Stereospecific Synthesis, Structure−Activity Relationship, and Oral Bioavailability of Tetrahydropyrimidin-2-one HIV Protease Inhibitors

George V. De Lucca,* Jing Liang, and Indawati De Lucca

DuPont Pharmaceuticals Company, Wilmington, Delaware 19880-0500

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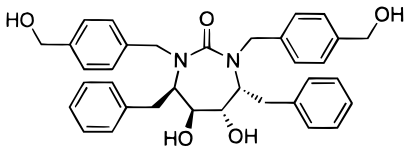
The use of tetrahydropyrimidinones as an alternate scaffold for designing HIVPR inhibitors has advantages, over the previously disclosed hexahydro-1,3-diazepin-2-ones, of being more unsymmetrical (different P1/P1′), less crystalline, more soluble, and more lipophilic (mono-ol vs diol). They show a better translation of K_i to IC_{90} for the more polar P2 groups that in general give the more potent enzyme inhibitors. Structure−activity relationship (SAR) studies of the tetrahydropyrimidinones showed that the phenylethyl P1′ substituent, the hydroxyl group, and the urea carbonyl are all critical for good activity. However, there was significant flexibility in the possible P2/P2′ substituents that could be used. Many analogues that contained identical or different P2/P2′ substituents, or only one P2 substituent, were found to have excellent enzyme potency and several had excellent antiviral potency. Several of these compounds were examined for oral bioavailability in the rat or the dog at 10 mg/kg. However, the oral bioavailability of the tetrahydropyrimidinones was, in general, less than the corresponding hexahydro-1,3-diazepin-2-ones. Unfortunately, when all factors are considered, including potency, protein binding, solubility, bioavailability, and resistance profile, the tetrahydropyrimidinones did not offer any advantage over the previously disclosed hexahydro-1,3-diazepin-2-ones series.

Introduction

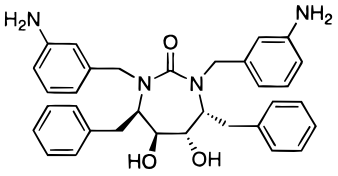
The human immunodeficiency virus (HIV) encodes an aspartyl protease which is responsible for the processing of the gag and gag-pol gene products. This processing is required for the production of mature, infectious virions and has been a prime target for intervention.[1,2] At Dupont Merck we have previously described the design and discovery of a novel class of cyclic urea based HIVPR inhibitors.[3] The C_2 symmetric hexahydro-1,3-diazepin-2-ones are complementary to the C_2 symmetric aspartic protease of HIV and are very potent inhibitors. This work resulted in the identification of two clinical candidates in this series, **DMP 323**[4] and **DMP 450**[5] (Figure 1).

As an extension of this work we recently disclosed the design and synthesis of tetrahydropyrimidinones, such as **I** (Figure 1), and showed by an X-ray crystallographic study that these bind to the active site of HIVPR in a fashion very similar to the hexahydro-1,3-diazepin-2-ones.[6] The carbonyl of **I** displaces the structural water molecule usually seen in structures of complexes with linear inhibitors and hydrogen bonds directly with the flap residues Leu 50/150. The hydroxyl group of **I** has hydrogen-bonding interactions with the catalytic aspartic acid residues Asp 25/125. The nitrogen substituents (P2, P2′) make good lipophilic contacts with the S2, S2′ specificity pockets of the enzyme and the C6 and C4 side chain substituents (P1, P1′) of **I** make good contact with the S1, S1′ specificity pockets of HIVPR. All these interactions are nearly identical to those seen with the hexahydro-1,3-diazepin-2-ones[4] and thus account for the near equipotency of these two classes of inhibitors.[6]

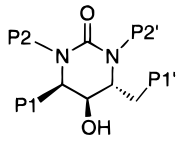
The C_2 symmetric cyclic ureas, such as **DMP 450** and **DMP 323**, are rigid, extremely complementary to the enzyme, and offer significant synthetic and cost advantages. However, they also have significant limitations due to their inherent crystallinity and low solubility. On the other hand, nonsymmetric ureas are more soluble and offer greater flexibility for adjusting the physical and chemical properties and designing favorable enzyme interactions.[4,7]



DMP 323



DMP 450



I

Figure 1. Structure of cyclic urea based clinical candidates **DMP 323** and **DMP 450** and the general structure of tetrahydropyrimidin-2-ones discussed in text.

Tetrahydropyrimidinones, as an alternate scaffold for HIVPR inhibitors, have the advantage of being more unsymmetrical (not C_2 symmetric with different P1/P1′)

* To whom correspondence should be addressed. E-mail: George.V.DeLucca@dupontpharma.com.

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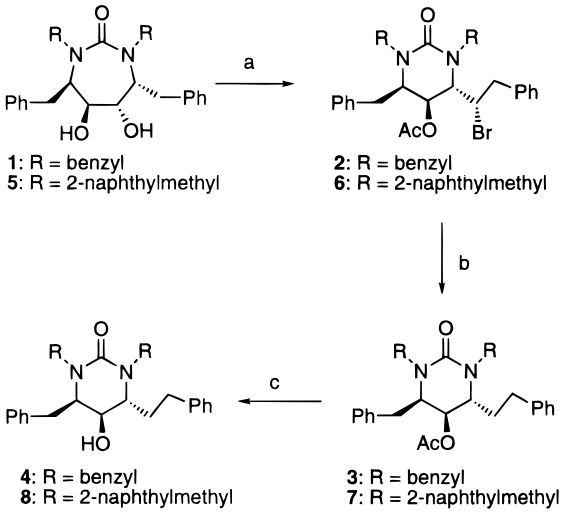
Scheme 1[a]



[a] Reagents and conditions: (a) acetoxyisobutyryl bromide/CH_2Cl_2; (b) Zn dust/acetic acid; (c) NaOH/MeOH.

and more lipophilic (mono-ol vs diol) than the hexahydro-1,3-diazepin-2-ones. This makes the tetrahydropyrimidinones less crystalline (as measured by their lower melting points) and consequently more soluble in typical organic solvents (CH_2Cl_2, $CHCl_3$). They also show a better translation of enzyme inhibition (K_i) to intracellular antiviral activity (IC_{90}) for analogues with the more polar P2 groups[8] that in general improve the potency of the enzyme inhibitors. Thus, the use of tetrahydropyrimidinones offered a way to better address the often conflicting issues of solubility, potency, and oral bioavailability. In this paper we wish to describe in detail our studies on the structure−activity relationship (SAR) and oral bioavailability of tetrahydropyrimidinones.

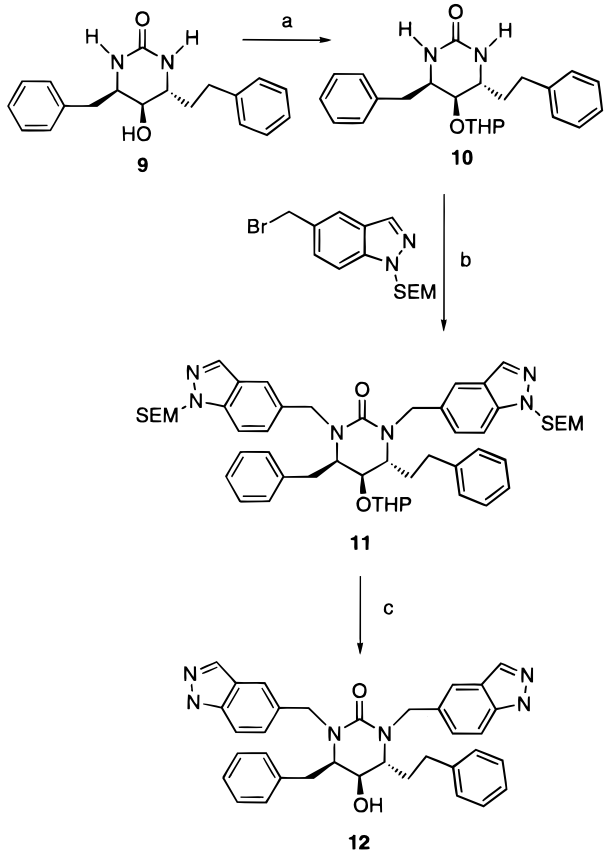
Chemistry

The stereospecific synthesis of symmetrically N,N′-disubstituted tetrahydropyrimidinones was accomplished using one of the two methods outlined in Schemes 1 and 2. The first method involved the rearrangement of the symmetrical hexahydro-1,3-diazepin-2-one analogues using 2-acetoxyisobutyryl bromide[9] as previously described.[6,10] The enantiomerically pure hexahydro-1,3-diazepin-2-one starting materials were readily prepared by the methods previously reported.[4] For example, when the diol **1**[4] was treated with 2-acetoxyisobutyryl bromide a nearly quantitative yield of the tetrahydropyrimidinone bromo acetate **2** was obtained. X-ray crystallographic analysis of **2** confirmed not only the assigned structure but also the absolute configuration of the phenethyl bromide substituent.[6]

The phenethyl bromide side chain of **2** was most conveniently reduced using Zn (dust) in acetic acid to give the phenethyl analogue **3** in nearly quantitative yield. Finally, the hydrolysis of the acetate **3** gave the desired alcohol **4** in excellent yield. Thus, the overall transformation of the diol **1** to the tetrahydropyrimidinone **4** was achieved efficiently with an overall yield of about 90%. This reaction sequence is quite general and was used to synthesize many tetrahydropyrimidinone analogues. [6,10]

While this three-step procedure (Scheme 1) was a very efficient method to synthesize tetrahydropyrimidinones

Scheme 2[a]



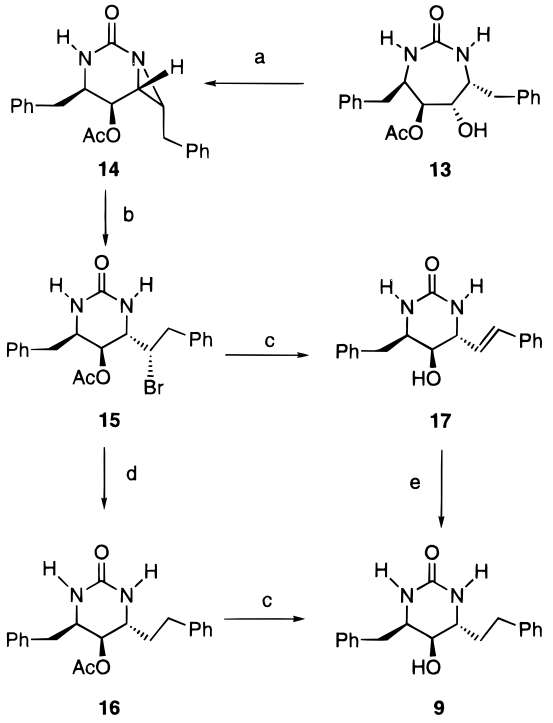
[a] Reagents and conditions: (a) DHP/$CHCl_3$/TsOH; (b) KO-*t*-Bu/THF; (c) HCl/MeOH reflux.

from the corresponding hexahydro-1,3-diazepin-2-ones, it had some practical limitations. If the two N,N′-substituents of the diazepin-2-one were not the same, then a mixture of the two possible regioisomeric tetrahydropyrimidinones products were obtained, and their separation required tedious chromatography. In addition, the N,N′-substituents of the hexahydro-1,3-diazepin-2-one had to be stable to the reaction conditions, namely stability toward acid bromides, reduction, and basic hydrolysis.

Thus, in some cases it was desirable to use the parent N,N′-unsubstituted tetrahydropyrimidinone **9** as the starting material. The hydroxyl group of **9** was protected as the THP ether **10** in quantitative yield (Scheme 2). The urea nitrogens were substituted using a variety of alkylating agents under our standard conditions.[4] For example, treatment of **10** with 5-(bromomethyl)-1-SEM-indazole[8,11] and 1 M solution of KOt-Bu (in THF) gave the dialkylated tetrahydropyrimidinone **11.** The protecting groups were removed under acidic conditions (HCl/MeOH) to give the indazole-substituted tetrahydropyrimidinone **12** in good yield.

We previously reported the stereospecific de novo synthesis of **9** from D-phenylalanine.[6] However, since the synthesis was long and the overall yield was not satisfactory, an alternate synthesis that used the parent N,N′-unsubstituted hexahydro-1,3-diazepin-2-one as the starting material was desirable. This became possible when we discovered[10] an unusual reaction of hexahydro-1,3-diazepin-2-ones with the fluorinating agent diethylamino sulfur trifluoride (DAST).

Scheme 3[a]



[a] Reagents and conditions: (a) DAST/CH_2Cl_2; (b) HBr(g)/dioxane; (c) NaOH/MeOH; (d) Zn dust/acetic acid; (e) H_2 10% Pd/C.

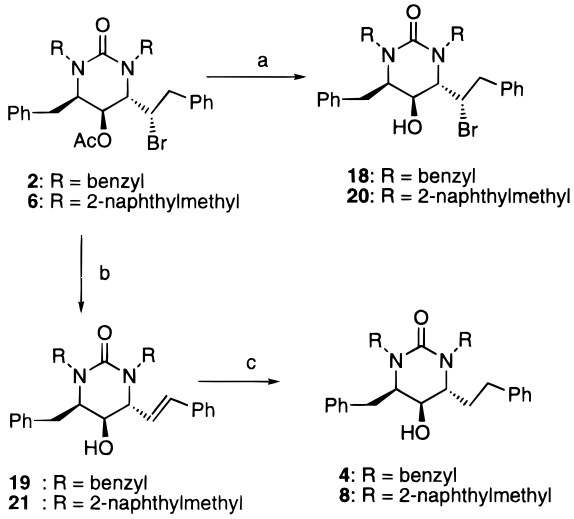
Treatment of the N,N′-unsubstituted monoacetate **13** with DAST did not give the expected fluoro analogue; instead, it provided the aziridine **14** in good yield (Scheme 3). Treatment of the aziridine **14** with HBr(g) gave a nearly quantitative yield of the phenethyl bromide **15**. The bromide **15** was reduced with zinc dust in acetic acid to give the phenethyl analogue **16** in excellent yield. Hydrolysis of **16** gave the unsubstituted tetrahydropyrimidinone **9** in excellent overall yield from the monoacetate **22**. Alternatively, the bromo acetate **15** was treated with excess NaOH or KOH to give the olefinic alcohol **17** in nearly quantitative yield. Hydrogenation of **17** gave the desired N,N′-unsubstituted tetrahydropyrimidinone **9**, again in excellent yield.

To explore the SAR of the P1′ group several substituted-phenethyl analogues were synthesized. For example, the intermediates bromo acetates **2** or **6** were hydrolyzed to give the bromo alcohols **18** or **20** using mildly basic conditions (0.01 M NaOH/MeOH) as shown in Scheme 4. Under more concentrated conditions (2 M NaOH or KOH in MeOH), the olefinic alcohols **19** and **21** were obtained in excellent yields. Hydrogenation of **19** or **21** gave the corresponding tetrahydropyrimidinones analogues **4** or **8** previously described in Scheme 1.

The rearrangement tendency of the hexahydro-1,3-diazepin-2-ones is a very general one and can be used to incorporate other substituents into the phenethyl side chain.[10] By using a variety of reactions it is possible to introduce a wide diversity of substituents (fluoro, bromo, oxygen, or nitrogen) as shown in the examples below.

Treating the diol **22**[4] with 1 equiv of DAST gave the rearranged 1-fluoro-2-phenethyl alcohol **23** as the major product. The structure of **23** was confirmed by the use of 2D COSY NMR experiments. The diol **22** was mono-protected with MEM-Cl to give the mono-MEM ether alcohol **24**, which was separated from diol and di-MEM

Scheme 4[a]



[a] Reagents and conditions: (a) 1 N NaOH/MeOH; (b) KOH(s)/MeOH; (c) H_2/10% Pd/C.

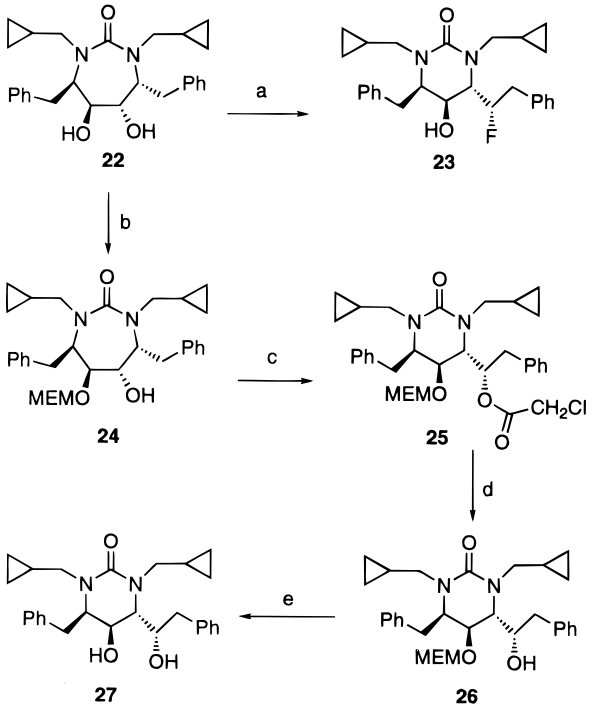
byproducts by chromatography. The free hydroxyl of **24** was treated under Mitsunobu conditions (Ph_3P, DEAD, chloroacetic acid) to give the rearranged chloroacetate **25**. The ester **25** was hydrolyzed to give a new mono-MEM ether alcohol **26** which was deprotected to give the non-C_2-symmetric diol **27**. A 2D COSY NMR of **27** shows that it is the rearranged tetrahydropyrimidinone analogue with one set of benzyl protons coupled to the proton α to a hydroxyl group and not coupled to the proton α to the nitrogen.

The reaction of **5**[4] (having a large 2-naphthyl P2 substituent) with 1 equiv of DAST gave the corresponding tetrahydropyrimidinone analogue **28** in good yield (Scheme 6). The diol **5** was converted to the mono-mesylate **29**. Reaction of the mesylate **29** with nucleophiles gave rearranged products. For example, the reaction of **29** with NaN_3 gave the azido analogue **30**. Treatment of **29** with NaI gave the trans olefin **21**, presumably via the phenethyl iodide which eliminates HI under the reaction conditions to give the observed olefin. The structure of the olefin **21** was further confirmed by hydrogenation to the phenethyl analogue **8**, both of which were prepared independently as shown in Scheme 4.

The aziridine **14** can be considered a protected form of the desired tetrahydropyrimidinone final product and was used to synthesize unsymmetrically substituted N,N′-analogues as summarized in Scheme 7. Alkylation of aziridine **14** with benzyl bromide gave the *N*-benzyl aziridine **31**. The acetate of **31** was removed under basic conditions to give the free alcohol **33**, whose structure was also confirmed by X-ray crystallography (Figure 2). The aziridine **31** was sequentially treated with HBr, zinc dust in acetic acid, and NaOH to give the mono-N-alkylated tetrahydropyrimidinone **36**.

The aziridine ring was opened by other acids in addition to HBr. For example, treatment of **31** with trifluoroacetic acid gave the corresponding trifluoroacetate (Scheme 7). Hydrolysis of the intermediate trifluoroacetate with NaOH gave the corresponding diol **34**. The aziridine **39**, containing the *N*-(3-benzyloxy)benzyl group, was hydrogenated, for a prolonged period of time, to remove the *O*-benzyl protecting groups and reduce

Scheme 5[a]



[a] Reagents and conditions: (a) 1 equiv DAST/CH_2Cl_2; (b) MEM-Cl/Et_3N; (c) DEAD/Ph_3P/chloroacetic acid; (d) NaOH/MeOH; (e) HCl/MeOH.

the aziridine ring and to give the tetrahydropyrimidinone phenol **40**.

