In Vitro and in Vivo Evaluation of Dihydropyrimidinone C-5 Amides as Potent and Selective α_{1A} Receptor Antagonists for the Treatment of Benign Prostatic Hyperplasia

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α_1 Adrenergic receptors mediate both vascular and lower urinary tract tone, and α_1 receptor antagonists such as terazosin (**1b**) are used to treat both hypertension and benign prostatic hyperplasia (BPH). Recently, three different subtypes of this receptor have been identified, with the α_{1A} receptor being most prevalent in lower urinary tract tissue. This paper explores 4-aryldihydropyrimidinones attached to an aminopropyl-4-arylpiperidine via a C-5 amide as selective α_{1A} receptor subtype antagonists. In receptor binding assays, these types of compounds generally display K_i values for the α_{1a} receptor subtype <1 nM while being greater than 100-fold selective versus the α_{1b} and α_{1d} receptor subtypes. Many of these compounds were also evaluated in vivo and found to be more potent than terazosin in both a rat model of prostate tone and a dog model of intra-urethral pressure without significantly affecting blood pressure. While many of the compounds tested displayed poor pharmacokinetics, compound **48** was found to have adequate bioavailability (>20%) and half-life (>6 h) in both rats and dogs. Due to its selectivity for the α_{1a} over the α_{1b} and α_{1d} receptors as well as its favorable pharmacokinetic profile, **48** has the potential to relieve the symptoms of BPH without eliciting effects on the cardiovascular system.

Introduction

Benign prostatic hyperplasia (BPH) is the progressive enlargement of the prostate gland. This condition is estimated to affect at least 50% of males over the age of 60 in the United States, an incidence that increases to greater than 85% by the age of 80.[1] The resulting symptoms of urinary obstruction (e.g. slow urinary stream, hesitancy, and large residual urine volume) are a result of two components, mechanical and dynamic. The mechanical component is due to increased prostatic mass, which has been attributed to 5α-dihydrotestosterone.[2] The enzyme responsible for conversion of testosterone to 5α-dihydrotestosterone is 5α-reductase, and inhibitors of this enzyme such as finasteride (**1a**) have been clinically proven to reduce the size of the prostate and alleviate symptoms of BPH in some patients.[3]

The dynamic component of BPH is attributed to endogenous adrenergic tone which also restricts flow through the urethra.[2] It has been demonstrated that adrenergic receptor antagonists, specifically α_1 receptor antagonists such as terazosin (**1b**), can also relieve symptoms of BPH by relaxing lower urinary tract tissue, thus reducing prostatic and urethral tone. These agents were initially developed for treatment of hypertension, thus when used for treating BPH may display undesired hypotensive side effects[4] (Figure 1).

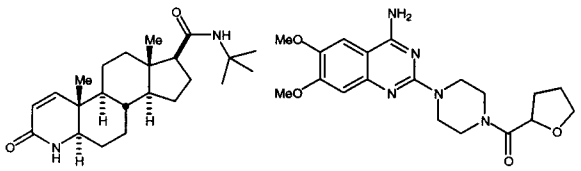

Figure 1. Approved pharmaceutical agents commonly employed for treatment of BPH.

Recently, three subtypes of α_1 receptors, α_{1A}, α_{1B}, and α_{1D}, have been identified.[5] These subtypes have different tissue distributions with the α_{1A} receptors predominating in lower urinary tract tissue, whereas this receptor subtype is less prevalent in the vasculature.[6] Therefore, agents that selectively block α_{1A} receptors over α_{1B} and α_{1D} should display a better therapeutic profile, especially in terms of cardiovascular effects. Tamsulosin (**1c**) is currently being marketed for BPH as the first "prostate selective" α_1 antagonist, and clinical data suggests that it has a better therapeutic index relative to terazosin.[7]

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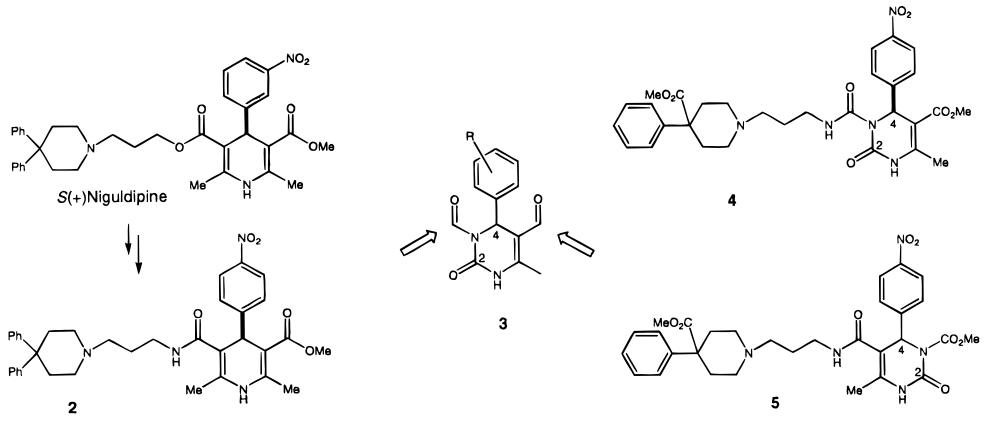
Scheme 1



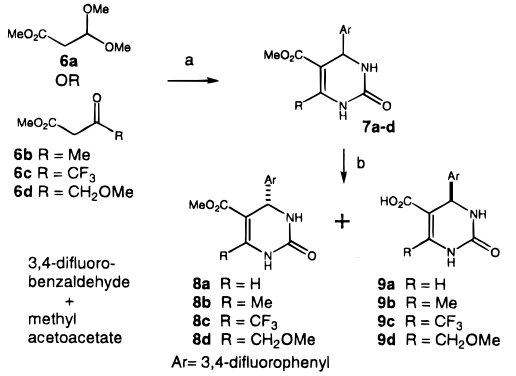
Soon after the cloning and expression of the three different α_1 receptor subtypes, the calcium channel blocker niguldipine (Scheme 1) was shown to be a potent antagonist of the α_{1a} receptor subtype with greater than 100-fold selectivity vs the other α_1 receptor subtypes. Several modifications of the niguldipine structure afforded **2** which maintained potency and selectivity vs the other α receptor subtypes but had attenuated calcium channel activity.[8] In analogy to previous work with calcium channel blockers,[9] the central heterocycle could be converted from the symmetrical 1,4-dihydropyridine to a dihydropyrimidinone (DHP, **3**), and this modification offers two logical sites of attachment of the piperidine containing side chain. The first is at N-3 of the DHP, exemplified by **4**, and compounds containing this general structure have been extensively documented as selective α_{1a} antagonists.[10−15] The success of this modification suggests that the exact structure of the central heterocycle is not critical and that the other mode of attachment of the piperidine containing side chain via amide bond formation of the DHP C-5 carboxylate might also provide potent and selective compounds. This line of reasoning led to the preparation of **5** which was found to have K_i values of 2.9, 537, and 1513 nM vs the α_{1a}, α_{1b}, and α_{1d} receptors, respectively. Herein we describe our efforts in this area to develop this alternate series of α_{1a} antagonists based on this encouraging lead.

Using some of the structure−activity relationships gleaned from the N-3 acyl variants (e.g. **4**) as a guide, we chose to modify the DHP C-4 aryl substituent to the optimal 3,4-difluorophenyl group (instead of 4-nitro as in **5**).[11] Substitution of the 4-phenyl group of the piperidine has been shown to increase potency,[12] and in this study we utilized 2-pyridyl and ortho and para nitrile and fluoro. Described below are the results from modification of the 1, 3, and 6 positions of the DHP ring, as well as the substituents of the 4-aryl piperidine, culminating in identification of **48**: a potent, selective, and bioavailable α_{1a} receptor antagonist.

Chemistry

The general strategy for the preparation of these compounds was to couple aminopropyl-4-arylpiperidines with resolved dihydropyrimidinones to afford enantiomerically enriched products. In several cases racemic products were prepared and resolved by preparative chiral HPLC.

Scheme 2[a]

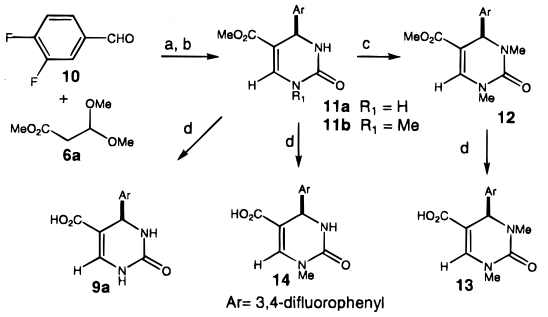


R	Time	Temperature	conversion	ee of **8**	ee of **9**
H	14 days	37 °C	<20%	<10%	80%
Me	10 days	37 °C	50%	>95%	>95%
CF_3	2 days	37 °C	55%	86%	81%
CF_3	1 day	23 °C	50%	>95%	nd
CH_2OMe	10 days	37 °C	50%	>95%	>95%

[a] (a) i. 3,4-Difluorobenzaldehyde, urea, Cu_2O, $BF_3{\cdot}OEt_2$, AcOH, THF, reflux, ii. for R = CF_3, PPA, 100 °C; (b) subtilistin, Tris, H_2O/AcN.

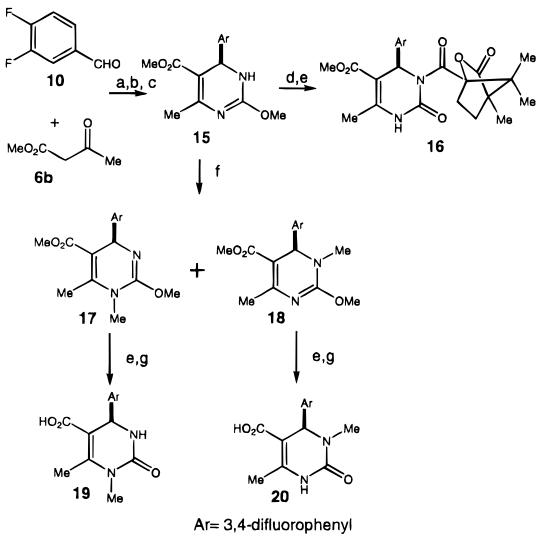
The dihydropyrimidinones in this study were prepared by the Biginelli reaction of 3,4-difluorobenzaldehyde, urea (or *N*-methylurea), and the appropriate acetoacetate (Scheme 2).[16] Interestingly, the Biginelli reaction with methyl trifluoroacetoacetate did not dehydrate under the standard reaction conditions, and the intermediate product had to be further treated with polyphosphoric acid at 100 °C to afford **7c**. Ikemoto et al.[17] demonstrated that dihydropyrimidinones could be resolved by selective enzymatic hydrolysis of the ester moiety, and the resulting acid **9d** was shown to be of the *R* configuration by X-ray crystallographic analysis. Resolution of compounds **7b** and **7d** proceeded smoothly under the reported conditions to give the desired acid in >95%ee. However, compound **7c** reacted much more rapidly and this substrate could be resolved in one-tenth the time at a lower temperature. Conversely, the hydrolysis of **7a** was much slower and stalled at less than 20% conversion, as if the product (**9a**) was an inhibitor of the enzyme. Therefore, an alternate strategy was followed (Scheme 3) whereby the Biginelli product **7a** was treated with LDA and *p*-nitrophenyl chloroformate followed by (+)-1-phenethylamine to give the diastereomeric N-3 acylated products which could be separated by silica gel chromatography. Treatment of

Scheme 3[a]



[a] (a) Urea or methylurea, Cu_2O, $BF_3{\cdot}OEt_2$, AcOH, THF, reflux; (b) i. LDA, *p*-nitrophenyl chloroformate, THF, −78 °C, ii. (*R*)-(+)-1-phenethylamine, Et_3N, DMF, iii. separate, iv. DBU, toluene, reflux; (c) NaH, MeI, THF; (d) NaOH, MeOH.

Scheme 4[a]

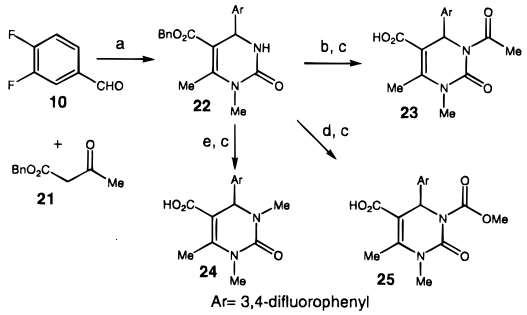


[a] (a) Piperidine, AcOH, 4 Å sieves, C_6H_6, rt; (b) *O*-methylisourea·H_2SO_4, $NaHCO_3$, DMF, 60 °C; (c) preparative chiral HPLC; (d) LDA, (*R*)-camphanic chloride, THF, −78 °C; (e) HCl, CH_2Cl_2/ether; (f) NaH, MeI, DMF; (g) NaOH, MeOH/H_2O.

the purified diastereomers with DBU in refluxing toluene afforded the resolved DHP esters, which could be carefully[18] hydrolyzed to the corresponding acids.[19]

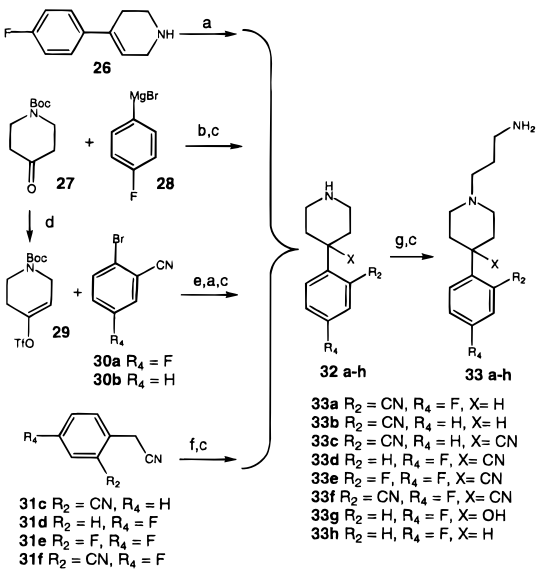
Several strategies were used to prepare N-substituted dihydropyrimidinones. In the case where there is no substituent at the DHP C-6 position, Biginelli reaction of **6a** with **10** and methylurea provided selectively the N-1 methylated DHP[20] which was resolved with (+)-1-phenylethylamine as described above to give **11b** (Scheme 3). This could be converted to its dimethylated counterpart **12** by treatment with NaH and MeI. Hydrolysis of **11** and **12** with NaOH provided the desired acids in good yield (Scheme 3). Selective methylation of the N-3 position could only be accomplished as outlined in Scheme 4. Reaction of *O*-methylisourea with the Knoevenagel product of methyl acetoacetate and 3,4-difluorobenzaldehyde[9] provided **15** which was resolved by preparative chiral HPLC (Scheme 4). Stereochemical determination of the resolved product was accomplished by acylating (−)-**15** with (1*R*)-camphanic chloride to give **16** as a crystalline solid suitable for X-ray structure determination. The desired *R* enantiomer (*R*)-**15** was then reacted with NaH and MeI to give a 1:1 mixture of **17** and **18** which could be separated by chromatography. Acidic hydrolysis of the heterocycle afforded the

Scheme 5[a]



[a] (a) Methylurea, Cu_2O, $BF_3{\cdot}OEt_2$, AcOH, THF, reflux; (b) Ac_2O, DMF, rt; (c) H_2, 1 atm, 10% Pd/C, EtOH/EtOAc; (d) NaH, MeOCOCl, THF, rt; (e) NaH, Me_2SO_4, toluene, rt.

