Design and Synthesis of Novel α_{1a} Adrenoceptor-Selective Antagonists. 4. Structure−Activity Relationship in the Dihydropyrimidine Series

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We have previously disclosed dihydropyridines such as **1a**,**b** as selective α_{1a} antagonists as a potential treatment for benign prostatic hyperplasia (BPH). The propensity of dihydropyridines toward an oxidation led us to find suitable replacements of the core unit. The accompanying papers describe the structure−activity relationship (SAR) of dihydropyrimidinones **2a**,**b** as selective α_{1a} antagonists. We report herein the SAR of dihydropyrimidines such as **4** and highlight the similarities and differences between the dihydropyrimidine and dihydropyrimidinone series of compounds.

Introduction

Benign prostatic hyperplasia (BPH) is a progressive condition characterized by a nodular enlargement of the prostate resulting in obstruction of the urethra.[1] Nonselective α_1 adrenoceptor antagonists such as prazosin and terazosin are presently used for the symptomatic relief of BPH.[2] It has been reported that the functional potency of a number of α_1 antagonists to relax the agonist-induced contraction of prostatic smooth muscle correlates well with the binding affinity for these antagonists for the α_{1a} subtype at the cloned human receptors.[3] The data seem to suggest that a potent and α_{1a}-selective antagonist can be an attractive drug candidate for treatment of BPH with fewer undesirable side effects that may be associated with the other subtypes.

We have recently disclosed the discovery of a number of dihydropyridines such as **1a**,**b** (Chart 1) as selective α_{1a} adrenoceptor antagonists.[4−6] Some of the compounds that belong to this class, however, exhibit less than optimal pharmacokinetic profiles. Mindful of the tendency of dihydropyridines to undergo metabolic oxidation, we reasoned that replacement of the dihydropyridine core unit with a dihydropyrimidinone (e.g. **2a**)[7] or a dihydropyrimidine (**3**) template might attenuate this propensity for oxidation and result in compounds with improved pharmacokinetic profiles. It was important that these analogues maintain the desirable binding affinity and subtype selectivity for the α_{1a} receptor observed for **1a**,**b** similar to that observed in the dihydropyrimidinone series (e.g. **2a**,**b**).[7,8] Structurally, dihydropyrimidines (**3**) are more closely related to the dihydropyridines (**1a**,**b**) than the dihydropyrimidinones (**2a**), and we needed to synthesize compounds such as **3** in order to evaluate their pharmacological properties. It became apparent that the dihydropyrimidines such as **3** are unstable, and we therefore decided to synthesize dihydropyrimidines represented by the general structure **4**. We have previously demonstrated that such a linker variation is well-tolerated in the dihydropyrimidinone series resulting in compounds such as **2b** that show excellent binding affinity and selectivity for the α_{1a} receptor.[8] The work described herein presents the synthesis of the dihydropyrimidines such as **4** and compares the SAR of the dihydropyrimidine series of compounds with that of the dihydropyrimidinones described in the accompanying papers.

Chemistry

Scheme 1 depicts a general synthetic route for the synthesis of dihydropyrimidines.[9] Thus, benzylidene **5** was reacted with acetamidine to afford tetrahydropyrimidine **6** which was dehydrated with *p*-toluenesulfonic acid without purification to afford intermediate **7**. This compound was then alkylated with either 5-bromo-1-chloropentane or 1,5-dibromopentane to yield halide **8a** or **8b** which was subsequently reacted with either a substituted piperidine or a piperazine to obtain the desired products **9**−**15** or **16**−**18**, respectively.

Methyl ester **21** was similarly prepared from benzylidene **19** (Scheme 2). To synthesize compounds **28** and **29**, compound **20** was initially converted to intermediate **24**. Reaction of 4-methoxycarbonyl-4-piperidine with **24** gave compound **26**, which upon hydrogenolysis afforded the carboxylic acid **27**. Subsequent coupling of **27** with ammonia or methylamine gave primary amide **28** and secondary amide **29**, respectively.