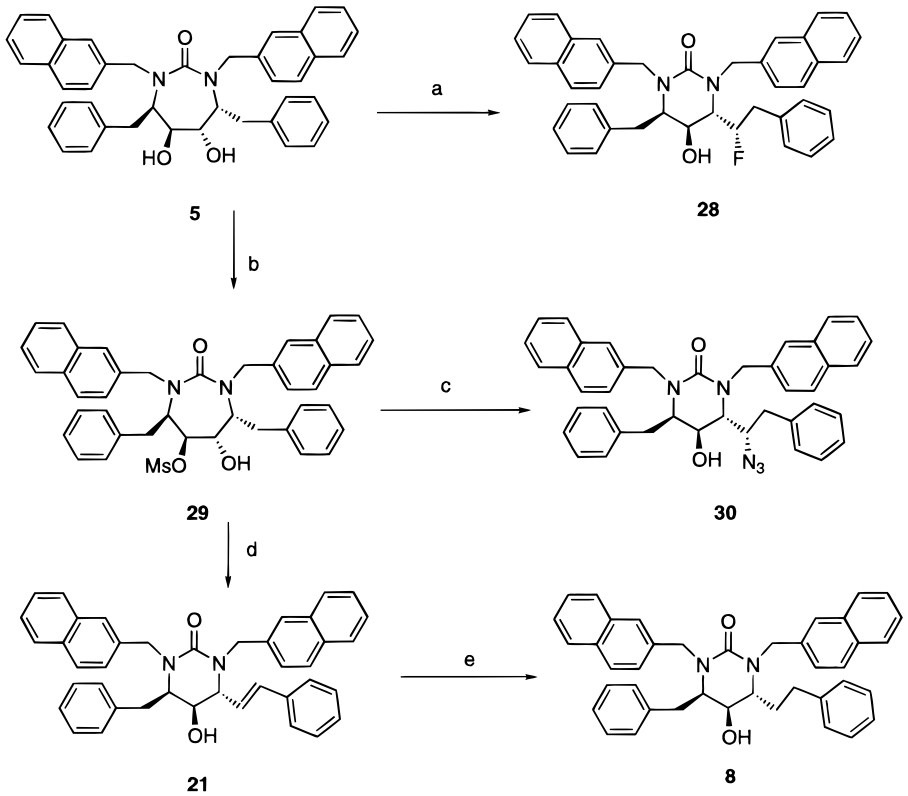
Suitably protected alcohols (such as **36** or **38**) were N-alkylated a second time to obtain unsymmetrical N,N′-dialkylated tetrahydropyrimidinones with defined regio-chemistry as shown in Scheme 8. For example, the alcohol of **38** was protected as the MEM ether **41**. Alkylation of the urea nitrogen with cyclopropylmethyl bromide under the usual conditions gave the dialkylated product **42**. The MEM group was removed under acidic (HCl/dioxane) conditions to give the free alcohol, and the cyano group was converted to the amidoxime with hydroxylamine to give the desired unsymmetrical N,N′-dialkylated tetrahydropyrimidinone **43**.

While one mono-N-alkylated tetrahydropyrimidinone isomer with defined regio-chemistry (such as **36** or **38**) was easily obtained from the aziridine **14**, the other regio-isomeric mono-N-alkylated product could not be preferentially synthesized. To obtain the other regio-isomer the sequence outlined in Scheme 9 was used. For example, the THP-protected tetrahydropyrimidinone **10** was alkylated with 3-nitrobenzyl bromide to give a mixture of mono-N-alkylated tetrahydropyrimidinones **44** and **45** which were separated by chromatography. The nitro group was reduced (H_2, 10% Pd/C), and the protecting group was removed (HCl/MeOH) to give corresponding mono-N-alkylated anilines **47** or **46**. The structure of **47** was determined by the independent synthesis starting with the aziridine **14** as shown in Scheme 9. Furthermore, the THP ether **49** was alkylated a second time to prepare the unsymmetrical N,N′-dialkylated tetrahydropyrimidinones **93**−**98** (Table 4).

Results and Discussion

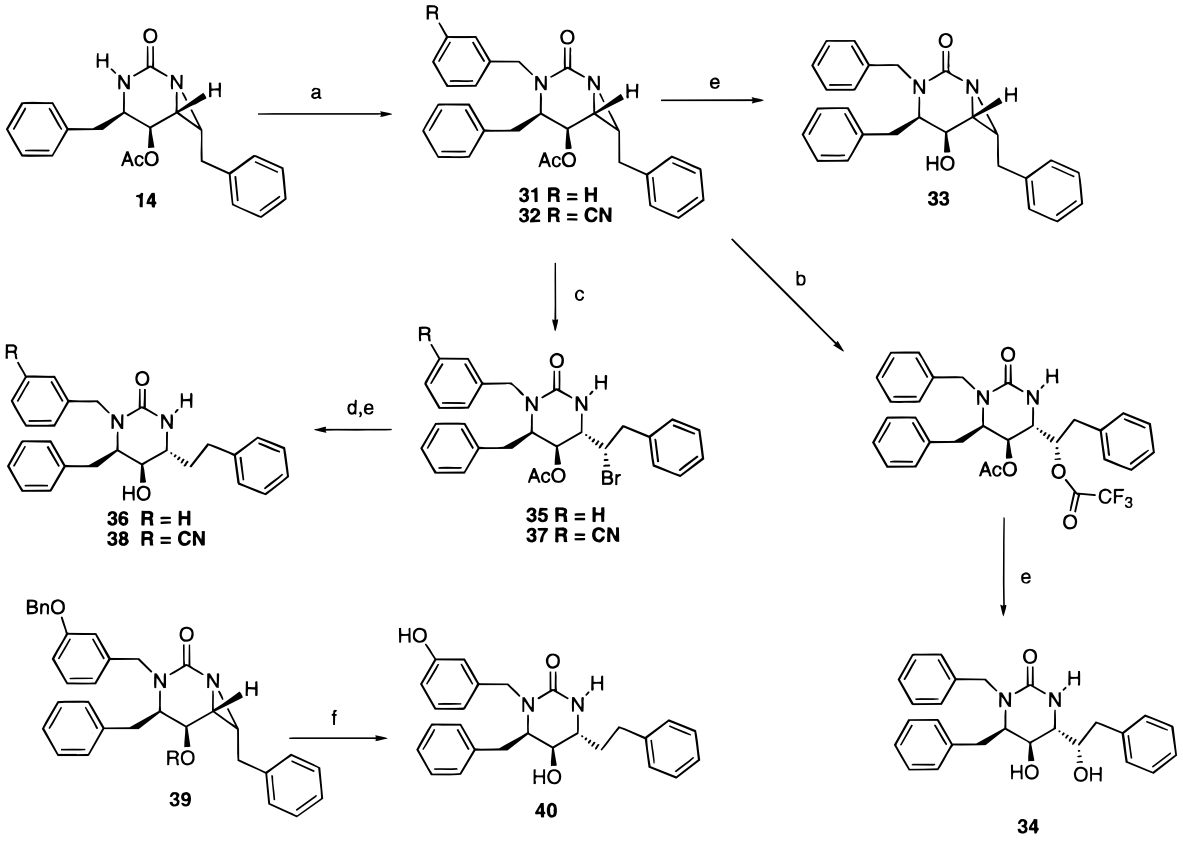
Identical P2/P2′ Substituents. We initially examined a variety of symmetrically N,N′-disubstituted P2 analogues keeping the P1/P1′ substituents constant (benzyl/phenethyl). The results are summarized in Table 1. Use of lipophilic P2 groups, such as the benzyl

Scheme 6[a]



[a] Reagents and conditions: (a) 1 equiv DAST/CH_2Cl_2; (b) Ms-Cl/Et_3N; (c) NaN_3/DMF; (d) NaI/DMF; (e) 50 psi H_2/10% Pd/C.

Scheme 7[a]



[a] Reagents and conditions: (a) NaH/DMF/Bn-Br; (b) CF_3COOH; (c) HBr(g)/dioxane; (d) Zn dust/acetic acid; (e) NaOH/MeOH; (f) H_2, 10% Pd/C.

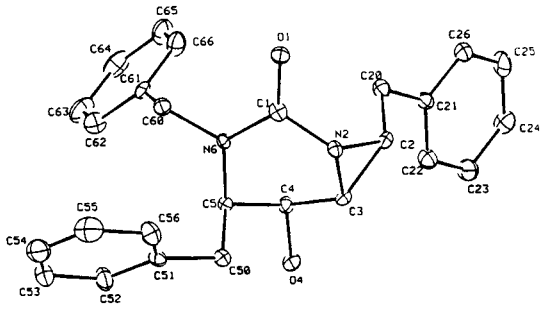
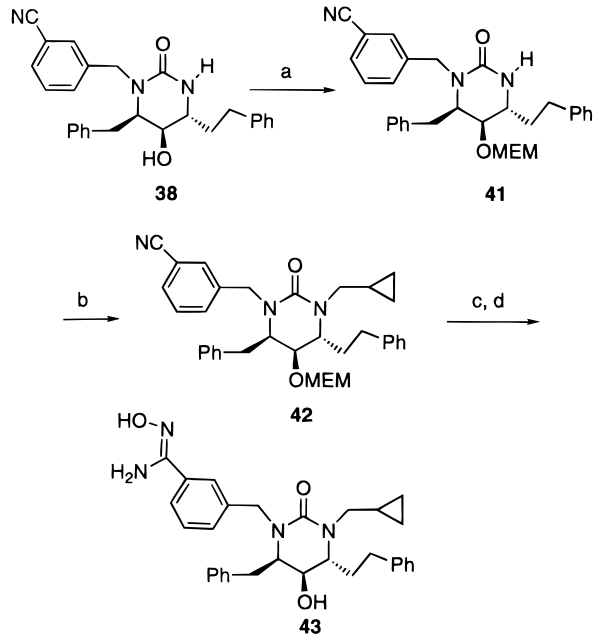


Figure 2. Small-molecule X-ray structure of aziridine **33**, which was used as the starting point for modeling studies shown in Figure 4.

analogue **50**, gave good enzyme potency (K_i = 11 nM). Introduction of hydrogen-bonding groups at the meta position of the *N*-benzyl substituents gave further improvements in potency.[6] The ketone **53**, the benzyl alcohol **54**, and the acid **55** all are subnanomolar inhibitors of HIVPR. Groups capable of forming multiple hydrogen bonds to the Asp 29, Asp 30, or Gly 48 residues, located near the edge of the S2 pockets, showed even greater potency.[6] For example the amide **56** (K_i = 0.09 nM) and the amidoxime **60** (K_i = 0.018 nM) are both extremely potent inhibitors of the enzyme. The X-ray crystal structure of **60** was previously disclosed[6] and showed an extensive network of hydrogen bonds with HIVPR, accounting for its potency. The antiviral potency of these analogues with hydrogen-bonding substituents are also very good with IC_{90} in the 30 to 50 nM range and in general are better than the corresponding hexahydro-1,3-diazepin-2-ones analogues.[7]

Scheme 8[a]

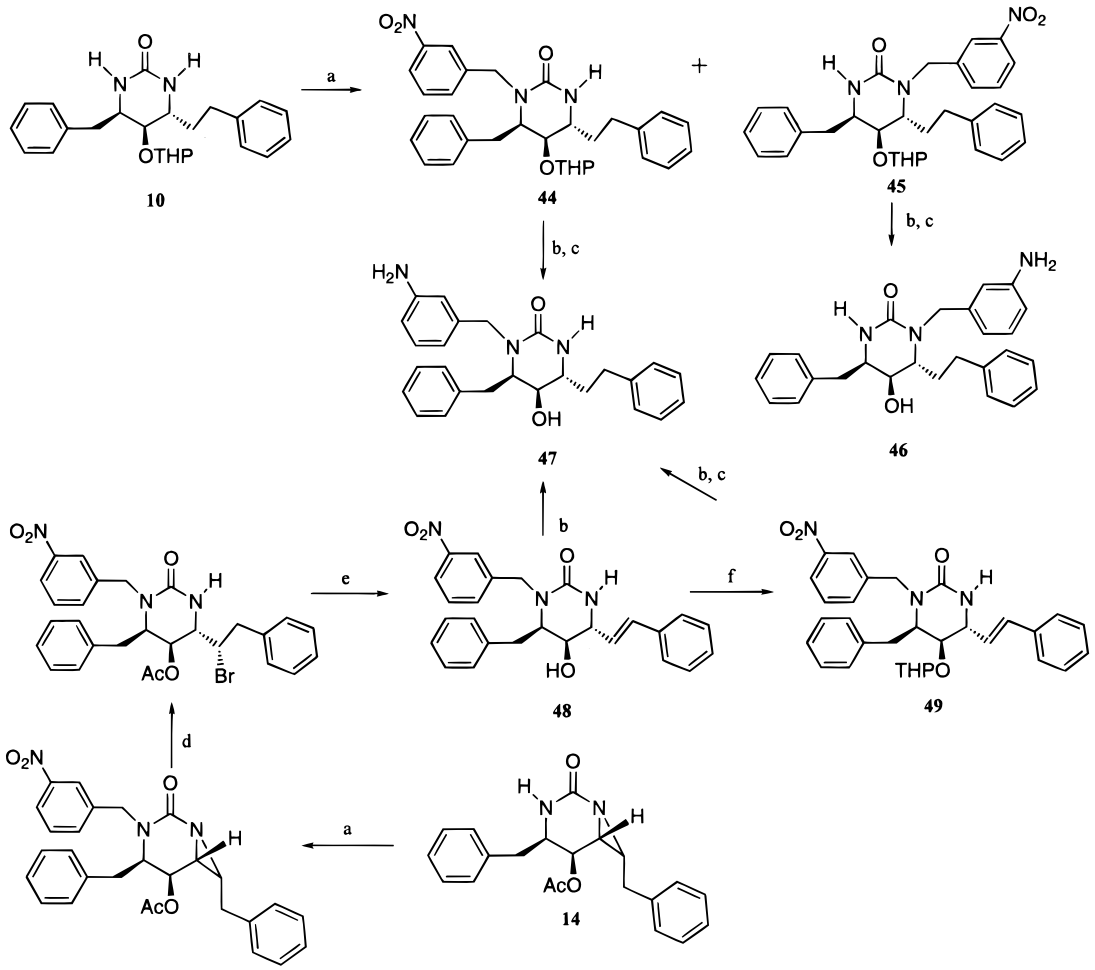


[a] Reagents and conditions: (a) MEM-Cl/Et_3N/CH_2Cl_2; (b) NaH/DMF/cyclopropylmethyl bromide; (c) HCl/dioxane; (d) NH_2OH·HCl/Et_3N/EtOH/reflux.

The better translation of K_i to IC_{90} for the tetrahydropyrimidinones is probably due to their increased lipophilicity.

To further improve the translation of some of the more polar analogues we introduced fluoro substituents in

Scheme 9[a]



[a] Reagents and conditions: (a) 3-NO_2-benzyl bromide/KO-*t*-Bu/THF; (b) 50 psi H_2/10% Pd/C; (c) HCl/MeOH; (d) HBr(g)/dioxane; (e) KOH/MeOH; (f) DHP/$CHCl_3$/TsOH.

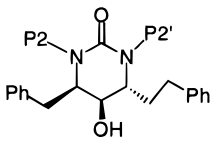
order to increase the lipophilicity of these analogues. Fluoro substituents were incorporated into the P2/P2′ phenyl groups ortho to the polar substituent (**59**, **63**, **65**, **66**), as well as into the P1/P1′ phenyl groups (**57**, **58**, **61**, **62**). The results were mixed; while the 4-fluoro aniline analogue **65** showed improved potency (K_i and IC_{90}) compared to the aniline analogue **64**, the 4-fluoro carboxamide analogue **59** showed a loss in potency compared to **56**. In the other cases there was little effect on potency or translation.

Some heterocycle containing substituents have been found to have the correct balance of hydrogen-binding ability and lipophilicity to produce excellent HIVPR inhibitors in the 1,3-diazepin-2-one series.[8,12,14] Introduction of these substituents into the tetrahydropyrimidinones also produced excellent results. For example, the pyrazole analogue **68** has an IC_{90} of 23 nM. The 5-indazole analogue **12** was the best with an IC_{90} of 6 nM. The heterocyclic amides, such as **73** and **74**, also exhibited good enzyme and antiviral potency. However, introduction of a polar amino group,[13] as in the 3-amino-5-indazole analogue **71**, decreased the antiviral potency to 383 nM.

To make more unsymmetrical inhibitors and to further explore the SAR of the P1′ substituent, several substituted-phenethyl analogues were examined. The results summarized in Table 3 show that an unsubstituted phenethyl P1′ group was the best. Any modification resulted in a significant loss in enzyme potency. For example the 1-fluoro-2-phenylethyl analogue **23** is 20-fold less potent than the corresponding phenethyl analogue **75**. Similar losses are seen with use of bromo, hydroxyl, or azido substituents. The incorporation of unsaturation into the side chain, as in the *trans*-styrene analogues **19** and **21**, also gave similar decreases in enzyme activity. We previously reported[6,15] that the benzyl-containing P1′ analogue **103**[6] (Figure 3) is 100-fold less potent than the phenethyl P1′ analogue **77**, and that the analogue lacking a P1′ substituent, **104**[15] (Figure 3), is over 100-fold less potent than the corresponding phenethyl analogue **4**. These results emphasize the critical importance of having a good lipophilic interaction between the P1 substituent of the inhibitor with the S1 specificity pocket of the enzyme.

The X-ray structure of tetrahydropyrimidinone **60**[6] complexed with HIVPR revealed that in order for the phenethyl side chain of the tetrahydropyrimidinone to interact optimally with the enzyme it has to be in a conformation in which there is an eclipsing interaction that is nearly anticlinal and thus is not the lowest energy conformer.[6] Any substituent on the phenethyl side chain would make this eclipsing conformation even more energetically unfavorable and thus lower the binding affinity for the enzyme.

Table 1. P2/P2′ SAR of Tetrahydropyrimidinone HIV Protease Inhibitors



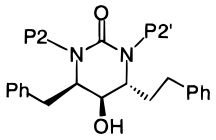
compd	P2/P2′	K_i[a] (nM)	IC_{90}[b] (nM)
9	H	970	
50	3-cyanobenzyl	11.00	1600
51	3-cyanobenzyl[c]	14.00	1560
52	3-cyano-4-fluorobenzyl	230	
53	3-acetylbenzyl	0.91	49
54	3-hydroxymethylbenzyl	0.49	109
55	3-carboxybenzyl	0.87	
56	3-(carboxamido)benzyl	0.09	35
57	3-(carboxamido)benzyl[c]	0.31	35
58	3-(carboxamido)benzyl[d]	0.15	90
59	3-(carboxamido)-4-fluorobenzyl	1.4	490
60	3-(carboxamido oxime)benzyl	0.02	49
61	3-(carboxamido oxime)benzyl[c]	0.02	49
62	3-(carboxamido oxime)benzyl[d]	0.01	117
63	3-(carboxamido oxime)-4-fluorobenzyl	0.06	51
64	3-aminobenzyl	1.70	365
65	3-amino-4-fluorobenzyl	0.25	36
66	4-amino-3-fluorobenzyl	8.00	539
67	3-(*N*-methyl-amino)benzyl	4.90	328
68	3-(pyrazol-3-yl)benzyl	0.10	22
12	indazol-5-yl-methyl[e]	0.02	6
69	indazol-6-yl-methyl	0.06	32
70	(3-methylindazol-5-yl)-methyl	0.10	18
71	3-aminoindazol-5-yl-methyl	0.03	383
72	3-aminobenzisoxazol-5-yl-methyl	0.41	132
73	3-(5-methyl-2-pyridylcarboxamido)-benzyl	0.08	26
74	3-(*N*-2-thiazolylcarboxamido)-benzyl	0.03	31

[a] Values were measured by cleavage of a fluorescent substrate using HPLC as described previously.[4,18] [b] Values were measured by a sensitive viral RNA-based detection system described previously.[4,19] Only compounds which displayed an antiviral IC_{90} concentration which was at least 3-fold less than the TC_{50} concentration are listed in the table. [c] The P1/P1′ phenyl groups contain a 4-fluoro substituent. [d] The P1/P1′ phenyl groups contain a 3,4-difluoro substituent. [e] See Scheme 2.

