Design and Synthesis of Novel α_{1a} Adrenoceptor-Selective Antagonists. 1. Structure−Activity Relationship in Dihydropyrimidinones

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Dihydropyrimidinones such as compound **12** exhibited high binding affinity and subtype selectivity for the cloned human α_{1a} receptor. Systematic modifications of **12** led to identification of highly potent and subtype-selective compounds such as (+)-**30** and (+)-**103**, with high binding affinity (K_i = 0.2 nM) for α_{1a} receptor and greater than 1500-fold selectivity over α_{1b} and α_{1d} adrenoceptors. The compounds were found to be functional antagonists in human, rat, and dog prostate tissues. Compound (+)-**103** exhibited excellent selectively to inhibit intraurethral pressure (IUP) as compared to lowering diastolic blood pressure (DBP) in mongrel dogs (K_b(DBP)/K_b(IUP) = 40) suggesting uroselectivity for α_{1a}-selective compounds.

Introduction

Benign prostatic hyperplasia (BPH) is a urological disorder in the aging male population which leads to a variety of symptoms including hesitancy in starting the urine flow, poor stream of urine flow, dribbling, nocturia, increased frequency of urination, and large residual volumes.[1−3] Obstructive symptoms associated with BPH result from a combination of two components: mechanical constriction of the urethra due to increased prostatic mass and a dynamic component attributable to increased noradrenergic tone in the hyperplasic prostate.[4,5]

As a part of our research program for the treatment of BPH, we have synthesized antagonists that bind selectively to the α_{1a} subtype compared to α_{1b} and α_{1d} adrenoceptors.[6−8] We have previously shown that the α_{1a} receptor subtype mediates the contraction of lower urinary tract and prostate smooth muscles.[9,10] It has been demonstrated that that α_{1a}-selective antagonists are able to effectively block the contraction of prostatic smooth muscle caused by a nonselective α_1 agonist after in vivo administration, without significant effects on blood pressure.[7] In contrast, nonselective α_1 antagonists, terazosin[11] and doxazosin,[12] show significant effects on lowering blood pressure at the doses required to block the contraction of prostate caused by an α_1 agonist in the dog model. This apparent lack of selectivity for α_{1a} receptor could contribute to some undesirable side effects such as orthostatic hypotension, dizziness, asthenia, and nasal congestion in patients.[13] After our initial reports,[5,9,10] several α_{1a} antagonists such as tamsulosin,[14] KMD-3213,[15] RS-97078,[16] GG-818,[17] and A-131701[18] have been reported to exhibit uroselectivity (Chart 1). The claims of uroselectivity exhibited by tamsulosin have been challenged by some researchers.[19,20]

Recently, we described the synthesis of a number of dihydropyridines such as **1** and **2** which were found to be potent and subtype-selective anatgonists for the α_{1a} adrenoceptor (Chart 2).[6,7] Although these compounds bear structural resemblance to the known calcium channel antagonist niguldipine, **1** and **2** show negligible affinity for the L-type calcium channel.[5,7] Dihydropyridine **2**, however, showed poor oral bioavailability in rats (5%). It is possible that the poor pharmacokinetic profile of **1** may be due to a rapid conversion of the dihydropyridine moiety into a pyridine moiety by oxidative metabolism. We reasoned that a dihydropyrimidinone in place of the dihydropyridine nucleus would not undergo such oxidative metabolism and, therefore, might exhibit a better pharmacokinetic profile. We were intrigued by the reports that certain dihydropyrimidinone derivatives adopt solid-state molecular conformations similar to dihydropyridines and show comparable pharmacological activity as calcium channel antagonists.[21−23] We therefore decided to synthesize a series of dihydropyrimidinone analogues of **1** and **2** and evaluate their binding affinities and selectivity for the α_{1a} adrenoceptor. In our initial design, we retained some of the optimal structural features derived from the dihydropyridine SAR, such as the nitrophenyl group and the distance between the dihydropyrimidinone moiety and piperidine end group. Synthesis and SARs in the dihydropyrimidinone are described in this paper.

Chemistry

The synthesis of compounds **9**−**12** is shown in Scheme 1. Dihydropyrimidine intermediates such as **5** were prepared utilizing a procedure similar to that described by Atwal et al.[21−23] Reaction of the benzylidine derivative **3** with *O*-methylisourea (**4**) in the presence of $NaHCO_3$ in DMF gave the dihydropyrimidine **5** as a

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Chart 1

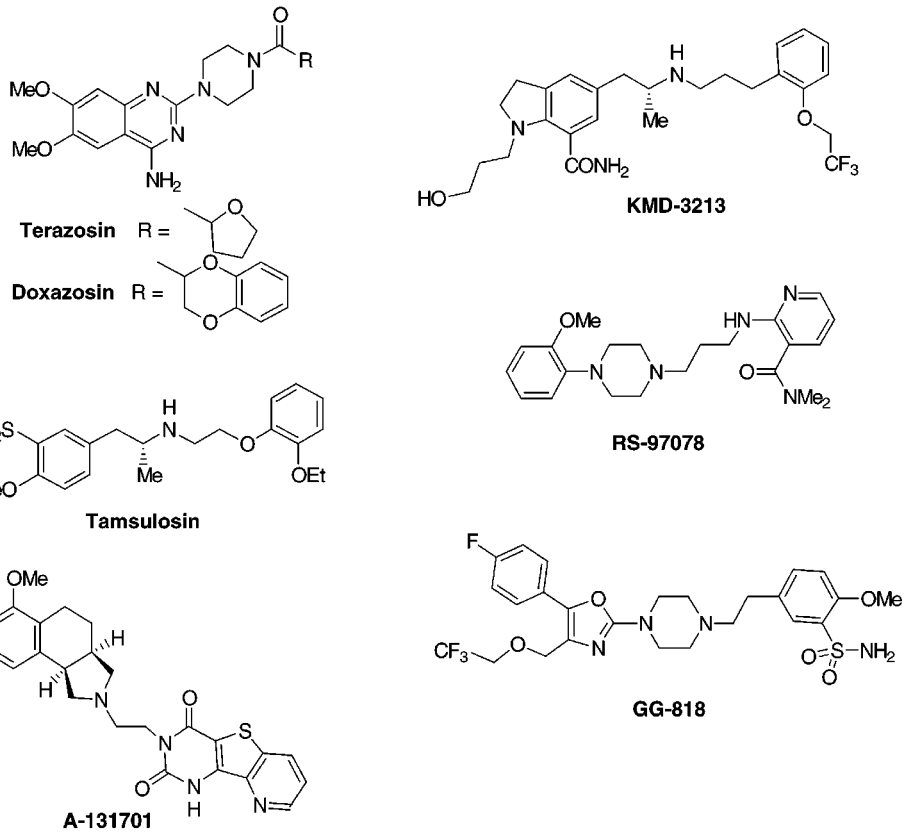
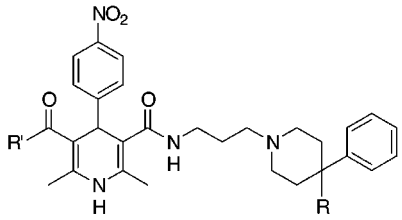


Chart 2



1 R' = MeO; R = Ph
2 R' = H_2N; R = CO_2Me

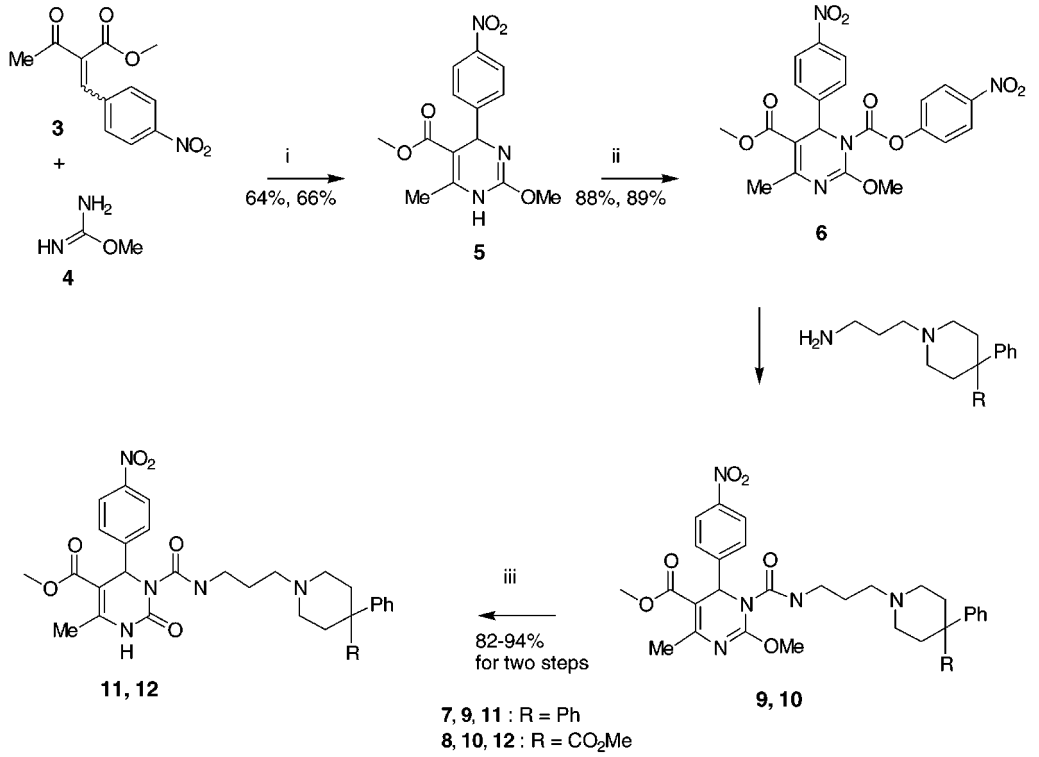
mixture of amine−imine tautomers. This compound, upon reaction with 4-nitrophenyl chloroformate, gave the carbamate ester **6**. Compound **6** was obtained via regiospecific acylation at the *N*-1 nitrogen.[21] The regiochemical preference was seen presumably to achieve conjugation of the double bond with the carbonyl group of the methyl ester. Reaction of **6** with 3-[4,4-diphenylpiperidin-1-yl]propylamine (**7**)[5] and 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (**8**)[7] gave the dihydropyrimidine derivatives **9** and **10**, respectively, which on treatment with aqueous HCl gave the dihydropyrimidinones **11** and **12**.

The resolution of enantiomers of the dihydropyrimidine **5** was achieved in two steps by using chiral auxiliary as shown in Scheme 2. First, the *p*-nitrophenyloxy carbamate **6,** derived from **5**, was reacted with (*S*)-(−)-α-methylbenzylamine to obtain a mixture of diastereomeric amides **13** and **14**,[21,22] and the diastereomers were separated by flash column chromatography. The α-methylbenzylaminocarbonyl moiety was then removed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the (+) and (−) enantiomers of dihydropyrimidine **5**. The absolute stereochemistry of the enantiomers was not assigned. The same sequence was repeated to obtain pure enantiomers of all the dihydropyrimidinones which are described in this paper. Compound (+)-**5** on reaction with 4-nitrophenyl chloroformate followed by reaction with amine **8** and subsequent treatment with aqueous HCl yielded (+)-**12**. A similar sequence of reactions starting with compound (−)-**5** gave (−)-**12**.

Scheme 3 describes the synthesis of dihydropyrimidinone analogues with modifications at the C-4 and C-5 positions. The methyl group at the C-4 position was changed to an ethyl group by starting with benzylidine **16** derived from the propionylacetic ester. A 2-cyanoethyl ester group provided a convenient access to modify the methyl ester substituent to other ester derivatives or amides.[7] The benzylidine derivatives **15** and **16** were reacted with *O*-methylisourea (**4**) to give the dihydropyrimidines **17** and **18**, respectively. Compounds **17** and **18**, upon reaction with 4-nitrophenyl chloroformate, gave the carbamate esters **19** and **20**, which upon further reaction with amine **8**, followed by treatment with aqueous HCl, gave **22** and **23**, respectively. Hydrolysis of the 2-cyanoethyl ester with aqueous NaOH gave carboxylic acids **24** and **28**. Reaction of these carboxylic acids with the corresponding alcohols in the presence of DMAP and EDC gave esters **25** and **29,** and a similar reaction with amines gave amides **26**, **27**, **30**, and **31**. Compounds (+)-**30** and (−)-**30** were synthesized from the resolved enantiomers of dihydropyrimidine **18** by the procedure similar to the one described for resolution of **12**.

