Design and Synthesis of Novel α_{1a} Adrenoceptor-Selective Antagonists. 2. Approaches To Eliminate Opioid Agonist Metabolites via Modification of Linker and 4-Methoxycarbonyl-4-phenylpiperidine Moiety[1,2]

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We have previously described compound **1a** as a high-affinity subtype selective α_{1a} antagonist. In vitro and in vivo evaluation of compound **1a** showed its major metabolite to be a μ-opioid agonist, 4-methoxycarbonyl-4-phenylpiperidine (**3**). Several dihydropyrimidinone analogues were synthesized with the goal of either minimizing the formation of **3** by modification of the linker or finding alternative piperidine moieties which when cleaved as a consequence of metabolism would not give rise to μ-opioid activity. Modification of the linker gave several compounds with good α_{1a} binding affinity (K_i = < 1 nM) and selectivity (>300-fold over α_{1b} and α_{1d}). In vitro analysis in the microsomal assay revealed these modifications did not significantly affect *N*-dealkylation and the formation of the piperidine **3**. The second approach, however, yielded several piperidine replacements for **3**, which did not show significant μ-opioid activity. Several of these compounds maintained good affinity at the α_{1a} adrenoceptor and selectivity over α_{1b} and α_{1d}. For example, the piperidine fragments of (+)-**73** and (+)-**83**, viz. 4-cyano-4-phenylpiperidine and 4-methyl-4-phenylpiperidine, were essentially inactive at the μ-opioid receptor (IC_{50} > 30 μM vs 3 μM for **3**). Compounds (+)-**73** and (+)-**83** were subjected to detailed in vitro and in vivo characterization. Both these compounds, in addition to their excellent selectivity (>880-fold) over α_{1b} and α_{1d}, also showed good selectivity over several other recombinant human G-protein coupled receptors. Compounds (+)-**73** and (+)-**83** showed good functional potency in isolated human prostate tissues, with K_bs comparable to their in vitro α_{1a} binding data. In addition, compound (+)-**73** also exhibited good uroselectivity (DBP K_b/IUP K_b > 20-fold) in the in vivo experiments in dogs, similar to **1a**.

Introduction

We have been interested[3−5] in developing α_{1a} adrenoceptor[6]-selective antagonists due to their potential to provide significant improvement in the treatment of benign prostatic hyperplasia (BPH)[7−9] over the clinically used nonselective α_1 adrenoceptor antagonists such as terazosin[10] and doxazosin.[11] In the preceding article,[2] we presented the biological rationale for design of α_{1a} adrenoceptor-selective antagonists. Therein, we presented the design and synthesis of several dihydropyrimidinone derivatives as potent α_{1a} adrenoceptor-selective antagonists. We identified compound **1a** as the lead candidate with excellent functional potency in the isolated human prostate tissue and presented data that showed good uroselectivity in dogs.

In vitro evaluation of **1a** in human liver microsomes and in vivo evaluation in rat and dog defined the metabolic pathway depicted in Chart 1, with the predominant (>50%) formation of **2** and 4-methoxycarbonyl-4-phenylpiperidine (**3**). Compound **2** was found to be devoid of α_{1a} antagonist activity and showed negligible cross-reactivity at several other G-protein coupled receptors and the L-type calcium channel. Metabolite **3**, however, was found to be a μ-opioid agonist (IC_{50} = 3 μM) and is a close analogue of the μ-opioid agonist meperidine (IC_{50} = 1.1 μM).[12] Hydrolysis of the piperidine-4-methoxycarbonyl ester to form the carboxylic acid **4** has been shown to occur. Meperidine is well-known for the undesirable narcotic and sedative properties. In addition, **3** showed a long plasma half-life (>12 h) in rats and dogs that raised concerns that this metabolite **3** may lead to opioid agonist liabilities on chronic administration of **1a**. These findings prompted us to search for compounds devoid of this potential liability.

We set out to attain these goals by two major approaches: (i) minimize the metabolic formation of 4-methoxycarbonyl-4-phenylpiperidine (**3**) by modification of the linker and (ii) replace this piperidine portion with other piperidines that do not have the μ-opioid

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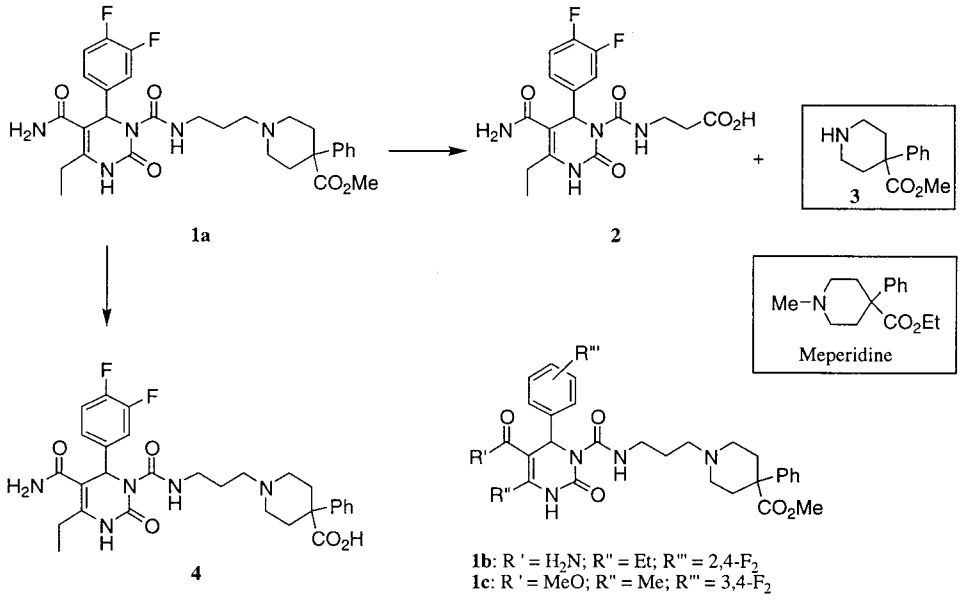
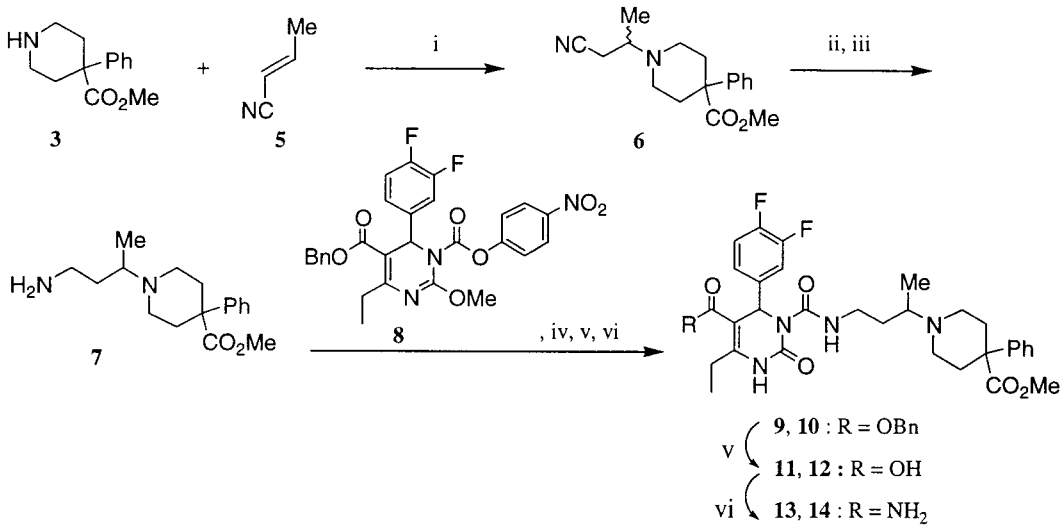
Chart 1

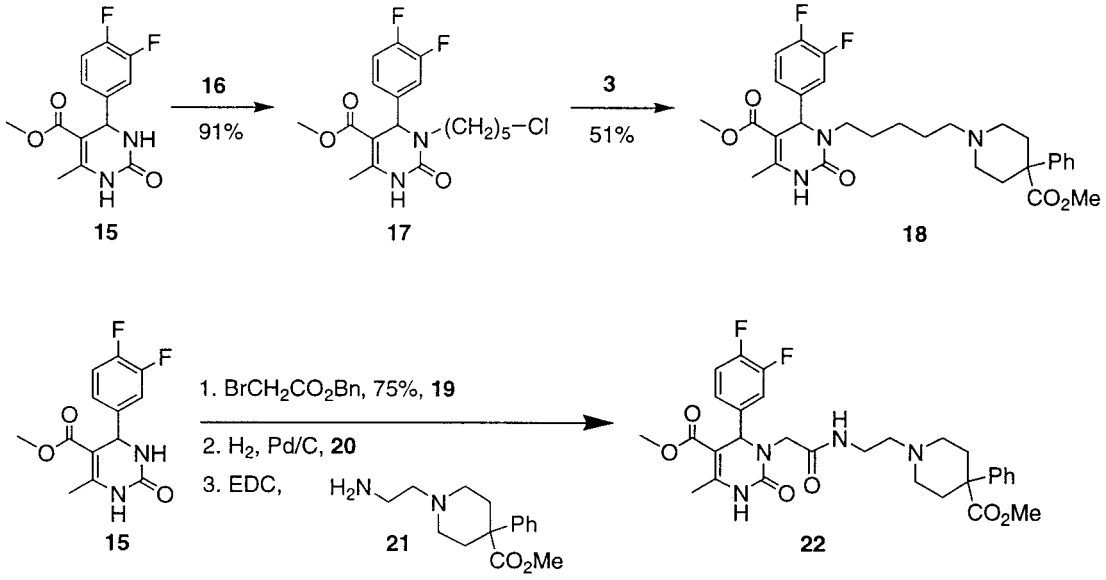


Scheme 1[a]

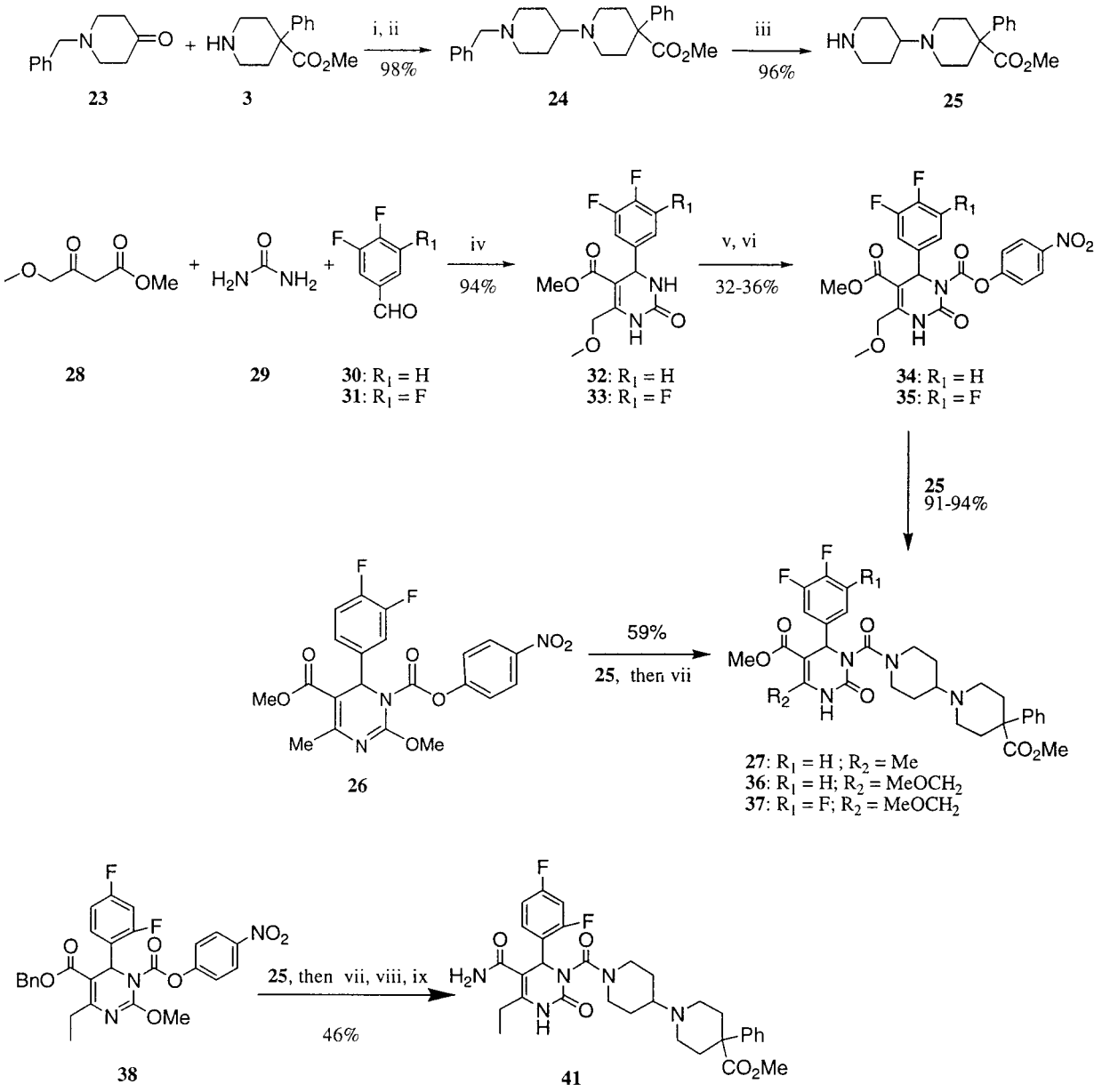


[a] (i) EtOH, reflux; (ii) HPLC separation of enantiomers; (iii) RaNi (H_2); (iv) 6 N HCl; (v) H_2, Pd−C, MeOH/water; (vi) EDC, NMM, NH_4OH, CH_2Cl_2.

Scheme 2



Scheme 3[a]



[a] (i) PTS, toluene; (ii) $NaBH_3CN$; (iii) H_2, Pd−C, MeOH/water; (iv) Cu_2O, HOAc, $BF_3{\cdot}OEt_2$, THF; (v) HPLC separation; (vi) LiHMDS, 4-nitrophenyl chloroformate; (vii) HCl; (viii) H_2, Pd−C, MeOH/water; (ix) EDC, NMM, NH_4OH, CH_2Cl_2.

agonist activity. The results from these studies are summarized here.