Since the tetrahydropyrimidinones were less crystalline and more soluble it was hoped that these physical characteristics would provide better pharmacokinetics. Several of these analogues were examined for oral bioavailability in the rat or dog at a dose of 10 mg/kg. The results of these studies, along with the corresponding hexahydro-1,3-diazepin-2-one analogues for comparison, are summarized in Table 2. As the data in Table 2 indicates, despite their favorable physical characteristics, the tetrahydropyrimidinones were less orally bioavailable than the corresponding hexahydro-1,3-diazepin-2-ones. In addition to the compounds listed in Table 2, the amidoximes **60**, **61**, and **63** were also examined for oral bioavailability in the rat, but no measurable blood levels were detected.

Different P2/P2′ Substituents. We next turned our attention to analogues having dissimilar P2/P2′ substituents in an effort to further decrease the symmetry and improve the potency and oral bioavailability of the tetrahydropyrimidinones. The results are summarized in Table 4. Having only one nitrogen substituent was not sufficient in most cases to make these monoalkylated analogues potent enough to be of interest. The exceptions were the amidoxime **83** and the aminoindazole **85** which did have subnanomolar enzyme activity.

Table 2. Oral Bioavailability of Tetrahydropyrimidinones



compd	P2/P2′	K_i[a] (nM)	IC_{90}[b] (nM)	Rat po[c] C_{max} (μM)
53	3-acetylbenzyl	0.09	9	0.18
	3-acetylbenzyl[d]	0.06	39	0.50
54	3-hydroxymethylbenzyl	0.49	109	0.24
	3-hydroxymethylbenzyl[e]	0.14	38	0.83
77	3-hydroxybenzyl	0.30	115	0.12
	3-hydroxybenzyl[e]	0.12	54	0.81
78	3-hydroxybenzyl[f]	12	2100	0.25
64	3-aminobenzyl	1.70	365	1.0
	3-aminobenzyl[e]	0.28	130	2.25
12	indazol-5-yl-methyl	0.02	6	0.25 (dog)
	indazol-5-yl-methyl[g]	0.014	7	1.0 (dog)
68	3-(pyrazol-3-yl)benzyl	0.10	22	0.16
	3-(pyrazol-3-yl)benzyl[d]	0.027	20	0.07

[a] Values were measured by cleavage of a fluorescent substrate using HPLC as described previously.[4,18] [b] Values were measured by a sensitive viral RNA-based detection system described previously.[4,19] Only compounds which displayed an antiviral IC_{90} concentration which was at least 3-fold less than the TC_{50} concentration are listed in the table. [c] Bioavailability was determined in groups of rats, unless otherwise indicated, dosed with compound in formulations containing propylene glycol, poly(ethylene glycol) 400, and water at 10 mg/kg as previously reported.[4,20] The maximum plasma concentration (C_{max}) is the observed peak plasma concentration after an oral dose. [d] Data for the corresponding 1,3-diazepin-2-one analogue (ref 12). [e] Data for the corresponding 1,3-diazepin-2-one analogue (ref 4). [f] Data for the analogue having 1-fluoro-2-phenylethyl as the P1′ substituent. [g] Data for the corresponding 1,3-diazepin-2-one analogue (ref 8).

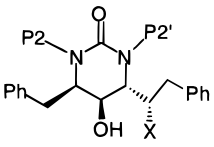
However, they were too polar and did not translate their good enzyme potency into good antiviral potency.

An interesting observation with the monoalkylated tetrahydropyrimidinones was that there was a difference in enzyme activity depending on the regioisomer. Having a P2 substituent (benzyl side) is 30- to 40-fold better than having a P2′ substituent (phenethyl side). For example, compare isomer **47** with **46**, or isomer **86** with **87**. This difference is probably due to changes in the conformation of the tetrahydropyrimidinone ring when the nitrogen on the phenethyl side is alkylated. It is also interesting to note that the lack of a P2′ group (as in **36**; K_i = 66 nM) does not cause as large a loss in the enzyme potency of the tetrahydropyrimidinones as the lack of a P1′ group (as in **104**;[15] K_i = 2,500 nM, Figure 3).

When both nitrogens are alkylated, there was very little difference in enzyme potency between the two regioisomers as one would expect for the interaction with a C_2 symmetric enzyme. Thus, the pairs of regioisomers that were prepared, **88**/**89**, **90**/**91**, and **92**/**93**, show nearly identical enzyme and antiviral potency. Many of the unsymmetrical P2/P2′ analogues also showed very good antiviral potency. In particular, the indazole (**92**, **93**) and the amidoxime (**98**) analogues all had antiviral potency less than 20 nM.

Since we were interested in potent inhibitors which could provide sufficient free drug at trough to inhibit both wild type and mutant variants of HIV with BID or TID dosing, we examined the effect of plasma protein binding on the antiviral potency of these analogues and we also examined them against a panel of mutant

Table 3. P1′ SAR of Tetrahydropyrimidinone Inhibitors of HIV Protease



compd	P2/P2′	X	K_i[a] (nM)	IC_{90}[b] (nM)
75	cyclopropylmethyl	H	9.8	5200
23	cyclopropylmethyl	F	201	
27	cyclopropylmethyl	OH	410	
36	benzyl (P2′ = H)	H	66	
34	benzyl (P2′ = H)	OH	320	
4	benzyl	H	15	2800
18	benzyl	Br	185	
19	benzyl	*c*	460	
8	2-naphthylmethyl	H	23	
30	2-naphthylmethyl	N_3	330	
28	2-naphthylmethyl	F	541	
20	2-naphthylmethyl	Br	100	
21	2-naphthylmethyl	*c*	280	
67	3-(*N*-methyl-amino)benzyl	H	4.90	328
76	3-(*N*-methyl-amino)benzyl	Br	23	
77	3-hydroxybenzyl	H	0.30	115
78	3-hydroxybenzyl	F	12	2100
54	3-hydroxymethylbenzyl	H	0.49	109
79	3-hydroxymethylbenzyl	Br	11	2100

[a] Values were measured by cleavage of a fluorescent substrate using HPLC as described previously.[4,18] [b] Values were measured by a sensitive viral RNA-based detection system described previously.[4,19] Only compounds which displayed an antiviral IC_{90} concentration which was at least 3-fold less than the TC_{50} concentration are listed in the table. [c] The P1′ group contains a *trans*-styrene substituent as shown in Scheme 4.

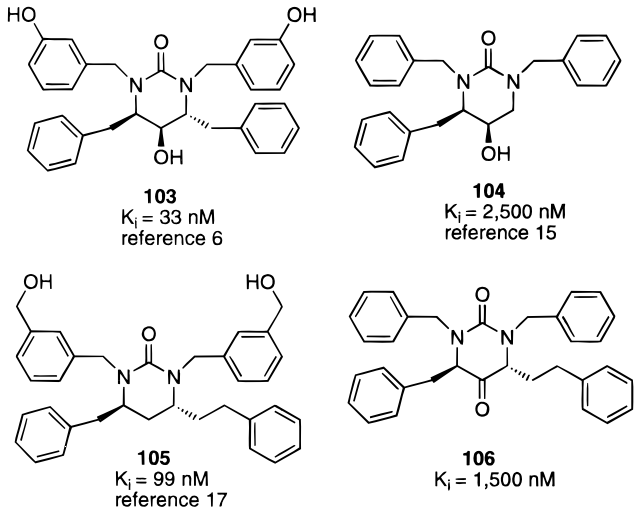


Figure 3. Structure of several tetrahydropyrimidin-2-ones discussed in the text.

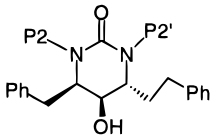
viruses as previously described.[5,7,16] Unfortunately, none of the tetrahydropyrimidinones showed any advantage over the analogous hexahydro-1,3-diazepin-2-ones, neither in terms of protein binding nor resistance profiles. In most cases the tetrahydropyrimidinones showed a greater loss of antiviral potency in the presence of plasma proteins (45 mg/mL serum albumin plus 1 mg/mL α-1-acid glycoprotein) than the hexahydro-1,3-diazepin-2-ones, probably due to their greater lipophilicity. The lack of any advantage precluded the further study, including pharmacokinetic evaluation, of these analogues.

1,3-Diazabicyclo[4.1.0]heptan-2-ones. The monoalkylated tetrahydropyrimidinones showed that it was possible to obtain subnamolar enzyme potency with inhibitors that contain just three interacting substituents (P1, P1′, P2) as in the amidoxime **83** and the aminoindazole **85**. If the tetrahydro-pyrimidinone scaffold could be modified to be less polar while maintaining the relative positions of the P1, P1′, and P2 substituents, then the translation of enzyme potency to antiviral potency could be improved. The aziridine **14** seemed like a potential candidate since it has one less N−H group than the tetrahydropyrimidinones which would decrease its polarity and enhance its cell penetration charateristics.

The small-molecule crystal structure[10] of the aziridine **33** (Figure 2) showed that its conformation was such that the P1/P2 benzyl groups as well as the hydroxyl group could be superimposed over that of the tetrahydropyrimidinone analogue. While the P1′ benzyl group of **33**, as found in its crystal structure, was not superimposable with the P1′ phenethyl group of the tetrahydropyrimidinone, rotation about the single bond achieves a good overlap. Computer models suggested that the energy difference in conformations would not preclude the adoption of this conformation. A computer model of **33** superimposed over the tetrahydropyrimidinone **60**[6] (in its HIV bound conformation) is shown in Figure 4. On the basis of this analysis, it was surprising to find that the aziridine **33** was a significantly less potent inhibitor (K_i = 3800 nM) of HIVPR than the corresponding tetrahydropyrimidinone **36** (K_i = 66 nM).

Other aziridine analogues were prepared, and the results are summarized in Table 5 along with the corresponding tetrahydropyrimidinone analogues for comparison. The results showed that the SAR of the aziridine series is nearly identical to the tetrahydropyrimidinone series. In both series the potency increases about 10-fold in going from the benzyl (**33**, **36**) to the carboxamide (**81**, **101**). It increases another 10-fold from the carboxamide to the amidoxime analogues (**83**, **102**). This suggests that both series are interacting with the enzyme in a similar binding mode. A possible explanation for this 100-fold difference in potency between aziridine and tetrahydropyrimidinone analogues may be due to the difference in the interaction of the urea carbonyl with the flap residues of HIVPR. As shown in Figure 4, while it is possible to overlap the P1/P1′/P2 and hydroxyl groups of the aziridine with the corresponding tetrahydropyrimidinone, the carbonyl of the two series cannot be overlapped properly. This difference in the placement of the carbonyl relative to the other recognition elements of the inhibitor, although small, may account for the loss in binding affinity. This suggests that the hydrogen-bonding interactions of the urea carbonyl with the flap residues is a very critical element in the recognition of tetrahydropyrimidinone inhibitors to HIVPR. The flap interaction may be nearly equal in importance to the hydrogen-bonding interaction of the hydroxyl group with the catalytic aspartic acids. For example, we previously reported that the deoxy analogue **105**[17] (K_i = 99 nM; Figure 3) showed a 200-fold loss in potency compared to the corresponding hydroxy analogue **54** (K_i = 0.49 nM). A similar loss in activity is also seen with the ketone analogue **106** (K_i

Table 4. Unsymmetrical P2/P2′ SAR of Tetrahydropyrimidinone HIVPR Inhibitors



compd	P2	P2′	K_i[a] (nM)	IC_{90}[b] (nM)
9	H	H	970	
36	benzyl	H	66	
38	3-cyanobenzyl	H	15	
80	3-cyano-4-fluorobenzyl	H	110	
40	3-hydroxybenzyl	H	2.60	4800
47	3-aminobenzyl	H	6.20	4330
81	3-(carboxamido)benzyl	H	5.60	
82	3-(carboxamido)-4-fluorobenzyl	H	14.0	
83	3-(carboxamido oxime)benzyl	H	0.24	370
84	3-(carboxamido oxime)-4-fluorobenzyl	H	1.40	3780
85	3-aminoindazol-5-yl-methyl	H	0.38	549
86	indazol-5-yl-methyl	H	1.20	590
87	H	indazol-5-yl-methyl	44	
46	H	3-aminobenzyl	157	
88	benzyl	3-cyano-4-fluorobenzyl	33	
89	3-cyano-4-fluorobenzyl	benzyl	40.0	
43	3-(carboxamido-oxime)benzyl[c]	cyclopropylmethyl	0.48	36
90	benzyl	3-aminoindazol-5-yl-methyl	0.65	71
91	3-aminoindazol-5-yl-methyl	benzyl	0.28	126
92	indazol-5-yl-methyl	3-aminobenzyl	0.08	13
93	3-aminobenzyl	indazol-5-yl-methyl	0.10	16
94	3-aminobenzyl	3-methylindazol-5-yl-methyl	0.13	32
95	3-aminobenzyl	3-cyanobenzyl	1.6	565
96	3-aminobenzyl	3-aminoindazol-5-yl-methyl	0.10	53
97	3-aminobenzyl	3-(carboxamido)benzyl	0.06	24
98	3-aminobenzyl	3-(carboxamido oxime)benzyl	0.02	17

[a] Values were measured by cleavage of a fluorescent substrate using HPLC as described previously.[4,18] [b] Values were measured by a sensitive viral RNA-based detection system described previously.[4,19] Only compounds which displayed an antiviral IC_{90} concentration which was at least 3-fold less than the TC_{50} concentration are listed in the table. [c] As shown in Scheme 8.

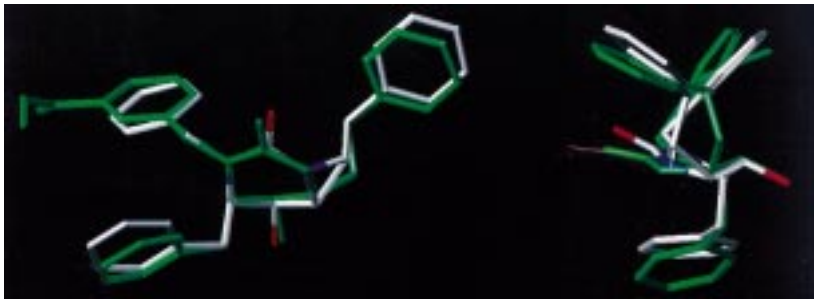


Figure 4. Computer model of a minimized conformation of aziridine **33** (color by atom) superimposed on tetrahydropyrimidin-2-one **60** (in green) as found in its bound conformation with HIV protease (as reported in ref 6). The P2′ substituent of **60** is omitted for clarity. View on the left highlights the good overlap found for the corresponding P1, P1′, and P2 groups of **33** with those of **60**. The view on the right highlights the difference in urea carbonyl trajectory between **33** and **60**.

= 1500 nM; Figure 3) compared to the corresponding hydroxy analogue **4** (K_i = 15 nM).

Conclusion

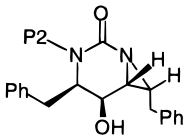
In this paper we reported our efforts to further explore the use of tetrahydropyrimidinones as an alternate scaffold for designing HIVPR inhibitors in order to try to exploit some of its advantages. Since the tetrahydropyrimidinones are more unsymmetrical (different P1/P1′) less crystalline, more soluble, and more lipophilic (mono-ol vs diol) than the corresponding hexahydro-1,3-diazepin-2-ones,[3] we hoped that the use of tetrahydropyrimidinones could better address the conflicting issues of solubility, potency, and oral bioavailability.

The SAR studies of the tetrahydropyrimidinones reported in this paper showed that the phenylethyl P1′ substituent, the hydroxyl group, and the urea carbonyl, are all critical for good activity. However, there was significant flexibility in the possible P2/P2′ substituents that could be used. Many analogues that contained identical or different P2/P2′ substituents, or only one P2 substituent, were found to have excellent enzyme potency and several had excellent antiviral potency.

A fair number of these compounds were examined for oral bioavailability in the rat or the dog at 10 mg/kg. However, despite the favorable physical charateristics listed above, the oral bioavailability of the tetrahydropyrimidinones were, in general, lower than the corresponding hexahydro-1,3-diazepin-2-ones. The reason for the lower oral bioavailability of the tetrahydropyrimidinones is not known, and further studies to establish a possible cause were not carried out.

Unfortunately, when all properties are considered, including potency, protein binding, solubility, bioavail-

Table 5. SAR of Diazabicyclo[4.1.0]heptan-2-ones HIVPR Inhibitors



compd	P2	K_i[a](nM)
99	H	3000
33	benzyl	3800
36[b]	benzyl	66
100	3-cyanobenzyl	2400
38[b]	3-cyanobenzyl	15
101	3-(carboxamido)benzyl	320
81[b]	3-(carboxamido)benzyl	5.60
102	3-(carboxamido oxime)benzyl	12
83[b]	3-(carboxamido oxime)benzyl	0.24

[a] Values were measured by cleavage of a fluorescent substrate using HPLC as described previously.[4,18] [b] Data for the corresponding tetrahydropyrimidinone analogue.

ability, and resistance profile, the tetrahydropyrimidinones did not offer any advantage over the hexahydro-1,3-diazepin-2-ones series and were not developed further.

Experimental Section

Biological Methods. Inhibition of HIVPR (K_i) was measured by the assay of the cleavage of a fluorescent substrate using HPLC as described previously.[4,18] The antiviral activity potency of compounds was assessed by measuring their effect on the accumulation of viral RNA transcripts 3 days after infection of MT-2 cells with HIV-1 RF as described previously.[4,19] The concentration of test compound which reduced the concentration of HIV viral RNA by 90% from the level measured in an untreated infected culture was designated IC_{90}. The cellular toxicity of compounds was assessed by measuring the extent of MTT dye reduction in uninfected MT-2 cell cultures grown for 3 days in the presence of various concentrations of test compound as previously described.[18,19] The compound concentration which decreased the level of MTT dye reduction by 50% was designated the TC_{50}. Only compounds which displayed an antiviral IC_{90} concentration which was at least 3-fold less than the TC_{50} concentration were considered to have a specific antiviral effect. Oral bioavailability of compounds was determined as previously reported.[4,20]

General. All reactions were carried out under an atmosphere of dry nitrogen. Commercial reagents were used without further purification. ^{1}H NMR (300 MHz) spectra were recorded using tetramethylsilane as an internal standard. TLC was performed on E. Merck 15710 silica gel plates. Medium-pressure liquid chromatography (MPLC) was carried out using EM Science silica gel 60 (230−400 mesh). HPLC chromatography was carried out using Jasco PV-987 pumps, Jasco UV-975 detectors, and Dupont Zorbax Sil or Zorbax NH_2 1-in. preparative columns. All final targets were obtained as noncrystalline amorphous solids unless specified otherwise. Mass spectra were measured with a HP5988A mass spectrometer with particle beam interface using NH_3 for chemical ionization or Finnigan MAT 8230 mass spectrometer with NH_3-DCI or VG TRIO 2000 for ESI. High-resolution mass spectra were measured on a VG 70-VSE instrument with NH_3 chemical ionization. Elemental analysis was performed by Quantitative Technologies, Inc., Bound Brook, NJ. For compounds where analysis was not obtained, HPLC analysis was used, and purity was determined to be >98% unless specified otherwise. The synthesis of compounds **4**, **9**, **50**, **54**, **56**, **59**, **60**, **64**, **65**, **66**, **67**, **75**, and **77** were previously reported in ref 6.