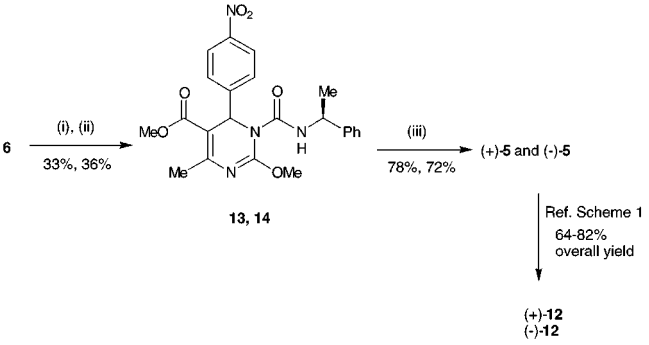
Schemes 4 and 5 depict the synthesis of dihydropyrimidinones **77**−**85**, (+)-**103**, and (+)-**104** by using the

Scheme 1[a]



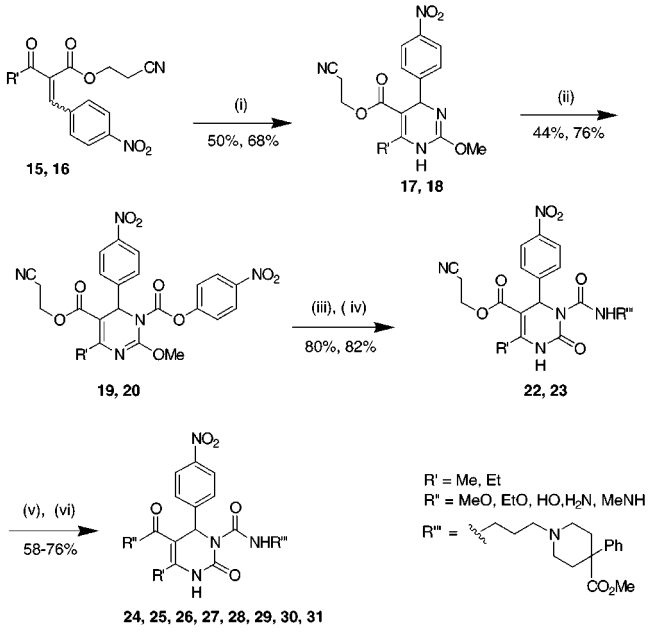
[a] (i) NaOAc, DMF; (ii) 4-nitrophenyl chloroformate, $NaHCO_3$, CH_2Cl_2, H_2O; (iii) HCl/THF.

Scheme 2[a]



[a] (i) (*S*)-(−)-α-Methylbenzylamine; (ii) separation of diastereomers; (iii) DBU.

Scheme 3[a]



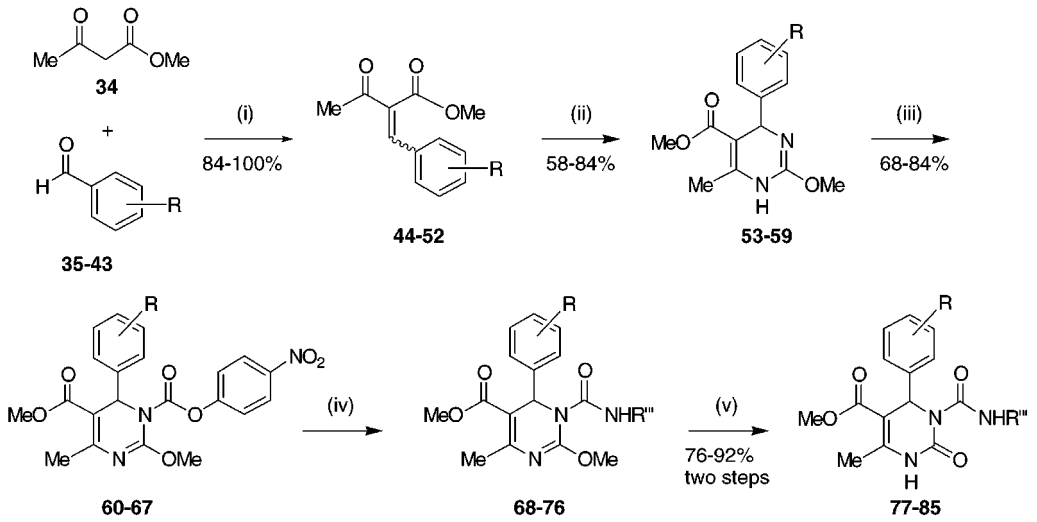
[a] (i) *O*-Methylisourea, $NaHCO_3$, EtOH; (ii) 4-nitrophenyl chloroformate, $NaHCO_3$, CH_2Cl_2, H_2O; (iii) amine **8** (H_2NR'''); (iv) 6 N HCl; (v) NaOH, acetone; (vi) EDC, DMAP, amine/alcohol, CH_2Cl_2.

sequence of reactions similar to the ones described previously.

Results and Discussion

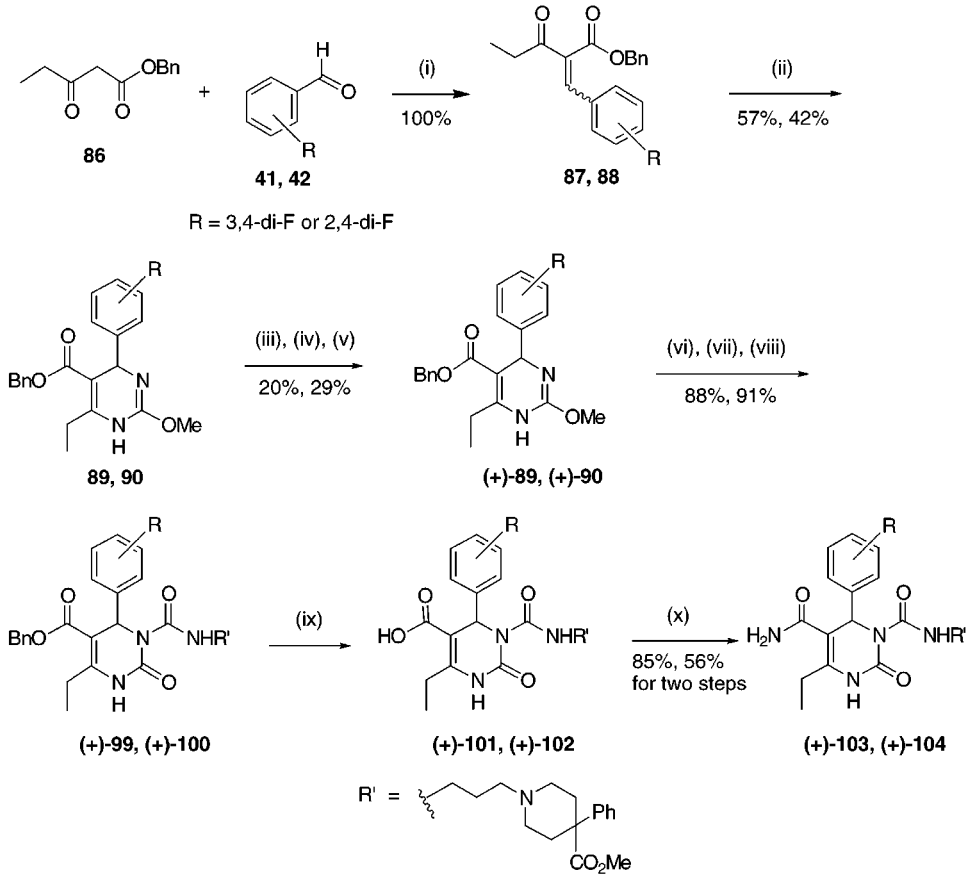
The binding profiles for the α_1 receptors of several structurally similar dihydropyridines and dihydropyrimidinones are summarized in Table 1. The dihydropyrimidinone **11**, containing a diphenylpiperidine side chain, had $K_i = 5$ nM at the cloned human α_{1a} adrenoceptor as compared to its dihydropyridine analogue **1** ($K_i = 0.4$ nM). Interestingly, the dihydropyrimidinone **12**, which contains 4-methoxycarbonyl-4-phenylpiperidine in the side chain, displayed better binding affinity ($K_i = 0.5$ nM) than its dihydropyridine analogue **2** ($K_i = 2.4$ nM). The subtype selectivity, however, was better for the dihydropyridine compounds (**1** and **2**) than the dihydropyrimidinones (**11** and **12**). Encouraged by these preliminary results, we tested both enantiomers of compound **12** in the binding assay. The more active enantiomer (+)-**12** showed higher affinity and improved subtype selectivity (>100-fold) for α_{1a} over the racemate and (−)-**12**. In addition, (+)-**12** showed >400-fold selectivity over α_2 adrenoceptor subtypes and even greater selectivity over the rat L-type calcium channel ($K_i > 10\ \mu$M). The active enantiomer (+)-**12** showed 10% oral bioavailability with a 90-min half-life in the rat and <10% bioavailability in the dog. These initial results prompted us to further investigate this ser-

Scheme 4[a]



[a] (i) Piperidine/HOAc; (ii) *O*-methylisourea, $NaHCO_3$, DMF; (iii) 4-nitrophenyl chloroformate, DMAP, CH_2Cl_2; (iv) amine **8**; (v) HCl.

Scheme 5[a]



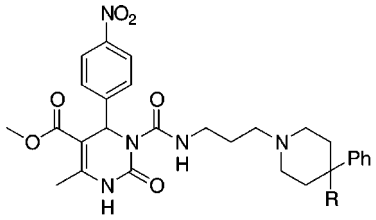
[a] (i) Piperidine, benzene; (ii) *O*-methylurea, $NaHCO_3$, DMF; (iii) 4-nitrophenyl chloroformate pyridine, CH_2Cl_2; (iv) *R*-(+)-phenethylamine and separate diastereomers; (v) DBU; (vi) 4-nitrophenyl chloroformate, pyridine, CH_2Cl_2; (vii) amine **8**; (viii) 6 N HCl; (ix) H_2, Pd−C, MeOH/water; (x) EDC, NMM, NH_4OH, CH_2Cl_2.

ies of compounds in order to optimize the selectivity for α_{1a} receptor and to improve their pharmacokinetic properties.

Replacement of the methyl ester in compound **12** with an ethyl ester (**25**) did not result in a significant change of affinity for the α_{1a} subtype (0.5 nM vs 0.3 nM). Interestingly, the carboxylic acid **24** showed lower α_{1a} affinity but greater than 150-fold selectivity over the other two α_1 subtypes. Replacement of the ester group in **12** by a primary amide group gave compound **26**, which showed comparable binding affinity ($K_i = 0.7$ nM) but better subtype selectivity than **12**. The methylamide **27** exhibited lower α_{1a} affinity than the primary amide **26**.

Compound **29**, containing an ethyl group at the C-4 position, showed a binding profile quite similar to that of **12** which contains a methyl group at the C-4 position of the dihydropyrimidinone. Compound **30**, an amide

Table 1. Binding Profiles of Dihydropyrimidinones versus Dihydropyridines at Recombinant Human α_1 Adrenoceptors



compd	K_i (nm)[a,b]		
	α_{1a}	α_{1b}	α_{1d}
terazosin	6.9	1.9	3.5
1	0.4	74	160
2	2.4	3700	8800
11 (R = Ph)	5.0	27	120
12 (R = CO_2Me)	0.5	28	100
(+)-**12** (R = CO_2Me)	0.4	81	180
(−)-**12** (R = CO_2Me)	2.1	19	80

[a] K_i values obtained by displacement of [^{3}H]prazosin from cloned human receptors. [b] All K_i values are ±5% SE or less for $n > 2$. In cases where $n = 2$, both K_i values are within 2-fold of each other and the values shown are the average of the two experiments.

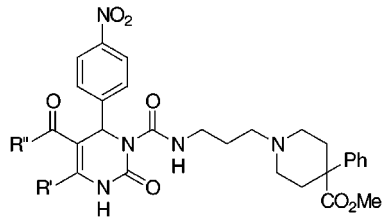
analogue of **29**, showed improved binding affinity and subtype selectivity. The methylamide **31** exhibited a lower affinity for α_{1a} (K_i = 1.2 nM) than the corresponding primary amide **30** but still showed greater than 100-fold selectivity against the α_{1b} and α_{1d} subtypes.

The improved α_{1a} adrenoceptor binding and selectivity profile of **30** prompted further characterization of the pure enantiomers of the compound. The (+) enantiomer of the compound (+)-**30** exhibited superior binding and selectivity profile compared to its antipode (−)-**30** and the racemate. This observation is consistent with the observation about the binding profile of the enantiomers of **12** that was described previously. Compound (+)-**30** showed greater than 1000-fold selectivity for the α_{1a} receptor over a number of recombinant human G-protein coupled receptors such as α_{2a}, α_{2b}, and α_{2c} adrenoceptors, histamine H_2, and 5HT (1A, 1B, 1D, and 2A) and for the rat L-type calcium channel. The selectivity over the histamine H_1 receptor was 100-fold.