Scheme 6[a]



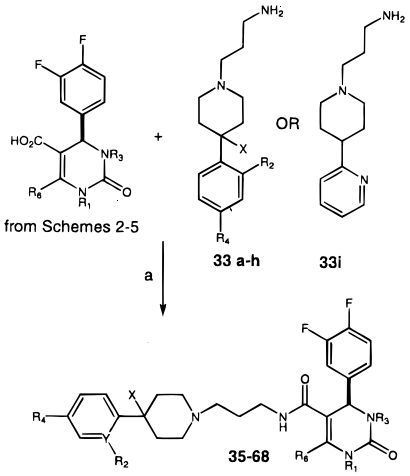
[a] (a) H_2, Pd/C, EtOH; (b) −78 °C, THF; (c) HCl, EtOAc, 0 °C; (d) LDA, $PhN(Tf)_2$, THF, −78 → rt; (e) BuLi, $ZnCl_2$, −78 → 0 °C, then $Pd(PPh_3)_4$, **29**, THF; (f) NaH or Cs_2CO_3, $(ClCH_2CH_2)_2NBoc$, 80 °C, DMF or DMSO; (g) $Br(CH_2)_3NHBoc$, Et_3N, DMF.

corresponding dihydropyrimidinones whose C-5 esters could be hydrolyzed (NaOH, MeOH/H_2O) to yield the acids **19** and **20** in essentially pure form after extractive workup. Racemic Biginelli product **22** was converted to the acylated variants **23** and **25** as well as the N-1,N-3 dimethylated DHP **24** as described in Scheme 5. Compounds produced from these acids were separated by preparative chiral chromatography after amide bond formation (Scheme 7).

The preparation of the aminopropyl-4-arylpiperidines is detailed in Scheme 6. Worthy of note is the preparation of piperidines wherein R_2 = CN and X = H. The arylzinc was generated from the corresponding bromide **30a** or **30b** by halogen metal exchange followed by transmetalation with $ZnCl_2$. Addition of $Pd(PPh_3)_4$ and the enol triflate **29** derived from piperidone **27** gave the coupled products which could be reduced to **32a** and **32b** in good yield. Each of the piperidines **32** was alkylated with 3-bromo-*N*-Boc-propylamine, and removal of the Boc protecting group afforded the required coupling fragments **33a**−**h.**

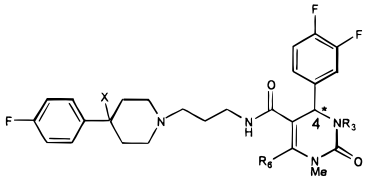
Amide bond formation between the requisite amines and DHP acids was accomplished with EDC and either HOBt or HOAt in DMF (Scheme 7). Racemic products

Scheme 7[a]



[a] (a) EDC, HOBt or HOAt, DMF, prep chiral chromatography if necessary.

Table 1. Comparison of in Vitro Binding Data for Epimeric C-4 Dihydropyrimidinones



					α_1 receptor subtype binding K_i (nM) ± SEM		
compd	C-4	R_3	R_6	X	α_{1a}	α_{1b}	α_{1d}
35	R	H	Me	H	0.18 ± 0.025	120 ± 40	590 ± 260
36	S	H	Me	H	20 ± 5.0	110 ± 15	600 ± 70
37	R	Me	Me	H	0.18 ± 0.023	20 ± 1.0	200 ± 23
38	S	Me	Me	H	11 ± 1.6	85 ± 23	410 ± 39
39	R	H	H	CN	0.12 ± 0.007	53 ± 4.5	240 ± 59
40	S	H	H	CN	2.3 ± 0.80	320 ± 210	710 ± 130

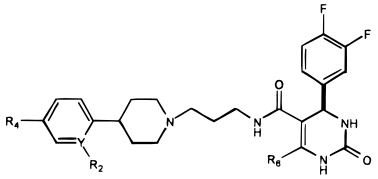
(derived from **23**−**25**) were resolved by preparative chiral chromatography.

Results and Discussion

In order to determine intrinsic potency and selectivity, all compounds were initially tested for their ability to displace [^{125}I]HEAT from human cloned α_{1a}, α_{1b}, and α_{1d}[21] receptors stably expressed in CHO, LM, and HEK cells, respectively.[22] As is demonstrated in Tables 1−4, **5** proved to be a good lead as most of the compounds prepared containing this basic architecture were quite potent and selective. Table 1 shows that both enantiomers show good subtype selectivity with the most potent compounds containing the (−)-(*R*)-DHP enantiomer. While this is the opposite enantiomer of that utilized in the best N-3 acyl variants, such as **4** (Scheme 1), the heterocycle has also been reversed so that the 4-aryl substituent on the DHP ring has the same relative orientation to the piperidine side chain. This implies that most of the important binding interactions for the α_{1a} receptor subtype reside in the proper placement of the 3,4-difluorophenyl moiety rather than the other elements on the heterocycle.

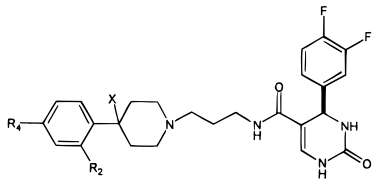
Using the more potent (−)-(*R*)-DHP enantiomer, it was possible to fine-tune the potency and selectivity of these compounds. Modifications of the DHP substructure in combination with several different 4-arylpiperidine side chains resulted in compounds with moderate differences in receptor subtype binding affinity, and these results are detailed in Tables 2−4.

Table 2. Comparison of in Vitro Binding Data for 4-Arylpiperidine Derivatives



				α_1 receptor subtype binding K_i (nM) ± SEM		
compd	Y−R_2	R_4	R_6	α_{1a}	α_{1b}	α_{1d}
41	C−CN	H	H	0.13 ± 0.015	290 ± 190	160 ± 80
42	C−CN	H	Me	0.25 ± 0.040	158 ± 71	168 ± 16
43	C−CN	H	CF_3	20 ± 5.5	700 ± 290	220 ± 58
44	C−CN	H	CH_2OMe	0.42 ± 0.025	285 ± 65	285 ± 25
45	C−H	F	H	0.17 ± 0.030	24 ± 1.5	68 ± 5.0
46	C−H	F	Me	0.39 ± 0.050	40 ± 15	240 ± 24
47	C−H	F	CF_3	19 ± 1.0	270 ± 30	1200 ± 400
48	C−H	F	CH_2OMe	0.24 ± 0.050	41 ± 5.5	260 ± 110
49	C−CN	F	H	0.07 ± 0.020	26 ± 5.0	62 ± 4.5
50	C−CN	F	Me	0.17 ± 0.050	87 ± 7.0	215 ± 45
51	C−CN	F	CF_3	4.2 ± 0.95	200 ± 15	270 ± 98
52	C−CN	F	CH_2OMe	0.14 ± 0.05	35 ± 1.0	260 ± 40
53	N	H	H	2.5 ± 0.15	1850 ± 150	>3000
54	N	H	Me	2.6 ± 0.20	>2000	>5000
55	N	H	CF_3	500 ± 40	>2000	>5000
56	N	H	CH_2OMe	0.45 ± 0.16	235 ± 5.0	495 ± 180

Table 3. Comparison of in Vitro Binding Data for 4-Piperidine Hydroxy and Nitrile Substituents

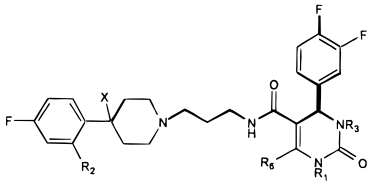


				α_1 receptor subtype binding K_i (nM) ± SEM		
compd	R_2	R_4	X	α_{1a}	α_{1b}	α_{1d}
45	H	F	H	0.17 ± 0.03	24 ± 1.5	68 ± 5.0
57	H	F	OH	0.91 ± 0.010	160 ± 0.0	880 ± 20
58	H	F	CN	0.17 ± 0.040	140 ± 26	810 ± 150
41	CN	H	H	0.13 ± 0.015	290 ± 190	160 ± 80
59	CN	H	CN	0.16 ± 0.070	970 ± 330	2400 ± 580

Trends noted among the 4-arylpiperidines (Table 2) were that the 2-cyanophenyl derivative is as potent as the 4-fluorophenyl derivative but displays greater selectivity (e.g. **41** vs **45**). Combination of the two gives a slight boost to potency as seen in the extraordinary binding affinity of **49** (70 pM) to the α_{1a} receptor subtype. The 2-pyridyl substituent, although imparting high selectivity, was found to be about 5−100-fold less potent than the others except when paired with the 6-methoxymethyl DHP (**56**).

The 4-position of the piperidine was also briefly examined as shown in Table 3. The hydroxy substituent caused a slight decrease in receptor binding affinity and a modest increase in selectivity relative to its unsubstituted counterpart (**57** vs **45**). The cyano substitution was quite remarkable in the additional selectivity against the α_{1b} and α_{1d} receptor subtypes without

Table 4. Comparison of in Vitro Binding Data for N-1 and N-3 Substituted Dihydropyrimidinones



						α_1 receptor subtype binding K_i (nM) ± SEM		
compd	R_1	R_3	R_2	R_6	X	α_{1a}	α_{1b}	α_{1d}
46	H	H	H	Me	H	0.39 ± 0.05	40 ± 15	240 ± 24
60	H	Me	H	Me	H	0.14 ± 0.040	4.8 ± 0.35	120 ± 10
35	Me	H	H	Me	H	0.18 ± 0.025	120 ± 40	590 ± 260
37	Me	Me	H	Me	H	0.18 ± 0.023	20 ± 1.0	200 ± 23
61	Me	$COCH_3$	H	Me	H	2.2 ± 0.10	33 ± 7.5	230 ± 39
62	Me	CO_2CH_3	H	Me	H	0.75 ± 0.010	25 ± 50	170 ± 98
63	Me	H	CN	Me	H	0.12 ± 0.062	130 ± 26	340 ± 30
64	Me	H	CN	Me	CN	0.60 ± 0.060	>2000	>4000
65	Me	H	H	Me	CN	0.39 ± 0.08	1100 ± 330	2200 ± 420
66	Me	H	CN	H	CN	0.18 ± 0.040	440 ± 20	630 ± 26
67	Me	Me	CN	H	CN	0.30 ± 0.00	72 ± 7.5	250 ± 8.5
68	Me	H	CN	H	H	0.068 ± 0.002	7.9 ± 0.25	69 ± 3.0

sacrificing α_{1a} potency, as is evident in compounds **58** and **59**.

The remaining area examined was the effect of substitution around the DHP nucleus. As evident in Table 2, the trifluoromethyl group at the DHP 6-position was detrimental to binding (**43**, **47**, **51**, and **55**), but hydrogen, methyl, and methoxymethyl provided excellent potency and greater than 100-fold selectivity versus the other α_{1a} subtypes, with a slight advantage in binding affinity noted for the unsubstituted variants (**41**, **45**, and **49**). There was concern that the polarity of these compounds may limit absorption; therefore, alkylation and acylation of the DHP nitrogens were examined for effects on binding affinity (Table 4).

Interestingly, methylation of N-1 improved selectivity while methylation of N-3 reduced it, with both having similar α_{1a} potencies (**35** and **60** vs **46**). Extraordinarily selective compounds were obtained by combining N-1 methylated DHPs with 4-cyanopiperidines (the trend toward selectivity noted in Table 3) as shown by **64**−**67**. Also worthy of note is that acylation of N-3 with acetyl (**61**) or carbomethoxy (**62**) resulted in a drop in both potency and selectivity even though this more closely mimics **4** (Scheme 1).

All of the compounds in Tables 1−4 that were greater than 100-fold selective for the α_{1a} receptor subtype over the other receptor subtypes were also counterscreened in vitro versus several G-protein coupled receptors (α_{2A}, α_{2B}, α_{2C}, human histamine H1, and several seratonin receptors). The results of these assays showed no compound to have less than 100-fold selectivity versus any of these receptors (data not shown). Since these compounds incorporate the structural changes that abolished calcium channel activity in **2** (no *m*-nitro group, ester→amide linkage, Scheme 1), we did not expect this activity to be a problem with the present compounds. The only compound tested in this regard, **48**, confirmed this as it displayed greater than 1000-fold selectivity (data not shown).

Based on these in vitro binding results, many of the compounds were further examined in vivo for pharmacodynamic effects and pharmacokinetic parameters. The compounds were initially tested in a model whereby the prostate of an anesthetized rat was exposed and connected to a force transducer. Compounds were evaluated for their inhibition (AD_{50}, Table 5) of contractile response induced by the α_{1a}-selective agonist A61603.[23] The pharmacodynamic duration of action could also be measured with repeated challenges with the agonist, and this is also listed in Table 5.

According to the data in Table 5, this series of compounds is quite potent in the rat assay. Some SAR information gleaned from this in vivo assay was that many compounds containing various fluoro and cyano substitutions on the 4-arylpiperidine were quite potent (AD_{50} values below 2 μg/kg), while the piperidine X substituent produced more of a trend with OH < H < CN (**57** vs **45** vs **58**). This is in contrast to the binding data (Table 3 above) whereby the X = OH substitution reduced potency. Methylation of the DHP N-1 position tended to slightly decrease activity (**50** vs **63**, **46** vs **35**, **49** vs **68**, **58** vs **39**) while there was no trend evident for additional methylation at N-3 (**35** vs **37** compared to **66** vs **67**). As noted in the binding assay, stereochemistry of the DHP was important as seen in the 10-fold potency difference between **39** and **40**.

The short pharmacodynamic duration of action for the majority of the compounds tested in this rat model (measured at antagonist concentration 4 times the AD_{50}) is difficult to explain. Compounds with respectable plasma half-lives were just as short acting as the others (e.g. **54** and **56**). One empirical observation noticed in this regard was that methylation at the DHP N-1 nitrogen tended to increase pharmacodynamic duration (**35**, **39**, **63**, and **65**−**68**).

