, 35.8, 29.9, 28.3, 27.8, 27.4, 25.2, 24.6, 21.3, 11.6, 5.6, 2.9 ppm; IR (mineral oil) 3445, 3416, 3285, 3259, 3198, 3155, 3100, 3086, 3041, 1714, 1679, 1656, 1641, 1614, 1592, 1561, 1437, 1398 cm^{-1}; MS (EI) m/z 510 (M^+). Anal. ($C_{29}H_{38}N_2O_6$) C, H, N.

[2-[[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]amino]-4-oxobutyl]carbamic acid, 1,1-dimethylethyl ester (37): 0.192 g (52%) of off-white solid; mp 188–191 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.87 (br s, 1 H), 7.76 (s, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.30 (dd, J = 8.0, 7.8 Hz, 1 H), 7.17 (d, J = 7.8 Hz, 1 H), 6.41 (br s, 1 H), 4.79 (br s, 1 H), 3.93 (d, J = 8.8 Hz, 1 H), 3.24 (t, J = 5.9 Hz, 2 H), 2.61 (m, 2 H), 2.45–2.36 (m, 4 H), 1.91–1.82 (m, 2 H), 1.75–1.71 (m, 2 H), 1.66–1.47 (m, 7 H), 1.45 (s, 9 H), 0.75 (m, 1 H), 0.62–0.55 (m, 2 H), 0.30–0.25 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.2, 165.7, 164.0, 161.2, 157.1, 142.1, 139.0, 129.7, 123.5, 118.8, 118.6, 110.7, 106.0, 79.8, 43.7, 39.2, 34.4, 30.7, 29.1, 28.8, 28.2, 27.1, 26.2, 25.7, 22.0, 13.0, 4.9, 3.8 ppm; IR (mineral oil) 3357, 3289, 3257, 3219, 3201, 3160, 3152, 3105, 3081, 3063, 3048, 3002, 1711, 1663, 1653, 1621, 1594, 1562, 1545, 1443, 1402, 1390 cm^{-1}; MS (EI) m/z 525 (M^+); HRMS calcd for $C_{30}H_{40}N_2O_6$ 525.2964, found 525.2999.

[2-[[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]amino]-1-(*S*)-methyl-2-oxoethyl]carbamic acid, 1,1-dimethylethyl ester (38): 0.288 g (77%) of off-white solid; mp 134–139 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.55 (br s, 1 H), 7.60 (d, J = 8.8 Hz, 1 H), 7.49 (d, J = 7.5 Hz, 1 H), 7.30–7.17 (m, 2 H), 5.04 (br s, 1 H), 4.30 (br s, 1 H), 3.88 (d, J = 8.8 Hz, 1 H), 2.61 (m, 2 H), 2.46 (m, 2 H), 1.73 (m, 2 H), 1.66–1.47 (m, 7 H), 1.45 (s, 9 H), 1.42 (d, J = 6.8 Hz, 3 H), 0.72 (m, 1 H), 0.61–0.50 (m, 2 H), 0.28–0.23 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.8, 165.6, 164.1, 161.3, 142.2, 129.7, 129.6, 123.8, 123.7, 119.0, 118.7, 110.7, 106.0, 50.7, 43.8, 30.7, 29.1, 28.8, 28.2, 26.2, 25.8, 25.7, 22.1, 17.2, 12.9, 5.0, 3.8 ppm; IR (mineral oil) 3399, 3299, 3223, 3153, 3077, 1669, 1660, 1612, 1593, 1557, 1489, 1446, 1405, 1393 cm^{-1}; MS (FAB) m/z 511 ($M + H^+$). Anal. ($C_{29}H_{38}N_2O_6$) C, H, N.