Molecular Modeling. Molecular modeling studies were performed using SYBYL version 6.0, commercially available from Tripos Associates, Inc., and viewed on a Silicon Graphics Indigo^2 workstation. Using the X-ray structure coordinates of **33**, the energy was calculated as 370.8 kcal/mol using the Tripos force field. The structure of **33** was allowed to relax by energy minimization to convergence using the MAXIMIN standard options [force field, Tripos; method, Powell; charge: Gasteiger-Huckel; dielectric constant, 1.0; termination, gradient 0.05 kcal/mol] to yield the relaxed X-ray structure of **33** with a calculated energy of 143.4 kcal/mol. Using the X-ray structure of amidoxime **60** (complexed with HIVPR as previously reported[6]) as a template, the relaxed structure **33** was manually docked to give the best overlap. An iterative process of manually adjusting the rotatable bonds in **33** to give the best overlap with the corresponding P1/P2/P1′ phenyl groups of tetrahydropyrimidinone **60** followed by energy minimization of **33** using MAXIMIN was used until the difference in conformation and energy was as small as possible. The final overlap is shown in Figure 4. The calculated energy of this final conformer of **33** was 143.9 kcal/mol, an energy value similar to that of the starting conformation (the relaxed X-ray structure of **33**).

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-1,3,6-tris-[phenylmethyl]-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (4). To a solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3,4,7-tetrakis-(phenylmethyl)-2*H*-1,3-diazepin-2-one **1**[4] (1.3 g, 2.6 mmol) in CH_2Cl_2 (40 mL) at room temperature was added 2-acetoxyisobutyryl bromide (1.7 g, 8.1 mmol), and the solution was stirred at room temperature for 15 min at which time TLC showed complete conversion. The solution was quenched with saturated $NaHCO_3$, and the organic layer was separated, washed with water and brine, dried, and concentrated to the corresponding bromo acetate. The crude bromo acetate was chromatographed (MPLC, silica gel, 30% EtOAc/hexane) to give 1.4 g of **2**. A fraction of the eluent from this chromatography was allowed to evaporate slowly to give crystals of the bromo acetate **2** that were of sufficient quality for single-crystal X-ray analysis.[6] For **2**: mp 178−180 °C; ^{1}H NMR ($CDCl_3$) δ 7.42−7.16 (m, 16 H), 6.89−6.79 (m, 4 H), 5.50 (d, J = 15 Hz, 1 H), 5.43 (d, J = 15 Hz, 1 H), 4.71 (t, J = 4 Hz, 1 H), 4.10 (d, J = 15 Hz, 1 H), 4.02 (m, 1 H), 3.87 (d, J = 15 Hz, 1 H), 3.71 (dd, J = 4 Hz, J = 7 Hz, 1 H), 3.58 (m, 1 H), 3.10 (dd, J = 6 Hz, J = 13 Hz, 1 H), 2.95 (dd, J = 3 Hz, J = 15 Hz, 1 H), 2.77 (dd, J = 10 Hz, J = 15 Hz), 2.65 (dd, J = 10 Hz, J = 13 Hz, 1 H), 1.61 (s, 3 H). Anal. ($C_{35}H_{35}N_2O_3Br$·0.2(C_6H_{14})) C, H, N.

The bromo acetate **2** (1.0 g) was dissolved in 50 mL of acetic acid and treated with Zn dust (7 g) and vigorously stirred at room temperature until TLC analysis showed complete conversion. The mixture was filtered and the solid washed thoroughly with EtOAc. The filtrate was washed with water, saturated $NaHCO_3$, and brine, dried, and evaporated to give the acetate. The crude acetate was chromatographed (MPLC silica gel 65% EtOAc/hexane) to give 820 mg of the acetate **3** as a white foam. The acetate **3** (400 mg, 0.68 mol) was dissolved in MeOH and treated with 1 N NaOH (5 mL), and the mixture was stirred at room temperature. The mixture was concentrated, and the residue was partitioned between 1 N HCl and EtOAc. The organic extract was washed with water and brine, dried, and concentrated, and the resulting residue was chromatographed (MPLC, silica gel, 65% EtOAc/hexane) to give 300 mg of **4** as a foam: ^{1}H NMR ($CDCl_3$) δ 7.37−7.15 (m, 16 H), 6.97 (m, 4 H), 5.46 (d, J = 15 Hz, 1 H), 5.42 (d, J = 14 Hz, 1 H), 3.89 (d, J = 14 Hz, 1 H), 3.82 (d, J = 15 Hz, 1 H), 3.41 (m, 1 H), 3.33 (m, 1 H), 3.17 (m, 1 H), 2.95 (m, 2 H), 2.85 (m, 2 H), 2.40 (t, J = 8 Hz, 2 H), 1.9 (m, 1 H), 1.61 (m, 2 H); CIMS (NH_3) m/z 491 (M + H$^+$, 100). Anal. ($C_{33}H_{34}N_2O_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[2-naphthylmethyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (8). Method 1. To a solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis-[2-naphthylmethyl]-4,7-bis-[phenylmethyl]-2*H*-1,3-diazepin-2-one **5**[4] (2.0 g, 3.3 mmol) in CH_2Cl_2 (40 mL) at room temperature was added 2-acetoxyisobutyryl bromide (2.0 g, 10 mmol) and the solution was stirred at room temperature for 10 min at which time TLC showed complete conversion. The solution was quenched with saturated $NaHCO_3$, and the organic layer was separated and

washed with water and brine. The organic layer was dried and concentrated. The residue was chromatographed (MPLC, silica gel, 30% EtOAc/hexane) to give 1.3 g of the 1-bromo-2-phenylethyl acetate tetrahydropyrimidinone **6**: ^{1}H NMR ($CDCl_3$) δ 7.89−7.78 (m, 6 H), 7.74 (m, 2 H), 7.60 (m, 1 H), 7.56−7.46 (m, 5 H), 7.19−7.13 (m, 4 H), 7.04 (m, 2 H), 6.47−6.74 (m, 2 H), 6.67 (d, J = 8 Hz, 2 H), 5.72 (d, J = 15 Hz, 1 H), 5.66 (d, J = 15 Hz, 1 H), 4.67 (m, 1 H), 4.28 (d, J = 15 Hz, 1 H), 4.13 (d, J = 15 Hz, 1 H), 4.06 (m, 1 H), 3.77 (dd, J = 4 Hz, J = 8 Hz, 1 H), 3.59 (m, 1 H), 3.20 (dd, J = 5 Hz, J = 13 Hz, 1 H), 2.85 (abx m, 2 H), 2.68 (dd, J = 5 Hz, J = 13 Hz, 1 H), 1.26 (s, 3 H); CIMS (NH_3) m/z 713 (M + H$^+$, 100) 711 (M + H$^+$, 95). Anal. ($C_{43}H_{39}N_2O_3Br$) C, H, N.

The 1-bromo-2-phenylethyl acetate **6** (0.4 g, 0.6 mmol) was dissolved in 50 mL of acetic acid and treated with Zn dust (1 g) and vigorously stirred at room temperature until TLC analysis showed complete conversion. The mixture was filtered and the solid washed thoroughly with EtOAc. The filtrate was washed with water, saturated $NaHCO_3$, and brine. The solution was dried and evaporated to give the phenethyl acetate **7**. The crude phenethyl acetate was dissolved in MeOH and treated with 1 N NaOH (5 mL) and the mixture stirred at room temperature. The mixture was concentrated, and the residue was partitioned between 1 N HCl and EtOAc. The organic extract was washed with water and brine, dried, and concentrated. The resulting residue was chromatographed (MPLC, silica gel, 50% EtOAc/hexane) to give 170 mg of **8** as a white foam.

Method 2. A solution of **21** (30 mg) in dioxane was treated with 10% Pd/C (30 mg) and hydrogenated at 50 psi for 3 h. The solution was filtered and concentrated, and the residue was chromatographed (HPLC, Zorbax Sil, 70% EtOAc/hexane) to give 10 mg of **8** as a white foam identical to that obtained using method 1 above. For **8**: ^{1}H NMR ($CDCl_3$) δ 7.87−7.77 (m, 6 H), 7.67 (s, 1 H), 7.61 (s, 1 H), 7.54−7.40 (m, 6 H), 7.26−7.16 (m, 6 H), 7.03−6.93 (m, 4 H), 5.66 (d, J = 15 Hz, 1 H), 5.63 (d, J = 15 Hz, 1 H), 4.06 (d, J = 15 Hz, 1 H), 4.01 (d, J = 15 Hz, 1 H), 3.41−3.34 (m, 2 H), 3.20 (m, 1 H), 3.08−2.81 (abx m, 2 H), 2.42 (m, 2 H), 1.90 (m, 1 H), 1.65 (m, 1 H), 1.60 (bs, 1 H); DCI MS (NH_3) m/z 591.5 (M + H$^+$, 100). Anal. ($C_{41}H_{38}N_2O_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (9). Method 1. A solution of **17** (7.0 g, 23 mmol) in THF/MeOH was treated with 3 g of 10% Pd/C and hydrogenated in a Parr bottle at 50 psi for 3 h at room temperature. The solution was filtered through Celite and the filtrate concentrated to give 6.3 g of **9**. The product was identical to that previously described.[6]

Method 2. A solution of **16** (0.5 g, 1.4 mmol) in methanol was treated with 5 mL of 1 N NaOH solution and stirred at room temperature for 8 h. The solution was concentrated to dryness and the residue acidified with 1 N HCl and extracted into ethyl acetate. The organic extract was washed with water and brine and then dried over $MgSO_4$. The solution was filtered and concentrated to give 0.3 g of **9**. Product was identical to that previously described:[6] mp 162−163 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.19 (m, 10 H), 6.69 (bs, 1 H), 5.00 (bs, 1 H), 4.61 (d, J = 8 Hz, 1 H), 3.60 (t, J = 7 Hz, 1 H), 3.49 (bm, 1 H), 3.38 (bm, 1 H), 3.30 (dd, J = 7 Hz, 14 Hz, 1 H, abx), 2.82 (dd, J = 7 Hz, 14 Hz, 1 H, abx), 2.78 (m, 1 H, abx) 2.57 (m, 1 H, abx), 1.62 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.1, 141.7, 137.2, 129.7, 129.2, 128.8, 128.8, 127.3, 126.4, 65.9, 57.1, 53.5, 38.4, 37.7, 32.4; CIMS (NH_3) m/z 311 (M + H$^+$, 100). Anal. ($C_{19}H_{22}N_2O_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-5-(tetrahydropyran-2-yl-oxy)-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (10). A solution of alcohol **9** (6.2 g, 20 mmol) in chloroform was treated with dihydropyran (12.0 g, 140 mmol) and TsOH·H_2O (0.4 g, 2 mmol) and stirred overnight at room temperature. The mixture was then washed with aqueous sodium bicarbonate and brine and then dried over $MgSO_4$. The solution was filtered and concentrated to give 7.8 g of **10** as white solid: mp 182−184 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.19 (m, 10 H), 4.83 (bs, 0.5 H), 4.78 (bs, 0.5 H), 4.69 (bs, 1 H), 4.45 (bs, 1 H), 3.97−3.42 (m, 5 H), 3.09−2.57 (m, 4 H), 1.92−1.51 (m, 8 H); CIMS (NH_3) m/z 395.3 (M + H$^+$, 100). Anal. ($C_{24}H_{30}N_2O_3$) C, H, N.

[4*R*,5*R*, 6*R*)-Tetrahydro-5-hydroxy-1,3-bis(1*H*-indazol-5-ylmethyl)-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (12). A solution of **10** (2.47 g, 6.3 mmol) and 5-(bromomethyl)-1-SEM-indazole[8,11] (4.70 g,13.8 mmol) in THF was treated dropwise with a 1 M solution of KO-*t*-Bu (in THF) via syringe. The resulting solution was stirred at room temperature for 30 min at which time analysis by TLC showed no starting material remained. The solution was concentrated to dryness and the residue chromatographed (MPLC, silica gel, 25% EtOAc/hexane) to give 4.3 g of **11** (75% yield). A solution of **11** (4.3 g, 4.6 mmol) in MeOH (150 mL) was treated with 50 mL of concentrated HCl and heated at reflux for 2 h. The solution was concentrated to half its volume on a rotary evaporator and made basic with 1 N NaOH. The solid precipitate was extracted into ethyl acetate, washed with water and brine, and dried over $MgSO_4$. The solution was filtered and concentrated and the residue chromatographed (MPLC, silica gel, 1.5% MeOH/EtOAc) to give 2.3 g (88% yield) of **12**: mp 130−134 °C; ^{1}H NMR ($CDCl_3$) δ 10.95 (bs, 1H), 10.87 (bs, 1 H), 7.84 (s, 1 H), 7.72 (s, 1 H), 7.50 (s, 1 H), 7.47 (s, 1 H), 7.35−7.15 (m, 10 H), 7.07 (2 overlapping d, J = 7 Hz, 2 H), 6.95 (2 overlapping d, J = 7 Hz, 2 H), 5.51 (d, J = 15 Hz, 1 H), 5.48 (d, J = 15 Hz, 1 H), 4.10 (d, J = 15 Hz, 1 H), 3.94 (d, J = 15 Hz, 1 H), 3.53 (m, 1 H), 3.42 (m, 1 H), 3.32 (m, 1 H), 2.94 (m, 2 H), 2.42 (m, 2 H), 1.90 (m, 1 H), 1.76 (m, 1 H), 1.62 (bs, H); CIMS (NH_3) m/z 571 (M + H$^+$, 100). Anal. ($C_{35}H_{34}N_6O_2$) C, H, N.

(4*R*,5*S*,6*R*,7*R*)-1,3-diaza-4,7-bis-(phenylmethyl)-5-(acetyloxy)-bicyclo[4.1.0]heptan-2-one (14). A solution of monoacetate **13**[4] (2.0 g, 5.0 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C in an ice bath and treated with DAST (0.8 mL, 6.0 mmol) via syringe. The solution was stirred at 0 °C for 30 min at which time TLC analysis showed complete consumption of **13**. The solution was diluted with saturated sodium bicarbonate, and the organic layer was separated and washed with water and brine, dried, and concentrated to give 1.9 g of **14** as a white solid. The solid was recrystallized from ethyl acetate: mp 222 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.00 (m, 10 H), 5.54 (d, J = 6 Hz, 1 H), 4.97 (dd, J = 5 Hz, J = 7 Hz, 1 H), 3.81 (m, 1 H), 3.26 (dd, J = 4 Hz, J = 15 Hz, 1 H), 3.16 (dd, J = 4 Hz, J = 14 Hz, 1 H), 3.00−2.84 (m, 3 H), 2.65 (dd, J = 8 Hz, J = 15 Hz, 1 H), 2.10 (s, 3 H); DCI MS (NH_3) m/z 351 (M + H$^+$, 100). Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

(4*S*,5*S*,6*R*)-Tetrahydro-5-(acetyloxy)-4-(1*S*-bromo-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (15). A solution of aziridine **14** (1.0 g, 2.9 mmol) in dioxane was cooled in an ice bath while HBr(g) was bubbled into the solution for 10 min. Ice bath was removed and the solution stirred at room temperature for 20 min. The solvent was removed under vacuum, and the residue was chromatographed (MPLC, silica gel, EtOAc) to give 900 mg of **15** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.36−7.11 (m, 10 H), 5.85 (bs, 1 H), 5.07 (bs, 1 H), 5.05 (m, 1 H), 4.23 (m, 1 H), 3.95 (m, 1 H), 3.61 (m, 1 H), 3.23 (d, J = 7 Hz, 2 H), 2.70 (abx m, 2 H), 2.12 (s, 3 H); CIMS (NH_3) m/z 433, 431 (M + H$^+$, 35).

(4*R*,5*R*,6*R*)-Tetrahydro-5-(acetyloxy)-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (16). A solution of bromo acetate **15** (900 mg, 2.1 mmol) in acetic acid was treated with 10 g of Zn dust and stirred overnight at room temperature. The solution is diluted with ethyl acetate and filtered through a fritted funnel, and the solids were washed with ethyl acetate. The filtrate was concentrated under vacuum, and the residue was chromatographed (MPLC, silica gel, EtOAc − 10% MeOH/EtOAc) to give 600 mg of **16** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.35−7.10 (m, 10 H), 6.08 (bs, 1 H), 5.28 (bs, 1 H), 4.80 (m, 1 H), 3.80 (m, 1 H), 3.42 (m, 1 H), 2.83 (abx m, 2 H), 2.77 (m, 1 H), 2,62 (m, 1 H), 2.12 (s, 3 H), 1.74 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.2, 156.3, 140.26, 135.40, 129.0, 128.9, 128.5, 128.3, 127.3, 126.2, 67.1, 53.5, 51.2, 36.9, 31.4, 20.9; CIMS (NH_3) m/z 353 (M + H$^+$, 100).