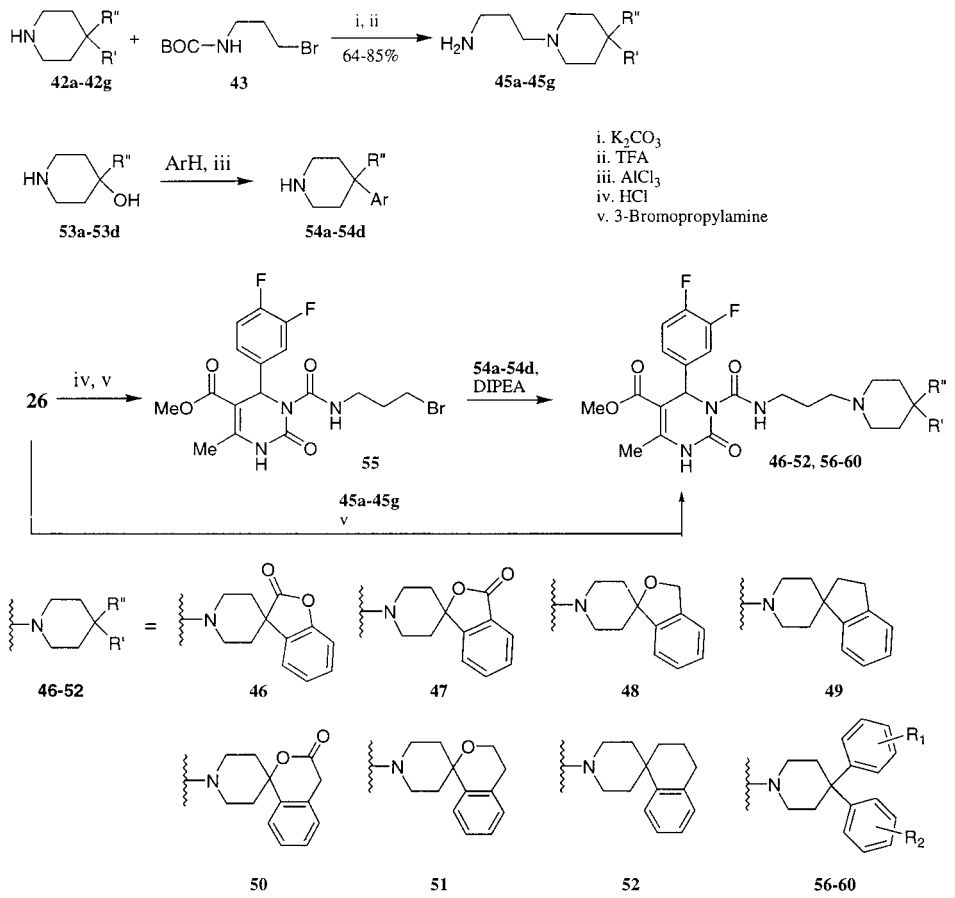
Chemistry

Schemes 1−3 describe the syntheses of compounds with linker modifications. Piperidine **3** was reacted with crotononitrile (**5**), and the resultant racemic nitrile **6** was resolved via chiral HPLC (Scheme 1). The individual enantiomers were then reduced to the enantiomeric amine **7** by Raney nickel-catalyzed hydrogenation. Independently, these amines were reacted with the (4-nitrophenyl)carbamoyldihydropyrimidine **8**[2] and subsequently treated with HCl to afford the benzyl esters **9** and **10**. These compounds on hydrogenation gave the carboxylic acids **11** and **12**, which upon coupling with ammonia gave products **13** and **14**.

Reaction of dihydropyrimidine **15** with 5-bromo-1-chloropentane (**16**) gave the chloride **17** which on reaction with piperidine **3** gave **18** (Scheme 2). Alkylation of dihydropyrimidine **15** with benzyl 2-bromoacetate gave **19**, which upon hydrogenation provided the carboxylic acid **20**. The 2-aminoethylpiperidine side chain **21** was prepared by reaction of piperidine **3** with 2-bromoethylamine. Subsequently, the carboxylic acid **20** was coupled with amine **21** in the presence of DMAP and EDC to provide **22**.

The piperidinylpiperidine derivative **24** was obtained by condensation of *N*-benzyl-4-piperidone (**23**) with piperidine **3** and subsequent reduction of the intermediate with $NaBH_3CN$ (Scheme 3). Hydrogenation of **24** with 10% Pd−C gave the piperidinylpiperidine **25**, which on reaction with dihydropyrimidine **26**[2] and treatment with HCl gave **27**. The racemic dihydropyrimidinone **32** was prepared by reaction of 3,4-difluorobenzaldehyde (**30**) with methyl 4-methoxyacetoacetate (**28**) and urea (**29**) in the presence of Cu_2O, boron

Scheme 4

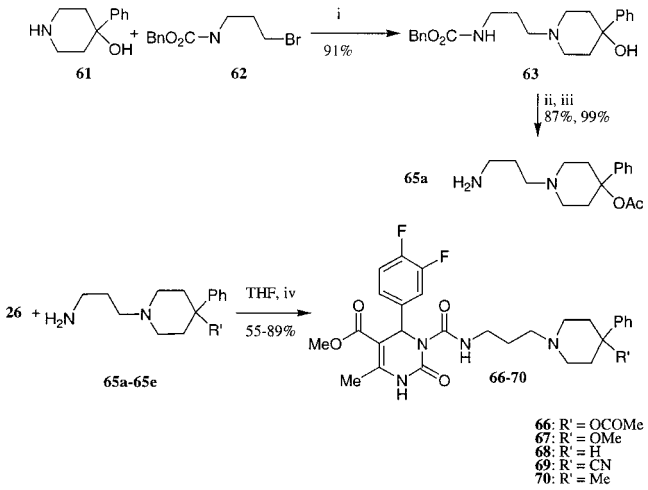


trifluoride−etherate, and acetic acid.[13] Compound **32** was resolved using a chiral HPLC column. The (+) enantiomer of **32** was reacted with LiHMDS followed by treatment with 4-nitrophenyl chloroformate to give the dihydropyrimidine carbamate ester **34**. Compound **34**, upon reaction with amine **25**, gave product **36**. The 3,4,5-trifluorophenyl-substituted dihydropyrimidine analogue **37** was prepared using a similar procedure. Compound **41** was prepared from the dihydropyrimidine benzyl ester intermediate **38** and amine **25** following a similar sequence of reactions described for **13** and **14** in Scheme 1.

Schemes 4−7 describe the syntheses of compounds with piperidine replacements. The spirocyclic piperidines **42a**−**42g**[14,15] were alkylated with 1-*N*-(*tert*-butoxycarbonyl)-3-bromopropylamine, and the resulting BOC-protected aminopiperidines **44** were treated with TFA to give the 3-aminopropylpiperidines **45a**−**45g** (Scheme 4). These amines, upon reaction with the pyrimidine **26** followed by treatment with HCl, gave **46**−**52**. Using a similar procedure, compound **56** was synthesized from **26** and 3-(4,4-diphenylpiperidin-1-yl)-propylamine.[3] The diarylpiperidines **54a**−**54d** were synthesized via a Friedel−Crafts reaction of 4-hydroxy-4-arylpiperidines **53a**−**53d** with substituted benzenes. Reaction of **26** with HCl followed by treatment with 3-bromopropylamine gave the 3-bromopropylcarbamoyldihydropyrimidine **55**. The diarylpiperidines **54a**−**54d** were reacted with the bromide **55** to afford products **57**−**60**.

Scheme **5** summarizes the synthesis of a series of compounds with modifications at the C-4 methoxycarbonyl piperidine position. Reaction of 4-hydroxy-4-phenylpiperidine (**61**) with 1-*N*-(benzyloxycarbonyl)-3-bromopropylamine (**62**) gave **63** which on acetylation with acetic anhydride followed by hydrogenolysis gave **65a**. Side chains **65b**−**65e** were synthesized following reported methods.[3,5] Reaction of **26** with amines **65a**−**65e** followed by treatment with HCl gave **66**−**70**.

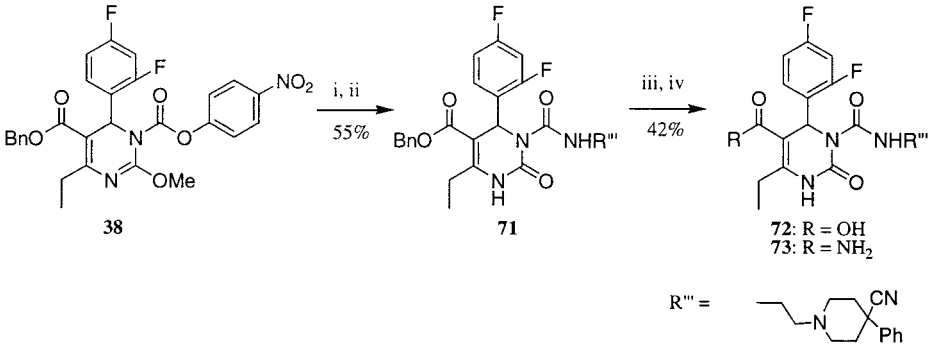
Scheme 5[a]



[a] (i) K_2CO_3; (ii) NaH, Ac_2O; (iii) H_2, 10% Pd−C; (iv) HCl.

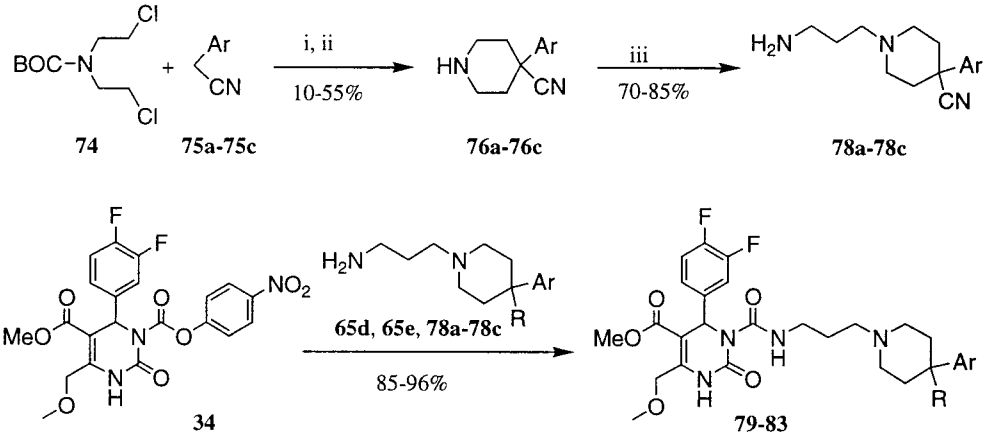
The synthesis of **73** is described in Scheme 6. Dihydropyrimidine **38**[2] was reacted with 3-(4-cyano-4-phenylpiperidin-1-yl)propylamine (**65d**) and subsequently treated with HCl to afford the benzyl ester **71**, which upon catalytic hydrogenation gave carboxylic acid **72**.

Scheme 6[a]



[a] (i) Amine **65d**; (ii) HCl; (iii) H_2, Pd−C, MeOH/water; (iv) EDC, NMM, NH_4OH, CH_2Cl_2.

Scheme 7. Synthesis of **79**−**83**[a]



[a] (i) NaH; (ii) TFA; (iii) (a) BOC-NH-$CH_2CH_2CH_2Br$, K_2CO_3, KI, acetone, (b) TFA; or (a) 3-bromopropylphthalimide, K_2CO_3, KI, DMF, (b) H_2N-NH_2, methanol.

Acid **72** was then converted to the amide **73** by reaction with ammonia in the presence of EDC and NMM.

Compound **79** was synthesized by the reaction of pyrimidinone **34**[2] with amine **65d**. The 4-aryl-4-cyanopiperidines **76a**−**76c** were synthesized from the corresponding 4-arylacetonitriles **75a**−**75c** by dialkylation with *N*-*tert*-butoxycarbonyl-bis(2-chloroethyl)amine (**74**) followed by treatment with TFA. The 3-aminopropyl moiety was introduced as described above or by reaction with 3-bromopropylphthalimide and subsequent treatment with hydrazine. Side chains **78a**−**78c** were reacted with the pyrimidinone **34** to provide compounds **80**−**82**. Compound **83** was synthesized by reaction of **34** with 3-(4-phenyl-4-methylpiperidin-1-yl)propylamine (**65e**).

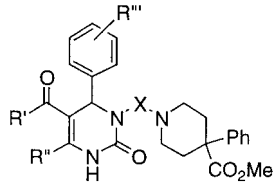
Results and Discussion

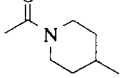
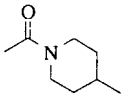
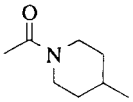
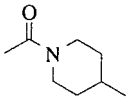
Initially, we used compound **1a**, its 2,4-difluoro analogue **1b**, or **1c** (see Chart 1) for the modifications of the linker and the piperidine. Later, we also made additional modifications on the dihydropyrimidinone moiety. In the first part of the discussion we present the structure−activity relationship (SAR) with respect to the α_{1a} binding affinity and selectivity of the resultant compounds. Subsequent discussions focus on the opioid activity of putative piperidine metabolites and additional in vitro and in vivo characterization.

Effect of Modification of the Linker on Binding Affinities. Introduction of a methyl group on the linker carbon adjacent to the piperidine nitrogen in order to minimize the *N*-dealkylation resulted in the two diastereomers **13** and **14** (Scheme 1). Among these, **13** showed higher binding affinity for the α_{1a} adrenoceptor than **14**. Compound **13** was 20 times weaker than **1a** but showed >300-fold subtype selectivity (Table 1). Changing the amide linker ($CONHCH_2CH_2CH_2$) between dihydropyrimidinone and piperidine moieties to an all carbon alkyl chain ($CH_2CH_2CH_2CH_2CH_2$) gave compound **18**. Rearrangement of the $CONHCH_2CH_2CH_2$ linker to $CH_2CONHCH_2CH_2$ gave **22** which reduced the distance between the two nitrogens by a methylene unit, while keeping the number of bonds between the dihydropyrimidinone and the piperidine constant.[3,4] Both compounds **18** and **22** showed good α_{1a} binding and selectivity profile (K_i = 0.1−0.2 nM, >1200-fold). In another approach, we conformationally restricted the linker with a piperidinyl moiety to minimize the *N*-dealkylation. The initial compound **27** in this series exhibited a significantly lower α_{1a} binding affinity (19 nM vs 0.1 nM for **1c**). However, when the dihydropyrimidinone C-4 methyl (R_2) group was changed to a 2-methoxymethyl (**36**) the α_{1a} affinity improved (K_i = 7.5 nM). Further improvement was seen (K_i = 1.7 nM) when a third fluorine was added on the C-6 phenyl ring to yield the dihydropyrimidinone **37** (K_i = 1.7 nM, >1800-fold). We also synthesized a close analogue of our earlier lead compound **1b** with this piperidylpiperidine modification (**41**); however, the compound showed a comparatively lower α_{1a} affinity (81 nM).

Effect of Spirocyclic Piperidine Modifications

Table 1. α_1 Binding Profile of Linker-Modified Dihydropyrimidinones



compd	R′	R″	R‴	X	K_i (nM)[a] α_{1a}	α_{1b}	α_{1d}
prazosin					0.6	0.6	0.3
SNAP 6201 (**1a**)	H_2N	Et	3,4-F_2	CO-NH-$(CH_2)_3$-	0.2	250	340
1b	H_2N	Et	2,4-F_2	CO-NH-$(CH_2)_3$-	0.2	220	340
1c	MeO	Me	3,4-F_2	CO-NH-$(CH_2)_3$-	0.1	45	140
13	H_2N	Et	3,4-F_2	CO-NH-$(CH_2)_2$-(CHMe)-	4.2	1480	2100
14	H_2N	Et	3,4-F_2	CO-NH-$(CH_2)_2$-(CHMe)-	58	1450	2260
18	MeO	Me	3,4-F_2	-$(CH_2)_5$-	0.1	140	150
22	MeO	Me	3,4-F_2	-CH_2-CO-NH-$(CH_2)_2$-	0.2	1050	610
27	MeO	Me	3,4-F_2		19	1940	2260
36	MeO	$MeOCH_2$	3,4-F_2		7.5	2630	5280
37	MeO	$MeOCH_2$	3,4,5-F_3		1.7	3130	5370
41	H_2N	Et	2,4-F_2		81	15500	14700

[a] All K_i values are ±5% SE or less for $n > 2$. In the case of $n = 2$, both K_i values were within 2-fold of each other and the value shown is the average of the two values.