Syntheses of compounds **36**−**41** and **43** are depicted in Scheme 3. Thus, dihydropyrimidine **7** (Scheme 3) was reacted with 1,4-dibromobutane (**30**) to obtain intermediate **33** which was then converted into compound **36** by reaction with 4-methoxycarbonyl-4-phenylpiperidine. Chiral dibromides **31** and **32** were prepared from known intermediates[10] and then treated with the substituted piperidines or piperazine to synthesize analogues **36**−

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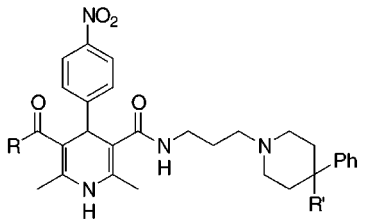
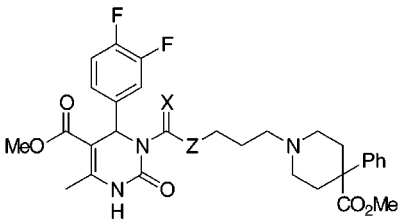
Chart 1



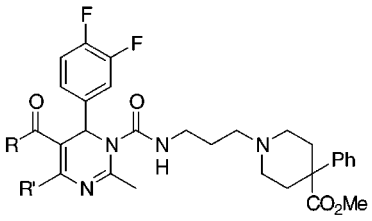
Dihydropyridines

1a R = OMe, R' = Ph
1b R = OMe, R' = CO_2Me



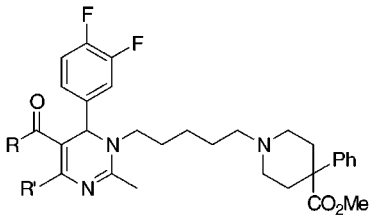
Dihydropyrimidinones

2a X = O; Z = NH
2b X = H, H; Z = CH_2



Dihydropyrimidine

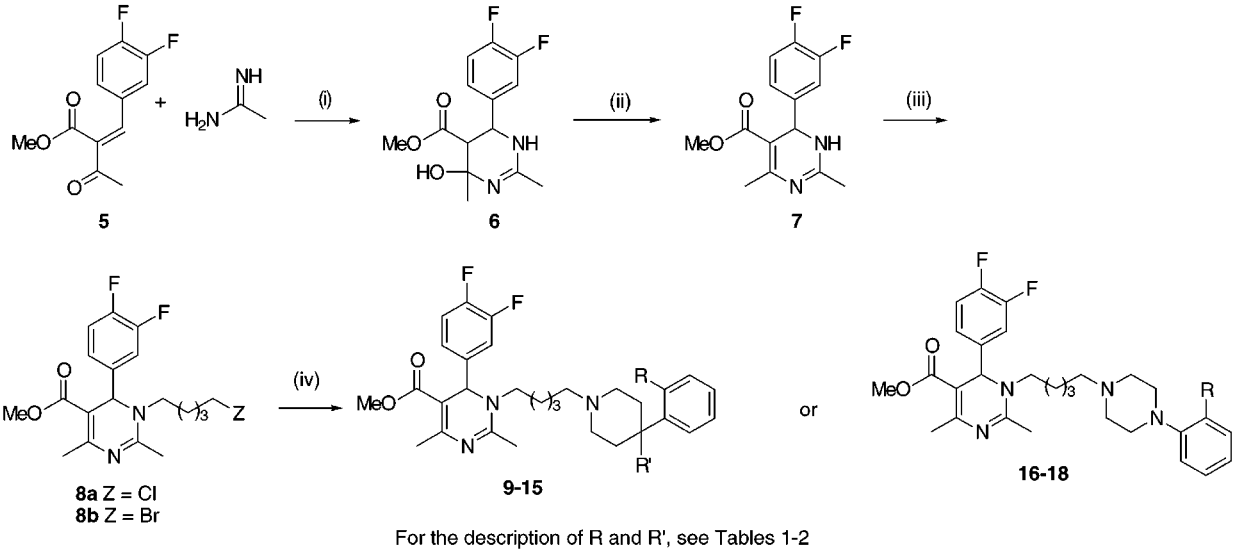
3



Dihydropyrimidine

4

Scheme 1[a]