[2-[[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3yl)methyl]phenyl]amino]-1(R)-methyl-2-oxoethyl]carbamic acid, 1,1-dimethylethyl ester (39): 0.058 g (33%) of white solid; mp 122–127 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.50 (br s, 1 H), 7.60 (d, J = 8.8 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.30–7.17 (m, 2 H), 5.02 (br s, 1 H), 4.31 (br s, 1 H), 3.88 (d, J = 8.0 Hz, 1 H), 2.61 (m, 2 H), 2.46 (m, 2 H), 1.73 (m, 2 H), 1.66–1.47 (m, 7 H), 1.45 (s, 9 H), 1.42 (d, J = 6.9 Hz, 3 H), 0.72 (m, 1 H), 0.62–0.53 (m, 2 H), 0.28–0.25 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.8, 165.6, 164.1, 161.3, 142.2, 129.7, 129.6, 123.8, 123.7, 119.0, 118.7, 110.7, 106.0, 50.7, 43.8, 30.7, 29.1, 28.8, 28.2, 26.2, 25.8, 25.7, 22.1, 17.2, 12.9, 5.0, 3.8 ppm; IR (mineral oil) 3399, 3297, 3255, 3153, 3077, 1671, 1611, 1593, 1557, 1488, 1446, 1404, 1393 cm^{-1}; MS (EI) m/z 510 (M^+). Anal. ($C_{29}H_{38}N_2O_6$) C, H, N.

2-[[[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]amino]-carbonyl]-1(S)-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester (40): 0.317 g (77%) of off-white solid; mp 132–136 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.68–7.49 (m, 2 H), 7.29 (m, 1 H), 7.18 (m, 1 H), 6.38 (br s, 1 H), 4.45 (br s, 1 H), 3.92 (d, J = 8.6 Hz, 1 H), 3.45–3.38 (m, 2 H), 2.78 (m, 2 H), 2.64–2.42 (m, 2 H), 1.92 (m, 2 H), 1.75–1.71 (m, 2 H), 1.66–1.55 (m, 10 H), 1.48 (s, 9 H), 0.73 (m, 1 H), 0.63–0.54 (m, 2 H), 0.29–0.24 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 164.0, 161.2, 129.8, 123.7, 123.6, 123.5, 118.8, 118.7, 118.6, 118.5, 110.7, 106.1, 105.9, 80.9, 47.1, 43.7, 43.6, 30.6, 29.1, 28.8, 28.3, 26.2, 25.7, 24.4, 22.0, 13.0, 12.9, 4.9, 3.8 ppm; IR (mineral oil) 3286, 3211, 3150, 3077, 1701, 1668, 1611, 1593, 1557, 1488, 1479, 1445, 1437, 1404 cm^{-1}; MS (EI) m/z 536 (M^+). Anal. ($C_{31}H_{40}N_2O_6$) C, H, N.

[2-[[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]amino]-1(*R*)-(1*H*-imidazol-4-ylmethyl)-2-oxoethyl]carbamic acid, 1,1-dimethylethyl ester (42): 0.196 g (68%) of white solid; mp 175–179 °C dec; ^{1}H NMR (DMSO) δ 9.90 (s, 1 H), 7.59 (s, 1 H), 7.53–7.48 (m, 2 H), 7.13 (t, J = 7.9 Hz, 1 H), 7.05–6.98 (m, 2 H), 6.81 (s, 1 H), 4.31 (m, 1 H), 3.36 (d, J = 9.7 Hz, 1 H), 2.94–2.77 (m, 2 H), 1.85 (m, 1 H), 1.63 (m, 2 H), 1.53 (m, 2 H), 1.36–1.27 (m, 8 H), 1.36 (s, 9 H), 0.66 (m, 1 H), 0.40–0.36 (m, 1 H), 0.18 (m, 1 H), 0.10 (m, 1 H) ppm; ^{13}C NMR (DMSO) δ 170.4, 159.7, 155.3, 145.3, 138.5, 134.7, 127.8, 122.7, 118.7, 118.6, 116.9, 116.8, 116.7, 116.6, 111.1, 105.1, 78.2, 55.1, 44.6, 30.3, 29.7, 29.3, 28.7, 28.2, 26.0, 25.5, 22.0, 12.7, 6.6, 3.9 ppm; IR (mineral oil) 3386, 3260, 3141, 3073, 1679, 1658, 1610, 1592, 1553, 1488, 1444, 1393 cm^{-1}; MS (EI) m/z 577 (M^+); HRMS calcd for $C_{32}H_{40}N_4O_6$ 577.3026, found 577.3058.