(4*S*,5*S*,6*R*)-Tetrahydro-5-(hydroxy)-4-(β-styrene)-6-(phen-

ylmethyl)-2(1*H*)-pyrimidinone (17). A solution of aziridine **14** (8.77 g, 25 mmol) in dioxane was cooled in an ice bath while HBr(g) was bubbled into the solution for 10 min. The ice bath was removed and solution stirred at room temperature for 20 min. The solvent was removed under vacuum, and the crude bromo acetate **15** was dissolved in MeOH and treated with 10 g of KOH. The solution was stirred at room temperature overnight. The solution was concentrated under vacuum and the residue acidified with 1 N HCl. The solid was extracted into chloroform (with a small amount of methanol to help dissolve it). The extract was dried over $MgSO_4$, filtered, and concentrated to give 7.0 g of **17** as a white solid: mp 231−233 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.36−7.21 (m, 10 H), 6.56 (d, J = 16 Hz, 1 H), 6.06 (dd, J = 5 Hz, J = 16 Hz, 1 H), 5.74 (bs, 1 H, exchanges), 4.95 (bs, 1 H, exchanges), 4.18 (m, 1 H), 3.75 (m, 1 H), 3.58 (m, 1 H), 3.01 (abx dd, J = 6 Hz, J = 14 Hz, 1 H), 2.81 (abx dd, J = 6 Hz, J = 14 Hz, 1 H); CIMS (NH_3) m/z 309 (M + H$^+$, 100). Anal. ($C_{19}H_{20}N_2O_2 \cdot 0.2H_2O$) C, H, N.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis-[phenylmethyl]-5-hydroxy-4-(1*S*-bromo-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (18): mp 135.0−137.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.18−7.17 (m, 16 H), 7.06−7.03 (m, 2 H), 6.88−6.85 (m, 2 H), 5.40 (d, J = 14 Hz, 1 H), 5.36 (d, J = 14 Hz, 1 H), 4.23 (d, J = 15 Hz, 1 H), 4.20−4.16 (m, 1 H), 3.81−3.75 (m, 1 H), 3.64−3.60 (m, 1 H), 3.48 (d, J = 15 Hz, 1 H), 3.38−3.31 (m, 1 H), 2.98−2.91 (m, 3 H), 2.74−2.65 (m, 1 H), 2.11−2.08 (m, 1 H); CIMS (M + NH_4^+) 588. HRMS calcd for $C_{33}H_{34}N_2O_2$-Br (M + H$^+$), 569.1804; found, 569.1784. Anal. ($C_{33}H_{33}N_2O_2$-Br$\cdot$0.2H_2O) C, H, N.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis-[phenylmethyl]-5-hydroxy-4-(*β*-styrene)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (19): mp 186.0−188.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.37−7.18 (m, 16 H), 7.10−7.05 (m, 4 H), 6.52 (d, J = 16 Hz, 1 H), 5.08−5.80 (dd, J = 7 Hz, 16 Hz, 2 H), 5.40 (d, J = 15 Hz, 1 H), 5.33 (d, J = 15 Hz, 1 H), 4.01 (d, J = 15 Hz, 1 H), 3.82−3.77 (m, 1 H), 3.57−3.53 (m, 1 H), 3.46−3.40 (m, 1 H), 3.35 (d, J = 15 Hz, 1 H), 2.97−2.91 (dd, J = 6 Hz, 13 Hz, 1 H), 2.68−2.61 (dd, J = 8 Hz, 13 Hz, 1 H), 2.02 (s, 1 H); CIMS (M + H$^+$) 489. HRMS calcd for $C_{33}H_{32}N_2O_2$ (M + H$^+$), 489.2542; found, 489.2555. Anal. ($C_{33}H_{32}N_2O_2 \cdot 0.8H_2O$) C, H, N.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis-[2-naphthylmethyl]-5-hydroxy-4-(1*S*-bromo-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (20). The 1-bromo-2-phenylethyl acetate **6** (100 mg, 0.14 mmol) was dissolved in MeOH (5 mL) and treated with 1 N NaOH (1 mL, 1.0 mmol) at room temperature for 1 h. The mixture was concentrated, and the residue was partitioned between 1 N HCl and EtOAc. The organic extract was washed with water and brine and dried over $MgSO_4$. The solution was filtered and concentrated to give 80 mg of **18** as a white solid: mp 85 °C (dec); ^{1}H NMR ($CDCl_3$) δ 7.89−7.78 (m, 7 H), 7.64 (m, 2 H), 7.50 (m, 4 H), 7.40−7.00 (m, 9 H), 6.67 (d, J = 8 Hz, 2 H), 5.60 (d, J = 15 Hz, 1 H), 5.56 (d, J = 15 Hz, 1 H), 4.21 (d, J = 15 Hz, 1 H), 3.76 (m, 1 H), 3.62 (d, J = 15 Hz, 1 H), 3.36 (m, 1 H), 3.01−2.90 (m, 3 H), 2.68 (dd, J = 5 Hz, J = 13 Hz, 1 H), 2.00 (d, J = 7 Hz, 1 H); CIMS (NH_3) m/z 669.2 (M + H$^+$, 67), 671.2 (M + H$^+$, 72), 589.2 ((M − HBr + H$^+$, 100). Anal. ($C_{41}H_{37}N_2O_2Br \cdot 0.2H_2O$) C, H, N.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis-[2-naphthalenylmethyl]-5-hydroxy-4-(*β*-styrene)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (21). Method 1. A solution of mesylate **29** (100 mg, 0.15 mmol) in DMF was treated with NaI (100 mg, 1.5 mmol) and heated at 80 °C for 2 h and then at 40 °C overnight. The solution was diluted with water and the solid extracted into ethyl acetate. The extracts were washed with water and brine and dried over $MgSO_4$. The solution was filtered and concentrated, and the solid residue was chromatographed (HPLC, Zorbax Sil, 50% EtOAc/hexane) to give 50 mg of **21** as a white solid.

Method 2. The 1-bromo-2-phenylethyl acetate **6** (100 mg, 0.14 mmol) was dissolved in MeOH (10 mL) and treated with solid KOH (1.0 g, 17.8 mmol) at room temperature for 1 h. The mixture was concentrated and the residue was partitioned between 1 N HCl and EtOAc. The organic extract was washed with water and brine, and dried over $MgSO_4$. The solution was filtered and concentrated to give 50 mg of **21** as a white solid identical to that obtained using method 1 above: ^{1}H NMR ($CDCl_3$) δ 7.93−7.65 (m, 6 H), 7.59 (m, 1 H), 7.55−7.40 (m, 6 H), 7.40−7.20 (m, 9 H), 7.12 (d, J = 8 Hz, 2 H), 6.55 (d, J = 16 Hz, 1 H), 5.91 (dd, J = 8 Hz, 16 Hz, 1 H), 5.70 (d, J = 15 Hz, 1 H), 5.55 (d, J = 15 Hz, 1 H), 4.14 (d, J = 15 Hz, 1 H), 3.80 (m, 1 H), 3.53 (d, J = 15 Hz, 1 H), 3.53 (m, 2 H), 2.98−2.70 (abx m, 2 H), 1.85 (d, J = 5 Hz, 1 H); DCI MS (NH_3) m/z 589 (M + H$^+$, 100). Anal. ($C_{41}H_{36}N_2O_2 \cdot 0.5H_2O$) C, H, N.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis-[cyclopropylmethyl]-5-hydroxy-4-(1*S*-fluoro-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (23). A solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis-[cyclopropylmethyl]-4,7-bis-[phenylmethyl]-2*H*-1,3-diazepin-2-one **22**[4] (0.112 g, 0.26 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C in an ice bath and treated with DAST (0.034 mL, 0.26 mmol) via syringe. The solution was stirred at 0 °C for 30 min at which time TLC showed complete conversion. The solution was diluted with water and the organic layer was separated, washed with water and brine, dried and concentrated. The residue was chromatographed (HPLC, Zorbax Sil, 65% EtOAc/hexane) to give 45 mg of **23** as a foam: ^{1}H NMR ($CDCl_3$) δ 7.36−7.21 (m, 8 H), 7.08−7.06 (m, 2 H), 4.83 (m, 0.5 H), 4.73 (m, 0.5 H), 4.05 (dd, J = 7 Hz, J = 15 Hz, 1 H), 3.86 (dd, J = 7 Hz, J = 15 Hz, 1 H), 3.81 (m, 1 H), 3.70 (m, 1 H), 3.61 (m, 1 H), 3.30 (abx m, 2 H), 2.91−2.61 (m, 4 H), 2.49 (d, J = 7 Hz, 1 H), 1.06 (m, 1 H), 0.96 (m, 1 H), 0.60−0.06 (m, 8 H); CIMS (NH_3) m/z 437.2 (M + H$^+$, 100). HRMS calcd for $C_{27}H_{34}N_2O_2F$ (M + H$^+$), 437.2604; found, 437.2593.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5-(2-methoxyethoxymethoxy)-6-hydroxy-1,3-bis-[cyclopropylmethyl]-4,7-bis-[phenylmethyl]-2*H*-1,3-diazepin-2-one (24). A solution of diol **22**[4] (2.06 g, 4.7 mmol) in CH_2Cl_2 (20 mL) was treated with MEM-Cl (0.71 g, 5.69 mmol) and diisopropylethylamine (1.53 g, 11.8 mmol), and the mixture was heated at reflux for 8 h. The mixture was washed with water, saturated sodium carbonate, and brine and then dried over $MgSO_4$. The mixture was filtered, concentrated, and the residue was chromatographed (HPLC, Zorbax Sil, 5% MeOH/$CHCl_3$) to give 1.3 g of **24** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.30−7.11 (m, 10 H), 4.95 (s, 2 H), 4.10 (m, 1 H), 3.89 (m, 3 H), 3.75−3.46 (m, 6 H), 3.41 (s, 3 H), 3.39−2.97 (m, 5 H), 1.98 (m, 2 H), 0.90 (m, 2 H), 0.40 (m, 4 H), 0.03 (m, 4 H); CIMS (NH_3) m/z 523 (M + H$^+$, 100).

(4*R*,5*S*,6*R*)-Tetrahydro-1,3-bis-[cyclopropylmethyl]-5-hydroxy-4-(1*S*-hydroxy-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (27). To a solution of **24** (1.0 g, 1.9 mmol) in THF were added triphenyl phosphine (1.0 g, 3.8 mmol), DEAD (0.7 g, 4.o mmol), and chloroacetic acid (0.40 g, 4.2 mmol), and the mixture was stirred for 20 h at room temperature. The mixture was evaporated, and the residue was chromatographed (MPLC, silica gel, 50% EtOAc/hexane) to give 0.9 g of chloroacetate **25** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.27−7.21 (m, 10 H), 5.39 (m, 1 H), 4.95 (d, J = 13 Hz, 1 H), 4.80 (d, J = 13 Hz, 1 H), 4.70 (s, 1 H), 4.27 (m, 1 H), 4.19 (m, 2 H), 4.00−3.70 (m, 5 H), 3.93 (s, 2 H), 3.48 (dd, J = 7 Hz, J = 15 Hz, 1 H), 3.37, (s, 3 H), 3.02−2.90 (m, 5 H), 1.90 (dd, J = 7 Hz, J = 15 Hz, 1 H), 1.22 (m, 2 H), 0.76 (m, 1 H), 0.57 (m, 2 H), 0.40−0.20 (m, 4 H), 0.0 (m, 1 H); CIMS (NH_3) m/z 599 (M + H$^+$, 100).

A solution of the chloroacetate **25** (0.9 g, 1.5 mmol) in methanol (15 mL) was treated with 4 mL of a 1 N NaOH solution and stirred at room temperature for 1 h. The solution was concentrated to dryness and the was residue extracted into ethyl acetate, washed with water and brine, and then dried over $MgSO_4$. The mixture was filtered and concentrated, and the residue was chromatographed (HPLC, Zorbax Sil, 85% EtOAc/hexane) to give 0.4 g of alcohol **26** as a viscous oil which slowly solidified over a few days: ^{1}H NMR ($CDCl_3$) δ 7.33−7.13 (m, 10 H), 4.92 (d, J = 7 Hz, 1 H), 4.84 (d, J = 7 Hz, 1 H), 4.28 (m, 1H), 4.20 (m, 1 H), 3.91−3.79 (m, 5 H), 3.60 (m, 2 H), 3.50 (dd, J = 7 Hz, J = 15 Hz, 1 H), 3.38 (s, 3 H), 3.06 (d, J = 7 Hz, 2 H), 2.94 (dd, J = 7 Hz, J = 15 Hz, 1 H), 2.82−2.62 (m, 2 H), 2.44 (d, J = 7 Hz, 1 H), 1.91 (dd, J = 7 Hz, J = 15 Hz,

1 H), 1.21 (m, 1 H), 0.81 (m, 1 H), 0.58 (m, 2 H), 0.45−0.25 (m, 4 H), 0.02 (m, 2 H); CIMS (NH_3) *m/z* 523 (M + H^+, 100).

A solution of **26** (70 mg, 0.13 mmol) in methanol was cooled in an ice bath while HCl gas was bubbled in for 20 min. The solution was allowed to warm to room temperature and stirred for 1 h. The solution was evaporated to dryness under vacuum, and the residue was chromatographed (HPLC, Zorbax Sil, 80% EtOAc/hexane) to give 48 mg of **27** as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.36−7.17 (m, 10 H), 4.24 (m, 2 H), 3.98 (dd, J = 8 Hz, J = 15 Hz, 1 H), 3.80 (m, 1 H), 3.72 (m, 1 H), 3.68 (dd, J = 8 Hz, J = 15 Hz, 1 H), 3.41 (d, J = 3 Hz, 1 H), 3.15−2.96 (m, 2 H, abx), 2. 85 (dd, J = 7 Hz, J = 15 Hz, 1 H), 2.79−2.51 (m, 2 H, abx), 2.19 (m, 1 H), 2.10 (dd, J = 7 Hz, J = 16 Hz, 1 H), 1.09 (m, 1 H), 0.82 (m, 1 H), 0.58−0.25 (m, 6 H), 0.05 (m, 2 H); CIMS (NH_3) *m/z* 435 (M + H^+, 100). HRMS calcd for $C_{27}H_{35}N_2O_3$ (M + H^+), 435.2648; found, 435.2638.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis-[2-naphthylmethyl]-5-hydroxy-4-(1*S*-fluoro-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (28). A solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis-[2-naphthylmethyl]-4,7-bis-[phenylmethyl]-2*H*-1,3-diazepin-2-one **5**[4] (0.10 g, 0.16 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C in an ice bath and treated with DAST (0.026 mL, 0.16 mmol) via syringe. The solution was stirred at 0 °C for 30 min at which time TLC showed complete conversion. The solution was diluted with water, and the organic layer was separated and washed with water and brine. The solution was dried, filtered, and concentrated, and the residue was chromatographed (HPLC, Zorbax Sil, 50% EtOAc/hexane) to give 35 mg of **28** as a foam: ^{1}H NMR ($CDCl_3$) δ 8.00−7.80 (m, 8 H), 7.68−7.54 (m, 6 H), 7.34−7.19 (m, 6 H), 7.06 (m, 2 H), 6.88 (d, J = 7 Hz, 2 H), 5.83 (d, J = 15 Hz, 1 H), 5.81 (d, J = 15 Hz, 1 H), 4.80 (m, 0.5 H), 4.63 (m, 0.5 H), 4.24 (d, J = 15 Hz, 1 H), 4.18 (d, J = 15 Hz, 1 H), 3.57 (m, 2 H), 3.31 (m, 1 H), 3.20 (m, 1 H, abx), 2.98 (m, 1 H, abx), 2.80−2.55 (m, 2 H), 1.95 (d, J = 8 Hz, 1 H); CIMS (NH_3) *m/z* 609 (M + H^+, 100). HRMS calcd for $C_{41}H_{38}N_2O_2F$ (M + H^+), 609.2917; found, 609.2911. Anal. ($C_{41}H_{37}N_2O_2F$·0.2(H_2O)) C, H, N.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5-(mesyloxy)-6-hydroxy-1,3-bis-[2-naphthylmethyl]-4,7-bis-[phenylmethyl]-2*H*-1,3-diazepin-2-one (29). A solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis-[2-naphthylmethyl]-4,7-bis-[phenylmethyl]-2*H*-1,3-diazepin-2-one **5**[4] (0.60 g, 1.0 mmol) in pyridine was treated with methanesulfonyl chloride (0.17 g, 1.5 mmol) and stirred at room temperature for 3 h. The mixture was diluted with 0.5 N HCl and extracted into ethyl acetate. The extracts were washed with water and brine and dried over $MgSO_4$. The solution was filtered and concentrated, and the solid residue was chromatographed (MPLC, silica gel, 40% EtOAc/hexane) to give 420 mg of **29** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.84−7.76 (m, 6 H), 7.58−7.40 (m, 6 H), 7.40−7.21 (m, 8 H), 7.09 (m, 4 H), 5.05 (d, J = 14 Hz, 1 H), 5.03 (d, J = 14 Hz, 1 H), 4.45 (dd, J = 4.5 HZ, 10 Hz, 1 H), 3.91 (m, 1 H), 3.78 (m, 1 H), 3.66 (m, 1 H), 3.44 (d, J = 14 Hz, 1 H), 3.22−2.85 (m, 5 H), 2.50 (s, 3 H), 2.26 (d, J = 4 Hz, 1 H); CIMS (NH_3) *m/z* 685 (M + H^+, 100).

(4*R*,5*S*,6*R*)-Tetrahydro-1,3-bis-[2-naphthylmethyl]-5-hydroxy-4-(1*S*-azido-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (30). A solution of **29** (100 mg, 0.15 mmol) in DMF was treated with NaN_3 (100 mg, 1.5 mmol) and heated at 80 °C for 2 h and then at 40 °C overnight. The solution was diluted with water and the solid extracted into ethyl acetate. The extracts were washed with water and brine and dried over $MgSO_4$. The solution was filtered and concentrated, and the solid residue was chromatographed (HPLC, Zorbax Sil, 50% EtOAc/hexane) to give 80 mg of **30** as a white solid: IR 2114; ^{1}H NMR ($CDCl_3$) δ 7.93−7.78 (m, 7 H), 7.63−7.39 (m, 8 H), 7.25−7.05 (m, 7 H), 6.73 (d, J = 7 Hz, 2 H), 5.76 (d, J = 7 Hz, 1 H), 5.68 (d, J = 7 Hz, 1 H), 4.10 (d, J = 7 Hz, 1 H), 3.78 (d, J = 7 Hz, 1 H), 3.62 (m, 1 H), 3.52 (m, 1 H), 3.29 (m, 2 H), 3.07−2.85 (abx m, 2 H), 2.56−2.31 (abx m, 2 H), 1.97 (d, J = 7 Hz, 1 H); DCI MS (NH_3) *m/z* 632 (M + H^+, 100). HRMS calcd for $C_{41}H_{38}N_5O_2$ (M + H^+), 632.3026; found, 632.3023. Anal. ($C_{41}H_{37}N_5O_2$·0.4(EtOAc)·0.4(hexane)) C, H, N.

(4*R*,5*S*,6*R*,7*R*)-1,3-Diaza-1,4,7-tris-(phenylmethyl)-5-(acetyloxy)-bicyclo[4.1.0]heptan-2-one (31). A solution of **14** (0.20 g, 0.57 mmol) in DMF was cooled in an ice bath and treated with NaH (30 mg, 0.7 mmol, 60% oil dispersion) and stirred for 30 min. Then benzyl bromide (0.12 g, 0.69 mmol) was added, and the solution was allowed to warm to room temperature for 1 h. The solution was diluted with water and extracted into ethyl acetate. The organic extract was washed with water and brine and then dried over $MgSO_4$. The solution was filtered and concentrated, and the residue was chromatographed (HPLC, Zorbax Sil, 50% EtOAc/hexane) to give 80 mg of **31** as a white solid. An additional 30 mg of the 5-benzyl ether compound was also obtained. For **31**: ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 13 H), 7.08 (m, 2 H), 5.05 (d, J = 15 Hz, 1 H), 4.53 (dd, J = 5 Hz, J = 7 Hz, 1 H), 3.77 (m, 1 H), 3.28 (dd, J = 4 Hz, J = 15 Hz, 1 H), 3.22 (abx m, 1 H), 3.05 (abx m, 1 H), 2.94 (m, 1 H), 2.83 (m, 1 H), 2.83 (d J = 15 Hz, 1 H), 2.55 (dd, J = 8 Hz, J = 15 Hz, 1 H), 1.95 (s, 3 H); DCI MS (NH_3) *m/z* 441 (M + H^+, 100).