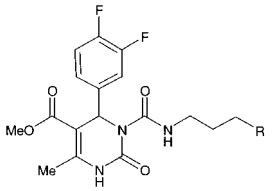
on Binding Affinities. The spirocyclic piperidine analogues were designed to avoid the formation of the piperidine-4-carboxylic acid derivatives such as **4** and to obtain piperidines with minimal μ-opioid activity. The variations included systematic modification of the piperidine 4-phenyl and 4-methoxycarbonyl moieties into lactones, ethers, and carbocycles (Table 2). The 6−5 spirocyclic lactone derivative **46** showed a 40-fold lower α_{1a} binding affinity (K_i 4.5 nM vs 0.1 nM for **1c**), and the reverse lactone (COO vs OCO) analogue **47** exhibited similar α_{1a} affinity (7.9 nM). The 6−5 spirocyclic ether (**48**) and the indane (**49**) analogues, however, exhibited improved binding affinity (K_i = 0.3 and 1.1 nM) and selectivity (>200-fold) for the α_{1a} adrenoceptor. The corresponding 6−6 spirocyclic piperidine analogues **50**−**52** showed significant improvement in the α_{1a} binding and selectivity relative to their five-membered counterparts **47**−**49**. However, these compounds showed significant cross-reactivity at either the α_2 receptor (e.g. **46** ≥ 26-fold selectivity over α_{2a}, α_{2c}) or histamine receptor (e.g. **46** ≥ 27-fold selectivity over H_1) (Table 2).

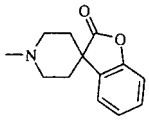
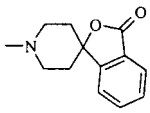
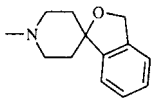
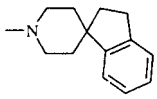
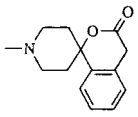
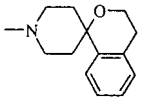
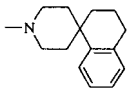
Effect of Diarylpiperidine Modifications on Binding Affinities. When tested at the μ-opioid receptor, 4,4-diphenylpiperidine (**54a**) showed an IC_{50} > 17 μM. This result suggested that we could use diarylpiperidines as replacements for **3** and thereby minimize the μ-opioid liability. Substitution of the piperidine moiety of **1c** with 4,4-diphenylpiperidine resulted in compound **56** with good α_{1a} affinity (K_i = 1.85 nM); however, it showed only ~20-fold selectivity over the α_{1b} subtype (Table 3). Further modification of the phenyl rings with a bis-4-chloro substitution (**54b**) resulted in lower affinity (**57**, K_i = 6.9 nM); however, a bis-4-fluoro substitution (**54c**) improved the α_{1a} binding as well as the selectivity (**58**, K_i = 0.16 nM, >125-fold). A 2- and 4′-dimethyl substitution (**54d**) improved the α_{1a} affinity of the analogue **59** to K_i = 0.06 nM and the subtype selectivity to over 1300-fold.

The μ-opioid activities of the diarylpiperidines are summarized in Table 4. We identified 4,4-bis(3,5-dimethylphenyl)piperidine (**54e**) to have weak activity at the μ-opioid receptor (IC_{50} = 27 μM). Its dihydropyrimidinone derivative **60** showed 4.6 nM affinity at the α_{1a} adrenoceptor with >186-fold over α_{1b} and α_{1d} adrenoceptors.

Effect of Modifications of the 4-Methoxycarbonyl Moiety of Piperidine on Binding Affinities. In this section, we replaced the 4-methoxycarbonyl group of the piperidine with acetoxy, methoxy, cyano, hydrogen, and methyl groups (Table 5). The reverse ester derivative **66** showed 3-fold less affinity (K_i = 0.3 nM vs 0.1 nM) than its methoxycarbonyl analogue **1c** but showed improved subtype selectivity (>2000-fold for both α_{1b} and α_{1d}). Replacement of the 4-methoxycarbonyl group with methoxy (**67**) resulted in 10-fold lower α_{1a} affinity but retained good selectivity over α_{1b} and α_{1d} (>250-fold). Interestingly, the analogue of **1c** unsubstituted at position 4 (**68**) retained good affinity (K_i = 0.21 nM) and selectivity (>170-fold). The 4-cyano-substituted compound **69** exhibited a significantly reduced affinity (K_i = 3.2 nM) and subtype selectivity

Table 2. α_1 Binding Profile of Spirocyclic Piperidine-Substituted Dihydropyrimidinones



compd	R	K_i (nM)[a] α_{1a}	α_{1b}	α_{1d}
1c		0.1	45	140
46		4.5	1490	1560
47		7.9	2820	1940
48		0.3	400	210
49		1.1	410	230
50		0.2	250	330
51		0.20	490	620
52		0.4	310	910

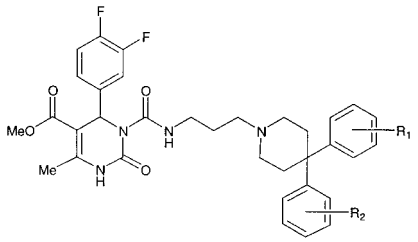
[a] All K_i values are ±5% SE or less for $n > 2$. In the case of $n = 2$, both K_i values were within 2-fold of each other and the value shown is the average of the two values.

(>70-fold) at the α_{1a} adrenoceptor. Substitution with a methyl group, however, provided compound **70** with excellent (>540-fold) α_1 adrenoceptor subtype selectivity. Synthesis of a close analogue of **1b** with 4-cyano-4-phenylpiperidine resulted in compound (+)-**73**, which showed good α_{1a} binding (K_i = 0.67 nM) affinity and >900-fold subtype selectivity.

Synthesis of additional analogues of **69** and **70** with a C-4 methoxymethyl group instead of a methyl group resulted in compounds **79** and **83** (Table 6), respectively, with excellent α_{1a} adrenoceptor binding profile. Further modification of the phenyl group of 4-phenyl-4-cyanopiperidine with a fluoro substitution provided several compounds (**80**−**82**) with good α_{1a} affinity, with the 4-fluoro analogue **82** being the best (K_i = 0.06 nM) among these compounds (Table 6).

Metabolism and Opioid Activity. We tested linker-modified analogues **13**, **18**, **22**, and **37** in the isolated rat/human liver microsomes and/or for their oral bioavailability and half-life in rats. The PK results revealed no improvement in half-life or bioavailability as compared to **1a**−**1c**. The fact that the half-life and/or bioavailability of linker-modified analogues were not improved suggested that either the levels of the piperidine metabolite were not significantly changed or the presence of a new linker had changed the route of the metabolism. In either case, the poor PK performance of the analogues precluded any further work in this area.

Table 3. α_1 Binding Profile of Diarylpiperidine-Substituted Dihydropyrimidinones



compd	R_1	R_2	K_i (nM)[a] α_{1a}	α_{1b}	α_{1d}
1c			0.1	45	140
56	H	H	1.9	36	190
57	4-Cl	4-Cl	6.9	84	560
58	4-F	4-F	0.2	20	120
59	2-CH_3	4-CH_3	0.06	80	250
60	3,5-dimethyl	3,5-dimethyl	4.6	860	750

[a] All K_i values are ±5% SE or less for $n > 2$. In the case of $n = 2$, both K_i values were within 2-fold of each other and the value shown is the average of the two values.

On the other hand, in the second approach several final products and their piperidines showed decreased μ-opioid activity. For example, compounds (+)-**73** and (+)-**83** and their piperidine fragments, 4-cyano-4-phenylpiperidine and 4-methyl-4-phenylpiperidine, were essentially inactive at the opioid receptor (IC_{50} > 30 μM vs 3 μM for **3**).

In Vitro and in Vivo Properties of (+)-73 and (+)-83. Compounds (+)-**73** and (+)-**83** were characterized in further in vitro and in vivo assays. Table 7 summarizes the in vivo properties of (+)-**73** and (+)-**83** in comparison to SNAP 6201 and terazosin. Both (+)-**73** and (+)-**83**, in addition to their excellent selectivities over α_{1b} and α_{1d}, were also found to be selective over several recombinant human G-protein coupled receptors. The panel of G-protein coupled receptors included α_{2a}, α_{2b}, α_{2c} adrenoceptors, histamine-H_1, and −H_2, 5HT-1A, -1B, -1D, and -2A, and dopamine (D_1, D_3, D_5) receptors and also at the rat L-type calcium channel, with selectivities ranging from 280-fold to greater than 1000-fold.

Compounds (+)-**73** and (+)-**83** showed good potencies with respect to the prostate in rat, dog, and human tissues, whereas terazosin showed good potencies in the prostate as well as the aorta (19 nM). In addition, in the phenylephrine-stimulated urethral pressure experiments in dog, compound (+)-**73** showed good potency (IUP K_b = 14 μg/kg) and uroselectivity (DBP K_b/IUP K_b = >20) compared to the poor selectivity seen for terazosin (DBP K_b/IUP K_b = ∼1).

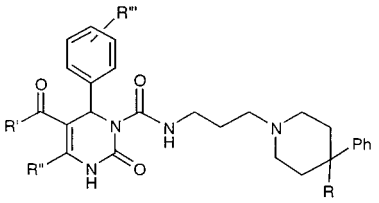
The pharmacokinetic profile of (+)-**73** was determined in male Sprague−Dawley rats and in male beagle dogs at 1 mg/kg iv and 3 mg/kg oral dose with quantification via HPLC. The results showed 8% oral bioavailability in rats with 35-min $t_{1/2}$ and 19% oral bioavailability and 138-min $t_{1/2}$ in dogs (Table 7). Using the HPLC quantification assay, (+)-**83** in the dog showed longer plasma

Table 4. Effect of 4,4′-Diaryl Substitution on Opioid Activity (IC_{50}, μM) of Selected Piperidines[a]

compd	R_1	R_2	opioid binding, [^{3}H]DAMGO (μM)
normeperidine	phenyl	carbethoxy	1.1
54a	phenyl	phenyl	17
54d	2-methylphenyl	4-methylphenyl	6
54e	3,5-dimethylphenyl	3,5-dimethylphenyl	27

[a] All IC_{50} values are ±30% SE or less for $n > 2$. In the case of $n = 2$, both IC_{50} values were within 2-fold of each other and the value shown is the average of the two values.

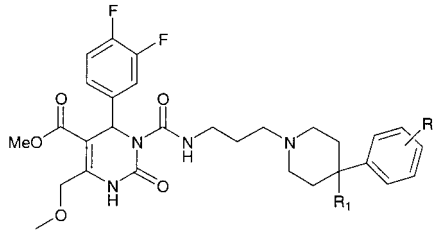
Table 5. α_{1a} Binding Profile of Dihydropyrimidinones **66**−**70**



					K_i (nM)[a]		
compd	R′	R″	R‴	R	α_{1a}	α_{1b}	α_{1d}
1c	MeO	Me	3,4-F_2	CO_2Me	0.1	45	140
66	MeO	Me	3,4-F_2	OCOMe	0.3	700	780
67	MeO	Me	3,4-F_2	OMe	1	250	370
68	MeO	Me	3,4-F_2	H	0.2	36	150
69	MeO	Me	3,4-F_2	CN	3.2	340	230
70	MeO	Me	3,4-F_2	Me	0.5	270	480
(+)-73	H_2N	Et	2,4-F_2	CN	0.7	610	1280

[a] All K_i values are ±5% SE or less for $n > 2$. In the case of $n = 2$, both K_i values were within 2-fold of each other and the value shown is the average of the two values.

Table 6. α_{1a} Binding Profile of Dihydropyrimidinones **79**−**83**



			K_i (nM)[a]		
compd	R_1	R	α_{1a}	α_{1b}	α_{1d}
1c			0.1	45	140
79	CN	H	0.1	130	260
80	CN	2-F	5.2	730	930
81	CN	3-F	0.2	150	180
82	CN	4-F	0.06	30	110
(+)-83	Me	H	0.5	440	640

[a] All K_i values are ±5% SE or less for $n > 2$. In the case of $n = 2$, both K_i values were within 2-fold of each other and the value shown is the average of the two values.

half-life (6.5 h vs 2.5 h for **1a**). Compound (+)-**83** showed 23% bioavailability and a half-life of 24 min in the rat (Table 7).

Summary

A series of dihydropyrimidinone analogues were synthesized with the goal of either minimizing the formation of meperidine-like metabolite **3** or finding replacement moieties that were devoid of the μ-opioid agonist activity. The initial approach involved the introduction of a methyl group on the linker carbon adjacent to the piperidine, all-alkyl carbon linker, and conformational restriction of the linker into a piperidine. Several compounds with good α_{1a} binding affinity (K_i = <1 nM) and selectivity (>300-fold over α_{1b} and α_{1d}) were obtained. In vitro analysis in the microsomal assay revealed these modifications did not significantly affect *N*-dealkylation and formation of the piperidine **3**. In addition, none of the compounds tested showed significant improvement in the pharmacokinetic profile, compared to **1a**.

In the second approach, however, we successfully identified several piperidines devoid of the μ-opioid activity, as replacements for **3**. For example, the piperidine pieces of (+)-**73** and (+)-**83**, viz. 4-cyano-4-phenylpiperidine and 4-methyl-4-phenylpiperidine, were essentially inactive at the μ-opioid receptor ($IC_{50} > 30$ μM vs 3 μM for **3**). Compounds (+)-**73** and (+)-**83** were subjected to further in vitro and in vivo characterization. Both these compounds, in addition to their excellent selectivity (>880-fold) over α_{1b} and α_{1d}, also showed good selectivity over several recombinant human G-protein coupled receptors. Similar to **1a**, compound (+)-**73** also exhibited good in vivo functional potency (IUP $K_b = 14$ μg/kg) in the dogs with a DBP K_b/IUP K_b ratio of >20 versus no selectivity seen for the nonselective α_1 adrenoceptor antagonist terazosin. Compound (+)-**83** in the isolated human prostate tissues showed good functional potency comparable to its in vitro binding affinity at the human α_{1a} adrenoceptor ($K_b = 0.66$ nM vs $K_i = 0.14$ nM). Neither (+)-**73** nor (+)-**83**, however, showed significantly improved pharmacokinetic profiles over **1b**. Another approach to address the issue of opioid active metabolites is described in the accompanying paper.[24]

Experimental Section

All protocols for the chemical and biological (in vitro and in vivo) experiments are described in the preceding manuscript.[2]

(+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-2-methylpropyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (14). (a) 3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropionitrile (6). To a solution of 4-methoxycarbonyl-4-phenylpiperidine (3.48 g, 15.8 mmol) in MeOH (25 mL) was added crotononitrile (5.32 g, 79.0 mmol) and the mixture was heated at reflux temperature for 4 h. Methanol and excess crotononitrile were evaporated and the residue was purified by column chromatography on silica gel (30−100% EtOAc in hexanes). ^{1}H NMR ($CDCl_3$): δ 1.16 (d, $J = 6.0$ Hz, 3 H), 1.86−1.96 (m, 2 H), 2.28−2.60 (m, 6 H), 2.68−2.80 (m, 2 H), 2.96−3,02 (m, 1 H), 3.62 (s, 3 H), 7.20−7.36 (m, 5 H).