The binding affinity of (+)-**30** at the recombinant rat,[25] dog,[26] and human α_{1a} adrenoceptors correlated well with the functional potency of the compound to antagonize the phenylephrine-induced contraction of isolated rat, dog, and human prostate tissues (Table 5). Compound (+)-**30** showed an oral bioavailability of 13% (iv: 1 mg/kg dose, AUC = 18 μmol min/L; po: 3 mg/kg dose, AUC = 9 μmol min/L) in rats and 32% (iv: 1 mg/kg dose, AUC = 23 μmol min/L; po: 3 mg/kg dose, AUC = 25 μmol min/L) in dogs with plasma half-life of 1.6 and 3.2 h, respectively.

The presence of a nitro substituent on the C-6 phenyl group of (+)-**30** was deemed to be a liability due to its potential for toxicity upon chronic administration.[24] A search was undertaken to synthesize analogues of (+)-**30**, with suitable replacements for the nitro group without compromising the desirable in vitro and in vivo profile of (+)-**30**. We decided to explore the SAR of the C-6 phenyl group by initially synthesizing analogues of **12** rather than **30** because the synthetic route to make analogues of **12** is shorter than that for **30**. The results of this study are summarized in Table 3. Replacement of the nitro group with a methyl or chloro group at the

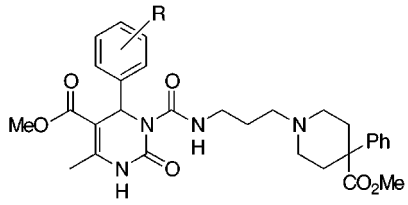
Table 2. Binding Profile of Dihydropyrimidinones with C-4 and C-5 Modifications at Recombinant Human α_1 Adrenoceptors



compd	R′	R″	K_i (nM)[a,b]		
			α_{1a}	α_{1b}	α_{1d}
12	Me	MeO	0.5	28	100
24	Me	HO	10	1600	2600
25	Me	EtO	0.3	15	91
26	Me	H_2N	0.7	100	140
27	Me	MeNH	2.1	100	270
29	Et	MeO	0.8	37	81
30	Et	H_2N	0.5	160	290
(+)-**30**	Et	H_2N	0.2	360	740
(−)-**30**	Et	H_2N	1.9	130	420
31	Et	MeNH	1.2	139	398

[a,b] For note, see Table 1.

Table 3. Binding Profile of Dihydropyrimidinones with C-6 Phenyl Ring Modifications at Recombinant Human α_1 Adrenoceptors

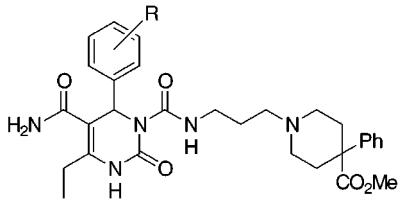


compd	R	K_i (nM)[a,b]		
		α_{1a}	α_{1b}	α_{1d}
12	4-NO_2	0.5	28	100
77	4-Me	8.0	77	220
78	3-Me	1.8	110	220
79	4-Cl	4.5	48	170
80	3-Cl	1.1	50	180
81	4-F	1.2	78	180
82	3-F	1.5	67	150
83	3,4-F_2	0.1	45	140
84	2,4-F_2	0.2	88	180
85	3,4-furazan	0.1	27	93

[a,b] For note, see Table 1.

C-4 position (**77** and **79**) of the phenyl ring reduced the α_{1a} affinity by about 10-fold. When the methyl or chloro substituent was placed at the 3-position (**78** and **80**) an improved α_{1a} binding profile was observed. A fluoro group at the 3- or 4-position (**81** and **82**) reduced the α_{1a} affinity and selectivity. The compounds containing difluoro substituents at the 3,4- or 2,4-positions gave compounds **83** and **84** which displayed improved binding affinities for the α_{1a} adrenoceptor and >400-fold selectivity over α_{1b} and α_{1d}. A 3,4-benzofurazanyl group, which has been used as an isostere for a nitrophenyl group in other programs,[21,22] was incorporated to give compound **85** which showed good binding and selectivity profile for the α_{1a} receptor. The easy accessibility of 3,4- and 2,4-difluorobenzaldehydes prompted us to use these substituents as the preferred groups on the C-6 phenyl ring for the synthesis of close analogues of **30** as shown Table 4.

Table 4. Binding Profile of (+)-**30** and Its Close Analogues at Recombinant Human α_1 Adrenoceptors



		K_i (nM)[a,b]		
compd	R	α_{1a}	α_{1b}	α_{1d}
(+)-**30**	4-NO_2	0.2	360	740
(+)-**103**	3,4-F_2	0.2	260	350
(+)-**104**	2,4-F_2	0.2	340	440

[a,b] For note, see Table 1.

Table 5. Comparison of Binding Affinities of (+)-**30** and (+)-**103** at the α_{1a} Adrenoceptors and Antagonism of Phenylephrine- or A-61603-Induced Contractions (K_b) of (+)-**30** and (+)-**103** in Isolated Prostate Tissue

	(+)-**30**		(+)-**103**	
species	K_i (nM)	K_b (nM)	K_i (nM)	K_b (nM)
rat	0.58	2.0[a]	0.27	1.00[a]
dog	1.9	0.85[a]	1.30	3.70[a]
human	0.19	0.04[b]	0.21	0.39[b]

[a] Phenylephrine was used as agonist. [b] A-61603 was used as agonist.

The compounds (+)-**103** [SNAP 6201(+)] and (+)-**104** displayed almost identical binding and selectivity profiles. In the initial binding experiments, (+)-**103** showed comparable binding affinity at the recombinant rat,[25] dog,[26] and human[9] α_{1a} adrenoceptors (K_i = 0.3, 1.3, and 0.2 nM, respectively) which correlated well with the potencies of the compound to antagonize phenylephrine- or A-61603-induced contraction of the prostate tissues as shown in Table 5. Thus the profile for **(+)-103** looked strikingly similar to that of **(+)-30,** and the compound was selected for detailed characterization.

In Vitro and in Vivo Evaluation of (+)-103. The results from a number of in vivo and in vitro experiments on **(+)-103** and terazosin are summarized in Table 6. While terazosin showed no subtype selectivity for the α_{1a} receptor, (+)-**103** showed >1000-fold selectivity for the α_{1a} receptor over a number of recombinant human G-protein coupled receptors such as α_2 and 5HT (1A, 1B, 1D, and 2A) receptors as well as the rat L-type calcium channel. The selectivity for the α_{1a} receptor over the histamine H_1 receptor was found to be 140-fold based on the binding affinities of (+)-**103** for the cloned human receptors.

Compound **(+)-103** was found to potently antagonize norepinephrine-induced contraction of isolated prostate and vas deferens tissues which predominantly express the α_{1a} subtype in rat, dog, and human. It, however, failed to inhibit the norepinephrine-induced contractions in the isolated rat aorta which predominantly express the α_{1d} subtype, at concentrations up to 1 μM.[27] The nonselective α_1 antagonist terazosin, on the other hand, antagonizes the norepinephrine-induced contractions in isolated rat aorta with almost identical K_b (19 and 25 nM, respectively). These results are in good agreement with the selectivity observed in the binding assays for the α_{1a} receptor over the α_{1d} receptor.

In the in situ rat prostate assay, compound **(+)-103** inhibited the contractile response to phenylephrine with AD_{50} = 20 μg/kg but needed a much higher dose (AD_{50} > 3 mg/kg) for inhibition of blood pressure effect elicited by phenylephrine in pithed rats. In contrast, the nonselective α_1 antagonist, terazosin, did not show much separation for doses required to inhibit the contractile response (AD_{50} = 52 μg/kg) versus doses required to lower blood pressure (AD_{50} = 65 μg/kg). In the phenylephrine-stimulated urethral and arterial pressure experiments in anesthetized dogs, compound (+)-**103** was found to inhibit intraurethral pressure (IUP) at doses 40-fold lower than those required to reduce diastolic blood pressure (DBP). The nonselective α_1 antagonist terazosin, in comparison, did not show difference in potency against these two effects in the same model (K_b(IUP) = 16.4 μg/kg and K_b(DBP) = 15.7 μg/kg). The ratio of K_b(IUP) over K_b(DBP) is one index of uroselectivity, i.e., selectivity of an antagonist for mediating urethral versus cardiovascular effects. This model is considered to be a good predictor of clinical urodynamic and hemodynamic profiles in humans,[28] and on the basis of the results described above, **(+)-103** will be expected to show less cardiovascular liability than terazosin. Compound (+)-**103** showed an oral bioavailability of 19% and 26% and plasma half-life of 2.0 and 2.5 h in rats and dogs, respectively. Interestingly, although **(+)-103** showed a short plasma half-life (2 h) in rats, it showed a longer duration of action (>4 h) in the in situ rat prostate experiment.

In vitro and in vivo metabolism experiment with (+)-**103** revealed a significant formation of 4-methoxycarbonyl-4-phenylpiperidine, which is an analogue of the known μ-opioid agonist, meperidine.[29] Issues relating to (+)-**103** metabolism will be further discussed in the accompanying papers.

Summary

We have designed and synthesized a novel series of dihydropyrimidinones as potent and selective α_{1a} adrenoceptor antagonists. Compound **12** was identified as a lead compound with good binding affinity and subtype selectivity for the α_{1a} receptor. Systematic modification of **12** led to the discovery of **30** as a potent and selective antagonist in the binding and functional assays. A 3,4-difluoro analogue of **30** was synthesized, and the resulting compound (+)-**103** (SNAP 6201) showed high affinity and selectivity for the α_{1a} adrenoceptor subtype. In the anesthetized dog model, this compound showed 40-fold selectivity to reduce the IUP versus DBP supporting our notion that this compound may be uroselective. On the basis of the lack of cardiovascular effects and the superior pharmacodynamic profiles of these α_{1a}-selective compounds in the animal models, we believe that they could offer a significant improvement over the current treatments of BPH.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded on a QE Plus 300 MHz spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Reactions were monitored by TLC (Merck type 60 F_{254}), and flash column chromatography was done on silica gel (Merck type 60 for column chromatography; 230−

Table 6. Summary and Comparison of the in Vitro and in Vivo Properties of (+)-**103** and Terazosin

assay	antagonist/agonist	(+)-**103**	terazosin
K_i α_{1a} human clones (nM)	[^{3}H]prazosin	0.2	4.0
$\alpha_{1b,1d}/\alpha_{1a}$	[^{3}H]prazosin	>1000	<1.0
$\alpha_{2a,b,c}/\alpha_{1a}$	[^{3}H]rauwolscine	>1000	<10
K_b rat prostate (nM)	A-61603	0.3	25
K_b rat aorta (nM)	norepinephrine	>1000	19
K_b rat vas deferens (nM)	norepinephrine	2.5	
K_b human prostate (nM)	A-61603	0.1	25
AD_{50} (in situ rat prostate)	phenylephrine	20	52
AD_{50}(DBP) rat (μg/kg)	phenylephrine	>3000	65
duration of action rat (h)	phenylephrine	>4	>4
K_b(IUP)[a] dog (μg/kg)	phenylephrine	4.2	16.4
K_b (DBP)[b] dog (μg/kg)	phenylephrine	187	15.7
rat F, $t_{1/2}$ (h)		15%,[c] 2.0	49%, 7.5
dog F, $t_{1/2}$ (h)		26%,[d] 2.5	

[a] Intraurethral pressure. [b] Diastolic blood pressure. [c] iv: 1 mg/kg dose, AUC = 70 μmol min/L. po: 3 mg/kg dose, AUC = 47 μmol min/L. [d] iv: 1 mg/kg dose, AUC = 29 μmol min/L. po: 3 mg/kg dose, AUC = 25 μmol min/L.

400 mesh) in the solvent systems indicated. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Abbreviations: EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP, 4-(*N*,*N*-dimethylamino)pyridine; NMM, *N*-methylmorpholine. The yields reported are of the isolated purified compounds and are not optimized.

5-Methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{*N*-[3-(4,4-diphenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (11). (a) 1,6-Dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-6-(4-nitrophenyl)pyrimidine (5). A mixture of methyl 2-{(4-nitrophenyl)-methylene}-3-oxobutyrate (**3**; 12.46 g, 0.05 mol), *O*-methylisourea hydrogen sulfate (**4**; 10.32 g, 0.06 mol), and NaOAc (9.84 g, 0.06 mol) in DMF (50 mL) was stirred and heated at 70−75 °C for 4 h. The mixture was cooled and poured into ice−water (300 mL). The precipitate formed was filtered, washed with water, and dried. The crude product was purified by flash column chromatography on silica gel using 10−30% EtOAc in hexanes as the gradient eluent (9.8 g, 64%). The ^{1}H NMR analysis of the product showed it to be a 19:1 mixture of the amine−imine tautomers, which was used as such in the next step. ^{1}H NMR ($CDCl_3$): δ 2.32, 2.38 (2 s, 3 H), 3.59, 3.70 (2 s, 3 H), 3.72, 3.85 (2 s, 3 H), 5.40, 5.66 (s, d, J = 3 Hz, 1 H), 5.50, 6.08 (s, d, J = 3 Hz, 1 H), 7.43, 7.45 (2 d, J = 9 Hz, 2 H), 8.10, 8.11 (2 d, J = 9 Hz, 2 H).