(4*R*,5*S*,6*R*,7*R*)-1,3-Diaza-1,4,7-tris-(phenylmethyl)-5-(hydroxy)-bicyclo[4.1.0]heptan-2-one (33). A solution of **31** (20 mg) in methanol was treated with 5 mL of 1 N NaOH and stirred at room temperature for 1 h. The solution was concentrated to dryness, and the residue was acidified with 1 N HCl and extracted into ethyl acetate. The organic extract was washed with water and brine and then dried over $MgSO_4$. The solution was filtered and concentrated, and the residue was chromatographed (HPLC, Zorbax Sil, 70% EtOAc/hexane) to give 15 mg of **33** as a white solid. The solid was recrystallized from ethyl acetate to give crystals suitable for X-ray analysis: ^{1}H NMR ($CDCl_3$) δ 7.41−7.21 (m, 13 H), 6.96 (m, 2 H), 5.08 (d, J = 15 Hz, 1 H), 3.63 (m, 1 H), 3.58−3.34 (m, 3 H), 3.04 (m, 1 H), 2.95 (m, 1 H), 2.81 (m, 1 H), 2.56 (d, J = 15 Hz, 1 H), 2.38 (dd, J = 10 Hz, J = 15 Hz, 1 H), 2.25 (bs, 1 H); DCI MS (NH_3) *m/z* 399 (M + H^+, 100).

(4*R*,5*S*,6*R*)-Tetrahydro-1,6-bis-(phenylmethyl)-5-hydroxy-4-(1*S*-hydroxy-2-phenylethyl)-2(1*H*)-pyrimidinone (34). The aziridine **31** (30 mg, 0.07 mmol) was dissolved in 1 mL of trifluoroacetic acid for 1 h. The solution was evaporated under vacuum and the residue made basic with saturated sodium bicarbonate and extracted into ethyl acetate. The extract was washed with water and brine and concentrated to dryness. The trifluoroacetate obtained was redissolved in methanol (5 mL) and treated with 1 N NaOH (1 mL) and stirred at room temperature for 2 h. The solution was acidified with 1 N HCl and extracted into methylene chloride. The extract was washed with water and brine and then dried over $MgSO_4$. The solution was filtered and concentrated to give 15 mg of **34** as a white solid: mp 193−194 °C; ^{1}H NMR ($CDCl_3$) δ 7.41−7.15 (m, 13 H), 6.95 (m, 2 H), 5.89 (bs, 1 H), 5.05 (d, J = 15 Hz, 1 H), 4.90 (m, 2 H), 3.41 (m, 2 H), 3.18−2.65 (m, 7 H); DCI MS (NH_3) *m/z* 417 (M + H^+, 100). Anal. ($C_{26}H_{28}N_2O_3$·0.66(CH_3OH)) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,6-bis-(phenylmethyl)-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (36). Using the same procedure detail above for the sequence **15**/**16**/**9**, the aziridine **31** was converted to **36**: mp 180 °C; ^{1}H NMR ($CDCl_3$) δ 7.36−7.15 (m, 13 H), 7.03 (m, 2 H), 5.16 (d, J = 15 Hz, 1 H), 4.98 (s, 1 H), 3.49 (m, 1 H), 3.36 (m, 2 H), 3.17 (d, J = 15 Hz, 1 H), 3.08 (dd, J = 5 Hz, J = 13 Hz, 1 H), 2.83 (dd, J = 9 Hz, J = 13 Hz, 1 H), 2.77 (m, 1 H), 2.62 (m, 1 H), 2.09 (d, J = 7 Hz, 1 H), 1.96 (m, 1 H), 1.73 (m, 1 H); DCI MS (NH_3) *m/z* 401 (M + H^+, 100). Anal. ($C_{26}H_{28}N_2O_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-cyanophenylmethyl)-6-phenylmethyl-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (38). Using the same procedure detail above for the synthesis of **36**, the aziridine **32** was converted to **38**: ^{1}H NMR ($CDCl_3$) δ 7.48 (d, J = 7 Hz, 1 H), 7.35−7.10 (m, 13 H), 5.35 (s, 1 H), 5.00 (d, J = 15 Hz, 1 H), 3.53 (m, 1 H), 3.38 (m, 2 H), 3.20 (d, J = 15 Hz, 1 H), 3.12 (dd, J = 5 Hz, J = 13 Hz, 1 H), 2.87−2.58 (m, 3 H), 2.29 (bs, 1 H), 2.05 (m, 1 H), 1.77 (m, 1 H); DCI MS (NH_3) *m/z* 426 (M + H^+, 100). HRMS calcd for $C_{27}H_{28}N_3O_2$ (M + H^+), 426.2181; found, 426.2159.

**(4*R*,5*R*,6*R*)-Tetrahydro-1-[3-hydroxyphenylmethyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyri-

midinone (40). A solution of **14** (1.4 g, 4.1 mmol) in DMF was cooled in an ice bath and treated with NaH (250 mg, 6.2 mmol, 60% oil dispersion) and stirred for 30 min. Then 3-benzyloxybenzyl bromide (1.4 g, 6.2 mmol) was added and solution was allowed to warm to room temperature for 1 h. The solution was diluted with water and extracted into ethyl acetate. The organic extract was washed with water and brine, and then dried over $MgSO_4$. The solution was filtered and concentrated and the residue was chromatographed (MPLC, silica gel, 50% EtOAc/hexane) to give 1 g of **39** (mixture of R = OAc and R = 3-benzyloxybenzyl) as a white solid. An additional 0.5 g of pure **39** (R = OH) was also obtained. For **39** (R = OH): mp 184−185 °C. Anal. ($C_{33}H_{32}N_2O_3$) C, H, N.

A solution of **39** (mixture of R = OAc and R = 3-benzyloxybenzyl) (1 g) in methanol was treated with 1 N NaOH and stirred at room temperature for 1 h. The solution was concentrated to dryness and the residue acidified with 1 N HCl and extracted into ethyl acetate. The organic extract was washed with water and brine and then dried over $MgSO_4$. The solution was filtered and concentrated, and the residue was chromatographed (MPLC, silica gel, 50% EtOAc/hexane) to give 800 mg of **39** (mixture of R = OH and R = 3-benzyloxybenzyl) as a white solid. A solution of **39** (mixture of R = OH and R = 3-benzyloxybenzyl) (800 mg) in ethanol was treated with 10% Pd/C (800 mg) and hydrogenated at 50 psi for 2 days. The solution was filtered through Celite and the filtrate concentrated. The residue was chromatographed (HPLC, Zorbax Sil, 3% MeOH/$CHCl_3$) to give 230 mg of **40** as a white solid. The 2D COSY was consistent with assigned structure: ^{1}H NMR ($CDCl_3$) δ 9.13 (s, 1H), 7.35−7.12 (m, 9 H), 6.83−6.80 (m, 4 H), 6.39 (d, J = 7 Hz, 1 H), 5.19 (bs, 1 H), 5.00 (d, J = 15 Hz, 1 H), 3.36 (m, 1 H), 3.16 (m, 2 H), 3.02 (abx m, 1 H), 2.98 (d, J = 15 Hz, 1 H), 2.70 (abx m, 1 H), 2.45 (m, 2 H), 1.86 (m, 1 H), 1.74 (d, J = 5 Hz, 1 H), 1.30 (m, 1 H); DCI MS (NH_3) m/z 417 (M + H$^+$, 100). HRMS calcd for $C_{26}H_{29}N_2O_3$ (M + H$^+$), 417.2178; found, 417.2163.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-(*N*-hydroxycarboximidamide)phenylmethyl)-3-cyclopropylmethyl-6-phenylmethyl-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (43). The alcohol **38** (0.5 g, 1.2 mmol) in methylene chloride was treated with MEM-Cl (0.29 g, 2.4 mmol) and DIEA (0.3 g, 2.4 mmol), and the solution was heated at reflux overnight. The solution was evaporated to dryness under vacuum and the residue chromatographed (MPLC, silica gel, EtOAc) to give 400 mg of the MEM ether **41** as an oil: DCI MS (NH_3) m/z 514.2 (M + H$^+$, 100).

A solution of the MEM ether **41** (0.25 g, 0.5 mmol) in DMF was treated with NaH (0.11 g, 3.0 mmol, 60% disp) and stirred at room temperature for 30 min. Cyclopropylmethyl bromide (0.39 g, 3.0 mmol) was added and the mixture heated at 70 °C for 1 h. The reaction mixture was diluted with 1 N HCl and extracted into ethyl acetate. The extract was washed with water and brine and then dried over $MgSO_4$. The solution was filtered and concentrated and the residue chromatographed (HPLC, Zorbax Sil, EtOAc) to give **42**: ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 1 H), 7.37−7.10 (m, 13 H), 4.84 (d, J = 15 Hz, 1 H), 4.69 (dd, J = 7 Hz, J = 22 Hz, 2 H), 3.90 (dd, J = 7 Hz, J = 15 Hz, 1 H), 3.80−3.60 (m, 5 H), 3.52 (m, 2 H), 3.36 (s, 3 H), 3.20 (d, J = 15 Hz, 1 H), 3.20 (d, J = 15 Hz, 1 H), 3.06−2.88 (m, 3 H), 2.52 (m, 2 H), 2.05 (m, 2 H), 1.07 (m, 1 H), 0.54 (m, 2 H), 0.32 (m, 2 H).

The MEM group was removed by dissolving **42** in 4 N HCl/dioxane and stirring at room temperature for 3 h. The solution was evaporated to dryness to give the crude alcohol. A solution of the crude alcohol (40 mg) in ethanol was converted to the amidoxime by treating with NH_2OH·HCl (60 mg) and Et_3N (80 mg) and heating at reflux for 2 h. The mixture was evaporated to dryness and the residue partitioned between EtOAc and water. The organic layer was washed with water and then concentrated. The residue was chromatographed (HPLC, Zorbax NH_2, 15% MeOH/CH_2Cl_2) to give **43** as a foam: mp 130−134 °C; ^{1}H NMR ($CDCl_3$) δ 7.50−6. 95 (m, 14 H), 5.15 (d, J = 15 Hz, 1 H), 4.84 (bs, 2 H), 3.90 (dd, J = 7 Hz, J = 15 Hz, 1 H), 3.90 (bs, 1 H), 3.76 (d, J = 15 Hz, 1 H), 3.57 (m, 1H), 3.43 (m, 1 H), 3.38 (m, 1 H), 3.52 (m, 2 H), 2.96 (m, 3 H), 2.78 (dd, J = 7 Hz, J = 15 Hz, 1 H), 2.42 (m, 2 H), 1.87 (m, 1 H), 1.64 (m, 1 H), 1.07 (m, 1 H), 0.54 (m, 2 H), 0.32 (m, 2 H); ESI MS (NH_3) m/z 513.3 (M + H$^+$, 100). Anal. ($C_{31}H_{36}N_4O_3$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-3-(3-aminophenylmethyl)-6-phenylmethyl-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (46). A solution of **10** (1.0 g, 2.5 mmol) in THF was alkylated (K-O-*t*-Bu/THF) with 1 equiv of 3-nitrobenzyl chloride (0.44 g, 2.5 mmol) to give a mixture of dialkylated products, **44** and **45**, and recovered starting material **10**. The mixture was chromatographed on silica gel (MPLC, 30% − 50%−100% EtoAc in hexane step gradient) to give 100 mg of **45** as the second monoalkylated product from the column (100% EtOAc). The nitro group was reduced (H_2; 10% Pd/C) and the THP protecting group removed with HCl/MeOH. The crude product was purified by chromatography (HPLC, Zorbax Sil, 10% MeOH/EtoAc) to give **46** as a white solid: mp 148−152 °C; ^{1}H NMR ($CDCl_3$) δ 7.33−7.00 (m, 11 H), 6.58−6.45 (m, 3 H), 5.14 (d, J = 15 Hz, 1 H), 4.54 (s, 1 H), 3.75−3.44 (m, 5 H), 3.23 (m, 1 H), 2.90 (abx dd, J = 7 Hz, J = 13 HZ), 2.76 (abx dd, J = 8 Hz, J = 13 HZ), 2.97 (m, 2 H), 2.10 (bs, 1 H), 1.98 (m, 1 H), 1.65 (m, 1 H); ESI MS (NH_3) m/z 416 (M + H$^+$, 100). HRMS calcd for $C_{26}H_{30}N_3O_2$ (M + H$^+$), 416.2338; found, 416.2328.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-aminophenylmethyl)-6-phenylmethyl-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (47). Method 1. A solution of **10** (1.0 g, 2.5 mmol) in THF was alkylated (K−Ot-Bu/THF) with 1 equiv of 3-nitrobenzyl chloride (0.44 g, 2.5 mmol) to give a mixture of dialkylated product, **44** and **45**, and recovered starting material **10**. The mixture was chromatographed on silica gel (MPLC, 30% − 50%−100% EtoAc in hexane step gradient) to give 200 mg of **44** as the first monoalkylated product from the column (50% EtOAc). The nitro group was reduced (H_2; THF, 10% Pd/C) and the THP protecting group removed with HCl/MeOH. The crude product was purified by chromatography (HPLC, Zorbax Sil, 10% MeOH/EtoAc) to give **47** as white solid.

Method 2. A solution of **49** in THF was hydrogenated (50 psi H_2; THF, 10% Pd/C) and the THP group was removed with HCl/MeOH. The product was purified by chromatography (HPLC, Zorbax Sil, 10% MeOH/EtoAc) to give **47** as a white solid identical in every respect as that obtained using method 1: mp 76−70 °C; ^{1}H NMR ($CDCl_3$) δ 7.33−7.10 (m, 10 H), 7.03 (t, J = 7 Hz, 1 H), 6.52 (d, J = 7 Hz, 1 H), 4.40 (d, J = 7 Hz, 1 H), 6.34 (s, 1 H), 5.08 (d, J = 15 Hz, 1 H), 5.03 (bs, 1 H), 3.59 (bs, 2 H), 3.49 (m, 1 H), 3.33 (m, 2 H),3.07 (d, J = 15 Hz, 1 H), 3.05 (abx m, 1 H), 2.81 (abx m, 1 H), 2.79 (m, 1 H), 2.63 (m, 1 H), 2.24 (bs, 1 H), 1.95 (m, 1 H), 1.69 (m, 1 H); ESI MS (NH_3) m/z 416 (M + H$^+$, 100). HRMS calcd for $C_{26}H_{30}N_3O_2$ (M + H$^+$), 416.2338; found, 416.2351.

(4*S*,5*S*,6*R*)-Tetrahydro-1-(3-nitrophenylmethyl)-6-phenylmethyl-5-hydroxy-4-(*β*-styrene)-2(1*H*)-pyrimidinone (48). A solution of **14** (1.0 g, 2.9 mmol) in THF was alkylated (K−Ot-Bu/THF) with 3-nitrobenzyl chloride (0.55 g, 3.3 mmol). Using the procedure describe for **17** above the alkylation product was treated with HBr and then KOH to give 0.5 g of nitro olefin **48**: ^{1}H NMR (DMSO-d_6) δ 8.07 (d, J = 8 Hz, 1 H), 7.83 (s, 1 H), 7.60−7.18 (m, 11 H), 6.78 (s, 1 H), 6.55 (d, J = 16 Hz, 1 H), 6.20 (dd, J = 7 Hz, J = 16 Hz, 1 H), 5.55 (s, 1 H), 4.86 (d, J = 15 Hz, 1 H), 3.89 (m, 1 H), 3.55 (m, 1 H), 3.44 (m, 2 H), 3.25 (s, 1 H), 3.07 (abx dd, J = 5 Hz, J = 13 Hz, 1 H), 2.73 (abx dd, J = 8 Hz, J = 13 Hz, 1 H); ESI MS (NH_3) m/z 444 (M + H$^+$, 100).

(4*S*,5*S*,6*R*)-Tetrahydro-1-(3-nitrophenylmethyl)-6-phenylmethyl-5-(tetrahydropyran-2-yl-oxy)-4-(*β*-styrene)-2(1*H*)-pyrimidinone (49). The alcohol of **48** was protected as the THP ether (using the procedure described for **10**) to give **49**. NMR shows mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 8.07 (m, 1 H), 7.80 (m, 1 H), 7.43−7.10 (m, 12 H), 6.70 (overlapping d, J = 16 Hz, 1 H), 6.10 (m, 1 H), 5.02−4.80 (m, 2 H), 4.62 (bs, 0.5 H), 4.49 (bs, 0.5 H), 4.25−4.02 (m, 1 H), 3.81−3.25 (m, 3 H), 3.40−3.20 (m, 2 H), 3.16−2.75 (m, 2 H), 1.80−1.31 (m, 6 H).