(b) 3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropionitrile (7). The racemic 3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropionitrile (1.53 g) was resolved by chiral HPLC [Chiralcel OD 20 × 250 mm #369-703-30604]; λ 254 nm; hexanes/ethanol, 80/20; 80 mg/injection; retention time of the desired enantiomer: 18.18 min. The first desired product was used to synthesize product **13** and the second peak to **14** (31 wt % isolation of the first peak and 35% of the second peak from the racemate).

(c) (+)-5-(Benzyloxycarbonyl)-6-(3,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropyl]carboxamido}-2-oxo-1,2,3,6-tetrahy-

Table 7. Summary and Comparison of in Vitro and in Vivo Properties of (+)-**73**, (+)-**83**, SNAP 6201, and Terazosin

assay	agonist/antagonist	(+)-**73**	(+)-**83**	SNAP 6201	terazosin
K_i, α_{1a} human clones (nM)	[^{3}H]prazosin	0.7	0.5	0.2	6.9
$\alpha_{1b,1d}/\alpha_{1a}$	[^{3}H]prazosin	>900	>400	>1000	<1.0
$\alpha_{2a,b,c}/\alpha_{1a}$	[^{3}H]rauwolscine	>1000	>280	>1000	<10.0
K_b rat prostate (nM)	phenylephrine	2.2	0.4	0.5	25
K_b rat aorta (nM)	norepinephrine	>1000	ND	>1000	19
K_b human prostate (nM)	A-61603	ND	0.7	0.1	25
AD_{50} rat prostate (μg/kg)	phenylephrine	18	69	20	52
duration of action rat (h)	A-61603	1.5	2	>4	3
IUP[a] K_b/DBP[b] K_b (dog)	phenylephrine	>20	ND	>30	1
K_b (IUP)[a] dog (μg/kg)	phenylephrine	14.2	ND	4.2	16.4
K_b (DBP)[b] dog (μg/kg)	phenylephrine	>300	ND	187	15.7
opioid K_i (μM)		51	100	4	
rat F, $t_{1/2}$ (h)		8,[c] 0.4	23,[d] 0.4	15,[e] 2.0	49, 7.5
dog F, $t_{1/2}$ (h)		32,[f] 2.3	ND, 6.5	26,[e] 2.5	

[a] Intraurethral pressure. [b] Diastolic blood pressure. [c] iv: 1 mg/kg dose, AUC = 49.7 μmol min/L. po: 3 mg/kg dose, AUC = 62.5 μmol min/L. [d] iv: 1 mg/kg dose, AUC = 25.6 μmol min/L. po: 3 mg/kg dose, AUC = 17.8 μmol min/L. [e] See ref 2 for details regarding SNAP 6201 and the in vitro and in vivo protocols for all compounds. [f] iv: 1 mg/kg dose, AUC = 32 μmol min/L. po: 3 mg/kg dose, AUC = 30 μmol min/L. ND, not determined; *F*, bioavailability.

dropyrimidine (9). To a solution of 3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropionitrile (first peak from HPLC, 475 mg, 1.65 mmol) in MeOH (10 mL) was bubbled NH_3 gas for 15 min. Raney Ni (80 mg, prewashed with water and then MeOH) was added to the mixture. The resulting suspension was hydrogenated at 150 psi overnight at room temperature. The suspension was filtered through a pad of Celite and the filtrate was concentrated to leave the amine **7** as an oil (462 mg, 96%), which was used as such in the next step.

To a stirred mixture of (+)-5-(benzyloxycarbonyl)-6-(3,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxy-1-[(4-nitrophenyloxy)carbonyl]pyrimidine[2] (**8**; 0.87 g, 1.6 mmol) in CH_2Cl_2 (20 mL) was added a solution of 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]-3-methylpropylamine (**7**; 0.70 g, 1.93 mmol) and K_2CO_3 (0.1 g) in THF (25 mL) at room temperature and stirring was continued for 8 h. The suspension was diluted with CH_2Cl_2 (150 mL) and washed with 10% KOH solution (2 × 10 mL). This solution was mixed with aqueous 10% HCl (2 mL) and stirred for 2 h. The mixture was treated with 10% aqueous KOH solution (10 mL); the organic layer was separated, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel to obtain the product as a white foam (0.52 g), which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 0.92 (d, J = 6.0 Hz, 3 H), 1.21 (t, J = 6.6 Hz, 3 H), 1.49−1.71 (m, 2 H), 1.83−1.87 (m, 2 H), 2.41−2.55 (m, 4 H), 2.65−2.73 (m, 4 H), 3.23−3.40 (m, 2 H), 3.64 (s, 3 H), 3.73 (t, J = 4.5 Hz, 1 H), 5.12 (ABq, d_A = 5.05, d_B = 5.20, J = 12.3 Hz, 2 H), 6.68 (s, 1 H), 6.98−7.37 (m, 14 H), 8.79 (t, J = 4.2 Hz, 1 H).

(e) (+)-6-(3,4-Difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic Acid (11). A solution of **9** (0.52 g, 0.755 mmol) in MeOH (10 mL) was added to a suspension of 10% Pd−C in MeOH (10 mL) and water (4 mL). The resulting suspension was hydrogenated under 100 psi for 10 h. It was then filtered through a pad of Celite and was washed with MeOH.[25] Solvents were evaporated from the filtrate and the residue was dissolved in THF, dried ($MgSO_4$), and concentrated to obtain the carboxylic acid **11** (0.45 g) as a white solid.

(f) (+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (13). To a solution of **11** in CH_2Cl_2 (40 mL) and NMM (0.30 mL, 2.7 mmol) was added EDC (0.44 g, 1.50 mmol) and the resulting mixture was cooled to 0 °C. Ammonia was bubbled through this solution for 30 min and the resulting suspension was stirred overnight at room temperature. The mixture was washed with saturated aqueous NH_4Cl solution (20 mL) followed by brine (20 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated. The residue was purified by column chromatography on silica gel using 10% MeOH in CH_2Cl_2 as the eluent to obtain product **13** as a white solid (0.18 g, 40% for two steps). $[\alpha]_D$ = +115 (c = 0.25, MeOH). ^{1}H NMR ($CDCl_3$): δ 0.93 (d, J = 6.3 Hz, 3 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.49−1.71 (m, 2 H), 1.87−1.94 (m, 2 H), 2.41−2.55 (m, 4 H), 2.65−2.73 (m, 4 H), 3.28−3.42 (m, 2 H), 3.64 (s, 3 H), 3.72 (t, J = 4.5 Hz, 1 H), 5.82 (br s, 2 H), 6.52 (s, 1 H), 7.07−7.36 (m, 8 H), 8.08 (br s, 1 H), 8.81 (t, J = 5.1 Hz, 1 H). It was converted to the HCl salt by treatment with 1 N HCl in ether. Mp: 212−216 °C. Anal. ($C_{32}H_{38}N_5O_5F_2Cl\cdot1.1CHCl_3$) C, H, N.

(+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (14). (a) (+)-5-(Benzyloxycarbonyl)-6-(3,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (10). The second HPLC fraction of 3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropionitrile (531 mg, 1.84 mmol) was reduced to the 3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropylamine using a similar procedure described earlier. It was reacted with **8** (0.620 g, 1.32 mmol) as described earlier to afford the product **10** (0.660 g, 72%). ^{1}H NMR ($CDCl_3$): δ 0.90 (d, J = 6.6 Hz, 3 H), 1.18 (t, J = 7.0 Hz, 3 H), 1.42−1.53 (m, 1 H), 1.60−1.68 (m, 2 H), 1.78−1.86 (m, 1 H), 1.92−2.02 (m, 1 H), 2.18−2.26 (m, 1 H), 2.40−2.70 (m, 6 H), 2.80−2.88 (m, 1 H), 3.24−3.38 (m, 2 H), 3.61 (s, 3 H), 5.12 (ABq, d_A = 5.05, d_B = 5.20, J = 12.3 Hz, 2 H), 6.68 (s, 1 H), 6.72 (s, 1 H), 6.97−7.37 (m, 14 H), 8.76 (t, J = 4.2 Hz, 1 H).

(b) (+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-3-methylpropyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (14). Prepared from **10** (0.660 g, 0.958 mmol) using a similar procedure described earlier to afford the product (0.293 g, 51%). ^{1}H NMR ($CDCl_3$): δ 0.90 (d, J = 6.6 Hz, 3 H), 1.20 (t, J = 7.0 Hz, 3 H), 1.46−1.72 (m, 3 H), 1.79−1.88 (m, 1 H), 1.92−2.02 (m, 1 H), 2.16−2.26 (m, m, 1 H), 2.40−2.80 (m, 7 H), 3.26−3.40 (m, 2 H), 3.60 (s, 3 H), 5.40 (br s, 2 H), 6.46 (s, 1 H), 6.72 (s, 1 H), 7.06−7.38 (m, 8 H), 8.78 (t, J = 5 Hz, 1 H). HCl salt Mp: 218−221 °C. $[\alpha]_D$ = + 80.0 (c = 0.25, MeOH). Anal. ($C_{32}H_{38}N_5O_5F_2Cl\cdot0.9\ H_2O$) C, H, N.

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-1-{*N*-[5-(4-methoxycarbonyl-4-phenyl)piperidin-1-yl)pentyl]carboxamido}-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (18). (a) 3-(5-Chloropentyl)-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (17). To a solution of 6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (**15**; 0.110, 0.426 mmol) in THF (10 mL) and HMPA (1.5 mL, 0.85 mmol) at 0 °C was added NaH (0.014 g, 1.27 mmol) in small portions over 2 min. After stirring at room temperature for 2 min, 1-bromo-5-chloropentane (**16**; 0.22 mL, 1.70 mmol) was added and the mixture was heated at reflux temperature for 30 min. The reaction mixture was cooled to 0

°C and carefully quenched by the addition of ice water (4 mL). The reaction mixture was concentrated and then partitioned between CH_2Cl_2 (25 mL) and water (5 mL). The organic layer was separated, mixed with aqueous 6 N HCl (3 mL), and stirred at room temperature for 15 min. To this was added saturated aqueous $NaHCO_3$ solution (15 mL) and the organic layer was separated. It was dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 3:2) to yield the product (0.142 g, 91%) as a syrup. ^{1}H NMR ($CDCl_3$): δ 1.42−1.79 (m, 7 H), 2.32 (s, 3 H), 2.74−2.83 (m, 1 H), 3.51 (t, J = 6.5 Hz, 2 H), 3.69 (s, 3 H), 5.26 (s, 1 H), 7.06−7.20 (m, 3 H), 8.23 (br s, J = 5.2 Hz, 1 H).

(b) 4-(3,4-Difluorophenyl)-5-methoxycarbonyl-3-[5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pentyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (18). To a stirred solution of **17** (0.173 g, 0.447 mmol) in dioxane (20 mL) were added 4-methoxycarbonyl-4-phenylpiperidine (**3**; 0.196 g, 0.89 mmol) and K_2CO_3 (0.186 g, 1.34 mmol) and the mixture was heated at reflux temperature for 24 h. It was cooled to room temperature, concentrated, and partitioned between EtOAc (25 mL) and water (5 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (EtOAc:MeOH, 9:1) to yield the product (0.130 g, 51%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.27−1.52 (m, 8 H), 1.94−2.88 (m, 10 H), 3.66 (s, 9 H), 3.68 (s, 3 H), 3.65−3.68 (m, 3 H), 5.25 (s, 1 H), 7.06−7.38 (m, 9 H), 8.76 (s, 1 H). HCl salt Mp: 140−145 °C. Anal. ($C_{31}H_{38}F_2N_3O_5Cl\cdot 1.0H_2O$) C, H, N.

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-1-{*N*-[(4-methoxycarbonyl-4-phenylpiperidin-1-yl)ethyl]acetamido}-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (22). (a) 6-(3,4-Difluorophenyl)-1-[(hydroxycarbonyl)-methyl]-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (20). A mixture of **15** (0.296 g, 1.00 mmol), benzyl 2-bromoacetate (0.229 g, 1.00 mmol), K_2CO_3 (600 mg), and KI (30 mg) in DMF (20 mL) was stirred and heated at 50−55 °C for 12 h. The mixture was cooled, poured into ice−water (150 mL), and extracted with ether (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was redissolved in THF (10 mL), mixed with aqueous 6 N HCl (3 mL), and stirred for 2 h. Solvent was evaporated and the residue was purified by column chromatography on silica gel (1:1 EtOAc/hexanes) to obtain the benzyl ester **19** (0.32 g, 75%). This intermediate (200 mg, 0.465 mmol) was dissolved in methanol/water (4:1, 15 mL) and mixed with Pearlman's catalyst (20 mg). The resulting suspension was hydrogenated at 100 psi for 4 h. TLC analysis confirmed the disappearance of the starting material. The catalyst was removed by filtration and the solvent was evaporated from the filtrate. The residue was dried under vacuum and used in the next step (0.135 g).

(b) 2-[4-Methoxycarbonyl-4-phenylpiperidin-1-yl]-ethylamine (21). A mixture of 4-methoxycarbonyl-4-phenylpiperidine (**3**; 1.2 g, 7.76 mmol), 2-bromoethylamine hydrobromide (3.28 g, 16 mmol), K_2CO_3 (2.7 g, 19.5 mmol), and KI (0.648 g, 3.9 mmol) in 1,4-dioxane (25 mL) was heated at reflux temperature for 36 h. Dioxane was evaporated under reduced pressure, and the residue was treated with ice-cold 6 N NaOH (400 mL) and extracted with CH_2Cl_2 (4 × 120 mL). The combined organic layers were dried (K_2CO_3) and concentrated. The residue was purified by column chromatography on silica gel using $CHCl_3$/MeOH/2 M NH_3 in MeOH (20:2:1) as the eluent to afford the product (0.855 g, 42%) as a viscous oil. ^{1}H NMR ($CDCl_3$): δ 1.90−2.10 (m, 2 H), 2.10−2.30 (br t, 2 H), 2.40−2.50 (br t, 2 H), 2.50−2.70 (m, 4 H), 2.80−2.90 (m, 4 H), 3.64 (s, 3 H), 7.20−7.45 (m, 5 H).

(c) 6-(3,4-Difluorophenyl)-5-methoxycarbonyl-1-{*N*-[(4-methoxycarbonyl-4-phenylpiperidin-1-yl)ethyl]acetamido}-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (22). A solution of the carboxylic acid **20** (20 mg), EDC (20 mg), DMAP (20 mg), and amine **21** (20 mg) in CH_2Cl_2 (10 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with more CH_2Cl_2 (20 mL) and washed with aqueous NH_4Cl solution (4 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by preparative thin-layer chromatography on silica gel using $CHCl_3$/MeOH/2 M NH_3 in MeOH (20:2:1) as the eluent (25 mg). MH^+ 585. $[\alpha]_D$ = + 108 (c = 0.5, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.80−2.00 (m, 2 H), 2.05−2.15 (m, 2 H), 2.20 (s, 3 H), 2.40−2.44 (m, 2 H), 2.50−2.65 (m, 2 H), 2.70−2.95 (m, 2 H), 3.20−3.40 (m, 2 H), 3.418, 3.473, 4.301, 4.355 (ABq, 2 H), 3.59 (s, 3 H), 3.64 (s, 3 H), 5.30 (s, 1 H), 6.60 (br t, 1 H, NH), 7.04−7.41 (m, 8 H), 7.95 (br s, 1 H, NH). HCl salt Mp: 247−250 °C. Anal. ($C_{30}H_{34}N_6O_6F_2Cl$) C, H, N.