The biggest challenge with this series of compounds was to overcome their uniformly poor pharmacokinetics in rats (Table 5). Nearly half of the compounds tested were not detected in plasma after oral dosing, and all but three were less than 15% bioavailable. Initially, we were concerned that the polarity of these compounds was limiting absorption (e.g. the log *P* of **52** is 0.65), and this was one of the motivations for methylation of the DHP nitrogens. However, in the Caco-2 model for GI absorption,[24] all of the compounds tested (**46, 58, 35, 37, 39, 65, 68, 63**) displayed adequate transport, indicating that absorption was probably not the most important factor in determining bioavailability in this series.[25] The in vitro metabolism of several of these compounds (**41, 42, 44, 48**−**50, 52, 63**) was examined using human liver microsomal preparations (10−50 μM substrate, microsomal protein 2 mg/mL, 1 h, LC−MS/MS detection). These experiments showed rapid N-dealkylation of the piperidine and the DHP N-3 methyl (when present), as well as desaturation of the DHP nucleus to a pyrimidine as the primary metabolic pathways. This "first-pass" effect is probably the major culprit in limiting bioavailability.

Nevertheless, compounds **48** and **63** escaped some of this first-pass metabolism in the rat, and therefore their pharmacodynamic and pharmacokinetic parameters in the dog were examined (Table 5). Gratifyingly, both of these compounds had good pharmacokinetic profiles in this species. However, analysis of plasma samples revealed that **63** underwent significant N-dealkylation of the DHP N-1 methyl group (as was seen in the

Table 5. In Vivo Data for Selected Compounds

	rat				dog			
			pharmacokinetics				pharmacokinetics	
compd	AD_{50}[a] (μg/kg)	duration[b] (h)	%F[c]	$t_{1/2}$ (min)[d]	IUP AD_{50}[e] (μg/kg)	DBP-20[f] (μg/kg)	%F[g]	$t_{1/2}$ (min)[d]
1b	52				97	74		
1c	3	3.5						
35	20	2.5	<6	72 ± 62				
37	9	1	17 ± 10	138 ± 65				
39	14	4	<6	66 ± 20				
40	145		8 ± 4	72 ± 18				
41	1.5	0.5	0	43 ± 4				
42	3	<0.5	0	162 ± 77	6	>300		
44	7	0.6	<6	108 ± 23				
45	2.2	0.5	0	60 ± 4	21	>300		
46	1.8	0.5	<6	102 ± 8	7	143		
48	4.6	1	26 ± 6	388 ± 128	25	>300	40 ± 5	466 ± 56
49	1.8	2	0	174 ± 31				
50	1.5	1.5	0	25 ± 6	5	>300		
52	2.8	1.5	<6	175 ± 80				
54	2.3	0.5	0	42 ± 4				
56	12	0.25	0	420 ± 37			48 ± 7	335 ± 37
57	1.2	0.5	0	37 ± 5				
58	7	0.75	0	140 ± 64				
59	3	1	0	45 ± 5				
63	7	2.5	15 ± 7	132 ± 19	10	>300	27 ± 11	128 ± 25
64	5	1	0	24 ± 7				
65	21	1.5	<6	45 ± 45				
66	4	3.5	0	<60				
67	13	3	<6	15 ± 3				
68	5	4	0	48 ± 30				

[a] Inhibition of A61603-induced prostate contraction, $n = 4$, and the data for each concentration was averaged (SEM < 10%). [b] Duration of action with repeated challenges of A61603 agonist, $n = 4$, and the data from each timepoint was averaged (SEM < 10%). [c] Bioavailability when dosed 1 mg/kg iv and 3 mg/kg po, $n = 3$. [d] Plasma half-life from iv dose, $n = 3$. [e] Inhibition of phenylephrine-induced contraction (SEM < 10%). [f] Dose effecting a 20 mmHg change in diastolic blood pressure (SEM < 10%). [g] Bioavailability when dosed 0.5 mg/kg iv and 1 mg/kg po, $n = 3$.

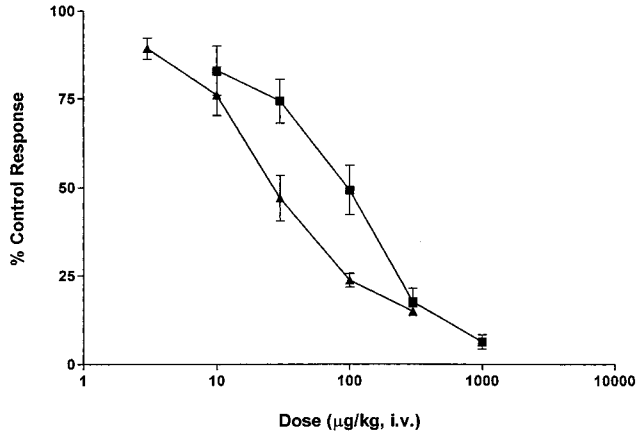


Figure 2. Inhibition of phenylephrine-induced increases in intra-urethral pressure by **48** (triangle, $n = 4$) and terazosin (square, $n = 3$) in anesthetized dogs.

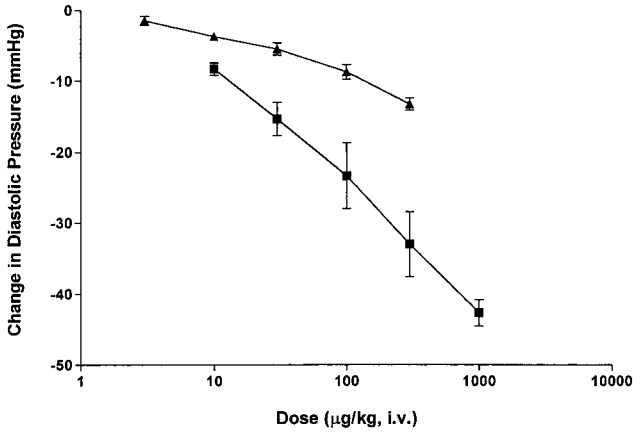


Figure 3. Effect of **48** (triangle, $n = 4$) and terazosin (square, $n = 3$) on baseline diastolic blood pressure in anesthetized dogs.

microsomal preparations) to give **50** as a major metabolite, a complication that could be avoided with **48**. The long half-life in dogs (7.8 h) suggests that **48** may be suitable for once-a-day dosing in humans.

Further characterization of **48** for pharmacodynamic efficacy and selectivity was done in a canine intra-urethral pressure (IUP) assay which allowed for the simultaneous monitoring of heart rate and blood pressure.[26] As demonstrated in Figure 2, **48** was more potent than terazosin for inhibition of phenylepherine-induced changes in intra-urethral pressure. Most importantly, the two compounds had distinct differences in their effect on baseline diastolic blood pressure (DBP) as demonstrated in Figure 3, with **48** having only a slight effect at high doses. The pharmacodynamic duration of **48** was also measured and found to be greater than 6 h (Figure 4), in contrast to the results in rat. Several other compounds (**42**, **45**, **46**, **50**, and **63**) were also examined in this model, and gratifyingly these selective α_{1A} receptor antagonists generally show the expected in vivo selectivity for the desired urodynamic effects over any undesired cardiovascular effects (Table 5) in accord with their receptor binding profile. As a result of these studies, compound **48** has potential for oral, once-a-day treatment of BPH based on its α_{1A} potency and selectivity, both in vitro and in vivo, as well as its favorable pharmacokinetic profile.

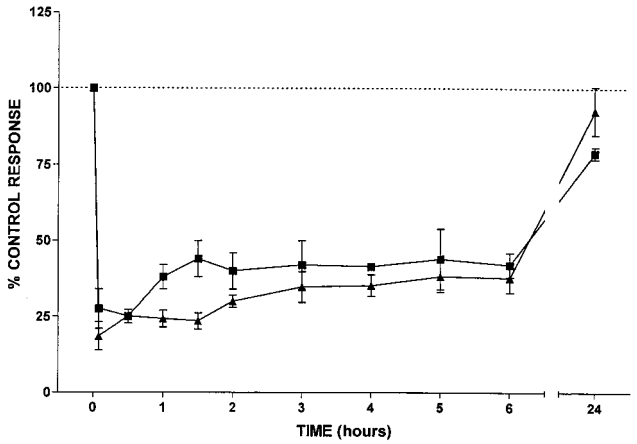


Figure 4. Pharmacodynamic inhibition of phenylephrine-induced increases in intra-urethral pressure in conscious dogs by **48** (squares, 100 μg/kg, iv, $n = 2$) and terazosin (triangle, 200 μg /kg, iv, $n = 2$).

Conclusions

The 4-aryldihydropyrimidinone heterocycle attached to an aminopropyl-4-arylpiperidine via a C-5 amide has proved to be an excellent template for selective α_{1A} receptor subtype antagonists. These types of compounds are exceptionally potent in both cloned receptor binding studies as well as in in vivo pharmacodynamic models of prostatic tone. Due to their selectivity for the α_{1A} over the α_{1B} and α_{1D} receptors, these compounds have lessened effects on the cardiovascular system. While most of the examples described above undergo rapid in vivo metabolism and clearance, **48** displayed sufficient bioavailability and plasma half-life in animal models to warrant further consideration for the treatment of BPH.

Experimental Section

Chemistry. General information: Melting points are uncorrected. Optical rotations were measured on Perkin-Elmer 241 digital polarimeter with a sodium lamp and reported as follows: $[\alpha]^{t°C}_{\lambda}$ (*c* g/100 mL, solvent). Infrared spectra were recorded on a Perkin-Elmer model 1600 FT-IR spectrometer. ^{1}H NMR spectra were recorded on Varian Unity-300 (300 MHz) or Varian Unity-plus 400 (400 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constants (Hz). Mass spectra were obtained on a VG ZAB-HF, with FAB ionization. Combustion analyses were performed on a Perkin-Elmer 2400-II analyzer.

Analytical thin-layer chromatography was performed on EM Reagent 0.25-mm silica gel 60-F plates. Flash chromatography was performed on EM silica gel 60 (230−240 mesh). Solvents for extraction and chromatography were HPLC grade. Unless otherwise noted, all reactions were conducted in oven (80 °C) or flame-dried glassware with magnetic stirring under an inert atmosphere of dry nitrogen.

4-(4-Nitrophenyl)-3-carbomethoxy-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid {3-[4-Phenyl-4-carbomethoxypiperidin-1-yl]propyl}amide (5). To a solution of 4-(4-nitrophenyl)-3-(2-cyanoethoxy)carbonyl-3-buten-2-one (5.68 g, 20.0 mmol) and *O*-methylisourea hydrogen sulfate (4.13 g, 24.0 mmol) in EtOH (80 mL) was added $NaHCO_3$ (3.36 g, 40 mmol). The resulting suspension was heated to 95−100 °C for 20 h. The reaction mixture was filtered to remove the solids and solvent was evaporated from the filtrates. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with brine (4 × 50 mL). The CH_2Cl_2 solution was dried (Na_2SO_4) and the solvent evaporated. The residue was purified by column chromatography on silica gel using hexane/EtOAc as eluent (10:1 to 1:1) to afford 4.95 g (72%) of 4-(4-nitrophenyl)-6-methyl-2-methoxy-3,4-dihydropyrimidine-5-carboxylic acid cyanoethoxy ester as an oil: ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 3H), 2.65−2.70 (m, 2H), 3.66 (s, 3H), 4.15 (t, $J = 5$ Hz, 2H), 5.60 (s, 1H), 7.49 (d, $J = 7.8$ Hz, 2H), 8.13 (d, $J = 7.8$ Hz, 2H). To this product (0.688 g, 2.00 mmol) in CH_2Cl_2 (20 mL) and pyridine (0.50 mL) was added methyl chloroformate (0.50 mL) at 0 °C. The reaction mixture was stirred for 2 h while warmed to room temperature. Solvent was evaporated and the crude product 4-(4-nitrophenyl)-3-carbomethoxy-6-methyl-2-methoxy-3,4-dihydropyrimidine-5-carboxylic acid cyanoethoxy ester (0.80 g, 100%) was used in the subsequent step without further purification: ^{1}H NMR ($CDCl_3$) δ 2.70 (s, 3H), 2.91 (t, $J = 6.3$ Hz, 2H), 4.12 (s, 3H), 4.16 (s, 3H), 4.55−4.65 (m, 2H), 6.55 (s, 1H), 7.70 (d, $J = 8.8$ Hz, 2H), 8.40 (d, $J = 8.8$ Hz, 2H). To this product (0.80 g, 2.0 mmol) in acetone (5 mL) at −10 °C was added 1 N NaOH (10 mL). The reaction mixture was stirred for 3 h at the same temperature. The acetone was evaporated at −5 °C under vacuum and the residue was diluted with H_2O (10 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 10 mL) and hexane (10 mL) was added. The mixture was stirred at −5 °C and 6 N HCl was added slowly until pH = 3−4. The precipitate formed was filtered and washed with H_2O (10 mL). To the crude product (0.50 g) in CH_2Cl_2 (40 mL) were added 1-(3-aminopropyl)-4-methoxycarbonyl-4-phenylpiperidine (0.553 g, 2.00 mmol), DMAP (0.55 g, 4.5 mmol) and EDC (0.767 g, 4.0 mmol) and the mixture was stirred at room temperature for 72 h. It was diluted with CH_2Cl_2 (150 mL) and washed thoroughly with saturated aqueous NH_4Cl (4 × 100 mL). The organic layer was treated with aqueous 6 N HCl (5 mL) and stirred for 2 h. It was washed with aqueous $NaHCO_3$ solution (2 × 100 mL) and dried (Na_2SO_4). Solvent was evaporated from the CH_2Cl_2 solution and the residue was purified by column chromatography on silica gel (hexanes−EtOAc 1:1; EtOAc; MeOH−EtOAc 10%-40%) to afford **5** (0.880 g, 74%): ^{1}H NMR ($CDCl_3$) δ 1.45−1.70 (m, 4H), 1.90−2.10 (m, 2H), 2.30−2.45 (m, 4H), 2.65−2.75 (m, 2H), 3.25−3.45 (m, 2H), 3.41 (s, 3H), 3.57 (s, 3H), 6.16 (s, 1H), 7.16−7.29 (m, 5H), 7.39 (d, $J = 8.6$ Hz, 2H), 7.96 (d, $J = 8.8$ Hz, 2H), 8.08 (br t, 1H, NH); mp 105−107 °C.

General Procedure for Preparation of Dihydropyrimidinones via Biginelli Reaction (see ref 16). To a well-stirred mixture of acetoacetate **6** (1 mmol), 3,4-difluorobenzaldehyde (1 mmol), and urea or methylurea (1.5 mmol) in THF (1 M in aldehyde) at room temperature were added sequentially copper(I) oxide (0.1 mmol) and acetic acid (0.1 mmol) followed by the dropwise addition of boron trifluoride diethyl etherate (1.3 mmol). The mixture was stirred and refluxed for 8−24 h. It was cooled and poured into a mixture of ice and sodium bicarbonate. The resulting mixture was filtered through Celite. The Celite was washed with dichloromethane. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried (sodium sulfate) and the solvent was evaporated. The crude product was purified by trituration, crystallization, or flash column chromatography on silica gel.