(b) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (6). To a well-stirred mixture of compound **5** (5.7 g, 18.7 mmol), $NaHCO_3$ (6.27 g, 0.074 mol), CH_2Cl_2 (200 mL), and water (50 mL) at 0−5 °C was added 4-nitrophenyl chloroformate (4.41 g, 2.18 mmol) in 5 min and the mixture was allowed to warm to room temperature. After 10 h, two layers were separated; the CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ solution (3 × 50 mL) and dried ($MgSO_4$), and the solvent was evaporated. The residue was recrystallized from CH_2Cl_2 and hexanes to give the product **6** as white crystals (12.8 g, 89%). ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3 H), 3.69 (s, 3 H), 3.94 (s, 3 H), 6.34 (s, 1 H), 7.36 (d, J = 9.1 Hz, 2 H), 7.46 (d, J = 8.7 Hz, 2 H), 8.14 (d, J = 8.7 Hz, 2 H), 8.26 (d, J = 9.1 Hz, 2 H). Mp: 168−169 °C. Anal. ($C_{21}H_{18}N_4O_9$) C, H, N.

(c) 1,6-Dihydro-1-{*N*-[3-(4,4-diphenylpiperidin-1-yl)-propyl]carboxamido} -2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)pyrimidine (9). To a stirred mixture of **6** (0.940 g, 2 mmol) and K_2CO_3 (0.552 g, 4 mmol) in anhydrous THF (20 mL) at room temperature under argon atmosphere was added a solution of 3-[4,4-diphenylpiperidin-1-yl]propylamine (**7**; 0.882 g, 3 mmol, 1.5 equiv) in THF (5 mL) and the stirring was continued for 1 h. Solvent was evaporated from the reaction mixture and the residue was redissolved in CH_2Cl_2 (50 mL). It was washed with 5% $NaHCO_3$ (3 × 25 mL) and brine (50 mL) and dried ($MgSO_4$). Solvent was evaporated and the residue was purified by flash column chromatography on silica gel using 10% methanol in EtOAc as the eluent to give the desired product **9** as an oil which became a white powder upon trituration with hexanes and drops of EtOAc (1.10 g, 88%). Mp: 95−96 °C. ^{1}H NMR ($CDCl_3$): δ 1.61−1.71 (m, 2 H), 2.26−2.33 (m, 2 H), 2.38 (s, 3 H), 2.39−2.50 (m, 8 H), 3.20−3.41 (m, 2 H), 3.65 (s, 3 H), 3.89 (s, 3 H), 6.65 (s, 1 H), 6.84 (br t, 1 H, NH), 7.08−7.29 (m, 10 H), 7.40 (d, J = 8.7 Hz, 2 H), 8.03 (d, J = 8.6 Hz, 2 H). Anal. ($C_{35}H_{39}N_5O_6$·0.75CH_2Cl_2) C, H, N.

(d) 5-Methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{*N*-[3-(4,4-diphenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine (11). To a stirred solution of **9** (0.208 g, 0.33 mmol) in THF (10 mL) at 5 °C under argon was added 3 N HCl (6 mL) and the mixture was allowed to warm to room temperature. After 2 h, solvents were evaporated completely, and the residue was treated with 40 mL of 10% $NaHCO_3$. The product was extracted with CH_2Cl_2 (2 × 15 mL) and the combined extracts were dried ($MgSO_4$). Solvent was evaporated and the residue was crystallized from hexane and EtOAc (0.20 g, 97%). Mp: 197−198 °C. ^{1}H NMR ($CDCl_3$): δ 1.63−1.67 (m, 2 H), 2.23−2.28 (m, 2 H), 2.34 (s, 3 H), 2.37−2.42 (m, 8 H), 3.20−3.41 (m, 2 H), 3.69 (s, 3 H), 6.75 (s, 1 H), 7.08−7.26 (m, 11 H), 7.46 (d, J = 8.7 Hz, 2 H), 8.08 (d, J = 8.7 Hz, 2 H), 8.77 (br t, 1 H, NH). Anal. ($C_{34}H_{37}N_5O_6$) C, H, N.

5-Methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (12). Prepared from **6** (0.47 g, 1 mmol) and 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (**8**; 0.332 g, 1.2 mmol, 1.2 equiv) following the procedure described above to give compound **10**, which on treatment with HCl gave product **12** (0.55 g, 86%). Mp: 180−181 °C. ^{1}H NMR ($CDCl_3$): δ 1.60−1.80 (m, 2 H), 1.85−1.95 (m, 2 H), 2.03−2.10 (m, 2 H), 2.28−2.33 (m, 2 H), 2.35 (s, 3 H), 2.48−2.50 (m, 2 H), 3.20−3.40 (m, 2 H), 3.60 (s, 3 H), 3.68 (s, 3 H), 6.75 (s, 1 H), 7.20−7.34 (m, 6 H), 7.46 (d, J = 8.8 Hz, 2 H), 8.07 (d, J = 8.8 Hz, 2 H), 8.78 (br t, 1 H, NH). Anal. ($C_{30}H_{35}N_5O_8$) C, H, N.

Preparation of (+)-12 and (−)-12. (a) (−)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{*N*-[2-phenylethyl]carboxamido}pyrimidine (13) and (+)-1,6-Dihydro-2-methoxy−5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{*N*-[2-phenylethyl] carboxamido}-pyrimidine (14). To a stirred solution of **6** (2.66 g, 5.6 mmol) in anhydrous THF (80 mL) at room temperature under argon atmosphere was added a solution of (*S*)−(−)-α-methylbenzylamine (0.82 g, 6.78 mmol, 1.2 equiv) in THF (5 mL) and the stirring was continued for 6 h. Solvent was evaporated from the reaction mixture, and the residue was redissolved in CH_2Cl_2 (50 mL). The solution was washed with 5% $NaHCO_3$ (3 × 25 mL) and brine (50 mL) and dried ($MgSO_4$). Solvent was evaporated and the residue was purified by flash chromatography on silica gel using 5−30% EtOAc in hexane as the gradient eluent. The first major product to elute was **13** and this compound was crystallized from isopropyl ether (0.85 g, 34%). Mp: 119−120 °C. $[\alpha]_D = -329$ (c = 1.3, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.47 (d, J = 7 Hz, 3 H), 2.40 (s, 3 H), 3.61 (s, 3 H),

3.95 (s, 3 H), 4.96 (quint, J = 6.5 Hz, 2 H), 6.66 (s, 1 H), 6.82 (d, J = 6.8 Hz, 1 H, NH), 7.22−7.36 (m, 5 H), 7.43 (d, J = 8.6 Hz, 2 H), 8.09 (d, J = 8.6 Hz, 2 H). Anal. ($C_{23}H_{24}N_4O_6$) C, H, N.

The second major compound to elute was **14** and it was crystallized from isopropyl ether (0.92 g, 36%). Mp: 138−140 °C. $[\alpha]_D$ = +172 (c = 1.131, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.47 (d, J = 7 Hz, 3 H), 2.42 (s, 3 H), 3.64 (s, 3 H), 3.91 (s, 3 H), 4.99 (quint, J = 6.5 Hz, 2 H), 6.70 (s, 1 H), 6.81 (d, J = 6.8 Hz, 1 H, NH), 7.22−7.35 (m, 5 H), 7.36 (d, J = 8.6 Hz, 2 H), 8.04 (d, J = 8.6 Hz, 2 H). Anal. ($C_{23}H_{24}N_4O_6$) C, H, N.

(b) (+)-5- Methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl] carboxamido}-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine [(+)-10]. A solution of **14** (0.226 g, 0.5 mmol) and DBU (0.076 g, 0.5 mmol) in CH_2Cl_2 (10 mL) was stirred and refluxed for 4 h and the solvent was evaporated. The residue was purified by column chromatography using 30% EtOAc in hexanes as the eluent to give (+)-**5** (0.120 g, 79%). $[\alpha]_D$ = +14.5° (c = 0.6, CH_2Cl_2).

Compound (+)-**5** (0.12 g, 0.393 mmol) was reacted with 4-nitrophenyl chloroformate (0.095 g, 0.472 mmol) as described earlier. After 2 h, saturated aqueous $NaHCO_3$ solution (10 mL) was added and the stirring continued for 30 min. The two layers were separated, the CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ solution (3 × 5 mL) and dried (Na_2SO_4), and the solvent was evaporated. The residue was redissolved in THF (10 mL) and mixed with K_2CO_3 (0.11 g, 0.8 mmol). To this was added a solution of amine **8** (0.138 g, 0.5 mmol) in THF (5 mL) and the mixture was stirred for 2 h. The solid was removed by filtration and the filtrate was cooled to 0−5 °C. To this was added 6 N HCl (0.5 mL) and the stirring was continued for 3 h. THF was evaporated from the mixture; the residue was redissolved in CH_2Cl_2 (20 mL), washed with 10% $NaHCO_3$ (4 × 5 mL), and dried ($MgSO_4$). Solvent was evaporated and the residue was purified by column chromatography using 1:1 hexanes/EtOAc to 100% EtOAc as gradient eluent. The oily product (+)-**12** was crystallized from hexanes and EtOAc (0.19 g, 82%). Mp: 137−139 °C. $[\alpha]_D$ = +108 (c = 0.665, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.60−1.80 (m, 2 H), 1.85−1.95 (m, 2 H), 2.03−2.10 (m, 2 H), 2.28−2.33 (m, 2 H), 2.35 (s, 3 H), 2.48−2.50 (m, 2 H), 3.20−3.40 (m, 2 H), 3.60 (s, 3 H), 3.68 (s, 3 H), 6.75 (s, 1 H), 7.20−7.34 (m, 5 H), 7.46 (d, J = 8.8 Hz, 2 H), 7.60 (br s, 1 H, N H), 8.07 (d, J = 8.8 Hz, 2 H), 8.78 (br t, 1 H, NH). Anal. ($C_{30}H_{35}N_5O_8 \cdot 0.2CH_2Cl_2 \cdot 0.2EtOAc$) C, H, N.

(−)-5- Methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine [(−)-12]. A solution of **13** (0.35 g, 0.774 mmol) and DBU (0.117 g, 0.774 mmol) in CH_2Cl_2 (10 mL) was stirred and refluxed for 8 h and the solvent evaporated. The crude product was purified by column chromatography using 30% EtOAc in hexanes as the eluent to give 0.152 g of (−)-**5**. This compound upon completion of the sequence of the reactions described above gave (−)-**12** (0.19 g, 64%). Mp: 138−140 °C. $[\alpha]_D$ = −106 (c = 0.395, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.60−1.80 (m, 2 H), 1.85−1.95 (m, 2 H), 2.03−2.10 (m, 2 H), 2.28−2.33 (m, 2 H), 2.35 (s, 3 H), 2.48−2.50 (m, 2 H), 3.20−3.40 (m, 2 H), 3.60 (s, 3 H), 3.68 (s, 3 H), 6.75 (s, 1 H), 7.20−7.34 (m, 6 H), 7.46 (d, J = 8.8 Hz, 2 H), 8.07 (d, J = 8.8 Hz, 2 H), 8.78 (br t, 1 H, NH). Anal. ($C_{30}H_{35}N_5O_8 \cdot 0.4CH_2Cl_2$) C, H, N.

Preparation of Compounds 29−30, and 31. (a) 5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-4-ethyl-2-methoxy-6-(4-nitrophenyl) pyrimidine (18). A mixture of 2-cyanoethyl 3-{(4-nitrophenyl)methylene}-4-oxopentanoate[7] (**16**; 5.00 g, 16.54 mmol), *O*-methylisourea hydrogen sulfate (3.422 g, 19.85 mmol), and $NaHCO_3$ (2.78 g, 33.08 mol) in EtOH (70 mL) was stirred and heated at 85−90 °C for 5 h. The solid was removed by filtration and ethanol was evaporated from the filtrate. The residue was redissolved in EtOAc (300 mL), washed with water (2 × 100 mL), and dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by flash column chromatography on silica gel using $CHCl_3$/methanol (30:1) as the eluent, to give the product **18** as a white solid (2.95 g, 50%). The ^{1}H NMR analysis of the product showed it to be a 5:1 mixture of the amine−imine tautomers and was used as such in the next step.