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[(3-cyanophenyl)methyl]-

5-hydroxy-4-(2-(4-fluorophenyl)ethyl)-6-(4-fluorophenylmethyl)-2(1*H*)-pyrimidinone (51): mp 63 °C; ^{1}H NMR ($CDCl_3$) δ 7.62−7.31 (m, 8 H), 7.02−6.80 (m, 8 H), 5.23 (d, J = 15 Hz, 1 H), 5.13 (d, J = 16 Hz, 1 H), 4.25 (d, J = 16 Hz, 1 H), 3.95 (d, J = 16 Hz, 1 H), 3.91 (m, 1 H), 3.46 (m, 2 H), 3.14 (m, 1 H), 2.88 (m, 2 H), 2.40 (m, 2 H), 1.90 (m, 1 H), 1.62 (m, 1 H); CI MS (NH_3) m/z 577 (M + H$^+$, 100). HRMS calcd for $C_{35}H_{31}N_4O_2F_2$ (M + H$^+$), 577.2415; found, 577.2429. Anal. ($C_{35}H_{30}N_4O_2F_2 \cdot 0.25H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[(3-cyano-4-fluorophenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (52): mp 70−74 °C; ^{1}H NMR ($CDCl_3$) δ 7.60−6.90 (m, 16 H), 5.14 (d, J = 15 Hz, 1 H), 4.98 (d, J = 16 Hz, 1 H), 4.30 (d, J = 16 Hz, 1 H), 3.84 (d, J = 16 Hz, 1 H), 3.56 (m, 2 H), 3.11 (m, 1 H), 2.87 (m, 2 H), 2.50−2.34 (m, 2 H), 1.90 (m, 1 H), 1.90 (bs, 1 H), 1.62 (m, 1 H); CI MS (NH_3) m/z 577 (M + H$^+$, 100). HRMS calcd for $C_{35}H_{31}N_4O_2F_2$ (M + H$^+$), 577.2415; found, 577.2408. Anal. ($C_{35}H_{30}N_4O_2F_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[(3-acetylphenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (53): mp 65−70 °C; ^{1}H NMR ($CDCl_3$) δ 7.89−7.82 (m, 4 H), 7.62−7.31 (m, 4 H), 7.25−7.15 (m, 6 H), 7.02−6.90 (m, 4 H), 5.34 (d, J = 15 Hz, 1 H), 5.30 (d, J = 16 Hz, 1 H), 4.05 (d, J = 16 Hz, 1 H), 4.00 (d, J = 16 Hz, 1 H), 3.51 (m, 1 H), 3.46 (m, 2 H), 3.18 (m, 1 H), 2.88 (m, 2 H), 2.58 (s, 3 H), 2.56 (s, 3 H), 2.40 (m, 2 H), 1.90 (m, 1 H), 1.90 (bs, 1 H), 1.62 (m, 1 H); CI MS (NH_3) m/z 575 (M + H$^+$, 100). Anal. ($C_{37}H_{38}N_2O_4 \cdot 0.25CDCl_3$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[(3-carboxyphenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (55): mp 112−116 °C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 8.05−7.91 (m, 4 H), 7.60−7.00 (m, 16 H), 5.41 (d, J = 16 Hz, 1 H), 5.23 (d, J = 16 Hz, 1 H), 4.02 (d, J = 16 Hz, 1 H), 3.59 (d, J = 16 Hz, 1 H), 3.60 (m, 1 H), 3.40 (m, 1 H), 3.20 (m, 1 H), 2.90 (abx m, 1 H), 2.70 (abx m, 1 H), 2.42 (m, 2 H), 1.94 (m, 1 H), 1.77 (m, 1 H); CI MS (NH_3) m/z 579 (M + H$^+$, 100). Anal. ($C_{35}H_{34}N_2O_6 \cdot 0.1CDCl_3$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[(3-carboxamidophenyl)methyl]-5-hydroxy-4-(2-(4-fluorophenyl)ethyl)-6-(4-fluorophenylmethyl)-2(1*H*)-pyrimidinone (57): mp 113−115 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (bs, 1 H), 7.45−7.25 (m, 3 H), 7.20−7.05 (m,4 H), 7.00−6.67 (m, 8 H), 5.20 (d, J = 16 Hz, 1 H), 4.80 (d, J = 16 Hz, 1 H), 4.58 (d, J = 16 Hz, 1 H), 3.96 (d, J = 16 Hz, 1 H), 3.60 (m, 2 H), 2.82 (m, 2 H), 2.32 (m, 2 H), 1.94 (m, 1 H), 1.90 (bs, 1 H), 1.57 (m, 1 H); ESI MS (NH_3) m/z 613 (M + H$^+$, 100). Anal. ($C_{35}H_{34}N_4O_4F_2 \cdot 0.75H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[(3-carboxamidophenyl)methyl]-5-hydroxy-4-(2-(3,4-difluorophenyl)ethyl)-6-(3,4-difluorophenylmethyl)-2(1*H*)-pyrimidinone (58): ^{1}H NMR ($CDCl_3$) δ 7.87 (bs, 1 H), 7.45−7.25 (m, 4 H), 7.10−6.67 (m, 6 H), 5.17 (d, J = 16 Hz, 1 H), 4.90 (d, J = 16 Hz, 1 H), 4.08 (d, J = 16 Hz, 1 H), 4.07 (d, J = 16 Hz, 1 H), 3.46 (m, 2 H), 2.83 (abx m, 1 H), 2.60 (abx m, 1 H), 2.39 (m, 2 H), 1.87 (m, 1 H), 1.68 (bs, 1 H); ESI MS (NH_3) m/z 649 (M + H$^+$, 100). Anal. ($C_{35}H_{32}N_4O_4F_4 \cdot 0.1CH_3OH \cdot 0.2CH_2Cl_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[(3-(*N*-hydroxycarboximidamide)-phenyl)methyl]-5-hydroxy-4-(2-(4-fluorophenyl)ethyl)-6-(4-fluorophenylmethyl)-2(1*H*)-pyrimidinone (61): mp 120−122 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.67 (bs, 1 H), 7.47 (m, 3 H), 7.40−7.15 (m, 4 H), 7.02−6.82 (m, 8 H), 5.22 (d, J = 15 Hz, 1 H), 4.93 (d, J = 15 Hz, 1 H), 4.01 (m, 1 H), 3.97 (d, J = 15 Hz, 1 H), 3.51 (m, 2 H), 3.20 (m, 1 H), 2.78 (m, 2 H, abx), 2.36 (m, 2 H), 1.90 (m, 1 H), 1.65 (m, 2 H); ESI MS (NH_3) m/z 643 (M + H$^+$, 100). Anal. ($C_{35}H_{36}N_6O_4F_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[(3-(*N*-hydroxycarboximidamide)-phenyl)methyl]-5-hydroxy-4-(2-(3,4-difluorophenyl)ethyl)-6-(3,4-difluorophenyl)-2(1*H*)-pyrimidinone (62): ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.63 (bs, 1 H), 7.47 (m, 3 H), 7.40−7.15 (m, 4 H), 7.02−6.62 (m, 6 H), 5.22 (d, J = 15 Hz, 1 H), 4.90 (d, J = 15 Hz, 1 H), 3.95 (d, J = 15 Hz, 1 H), 3.51 (m, 2 H), 3.20 (m, 1 H), 2.82 (m abx, 1 H), 2.58 (m abx, 1 H), 2.39 (m, 2 H), 1.90 (m, 1 H), 1.65 (m, 2 H); ESI MS (NH_3) m/z 679 (M + H$^+$, 100). Anal. ($C_{35}H_{34}N_2O_4F_4 \cdot 0.2CH_2Cl_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[(3-(*N*-hydroxycarboximidamide)-4-fluoro-phenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (63): mp 125−128 °C; ^{1}H NMR (DMSO-d_6) δ 9.63 (s, 1 H), 9.61 (s, 1 H), 7.56 (m, 1 H), 7.42 (m, 1 H), 7.36−7.00 (m, 14 H), 5.80 (bs, 4 H), 5.45 (bs, 1 H), 5.01 (d, J = 15 Hz, 1 H), 4.90 (d, J = 15 Hz, 1 H), 4.10 (d, J = 15 Hz, 1 H), 3.52 (m,1 H), 3.21 (m, 1 H), 3.11 (m, 1 H), 2.82 (m abx, 1 H), 2.52(m abx, 1 H), 2.39 (m, 2 H), 1.88 (m, 2 H); ESI MS (NH_3) m/z 643 (M + H$^+$, 100). Anal. ($C_{35}H_{36}N_6O_4F_2 \cdot 0.75H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis-[(3-(pyrazol-3-yl)phenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (68): mp 121−125 °C; ^{1}H NMR ($CDCl_3$) δ 10.95 (bs, 1H), 8.00 (bs, 1 H), 7.84 (s, 1 H), 7.58−7.42 (m, 4 H), 7.35−6.95 (m, 12 H), 6.85 (m, 2 H), 6.53 (m, 2 H), 5.31 (d, J = 15 Hz, 1 H), 5.08 (bs, 1 H), 4.30 (bs, 1 H), 3.98 (d, J = 15 Hz, 1 H), 4.10 (d, J = 16 Hz, 1 H), 3.94 (d, J = 15 Hz, 1 H), 3.5 (bs, 1 H), 3.43 (m, 2 H), 3.22 (m, 1 H), 2.84 (m, 2 H), 2.34 (m, 2 H), 1.90 (m, 1 H), 1.59 (m, 1 H); ESI MS (NH_3) m/z 623 (M + H$^+$, 100); HRMS calcd for $C_{39}H_{39}N_6O_2$ (M + H$^+$) 623.3135; found, 623.3123. Anal. ($C_{39}H_{38}N_6O_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-1,3-bis[(1*H*-indazol-6-yl)methyl]-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (69): mp 130−133 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.94 (s, 1 H), 7.82 (s, 1 H), 7.63−7.43 (m, 4 H), 7.20−7.05 (m, 6 H), 7.07−6.93 (m, 4 H), 6.85 (m, 2 H), 5.32 (d, J = 15 Hz, 1 H), 5.27 (d, J = 15 Hz, 1 H), 4.40 (d, J = 16 Hz, 1 H), 4.00 (d, J = 15 Hz, 1 H), 3.53 (m, 1 H), 3.45 (m, 1 H), 3.30 (m, 1 H), 2.90 (m, 2 H), 2.30 (m, 2 H), 1.82 (m, 1 H), 1.50 (m, 1 H); CIMS (NH_3) m/z 571 (M + H$^+$, 100). Anal. ($C_{35}H_{34}N_6O_2 \cdot 0.75H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-1,3-bis[(3-methyl-1*H*-indazol-5-yl)methyl]-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (70): mp 143−146 °C; ^{1}H NMR ($CDCl_3$) 7.52 (s, 1 H), 7.39−6.95 (m, 17 H), 5.32 (d, J = 15 Hz, 1 H), 5.47 (d, J = 15 Hz, 1 H), 4.14 (d, J = 16 Hz, 1 H), 3.65 (d, J = 15 Hz, 1 H), 3.53 (m, 1 H), 3.40−3.20 (m, 3 H), 2.82 (m, 2 H), 2.48 (s, 3 H), 2.45 (s, 3 H), 2.46 (m, 2 H), 1.91 (m, 1 H), 1.79 (m, 1 H); CIMS (NH_3) m/z 599 (M + H$^+$, 100). Anal. ($C_{37}H_{38}N_6O_2 \cdot H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-1,3-bis[(3-amino-1*H*-indazol-5-yl)methyl]-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (71): mp 150−154 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.46 (s, 1 H), 7.36 (s, 1 H), 7.28−6.93 (m, 14 H), 5.35 (d, J = 15 Hz, 2 H), 3.97 (d, J = 16 Hz, 1 H), 3.93 (d, J = 15 Hz, 1 H), 3.48−3.35 (m, 2 H), 3.23 (m, 1 H), 2.83 (m, 2 H), 2.39 (m, 2 H), 1.82 (m, 1 H), 1.62 (m, 1 H); CIMS (NH_3) m/z 601 (M + H$^+$, 100). Anal. ($C_{35}H_{36}N_8O_2 \cdot 0.25H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-1,3-bis[(3-amino-benzisoxazol-5-yl)methyl]-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (72): mp 143−146 °C; ^{1}H NMR ($CDCl_3$) δ 7.46 (s, 1 H), 7.40−7. 10 (m, 11 H), 7.05−6.93 (m, 4 H), 5.35 (d, J = 15 Hz, 1 H), 5.30 (d, J = 15 Hz, 1 H), 4.57 (bs, 2 H), 4.42 (bs, 2 H), 4.16 (d, J = 16 Hz, 1 H), 3.91 (d, J = 15 Hz, 1 H), 3.48−3.35 (m, 2 H), 3.23 (m, 1 H), 2.83 (m, 2 H), 2.69 (bs, 1 H), 2.40 (m, 2 H), 1.82 (m, 1 H), 1.60 (m, 1 H); CIMS (NH_3) m/z 603 (M + H$^+$, 100). HRMS calcd for $C_{35}H_{35}N_6O_4$ (M + H$^+$), 603.2720; found, 603.2696.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-1,3-bis[(3-(5-methylpyrid-2-yl)carboxamidophenyl)methyl]-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (73): mp 118−120 °C; ^{1}H NMR ($CDCl_3$) δ 9.18 (s, 1 H), 8.91 (s, 1 H), 8.25 (m, 2 H), 8.10−7.90 (m, 3 H), 7.81−7.63 (m, 4 H), 7.40−6.88 (m, 15 H), 5.39 (d, J = 15 Hz, 1 H), 5.24 (d, J = 15 Hz, 1 H), 4.41 (bs, 1 H), 4.16 (d, J = 16 Hz, 1 H), 3.96 (d, J = 15 Hz, 1 H), 3.48−3.35 (m, 2 H), 3.23 (m, 1 H), 2.83 (m, 2 H), 2.40 (m, 2 H), 2.36 (s, 3 H), 2.28 (s, 3 H), 1.82 (m, 1 H), 1.60 (m, 1 H); CIMS (NH_3) m/z 759 (M + H$^+$, 100). Anal. ($C_{47}H_{46}N_6O_4 \cdot 2H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-1,3-bis[(3-(thiazol-2-yl)carboxamidophenyl)methyl]-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (74): mp 143−146 °C; ^{1}H

NMR ($CDCl_3$) δ 8.18 (s, 1 H), 7.96 (s, 1 H), 7.85 (m, 2 H), 7.50−6.88 (m, 20 H), 5.21 (d, J = 15 Hz, 2 H), 4.41 (bs, 1 H), 4.16 (d, J = 16 Hz, 1 H), 4.06 (d, J = 15 Hz, 1 H), 3.60−3.23 (m, 4 H), 2.83 (m, 2 H), 2.30 (m, 2 H), 1.82 (m, 1 H), 1.60 (m, 1 H); CIMS (NH_3) m/z 743 ($M + H^+$, 100). Anal. ($C_{41}H_{38}N_6O_4S_2 \cdot 0.33H_2O$) C, H, N.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis-[3-(*N*-methyl)phenylmethyl]-5-hydroxy-4-(1*S*-bromo-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (76): mp 188−189 °C; ^{1}H NMR ($CDCl_3$) δ 7.26−7.00 (m, 12 H), 6.86−6.36 (m, 8 H), 5.39 (d, J = 15 Hz, 2 H), 4.18 (m, 1 H), 4.10 (d, J = 15 Hz, 1 H), 3.70 (m, 2 H), 3.60 (m, 1 H), 3.43 (d, J = 14 Hz, 1 H), 3.31 (m, 1 H), 3.10−2.6 (m abx, 4 H), 2.83 (s, 3 H), 2.70 (s, 3 H); CIMS (NH_3) m/z 628 ($M + H^+$, 100). Anal. ($C_{35}H_{39}N_4O_2Br$) C, H, N.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis-[3-hydroxyphenylmethyl]-5-hydroxy-4-(1*S*-fluoro-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (78): ^{1}H NMR ($CDCl_3$) δ 7.26−7.06 (m, 7 H), 7.00−6.65 (m, 11 H), 5.37 (d, J = 15 Hz, 2 H), 5.10 (d, J = 15 Hz, 1 H), 4.60 (m, 0.5 H), 4.45 (m, 0.5 H), 3.70 (m, 2 H), 4.14 (d, J = 14 Hz, 1 H), 3.90 (d, J = 14 Hz, 1 H), 3.41 (m, 2 H), 3.32 m, 1 H), 3.00−2.60 (m abx, 4 H), 1.85 (bs, 3 H); CIMS (NH_3) m/z 541 ($M + H^+$, 100). Anal. ($C_{33}H_{33}N_2O_4F \cdot 0.8H_2O$) C, H, N.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis-[3-(hydroxymethyl)phenylmethyl]-5-hydroxy-4-(1*S*-fluoro-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (79): ^{1}H NMR ($CDCl_3$) δ 7.49 (s, 1 H), 7.41−7.00 (m, 15 H), 6.80 (m, 2 H), 5.27 (d, J = 15 Hz, 1 H), 5.25 (d, J = 15 Hz, 1 H), 4.67 (d, J = 6 Hz, 2 H), 4.54 (d, J = 6 Hz, 2 H), 4.18 (m, 1 H), 4.25 (d, J = 15 Hz, 1 H), 4.09 (m, 1 H), 3.76 (m, 1 H), 3.60 (d, J = 15 Hz, 1 H), 3.60 (m, 1 H), 3.33 (m, 1 H),91 (m, 3 H), 2.63 (abx m, 1 H), 2.25 (bs, 3 H); CIMS (NH_3) m/z 541 ($M + H^+$, 100). HRMS calcd for $C_{35}H_{38}N_2O_4Br$ ($M + H^+$), 629.2015; found 629.2032.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-cyano-4-fluorophenylmethyl)-6-phenylmethyl-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (80): mp 62−66 °C; ^{1}H NMR ($CDCl_3$) δ 7.40−7.00 (m, 13 H), 5.57 (s, 1 H),4.89 (d, J = 15 Hz, 1 H), 3.56 (m, 1 H), 3.38 (m, 2 H), 3.20 (d, J = 15 Hz, 1 H), 3.15 (dd, J = 5 Hz, J = 13 Hz, 1 H), 2.87−2.58 (m, 3 H), 2.39 (bs, 1 H), 2.05 (m, 1 H), 1.77 (m, 1 H); DCI MS (NH_3) m/z 443 ($M + H^+$, 100). Anal. ($C_{27}H_{26}N_3O_2F$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-carboxamidophenylmethyl)-6-phenylmethyl-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (81): ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 7 Hz, 1 H), 7.55 (s, 1 H), 7.35−7.10 (m, 11 H), 6.70 (bs, 1 H), 6.43 (bs, 1 H), 5.40 (s, 1 H), 4.95 (d, J = 15 Hz, 1 H), 3.43 (m, 1 H), 3.38−3.20 (m, 2 H), 3.20 (d, J = 15 Hz, 1 H), 3.12 (dd, J = 4 Hz, J = 13 Hz, 1 H), 2.80−2.43 (m, 3 H), 190 (bs, 1 H), 1.91 (m, 1 H), 1.59 (m, 1 H); DCI MS (NH_3) m/z 443 ($M + H^+$, 100). HRMS calcd for $C_{27}H_{30}N_3O_3$ ($M + H^+$), 444.2287, found, 444.2281. Anal. ($C_{27}H_{29}N_3O_3 \cdot 0.25EtOAc$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-carboxamido-4-fluorophenylmethyl)-6-phenylmethyl-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (82): mp 92−94 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (m, 1 H), 7.35−7.10 (m, 12 H), 7.00 (m, 1 H), 6.67 (bs, 1 H), 6.00 (bs, 1 H), 5.00 (s, 1 H),4.97 (d, J = 15 Hz, 1 H), 3.59 (m, 1 H), 3.45 (m, 1 H), 3.38 (m, 1 H), 3.20 (d, J = 15 Hz, 1 H), 3.07 (abx dd, J = 5 Hz, J = 13 Hz, 1 H), 2.83−2.58 (m, 3 H), 2.54 (d, J = 6 Hz, 1 H), 2.00 (m, 1 H), 1.75 (m, 1 H); DCI MS (NH_3) m/z 462 ($M + H^+$, 100). HRMS calcd for $C_{27}H_{29}N_3O_3F$ ($M + H^+$), 462.2193; found, 462.2175. Anal. ($C_{27}H_{28}N_3O_3F \cdot 0.5H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-(*N*-hydroxycarboximidamide)phenylmethyl)-6-phenylmethyl-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (83): mp 106−109 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (d, J = 7 Hz, 1 H), 7.35−6.86 (m, 14 H), 5.59 (s, 1 H), 4.96 (d, J = 15 Hz, 1 H), 4.91 (bs, 2 H), 3.45 (m, 1 H), 3.38 (m, 1 H), 3.25 (m, 1 H), 3.05 (d, J = 15 Hz, 1 H), 3.12 (dd, J = 4 Hz, J = 13 Hz, 1 H), 2.77−2.40 (m, 3 H), 2.29 (bs, 1 H), 1.85 (m, 1 H), 1.57 (m, 1 H); ESI MS (NH_3) m/z 459 ($M + H^+$, 100). Anal. ($C_{27}H_{30}N_4O_3$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-(*N*-hydroxycarboximidamide)-4-fluorophenylmethyl)-6-phenylmethyl-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (84): mp 200−202 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 1 H), 7.25−6.85 (m, 14 H), 5.45 (s, 1 H), 5.10 (bs, 2 H), 4.96 (d, J = 15 Hz, 1 H), 3.45 (m, 1 H), 3.38 (m, 1 H), 3.30 (m, 1 H), 3.11 (d, J = 15 Hz, 1 H), 3.05 (dd, J = 4 Hz, J = 13 Hz, 1 H), 2.79−2.40 (m, 3 H), 2.24 (bs, 1 H), 1.85 (m, 1 H), 1.65 (m, 1 H); ESI MS (NH_3) m/z 477 ($M + H^+$, 100). Anal. ($C_{27}H_{29}N_4O_3F \cdot 0.25H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-1-[(3-amino-1*H*-indazol-5-yl)methyl]-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (85): mp 122−126 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.35−6.90 (m, 13 H), 5.22 (s, 1 H), 5.07 (d, J = 15 Hz, 1 H), 3.53 (m, 3 H), 3.10 (d, J = 15 Hz, 1 H), 3.10 (m, 1 H), 2.80−2.50 (m, 3 H), 2.00 (m, 1 H), 1.62 (m, 1 H); ESI MS (NH_3) m/z 456 ($M + H^+$, 100). Anal. ($C_{27}H_{29}N_5O_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-1-[(1*H*-indazol-5-yl)methyl]-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (86): mp 102−104 °C; ^{1}H NMR ($CDCl_3$) δ 10.50 (bs, 1 H), 7.78 (s, 1 H), 7.35−7.00 (m, 13 H), 5.19 (bs, 1 H), 5.19 (d, J = 15 Hz, 1 H), 3.50−3.30 (m, 3 H), 3.28 (d, J = 15 Hz, 1 H), 3.10 (abx m, 1 H), 2.86−2.57 (m, 3 H), 1.98 (m, 1 H), 1.63 (m, 1 H); ESI MS (NH_3) m/z 441 ($M + H^+$, 100). HRMS calcd for $C_{27}H_{29}N_4O_2$ ($M + H^+$), 441.2291; found, 441.2313. Anal. ($C_{27}H_{28}N_4O_2 \cdot 0.25H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-3-[(1*H*-indazol-5-yl)methyl]-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (87): mp 237−238 °C; ^{1}H NMR (DMSO-d_6) δ 13.10 (bs, 1 H), 7.98 (s, 1 H), 7.55−7.10 (m, 11 H), 6.99 (d, J = 6 Hz, 2 H), 5.00 (bs, 1 H), 4.83 (d, J = 15 Hz, 1 H), 4.13 (d, J = 15 Hz, 1 H), 3.61 (m, 1 H), 3.20 (bs, 1 H), 3.37 (bs, 1 H), 3.07 (bs, 1 H), 2.91−2.71 (abx m, 2 H), 2.27 (m, 2 H), 1.78 (m, 1 H), 1.50 (m, 1 H); ESI MS (NH_3) m/z 441 ($M + H^+$, 100). HRMS calcd for $C_{27}H_{29}N_4O_2$ ($M + H^+$), 441.2291; found, 441.2284. Anal. ($C_{27}H_{28}N_4O_2 \cdot 0.1CDCl_3 \cdot CD_3OD$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,6-bis-(phenylmethyl)-3-(3-cyano-4-fluorophenylmethyl)-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (88): mp 65−68 °C; ^{1}H NMR ($CDCl_3$) δ 7.55−7.10 (m, 14 H), 7.00−6.90 (m, 4 H), 5.45 (d, J = 15 Hz, 1 H), 5.17 (d, J = 15 Hz, 1 H), 4.01 (d, J = 15 Hz, 1 H), 3.82 (d, J = 15 Hz, 1 H), 3.42 (m, 2 H), 3.18−3.00 (m, 2 H), 2.81 (abx m, 1 H), 2.38 (m, 2 H), 1.80 (m, 1 H), 1.57 (m, 1 H), 1.80 (bs, 1 H); ESI MS (NH_3) m/z 534 ($M + H^+$, 100). HRMS calcd for $C_{27}H_{29}N_4O_2$ ($M + H^+$), 534.2557; found, 534.2541.