4-(−)-(3,4-Difluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (7a): purified by trituration with CH_2Cl_2; ^{1}H NMR δ_H (300 MHz, DMSO) 9.29 (d, 1H, $J = 5.37$ Hz), 7.75 (s, 1H), 7.50−7.35 (m, 1H), 7.30−7.20 (m, 2H), 7.15−7.05 (m, 1H), 5.155 (d, 1H, $J = 2.68$ Hz), 3.565 (s, 3H).

4-(3,4-Difluorophenyl)-2-oxo-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (7b): purified by crystallization from toluene; ^{1}H NMR (300 MHz, DMSO) δ 9.3 (s, 1H), 7.81 (s, 1H), 7.40 (m, 1H), 7.22 (m, 1H), 7.07 (m, 1H), 5.15 (s, 1H), 3.54 (s, 3H), 2.26 (s, 1H).

4-(3,4-Difluorophenyl)-2-oxo-6-trifluoromethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (7c): general procedure afforded a hydrated product which was crystallized from toluene; ^{1}H NMR ($CDCl_3$) δ 7.25−7.12 (m, 3H), 6.22 (s, 1H), 5.71 (s, 1H), 5.55 (s, 1H), 4.85 (d, 1H, $J = 7$

Hz), 3.50 (s, 3H), 3.08 (d, 1H, J = 7 Hz); MS (FAB/glycerol: M + H = 355). Dehydration was accomplished by heating the hydrated product 13.5 g (38 mmol) in 170 g polyphosphoric acid to 100 °C with manual stirring for 30 min. The reaction was then poured over 2L of ice. To this was added 500 mL EtOAc and 300 mL H_2O and the mixture stirred vigorously for 30 min. The layers were separated and the aqueous layer was extracted again with 300 mL EtOAc and the combined extracts washed with 500 mL brine, dried over Na_2SO_4, filtered, and concentrated to give 12 g of **7c** as an essentially pure tan solid: ^{1}H NMR (300 MHz, DMSO) δ 9.93 (s, 1H), 8.12 (s, 1H), 7.49 (m, 1H), 7.33 (m, 1H), 7.13 (m, 1H), 5.3 (s, 1H), 3.62 (s, 3H).

4-(3,4-Difluorophenyl)-2-oxo-6-methoxymethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (7d): flash chromatography (50% EtOAc/hexanes followed by 100% EtOAc) afforded **7d** as a foam in 94% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (br s, 1H), 7.20−7.00 (m, 3H), 6.60 (br s, 1H), 5.39 (s, 1H), 4.65 (s, 2H), 3.65 (s, 3H), 3.48 (s, 3H).

4-(3,4-Difluorophenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester (11): crystallized from toluene; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.2−7.1 (m, 3H), 6.02 (s, 1H), 5.34 (s, 1H), 3.66 (s, 3H), 3.20 (s, 3H).

4-(3,4-Difluorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Benzyl Ester (22). Prepared using a slight modification of the general procedure: Benzyl acetoacetate (28.8 g, 150 mmol), methylurea (11.26 g, 152 mmol) and 3,4-difluorobenzaldehyde (21.3 g, 150 mmol) were combined in ethanol (60 mL) and concentrated HCl (24 drops) was added. The reaction mixture was refluxed for 5 h. The solvent was removed in vacuo and ethanol (30 mL) and hexane (250 mL) added providing **22** (41.28 g, 74%) as a pale yellow solid by filtration. Another portion of product (2.71 g, 5%) was obtained from the mother liquor: ^{1}H NMR ($CDCl_3$) δ 7.40−7.25 (m, 3H), 7.25−7.15 (m, 2H), 7.10−6.80 (m, 3H), 6.06 (br s, 1H), 5.35 (d, 1H), 5.10 (AB q, 2H), 3.25 (s, 3H), 2.55 (s, 3H).

General Procedure for Enzymatic Resolution. To a 5-L flask equipped with a reflux condenser and an overhead mechanical stirred were added a solution of 15 g tris·base and 5.9 g tris·HCl in 3.2 L H_2O followed by a suspension of 9 g dihydropyrimidinone in 400 mL acetonitrile (50 mL rinse). To this was added 2 L of a water/propylene glycol solution of subtilistin enzyme and the reaction heated to 37 °C for 10−14 days (23 °C for 1 day for **7c**) with vigorous stirring. The reaction was then cooled and extracted 3 × 2 L toluene which were combined, dried over Na_2SO_4, filtered and concentrated to give the resolved (+) esters **8b**−**d**. **8b:** $[\alpha]_D^{24}$ = +40 (c = 0.79 MeOH). **8c:** $[\alpha]_D^{24}$ = +144 (c = 1.09 CH_2Cl_2). **8d:** $[\alpha]_D^{24}$ = +84 (c = 0.5 $CHCl_3$). The aqueous layer was acidified to pH = 3 with 200 mL 1 N HCl and extracted 2 × 1 L EtOAc, filtered, dried over Na_2SO_4, filtered and concentrated to give the (−)-DHP acids **9b**−**d** along with some residual propylene glycol. Esterification with CH_2N_2 afforded an analytical sample for assay (Chiracel OD 4.6 × 250 mm 3:2 hexane (0.1% diethylamine)/ethanol, ee shown in Scheme 2).

4-(3,4-Difluorophenyl)-2-oxo-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (9b): ^{1}H NMR (300 MHz, DMSO) δ 9.18 (s, 1H), 7.77 (s, 1H), 7.40 (m, 1H), 7.21 (m, 1H), 7.09 (m, 1H), 5.15 (s, 1H), 2.22 (s, 3H).

4-(3,4-Difluorophenyl)-2-oxo-6-trifluoromethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (9c): ^{1}H NMR (300 MHz, DMSO) δ 9.75 (s, 1H), 8.02 (s, 1H), 7.49 (m, 1H), 7.31 (m, 1H), 7.12 (m, 1H), 5.28 (s, 1H).

4-(3,4-Difluorophenyl)-2-oxo-6-methoxymethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (9d): ^{1}H NMR (400 MHz, DMSO) δ 12.32 (s, 1H), 8.58 (s, 1H), 7.82 (s, 1H), 7.41 (m, 1H), 7.22 (m, 1H), 7.09 (m, 1H), 5.16 (s, 1H), 4.60 (d, 1H, J = 13.5 Hz), 4.44 (d, 1H, J = 13.5 Hz), 3.30 (s, 3H).

General Procedure for Chemical Resolution with (+)-(*R*)-1-Phenylethylamine (Scheme 3). To a −78 °C solution of 4 g (14 mmol) **(±)-11b** in 70 mL THF was added 7 mL (14 mmol, 2 M solution in THF/heptane/ethylbenzene) LDA. The reaction mixture was stirred for 15 min, then a −78 °C solution of 3.13 g (15.5 mmol) *p*-nitrophenyl chloroformate in 10 mL THF was added very quickly via a large bore cannula. After stirring 45 min at −78 °C, the reaction mixture was poured into 300 mL EtOAc and washed with 200 mL saturated aqueous sodium bicarbonate solution, 200 mL 5% aqueous K_2CO_3 solution, 200 mL water, and 200 mL brine; then dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was dissolved in 50 mL DMF and to this were added 2 mL (14 mmol) triethylamine and 1.83 mL (14 mmol) (*R*)-1-phenethylamine. The reaction mixture was stirred 3 h at room temperature, diluted with 400 mL ethyl acetate, washed with 3 × 150 mL 10% aqueous K_2CO_3 solution, 1 × 200 mL water, and 1 × 200 mL brine; then dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash chromatography (6 × 18 cm silica gel, linear gradient 0−5% MeOH/1% NH_4OH/CH_2Cl_2) followed by purification of the mixed fractions by flash chromatography (5 × 15 cm silica gel, linear gradient 0−12% MeOH/1% NH_4OH/CH_2Cl_2) afforded 1.9 g "hi R_f diastereomer": ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (d, 1H, J = 6.84 Hz), 7.36−7.04 (m, 4H), 6.59 (s, 1H), 4.95 (quint, 1H, J = 6.84 Hz), 3.67 (s, 3H), 3.27 (s, 3H), 1.48 (d, 3H, J = 7.08 Hz); and 1.7 g "lo R_f diastereomer": ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (d, 1H, J = 7.08 Hz), 7.34−7.00 (m, 4H), 6.67 (s, 1H), 5.00 (quint, 1H, J = 6.92 Hz), 3.73 (s, 3H), 3.27 (s, 3H), 1.50-(d, 3H, J = 6.84 Hz). A solution of 1.7 g (4.3 mmol) of the "hi R_f diastereomer" and 3 mL (20 mmol) DBU in 50 mL toluene was heated to 110 °C for 16 h then cooled to room temperature. To this was added 2 mL concentrated aqueous NH_4OH solution and the reaction stirred 5 min, then 200 mL ethyl acetate and 200 mL 10% aqueous $KHSO_4$ solution were added and the layers mixed and separated. The ethyl acetate layer was washed with 200 mL water and 200 mL brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash chromatography (5 × 15 cm silica gel, linear gradient 50−90% EtOAc/hexanes) afforded 1.0 g of **(+)-11b** optical rotation: $[\alpha]_D^{25}$ = +121 (c = 0.48 CH_2Cl_2). The same procedure on the "lo R_f diastereomer" afforded 0.9 g of **(−)-11b** with optical rotation: $[\alpha]_D^{25}$ = −126 (c = 0.6 CH_2Cl_2). HPLC analysis on a Chiracel OD 250 × 4.6 mm column, 70% hexane(0.1% diethylamine)/30% ethanol 1 mL/min gave retention times of 5.6 min for the (+) enantiomer (93%ee) and 6.2 min for the (−) enantiomer (91% ee). Hydrolysis of the ester was effected by treatment of 0.55 g (2 mmol) **(−)-11** in 7.5 mL MeOH with 2.5 mL NaOH (2.5 M aqueous solution) for 14 h at 23 °C then 8 h at 60 °C. The reaction mixture was cooled, 50 mL H_2O added and washed with 50 mL EtOAc. The aqueous layer was acidified to pH 1 and extracted 3 × 25 mL EtOAc. The combined extracts were dried over Na_2SO_4, filtered and concentrated to give 0.5 g **14**.

(−)-4-(3,4-Difluorophenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (14): optical rotation $[\alpha]_D^{25}$ = −110 (c = 0.34 MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ 7.50 (s, 1H), 7.27−7.10 (m, 3H), 5.25 (s, 1H), 3.20 (s, 3H).

The same procedure provided **(−)-4-(3,4-difluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (9a):** ^{1}H NMR (300 MHz, DMSO) δ 9.17 (d, 1H, J = 5.37 Hz), 7.69 (s, 1H), 7.50−7.35 (m, 1H), 7.30−7.20 (m, 2H), 7.15−7.05 (m, 1H), 5.13 (d, 1H, J = 2.44).

(−)-4-(3,4-Difluorophenyl)-1,3-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid (13). To a solution of 0.36 g (1.3 mmol) **11b** in 3 mL DMF was added 0.068 g (2.8 mmol) sodium hydride. After the gas evolution has ceased (5 min), 0.10 mL (1.6 mmol) methyl iodide was added and the reaction mixture was stirred 2 h at room temperature then poured into 100 mL EtOAc and washed 100 mL 5% aqueous $KHSO_4$ solution, 100 mL water, and 100 mL brine; then dried over Na_2SO_4, filtered and concentrated in vacuo to give **12** as an essentially pure viscous oil. Without further purification, **12** was dissolved in 5 mL MeOH and to this was added 0.2 mL (0.5 mmol, 2.5 M solution in water) NaOH, 2 mL THF, and 0.8 mL (2 mmol, 2.5 M solution in water) NaOH. The initially heterogeneous reaction mixture slowly became homogeneous, and after 6 h, the reaction was poured into 75

mL EtOAc and extracted 2 × 75 mL H_2O. The aqueous layer was acidified to pH = 1 with concentrated HCl solution, then solid NaCl was added, and the mixture extracted 3 × 50 mL EtOAc. The combined ethyl acetate extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Toluene (50 mL) was added and removed in vacuo two times, and the residue was dissolved in 1 mL CH_2Cl_2 and 0.33 g of essentially pure **13** was obtained by adding hexane: $[\alpha]_D^{25} = -150$ (c = 0.37 MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.45 (s, 1H), 7.28−7.12 (m, 3H), 5.25 (s, 1H), 3.21 (s, 3H), 2.82 (s, 3H).

4-(3,4-Difluorophenyl)-6-methyl-2-methoxy-3,4-dihydropyrimidine-5-carboxylic Acid Methyl Ester (15). To a solution of methyl acetoacetate **6b** (8.0 g, 0.069 mol), 3,4-difluorobenzaldehyde **10** (9.8 g, 0.069 mol), acetic acid (0.490 g, 0.008 mole) and piperidine (0.69 g, 0.008 mol) in benzene (1.5 L) was added molecular sieves (37.9 g) and the mixture was stirred at room temperature for 48 h. The molecular sieves were removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified by trituration from hexane to yield the intermediate methyl 2-[(3,4-difluorophenyl)methylene]-3-oxobutyrate product as a yellow solid (12 g, 72%) as a mixture of cis and trans isomers. A suspension of the methyl 2-[(3,4-difluorophenyl)methylene]-3-oxobutyrate thus obtained (12 g, 49.9 mmol), *O*-methylisourea hemisulfate (11.15 g, 67.76 mmol, 1.5 equiv), and sodium bicarbonate (17 g, 203 mmol, 3 equiv) in DMF (110 mL) was stirred at 60 °C for 8 h. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The residue was purified by chromatography on silica gel eluting with 25−30% EtOAc/hexane, to give the product as a pale yellow solid (12.43 g, 84%): ^{1}H NMR ($CDCl_3$) δ 7.2−7.0 (m, 3H), 6.0 (s, 1H), 5.56 (s, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.33 (s, 3H). This material was resolved via preparative chiral HPLC (Chiracel OD, 60 mL/min, 5% ethanol/0.1% diethylamine/hexane) to afford **(+)-15** $[\alpha]_D^{25}$ = +28 (c = 0.1 MeOH) with greater than 95% ee. (Note the (+) isomer of **15** affords the (−) acid **20** after hydrolysis.)

4-(3,4-Difluorophenyl)-2-methoxy-1,4-dimethyl-3,4-dihydropyrimidine-5-carboxylic Acid Methyl Ester (17). To a suspension of a 60% oil dispersion of NaH (96 mg, 2.2 mmol) in DMF (3 mL) at 0 °C was added a DMF solution (5 mL) of **(+)15** (592 mg, 2.0 mmol). After the mixture was stirred 30 min, a DMF solution (2 mL) of methyl iodide (312 mg, 2.2 mmol) was added and the reaction stirred at rt for 45 min. The DMF was removed in vacuo, the residue treated with water and extracted with ethyl acetate (3×). The extracts were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo to give a crude oil (800 mg). Flash chromatography on silica gel (3% to 6% diethyl ether in methylene chloride) gave **18** (288 mg) and **17** (268 mg) as colorless oils (91.1% overall). The regiochemical assignment was made on the derivative prepared as follows. Upper component **18**: R_f = 0.54 (5% ether in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.26−7.00 (m, 3H), 5.18 (s, 1H), 3.90 (s, 3H), 3.62 (s, 3H), 2.83 (s, 3H), 2.36 (s, 3H). Lower component **17:** R_f = 0.33 (5% ether in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.27−6.98 (m, 3H), 5.55 (s, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.11 (s, 3H), 2.49 (s, 3H).