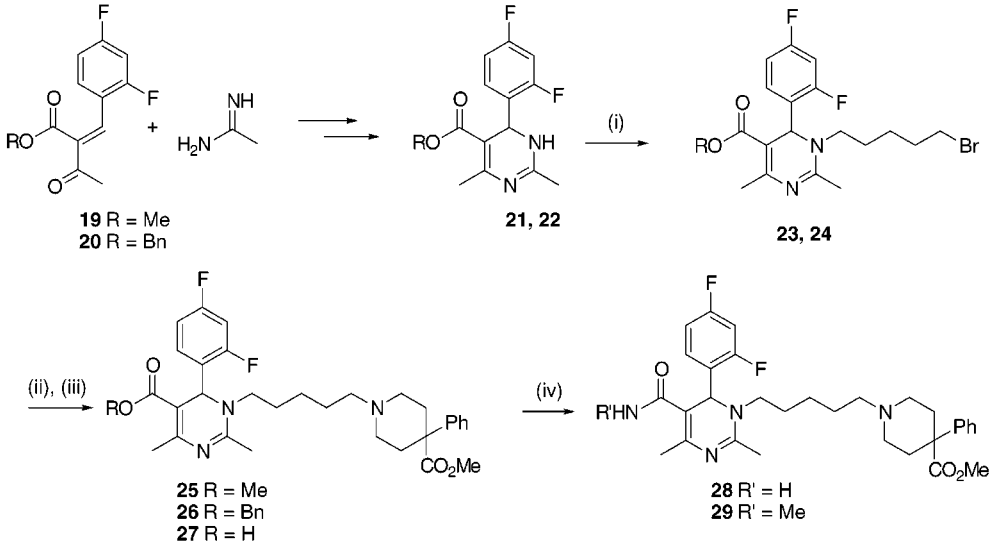
[a] (i) *t*-BuOK, DMF; (ii) *p*-TsOH; (iii) $Br(CH_2)_5$-Z, where Z = Cl or Br; (iv) substituted piperidines or piperazines.

41. Reaction of **7** with α,α′-dibromo-*m*-xylene yielded intermediate **42**, which was subsequently elaborated to afford **43**. Compounds **50** and **51** (Scheme 4) were synthesized from amidine **45**[11] and acetamide, by procedures similar to the ones described previously.

Results and Discussion

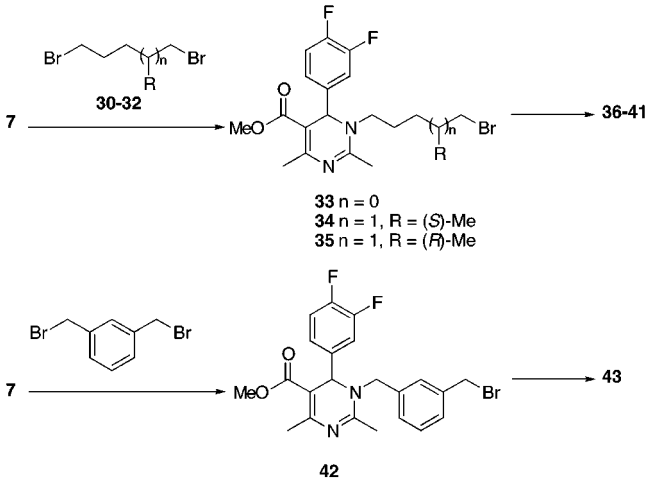
The binding affinities of a number of dihydropyrimidines containing a 4-methoxycarbonyl-4-phenylpiperidine moiety are compared with those of dihydropyridine **1a** and dihydropyrimidinone **2b** in Table 1. (For the protocols for in vivo and in vitro binding studies, please refer to ref 7.) Dihydropyrimidine **9** displays comparable binding affinity (1.0 nM) and selectivity (>400-fold) for the α_{1a} receptor over α_{1b}, α_{1d}, and α_2 receptors similar to dihydropyridine **1a** (0.2 nM) and dihydropyrimidinone **2b** (0.1 nM). The affinity and selectivity is found to be mainly associated with in the (+) enantiomer, an observation which parallels the SAR in the dihydropyrimidinone series. The (−) enantiomer shows significantly lower binding affinity and selectivity for the α_{1a} receptor over α_{1b}, α_{1d}, and α_2 receptors. As in the case of dihydropyrimidinones, the substitution on the C-6 aryl ring does not have a pronounced effect on the binding and selectivity profile as evident by the binding affinities for **9** and **25**. When the methyl ester functionality at the C-5 position of **25** was replaced by a primary amide or a secondary amide, the resulting compounds (**28** and **29**, respectively) show lower binding affinity and selectivity for the α_{1a} receptor. In the dihydropyrimidinone series, both an ester and an amide functionality at the C-5 position are well-tolerated.[7] In vitro and in vivo metabolism study of compound **(+)-9** indicate that the compound undergoes *N*-dealkylation to produce 4-methoxycarbonyl-4-phenylpiperidine as the major metabolite. 4-Methoxycarbonyl-4-phenylpiperidine was found to be an agonist of opioid receptors and has long half-life in rats and dogs. The structural similarity

Scheme 2[a]



[a] (i) $Br(CH_2)_5Br$; (ii) 4-methoxycarbonyl-4-phenylpiperidine; (iii) H_2, Pd−C; (iv) NH_3 or $MeNH_2$, EDC.