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-1-{*N*-(4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidin-1-yl)-carboxamido]-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (27). (a) 1-Benzyl-4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidine (24). A mixture of 4-methoxycarbonyl-4-phenylpiperidine (**3**; 6.50 g, 29.6 mmol), 1-benzyl-4-piperidone (**23**; 5.62 g, 29.6 mmol), and *p*-toluenesulfonic acid (100 mg) in toluene (80 mL) was heated at reflux temperature for 14 h while the water formed was trapped using a Dean−Stark apparatus. Solvent was evaporated and the residue was dissolved in methanol (200 mL) and cooled to 0−5 °C. Sodium cyanoborohydride (1.86 g, 29.6 mmol) was added in portions in about 30 min and the mixture was stirred for 12 h. Solvent was evaporated and the residue was treated with ice−water (400 g). The mixture was extracted with CH_2Cl_2 (4 × 50 mL) and the combined extracts were washed with brine (3 × 100 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was crystallized from 2-propanol and hexanes to get product **24** as white crystals (8.50 g, 73%). Mp: 112−113 °C. ^{1}H NMR ($CDCl_3$): δ 1.50−1.60 (m, 2 H), 1.68−1.80 (m, 2 H), 1.85−2.00 (m, 4 H), 2.20−2.35 (m, 3 H), 2.50−2.60 (m, 2 H), 2.85−2.95 (br t, 4 H), 3.45 (s, 2 H), 3.60 (s, 3 H), 7.20−7.40 (m, 10 H).

(b) 4-[4-Methoxycarbonyl-4-phenylpiperidin-1-yl]piperidine (25). 1-Benzyl-4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidine (**24**; 3.92 g, 10 mmol) was dissolved in a freshly prepared solution of formic acid in methanol (4.4%, 200 mL) and cooled to 0 °C. To this was added 10% Pd−C (1.0 g) cautiously in about 45 min and the mixture was stirred and allowed to warm to room temperature. After 8 h, the catalyst was removed by filtration and washed with more methanol (50 mL). Solvent was evaporated from the filtrate, the residue was treated with ice-cold NaOH (6 N, 50 mL), and the mixture was extracted with ether (4 × 50 mL). Evaporation of solvent from the combined dried (Na_2SO_4) extracts left the product as a viscous oil (2.90 g, 96%). The ^{1}H NMR analysis confirmed the product to be pure and was used in the next step. ^{1}H NMR ($CDCl_3$): δ 1.30−1.50 (m, 2 H), 1.70−1.80 (m, 2 H), 1.85−2.00 (m, 2 H), 2.25−2.40 (m, 3 H), 2.50−2.65 (m, 4 H), 2.85−2.95 (br d, 2 H), 3.05−3.15 (br d, 2 H), 3.60 (s, 3 H), 7.20−7.40 (m, 5 H).

(c) 6-(3,4-Difluorophenyl)-5-methoxycarbonyl-1-{*N*-(4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidin-1-yl)carboxamido}-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (27). Prepared from **26** (138 mg, 0.30 mmol) and **25** (100 mg, 0.33 mmol) using a similar procedure described earlier (108 mg, 59%). ^{1}H NMR (CD_3OD): δ 1.70−1.85 (m, 2 H), 2.05−2.30 (m, 4 H), 2.80−3.00 (m, 4 H), 3.00−3.20 (br t, 2 H), 3.35−3.45 (m, 1 H), 3.55−3.65 (m, 4 H), 3.67 (s, 3 H), 3.69 (s, 3 H), 5.80 (s, 1 H), 7.00−7.60 (m, 8 H). Anal. ($C_{33}H_{37}N_4O_6F_2Cl\cdot 0.4CH_2Cl_2$) C, H, N.

(+)-6-(3,4-Difluorophenyl)-5-methoxycarbonyl-1-{*N*-(4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidin-1-yl)carboxamido}-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (36). (a) 6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (32). To a well-stirred mixture of methyl 4-methoxyacetoacetate (**28**; 50 g, 0.351 mol), 3,4-difluorobenzaldehyde (**30**; 51.39 g, 0.351 mmol), and urea (**29**; 31.64 g, 0.527 mol) in THF (300 mL) at room temperature were added copper(I) oxide (5.06 g, 0.035 mol) and acetic acid (2.05 mL) sequentially followed by dropwise addition of boron trifluoride−diethyl etherate (56 mL, 0.456 mole). The mixture was stirred and

heated at reflux temperature for 8 h, whereupon TLC (1/1 EtOAc/hexanes) indicated completion of the reaction. It was cooled and poured into a mixture of ice (500 g) and $NaHCO_3$ (100 g) and the resulting mixture was filtered through Celite. The Celite pad was washed with CH_2Cl_2 (400 mL). The organic layer was separated from the filtrate and the aqueous layer was extracted with more CH_2Cl_2 (3 × 300 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (50% EtOAc in hexanes, then EtOAc) to give the product **32** as a pale yellow foam, which on trituration with hexanes became a white powder (103 g, 94%). ^{1}H NMR ($CDCl_3$): δ 3.47 (s, 3 H), 3.65 (s, 3 H), 4.65 (s, 2 H), 5.39 (s, 1 H), 6.60 (br s, 1 H, NH), 7.00−7.20 (m, 3 H), 7.72 (br s, 1 H, NH).

(b) (+)-6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine [(+)-32]. The **32** was resolved by chiral HPLC [Chiralcel OD 20 × 250 mm #369-703-30604]; λ 254 nm; hexanes/ethanol, 90/10; 85 mg/injection; retention time of the desired enantiomer: 16.94 min. The first enantiomer peak to elute gave (+)-**32** (40−42 wt % isolation of the desired enantiomer from the racemate). $[\alpha]_D = +84$ ($c = 0.5$, $CHCl_3$).

(c) (+)-6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-1-[(4-nitrophenyloxy)carbonyl]-2-oxo-1,2,3,6-tetrahydropyrimidine (34). To a solution of (+)-**32** (1.98 g, 6.34 mmol) in anhydrous THF (20 mL) at −78 °C under argon atmosphere was added a solution of LiHMDS in THF (1.0 M, 18.0 mL, 18.0 mmol) over 2−3 min and the mixture was stirred for 10 min. This solution was added over 6 min via a cannula to a stirred solution of 4-nitrophenyl chloroformate (4.47 g, 22.2 mmol) in THF (20 mL) at −78 °C. The stirring was continued for 10 min and the mixture was poured onto ice (50 g) and extracted with $CHCl_3$ (2 × 50 mL). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash column chromatography using hexanes/EtOAc (4:1 to 3.5:1) as eluent. The product was obtained as a yellow syrup, which on trituration with hexanes became a white powder (2.4 g, 79%). ^{1}H NMR ($CDCl_3$): δ 3.52 (s, 3 H), 3.74 (s, 3 H), 4.65−4.80 (q, $J = 16.5$ Hz, 2 H), 6.32 (s, 1 H), 7.10−7.30 (m, 4 H), 7.36 (d, $J = 9$ Hz, 2 H), 8.27 (d, $J = 9$ Hz, 2 H).

(d) (+)-6-(3,4-Difluorophenyl)-5-methoxycarbonyl-1-{*N*-(4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidin-1-yl)carboxamido}-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (36). Prepared from **34** (120 mg, 0.25 mmol) and the amine **25** (80 mg, 0.27 mmol) using a similar procedure described earlier to afford the product (0.146 g, 91%). ^{1}H NMR (CD_3OD): δ 1.70−1.80 (m, 2 H), 2.00−2.20 (m, 4 H), 2.80−3.00 (m, 4 H), 3.00−3.20 (br t, 2 H), 3.35−3.45 (m, 1 H), 3.40 (s, 3 H), 3.55−3.65 (m, 4 H), 3.60 (s, 3 H), 3.72 (s, 3 H), 4.60 (ABq, $J = 12$ Hz, 2 H), 5.75 (s, 1 H), 7.05−7.50 (m, 8 H). Anal. ($C_{33}H_{39}N_4O_7F_2Cl\cdot 0.4CH_2Cl_2$) C, H, N.

(+)-5-Methoxycarbonyl-1-{*N*-(4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidin-1-yl)carboxamido}-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydro-6-(3,4,5-trifluorophenyl)-pyrimidine (37). (a) 5-Methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4,5-trifluorophenyl)-pyrimidine (33). Prepared from 3,4,5-trifluorobenzaldehyde (37.0 g, 230 mmol), methyl 4-methoxyacetoacetate (33.6 g, 230 mmol), and urea (20.7 g, 345 mmol) using a similar procedure described earlier. The product was obtained as a white powder (72.9 g, 94%).

(b) (+)-5-Methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydro-6-(3,4,5-trifluorophenyl)pyrimidine [(+)-33]. The racemic **33** was resolved by chiral HPLC [Chiralcel OD 20 × 250 mm #369-703-30604]; λ 254 nm; hexanes/ethanol, 90/10; 80 mg/injection; retention time of the desired enantiomer: 16.94 min. The first enantiomer peak to elute gave (+)-**33** (40−42 wt % isolation of the desired enantiomer from the racemate). $[\alpha]_D = +86.8$ ($c = 0.5$, $CHCl_3$).

(c) (+)-5-Methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydro-6-(3,4,5-trifluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (35). Prepared from (+)-**33** (1.34 g, 4.05 mmol), LiHMDS (4.5 mL, 1.0 M), and 4-nitrophenyl chloroformate (0.804 g, 4 mmol) using a similar procedure described earlier (1.75 g, 85%). $[\alpha]_D = +86.8$ ($c = 0.5$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 3.53 (s, 3 H), 3.75 (s, 3 H), 4.65−4.80 (q, $J = 16.5$ Hz, 2 H), 6.29 (s, 1 H), 7.03−7.08 (m, 2 H), 7.38 (d, $J = 9$ Hz, 2 H), 8.29 (d, $J = 9$ Hz, 2 H).

(d) (+)-5-Methoxycarbonyl-1-{*N*-(4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidin-1-yl)carboxamido}-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydro-6-(3,4,5-trifluorophenyl)pyrimidine (37). Prepared from **35** (50 mg, 0.101 mmol) and the amine **25** (50 mg, 0.165 mmol) using a similar procedure described earlier to afford the product (66 mg, 99%). $[\alpha] = +135$ ($c = 0.65$, MeOH). HCl salt Mp: 178−181 °C. ^{1}H NMR (CD_3OD): δ 1.70−1.80 (m, 2 H), 2.00−2.20 (m, 4 H), 2.80−3.00 (m, 4 H), 3.00−3.20 (br t, 2 H), 3.35−3.45 (m, 1 H), 3.40 (s, 3 H), 3.55−3.65 (m, 4 H), 3.60 (s, 3 H), 3.72 (s, 3 H), 4.60 (ABq, $J = 12$ Hz, 2 H), 5.75 (s, 1 H), 7.05−7.50 (m, 7 H). Anal. ($C_{33}H_{38}ClF_3N_4O_7.0.4CH_2Cl_2$) C, H, N.

(+)-5-Carboxamido-6-(2,4-difluorophenyl)-4-ethyl-1-{*N*-(4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidin-1-yl)carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine(41).(a)(+)-5-Benzyloxycarbonyl-6-(2,4-difluorophenyl)-4-ethyl-1-{*N*-(4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidin-1-yl)carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (39). To a solution of **38**[2] (140 mg, 0.254 mmol) and **25** (82 mg, 0.272 mmol) in THF (15 mL) was added K_2CO_3 (0.50 g). The resulting suspension was stirred over 10 h at room temperature before filtered. The filtrate was cooled in an ice bath and 6 N HCl (5 mL) was added. The resulting mixture was warmed to room temperature and stirred for 30 min before adjusting the pH to 8 with aqueous 10% NaOH. The mixture was extracted with EtOAc (50 mL). The organic layer was washed with 10% K_2CO_3 (20 mL) and brine (50 mL), dried (K_2CO_3), and concentrated and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/2 N NH_3 in MeOH = 100:3:1) to afford the desired product (184 mg, 97%). $[\alpha] = +72$ ($c = 0.58$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.19 (t, $J = 7$ Hz, 3 H), 1.55−1.70 (m, 4 H), 1.80−1.94 (m, 2 H), 2.10−2.38 (m, 4 H), 2.48−2.60 (m, 2 H), 2.62−2.85 (m, 4 H), 3.61 (s, 3 H), 4.86−5.06 (m, 2 H), 6.64−6.74 (m, 2 H), 7.03−7.12 (m, 2 H), 7.22−7.38 (m, 10 H).

(b) (+)-6-(2,4-Difluorophenyl)-4-ethyl-1-{*N*-(4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidin-1-yl)carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic Acid (40). To a solution of **39** (166 mg, 0.240 mmol) in MeOH (10 mL) was added 10% Pd−C (25 mg) in portions in about 10 min. The resulting suspension was hydrogenated at 100 psi for 6 h at room temperature. The mixture was filtered through a pad of Celite and the filtrate was concentrated to leave the product as a white solid (135 mg, 92%).[25] The product was used in the next step without further purification. $[\alpha] = +96$ ($c = 0.75$, 20% MeOH−$CHCl_3$).

(c) (+)-5-Carboxamido-6-(2,4-difluorophenyl)-4-ethyl-1-{*N*-(4-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]piperidin-1-yl)carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (41). To a solution of **40** (115 mg, 0.188 mmol) in CH_2Cl_2 (30 mL) were added EDC (107 mg, 0.564 mmol) and DMAP (69 mg, 0.564 mmol). The resulting mixture was stirred at room temperature for 1 h. Then NH_3 gas was bubbled through the solution for 3 h. The resulting mixture was stirred over 2 days before washed with aqueous NH_4Cl (30 mL × 3) and brine (3 × 30 mL). The organic phase was dried (K_2CO_3), concentrated, and purified by column chromatography ($CHCl_3$/MeOH/2 M NH_3 in MeOH = 100:4:1) to afford the product as a white solid (80 mg, 70%). $[\alpha] = +107°$ ($c = 0.88$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.05−1.25 (m, 6 H), 1.65−1.98 (m, 4 H), 2.06−2.38 (m, 4 H), 2.46−2.80 (m, 6 H), 3.10−3.33 (m, 2 H), 3.61 (s, 3 H), 6.53 (s, 1 H), 6.75−6.95 (m, 3 H), 7.20−7.38 (m, 5 H), 7.60−7.70 (m, 1 H), 11.20−11.30 (m, 1 H). HCl salt Mp: 122−124 °C. Anal. ($C_{32}H_{38}N_5O_5ClF_2\cdot 0.25CHCl_3$) C, H, N.