(−)-4-(3,4-Difluorophenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid (20). To a solution of **18** (278 mg, 0.896 mmol) dissolved in methylene chloride (4 mL) was added 1 N HCl in ether (1.66 mL), and stirred at room temperature for 2 h. The solvent was removed in vacuo, the residue treated with water and saturated sodium bicarbonate (aq) to adjust the pH = 9.0, and extracted with ethyl acetate (3×). The extracts were combined, washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give a white foam (296 mg). Crystallization from diethyl ether gave the product as white crystals (200 mg, 75%): $[\alpha_D]$ = −113 (c = 0.20 CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.60 (br s, 1H), 7.19−7.07 (m, 3H), 5.19 (s, 1H), 3.67 (s, 3H), 2.86 (s, 3H), 2.34 (s, 3H). X-ray crystallographic analysis of this intermediate established the regiochemistry of the alkylation (vide infra). This ester (650 mg, 2.19 mmol) was dissolved in methanol (10 mL), treated with 2.5 N sodium hydroxide (10 mL), and warmed to 50 °C for 8 h. The solvent was removed in vacuo, the remaining aqueous phase treated with 10% $KHSO_4$ (aq), and extracted with ethyl acetate (3×). The extracts were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated to dryness in vacuo to give a crude oil. Crystallization from diethyl ether gave **20** as a white solid (475 mg, 76.9%): $[\alpha_D]$ = −128 (c = 0.20 MeOH); ^{1}H NMR (DMSO) δ 9.37 (s, 1H), 7.47−7.38 (m, 1H), 7.31−7.24 (m, 1H), 7.14−7.07 (m, 1H), 5.19 (s, 1H), 2.71 (s, 3H), 2.23 (s, 3H).

The same procedure on **17** afforded **(−)-4-(3,4-difluorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid (19):** crystallized from diethyl ether; $[\alpha_D]$ = +48 (c = 0.145 MeOH); ^{1}H NMR (DMSO) δ 7.98 (d, 1H, J = 3.9 Hz), 7.45−7.35 (m, 1H), 7.25−7.17 (m, 1H), 7.10−7.03 (m, 1H), 5.12 (d, 1H, J = 3.9 Hz), 3.08 (s, 3H), 2.50 (s, 3H).

3-((1*S*)-3-Oxa-4,7,7-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carboxy)-4(*R*)-4-(3,4-difluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid, Methyl Ester (16). To a solution of 0.10 g (0.34 mmol) **15** in 1 mL CH_2Cl_2 were added 0.14 mL (1 mmol) Et_3N, 0.005 g DMAP, and 0.11 g (0.51 mmol) (1*S*)-(−)-camphanic chloride. The reaction mixture was stirred 5 min then diluted with ether, washed with water, saturated sodium bicarbonate solution, and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness in vacuo. Purification by flash chromatography (50% EtOAc:hexanes) afforded 0.168 g: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.05 (m, 3H), 6.11 (s, 1H), 3.90 (s, 3H), 3.70 (s, 3H), 2.49(s, 3H), 2.42(m, 1H), 2.19 (m, 1H), 1.97 (ddd, 1H, J = 13, 13, and 4.6 Hz), 1.73 (m, 1H), 1.23 (s, 3H), 1.10 (s, 3H), 0.87 (s, 3H). The dihydropyrimidine thusly generated (0.075 g, 0.15 mmol) in 1.5 mL CH_2Cl_2 was treated with 1.6 mL (1.6 mmol, 1 M etheral solution) HCl and the mixture stirred vigorously for 2 h. The reaction mixture was purged with argon and concentrated. Crystallization from hexane/ethanol afforded **16** as X-ray quality crystals (vide infra): ^{1}H NMR ($CDCl_3$) δ 7.23−7.07 (m, 3H), 6.10 (s, 1H), 3.75 (s, 3H), 2.76(m, 1H), 2.44(s, 3H), 2.37 (m, 1H), 1.92 (ddd, 1H, J = 13, 13, and 4.6 Hz), 1.72 (m, 1H), 1.59 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H).

4-(3,4-Difluorophenyl)-1,6-dimethyl-3-acetyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid (23). To a solution of 3 g (8 mmol) **22** in 30 mL DMF was added 3.8 mL (40 mmol) acetic anhydride and 0.4 g (10 mmol, 60% in mineral oil) NaH. The reaction mixture was heated to 80 °C for 4 h, then cooled and diluted with ether, washed with 1 N aq HCl, water, dilute aqueous LiCl solution, and brine. The ether layer was then dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (silica gel, linear gradient 25% EtOAc/hexanes to 30% EtOAc/hexanes afforded 1.91 g of benzyl ester that was dissolved in 70 mL EtOH and 30 mL EtOAc and treated with 0.19 g Pd (10% on carbon) and 1 atm H_2 for 3 h. The reaction mixture was filtered through Celite and concentrated in vacuo to give 1.54 g (59%) of **23**: ^{1}H NMR ($CDCl_3$) δ 7.15−7.05 (m, 2H), 7.00−6.90 (m, 1H), 6.65 (s, 1H), 3.25 (s, 3H), 2.60 (s, 3H), 2.55 (s, 3H).

4-(3,4-Difluorophenyl)-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid (24). To a suspension of **22** (10 g, 26.9 mmol) in toluene (200 mL) was added dimethyl sulfate (3.05 mL, 32.2 mmol) followed by NaH (60% dispersion in oil, 1.13 g, 28.2 mmol) in portions. The reaction mixture was stirred at 60 °C for 3 h, allowed to cool to room temperature and diluted with diethyl ether and water. The organic layer was separated, washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 30% ethyl acetate in hexane to 40%) to provide the ester (5.22 g, 50%). The benzyl ester (400 mg, 1.03 mmol) in 20 mL of 1:1 EtOAc/EtOH was treated with 0.03 g Pd (10% on carbon) under 1 atm H_2 for 2 h. Filtration through Celite and removal of the solvent in vacuo afforded 290 mg (94.5%) of **24**: ^{1}H NMR

($CDCl_3$) δ 7.15−7.05 (m, 2H), 7.00−6.95 (m, 1H), 5.25 (s, 1H), 3.25 (s, 3H), 2.95 (s, 3H), 2.55 (s, 3H).

4-(3,4-Difluorophenyl)-1,6-dimethyl-3-carbomethoxy-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid (25). To a solution of 3 g (8 mmol) **22** in 50 mL THF were added 3.11 mL (40 mmol) methyl chloroformate and 0.4 g (10 mmol, 60% in mineral oil) NaH. The reaction mixture was heated to 80 °C and additional portions of NaH and methyl chloroformate were added until the reaction was judged complete by TLC. The reaction mixture was then cooled, quenched with methanol, and diluted with ether, washed with 1 N aq HCl, water, dilute aqueous LiCl solution, and brine. The ether layer was then dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (silica gel, linear gradient 3:3:1 CH_2Cl_2/hexanes/ether to 1:1:1 CH_2Cl_2/hexanes/ether afforded 2.5 g of benzyl ester that was dissolved in 100 mL EtOH and 50 mL EtOAc and treated with 0.25 g Pd (10% on carbon) and 1 atm H_2 for 1.5 h. The reaction mixture was filtered through Celite and concentrated in vacuo to give 1.5 g (57%) of **25**: ^{1}H NMR ($CDCl_3$) δ 7.20−7.05 (m, 2H), 7.00−6.90 (m, 1H), 6.35 (s, 1H), 3.95 (s, 3H), 3.20 (s, 3H), 2.55 (s, 3H).

Trifluoromethanesulfonic Acid 1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl Ester (29). To a solution of diisopropylamine (13.4 mL, 0.096 mol) in tetrahydrofuran (400 mL), cooled to −78 °C was added *n*-butyllithium (2.5 M in hexanes, 38.4 mL, 0.096 mol) followed by addition of 1-*tert*-butoxycarbonyl-4-piperidone **27** (16 g, 0.080 mol) in tetrahydrofuran (200 mL). After stirring for 10 min, a solution of *N*-phenyltrifluoromethane sulfonimide (31.4 g, 0.088 mol) in tetrahydrofuran (100 mL) was added. The reaction mixture was stirred for 15 min at −78 °C, allowed to warm to room temperature and quenched with saturated bicarbonate solution. The reaction was diluted with ether and washed with 15% potassium hydrogen sulfate, saturated bicarbonate solution, 1 N sodium hydroxide × 4, water × 2 and brine. Drying and solvent evaporation gave a solid; flash chromatography (silica gel, hexanes−ethyl acetate, 95:5) gave **29** (20.2 g, 76%): ^{1}H NMR ($CDCl_3$) δ 5.76 (br s, 1H), 4.04 (d, 2H, J = 2.6 Hz), 3.63 (t, 2H, J = 5.6 Hz), 1.48 (s, 9H), 2.44 (m, 2H).

4-(2-Cyano-4-fluorophenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (70). A solution of 2-bromo-5-fluorobenzonitrle **30a** (8.1 g, 40.5 mmol) in THF-(50 mL) at was added rapidly to a solution of *n*-BuLi (20 mL, 2.5 M, 50 mmol) in THF at −78 °C and the resulting dark solution stirred at −78 °C for 5 min. To this solution was added $ZnCl_2$ (0.5 M in THF, 89 mL) and the solution was warmed to 0 °C. Palladium tetrakistriphenylphosphine (1.5 g, 1.3 mmol) was added followed by **29** (9 g, 27.16 mmol). The reaction was heated to 40 °C for 30 min and then cooled to room temperature and poured into saturated aqueous sodium bicarbonate (1 L). The mixture was extracted with ethyl acetate (3 × 300 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 15% to 30% ethyl acetate/hexanes to give 7.9 g of **70**: ^{1}H NMR ($CDCl_3$) δ 7.4−7.25 (m, 3H), 5.95 (br s, 1H), 4.09 (br s, 2H), 3.65−3.60 (m, 2H), 2.50 (m, 2H), 1.50 (s, 9H).

4-(2-Cyano-4-fluorophenyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (71). To a solution of **70** (7.89 g, 26.1 mmol) in absolute ethanol (270 mL) was added 10% palladium on carbon (3.95 g) and acetic acid (0.79 mL) and the mixture hydrogenated at 60 psi for 2.5 h. The catalyst was removed by filtration through Celite and the filtrate concentrated to dryness. Purification by flash chromatography (silica gel, 10% to 15% ethyl acetate:hexane) gave **71** as a colorless oil (5.75 g, 72.3%): ^{1}H NMR ($CDCl_3$) δ 7.35−7.25 (m, 3H), 4.30−4.11 (br d, 2H), 3.15−3.06 (m, 1H), 2.91−2.82 (t, 2H), 1.87−1.82 (br d, 2H), 1.68−1.62 (m, 2H), 1.49 (s, 9H).

5-Fluoro-2-piperidin-4-ylbenzonitrile Hydrochloride (32a). An ethyl acetate solution (56 mL) of **71** (5.64 g, 18.5 mmol) was cooled to 0 °C and hydrogen chloride gas was bubbled through the solution until saturated (10 min). The solution was stirred at 0 °C for 20 min and then concentrated in vacuo to give **32a** as a white solid (4.46 g, 100%): ^{1}H NMR (CD_3OD) δ 7.61−7.53 (m, 2H), 7.53−7.43 (m, 1H), 3.60−3.50 (m, 2H), 3.40−3.16 (m, 3H), 2.18−1.94 (m, 4H).

2-(1-*tert*-Butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)benzonitrile (72). To a suspension of **29** (10.5 g, 0.032 mol) and tetrakis(triphenylphosphine) palladium(0) (1.8 g, 1.6 mmol) in tetrahydrofuran (95 mL) was added iodo(2-cyanophenyl)zinc (0.5 M in tetrahydrofuran, 94 mL, 0.047 mol) dropwise. The reaction mixture was stirred at room temperature for 0.5 h and quenched with saturated bicarbonate solution. The mixture was diluted with ethyl acetate and washed with water × 2 and brine. Drying and solvent evaporation gave an oil (13 g), purification by flash chromatography (silica gel, hexanes−ethyl acetate, 92:8) gave **72** (8.7 g, 97%): ^{1}H NMR ($CDCl_3$) δ 7.66 (bd, 1H, J = 8 Hz), 7.54 (bt, 1H, J = 7.6 Hz), 7.34 (m, 2H), 5.98 (m, 1H), 4.12 (d, 2H, J = 3.2 Hz), 3.67 (t, 2H, J = 6.0 Hz), 2.53 (m, 2H), 1.50 (s, 9H).

2-(1-*tert*-Butoxycarbonylpiperidin-4-yl)benzonitrile (73). To a solution of **72** (5.3 g, 0.019 mol) and acetic acid (0.28 mL, 4.9 mmol) in ethanol (200 mL), degassed with argon was added palladium on carbon (10%, 1.8 g). The reaction was hydrogenated on a Parr apparatus at 50 psi for 15 h. The mixture was recharged twice with acetic acid (0.14 mL, 0.28 mL) and palladium on carbon (900 mg, 1.8 g), hydrogenated as above and filtered through Celite. Solvent evaporation gave **73** (4.9 g, 91%): ^{1}H NMR ($CDCl_3$) δ 7.63 (bd, 1H, J = 7.7 Hz), 7.56 (bt, 1H, J = 7.7 Hz), 7.31 (m, 2H), 4.27 (bs, 2H), 3.14 (tt, 1H, J = 12 Hz, J = 4 Hz), 2.88 (bt, 2H, J = 14 Hz), 1.86 (bd, 2H, J = 13.4 Hz), 1.49 (s, 9H), 1.64 (m, 2H).

2-(Piperidin-4-yl)benzonitrile Hydrochloride (32b). To a solution of **73** (1.7 g, 5.9 mmol) in 50 mL ethyl acetate, cooled to 0 °C was added hydrogen chloride gas, bubbled vigorously for 5 min. The reaction mixture was stirred for 10 min at 0 °C, purged with argon and concentrated. Flushing with ethyl acetate × 3 and concentration provided **32b** (1.3 g, 100%): ^{1}H NMR (DMSO) δ 9.10 (bd, 2H), 7.83 (bd, 1H, J = 7.0 Hz), 7.74 (bt, 1H, J = 7.7 Hz), 7.46 (m, 2H), 3.36 (m, 2H), 3.21 (tt, 1H, J = 12 Hz, J = 3.8 Hz), 3.07 (m, 2H), 1.98 (m, 4H).