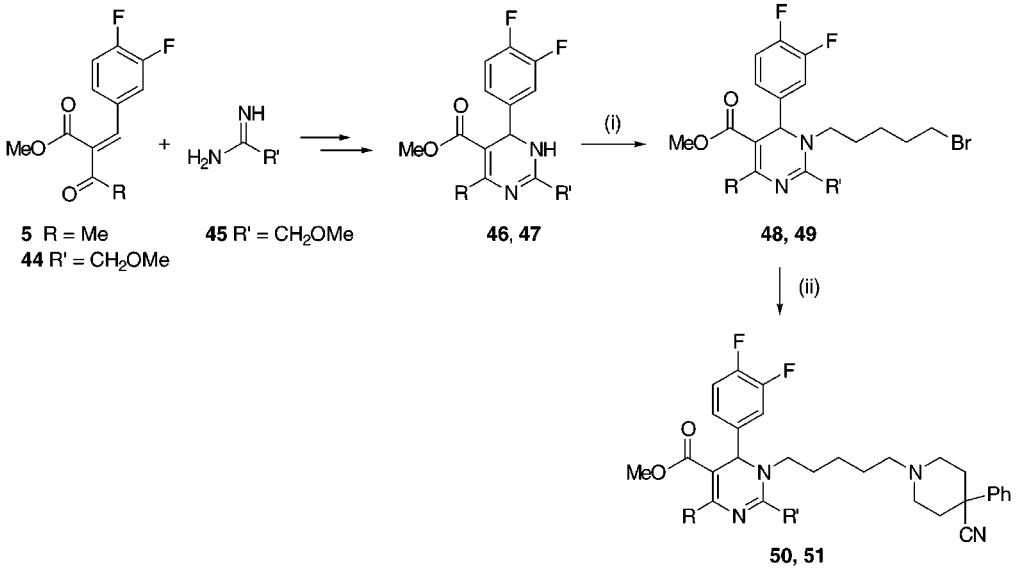
Scheme 3



between this metabolite and a known sedative, meperidine,[12] which has sedative and habit-forming properties associated with it,[13] raised concerns regarding safety upon chronic administration. We therefore decided to replace the 4-methoxycarbonyl-4-phenylpiperidine moiety with some preferred piperidines and piperazines.[8,14] Binding profiles of these compounds are presented in Table 2.

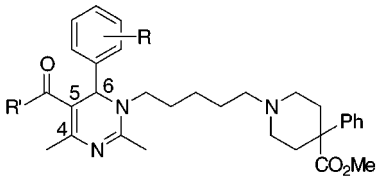
The methoxycarbonyl group on the 4-position of the piperidine ring of **(+)-9** does not appear to be essential for the binding affinity as evident from the binding profile for compound **10** (Table 2). An analogue of **10** containing an *o*-trifluoromethyl group on the phenyl ring (**9b**) show increased affinity for the rat L-type calcium channel, whereas compound **12** containing a 4-(2-methoxyphenyl)piperidine moiety displays a binding and selectivity profile similar to **10**. Substitution of the methoxycarbonyl group on the 4-position of the piperidine in **(+)-9** with a cyano group results in compound **13** which shows high binding affinity and good selectivity for the α_{1a} receptor. The diarylpiperidine-containing compounds **(+)-14** and **(+)-15** also exhibit excellent

Scheme 4[a]



[a] (i) $Br(CH_2)_5Br$; (ii) 4-cyano-4-phenylpiperidine.