6-(3,4-Difluorophenyl)-1-{*N*-[3-[4-(6′-hydroxyphenylisonipecotic acid lactone)-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (46). (a) *N*-(*tert*-Butoxycarbonylaminopropyl)-

4-(6′-hydroxyphenyl)isonipecotic Acid Lactone. To a stirred solution of the 4-phenylisonipecotic acid lactone[15] (**42a**; 0.736 g, 3.64 mmol) in dioxane (20 mL) were added *N*-(*tert*-butoxycarbonyl)-3-bromopropylamine (**43**; 0.953 g, 4 mmol) and K_2CO_3 (1.00 g, 7.28 mmol) and the mixture was heated at reflux temperature for 24 h. The reaction mixture was cooled to room temperature, concentrated, and partitioned between $CHCl_3$ (40 mL) and water (5 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (EtOAc:MeOH, 9:1) to yield the product as a colorless oil (0.574 g, 44%). ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9 H), 1.73 (t, J = 6.3 Hz, 2 H), 2.00−2.05 (m, 4 H), 2.59 (t, J = 6.3 Hz, 2 H), 2.70−2.84 (m, 4 H), 3.24 (d, J = 5.8 Hz, 2 H), 5.59 (br s, 1 H), 7.12 (t, J = 8.1 Hz), 7.28−7.33 (m, 2 H).

(b) *N*-(3-Aminopropyl)-4-(6′-hydroxyphenyl)isonipecotic Acid Lactone (45a). To *N*-(*tert*-butoxycarbonylaminopropyl)-4-(6′-hydroxyphenyl)isonipecotic acid lactone (0.254 g, 0.707 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (1 mL) and the solution stirred at room temperature for 1 h. It was concentrated, neutralized with aqueous 10% KOH solution and extracted with CH_2Cl_2 (25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give 0.183 g (100%) of the product which was used as such in the next step.

(c) 6-(3,4-Difluorophenyl)-1-{*N*-[3-[4-(6′-hydroxyphenylisonipecotic acid lactone)-1-yl] propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (46). Prepared from amine **45a** (0.054 g, 0.207 mmol) and **26** (0.080 g, 0.173 mmol) using a similar procedure described earlier to give the product (0.055 g, 56%) as a syrup. ^{1}H NMR ($CDCl_3$): δ 1.63−1.76 (m, 4 H), 2.14−2.19 (m, 2 H), 2.40−2.48 (m, 7 H), 2.86 (d, J = 11 Hz, 2 H), 3.30−3.41 (m, 2 H), 3.68 (s, 3 H), 6.68 (s, 1 H), 7.01−7.17 (m, 3 H), 7.38 (d, J = 7.4 Hz, 1 H), 7.49 (t, J = 7.4 Hz, 1 H), 7.63 (t, J = 7.4 Hz, 1 H), 7.83 (d, J = 7.4 Hz, 1 H), 8.83 (t, J = 5.4 Hz, 1 H). HCl salt Mp: 173−176 °C. Anal. ($C_{27}H_{31}F_2N_4O_6Cl\cdot 1.0H_2O$) C, H, N.

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{*N*-[[spiro(isobenzofuran-1(3*H*),4′-piperidin)-3-one]-1-propyl]carboxamido}-1,2,3,6-tetrahydropyrimidine (47). (a) *N*-(*tert*-Butoxycarbonylaminopropyl)spiro-(isobenzofuran-1(3*H*),4′-piperidin)-3-one. Prepared from spiro(isobenzofuran-1(3*H*),4′-piperidin)-3-one[15] (**42b**; 0.393 g, 19.3 mmol) and *N*-(*tert*-butoxycarbonyl)-3-bromopropylamine (0.506 g, 21.2 mmol) using a similar procedure described earlier to give the required product as a colorless oil (0.438 g, 63%). ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9 H), 1.70−1.76 (m, 4 H), 2.19−2.23 (m, 2 H), 2.47−2.57 (m, 4 H), 2.95 (d, J = 11 Hz, 2 H), 3.24 (d, J = 5.89 Hz, 2 H), 5.50 (s, 1 H), 7.40 (d, J = 7.35 Hz, 1 H), 7.55 (t, J = 7.35 Hz, 1 H), 7.68 (d, J = 7.35 Hz, 1 H), 7.89 (d, J = 7.36 Hz, 1 H).

(b) *N*-(3-Aminopropyl)spiro(isobenzofuran-1(3*H*),4′-piperidin)-3-one (45b). Prepared from *N*-(*tert*-butoxycarbonylaminopropyl)spiro(isobenzofuran-1(3*H*),4′-piperidin)-3-one (0.438 g, 12.1 mmol) and trifluoroacetic acid (1 mL) using a similar procedure described earlier to give the amine **45b** (0.150 g, 47%) which was used as such in the next step.

(c) 6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{*N*-[[spiro(isobenzofuran-1(3*H*),4′-piperidin)-3-one]-1-propyl]carboxamido}-1,2,3,6-tetrahydropyrimidine (47). Prepared from **26** (0.060 g, 0.129 mmol) and **45b** (0.037 g, 0.142 mmol) using a similar procedure described earlier to give the product (0.072 g, 97%) as a syrup. ^{1}H NMR ($CDCl_3$): δ 1.63−1.76 (m, 4 H), 2.14−2.19 (m, 2 H), 2.40−2.48 (m, 7 H), 2.86 (d, J = 11 Hz, 2 H), 3.30−3.41 (m, 2 H), 3.68 (s, 3 H), 6.68 (s, 1 H), 7.01−7.17 (m, 3 H), 7.38 (d, J = 7.4 Hz, 1 H), 7.49 (t, J = 7.4 Hz, 1 H), 7.63 (t, J = 7.4 Hz, 1 H), 7.83 (d, J = 7.4 Hz, 1 H), 8.83 (t, J = 5.4 Hz, 1 H). HCl salt Mp: 185−187 °C. Anal. ($C_{29}H_{32}F_2N_5O_6Cl_2\cdot 1.0H_2O$) C, H, N.

6-(3,4-Difluorophenyl)-1-{*N*-[[4-(isobenzofuranyl)piperidin-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (48). (a) *N*-(*tert*-Butoxycarbonylaminopropyl)-4-(isobenzofuranyl)-piperidine. Prepared from 4-(isobenzofuranyl)piperidine[15] (**42c**; 0.566 g, 3.27 mmol) and *N*-(*tert*-butoxycarbonyl)-3-bromopropylamine (0.772 g, 3.27 mmol) using a similar procedure described earlier to give the product (0.856 g, 79%). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9 H), 1.63−2.04 (m, 6 H), 2.33−2.52 (m, 4 H), 2.87 (d, J = 11.0 Hz, 2 H), 3.20 (br s, 2 H), 5.07 (s, 2 H), 5.6 (br s, 1 H), 7.13−7.28 (m, 4 H).

(b) *N*-(Aminopropyl)-4-(isobenzofuranyl)piperidine (45c). Prepared from **42** (0.50 g, 1.51 mmol) using a similar procedure described earlier (0.340 g, 98%).

(c) 6-(3,4-Difluorophenyl)-1-{*N*-[[4-(isobenzofuranyl)-piperidin-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (48). Prepared from **26** (0.052 g, 0.112 mmol) and **45c** (0.032 g, 0.123 mmol) using a similar procedure described earlier (0.040 g, 64%). ^{1}H NMR ($CDCl_3$): δ 1.73−1.78 (m, 7 H), 1.93−2.04 (m, 2 H), 2.33−2.48 (m, 6 H), 2.83 (d, J = 11.8 Hz, 2 H), 3.35−3.41 (m, 2 H), 3.71 (s, 3 H), 5.06 (s, 2 H), 6.75 (s, 1 H), 7.04−7.26 (m, 7 H), 8.82 (t, J = 5.1 Hz, 1 H). HCl salt Mp: 178−182 °C. Anal. ($C_{29}H_{34}F_2N_4O_5Cl_2\cdot 0.6H_2O$) C, H, N.

6-(3,4-Difluorophenyl)-1-{*N*-[[4-(dihydroindenyl)piperidin-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (49). (a) *N*-(*tert*-Butoxycarbonylaminopropyl)-4-(dihydroindenyl)-piperidine. Prepared from 4-(dihydroindenyl)piperidine[15] (**42d**; 0.790 g, 4.22 mmol) and *N*-(*tert*-butoxycarbonyl)-3-bromopropylamine (1.10 g, 4.64 mmol) using a similar procedure described earlier (0.886 g, 61%). ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9 H), 1.55 (d, J = 11.3 Hz, 2 H), 1.69 (t, J = 6.3 Hz, 2 H), 1.88−2.47 (m, 6 H), 2.47 (t, J = 6.3 Hz, 2 H), 2.88 (t, J = 3.3 Hz, 4 H), 3.23 (d, J = 5.6 Hz, 2 H), 5.85 (br s, 1 H), 7.18 (s, 4 H).

(b) *N*-(3-Aminopropyl)-4-(dihydroindenyl)piperidine (45d). Prepared from **42d** (0.180 g, 0.52 mmol) using a similar procedure described earlier (0.156 g, 100%).

(c) 6-(3,4-Difluorophenyl)-1-{*N*-[[4-(dihydroindenyl)-piperidin-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (49). Prepared from **26** (0.050 g, 0.108 mmol) and *N*-(3-aminopropyl)-4-(dihydroindenyl)piperidine (**45d**; 0.053 g, 0.216 mmol) using a similar procedure described earlier (0.060 g, 100%). ^{1}H NMR ($CDCl_3$): δ 1.52 (d, J = 13.2 Hz, 2 H), 1.70−2.07 (m, 8 H), 2.12 (t, J = 10.3 Hz, 2 H), 2.42 (s, 4 H), 2.86−2.91 (m, 3 H), 3.32−3.43 (m, 2 H), 3.72 (s, 3 H), 6.71 (s, 1 H), 7.04−7.19 (m, 7 H), 8.82 (t, J = 5.2 Hz, 1 H). HCl salt Mp: 150−153 °C. Anal. ($C_{30}H_{36}F_2N_4O_6Cl_2$) C, H, N.

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{*N*-[[spiro(isobenzopyran-1(3*H*),4′-piperidin)-3-one]-1-propyl]carboxamido}-1,2,3,6-tetrahydropyrimidine (50). (a) *N*-(*tert*-Butoxycarbonylaminopropyl)spiro(isobenzo-pyran-1(3*H*),4′-piperidin)-3-one. Prepared from spiro(isobenzopyran-1(3*H*),4′-piperidin)-3-one[15] (**42e**; 0.242 g, 1.11 mmol) and *N*-(*tert*-butoxycarbonyl)-3-bromopropylamine (0.291 g, 1.22 mmol) using a similar procedure described earlier (0.237 g, 57%). ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 9 H), 1.65 (t, J = 6.47 Hz, 2 H), 1.96 (d, J = 15.6 Hz, 2 H), 2.22 (t, J = 2.5 Hz, 2 H), 2.46−2.56 (m, 4 H), 2.80−2.84 (m, 2 H), 3.17−3.18 (m, 2 H), 3.73 (s, 2 H), 5.58 (br s, 1 H), 7.12 (s, 1 H), 7.22−7.27 (m, 3 H).

(b) *N*-(Aminopropyl)spiro(isobenzopyran-1(3*H*),4′-piperidin)-3-one (45e). Prepared from *N*-(*tert*-butoxycarbonylaminopropyl)spiro(isobenzopyran-1(3*H*),4′-piperidin)-3-one (0.237 g, 0.72 mmol) using a similar procedure described earlier (0.150 g, 87%).

(c) 6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{*N*-[[spiro(isobenzopyran-1(3*H*),4′-piperidin)-3-one]-1-propyl}]arboxamido}-1,2,3,6-tetrahydropyrimidine (50). Prepared from **26** (0.077 g, 0.166 mmol) and *N*-(aminopropyl)spiro(isobenzopyran-1(3*H*),4′-piperidin)-3-one (**45e**; 0.050 g, 0.183 mmol) using a similar procedure described earlier (0.072 g, 72%). ^{1}H NMR ($CDCl_3$): δ 1.72 (t, J = 6.1 Hz, 2 H), 1.93 (d, J = 16.2 Hz, 2 H), 2.19 (t, J = 6.9 Hz, 2 H), 2.38 (s, 3 H), 2.43−2.55 (m, 4 H), 2.81 (s, 2 H), 3.28−3.42 (m, 2 H), 3.67 (s, 3 H), 3.73 (s, 3 H), 6.66 (s, 1 H), 7.0−7.25 (m, 4 H), 7.28 (s, 2 H), 7.45 (s, 1 H), 8.82 (t, J = 5.2 Hz,

1 H). HCl salt Mp: 165−168 °C. Anal. ($C_{30}H_{34}F_2N_4O_6Cl_2 \cdot 2.0H_2O$) C, H, N.

1-{*N*-[[4-(Benzopyranyl)piperidin-1-yl]propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (51). (a) [4-(Benzopyranyl)piperidin-1-yl]propylamine (45f). Prepared using a similar procedure described for **45e**.

(b) 1-{*N*-[[4-(Benzopyranyl)piperidin-1-yl]propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (51). Prepared from **26** (0.048 g, 0.103 mmol) and [4-(benzopyranyl)piperidin-1-yl]propylamine (**45f**; 0.053 g, 0.207 mmol) using a similar procedure described earlier (0.066 g, 100%). $[\alpha]_D = +69$ (c = 1.32, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.70−2.06 (m, 6 H), 2.43−2.47 (m, 7 H), 2.75−2.82 (m, 4 H), 3.33−3.42 (m, 2 H), 3.72 (s, 3 H), 3.89 (t, J = 5.1 Hz, 2 H), 6.71 (s, 1 H), 7.05−7.21 (m, 7 H), 8.85 (t, J = 5.2 Hz, 1 H). HCl salt Mp: 150−152 °C. Anal. ($C_{30}H_{36}F_2N_4O_5Cl_2 \cdot 2.5H_2O$) C, H, N.

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{*N*-[[4-(tetralinyl)piperidin-1-yl]propyl]carboxamido}-1,2,3,6-tetrahydropyrimidine (52). (a) *N*-(*tert*-Butoxycarbonylaminopropyl)-4-(tetralinyl)piperidine. Prepared from 4-(tetralinyl)piperidine[15] (**42g**; 0.512 g, 2.56 mmol) and *N*-(*tert*-butoxycarbonyl)-3-bromopropylamine (0.666 g, 2.80 mmol) using a similar procedure described earlier (0.258 g, 28%). ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9 H), 1.59−2.83 (m, 18 H), 3.23−3.25 (m, 2 H), 6.27 (br s, 1 H), 7.05−7.14 (m, 2 H).

(b) *N*-(Aminopropyl)-4-(tetralinyl)piperidine (45g). Prepared from *N*-(*tert*-butoxycarbonylaminopropyl)-4-(tetralinyl)-piperidine (0.258 g, 0.720 mmol) using a similar procedure described earlier (0.183 g, 99%).

(c) 6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydro-1-{*N*-[[4-(tetralinyl)piperidin-1-yl]propyl]carboxamido}pyrimidine (52). Prepared from **26** (0.025 g, 0.054 mmol) and *N*-(aminopropyl)-4-(tetralinyl)-piperidine (**45g**; 0.029 g, 0.010 mmol) using a similar procedure described earlier (0.026 g, 87%). ^{1}H NMR ($CDCl_3$): δ 1.57 (d, J = 13.2 Hz, 2 H), 1.73−2.27 (m, 9 H), 2.41 (s, 6 H), 2.75 (s, 4 H), 3.31−3.45 (m, 2 H), 3.71 (s, 3 H), 6.70 (s, 1 H), 7.00−7.39 (m, 6 H), 7.48 (d, J = 7.7 Hz, 1 H), 8.83 (s, 1 H). HCl salt Mp: 148−152 °C. Anal. ($C_{31}H_{38}F_2N_4O_5Cl_2 \cdot 1.0H_2O$) C, H, N.