2-Cyano-4-fluorophenylacetonitrile (31f). A solution of 1.0 g (7.2 mmol) 2,5-difluorobenzonitrile, 1.2 mL (8.4 mmol) *tert*-butyl cyanoacetate, and 3.5 g (10.7 mmol) cesium carbonate in 30 mL DMSO was heated to 100 °C for 2 h. The reaction was cooled to room temperature, diluted with 600 mL ether, washed with 300 mL 10% $KHSO_4$, 300 mL dilute brine, and 300 mL brine. The ether layer was dried over $MgSO_4$, filtered, and concentrated to give 1.6 g of an oil (TLC R_f =0.34 (20% EtOAc:hexanes)). This oil was dissolved in 100 mL 1,2-dichloroethane and 0.5 mL trifluoroacetic acid was slowly added. The reaction was heated to reflux for 4 h, cooled, diluted with 200 mL ether, washed with 100 mL saturated aqueous sodium bicarbonate solution, 100 mL brine, then dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (4 × 12 cm silica gel, linear gradient 20−50% EtOAc:hexanes) afforded 0.30 g (26%) of **31f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (m, 1H), 7.41 (m, 2H), 3.95 (s, 2H).

4-Cyano-4-(2-cyano-4-fluorophenyl)piperidine-1-carboxylic Acid *tert*-Butyl Ester (75). To a solution of 0.098 g (0.61 mmol) **31f** and 0.17 g (0.07 mmol) *N*-Boc-di(2-chloroethyl)amine in 3 mL DMSO was added 0.69 g (2.1 mmol) cesium carbonate. The reaction was stirred 24 h at room temperature, then diluted with 100 mL ethyl acetate, washed with 100 mL aqueous 10% $KHSO_4$ solution, 100 mL saturated sodium bicarbonate solution, 100 mL brine; then dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash chromatography (3 × 12 cm silica gel, linear gradient 0−4% acetone/CH_2Cl_2) afforded 0.049 g (24%) of **75**: TLC R_f = 0.25 (30% EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 1H), 7.50 (m, 1H), 7.37 (m, 1H), 4.37 (br m, 2H), 3.25 (br m, 2H), 2.30 (m, 4H), 1.50 (s, 9H).

4-Cyano-4-(2-cyano-4-fluorophenyl)piperidine (32f). To a 0 °C solution of 0.53 g (1.63 mmol) **75** in 10 mL ethyl acetate was bubbled through HCl gas for 5 min. The heterogeneous reaction mixture was stirred 5 more minutes at 0 °C, then diluted with 70 mL EtOAc and extracted 2 × 75 mL H_2O. The

combined aqueous extracts were brought to pH 11 with 3 mL 50% aqueous NaOH and extracted 3 × 50 mL ethyl acetate, adding solid NaCl to each extraction. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give 0.33 g of an oil that was used immediately without further purification.

4-Cyano-4-(2-cyanophenyl)piperidine (32c) prepared in analogy to **33f** and used immediately without further purification.

4-(4-Fluorophenyl)-*tert*-butoxycarbonylpiperidine-4-carbonitrile (76). To a solution of bis(2-chloroethyl)-*tert*-butoxycarbonylamine (3.0 g, 12.39 mmol) in 75 mL of DMF was added 4-fluorobenzylacetonitrile (1.515 g, 11.27 mmol). This solution was cooled to 0 °C, and a 60% dispersion of sodium hydride was added portion wise (1.17 g, 29.25 mmol). The solution was stirred for 20 min, warmed to r.t., then heated to 80 °C for 24 h. It was poured onto water, and extracted with ethyl acetate. The combined organic layers were washed with saturated sodium chloride, dried with magnesium sulfate, and concentrated in vacuo. Purification by flash chromatography (silica gel, 25% ethyl acetate, hexane) afforded **76** (1.47 g, 43%): ^{1}H NMR ($CDCl_3$) δ 7.50−7.40 (m, 2H), 7.15−7.05 (m, 2H), 4.40−4.20 (br m, 2H), 3.30−3.10 (br m, 2H), 2.15−2.05 (m, 2H), 2.00−1.85 (m, 2H), 1.49 (s, 9H).

4-(4-Fluorophenyl)piperidine-4-carbonitrile Hydrochloride (32d). A solution of **76** (840 mg, 2.74 mmol) in 50 mL ethyl acetate was cooled to 0 °C. Hydrogen chloride gas was bubbled through the solution for 2 min. It was stirred for 10 min and then concentrated in vacuo to give the product (340 mg, 98%): ^{1}H NMR (CD_3OD) δ 7.65−7.55 (M, 2H), 7.30−7.20 (m, 2H), 3.68−3.60 (m, 2H), 3.45−3.00 (m, 2H), 2.50−2.25 (m, 4H).

4-(2,4-Difluorophenyl)piperidine-4-carbonitrile hydrochloride (32e): prepared in analogy to **33d**. ^{1}H NMR (CD_3OD) δ 7.65−7.55 (m, 1H), 7.20−7.05 (m, 2H), 3.70−3.60 (m, 2H), 3.45−3.00 (m, 2H), 2.60−2.50 (m, 2H), 2.50−2.35 (m, 2H).

4-(4-Fluorophenyl)piperidine Hydrochloride (32h). To a solution of 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride **26** (10 g) in methanol (200 mL) was added 10% palladium on charcoal (0.5 g) and the mixture was hydrogenated at 50 psi H_2 for 3 h. The catalyst was removed by filtration and solvent was evaporated to leave **32h** (10 g) as a white powder, which was used in the next step without purification: mp 181−182 °C; ^{1}H NMR ($CDCl_3$) δ 9.71 (br s, 1H), 9.60 (br s, 1H), 7.19−7.22 (m, 2H), 6.96−7.03 (m, 2H), 3.60−3.64 (br d, 2H), 2.91−3.07 (br q, 2H), 2.70−2.80 (m, 1H), 2.14−2.29 (m, 2H), 1.95−2.03 (br d, 2H).

3-Bromo-1-*tert*-butoxycarbonylpropylamine (77). To a suspension of 3-bromopropylamine hydrobromide (5.0 g, 0.023 mol) and di-*tert*-butyl dicarbonate (5.0 g, 0.023 mol) in methylene chloride (125 mL), cooled to 0 °C was added triethylamine (3.2 mL, 0.023 mol). The reaction mixture was stirred for 3 h at room temperature, diluted with methylene chloride and washed twice with water and brine. Drying and solvent evaporation gave 3-bromo-1-*tert*-butoxycarbonylpropylamine (5.3 g, 96%): ^{1}H NMR ($CDCl_3$) δ 4.64 (bs, 1H), 3.43 (m, 2H), 3.28 (m, 2H), 2.05 (m, 2H), 1.46 (s, 9H).

Representative Procedure for Conversion of 32 to 33. Note: **32g** was purchased from Sigma and **32i** was prepared according to Lunn, G. *J. Org. Chem.* **1992**, *57*, 6317−6320.

2-[1-(3-*tert*-Butoxycarbonylaminopropyl)piperidin-4-yl]benzonitrile (78). A suspension of **32b** (600 mg, 2.7 mmol), 3-bromo-1-*tert*-butoxycarbonylpropylamine (0.67 g, 2.8 mmol) and triethylamine (0.77 mL, 5.5 mmol) in DMF (12 mL) was stirred at room temperature for 15 h. The reaction mixture was diluted with ethyl acetate and washed with saturated bicarbonate solution, water (twice), and brine. Drying and solvent evaporation gave an oil. Purification by flash chromatography (silica gel, ethyl acetate) gave **78** (0.61 g, 66%): ^{1}H NMR ($CDCl_3$) δ 7.62 (bd, 1H, J = 7.7 Hz), 7.54 (bt, 1H, J = 7.7 Hz), 7.39 (bd, 1H, J = 7.9 Hz), 7.29 (m, 1H), 5.61 (bs, 1H), 3.22 (m, 2H), 2.97−3.08 (m, 3H), 2.47 (t, 2H, J = 6.7 Hz), 2.12 (bt, 2H, J = 10.8 Hz), 1.89 (m, 2H), 1.80 (bt, 2H, J = 12 Hz), 1.69 (m, 2H), 1.45 (s, 9H).

2-[1-(3-Aminopropyl)piperidin-4-yl]benzonitrile Hydrochloride (33b). To a solution of **78** (0.73 g, 2.1 mmol) in ethyl acetate (100 mL), cooled to 0 °C was added hydrogen chloride gas, bubbled vigorously for 5 min. The reaction mixture was stirred for 10 min at 0 °C, purged with argon and concentrated. Flushing with ethyl acetate (twice) and concentration gave 2-[1-(3-aminopropyl)piperidin-4-yl]benzonitrile hydrochloride (0.66 g, 100%): ^{1}H NMR (DMSO) δ 11.1 (bd, 1H), 8.14 (bs, 2H), 7.84 (bd, 1H, J = 7.9 Hz), 7.75 (bt, 1H, J = 8 Hz), 7.47 (m, 2H), 3.56 (bd, 2H, J = 11.7 Hz), 3.18 (m, 4H), 2.95 (m, 2H), 2.28 (m, 2H), 2.10 (m, 2H), 2.00 (m, 2H).

2-[1-(3-Aminopropyl)piperidin-4-yl]-4-fluorobenzonitrile hydrochloride (33a): ^{1}H NMR (CD_3OD) δ 7.65−7.50 (m, 2H), 7.5−7.43 (m, 1H), 3.75−3.65 (m, 2H), 3.40−3.1 (m, 3H), 2.25−2.1 (m, 4H).

1-(3-Aminopropyl)-4-(2-cyanophenyl)piperidine-4-carbonitrile hydrochloride (33c): ^{1}H NMR ($CDCl_3$) δ 7.97−7.95 (d, 1H, J = 7.1 Hz), 7.83−7.80 (t, 1H, J = 7.1), 7.72−7.63 (m, 2H), 3.95−3.90 (d, 2H, J = 15 Hz), 3.51−3.29 (m, 4H), 3.12−3.07 (t, 2H, J = 7.8), 2.93−2.88 (br m, 2H), 2.67−2.55 (m, 2H), 2.22−2.01 (m, 2H).

1-(3-Aminopropyl)-4-(4-fluorophenyl)piperidine-4-carbonitrile hydrochloride (33d): ^{1}H NMR (CD_3OD) δ 7.66−7.61 (m, 2H), 7.26−7.20 (m, 2H), 3.85−8.81 (m, 2H), 3.45−3.25 (m, 4H), 3.10 (t, 2H, J = 7.6 Hz), 2.60−2.52 (m, 4H), 2.28−2.15 (m, 2H).

1-(3-Aminopropyl)-4-(2,4-difluorophenyl)piperidine-4-carbonitrile hydrochloride (33e): ^{1}H NMR (CD_3OD) δ 7.66−7.55 (m, 2H), 7.21−7.05 (m, 2H), 3.90−3.85 (m, 2H), 3.55−3.25 (m, 4H), 3.15−3.05 (m, 2H), 2.70−2.55 (m, 4H), 2.30−2.015 (m, 2H).

1-(3-Aminopropyl)-4-cyano-4-(2-cyano-4-fluorophenyl)-piperidine hydrochloride (33f): ^{1}H NMR (300 MHz, CD_3OD) δ 7.82 (dd, 1H, J = 8.06 and 2.93 Hz), 7.75 (dd, 1H, J = 8.79 and 4.88 Hz), 7.60 (m, 1H), 3.95 (d, 2H, J = 13.0 Hz), 3.41 (m, 4H), 3.10 (t, 2H, J = 7.57 Hz), 2.90 (m, 2H), 2.63 (br t, 2H, J = 14.7 Hz), 2.23 (m, 2H).

1-(3-Aminopropyl)-4-(4-fluorophenyl)-4-hydroxypiperidine hydrochloride (33g): ^{1}H NMR (CD_3OD) δ 7.6−7.45 (m, 2H), 7.15−7.05 (m, 2H), 3.65−3.40 (m, 4H), 3.3−3.25 (m, 2H), 3.15−3.05 (t, J = 8.2 Hz, 2H), 2.55−2.40 (m, 2H), 2.30−2.15 (m, 2H), 2.05−1.8 (m, 2H).

1-(3-Aminopropyl)-4-(4-fluorophenyl)piperidine (33h): ^{1}H NMR ($CDCl_3$) δ 7.14−7.20 (m, 2H), 6.93−7.00 (m, 2H), 3.03−3.07 (br d, 2H), 2.70−2.85 (br t, 2H), 2.40−2.55 (m, 3H), 1.96−2.07 (m, 4H), 1.60−1.83 (m, 6H).

1-(3-Aminopropyl)-4-(2-pyridyl)piperidine (33i): ^{1}H NMR (CD_3OD) δ 8.48 (dd, J = 0.9 Hz, J = 4.2 Hz, 1H), 7.16 (dt, J = 0.9 Hz, J = 8.7 Hz, 1H), 7.05−7.09 (m, 4H), 3.02−3.06 (br m, 2H), 2.37−2.75 (m, 3H), 2.02−2.06 (m, 2H), 1.50−1.99 (m, 10H).

Representative Procedure for Amide Bond Formation between Amines 33a−h and Dihydropyrimidinone Acids. 4-(*R*)-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid {3-[4-(2-Cyano-4-fluorophenyl)piperidin-1-yl]propyl}amide (52). A solution of **33a** (90 mg, 0.296 mmol), triethylamine (95.6μL, 0.688 mmol), **9d** (88.3 mg, 0.296 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (56.6 mg, 0.296 mmol), and 1-hydroxybenzotriazole hydrate (40.0 mg, 0.296 mmol) were combined in dimethylformamide (2 mL) and stirred for 24 h. After removal of the solvent in vacuo, the residue was treated with 100 mL saturated aqueous sodium bicarbonate and extracted 3 × 75 mL ethyl acetate. The extracts were combined, washed with 150 mL brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, 160/10/1 methylene chloride/methanol/concentrated ammonium hydroxide) gave 93.0 mg (63.8%) of **52** as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46−7.38 (m, 3H), 7.24−7.07 (m, 4H), 6.77 (br s, 1H), 5.68 (s, 1H), 5.40 (s, 1H), 4.53 (d, 1H, J = 14 Hz), 4.34 (d, 1H, J = 14 Hz), 3.43 (s, 3H), 3.43−3.36 (m, 1H), 3.27−3.18 (m, 1H), 3.02−2.86 (m, 3H), 2.40−2.33 (m, 2H), 2.16−1.99 (m, 2H), 1.90−1.60 (m, 6H). Anal. C,H,N.

The following examples were prepared essentially as described above. Compounds that were not solid as the free base were treated with 1 N etheral HCl in ethyl acetate and the solvent removed in vacuo to give the mono- or di-HCl salt as indicated by C,H,N analysis. Racemic compounds were resolved to give individual enantiomers (**35**&**36**, **37**&**38**, **39**&**40**) by preparative chiral HPLC (Chiralpak AD, 70:30 0.1% diethylamine in hexane:ethanol).