[2-[[3-[Cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]amino]-1(*S*)-(1*H*-imidazol-4-ylmethyl)-2-oxoethyl]carbamic Acid, 1,1-Dimethylethyl Ester (41). An intermediate, [2-[[3-

[cyclopropyl(5,6,7,8,9,10-hexahydro-4-hydroxy-2-oxo-2*H*-cycloocta[*b*]pyran-3-yl)methyl]phenyl]amino]-1-[[1(*S*)-[(4-methylphenyl)sulfonyl]-1*H*-imidazol-5-yl]methyl]-2-oxoethyl]-carbamic acid, 1,1-dimethylethyl ester (**43**), was prepared from **24** as described in the representative procedure above: 0.349 g (48%) of white solid; mp 120–124 °C dec; ^{1}H NMR ($CDCl_3$) δ 9.85 (br s, 1 H), 8.59 (br s, 1 H), 7.88 (d, J = 8.0 Hz, 2 H), 7.51 (d, J = 7.2 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 2 H), 7.28–7.15 (m, 2 H), 6.55 (br s, 1 H), 5.92 (d, J = 7.2 Hz, 1 H), 4.79 (br s, 1 H), 3.90 (d, J = 8.9 Hz, 1 H), 3.43–3.29 (m, 1 H), 3.02–2.89 (m, 1 H), 2.59 (m, 2 H), 2.49–2.40 (m, 2 H), 2.45 (s, 3 H), 1.74 (m, 2 H), 1.61–1.36 (m, 8 H), 1.32 (s, 9 H), 0.74 (m, 1 H), 0.58–0.51 (m, 2 H), 0.27 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 165.6, 161.4, 161.3, 146.3, 142.3, 138.1, 136.0, 130.5, 130.4, 130.1, 129.6, 127.2, 126.9, 123.8, 119.1, 118.7, 115.0, 114.9, 110.7, 105.9, 43.8, 30.7, 30.5, 29.9, 29.1, 28.9, 28.1, 26.2, 25.7, 22.1, 21.6, 14.1, 13.0, 5.0, 3.8 ppm; IR (mineral oil) 3384, 3297, 3223, 3148, 3105, 3076, 1672, 1612, 1595, 1558, 1488, 1446, 1401 cm^{-1}; MS (EI) m/z 731 (M^+).

In a 25-mL, two-necked, round-bottomed flask with a nitrogen inlet, **43** (0.204 g, 0.51 mmol) was dissolved in 5 mL of THF. Hydroxybenztriazole (HOBT) (0.207 g, 1.54 mmol) was added, and the solution was stirred at room temperature for 16 h. The reaction mixture was then concentrated *in vacuo*. Column chromatography on 30 g of silica gel (elution with 2–15% MeOH/CH_2Cl_2) yielded 0.255 of **41** contaminated with HOBT. The mixture was partitioned between chloroform and saturated $NaHCO_3$, and the organic layer was concentrated to give 0.221 g (75%) of **41** as a white solid: mp 160–165 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.88 (s, 1 H), 7.58 (s, 1 H), 7.53–7.48 (m, 2 H), 7.14 (dd, J = 7.9, 7.9 Hz, 1 H), 7.05–6.98 (m, 2 H), 6.81 (s, 1 H), 4.31 (m, 1 H), 3.35 (d, J = 10.1 Hz, 1 H), 2.94–2.77 (m, 2 H), 1.85 (m, 1 H), 1.63 (m, 2 H), 1.53 (m, 2 H), 1.42–1.23 (m, 8 H), 1.36 (s, 9 H), 0.67 (m, 1 H), 0.41–0.37 (m, 1 H), 0.20 (m, 1 H), 0.10 (m, 1 H) ppm; ^{13}C NMR (DMSO-d_6) δ 170.5, 159.7, 155.3, 145.0, 138.5, 134.7, 127.8, 122.6, 118.7, 118.6, 116.9, 116.8, 116.7, 116.6, 110.8, 105.4, 78.2, 55.1, 44.7, 30.3, 29.7, 29.3, 28.7, 28.2, 26.0, 25.5, 22.0, 12.6, 6.6, 3.9 ppm; IR (mineral oil) 3292, 3146, 3075, 1705, 1660, 1610, 1592, 1553, 1488, 1442, 1427, 1393 cm^{-1}; MS (EI) m/z 577 (M^+); HRMS calcd for $C_{32}H_{40}N_4O_6$ 577.3026, found 577.3042.