Table 1. Effect of C-5 and C-6 Substituents on α_1 Binding Affinities at Recombinant Human α_1 and α_2 Adrenoceptors



			K_i (nM)[a,b]			fold selective of
compd	R	R′	α_{1a}	α_{1b}	α_{1d}	α_{1a} over $\alpha_{2a,b,c}$
1a			0.2	180	630	>1000
2b			0.1	140	150	>1000
9	3,4-di-F	OMe	1.0	480	680	>1000
(+)-9	3,4-di-F	OMe	0.1	190	180	>500
(−)-9	3,4-di-F	OMe	13	700	550	<25
25	2,4-di-F	OMe	0.5	160	700	>1000
28	2,4-di-F	NH_2	4.2	410	690	<10
29	2,4-di-F	NHMe	14	870	1900	<80

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

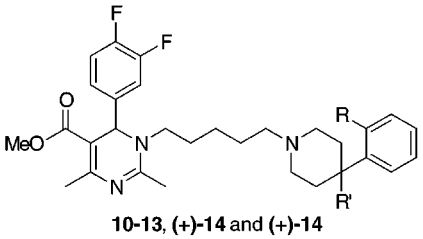
binding profiles. Compounds **17** and **18** that contain substituted phenylpiperazine moieties show good binding affinities for the α_{1a} receptor, as is the case with dihydropyrimidinone series. Compound **16** displays poor selectivity for the α_{1a} receptor over α_2 adrenoceptors. Similar substitution in the dihydropyrimidinone series leads to compounds with significantly higher selectivity for the α_{1a} receptor over α_2 receptors.

The effect of modification of the tether linking the dihydropyrimidine core unit with piperidines or piperazines on the binding profiles of the resulting compounds is shown in Table 3. A linker comprising a five-methylene spacer, as in **(+)-9**, was found to be the optimal, yielding compounds with good binding affinity and selectivity for the α_{1a} receptor. Compound **36** containing a four-methylene tether shows a 30-fold decrease in the binding affinity for the α_{1a} receptor resulting in poor selectivity over α_2 receptors. Compound **43** with a conformationally restricted linker exhibits a suboptimal binding profile. The presence of a methyl group on the linker, such as the one in **(+)-37**, results in a 15-fold decrease in the binding affinity for α_{1a} receptor. Interestingly, compound **(+)-38**, a close analogue of **(+)-37**, which differs only in the substitution at the 4-position of the piperidine ring (CN instead of CO_2Me), displays a similar binding profile for α_1 receptors but has improved selectivity over the α_2 receptors. It is important to note that the absolute configuration at the carbon bearing the methyl group is crucial and the (*S*) isomer is found to give compounds that show significantly better binding and selectivity profiles than the (*R*) isomer (compound **(+)-38** versus compound **(+)-39**). A similar observation was made for the piperazine-containing compounds **(+)-40** and **(+)-41** for their binding affinity at the α_{1a} receptor. Both compounds, however, fail to meet the required criteria of 100-fold selectivity over the α_2 adrenoceptors. The initial rationale behind design of these substituted linkers was to slow the metabolic *N*-dealkylation at the carbon bearing the piperidine or piperazine.[8] Analysis of the metabolites of some of the compounds presented in Table 3, however, revealed that *N*-dealkylation still remains to be the major metabolic pathway.

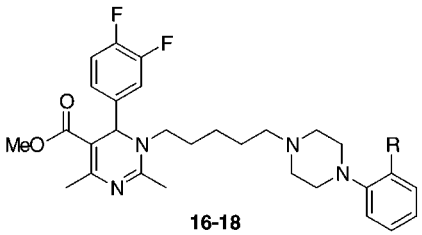
Modifications at the C-2 and C-4 positions of the dihydropyrimidine core were briefly explored, and some representative examples are shown in Table 4. These positions appear to accommodate bulky groups as indicated by the binding and selectivity profiles for **50** and **51**.

The results from a number of in vitro and in vivo assays for **(+)-14**, **(+)-15**, and **(+)-18** are summarized in Table 5. All three compounds show greater than 100-fold selectivity for the α_{1a} receptor over α_{1b}, α_{1d}, and α_2 receptors and greater than 10000-fold selectivity over rat L-type calcium channel. Compound **(+)-14** displayed binding affinity at isolated human prostate of 0.33 nM which is good agreement with the binding affinity (K_i = 0.4 nM) at the cloned human α_{1a} receptor. Compound **(+)-14** shows a much lower binding affinity for isolated human aorta (K_i = 110 nM) as expected based on the selectivity for the α_{1a} over α_{1d} receptor in