(4*R*)-4-(3,4-Difluorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide (35): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (br s, 1H),7.35−6.95 (m, 7H), 5.45 (br s, 1H), 5.25 (br s, 1H), 3.60−3.44 (m, 1H), 3.30−3.15 (m, 1H), 3.15 (s, 3H), 3.10−2.95 (m, 1H), 2.85−2.65 (m, 1H), 2.60−2.30 (m, 3H), 2.18 (s, 3H), 1.80−1.30 (m, 8H); optical rotation $[\alpha]^{23}_D$ −97 (*c* = 0.18, $CDCl_3$). Anal. C,H,N.

(4*S*)-4-(3,4-Difluorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide (36): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (br s, 1H),7.35−6.95 (m, 7H), 5.45 (br s, 1H), 5.25 (br s, 1H), 3.60−3.44 (m, 1H), 3.30−3.15 (m, 1H), 3.15 (s, 3H), 3.10−2.95 (m, 1H), 2.85−2.65 (m, 1H), 2.60−2.30 (m, 3H), 2.18 (s, 3H), 1.80−1.30 (m, 8H); optical rotation $[\alpha]^{23}_D$ +88 (*c* = 0.22, $CDCl_3$). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide (37): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.85 (br s, 1H), 8.05 (br s, 1H), 7.50−7.00 (m, 7H), 5.25 (s, 1H), 3.60−2.70 (m, 9H), 3.10 (s, 3H), 2.75 (s, 3H), 2.15 (s, 3H), 2.10−1.70 (m, 6H); optical rotation $[\alpha]^{23}_D$ −30 (*c* = 0.12, MeOH). Anal. C,H,N.

(4*S*)-4-(3,4-Difluorophenyl)-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide (38): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.85 (br s, 1H), 8.05 (br s, 1H), 7.50−7.00 (m, 7H), 5.25 (s, 1H), 3.60−2.70 (m, 9H), 3.10 (s, 3H), 2.75 (s, 3H), 2.15 (s, 3H), 2.10−1.70 (m, 6H); optical rotation $[\alpha]^{23}_D$ +40 (*c* = 0.1, MeOH). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-cyano-4-(4-fluorophenyl)piperidin-1-yl]propyl}amide hydrochloride (39): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46−7.40 (m, 2H), 7.20−7.11 (m, 5H), 6.95 (s, 1H), 5.95 (s, 1H), 5.43 (s, 1H), 5.26 (s, 1H), 3.31−3.27 (m, 2H), 2.97−2.90 (m, 2H), 2.45−2.38 (m, 4H), 2.01−1.89 (m, 4H); optical rotation $[\alpha]^{23}_D$ −16.80 (*c* = 0.25, CH_3OH). Anal. C,H,N.

(4*S*)-4-(3,4-Difluorophenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-cyano-4-(4-fluorophenyl)piperidin-1-yl]propyl}amide (40): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46−7.40 (m, 2H), 7.20−7.11 (m, 5H), 6.95 (s, 1H), 5.95 (s, 1H), 5.43 (s, 1H), 5.26 (s, 1H), 3.31−3.27 (m, 2H), 2.97−2.90 (m, 2H), 2.45−2.38 (m, 4H), 2.01−1.89 (m, 4H); optical rotation $[\alpha]^{23}_D$ +39.84 (*c* = 0.26, CH_3OH). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(2-cyanophenyl)piperidin-1-yl]propyl}amide (41): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.69−7.62 (m, 2H), 7.49−7.46 (m, 1H), 7.40−7.37 (m, 1H), 7.25−7.13 (m, 3H), 5.43 (s, 1H), 3.24−3.22 (m, 2H), 3.05−2.97 (m, 3H), 2.35−2.32 (m, 2H), 2.12−2.08 (m, 2H), 1.85−1.66 (m, 6H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(2-cyanophenyl)piperidin-1-yl]propyl}amide (42): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65−7.52 (m, 2H), 7.34−7.25 (m, 2H), 7.22−7.00 (m, 5H), 5.47 (br s, 2H), 3.51−3.40 (m, 1H), 3.28−3.18 (m, 1H), 3.04−2.88 (m, 2H), 2.84−2.75 (m, 1H), 2.50−2.31 (m, 2H), 2.12 (s, 3H), 2.11−1.96 (m, 2H), 1.94−1.84 (m, 1H), 1.82−1.72 (m, 1H), 1.70−1.52 (m, 4H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-6-trifluoromethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(2-cyanophenyl)piperidin-1-yl]propyl}amide (43): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66−7.52 (m, 2H), 7.48 (br s, 1H), 7.34−7.08 (m, 6H), 5.70 (br s, 1H), 5.56 (s, 1H), 3.40−3.30 (m, 1H), 3.29−3.17 (m, 1H), 3.03−2.84 (m, 2H), 2.74−2.67 (m, 1H), 2.50−2.26 (m, 2H), 2.12−1.94 (m, 2H), 1.90−1.75 (m, 2H), 1.70−1.40 (m, 4H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(2-cyanophenyl)piperidin-1-yl]propyl}amide hydrochloride (44): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.79−7.67 (m, 2H), 7.55−7.41 (m, 2H), 7.33−7.13 (m, 3H), 5.44 (s, 1H), 4.35 (s, 2H), 3.66−3.50 (m, 3H), 3.42 (s, 3H), 3.39−3.23 (m, 2H), 3.20−3.06 (m, 2H), 3.05−2.93 (m, 2H), 2.22−2.03 (m, 4H), 1.96−1.85 (m, 2H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide (45): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.29−6.97 (m, 7H), 5.43 (s, 1H), 3.23−3.18 (m, 2H), 2.99−2.96 (m, 2H), 2.53−2.50 (m, 1H), 2.29−2.26 (m, 2H), 2.07−1.99 (m, 2H), 1.77−1.64 (m, 6H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide hydrochloride (46): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.31−7.04 (m, 7H), 5.37 (s, 1H), 3.54−3.40 (m, 2H), 3.05−2.93 (m, 4H), 2.18 (s, 3H), 2.01−1.87 (m, 4H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-2-oxo-6-trifluoromethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide hydrochloride (47): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.35−7.21 (m, 7H), 5.38 (s, 1H), 3.60−3.57 (m, 2H), 3.20−2.91 (m, 6H), 2.19−1.82 (m, 6H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide (48): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21−6.89 (m, 7H), 5.65 (s, 1H), 5.43 (s, 1H), 4.54−4.49 (d, 1H, *J* = 13.92 Hz), 4.36−4.31 (d, 1H, *J* = 13.91 Hz), 3.42 (s, 3H), 3.36−3.17 (m, 1H), 2.96−2.93 (d, 1H, *J* = 10.25 Hz), 2.86−2.82 (d, 1H, *J* = 10.74), 2.51−2.24 (m, 3H), 2.05−1.52 (m, 10H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(2-cyano-4-fluorophenyl)piperidin-1-yl]propyl}amide hydrochloride (49): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.61−7.46 (m, 3H), 7.31−7.20 (m, 3H), 5.43 (s, 1H), 3.42−3.39 (m, 1H), 3.26−2.87 (m, 5H), 2.13−1.83 (m, 6H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(2-cyano-4-fluorophenyl)piperidin-1-yl]propyl}amide (50): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.36 (m, 3H), 7.22−7.03 (m, 3H), 6.93 (s, 1H), 5.55 (s, 1H), 5.47 (s, 1H), 4.77 (s, 1H), 3.51−3.40 (m, 1H), 3.28−3.15 (m, 1H), 3.04−2.87 (m, 2H), 2.83−2.75 (m, 1H), 2.45−2.29 (m, 2H), 2.13 (s, 3H), 2.10−1.96 (m, 2H), 1.94−1.83 (m, 1H), 1.82−1.72 (m, 1H), 1.70−1.48 (m, 4H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-6-trifluoromethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(2-cyano-4-fluorophenyl)piperidin-1-yl]propyl}amide (51): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.07 (m, 8H), 5.74 (s, 1H), 5.55 (s, 1H), 3.41−3.29 (m, 1H), 3.28−3.17 (m, 1H), 3.03−2.86 (m, 2H), 2.74−2.67 (m, 1H), 2.50−2.28 (m, 2H), 2.12−1.94 (m, 2H), 1.90−1.72 (m, 2H), 1.70−1.41 (m, 4H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid [3-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′]bipyridinyl-1′-yl)propyl]amide dihydrochloride (52): ^{1}H NMR (CD_3OD, 300 MHz) δ 8.79−8.77 (m, 1H), 8.56−8.53 (m, 1H), 8.00−7.92 (m, 2H), 7.31−7.19 (m, 3H), 5.44 (s, 1H), 4.28−4.23 (m, 1H), 3.70−3.64 (m, 1H), 3.50−3.05 (m, 6H), 2.38−1.85 (m, 6H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid [3-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′]bipyridinyl-1′-yl)propyl]amide (53): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.97 (br s, 1H), 8.82 (d, 1H, *J* = 4 Hz), 8.56 (br s, 1H), 7.63 (t, 1H, *J* = 7 Hz), 7.25−7.04 (m, 5H), 6.26 (br s, 1H), 5.64 (d, 1H, *J* = 5 Hz), 3.68−3.60 (m, 1H), 3.38−3.26 (m, 1H), 3.17−3.02 (m, 2H), 2.77−2.50 (m, 3H), 2.31

(s, 3H), 2.14−1.98 (m, 2H), 1.91−1.79 (m, 2H), 1.78−1.69 (m, 2H), 1.63−1.58 (m, 2H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-6-trifluoromethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid [3-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′]bipyridinyl-1′-yl)propyl]-amide (54): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (d, 1H, J = 5 Hz), 8.57 (br s, 1H), 8.68 (t, 1H, J = 8 Hz), 7.42 (br s, 1H), 7.28−7.10 (m, 5H), 6.67 (br s, 1H), 5.60 (s, 1H), 3.50−3.30 (m, 2H), 3.10−3.01 (m, 1H), 2.96−2.87 (m, 1H), 2.77−2.63 (m, 1H), 2.60−2.41 (m, 2H), 2.10−1.95 (m, 2H), 1.92−1.81 (m, 2H), 1.80−1.56 (m, 4H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid [3-(3′,4′,5′,6′-tetrahydro-2′*H*-[2,4′]bipyridinyl-1′-yl)propyl]-amide dihydrochloride (55): ^{1}H NMR (CD_3OD, 300 MHz) δ 8.86−8.80 (m, 1H), 8.20−8.09 (m, 1H), 8.10−7.97 (m, 2H), 7.35−7.17 (m, 3H), 5.28 (s, 1H), 4.36 (s, 2H), 3.75−3.62 (m, 3H), 3.43 (s, 3H), 3.40−3.27 (m, 2H), 3.26−3.11 (m, 2H), 3.10−3.00 (m, 2H), 2.41−2.19 (m, 4H), 2.00−1.92 (m, 2H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]propyl}amide hydrochloride (56): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.55−7.43 (m, 2H), 7.30−7.08 (m, 5H), 5.44 (s, 1H), 3.45−3.40 (m, 1H), 3.07−2.99 (m, 2H), 2.31−2.20 (m, 2H), 2.02−1.90 (m, 4H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-cyano-4-(fluorophenyl)piperidin-1-yl]propyl}amide hydrochloride (57): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.63−7.58 (m, 2H), 7.30−7.18 (m, 5H), 5.42 (s, 1H), 3.78−3.63 (m, 1H), 3.53−3.42 (m, 1H), 3.20−3.05 (m, 2H), 2.58−2.34 (m, 6H), 2.01−1.85 (m, 3H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-cyano-4-(2-cyanophenyl)piperidin-1-yl]propyl}amide hydrochloride (58): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87−7.49 (m, 5H), 7.25−7.05 (m, 3H), 6.72 (m, 1H), 5.88 (s, 1H), 5.49 (s, 1H), 5.30 (s, 1H), 3.40−3.25 (m, 2H), 3.13−3.03 (m, 2H), 2.58−2.46 (m, 4H), 2.22−2.15 (m, 2H), 1.85−1.62 (m, 3H), 1.3−1.15 (m, 2H). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide (59): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17−6.97 (m, 8H), 5.52 (br s, 1H), 5.52 (s, 1H), 3.59−3.48 (m, 1H), 3.26−3.14 (m, 1H), 3.03−2.92 (m, 1H), 2.86 (s, 3H), 2.72−2.62 (m, 1H), 2.50−2.24 (m, 3H), 2.10 (s, 3H), 2.08−1.96 (m, 1H), 1.95−1.80 (m, 2H), 1.74−1.50 (m, 4H), 1.40−1.28 (m, 1H); optical rotation $[\alpha]^{23}_D$ −82.2 (c = 0.135, MeOH). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-1,6-dimethyl-3-acetyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide hydrochloride (60): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.70 (br s, 1H), 7.90 (br s, 1H), 7.35−6.90 (m, 7H), 6.43 (s, 1H), 3.70−3.30 (m, 4H), 3.19 (s, 3H), 3.00−1.85 (m, 11H), 2.50 (s, 3H), 2.41 (s, 3H); MS (FAB) M + 1 = 543.3. Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-1,6-dimethyl-3-carbomethoxy-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}amide hydrochloride (61): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.45 (br s, 1H), 8.41 (br t, 1H, J = 6 Hz), 7.50−7.14 (m, 7H), 5.96 (s, 1H), 3.79 (s, 3H), 3.51−3.35 (m, 4H), 3.34−3.20 (m, 2H), 3.20−2.73 (m, 3H), 3.06 (s, 3H), 2.22 (s, 3H), 2.20−1.80 (m, 6H); MS (ES) M + 1 = 559.3. Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(2-cyano-4-fluorophenyl)piperidin-1-yl]propyl}amide (62): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.29 (m, 2H), 7.25−7.02 (m, 5H), 5.34 (s, 1H), 5.25 (s, 1H), 3.48−3.39 (m, 1H), 3.30−3.21 (m, 1H), 3.19 (s, 3H), 3.04−2.90 (m, 2H), 2.88−2.80 (m, 1H), 2.50−2.32 (m, 2H), 2.17 (s, 3H), 2.16−2.00 (m, 2H), 1.95−1.87 (m, 1H), 1.82−1.75 (m, 1H), 1.68−1.43 (m, 4H); optical rotation $[\alpha]^{23}_D$ −45.9 (c = 0.185, MeOH). Anal. C,H,N.

(4*R*)-4-(3,4-Difluorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[2-cyano-(4-fluorophenyl)piperidin-1-yl]propyl}amine hydrochloride (63): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.72 (m, 2H), 7.53 (m, 1H), 7.28−7.06 (m, 3H), 5.24 (s, 1H), 3.21 (m, 2H), 3.15 (s, 3H), 3.04 (br t, 2H, J = 9.71 Hz), 2.45 (m, 4H), 2.36 (t, 2H, J = 7.14 Hz), 2.16 (s, 3H), 2.15 (m, 2H), 1.64 (quint, 2H, J = 6.8 Hz); MS (FAB): M + H = 551.1. Anal. C,H,N.