6-(3,4-Difluorophenyl)-1-{*N*-[3-(4,4-diphenylpiperidin-1-yl)propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (56). Prepared from **26** (231 mg, 0.500 mmol) and 3-(4,4-diphenylpiperidin-1-yl)-propylamine[3] (220 mg, 0.750 mmol) using a similar procedure described earlier (286 mg, 93%). HCl salt Mp: 161−164 °C. ^{1}H NMR ($CDCl_3$): α 1.25 (m, 4 H), 1.68 (q, J = 7.6 Hz, 2 H), 2.39 (s, 3 H), 2.60−2.20 (m, 6 H), 3.60−3.20 (m, 3 H), 3.69 (s, 3 H), 6.67 (s, 1 H), 7.80 (b, 1 H), 8.81 (m, 1 H). Anal. ($C_{34}H_{37}F_2N_4O_4Cl \cdot 0.25C_6H_{14}$) C, H, N.

General Procedure for the Preparation of Compounds 57−60. General Procedure for the Preparation of 4,4-Diarylpiperidines 54a−54d. A mixture of 4-aryl-4-hydroxypiperidine (**53a**−**53d**; 0.50 g), substituted benzene (3.0 mL), and $AlCl_3$ (1.0 g) was stirred at room temperature for 3 days. The reaction mixture was treated with ice−water (10 mL) and diluted with *tert*-butyl methyl ether; the resulting hydrochloride salt formed was filtered, washed with water and ether, dried, and used in the next step after spectral characterization. Full experimental details for **54e** will be given below due to the unexpected product (**54e**) obtained from the Friedel−Crafts reaction of 4-hydroxy-4-(4-methylphenyl)piperidine and *m*-xylene. Other examples of this highly unusual reaction will be reported in due course.

Bis-4-(3,5-dimethylphenyl)piperidine Hydrochloride (54e). To a turbid solution of 4-hydroxy-4-(4-methylphenyl)-piperidine (3.14 mmol, 0.60 g) in *m*-xylene (10 mL) at room temperature was added anhydrous aluminum chloride (4.32 mmol, 0.58 g) in one portion (isotherm was observed) and the resulting suspension was allowed to stir overnight under argon atmosphere. The dark solution was then poured over an ice−water bath and was stirred vigorously for 1 h. The resulting off-white solid was filtered through a sintered glass funnel and washed with 50 mL of CH_2CL_2 and 50 mL of Et_2O. The off-white powder was dried under vacuum and used in the next step without further purification (0.36 g, 35% yield). Mass spectrum (ESMS, MH^+) was consistent with the proposed structure. The regiochemistry of the methyl groups was assigned based on the symmetrical nature of the ^{1}H NMR spectrum and lack of splitting for the aromatic protons. The ^{1}H NMR spectrum was also recorded in DMSO-d_6 and was identical to the one in CD_3OD. Mp: = 246−252 °C. ^{1}H NMR (CD_3OD): δ 2.24 (s, 12 H), 2.59 (br s, 4 H), 3.17 (br s, 4 H), 6.82 (s, 2 H), 6.91 (s, 4 H). Mass spectrum (ESMS, MH^+, low res.): 293 (100%). Anal. Calcd for $C_{21}H_{28}ClN.0.5CH_2Cl_2$: C, 69.35; H, 7.85; N, 3.76. Found: C, 69.76; H, 7.61; N, 3.99.

1-(3-Bromopropylcarbamoyl)-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (55). To a well-stirred solution of **26** (4.1 g, 9.1 mmol) in THF (20 mL) was added aqueous HCl (10%, 10 mL) at room temperature and the resulting solution was stirred overnight. THF was evaporated under reduced pressure and the resulting residue was extracted with EtOAc (3 × 20 mL), washed with brine (10 mL), and then dried (Na_2SO_4). The solvent was evaporated under reduced pressure to obtain (+)-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]-2-oxo-1,2,3,6-tetrahydropyrimidine as a viscous oil (3.8 g). It was redissolved in THF (20 mL) and mixed with 3-bromopropylamine hydrobromide (2.33 g, 10.8 g) and $NaHCO_3$ (1.81 g, 21.5 mmol) and the resulting suspension was stirred at room temperature overnight. Solvent was evaporated under reduced pressure and the resulting residue was treated with water (10 mL) and then extracted with EtOAc (3 × 20 mL). The EtOAc extracts were combined and dried (Na_2SO_4) and the solvent was evaporated to obtain the product (3.28 g, 83%). ^{1}H NMR ($CDCl_3$): δ 2.05−2.15 (m, 2 H), 2.43 (s, 3 H), 3.40−3.56 (m, 4 H), 3.72 (s, 3 H), 6.69 (s, 1 H), 7.08−7.27 (m, 3 H), 7.57 (br s, 1 H), 8.84 (br t, 1 H). Anal. ($C_{17}H_{18}N_3O_4F_2Br$) C, H, N.

Reaction of Piperidines 54a−54d and (3-Bromopropyl)carbamoyldihydropyrimidinone 55. A mixture of **55** (45 mg, 0.10 mmol), 4,4-diarylpiperidine hydrochloride (0.10 mmol), and diisopropylethylamine (0.5 mL) in dioxane (2.0 mL) was heated at reflux temperature for 2 days. The mixture was cooled and the crude product was purified by preparative thin-layer chromatography on silica gel using 2−3% MeOH in EtOAc as eluent. The products were converted to their HCl salts by treatment with 1 N HCl in ether.

1-{[3-[Bis-4-(4-chlorophenyl)piperidin-1-yl]propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (57). (a) Bis-4-(4-chlorophenyl)piperidine Hydrochloride (54a). Prepared from 4-(4-chlorophenyl)-4-hydroxypiperidine and chlorobenzene. Yield: 92%. ^{1}H NMR (CD_3OD): δ 7.60−7.30 (m, 8 H), 3.18 (m, 4 H), 2.65 (m, 4 H). Anal. ($C_{17}H_{18}N_1Cl_3$) C, H, N.

(b) 1-{[3-[Bis-4-(4-chlorophenyl)piperidin-1-yl]propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (57). Yield: 71%. ^{1}H NMR ($CDCl_3$): δ 8.83 (t, J = 7 Hz, 1 H), 7.40−6.90 (m, 12 H), 6.03 (br s, 1 H), 3.72 (s, 3 H), 3.60−3.20 (m, 2 H), 2.76 (m, 2 H), 2.58 (m, 4 H), 2.39 (s, 3 H), 1.85 (q, J = 7.6 Hz, 2 H), 1.42 (m, 4 H). Anal. ($C_{34}H_{35}Cl_3N_4F_2O_4 \cdot 1.0\ Et_2O$) C, H, N.

6-(3,4-Difluorophenyl)-1-{[3-[4-bis(4-fluorophenyl)piperidin-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (58). (a) Bis-4-(4-fluorophenyl)piperidine Hydrochloride (54b). Prepared from 4-(4-fluorophenyl)-4-hydroxypiperidine and fluorobenzene. Yield: 69%. ^{1}H NMR (CD_3OD): δ 7.40−7.05 (m, 8 H), 3.19 (m, 4 H), 2.65 (m, 4 H).

(b) 6-(3,4-Difluorophenyl)-1-{[3-[4-bis(4-fluorophenyl)-piperidin-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (58). Yield: 80%. ^{1}H NMR ($CDCl_3$): δ 8.81 (m, 1 H), 7.80 (b, 1 H), 7.30−6.80 (m, 11 H), 6.67 (s, 1 H), 3.69 (s, 3 H), 3.60−3.20 (m, 3 H),

2.60−2.20 (m, 6 H), 2.39 (s, 3 H), 1.68 (q, J = 7.6 Hz, 2 H), 1.25 (m, 4 H). Anal. ($C_{34}H_{35}F_4N_4O_4Cl\cdot 1H_2O$) C, H, N.

6-(3,4-Difluorophenyl)-1-{*N*-[3-[4-(4-methylphenyl)-4-(2-methylphenyl)piperidin-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (59). (a) 4-(4-Methylphenyl)-4-(2-methylphenyl)-piperidine Hydrochloride (54c). Yield: 99%. MS: 266 (M + 1, 100%). Anal. ($C_{19}H_{24}NCl\cdot 0.15CH_2Cl_2$) C, H, N.

(b) 6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-1-{*N*-[3-[4-(4-methylphenyl)-4-(2-methylphenyl)piperidin-1-yl]propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (59). Yield: 64%. HCl salt Mp: 143−147 °C. $[\alpha]_D$ = +79.8° (c = 0.25, MeOH). Anal. ($C_{37}H_{44}N_4O_4F_2Cl\cdot 0.5CH_2Cl_2$) C, H, N.

6-(3,4-Difluorophenyl)-1-{[3-[4-bis(3,5-dimethylphenyl)-piperidin-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (60). Yield: 77%. Mp: 176−180 °C. [α] = +93.6 (c = 0.28, MeOH). ^{1}H NMR ($CDCl_3$): δ 8 (m, 2 H), 2.25 (s, 12 H), 2.30 (t, J = 6.9 Hz, 2 H), 2.37−2.42 (m, 7 H), 2.47 (br s, 4 H), 3.22−3.41 (m, 2 H), 3.71 (s, 3 H), 6.68 (s, 1 H), 6.77 (s, 2 H), 6.85 (s, 4 H), 7.01−7.20 (m, 4 H), 8.77 (t, J = 5.4 Hz, 1 H). Anal. ($C_{38}H_{45}F_2N_4O_4Cl\cdot 0.7CH_2Cl_2$) C, H, N.

1-{*N*-[3-[4-Acetoxy-4-phenylpiperidin-1-yl]propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (66). (a) *N*-Benzyloxycarbonyl-3-(4-hydroxy-4-phenylpiperidin-1-yl)-propylamine (63). A mixture of 4-hydroxy-4-phenylpiperidine (**61**; 5.00 g, 0.028 mol), *N*-benzyloxycarbonyl-3-bromopropylamine (**62**; 8.45 g, 0.031 mol), and K_2CO_3 (7.795 g, 0.0564 mol) in acetone (200 mL) was stirred and heated at reflux temperature for 12 h. Acetone was evaporated at reduced pressure, and the residue was treated with ice-cold water (400 mL) and extracted with CH_2Cl_2 (4 × 120 mL). Solvent was evaporated from the combined dried (Na_2SO_4) extracts and the residue was found to be pure product (9.50 g, 91%) by TLC and ^{1}H NMR. It was used in the next step as such without any further purification.

(b) *N*-Benzyloxycarbonyl-3-(4-acetoxy-4-phenylpiperidin-1-yl)propylamine. To a solution of **63** (0.50 g, 1.36 mmol) in THF (20 mL) at 0 °C was added NaH (60% suspension in paraffin, 65 mg, 1.63 mmol) and the mixture was stirred for 1.5 h. To this suspension was added acetyl bromide (0.12 mL, 1.63 mmol) and the mixture was stirred at 0 °C for 30 min and at room temperature for 3 h. Solvent was evaporated and the residue was mixed with CH_2Cl_2 (100 mL) and washed with water (2 × 20 mL). The organic layer was dried (Na_2SO_4) and concentrated to obtain the product as a viscous oil (0.485 g, 87%). The ^{1}H NMR showed this product to be pure and it was used in the next step without any further purification. ^{1}H NMR ($CDCl_3$): δ 1.82−1.92 (m, 4 H), 2.01 (s, 3 H), 2.24−2.33 (m, 2 H), 2.42−2.50 (m, 4 H), 2.78−2.84 (m, 2 H), 3.24 (m, 2 H), 5.05 (s, 2 H), 6.00 (br s, 1 H), 7.28−7.38 (m, 10 H).

(c) 3-(4-Acetoxy-4-phenylpiperidin-1-yl)propylamine (65a). A mixture of *N*-benzyloxycarbonyl-3-(4-acetoxy-4-phenylpiperidin-1-yl)propylamine (3.0 g, 7.3 mmol) and 10% Pd−C (0.3 g) in 1.0 M NH_3 in MeOH (50 mL) was hydrogenated at 70 psi at room temperature for 4 h. The catalyst was removed by filtration and the solvent was evaporated to leave the product as a viscous oil (2.01 g, 99%). ^{1}H NMR showed it to be pure product and was used in the next step without any purification. ^{1}H NMR ($CDCl_3$): δ 1.70−1.82 (m, 4 H), 2.01 (s, 3 H), 2.25−2.35 (m, 2 H), 2.42−2.55 (m, 4 H), 2.82−2.92 (m, 4 H), 7.18−7.36 (m, 5 H).

(d) 1-{*N*-[3-[4-Acetoxy-4-phenylpiperidin-1-yl]propyl]-carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (66). Prepared from **26** (0.295 g, 0.64 mmol) and **65a** (0.23 g, 0.832 mmol) using a similar procedure described earlier (0.210 g, 55%). ^{1}H NMR ($CDCl_3$): δ 1.70−1.78 (m, 2 H), 2.02 (s, 3 H), 2.22−2.30 (m, 2 H), 2.34 (s, 3 H), 2.36−2.44 (m, 4 H), 2.72−2.80 (m, 2 H), 3.24−3.40 (m, 2 H), 3.68 (s, 3 H), 6.66 (s, 1 H), 7.02−7.32 (m, 8 H), 8.80 (t, J = 7 Hz, 1 H). HCl salt Mp: 95−97 °C. Anal. ($C_{30}H_{35}N_4O_6F_2Cl\cdot 0.8CHCl_3$) C, H, N.

4-(3,4-Difluorophenyl)-6-methyl-2-oxo-3-{(4-methoxy-4-phenylpiperidin-1-yl)propyl}-5-methoxycarbonyl-1,2,3,4-tetrahydropyrimidine (67). To a solution of **26** (0.06 g, 0.129 mmol) in dry CH_2Cl_2 (10 mL) was added 3-(4-methoxy-4-phenylpiperidin-1-yl)propylamine[5] (**65b**; 0.072 g, 0.259 mmol) and the solution was stirred at room temperature for 24 h. The reaction mixture was stirred for another 1 h after addition of 6 N HCl (2 mL). It was basified with 10% aqueous KOH solution (pH = 9) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc:MeOH, 9:1) to obtain the product as a syrup (0.056 g, 77%). ^{1}H NMR ($CDCl_3$): δ 1.76−2.00 (m, 4 H), 2.39−2.44 (m, 6 H), 2.72−2.85 (m, 2 H), 2.95 (s, 3 H), 3.30 (m, 2 H), 3.71 (s, 3 H), 6.70 (s, 1 H), 7.04−7.41 (m, 8 H), 8.83 (t, J = 5.2 Hz, 1 H). HCl salt Mp: 170−174 °C. Anal. ($C_{29}H_{36}F_2N_4O_5Cl\cdot 1.3H_2O$) C, H, N.

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{*N*-[3-(4-phenylpiperidin-1-yl)propyl]carboxamido}-1,2,3,6-tetrahydropyrimidine (68). Prepared from **26** (100 mg, 0.217 mmol) and 3-(4-phenylpiperidin-1-yl)propylamine (**65c**; 95 mg, 0.433 mmol) using a similar procedure described earlier (105 mg, 89%). ^{1}H NMR ($CDCl_3$): δ 1.76−1.90 (m, 6 H), 2.02−2.25 (m, 2 H), 2.45 (s, 3 H), 2.46−2.58 (m, 2 H), 3.02−3.10 (m, 2 H), 3.36−3.46 (m, 2 H), 3.68 (s, 3 H), 3.98 (s, 3 H), 6.60 (s, 1 H), 7.02−7.38 (m, 8 H). HCl salt Mp: 133−136 °C. Anal. ($C_{28}H_{33}F_2N_4O_4Cl\cdot 0.2CH_2Cl_2$) C, H, N.