Acknowledgment. We would like to thank Steven J. Ray for the preparation of compounds **18** and **19**.

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(6) Similar results were observed with the seven-membered ring analog of compound **1**. See ref 5 for details.

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(8) Conformational analysis of the C-6 α-substituted cycloalkyl rings was carried out as follows. X-ray crystal structures of unsubstituted seven- and eight-membered cyclic analogs were removed from the protein and propyl groups were attached at the C-6 α position on the cycloalkyl ring. The Monte Carlo Multiple Minimum facility in BatchMin 3.5ᵉ was then used to search the ring conformational space. The search covered 1000 steps for the eight-membered ring and 500 steps for the seven-membered ring. Each Monte Carlo step was minimized using the BatchMin MM2* forcefield, and duplicates were eliminated. The final energy differences reported in the text corresponded to the difference between the overall lowest energy conformation in a particular run (invariably having the propyl group equatorial) and the lowest energy conformation that also had the propyl in the desired axial or pseudoaxial orientation, which would point toward the S2′ subsite.

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(10) Isolation of the four stereoisomers of **11** was accomplished using chiral HPLC separation techniques. First **2** was separated into its two component enantiomers as described in ref 5, then each of these was alkylated using iodopropane as described in Scheme 1 and the resulting diastereomeric mixtures were separated. The (−)-enantiomer of **2** (**2a**, K_i = 38 ± 3 nM) was used to make the mixture **11a** (K_i = 30 nM), which was subsequently separated into the diastereomers **11b** (K_i = 210 ± 65 nM) and **11c** (K_i = 15 ± 2.8 nM). Likewise, the (+)-enantiomer of **2** (**2b**, K_i = 13 ± 2.2 nM) was alkylated to give the diastereomeric mixture **11d** (K_i = 11 nM), which was separated into **11e** (K_i = 9 ± 1 nM) and **11f** (K_i = 90 ± 30 nM).

(11) The use of *meta*-carboxamide substitution on the phenyl ring has recently proven useful in related templates. See: Thaisrivongs, S.; Watenpaugh, K. D.; Howe, W. J.; Tomich, P. K.; Dolak, L. A.; Chong, K.-T.; Tomich, C.-S. C.; Tomaselli, A. G.; Turner, S. R.; Strohbach, J. W.; Mulichak, A. M.; Janakiraman, M. N.; Moon, J. B.; Lynn, J. C.; Horng, M.-M.; Hinshaw, R. R.; Curry, K. A.; Rothrock, D. J. Structure-Based Design of Novel HIV Protease Inhibitors: Carboxamide-Containing 4-Hydroxycoumarins and 4-Hydroxy-2-pyrones as Potent Non-peptidic Inhibitors. *J. Med. Chem.* **1995**, *38*, 3624–3637.

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(17) A detailed discussion and experimental data related to these issues are beyond the scope of this paper and will be presented at a later date.

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JM950453S