(b) 5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-4-ethyl-2-methoxy-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (20). Prepared from **18** (2.64 g, 7.36 mmol) and 4-nitrophenyl chloroformate (1.485 g, 7.36 mmol) using a similar procedure described earlier to give the product **20** as a viscous oil (1.70 g, 44%). ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7 Hz, 3 H), 2.61−2.68 (m, 2 H), 2.88−2.92 (m, 2 H), 3.97 (s, 3 H), 4.32 (t, J = 7 Hz, 2 H), 6.34 (s, 1 H), 7.37 (d, J = 9.2 Hz, 2 H), 7.50 (d, J = 8.7 Hz, 2 H), 8.18 (d, J = 8.7 Hz, 2 H), 8.28 (d, J = 9.2 Hz, 2 H).

(c) 5-(2-Cyanoethoxycarbonyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-6-(4-nitrophenyl)−1,2,3,6-tetrahydropyrimidine (23). To a well-stirred mixture of **20** (0.940 g, 2 mmol) and K_2CO_3 (0.552 g, 4 mmol) in anhydrous THF (20 mL) at room temperature under argon atmosphere was added a solution of amine **8** (0.882 g, 3 mmol, 1.5 equiv) in THF (5 mL) and the stirring was continued for 1 h. Solvent was evaporated from the reaction mixture; the residue was redissolved in CH_2Cl_2 (50 mL), washed with 5% $NaHCO_3$ (3 × 25 mL) and brine (50 mL), and dried ($MgSO_4$). Solvent was evaporated and the residue was purified by flash chromatography on silica gel using 10% methanol in EtOAc as the eluent to give 5-(2-cyanoethoxycarbonyl)-1,6-dihydro-4-ethyl-2-methoxy-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]-carboxamido}-6-(4-nitrophenyl)pyrimidine (**21**) as an oil, which on trituration with hexanes and drops of EtOAc became a white powder (1.71 g, 80%). Mp: 62−63 °C. ^{1}H NMR ($CDCl_3$): δ 1.16 (t, J = 7.5 Hz, 3 H), 1.62−1.78 (m, 2 H), 1.80−1.84 (m, 2 H), 2.06−2.18 (m, 2 H), 2.28−2.36 (m, 2 H), 2.50−2.53 (m, 4 H), 2.58−2.63 (m, 2 H), 2.70−2.84 (m, 4 H), 3.25−3.40 (m, 2 H), 3.61 (s, 3 H), 3.92 (s, 3 H), 4.26 (m, 2 H), 6.66 (s, 1 H), 6.82 (br t, 1 H, NH), 7.22−7.33 (m, 6 H), 7.43 (d, J = 7.8 Hz, 2 H), 8.10 (d, J = 7.8 Hz, 2 H). Anal. ($C_{34}H_{40}N_6O_8 \cdot 0.1C_6H_{12} \cdot 0.5H_2O$) C, H, N. This compound upon treatment with aqueous HCl and subsequent workup as described earlier gave product **23**, which was used in the next step without further characterization.

(d) 4-Ethyl-1-{*N*-[3-[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl] carboxamido}-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic Acid (28). To a stirred solution of **23** (4.40 g, 6.8 mmol) in acetone (50 mL) at 0 °C was added aqueous NaOH solution (1 N, 27.2 mL, 4 equiv) dropwise and the stirring was continued until the disappearance of the starting material (1 h). Most of the acetone from the mixture was evaporated under reduced pressure while keeping the temperature at 0 °C and the residue pH was adjusted to 7.0 by the addition of 1 N HCl. The white precipitate of the carboxylic acid **24** formed was filtered and dried under vacuum (3.59 g, 89%). ^{1}H NMR ($CDCl_3$): δ 1.07 (t, J = 7.5 Hz, 3 H), 1.55−1.70 (m, 2 H), 1.72−1.84 (m, 2 H), 1.84−2.15 (m, 2 H), 2.20−2.40 (m, 4 H), 2.70−2.90 (m, 2 H), 3.10−3.40 (m, 4 H), 3.51 (s, 3 H), 6.54 (s, 1 H), 7.18−7.38 (m, 6 H), 7.41 (d, J = 7.8 Hz, 2 H), 8.15 (d, J = 7.8 Hz, 2 H), 8.79 (br t, 1 H, N H), 10.05 (br s, 1 H, COO*H*). This product was used in the next step without further characterization.

(e) 4-Ethyl-5-methoxycarbonyl-1-{*N*-[3-[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (29). A mixture of the carboxylic acid **28** (0.350 g, 0.59 mmol), EDC (0.2264 g, 1.18 mmol, 2 equiv), and DMAP (0.1443 g, 1.18 mmol, 2 equiv) in anhydrous CH_2Cl_2 was stirred at room temperature for 2 h. To this was added methanol (5 mL) and the stirring was continued for 12 h. The reaction mixture was worked-up and purified using a similar process described above to obtain the product **29** as a white powder. Yield: 68%. Mp: 75−77 °C. ^{1}H NMR ($CDCl_3$): δ 1.19 (t, J = 7.5 Hz, 3 H), 1.68−1.73 (m, 2 H), 1.90−2.00 (m, 2 H), 2.03−2.14 (m, 2 H), 2.32 (t, J = 7.1 Hz, 2 H), 2.49−2.53 (m, 2 H), 2.61−2.95 (m, 4 H), 3.22−

3.40 (m, 2 H), 3.61 (s, 3 H), 3.69 (s, 3 H), 6.45 (s, 1H), 7.09−7.35 (m, 5 H), 7.46 (d, J = 7.8 Hz, 2 H), 8.09 (d, J = 7.8 Hz, 2 H), 8.79 (br t, 1 H, NH). Anal. ($C_{31}H_{37}N_5O_8 \cdot 0.7H_2O$) C, H, N.

5-Carboxamido-4-ethyl-1-{*N*-[3-(4-methoxycarbonylphenylpiperidin-1-yl) propyl]carboxamido}-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (30). A mixture of carboxylic acid **28** (0.350 g, 0.59 mmol), EDC (0.2264 g, 1.18 mmol, 2 equiv), and DMAP (0.1443 g, 1.18 mmol, 2 equiv) in anhydrous CH_2Cl_2 was stirred at room temperature for 2 h. To this was added 40% aqueous NH_3 (0.6 mL) and the stirring was continued for 12 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous NH_4Cl solution (3 × 20 mL). Solvent was evaporated after drying over $MgSO_4$ and the residue was purified by column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (500/16/8) as the eluent to obtain the desired product **30** as a pale yellow powder (0.24 g, 69%). mp 107−109 °C. ^{1}H NMR ($CDCl_3$): δ 1.20 (t, J = 7.5 Hz, 3 H), 1.66−1.72 (m, 2 H), 1.79−2.00 (m, 3 H), 2.00−2.20 (m, 2 H), 2.29−2.35 (m, 2 H), 2.42−2.60 (m, 2 H), 2.62−2.82 (m, 3 H), 3.20−3.40 (m, 2 H), 3.60 (s, 3 H), 5.70 (br m, 2 H, NH_2), 6.59 (s, 1 H), 7.20−7.39 (m, 6 H), 7.52 (d, J = 7.8 Hz, 2 H), 8.13 (d, J = 7.8 Hz, 2 H), 8.82 (t, 1 H). Anal. ($C_{30}H_{36}N_6O_7 \cdot 0.8H_2O$) C, H, N.

4-Ethyl-5-(*N*-methylcarboxamido)-1-{*N*-[3-(4-methoxycarbonylphenylpiperidin-1-yl)propyl]carboxamido}-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (31). Prepared from the carboxylic acid **28** and methylamine following a similar procedure described for compound **30**. Yield: 48%. Mp: 160−162 °C. ^{1}H NMR ($CDCl_3$): δ 1.19 (t, J = 7.5 Hz, 3 H), 1.68−1.73 (m, 2 H), 1.90−2.00 (m, 2 H), 2.03−2.14 (m, 2 H), 2.32 (t, J = 7.1 Hz, 2 H), 2.49−2.53 (m, 2 H), 2.61−2.95 (m, 4 H), 2.80 (d, J = 5 Hz, 3 H), 3.22−3.40 (m, 2 H), 3.61 (s, 3 H), 3.69 (s, 3 H), 5.60 (bs, 1 H, NH), 6.50 (s, 1 H), 7.20−7.40 (m, 5 H), 7.46 (d, J = 7.8 Hz, 2 H), 8.09 (d, J = 7.8 Hz, 2 H), 8.79 (br t, 1 H, NH). Anal. ($C_{31}H_{38}N_6O_7Cl \cdot 1.2CH_2Cl_2$) C, H, N.

Preparation of Products 24−27. These products were synthesized using a similar procedure described for **29**−**31**.

5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]-pyrimidine (19). Yield: 68%. ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3 H), 2.67 (t, J = 7 Hz, 2 H), 3.97 (s, 3 H), 4.32 (t, J = 7 Hz, 2 H), 6.34 (s, 1 H), 7.37 (d, J = 9.2 Hz, 2 H), 7.50 (d, J = 8.7 Hz, 2 H), 8.18 (d, J = 8.7 Hz, 2 H), 8.28 (d, J = 9.2 Hz, 2 H).

5-(2-Cyanoethoxycarbonyl)-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (22). Yield: 70%. ^{1}H NMR ($CDCl_3$): δ 2.00−2.10 (m, 2 H), 2.41 (s, 3 H), 2.40−2.95 (m, 10 H), 3.25−3.40 (m, 4 H), 3.62 (s, 3 H), 4.20−4.32 (m, 2 H), 6.71 (s, 1 H), 7.20−7.33 (m, 5 H), 7.49 (d, J = 7.8 Hz, 2 H), 8.08 (d, J = 7.8 Hz, 2 H), 8.70−8.90 (m, 2 H).

1-{*N*-[3-[4-(4-Methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic Acid (24). Yield: 89%. Mp: 195 °C dec. ^{1}H NMR ($CDCl_3$): δ 1.60−2.00 (m, 4 H), 2.00−2.20 (m, 2 H), 2.25 (s, 3 H), 2.49−2.53 (m, 2 H), 2.76−2.80 (m, 4 H), 3.34−3.41 (m, 2 H), 3.61 (s, 3 H), 6.60 (s, 1 H, NH), 7.21−7.40 (m, 5 H), 7.40 (d, J = 7.8 Hz, 2 H), 8.18 (d, J = 7.8 Hz, 2 H), 8.81 (br t, 1 H, NH), 10.02 (bs, 1 H). Anal. ($C_{29}H_{33}N_5O_8 \cdot 1.05CH_2Cl_2$) C, H, N.

5-Ethoxycarbonyl-1-{*N*-[3-[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (25). Yield: 67%. Mp: 76−78 °C. ^{1}H NMR ($CDCl_3$): δ 1.22 (t, J = 7.2 Hz, 3 H), 1.90−2.10 (m, 4 H), 2.31 (t, J = 7.1 Hz, 2 H), 2.35 (s, 3 H), 2.49−2.53 (m, 2 H), 2.76−2.80 (m, 2 H), 3.34−3.41 (m, 2 H), 3.61 (s, 3 H), 4.14 (q, J = 7.1 Hz, 2 H), 6.74 (s, 1 H, NH), 7.21−7.35 (m, 5 H), 7.48 (d, J = 7.8 Hz, 2 H), 8.09 (d, J = 7.8 Hz, 2 H), 8.81 (br t, 1 H, NH). Anal. ($C_{31}H_{37}N_5O_8 \cdot 0.2CH_2Cl_2$) C, H, N.

5-Carboxamido-1-{*N*-[3-[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (26). Yield: 71%. Mp: 202−204 °C. ^{1}H NMR ($CDCl_3$): δ 1.69 (t, J = 6.9 Hz, 2 H), 1.85−1.90 (m, 2 H), 2.03−2.14 (m, 2 H), 2.30 (s, 3 H), 2.48−2.53 (m, 2 H), 2.76−2.81 (m, 2 H), 3.22−3.41 (m, 2 H), 3.45 (s, 3 H), 3.61 (s, 3 H), 5.61 (br s, 2 H, NH), 6.61 (s, 1 H, NH), 7.09−7.34 (m, 5 H), 7.51 (d, J = 7.8 Hz, 2 H), 8.12 (d, J = 7.8 Hz, 2 H), 8.82 (br t, 1 H, NH). Anal. ($C_{29}H_{34}N_6O_7 \cdot 0.3EtOAc$) C, H, N.