4-(*R*)-(3,4-Difluorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(4-fluorophenyl)-4-cyanopiperidin-1-yl]propyl}amide (64): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−6.95 (m, 7H), 6.38 (br s, 1H), 5.35 (s, 1H), 5.25 (s, 1H), 3.50−3.35 (m, 1H), 3.35−3.15 (m, 1H),), 3.15 (s, 3H),), 3.00−2.90 (m, 1H), 2.90−2.75 (m, 1H), 2.55−2.30 (m, 3H), 2.18 (s, 3H), 2.15−1.70 (m, 7H); optical rotation $[\alpha]^{23}_D$ −80 (c = 0.23, $CDCl_3$); MS (FAB) M + H = 526.4. Anal. C,H,N.

4-(*R*)-(3,4-Difluorophenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[2-cyano-(4-fluorophenyl)-4-cyanopiperidin-1-yl]propyl}amine hydrochloride (65): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.83 (d, 1H, J = 5.13 Hz), 7.74 (m, 1H), 7.61 (m, 1H), 7.53 (s, 1H), 7.23 (m, 2H), 7.15 (m, 1H), 5.40 (s, 1H), 3.83 (m, 1H), 3.62 (m, 1H), 3.40−3.00 (m, 6H), 3.17 (s, 3H), 2.84 (m, 2H), 2.49 (m, 2H), 1.99 (m, 2H); MS (FAB) M + H = 537.2. Anal. C,H,N.

4-(*R*)-(3,4-Difluorophenyl)-1,3-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[2-cyano-(4-fluorophenyl)-4-cyanopiperidin-1-yl]propyl}amine hydrochloride (66): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.83 (dd, 1H J = 7.87 and 2.74 Hz), 7.77 (m, 1H), 7.61 (m, 1H), 7.32 (s, 1H), 7.27 (m, 2H), 7.17 (m, 1H), 5.37 (s, 1H), 3.84 (d, 1H, J = 13.4 Hz), 3.64 (d, 1H, J = 12.5 Hz), 3.40−3.10 (m, 8H), 3.22 (s, 3H), 2.83 (s, 3H), 2.50 (m, 2H), 1.98 (m, 2H); MS(FAB) M + H = 551.1. Anal. C,H,N.

4-(*R*)-(3,4-Difluorophenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid {3-[4-(2-cyano-4-fluorophenyl)piperidin-1-yl]propyl}amide (67): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.15 (m, 6H), 6.96 (s, 1H), 6.59 (br s, 1H), 5.46 (d, 1H, J = 2.44 Hz), 5.26 (d, 1H, J = 2.4 Hz), 3.41−3.24 (m, 2H), 3.17 (s, 3H), 3.00 (m, 2H), 2.40 (m, 2H), 2.07 (m, 2H), 1.89 (t, 1H, J = 14.2 Hz), 1.65 (m, 4H). Anal. C,H,N.

2-(3,4-Difluorophenyl)benzoic acid [4-(2-cyanophenyl)-piperidin-1-yl]propyl}amide hydrochloride (68): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.79−7.66 (m, 2H), 7.60−7.40 (m, 6H), 7.39−7.30 (m, 2H), 7.26−7.18 (m, 1H), 3.71−3.61 (m, 2H), 3.27−3.07 (m, 5H), 2.22−2.01 (m, 6H), 1.99−1.88 (m, 2H); MS (FAB) M + H = 460.1. Anal. C,H,N.

X-ray Crystallography. Compound **16**: $C_{23}H_{24}F_2N_2O_6$, M_r = 462.454, monoclinic, $C2$; a = 27.420(4), b = 7.362(2), c = 12.323(3) Å; β = 114.30(1)°, V = 2267(2) Å^3, Z = 4, D_x = 1.355 g cm^{-3}; monochromatized radiation λ(Cu Kα) = 1.541838 Å, μ = 0.89 mm^{-1}, F(000) = 968, T = 294 K. Data were collected on a Rigaku AFC5 diffractometer to a θ limit of 72.88° which yielded 2294 unique reflections. The structure was solved by direct methods (SHELXS86)[27] and refined using full-matrix least-squares on F^2 (SHELXL-93).[28] The final model was refined using 304 parameters and all 2294 data. All non-hydrogen atoms were refined with anisotropic thermal displacements. The final agreement statistics were: R = 0.043 (based on 2171 reflections with $I \geq 2\sigma(I)$), wR = 0.121, S = 1.02 with $(\Delta/\sigma)_{max} < 0.01$. The maximum peak height in a final difference Fourier map was 0.369 eÅ^{-3} and this peak was without chemical significance.

Compound **18a**: $C_{14}H_{14}F_2N_2O_3$, M_r = 296.276, orthorhombic, $P2_12_12_1$; a = 11.259(2), b = 16.444(2), c = 7.416(1) Å; V = 1373.0(7) Å^3, Z = 4, D_x = 1.433 g cm^{-3}; monochromatized radiation λ(Cu Kα) = 1.541838 Å, μ = 0.99 mm^{-1}, F(000) = 616, T = 294 K. Data were collected on a Rigaku AFC5 diffractometer to a θ limit of 72.93° which yielded 1586 unique reflections. The structure was solved by direct methods (SHELXS86)[27] and refined using full-matrix least-squares on F^2 (SHELXL-93).[28] The final model was refined using 194 parameters and all 1586 data. All non-hydrogen atoms were

refined with anisotropic thermal displacements. The final agreement statistics were: $R = 0.047$ (based on 1289 reflections with $I \geq 2\sigma(I)$), $wR = 0.130$, $S = 1.05$ with $(\Delta/\sigma)_{max} < 0.01$. The maximum peak height in a final difference Fourier map was 0.401 eÅ^{-3} and this peak was without chemical significance.

The atomic coordinates for both structures have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

Biological Methods. Binding assay: The radioligand binding assays (Tables 1−4) utilizing the cloned human α_{1a}, α_{1b} and α_{1d} receptors expressed in mammalian cells was preformed as described in ref 22.

Caco-2 cell assay: Caco-2 cells, passage numbers 20−22, were cultured on Millicell culture plate inserts (0.4-μm pore, 12-mm diameter; Millipore) for 18−30 days prior to use. Dosing solutions (400 μL/filter) consisting of 100 μM drug, 0.1 mg/ml lucifer yellow (LY) and 0.5% (v/v) dimethyl sulfoxide (DMSO) in Hanks' balanced salt solution (HBSS), pH 6.5, were applied to the apical surface of the cells. Inserts were placed in 12-well culture plates containing 1.5 mL receiver solution (HBSS, pH 7.4). Plates were maintained in a 37 °C incubator at room atmosphere for the duration of the study. At 30 min, the cell inserts were transferred to fresh receiver solution. Following an additional 60 min incubation, inserts were removed and set aside for collection of the donor solution.

Lucifer yellow (LY) transport: Monolayer integrity was assessed by detection of LY, a fluorescent marker which is transported paracellularly (through tight junctions between cells), in the receivers. Receivers were analyzed in a Cambridge Technology, Inc. microplate fluorometer at 460λ excitation and 530λ emission. Fluorescence in receivers was compared to that of a standard (1:100 dilution of dosing solution) to obtain the percent of LY dose transported.

Drug transport: Receivers (1.5 mL) were collected at 30 and 90 min, acidified with 1 μL trifluoroacetic acid (TFA), and pooled with 0.5 mL methanol rinse of the receiver vessel. Dosing and donor (following 90-min incubation) solutions were diluted 1:25 in methanol/water to a final concentration of 25% methanol. Samples were analyzed by gradient elution HPLC (10−90% acetonitrile + 0.1% TFA) on a Shimadzu 10A with 4.6 mm × 15 cm Zorbax RX-C8 column, using UV detection at 220λ. Drug concentrations were determined relative to dosing solution peak area (adjusted for dilution).

In vivo rat model: Male Sprague−Dawley rats (300−400 gm) were anesthetized with urethane (1.75 gm/kg, ip) and placed on a heating pad thermostatically controlled via a rectal probe to maintain body temperature at 37 °C. To facilitate breathing, a short length of PE 205 tubing was inserted through a small incision in the trachea and sutured in place. The left femoral vein was cannulated with saline filled PE 50 tubing for drug administration. The prostate was exposed through a midline incision and freed with minimal bleeding from adherent connective tissue and the bladder neck. A suture was placed through the rear portion of the prostate and firmly taped to the tail. The anterior portion of the prostate was then attached via a suture to a Grass force transducer linked to a Hewlett-Packard 7754B chart recorder. A resting tension of 2 g was applied to the tissue and the animal was given atropine (1 mg/kg, iv) followed 20 min later by propranolol (1 mg/kg, iv). After another 20 min, an iv priming dose of 30 ng/kg of A61603[23] or 10 μg/kg of phenylephrine was administered to test the responsiveness of the tissue. For the determination of antagonist potency (AD_{50}), rats were then treated iv with rising noncumulative doses of test compound 5 min before administration of successive doses ($\sim ED_{50}$) of A61603 (30 ng/kg iv) or phenylephrine (10 μg/kg iv) administered roughly every 20 min. For the duration studies, the effect of submaximal doses of antagonist on the contractile effect of repeated injections of the agonists was determined. Control studies indicated that the contractile response of repeated submaximal dosings of either A61603 or phenylephrine were constant over a period of at least 4 h. For each compound tested, four rats were used in parallel and the data for each concentration or time point was averaged (SEM < 10%). Data were analyzed for AD_{50} values by nonlinear regression (Graph Pad In Plot).

In vivo dog models: Adult male dogs of mixed breed obtained from Covance Research Products, Inc. (Denver, PA), weighing 10−17 kg, were used in this study. The dogs were fasted 12 h before the experiment, water ad libitum. They were cared for according to National Institutes of Health guidelines on canine care, and the experimental protocols described herein was reviewed and approved by the Institutional Animal Care and Use Committee of Merck Research Laboratories.

1. Determination of potency: Animals (8 months to 2 years of age) were anesthetized with sodium pentobarbital (Butler Co., Columbus, OH) at 35 mg/kg, iv followed by a continuous intravenous infusion of this substance in 0.9% NaCl at 5 mg/kg/h. They were intubated and ventilated with room air using a positive displacement large animal ventilator (Harvard Apparatus, Inc., South Natick, MA). A temperature controller (YSI Scientific Division, Yellow Springs, OH) with heating pad (circulating water) and esophageal probe, were used to maintain body temperature at 37 °C. Polyethylene catheters (PE-260) were placed in the aorta via the femoral arteries, and vena cava via the femoral veins. The arterial catheters were used for measuring arterial pressure and administering phenylephrine. The venous catheters were used for administering anesthesia and the antagonists. A suprapubic incision (approximately 0.25-in. lateral to the penis) was made to expose the urinary bladder and urethra. The ureters were tied off to the bladder to prevent filling, and catheterized with polyethylene tubing (PE-90). The bladder was retracted to facilitate dissection of the proximal and distal urethra, and the bladder dome was incised to allow drainage. A piece of umbilical tape (1/8th in. wide) was passed under the urethra at the bladder neck and another piece under the distal urethra approximately 1−2 cm distal to the prostate. A Mikro-tip catheter transducer (Millar Instruments, Inc., Houston, TX) was advanced into the urethra through the incision in the bladder dome. The neck of the bladder was ligated with the umbilical tape and a purse string suture was made at the bladder dome using 3-0 silk to secure the transducer. The tip of the transducer was slowly withdrawn until it was positioned in the prostatic urethra. The position of the Millar catheter was verified by gently squeezing the prostate and noting the large change in urethral pressure. Finally, the distal urethra was ligated with the umbilical tape distal to the prostate. Diastolic blood pressure (DBP) was monitored using a blood pressure transducer (Argon, Athens, TX). Heart rate was monitored using ECG leads and subdermal electrodes. These and the blood pressure transducers were all interfaced to a computerized data acquisition system (Modular Instruments, Inc., Malvern, PA).

Phenylephrine, a nonselective α_1-AR agonist (10 ug/kg) (Sigma Chemical Co., St. Louis, MO) was dissolved in 0.9% saline and administered at 0.05 mL/kg, iv every 30 min for submaximal increases in urethral pressure. Twenty minutes after the last control response, baseline control values were recorded for DBP and HR, and vehicle or α_1-AR antagonist was given iv (0.5 mL/kg) in increasing concentrations every 30 min. Antagonists were dissolved in 0.8 mM HCl/20% PEG 200 (final concentrations) in 5% dextrose/H_2O (D5W), and subsequent dilutions made in D5W. Ten minutes post-dose, the effects of PE-induced increases in IUP and baseline DBP and HR were reevaluated.

2. Duration of action in conscious male dogs: Animals at least 2 years old or more were placed in Alice King Chatham dog slings. The tip of a 7 French, double lumen Swan-Ganz balloon catheter was lubricated with a water soluble jelly, inserted into the urethral orifice, and advanced approximately 40 cm until well inside the urinary bladder. The balloon was then inflated with 1 mL of room air, and the catheter slowly withdrawn just past the first resistance that was felt at the bladder neck. The balloon port of the catheter was connected

to a pressure transducer interfaced to a computerized data acquisition system (Modular Instruments, Inc.) for the measurement of intraurethral pressure (IUP). Urine was allowed to drain freely through the other port of the catheter into a flask. A 22- and an 18-g. iv intra-catheter attached to sterile Tygon tubing with 20-g tubing adapters were inserted into each saphenous vein for injecting drugs and withdrawing blood, respectively.

Phenylephrine (PE), an α_1 adrenergic agonist, dissolved in 0.9% saline and solution-filtered using an Acrodisc filter (0.2 μm), was administered at 10 μg/kg, iv (0.05 mL/kg volume) to elicit a submaximal increase in IUP. PE was given 3 times, 20 min apart, for an average control increase in IUP. Following administration of an α_1 antagonist or vehicle, PE was administered at 5 (iv), 15 (oral), 30, 60, 90, 120, 180, 240, 300, and 360 min, and the effects on IUP were reevaluated. The dog was taken back to its cage and fed. The next day the dog was recatheterized for the 24 h reading. The antagonists were normally dissolved in 0.8 mM HCl/PEG 200/D5W, filtered for iv administration and injected at 0.1 mL/kg, or given orally by gavage at 2 mL/kg. Each animal was given at least 1 week's rest between experiments.

Pharmacokinetics: Two groups of three male Sprague−Dawley rats (∼0.25 kg), surgically prepared with a cannula implanted in the right jugular vein, received intravenous (1 mg/kg) or oral (3 mg/kg) doses of test compound. Two groups of three male beagle dogs (∼11 kg), surgically prepared with a cannula implanted in the right jugular vein, received intravenous (0.5 mg/kg) or oral (1 mg/kg) doses of test compound. Blood samples were drawn at preselected time points and plasma was obtained by centrifugation and stored at −20 °C until analyzed by LC−MS.

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Supporting Information Available: Analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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