(4*R*,5*R*,6*R*)-Tetrahydro-3,6-bis-(phenylmethyl)-1-(3-cyano-4-fluorophenylmethyl)-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (89): mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 2 H), 7.40−7.10 (m, 12 H), 7.10−6.90 (m, 4 H), 5.38 (d, J = 15 Hz, 1 H), 4.97 (d, J = 15 Hz, 1 H), 4.10 (d, J = 15 Hz, 1 H), 3.91 (d, J = 15 Hz, 1 H), 3.42 (m, 2 H), 3.18 (m, 1 H), 2.80 (abx m, 2 H), 2.42 (m, 2 H), 1.90 (m, 1 H), 1.61 (m, 1 H), 1.58 (bs, 1 H); ESI MS (NH_3) m/z 534 ($M + H^+$, 100). HRMS calcd for $C_{27}H_{29}N_4O_2$ ($M + H^+$), 534.2557; found, 534.2552.

(4*R*,5*R*,6*R*)-Tetrahydro-1,6-bis-(phenylmethyl)-3-[(3-amino-1*H*-indazol-5-yl)methyl]-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (90): mp 109−113 °C; δ 9.20 (bs, 1 H), 7.40−7.10 (m, 14 H), 7.00−6.90 (m, 4 H), 5.65 (d, J = 15 Hz, 1 H), 5.21 (d, J = 15 Hz, 1 H), 4.10 (bs, 2 H), 3.96 (d, J = 15 Hz, 1 H), 3.85 (d, J = 15 Hz, 1 H), 3.42 (m, 3 H), 3.08−2.81 (abx m, 2 H), 2.42 (m, 2 H), 1.80 (m, 1 H), 1.57 (m, 1 H); ESI MS (NH_3) m/z 546 ($M + H^+$, 100). Anal. ($C_{34}H_{35}N_5O_2 \cdot 0.85H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-3,6-bis-(phenylmethyl)-1-[(3-amino-1*H*-indazol-5-yl)methyl]-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (91): mp 104−108 °C; ^{1}H NMR ($CDCl_3$) δ 9.20 (bs, 1 H), 7.40−7.05 (m, 14 H), 7.00−6.90 (m, 4 H), 5.46 (d, J = 15 Hz, 1 H), 5.41 (d, J = 15 Hz, 1 H), 4.10 (bs, 2 H), 3.91 (d, J = 15 Hz, 1 H), 3.86 (d, J = 15 Hz, 1 H), 3.42 (m, 1 H), 3.35 (m, 1 H), 3.18 (m, 1 H), 2.98−2.80 (abx m, 2 H), 2.40 (m, 2 H), 1.82 (m, 1 H), 1.60 (m, 1 H), 1.3 (bs, 1 H); ESI MS (NH_3) m/z 546 ($M + H^+$, 100). Anal. ($C_{34}H_{35}N_5O_2 \cdot 0.66H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1-[1*H*-indazol-5-ylmethyl]-3-(3-aminophenyl-methyl)-4-(2-phenylethyl)-5-hydroxy-6-(phenylmethyl)-2(1*H*)-pyrimidinone (92): mp 96−101 °C; ^{1}H NMR ($CDCl_3$) δ 10.50 (bs, 1 H), 7.90 (s, 1 H), 7.51 (s, 1 H), 7.40−6.90 (m, 13 H), 6.70−6.50 (m, 3 H), 5.45 (d, J = 15 Hz,

1 H), 5.35 (d, J = 15 Hz, 1 H), 3.95 (d, J = 15 Hz, 1 H), 3.75 (d, J = 15 Hz, 1 H), 3.60 (bs, 2 H), 3.50−3.16 (m, 3 H), 2.90 (abx m, 2 H), 2.40 (abx m, 2 H), 1.85 (m, 1 H), 1.60 (m, 1 H), 1.20 (bs, 1 H); ESI MS (NH_3) m/z 546 ($M + H^+$, 100). HRMS calcd for $C_{27}H_{29}N_4O_2$ ($M + H^+$), 545.2869; found, 546.2879.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-aminophenyl-methyl)-3-[1*H*-indazol-5-ylmethyl]-4-(2-phenylethyl)-5-hydroxy-6-(phenylmethyl)-2(1*H*)-pyrimidinone (93): mp 100−105 °C; ^{1}H NMR ($CDCl_3$) δ 10.50 (bs, 1 H), 7.82 (s, 1 H), 7.45 (s, 1 H), 7.40−6.98 (m, 13 H), 6.65−6.55 (m, 3 H), 5.47 (d, J = 15 Hz, 1 H), 5.41 (d, J = 15 Hz, 1 H), 3.90 (d, J = 15 Hz, 1 H), 3.81 (d, J = 15 Hz, 1 H), 3.65 (bs, 2 H), 3.50−3.23 (m, 3 H), 2.93 (abx m, 2 H), 2.42 (abx m, 2 H), 1.90 (m, 1 H), 1.62 (m, 1 H), 1.20 (bs, 1 H); ESI MS (NH_3) m/z 546 ($M + H^+$, 100). HRMS calcd for $C_{27}H_{29}N_4O_2$ ($M + H^+$), 545.2869; found, 546.2873.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-aminophenyl-methyl)-3-[3-methyl-1*H*-indazol-5-ylmethyl]-4-(2-phenylethyl)-5-hydroxy-6-(phenylmethyl)-2(1*H*)-pyrimidinone (94): mp 116−120 °C; ^{1}H NMR ($CDCl_3$) δ 10.40 (bs, 1 H), 7.40−6.98 (m, 14 H), 6.66−6.49 (m, 3 H), 5.51 (d, J = 15 Hz, 1 H), 5.36 (d, J = 15 Hz, 1 H), 3.93 (d, J = 15 Hz, 1 H), 3.76 (d, J = 15 Hz, 1 H), 3.65 (bs, 2 H), 3.60−3.23 (m, 3 H), 2.96 (m, 2 H), 2.45 (m, 2 H), 2.45 (s, 3 H), 2.40 (bs, 1 H), 1.90 (m, 1 H), 1.65 (m, 1 H); ESI MS (NH_3) m/z 280.9 ($M + 2H^{+2}$, 100). Anal. ($C_{35}H_{37}N_5O_2 \cdot 0.5H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-aminophenyl-methyl)-3-[3-cynanophenyl-methyl]-4-(2-phenylethyl)-5-hydroxy-6-(phenylmethyl)-2(1*H*)-pyrimidinone (95): mp 102.0−104.0 °C; ^{1}H NMR (CD_3OD) δ 7.68 (bs, 1 H), 7.62−7.58 (m, 2 H), 7.53−7.45 (m, 2 H), 7.39−7.12 (m, 11 H), 7.03−6.97 (m, 2 H), 5.00 (d, J = 15 Hz, 1 H), 4.26 (d, J = 16 Hz, 1 H), 4.19 (d, J = 16 Hz, 1 H), 3.94−3.86 (m, 1 H), 3.73−3.68 (m, 1 H), 3.61 (m, 1 H), 3.29 (bs, 2 H), 3.18−3.17 (m, 1 H), 2.96−2.89 (m, 1 H), 2.81−2.75 (m, 1 H), 2.36−2.31 (m, 2 H); 2.03−1.90 (m, 1 H), 1.71−1.65 (m, 1 H); CI MS 548 ($M + NH_4^+$, 100). HRMS calcd for $C_{34}H_{35}N_4O_2$ ($M + H^+$), 531.2760; found, 531.2753. Anal. ($C_{34}H_{34}N_4O_2 \cdot 0.33(i\text{-}C_3H_7OH) \cdot CD_3OD$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-aminophenyl-methyl)-3-[3-amino-1*H*-indazol-5-ylmethyl]-4-(2-phenylethyl)-5-hydroxy-6-(phenylmethyl)-2(1*H*)-pyrimidinone (96): mp 129.0−132.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.36 (bs, 1 H), 7.25−6.91 (m, 13 H), 6.63−6.55 (m, 3 H), 5.48 (d, J = 16 Hz, 1 H), 5.27 (d, J = 15 Hz, 1 H), 3.90 (d, J = 14 Hz, 1 H), 3.87 (d, J = 15 Hz, 1 H), 3.54−3.43 (m, 2 H), 3.40−3.30 (m, 1 H), 3.00−2.83 (m, 2 H), 2.43−2.37 (m, 2 H), 1.96−1.82 (m, 1 H), 1.65−1.52 (m, 1 H); ESI MS 281.4 ($M + 2H^{+2}$, 100). HRMS calcd for $C_{34}H_{37}N_6O_2$ ($M + H^+$), 561.2978; found, 561.2968. Anal. ($C_{34}H_{36}N_6O_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-aminophenyl-methyl)-3-[3-carboxamidophenyl-methyl]-4-(2-phenylethyl)-5-hydroxy-6-(phenylmethyl)-2(1*H*)-pyrimidinone (97): mp 197.0−109.0 °C; ^{1}H NMR (CD_3OD) δ 7.92 (bs, 1 H), 7.79−7.76 (m, 1 H), 7.55−7.52 (m, 1 H), 7.45−7.40 (m, 1 H), 7.29−6.99 (m, 11 H), 6.63−6.59 (m, 1 H), 6.50 (bs, 1 H), 6.45−6.43 (m, 1 H), 5.13 (d, J = 15 Hz, 1 H), 5.11 (d, J = 15 Hz, 1 H), 4.25 (d, J = 15 Hz, 1 H), 3.60−3.57 (m, 1 H); 3.44−3.42 (m, 1 H), 3.32−3.24 (m, 2 H), 3.20−3.16 (m, 1 H), 2.88−2.86 (m, 1 H), 2.69−2.63 (m, 1 H), 2.40−2.34 (m, 2 H), 1.87−1.81 (m, 2 H); ESI MS 549.5 ($M + H^+$, 100). HRMS calcd for $C_{34}H_{37}N_4O_3$ ($M + H^+$), 549.2866; found, 549.2866. Anal. ($C_{34}H_{36}N_4O_3 \cdot 0.15DMSO$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1-(3-aminophenyl-methyl)-3-[(3-(*N*-hydroxycarboximidamide)phenyl-methyl]-4-(2-phenylethyl)-5-hydroxy-6-(phenylmethyl)-2(1*H*)-pyrimidinone (98): mp 115.0−117.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (bs, 1 H), 7.29−6.90 (m, 13 H);, 6.56−6.50 (m, 3 H), 5.21 (d, J = 15 Hz, 1 H), 5.19 (d, J = 15 Hz, 1 H), 5.05 (bs, 1 H), 3.97 (d, J = 15 Hz, 1 H), 3.83 (d, J = 15 Hz, 1 H), 3.42−3.38 (m, 2 H), 3.16−3.15 (m, 1 H), 2.88−2.75 (m, 2 H);, 2.23−2.24 (m, 2 H), 1.89−1.81 (m, 1 H), 1.55−1.46 (m, 1 H); ESI MS 282.9 ($M + 2H^{+2}$, 100). HRMS calcd for $C_{34}H_{38}N_5O_3$ ($M + H^+$), 564.2975; found, 564.2999. Anal. ($C_{34}H_{37}N_5O_3 \cdot 0.3C_4H_8O_2$) C, H, N.

(4*R*,5*S*,6*R*,7*R*)-1,3-diaza-4,7-bis-(phenylmethyl)-5-(hydroxy)-bicyclo[4.1.0]heptan-2-one (99). Method 1. A solution of acetate **14** (100 mg, 0.29 mmol) in methanol (5 mL) was treated with 1 N NaOH (10 drops from 2 mL disposable pipet) and stirred at room temperature for 30 min. The solution was diluted with water and the precipitate extracted into methylene chloride. The extracts were washed with water and dried over $MgSO_4$. The mixture was filtered and concentrated to give 30 mg of **99** as a white solid: ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.38−7.16 (m, 10 H), 3.97 (dd, J = 5 Hz, J = 7 Hz, 1 H), 3.52 (m, 1 H), 3.40−3.20 (m, 2 H), 3.00−2.74 (m, 3 H), 2.51 (dd, J = 10 Hz, J = 15 Hz, 1 H); DCI MS (NH_3) m/z 309 ($M + H^+$, 100). Anal. ($C_{21}H_{22}N_2O_3 \cdot 0.25(CH_3OH)$) C, H, N.

Method 2. A solution of acetate **14** (350 mg, 1.0 mmol) in THF was cooled in an ice bath and treated with LAH (76 mg, 2.0 mmol) and stirred while allowing the solution to warm to room temperature for 3 h. The solution was diluted with water and extracted into ethyl acetate. The extracts were washed with water and brine and dried over $MgSO_4$. The mixture was filtered and concentrated to give 300 mg of **99** as a white solid. Recrystallized from EtOAc/hexane: mp 170−176 °C (dec): ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.38−7.16 (m, 10 H), 3.97 (dd, J = 5 Hz, J = 7 Hz, 1 H), 3.52 (m, 1 H), 3.40−3.20 (m, 2 H), 3.00−2.74 (m, 3 H), 2.51 (dd, J = 10 Hz, J = 15 Hz, 1 H); DCI MS (NH_3) m/z 309 ($M + H^+$, 100). Anal. ($C_{21}H_{22}N_2O_3 \cdot 0.2(EtOAc) \cdot 0.2(hexane)$) C, H, N.

(4*R*,5*S*,6*R*,7*R*)-1,3-diaza-1-[(3-cyanophenyl)methyl]-4,7-bis-(phenylmethyl)-5-(hydroxy)-bicyclo[4.1.0]heptan-2-one (100): ^{1}H NMR ($CDCl_3$) δ 7.51−7.16 (m, 14 H), 4.96 (d, J = 15 Hz, 1 H), 3.65 (m, 1 H), 3.51−3.30 (m, 3 H), 3.00 (m, 1 H), 2.98 (m, 1 H), 2.82 (m, 1 H), 2.64 (d, J = 15 Hz, 1 H), 2.31 (dd, J = 10 Hz, J = 15 Hz, 1 H), 1.6 (bs, 1 H); DCI MS (NH_3) m/z 424 ($M + H^+$, 100). Anal. ($C_{27}H_{25}N_3O_2$) C, H, N.

(4*R*,5*S*,6*R*,7*R*)-1,3-diaza-1-[3-carboxamidophenylmethyl]-4,7-bis-(phenylmethyl)-5-(hydroxy)-bicyclo[4.1.0]-heptan-2-one (101): ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 7 Hz, 1 H), 7.41−7.11 (m, 13 H), 6.40 (bs, 1 H), 6.05 (bs, 1 H), 4.91 (d, J = 15 Hz, 1 H), 4.20 (bs, 1 H), 3.63 (m, 1 H), 3.58−3.20 (m, 3 H), 3.01−2.72 (m, 3 H), 2.60 (d, J = 15 Hz, 1 H), 2.32 (dd, J = 10 Hz, J = 15 Hz, 1 H); DCI MS (NH_3) m/z 442 ($M + H^+$, 100). Anal. ($C_{27}H_{27}N_3O_3 \cdot 0.15DMSO$) C, H, N.

(4*R*,5*S*,6*R*,7*R*)-1,3-diaza-1-[(*N*-hydroxycarboximidamide)phenylmethyl]-4,7-bis-(phenylmethyl)-5-(hydroxy)-bicyclo[4.1.0]heptan-2-one (102): ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.46−7.01 (m, 14 H), 5.01 (d, J = 15 Hz, 1 H), 3.60−3.20 (m, 4 H), 3.04−2.71 (m, 3 H), 2.56 (d, J = 15 Hz, 1 H), 2.37 (dd, J = 10 Hz, J = 15 Hz, 1 H); ESI MS (NH_3) m/z 457 ($M + H^+$, 100). Anal. ($C_{27}H_{28}N_4O_3 \cdot 0.85EtOAc$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3,6-tris-[phenylmethyl]-5-oxo-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (106): ^{1}H NMR ($CDCl_3$) δ 7.46−7.00 (m, 20 H), 5.36 (d, J = 15 Hz, 1 H), 4.92 (d, J = 14 Hz, 1 H), 3.96 (d, J = 14 Hz, 1 H), 3.95 (m, 1 H), 3.72 (d, J = 15 Hz, 1 H), 3.55 (m, 1 H), 3.09 (d, J = 7 Hz, 1 H), 2.60 (abx m, 1 H), 2.41 (abx m, 1 H), 1.99 (m, 2 H); ^{13}C NMR ($CDCl_3$) 204.0, 156.8, 140.2, 136.8, 136.7, 135.7, 129.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127.8, 127.6, 127.2, 126.1, 64.2, 62.0, 49.3, 49.1, 36.8, 32.1, 30.8; CIMS (NH_3) m/z 506 ($M + NH_4^+$, 100).

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