1-{*N*-[3-[4-(4-Methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]carboxamido}-4-methyl-5-(*N*-methylcarboxamido)-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (27). Yield: 88%. Mp: 168−170 °C. ^{1}H NMR ($CDCl_3$): δ 1.66−1.71 (m, 2 H), 1.90−1.95 (m, 2 H), 2.03−2.14 (m, 2 H), 2.23 (s, 3 H), 2.32 (t, J = 7.1 Hz, 2 H), 2.49−2.53 (m, 2 H), 2.78−2.81 (m, 4 H), 3.22−3.41 (m, 2 H), 3.64 (s, 3 H), 5.58 (br s, 1 H, NH), 6.56 (s, 1 H, NH), 7.09−7.34 (m, 5 H), 7.47 (d, J = 7.4 Hz, 2 H), 8.09−8.13 (d, J = 7.4 Hz, 2 H), 8.83 (br t, 1 H, NH). Anal. ($C_{30}H_{37}N_6O_7Cl \cdot 1.2CH_2Cl_2$) C, H, N.

(+)-5-Carboxamido-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl) propyl]carboxamido}-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine [(+)-30]. (a) 5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-4-ethyl-2-methoxy-6-(4-nitrophenyl)−1-{*N*-[2-phenylethyl]-carboxamido}pyrimidine (32). To a stirred solution of **20** (17.5 g, 33.43 mmol) in anhydrous THF (200 mL) at room temperature under argon atmosphere was added (*R*)−(+)-α-methylbenzylamine (4.86 g, 40.11 mmol) and the stirring was continued for 16 h. Solvent was evaporated from the reaction mixture and the residue was purified by flash chromatography on silica gel using toluene/EtOAc (20:3) as the eluent. The first major product to elute was **32** as a viscous oil (6.11 g, 36%). $[\alpha]_D$ = +299.5 (c = 1.95, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7 Hz, 3 H), 1.47 (d, J = 7 Hz, 3 H), 2.61 (t, 2 H), 2.7−2.92 (m, 2 H), 3.98 (s, 3 H), 4.20−4.32 (m, 2 H), 4.96 (quint, J = 6.5 Hz, 2 H), 6.66 (s, 1 H), 6.82 (d, J = 6.8 Hz, 1 H, NH), 7.22−7.36 (m, 5 H), 7.45 (d, J = 8.6 Hz, 2 H), 8.11 (d, J = 8.6 Hz, 2 H). The second major compound to elute was **33**, the other diastereomer (5.92 g, 35%). $[\alpha]_D$ = −105.1 (c = 3.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.20 (t, J = 7 Hz, 3 H), 1.48 (d, J = 7 Hz, 3 H), 2.62 (t, 2 H), 2.82 (q, 2 H), 3.94 (s, 3 H), 4.20−4.32 (m, 2 H), 4.96 (quint, J = 6.5 Hz, 2 H), 6.69 (s, 1 H), 6.84 (d, J = 6.8 Hz, 1 H, NH), 7.22−7.36 (m, 5 H), 7.39 (d, J = 8.6 Hz, 2 H), 8.06 (d, J = 8.6 Hz, 2 H).

(b) (+)-5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-4-ethyl-2-methoxy-6-(4-nitrophenyl) pyrimidine [(+)-18]. To a stirred solution of **32** (2.62 g, 5.182 mmol) in toluene (40 mL) was added DBU (0.237, 1.55 mmol) at room temperature and the resulting solution was heated at 90 °C for 3.5 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel using $CHCl_3$/EtOAc (9:1) as the eluent, to give 1.32 g (71%) of (+)-**18**. $[\alpha]_D$ = + 4.0 (c = 3.25, $CHCl_3$).

(c) (+)-5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-4-ethyl-2-methoxy-6-(4-nitrophenyl)−1-[(4-nitrophenyloxy)carbonyl]pyrimidine [(+)-20]. Prepared using a similar procedure described earlier to give the product as a white solid (2.25 g, 95%). ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7 Hz, 3 H), 2.61−2.68 (m, 2 H), 2.88−2.92 (m, 2 H), 3.97 (s, 3 H), 4.32 (t, J = 7 Hz, 2 H), 6.34 (s, 1 H), 7.37 (d, J = 9.2 Hz, 2 H), 7.50 (d, J = 8.7 Hz, 2 H), 8.18 (d, J = 8.7 Hz, 2 H), 8.28 (d, J = 9.2 Hz, 2 H). $[\alpha]_D$ = + 317 (c = 3.9, $CHCl_3$).

(d) (+)-5-(2-Cyanoethoxycarbonyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydro pyrimidine [(+)-23]. Prepared from (+)-**20** (3.60 g, 6.878 mmol) and amine **8** (2.47 g, 8.94 mmol) following a similar procedure described earlier to obtain the desired product as a white powder (4.40 g, 98.5%). ^{1}H NMR ($CDCl_3$): δ 1.23 (t, J = 7.5 Hz, 3 H), 2.0−2.1 (m, 2 H), 2.40−2.95 (m, 12 H), 3.25−3.50 (m, 4 H), 3.65 (s, 3 H), 4.27−4.32 (m, 2 H), 6.64 (s, 1 H), 7.20−7.33 (m, 5 H), 7.49 (d, J = 7.8 Hz, 2 H), 8.08 (d, J = 7.8 Hz, 2 H), 8.70−8.90 (m, 2 H). $[\alpha]_D$ = +112 (c = 2.15, $CHCl_3$). This product was used in the next step without further analysis.

(e) (+)-5-Carboxamido-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl) propyl]carboxamido}-6-(4-

nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine [(+)-30]. To a stirred solution of (+)-**23** (4.40 g, 6.8 mmol) in acetone (50 mL) at 0 °C was added aqueous NaOH solution (1 N, 27.2 mL, 4 equiv) dropwise and the stirring continued until the disappearance of the starting material by TLC (1 h). Most of the acetone from the mixture was evaporated under reduced pressure while maintaining the temperature at 0 °C and the pH of the residue was adjusted to 7.0 by the addition of 1 N HCl. The white precipitate of the carboxylic acid (+)-**28** formed was filtered and dried under vacuum (3.59 g, 89%). ^{1}H NMR ($CDCl_3$): δ 1.07 (t, J = 7.5 Hz, 3 H), 1.55−1.70 (m, 2 H), 1.72−1.84 (m, 2 H), 1.84−2.15 (m, 2 H), 2.20−2.40 (m, 4 H), 2.70−2.90 (m, 2 H), 3.10−3.40 (m, 4 H), 3.51 (s, 3 H), 6.54 (s, 1 H), 7.18−7.38 (m, 6 H), 7.41 (d, J = 7.8 Hz, 2 H), 8.15 (d, J = 7.8 Hz, 2 H), 8.79 (br t, 1 H, N H), 10.05 (br S, 1 H, COO*H*). This product was used in the next step without further characterization.

A mixture of carboxylic acid (+)-**28** (0.350 g, 0.59 mmol), EDC (0.226 g, 1.18 mmol, 2 equiv), and DMAP (0.144 g, 1.18 mmol, 2 equiv) in anhydrous CH_2Cl_2 was stirred at room temperature for 2 h. To this was added 40% aqueous ammonia (0.6 mL) and the stirring was continued for 12 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous NH_4Cl solution (3 × 20 mL). Solvent was evaporated from the dried ($MgSO_4$) CH_2Cl_2 solution and the residue was purified by column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (500/16/8) as the eluent to give (+)-**30** as a pale yellow powder (0.24 g, 69%). Mp: 107−109 °C. ^{1}H NMR ($CDCl_3$): δ 1.20 (t, J = 7.5 Hz, 3 H), 1.66−1.72 (m, 2 H), 1.79−2.00 (m, 3 H), 2.00−2.20 (m, 2 H), 2.29−2.35 (m, 2 H), 2.42−2.60 (m, 2 H), 2.62−2.82 (m, 3 H), 3.20−3.40 (m, 2 H), 3.60 (s, 3 H), 5.70 (br m, 2 H, NH_2), 6.59 (s, 1 H), 7.20−7.39 (m, 6 H), 7.52 (d, J = 7.8 Hz, 2 H), 8.13 (d, J = 7.8 Hz, 2 H), 8.82 (t, 1 H). $[\alpha]_D$ = +115.7 (c = 1.4, $CHCl_3$). Anal. ($C_{30}H_{36}N_6O_7 \cdot 0.8H_2O$) C, H, N.

Preparation of Compounds 77−85. These compounds were prepared using the general procedure described for **83**. Some final products were characterized as free bases and the rest of them were characterized as their HCl salts.

5-Methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-6-(4-methylphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (77). (a) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-methylphenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (60). Yield: 63%. ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3 H), 2.50 (s, 3 H), 3.72 (s, 3 H), 3.98 (s, 3 H), 6.38 (s, 1 H), 7.24−7.60 (m, 6 H), 8.26−8.34 (d, J = 7 H, 2 H).

(b) 77. Yield: 93%. Mp: 43−46 °C. ^{1}H NMR ($CDCl_3$): δ 1.62−1.78 (m, 4 H), 1.90−2.04 (m, 2 H), 2.04−2.16 (m, 2 H), 2.30 (s, 3 H), 2.30−2.36 (m, 2 H), 2.39 (s, 3 H), 2.50−2.58 (m, 2 H), 2.78−2.88 (m, 2 H), 3.24−3.44 (m, 2 H), 3.64 (s, 3 H), 3.70 (s, 3 H), 6.48 (s, 1 H), 6.78 (s, 1 H), 7.05−7.40 (m, 9 H), 8.82 (b t, 1 H, NH). Anal. ($C_{31}H_{38}N_4O_6 \cdot 0.5C_4H_8O_2$) C, H, N.

5-Methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-6-(3-methylphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (78). (a) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(3-methylphenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (61). Yield: 62%. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 2.50 (s, 3 H), 3.70 (s, 3 H), 3.98 (s, 3 H), 6.38 (s, 1 H), 7.24−7.60 (m, 6 H), 8.26−8.34 (d, J = 7 H, 2 H).

(b) 78 HCl. Yield: 73%. Mp: 130−135 °C. ^{1}H NMR ($CDCl_3$): δ 1.62−1.78 (m, 4 H), 1.90−2.04 (m, 2 H), 2.04−2.16 (m, 2 H), 2.30 (s, 3 H), 2.30−2.36 (m, 2 H), 2.39 (s, 3 H), 2.50−2.58 (m, 2 H), 2.78−2.88 (m, 2 H), 3.24−3.44 (m, 2 H), 3.64 (s, 3 H), 3.70 (s, 3 H), 6.48 (s, 1 H), 6.78 (s, 1 H), 7.05−7.40 (m, 9 H), 8.82 (b t, 1 H, NH). Anal. ($C_{31}H_{39}N_4O_6Cl$) C, H, N.

6-(4-Chlorophenyl)-5-methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (79). (a) 6-(4-Chlorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl−1-[(4-nitrophenyloxy)carbonyl]pyrimidine (62). Yield: 63%. ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3 H), 3.72 (s, 3 H), 3.98 (s, 3 H), 6.38 (s, 1 H), 7.24−7.41 (m, 6 H), 8.26−8.34 (m, 2 H).

(b) 79. Yield: 84%. Mp: 65−68 °C. ^{1}H NMR ($CDCl_3$): δ 1.66−1.75 (m, 2 H), 1.90−2.18 (m, 4 H), 2.30−2.44 (m, 5 H), 2.50−2.62 (m, 2 H), 2.80−2.90 (m, 2 H), 3.25−3.44 (m, 2 H), 3.65 (s, 3 H), 3.73 (s, 3 H), 6.70 (s, 1 H), 7.15−7.48 (m, 8 H), 8.81 (b t, 1 H, NH). Anal. ($C_{30}H_{35}N_4O_6Cl$) C, H, N.

6-(3-Chlorophenyl)-5-methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (80). (a) 6-(3-Chlorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl−1-[(4-nitrophenyloxy)carbonyl]pyrimidine (63). Yield: 50%. ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3 H), 3.68 (s, 3 H), 3.95 (s, 3 H), 6.25 (s, 1 H), 6.92−8.30 (m, 8 H).

(b) 80 HCl. Yield: 88%. Mp: 132−136 °C. ^{1}H NMR (CD_3OD): δ 1.90−2.12 (m, 4 H), 2.38 (s, 3 H), 2.78−2.91 (m, 2 H), 2.94−3.14 (m, 4 H), 3.30−3.40 (m, 2 H), 3.50−3.60 (m, 2 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 6.60 (s, 1 H), 7.20−7.52 (m, 9 H). Anal. ($C_{30}H_{36}N_4O_6Cl_2$) C, H, N.

6-(4-Fluorophenyl)-5-methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (81). (a) 6-(4-Fluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (64). Yield: 68%. ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3 H), 3.68 (s, 3 H), 3.95 (s, 3 H), 6.25 (s, 1 H), 6.92−8.30 (m, 8 H).