(+)-1-{*N*-[[4-Cyano-4-phenylpiperidin-1-yl]propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (69). Prepared from **26** (30 mg, 0.067 mmol) and **65d** (30 mg, 0.123 mmol) using a similar procedure described earlier to afford the product (30 mg, 81%). (M + 1): 552. ^{1}H NMR ($CDCl_3$): δ 1.70−1.78 (m, 2 H), 2.04−2.16 (m, 2 H), 2.34 (s, 3 H), 2.35−2.43 (m, 2 H), 2.44−2.52 (m, 4 H), 2.98−3.02 (m, 2 H), 3.32−3.42 (m, 2 H), 3.64 (s, 3 H), 6.68 (s, 1 H), 7.02−7.49 (m, 8 H), 8.84 (t, J = 7 Hz, 1 H). HCl salt Mp: 140−143 °C. Anal. ($C_{29}H_{32}F_2N_5O_4Cl$) C, H, N.

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-1-{*N*-[3-(4-methyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (70). Prepared from **26** and **65e**[5] using a similar procedure described earlier in 0.16 mmol scale. Yield: 71%. $[\alpha]_D$ = + 92.7 (c = 0.18, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 3 H), 1.69−1.87 (m, 6 H), 2.09−2.15 (m, 2 H), 2.31 (t, J = 7.5 Hz, 2 H), 2.32−2.50 (m, 4 H), 2.40 (s, 3 H), 3.30−3.36 (m, 2 H), 3.71 (s, 3 H), 6.69 (s, 1 H), 7.02−7.38 (m, 9 H), 8.78 (t, J = 5.7 Hz, 1 H). The HCl salt was hygroscopic. Anal. ($C_{29}H_{35}N_4O_4F_2Cl\cdot 0.7CH_2Cl_2$) C, H, N.

(+)-5-Carboxamido-1-{*N*-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]carboxamido}-6-(2,4-difluorophenyl)-4-ethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (73). (a) (+)-5-(Benzyloxycarbonyl)-1-{*N*-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]carboxamido}-6-(2,4-difluorophenyl)-4-ethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (71). A mixture of (+)-5-(benzyloxycarbonyl)-6-(2,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxy-1-[(4-nitrophenyloxy)carbonyl]pyrimidine[2] (**38**; 6.50 g, 11.81 mmol) and 3-[4-cyano-4-phenylpiperidin-1-yl]-propylamine[5] (**65d**; 3.60 g, 15.36 mmol) in THF (500 mL) was stirred at room temperature for 18 h. It was cooled to 0 °C and aqueous 10% HCl (2 mL) was added and stirred for 2 h. The mixture was washed with aqueous NaOH (0.5 N, 30 mL) and dried (Na_2SO_4) and the solvent evaporated. The residue was purified by column chromatography on silica gel using $CHCl_3$/MeOH/2 M NH_3 in MeOH (100/2/1) as the eluent to obtain product **71** as a white foamy solid (7.05 g, 93%). ^{1}H NMR ($CDCl_3$): δ 1.16 (t, J = 7.5 Hz, 3 H), 1.64−1.68 (m, 2 H), 1.99−2.08 (m, 4 H), 2.34−2.42 (m, 4 H), 2.60−2.80 (m, 2 H), 2.89 (br d, J = 12 Hz, 2 H), 3.18−3.40 (m, 2 H), 5.26 (q, J = 11 Hz, 2 H), 6.60−7.45 (m, 14 H), 8.86 (br t, 1 H, NH).

(b) 1-{*N*-[3-(4-Cyano-4-phenylpiperidin-1-yl)propyl]-carboxamido}-6-(2,4-difluorophenyl)-4-ethyl-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic Acid (72). To a suspension of 10% Pd−C (2.1 g) in MeOH (100 mL) and H_2O (20 mL) was added a solution of **71** (7.55 g, 11.2 mL) in

methanol (100 mL) and the mixture was hydrogenated at 80 psi for 14 h.[25] The black suspension was filtered through a pad of Celite and washed thoroughly with MeOH (2.0 L) and MeOH/$CHCl_3$ (1:2, 200 mL). Solvent was evaporated from the combined filtrate to leave the product **72** as a white solid (6.06 g, 98%). It was used in the next step without further purification.

(c) (+)-5-Carboxamido-1-{*N*-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]carboxamido}-6-(2,4-difluorophenyl)-4-ethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (73). A mixture of **72** (6.30 g, 11.2 mmol), EDC (4.29 g, 22.4 mmol, 2 equiv), and DMAP (3.41 g, 27.95 mmol, 2.5 equiv) in anhydrous CH_2Cl_2 (400 mL) was stirred at room temperature for 2 h. To this was added 40% aqueous NH_3 (6.13 g, 5 equiv) and the stirring continued for 12 h. The mixture was diluted with CH_2Cl_2 (200 mL) and washed with saturated aqueous NH_4Cl solution (3 × 200 mL). Solvent was evaporated from the dried (Na_2SO_4) organic layer and the residue was purified by column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in methanol (100/2/1) as the eluent to obtain the desired product as a white powder (5.45 g, 87%). ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.6 Hz, 3 H), 1.66−1.68 (m, 4 H), 2.04−2.09 (m, 4 H), 2.36−2.44 (m, 4 H), 2.60−2.78 (m, 2 H), 2.91 (br d, 2 H), 3.20−3.40 (m, 2 H), 5.70 (br s, 2 H), 6.55 (s, 1 H), 6.64−6.84 (m, 2 H), 7.20−7.55 (m, 6 H), 8.88 (br t, 1 H, NH). HCl salt Mp: 196−197 °C. $[\alpha]_D$ = +126 (c = 0.505, 1:1 $CHCl_3$/MeOH). Anal. ($C_{29}H_{33}N_6O_3F_2Cl$) C, H, N.

(+)-1-{*N*-[[4-Cyano-4-phenylpiperidin-1-yl]propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (79). To a solution of **34** (223 mg, 46.8 mmol) in CH_2Cl_2 (20 mL) was added 3-(4-cyano-4-phenylpiperidin-1-yl)propylamine (**65d**; 137 mg, 56 mmol). The resulting mixture was stirred at room temperature for 2 h and the solvent evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/2 M NH_3 in MeOH = 100:12:6) to afford the desired product (230 mg, 82%). $[\alpha]_D$ = 129° (c = 0.625, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.70−1.78 (m, 2 H), 2.00−2.20 (m, 4 H), 2.38−2.50 (m, 4 H), 2.94−3.00 (m, 2 H), 3.25−3.45 (m, 2 H), 3.45 (s, 3 H), 3.67 (s, 3 H), 4.65 (s, 2 H), 6.65 (s, 1 H), 6.97−7.45 (m, 8 H), 7.65 (br s, 1 H), 8.92 (t, J = 7 Hz, 1 H). HCl salt Mp: 118−119 °C. Anal. ($C_{30}H_{35}F_2N_5O_5Cl\cdot 1.2H_2O$) C, H, N.

1-{[3-[4-Cyano-4-(2-fluorophenyl)piperidin-1-yl]propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (80). (a) 4-Cyano-4-(2-fluorophenyl)piperidine (76a). To a solution of 2-fluorophenylacetonitrile (**75a**; 1.35 g, 10 mmol) and *N*-*tert*-butoxycarbonyl-bis(2-chloroethyl)amine (**74**; 2.42 g, 10 mmol) in DMF (30 mL) at 0 °C was added NaH (0.76 g, 95%, 30 mmol) carefully over 10 min. The resulting suspension was stirred and heated at 60 °C for 24 h. The reaction mixture was cooled and quenched with ice−water (100 mL) and the mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were dried ($MgSO_4$) and concentrated and the residue was purified by column chromatography on silica gel (20% EtOAc/hexanes) to yield the BOC-protected piperidine. It was dissolved in CH_2Cl_2 (10 mL) and treated with TFA (10 mL). The resulting mixture was stirred for 3 h and the solvent was evaporated. The residue was treated with aqueous 1 N NaOH, adjusted the pH to 10, and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were dried (K_2CO_3), concentrated, and purified by column chromatography on silica gel (80% EtOAc in hexanes) to yield the desired piperidine **76a** (933 mg, 30%).

(b) 1-*N*-(3-Aminopropyl)-4-cyano-4-(2-fluorophenyl)-piperidine (78a). To a solution of 4-cyano-4-(2-fluorophenyl)-piperidine (**76a**; 933 mg, 3.00 mmol) and *N*-(3-bromopropyl)-phthalimide (965 mg, 3.60 mmol) in DMF (20 mL) were added K_2CO_3 (2.00 g) and KI (100 mg). The resulting suspension was stirred vigorously at 80 °C for 12 h and then quenched with ice−water (60 mL). The mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers was dried ($MgSO_4$), concentrated, and purified by column chromatography on silica gel (30% EtOAc in hexanes) to yield the phthalimide-protected intermediate. It was dissolved in MeOH (40 mL) and treated with hydrazine (3.0 mL). The resulting mixture was heated at reflux temperature overnight. The white solid formed was filtered and the solvent was evaporated from the filtrate. The residue was purified by column chromatography on silica gel using $CHCl_3$:MeOH:2 M NH_3 in MeOH (100:8:4) as the eluent to yield the desired amine **78a** (607 mg, 55%) as a colorless oil.

(c) 1-{[3-[4-Cyano-4-(2-fluorophenyl)piperidin-1-yl]-propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (80). Prepared from **34** (25 mg, 0.052 mmol) and 1-*N*-(3-aminopropyl)-4-cyano-4-(2-fluorophenyl)piperidine (**78a**; 26 mg, 0.10 mmol) using a similar procedure described earlier (25 mg, 81%). ^{1}H NMR ($CDCl_3$): δ 1.70−1.78 (m, 2 H), 2.00−2.08 (m, 4 H), 2.38−2.50 (m, 4 H), 2.94−3.00 (m, 2 H), 3.30−3.47 (m, 2 H), 3.48 (s, 3 H), 3.70 (s, 3 H), 4.68 (s, 2 H), 6.67 (s, 1 H), 6.97−7.45 (m, 7 H), 7.69 (br s, 1 H), 8.97 (t, J = 7 Hz, 1 H). HCl salt Mp: 132−135 °C. Anal. ($C_{30}H_{33}F_3N_5O_5Cl\cdot 0.5CH_2Cl_2$) C, H, N.

(+)-1-{[3-[4-Cyano-4-(3-fluorophenyl)piperidin-1-yl]propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (81). (a) 4-Cyano-4-(3-fluorophenyl)piperidine (76b). Prepared from 3-fluorophenylacetonitrile (1.35 g, 10.0 mmol), *N*-*tert*-butoxycarbonyl-bis(2-chloroethyl)amine (2.42 g, 10.0 mmol), and NaH (0.76 g, 95%, 30 mmol) using a similar procedure described earlier (995 mg, 32%).

(b) 1-*N*-(3-Aminopropyl)-4-cyano-4-(3-fluorophenyl)-piperidine (78b). Prepared from **76b** (995 mg, 3.20 mmol) and *N*-(3-bromopropyl)phthalimide (965 mg, 3.60 mmol) using a similar procedure described earlier (colorless oil, 640 mg, 58%).

(c)(+)-1-{[3-[4-Cyano-4-(3-fluorophenyl)piperidin-1-yl]-propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (81). Prepared from **34** (25 mg, 0.052 mmol) and **78b** (26 mg, 0.10 mmol) using a similar procedure described earlier (25 mg, 81%). ^{1}H NMR ($CDCl_3$): δ 1.70−1.78 (m, 2 H), 2.00−2.08 (m, 4 H), 2.38−2.50 (m, 4 H), 2.94−3.00 (m, 2 H), 3.30−3.47 (m, 2 H), 3.48 (s, 3 H), 3.70 (s, 3 H), 4.68 (s, 2 H), 6.67 (s, 1 H), 6.97−7.45 (m, 7 H), 7.69 (br s, 1 H), 8.97 (t, J = 7 Hz, 1 H). HCl salt Mp: 124−127 °C. Anal. ($C_{30}H_{33}F_3N_5O_5Cl\cdot 0.5CH_2Cl_2$) C, H, N.

(+)-1-{*N*-[3-[4-Cyano-4-(4-fluorophenyl)piperidin-1-yl]-propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (82). (a) 4-Cyano-4-(4-fluorophenyl)piperidine (76c). Prepared from 4-fluorophenylacetonitrile (1.35 g, 10.0 mmol), *N*-*tert*-butoxycarbonyl-bis(2-chloroethyl)amine (2.42 g, 10.0 mmol), and NaH (0.76 g, 95%, 30 mmol) using a similar procedure described earlier (2.0 g, 64%).

(b) 1-*N*-(3-Aminopropyl)-4-cyano-4-(4-fluorophenyl)-piperidine (78c). Prepared from **76c** (1.55 g, 5.0 mmol) and *N*-(3-bromopropy)phthalimide (1.480 g, 5.50 mmol) using a similar procedure described earlier (colorless oil, 1.10 g, 64%).

(c) (+)-1-{*N*-[3-[4-Cyano-4-(4-fluorophenyl)piperidin-1-yl]propyl]carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (82). Prepared from **34** (25 mg, 0.052 mmol) and **78c** (26 mg, 0.10 mmol) using a similar procedure described earlier (30 mg, 96%). ^{1}H NMR ($CDCl_3$): δ 1.74 (m, 2 H), 2.06 (m, 4 H), 2.49 (m, 4 H), 3.00 (m, 2 H), 3.40 (m, 2 H), 3.48 (s, 3 H), 3.70 (s, 3 H), 4.67 (s, 2 H), 6.67 (s, 1 H), 7.08 (m, 4 H), 7.18 (m, 1 H), 7.48 (m, 2 H), 7.67 (bs, 1 H), 8.97 (bt, 1 H). HCl salt, white solid; Mp: 103−106 °C. CIMS: m/e = 600 (MH^+). $[\alpha]_D$ = 106.0 (c = 0.205, MeOH). Anal. ($C_{30}H_{33}F_3N_5O_5Cl\cdot 0.9CHCl_3$) C, H, N.

(+)-1-{*N*-[3-[4-Methyl-4-phenylpiperidin-1-yl]propyl]-carboxamido}-6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (83). Prepared from **34** and amine **65e** using a similar procedure described earlier. Yield: 0.12 g (81%). $[\alpha]_D$ = + 82.1 (c = 0.31, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.14 (s, 3 H), 1.61−1.72 (m, 4 H),

2.03−2.08 (m, 2 H), 2.25 (t, J = 7.2 Hz, 2 H), 2.30−2.42 (m, 4 H), 3.19−3.31 (m, 2 H), 3.40 (s, 3 H), 3.63 (s, 3 H), 4.60 (s, 2 H), 6.60 (s, 1 H), 6.97−7.29 (m, 8 H), 7.63 (br s, 1 H), 8.78 (t, J = 5.7 Hz, 1 H). The HCl salt was hygroscopic. Anal. ($C_{30}H_{37}N_4O_5F_2Cl\cdot1.0CH_2Cl_2$) C, H, N.

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