(b) 81 HCl. Yield: 84%. Mp: 140−144 °C. ^{1}H NMR (CD_3OD): δ 1.90−2.12 (m, 4 H), 2.38 (s, 3 H), 2.78−2.91 (m, 2 H), 2.94−3.14 (m, 4 H), 3.30−3.40 (m, 2 H), 3.50−3.60 (m, 2 H), 3.62 (s, 3 H), 3.66 (s, 3 H), 6.94−7.52 (m, 9 H). Anal. ($C_{30}H_{36}N_4O_6ClF$) C, H, N.

6-(3-Fluorophenyl)-5-methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (82). (a) 6-(3-Fluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl−1-[(4-nitrophenyloxy)carbonyl]pyrimidine (65). Yield: 46%. ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3 H), 3.66 (s, 3 H), 3.85 (s, 3 H), 6.30 (s, 1 H), 6.92−7.30 (m, 3 H), 7.35 (d, J = 7 Hz, 2 H), 7.50 (d, J = 6.8 Hz, 1 H), 8.20 (d, J = 7 Hz, 2 H).

(b) 82 HCl. Yield: 83%. Mp: 120−124 °C. ^{1}H NMR (CD_3OD): δ 1.92−2.18 (m, 4 H), 2.38 (s, 3 H), 2.82−2.92 (m, 2 H), 2.95−3.18 (m, 4 H), 3.35−3.42 (m, 2 H), 3.50−3.68 (m, 2 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 6.60 (s, 1 H), 6.95−7.52 (m, 9 H). Anal. ($C_{30}H_{36}N_4O_6ClF \cdot 0.25C_6H_{14}$) C, H, N.

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (83). (a) Methyl 2-{(3,4-Difluorophenyl)methylene}-3-oxobutyrate (50). A mixture of 3,4-difluorobenzaldehyde (**41**; 14.2 g, 0.1 mol), methyl acetoacetate (**34**; 12.2 g, 0.105 mol), piperidine (0.430 g, 5 mmol), and acetic acid (0.30 g, 5 mmol) in benzene (150 mL) was stirred and refluxed with a Dean−Stark trap for 8 h. Benzene was evaporated; the residue was dissolved in EtOAc (200 mL) and washed with brine (50 mL), saturated $KHSO_4$ solution (50 mL), and saturated $NaHCO_3$ solution in sequence. The EtOAc solution was dried ($MgSO_4$), solvent evaporated under reduced pressure, and the residue purified by column chromatography on silica gel (EtOAc/hexanes, 10−15%). The product **50** was obtained as a yellow oil (0.98 g, 98%) and was used in the next step without any further characterization.

(b) 6-(3,4-Difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine (57). A mixture of **50** (8.8 g, 36.6 mmol), *O*-methylisourea hydrogen sulfate (9.4 g, 55 mmol), and $NaHCO_3$ (12.3 g, 0.146 mol) in DMF (30 mL) was stirred and heated at 70 °C for 16 h. The mixture was cooled, diluted with EtOAc (300 mL), washed with water (5 × 300 mL) and brine (300 mL), and dried ($MgSO_4$). Solvent was evaporated and the crude product was purified by flash column chromatography on silica gel using 10−20% EtOAc in hexanes as the gradient eluent, to leave the product **57** as an oil (3.82 g, 30%). ^{1}H NMR ($CDCl_3$): δ 2.32, 2.39 (2 s, 3 H), 3.58, 3.64 (2 s, 3 H), 3.72, 3.85 (2 s, 3 H), 5.55 (s, 1 H), 6.13−7.80 (m, 4 H).

(c) 6-(3,4-Difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl−1-[(4-nitrophenyloxy)carbonyl]pyrimidine (65). To a solution of **57** (2.82 g, 9.52 mmol) and DMAP (1.16 g, 9.52 mmol) in CH_2Cl_2 (50 mL), at 0−5 °C, was added 4-nitrophenyl chloroformate (1.82 g, 9.04 mmol) and the mixture was allowed to warm to room temperature. After 12 h, solvent was evaporated and the residue was purified by flash column chromatography (SiO_2, EtOAc/hexanes, 10−15%) to obtain the product **65** as white crystals (3.72 g, 85%), mp 172−174 °C. ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 3 H), 3.72 (s, 3 H), 3.97 (s, 3 H), 6.26 (s, 1 H), 7.00−7.30 (m, 3 H), 7.38 (d, J = 9.3 Hz, 2 H), 8.32 (d, J = 9.3 Hz, 2 H).

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (83). Prepared from **65** and amine **8** using a similar procedure described earlier followed by treatment with HCl. Yield: 97%. Mp: 130−134 °C. ^{1}H NMR (CD_3OD): δ 1.92−2.16 (m, 4 H), 2.38 (s, 3 H), 2.82−3.20 (m, 6 H), 3.35−3.68 (m, 4 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 6.60 (s, 1 H), 7.08−7.48 (m, 8 H). Anal. ($C_{30}H_{35}N_4O_6F_2Cl\cdot0.25H_2O$) C, H, N.

6-(2,4-Difluorophenyl)-5-methoxycarbonyl-1-{*N*-[3-[4-(4-methoxycarbonyl)-4-phenylpiperidin-1-yl]propyl]-carboxamido}-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (84). (a) 6-(2,4-Difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl−1-[(4-nitrophenyloxy)carbonyl]pyrimidine (66). Yield: 14%. ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 3 H), 3.72 (s, 3 H), 4.00 (s, 3 H), 6.60 (s, 1 H), 6.80−7.20 (m, 3 H), 7.40 (d, J = 9.3 Hz, 2 H), 8.34 (d, J = 9.3 Hz, 2 H).

(b) 84 HCl. Yield: 93%. Mp: 115−118 °C. ^{1}H NMR (CD_3OD): δ 1.92−2.14 (m, 4 H), 2.38 (s, 3 H), 2.82−2.92 (m, 2 H), 2.95−3.18 (m, 4 H), 3.35−3.42 (m, 2 H), 3.58−3.68 (m, 2 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 6.66 (s, 1 H), 7.27−7.90 (m, 8 H). Anal. ($C_{31}H_{36}N_4O_7F_2\cdot1.25C_3H_6O$) C, H, N.

6-(Benzofurazan-5-yl)-5-methoxycarbonyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (85). (a) 6-(Benzofurazan-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl−1-[(4-nitrophenyloxy)carbonyl]-pyrimidine (67). Yield: 89%. Mp: 180−183 °C. ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3 H), 3.75 (s, 3 H), 3.98 (s, 3 H), 6.37 (s, 1 H), 7.40 (d, J = 9.3 Hz, 2 H), 7.52 (d, J = 9.0 Hz, 1 H), 7.68 (s, 1 H), 7.84 (d, J = 9.0 Hz, 1 H), 8.32 (d, J = 9.3 Hz, 2 H).

(b) 85 HCl. Yield: 92%. Mp: 183−185 °C. ^{1}H NMR (CD_3OD): δ 1.92−2.14 (m, 4 H), 2.38 (s, 3 H), 2.82−2.92 (m, 2 H), 2.95−3.18 (m, 4 H), 3.35−3.42 (m, 2 H), 3.58−3.68 (m, 2 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 6.70 (s, 1 H), 7.27−7.90 (m, 8 H). Anal. ($C_{30}H_{35}N_6O_7Cl\cdot0.25\ H_2O$) C, H, N.

(+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine [(+)-103]. (a) Benzyl 3-[(3,4-Difluorophenyl)methylene]-4-oxopentanoate (87). A solution of benzyl propionylacetate (**86**; 36.3 g, 176 mmol), 3,4-difluorobenzaldehyde (**41**; 25.0 g, 176 mmol), piperidine (0.86 mL, 9.0 mmol), and acetic acid (0.49 mL, 9.0 mmol) were refluxed with removal of water using Dean−Stark apparatus for 5 h. The solvent was removed under vacuum and the residue was dissolved in EtOAc. It was washed with water (100 mL) followed by brine (100 mL) and dried (Na_2SO_4). Solvent was evaporated to get pale yellow syrup (60.2 g). It was used in the next step without further purification.

(b) 5-(Benzyloxycarbonyl)-6-(3,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxypyrimidine (89). A suspension of **87** (16.0 g, 48.0 mmol), *O*-methylisourea hydrogen sulfate (16.65 g, 97 mmol), and $NaHCO_3$ (16.3 g, 130 mmol) in DMF (190 mL) was stirred at 70 °C for 20 h. After cooling to room temperature, the mixture was filtered and the filtrate was diluted with EtOAc (300 mL), then washed with water (4 × 100 mL) and brine (200 mL), and dried (Na_2SO_4). After removal of solvents, the residue was purified by column chromatography (SiO_2, EtOAc/hexanes, 10−30%) to get **89** as a colorless oil (10.6 g, 58%). The ^{1}H NMR analysis showed it to be a mixture of amine/imine tautomers and was used in the next step without further characterization.

(c) 5-(Benzyloxycarbonyl)-6-(3,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxy-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (91). To a well-stirred solution of **89** (17.0 g, 44 mmol) and DMAP (6.99 g, 57 mmol) in CH_2Cl_2 (200 mL) was added a powder of 4-nitrophenyl chloroformate (11.54 g, 57 mmol) at room temperature. The reaction mixture was stirred for 12 h and then the solvent was removed in vacuum. The residue was purified by chromatography (SiO_2, EtOAc/hexanes 10−30%) to get **91** as a colorless viscous oil (12.6 g, 50%). ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7.2 Hz, 3 H), 2.81−2.98 (m, 3 H), 3.97 (s, 3 H), 5.14 (AB_q, d_A= 5.08, d_B= 5.20, J = 12.3 Hz, 2 H), 6.28 (s, 3 H), 7.03−7.29 (m, 8 H), 7.35 (d, J = 9.2 Hz, 2 H), 8.26 (d, J = 9.2 Hz, 2 H).

(d) 5-(Benzyloxycarbonyl)-6-(3,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxy-1-{*N*-[2-phenylethyl]-carboxamido}pyrimidine (92). To a stirred mixture of **91** (12.6 g, 22.86 mmol) in THF (150 mL) was added a solution of (*R*)−(+)-α-methylbenzylamine (3.53 mL, 27.44 mmol) at room temperature. The stirring was continued for 12 h and the solvent was evaporated under vacuum. The yellow residue was dissolved in $CHCl_3$ (200 mL) and washed with 10% K_2CO_3 solution (2 × 30 mL). The organic layer was dried (Na_2SO_4) and solvent was evaporated under vacuum. The resulting mixture of diastereomers was separated by column chromatography over silica gel with hexanes:ether (9:1 to 4:1). First major product to elute was **92** as a colorless oil (3.8 g, 60%). $[\alpha]_D$ = + 267 (c = 0.76, $CHCl_3$). ^{1}H NMR: δ 1.22 (t, J = 7.5 Hz, 3 H), 1.52 (d, J = 6.9 Hz, 3 H), 2.88 (q, J = 6.0 Hz, 2 H), 3.99 (s, 3 H), 4.99 (m, 1 H), 5.09 (AB_q, d_A= 5.00, d_B= 5.19, J = 12.6 Hz, 2 H), 6.66 (s, 1 H), 6.99−7.36 (m, 13 H). Second major product to elute was (−)-5-(benzyloxycarbonyl)-6-(3,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxy-1-{*N*-[2-phenylethyl]carboxamido}pyrimidine (**93**) (3.2 g, 51.2%). $[\alpha]_D$ = −146.89 (c = 0.38, $CHCl_3$). ^{1}H NMR($CDCl_3$): δ 1.22 (t, J = 7.2 Hz, 3 H), 1.49 (d, J = 6.6 Hz, 3 H), 2.88 (q, J = 6.0 Hz, 2 H), 3.94 (s, 3 H), 5.03 (m, 1 H), 5.11 (AB_q, d_A = 5.02, d_B = 5.19, J = 12.6 Hz, 2 H), 6.68 (s, 1 H), 6.91−7.34 (m, 13 H).

(e) (+)-5-(Benzyloxycarbonyl)-6-(3,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxypyrimidine [(+)-89]. To a stirred solution of **92** (1.83 mmol, 1.0 g) in toluene (10 mL) was added DBU (0.81 mmol, 0.12 mL) at room temperature and the resulting solution was refluxed for 5 h and then stirred for 12 h at room temperature. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with 3:1 EtOAc/hexanes as the eluting system to give (+)-**89** (0.56 g, 77%).

(f) (+)-5-(Benzyloxycarbonyl)-6-(3,4-diflurophenyl)-1,6-dihydro-4-ethyl-2-methoxy-1-[(4-nitrophenyloxy)carbonyl]pyrimidine [+-(91)]. To a well-stirred solution of (+)-**89** (17.0 g, 44.04 mmol) and DMAP (6.99 g, 57.25 mmol) in CH_2Cl_2 (200 mL) was added a powder of 4-nitrophenyl chloroformate (11.54 g, 57.25 mmol) at room temperature. The reaction mixture was stirred for 12 h and then the solvent was evaporated under vacuum. The residue was purified by chromatography (SiO_2, EtOAc/hexanes 10−30%) to get (+)-**91** as a colorless viscous oil (19.3 g, 76%).

(g) (+)-5-(Benzyloxycarbonyl)-6-(3,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine [(+)-99]. To a stirred mixture of (+)-**91** (0.55 g, 1.12 mmol) in THF (5 mL) was added a solution of 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (**8**; 0.31 g, 1.12 mmol) in THF (5 mL) at room temperature. The stirring was continued for 12 h. A solution of 10% HCl in water (2 mL) was added and stirred for 2 h. The solvent was then evaporated under vacuum and the residue was extracted with ethyl acetate (3 × 10 mL). It was washed with 10% aq KOH solution and dried (Na_2SO_4) and solvent was evaporated under vaccum to obtain (+)-**99** as a white foam (0.73 g, 96.6%), the purity of which was characterized as its HCl salt. Anal. ($C_{37}H_{41}ClF_2N_4O_6\cdot0.5CHCl_3$) C, H, N.

(h) 6-(3,4-Difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic Acid [(+)-101]. To a suspension of 10% Pd−C (0.14 g, 20% by wt) in MeOH (3 mL) was added the solution of (+)-**99** at room temperature with constant stirring. A balloon filled with H_2 was attached and the reaction mixture was stirred for 48 h. The black suspension was filtered through a pad of Celite and the filtrate was concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 10% MeOH in EtOAc) to obtain (+)-**101** as a white solid. mp 184−186 °C. $[\alpha]_D$ = + 142 (c = 0.25, $CHCl_3$). Anal. ($C_{30}H_{35}ClF_2N_4O_6 \cdot 0.3CHCl_3$) C, H, N.

(i) (+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine [(+)-103]. To a solution of carboxylic acid (+)-**101** (0.22 g, 0.375 mmol) in CH_2Cl_2 (3 mL) were added DMAP (0.14 g, 1.12 mmol) and EDC (0.21 g, 1.12 mmol) under argon and the resulting solution was stirred at room temperature for 2 h. To this was then added saturated NH_4OH (0.3 mL) and the solution was stirred for 48 h. The solution was washed with water (5 mL) and dried over (Na_2SO_4). The solvent was evaporated under vacuum and the residue was purified by column chromatography (SiO_2, 10% MeOH in $CHCl_3$) to obtain (+)-**103** as a white solid (0.1 g, 45%). HCl salt mp 136−138 °C. $[\alpha]_D$ = +111.44 (c = 0.18, MeOH). ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7.5 Hz, 3 H), 1.60−1.75 (m, 2 H), 1.92−2.10 (m, 2 H), 2.33 (t, J = 6.6 Hz, 2 H), 2.44−2.52 (m, 2 H), 2.53−2.84 (m, 4 H), 3.27−3.32 (m, 2 H), 3.60 (s, 3 H), 5.60 (br s, 2 H), 6.47 (s, 1 H), 7.05−7.33 (m, 8 H), 8.80 (br t, 1 H). Anal. ($C_{30}H_{35}ClF_2N_4O_6 \cdot 1.0CHCl_3$) C, H, N.

(+)-5-Carboxamido-6-(2,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine [(+)-104]. (a) Benzyl 3-[(2,4-Difluorophenyl)methylene]-4-oxopentanoate (88). Prepared from benzyl propionylacetate (157 g, 0.758 mol) and 2,4-difluorobenzaldehyde (107.65 g, 0.758 mol) following a similar procedure described above (251 g).

(b) 5-(Benzyloxycarbonyl)-6-(2,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxypyrimidine (90). Prepared using a similar procedure described above and the product was obtained as a pale yellow oil (39 g, 42%).

(c) 5-(Benzyloxycarbonyl)-6-(2,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxy-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (94). Prepared from **90** (22.5 g, 59.3 mmol) and 4-nitrophenyl chloroformate (15.3 g, 75.8 mmol) using a similar procedure described above to give the product as a viscous oil (32.0 g, 98%). ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7.2 Hz, 3 H), 2.81−3.00 (m, 2 H), 4.00 (s, 3 H), 5.14 (AB_q, d_A = 5.08, d_B = 5.16, J = 12.3 Hz, 2 H), 6.59 (s, 1 H), 6.75−6.81 (m, 2 H), 7.18−7.40 (m, 8 H), 8.28 (d, J = 9.0 Hz, 2 H).

(d) 5-(Benzyloxycarbonyl)-6-(2,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxy-1-{*N*-[2-phenylethyl]carboxamido}pyrimidine (95). To a stirred solution of **94** (32 g, 58.17 mmol) in CH_2Cl_2 (200 mL) was added (*R*)−(+)-α-methylbenzylamine (9.16, 75.6 mmol) at room temperature and the stirring was continued for 12 h. The mixture was diluted with CH_2Cl_2 (200 mL) and washed with 0.5 N NaOH solution (2 × 60 mL). The organic layer was dried (Na_2SO_4) and filtered and solvent evaporated. The resulting mixture of diastereomers was separated by column chromatography (SiO_2, 3% EtOAc in toluene). The first major product to elute was **95** (12.15 g, 38%). $[\alpha]_D$ = + 214 (c = 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.5 Hz, 3 H), 1.43 (d, J = 7 Hz, 3 H), 2.78 (q, J = 6.0 Hz, 2 H), 3.97 (s, 3 H), 4.99 (m, 1 H), 5.09 (AB_q, d_A = 5.00, d_B = 5.19, J = 12.6 Hz, 2 H), 6.76 (s, 1 H), 6.66−7.40 (m, 13 H). The second major product to elute was the other diastereomer **96** and no effort was made to isolate it.

(e) (+)-5-(Benzyloxycarbonyl)-6-(2,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxypyrimidine [(+)-90]. Prepared from **95** (11.15 g, 20.41 mmol) using a similar procedure described earlier to give (+)-**90** as a viscous oil (6.15 g, 78%). $[\alpha]_D$ = + 296 (c = 1.07 g, $CHCl_3$).

(f) (+)-5-(Benzyloxycarbonyl)-6-(2,4-difluorophenyl)-1,6-dihydro-4-ethyl-2-methoxy-1-[(4-nitrophenyloxy)carbonyl]pyrimidine [(+)-94]. Prepared from (+)-**90** (4.1 g, 10.62 mmol) following a similar procedure described earlier (5.37 g, 92%).

(g) (+)-5-(Benzyloxycarbonyl)-6-(2,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine [(+)-100]. Prepared from (+)-**94** (0.55 g, 1.12 mmol) and 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (**8**; 0.31 g, 1.12 mmol) followed by treatment with HCl, using a similar procedure described earlier. Yield: 99%. Mp: 50−54 °C. $[\alpha]_D$ = +109 (c = 0.98, $CHCl_3$).

(h) 6-(2,4-Difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic Acid [(+)-102]. Prepared using a similar procedure described earlier for (+)-**102**. Yield: 97%. Mp: 145 °C dec. $[\alpha]_D$ = +148 (c = 1.1, $CHCl_3$).

(+)-5-Carboxamido-6-(2,4-difluorophenyl)-4-ethyl-1-{*N*-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-2-oxo-1,2,3,6-tetrahydropyrimidine [(+)-104]. Prepared from (+)-**102** (0.22 g, 0.375 mmol) using a similar procedure described earlier. Yield: 58%. Mp: 72−76 °C. $[\alpha]_D$ = +131.7 (c = 0.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7.5 Hz, 3 H), 1.60−1.75 (m, 2 H), 1.95−2.0 (m, 2 H), 2.00−2.20 (m, 2 H), 2.30 (t, J = 6.6 Hz, 2 H), 2.44−2.60 (m, 2 H), 2.58−2.84 (m, 4 H), 3.27−3.35 (m, 2 H), 3.60 (s, 3 H), 6.00 (br s, 2 H), 6.55 (s, 1 H), 6.70−6.90 (m, 2 H), 7.05−7.33 (m, 6 H), 8.50 (s, 1 H), 8.85 (br t, 1 H, NH). ($C_{30}H_{35}ClF_2N_4O_6 \cdot 0.9\ CHCl_3$) C, H, N.

Biological Methods. Binding Assays: Equilibrium competition binding assays were performed in membrane preparations from cells lines expressing the recombinant human, rat, and dog[25] α_1 adrenoceptors using [^{3}H]prazosin as ligand as described elsewhere.[6,10] The affinities at the L-type calcium channel were determined from the displacement of [^{3}H]-nitrendipine from rat brain membrane preparations.[30] Binding affinities (K_i) at the human α_{2a}, α_{2b}, and α_{2c} adrenoceptors, histamine H_1 and H_2, and 5HT 1A, 1B, 1D, and 2A receptors were determined by radioligand competition binding assays in membrane preparations of cells expressing the human recombinant receptors, as described elsewhere.[31−36] All K_i values are ±5% SE or less for n > 2. In cases where n = 2, both K_i values are within 2-fold of each other and the values shown are the average of the two experiments.

Functional α_1 Antagonism in Isolated Rat, Dog, and Human Prostate Tissues: Assays were performed using phenylephrine (rat and dog prostates) or A61603[37] (human prostate) as the agonists, and K_b values were determined as described previously.[38]

[^{3}H]Prazosin/[^{125}I]HEAT Binding in Human and Dog Prostate Membranes: Competition binding assays in human prostate membrane preparations were performed using [^{3}H]-prazosin and in rat and dog prostate membranes using [^{125}I]-HEAT as described previously.[7,29]

In Vitro Metabolism Experiments: The in vitro metabolism was studied using suspensions of freshly isolated hepatocytes and microsomal preparations from rat, dog, and human. The compounds were incubated with liver microsomal protein and NADPH for 60 min. Following centrifugation, the supernatant was dried, reconstituted with 30% acetonitrile, and analyzed by electrospray LC−MS/MS.

In Situ Rat Prostate Experiment: Male Sprague−Dawley rats (300−400 g) were anesthetized with urethane and placed on a thermostatically controlled heating pad to maintain rectal temperature at 37 °C. A short piece of PE 205 tubing was placed through a small incision in the trachea to facilitate breathing, and the left femoral vein was cannulated for drug administration. The prostate was exposed through a midline incision, freed from adherent connective tissue, and the bladder neck suture was placed through the rear aspect

and secured to the tail. The anterior portion of the prostate was attached to a force transducer, and a resting tension of 2 g was applied to the tissue. Animals were pretreated with atropine (1 mg/kg) and prolanolol (1 mg/kg). Preliminary experiments demonstrated that responses to phenylephrine (10 μg/kg) and (*R*)-A-61603[30] (30 ng/kg) were stable for at least 5 h. For AD_{50} (dose of an antagonist to produce 50% inhibition) determinations, animals were treated with rising noncumulative doses of antagonist at 20-min intervals. Agonist was administered 5 min after each antagonist dose. AD_{50} values were determined with GraphPad Prism. In the duration of action studies, agonist was administered 5 min following antagonist and every 30 min thereafter for up to 4 h.

In Vivo Functional Assays: Male mongrel dogs (9−14 kg) were anesthetized with pentobarbital sodium (35 mg/kg, iv plus 4−5 mg/kg/h iv infusion). The dogs were intubated and ventilated with room air using a Harvard instruments positive displacement large animal ventilator. Polyethylene catheters were placed in the aorta via the femoral artery and vena cava via the femoral veins (two catheters, one in each vein) for the measurement of arterial pressure and the administration of drugs, respectively. A Millar microtip pressure transducer was advanced into the urethra via the bladder dome and positioned so that the tip of the transducer was in the prostatic urethra. The position of the catheter was verified by gently squeezing the prostate and noting the large change in urethral pressure. The catheter was held in position by ligatures at the bladder dome, bladder neck, and distal urethra. Phenylephrine, an α_1 adrenergic agonist, was administered intravenously (0.1−300 mg/kg, bolus) in order to construct control dose−response curves for changes in intraurethral pressure (IUP) and diastolic blood pressure (DBP). Inhibition of phenylephrine dose−response curves by successive doses of antagonist (30, 100, 300 mg/kg, iv) was determined for both IUP and DBP. The potency is given as the K_b (μg/kg) as determined by the method of Arunlaksana and Schild.[39] Relative selectivity was calculated as the ratio of DBP and IUP K_b values.

Pharmacokinetic Assays: Male Sprague−Dawley rats (0.2−0.25 kg) and male beagle dogs (ca. 8 kg) were dosed with 1−3 mg/kg iv and 3−10 mg/kg oral doses (3−4 animals), and the plasma samples were analyzed from 0.08−24 h, using standard protocols either by radioreceptor assay or by LC−MS/MS quantification. Computation of pharmacokinetic parameters was performed with the aid of TOPFIT software.

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