Table 2. Effect of Substituted Piperidines and Piperazines on α_1 Binding Affinities at Recombinant Human α_1 and α_2 Adrenoceptors



10-13, (+)-14 and (+)-14

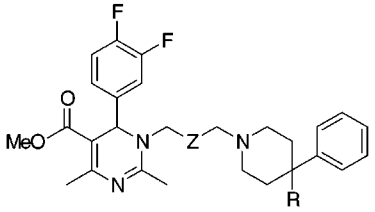


16-18

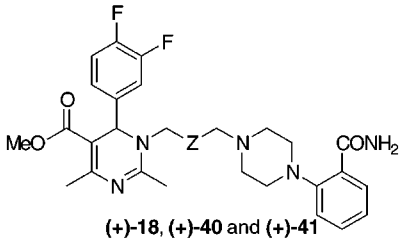
			K_i (nM)[a,b]			fold selective of
compd	R	R′	α_{1a}	α_{1b}	α_{1d}	α_{1a} over $\alpha_{2a,b,c}$
(+)-9	H	CO_2Me	0.1	190	180	>500
10	H	H	0.4	93	220	>300
11	CF_3	H	1.1	500	1100	>150[c]
12	OMe	H	0.3	140	120	>100
13	H	CN	1.0	490	1100	>300
(+)-14	H	Ph	0.4	100	180	>180
(+)-15	Me	4-Me-Ph	0.1	250	440	>400
16	OMe		0.4	67	65	<100
17	CO_2Me		0.5	34	79	>100
(+)-18	$CONH_2$		0.6	240	580	>100

[a,b] Please see notes in Table 1. [c] Selectivity for α_{1a} over rat L-type Ca^{2+} channel < 100.

Table 3. Effect of Linker Variation on α_1 Binding Affinities at Recombinant Human α_1 and α_2 Adrenoceptors



(+)-9, 13 and 36-39

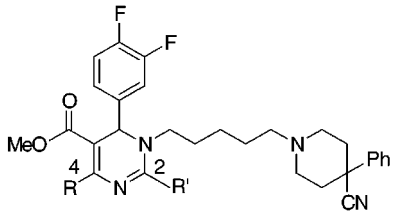


(+)-18, (+)-40 and (+)-41

compd	Z	R	K_i (nM)[a,b] α_{1a}	α_{1b}	α_{1d}	fold selective of α_{1a} over $\alpha_{2a,b,c}$
(+)-9	$(CH_2)_3$	CO_2Me	0.1	480	680	>500
36	$(CH_2)_2$	CO_2Me	3.6	440	610	<80
43	3′,5′-phenyl	CO_2Me	6.8	320	570	>130
(+)-37	$(CH_2)_2CH$-(*S*)-CH_3	CO_2Me	1.6	430	910	<50
13	$(CH_2)_3$	CN	1.0	490	1100	>300
(+)-38	$(CH_2)_2CH$-(*S*)-CH_3	CN	1.2	480	1100	>120
(+)-39	$(CH_2)_2CH$-(*R*)-CH_3	CN	22	1700	1600	<10
(+)-18	$(CH_2)_3$		0.6	240	580	>130
(+)-40	$(CH_2)_2CH$-(*S*)-CH_3		3.5	810	1700	<100
(+)-41	$(CH_2)_2CH$-(*R*)-CH_3		20	1500	1700	<10

[a,b] Please see notes in Table 1.

Table 4. Effect of C-2 and C-4 Substituents on α_1 Binding Affinities at Recombinant Human α_1 and α_2 Adrenoceptors



compd	R	R′	K_i (nM)[a,b] α_{1a}	α_{1b}	α_{1d}	fold selective of α_{1a} over $\alpha_{2a,b,c}$
13	Me	Me	1.0	490	1100	>300
50	Me	$MeOCH_2$	0.4	310	480	>700
51	$MeOCH_2$	Me	0.4	400	680	>4000

[a,b] Please see notes in Table 1.

the binding assays.[15,16] Dihydropyrimidinones show similar selectivity profiles in the tissue binding experiments.

Compounds **(+)-14**, **(+)-15**, and **(+)-18** antagonize the phenylephrine-induced contraction of isolated rat prostate with a much weaker K_b (60, 27, and 7 nM, respectively) compared to the binding affinities for cloned human receptors (K_i = 0.4, 0.1, and 0.6 nM, respectively). In the dihydropyrimidinone series, the correlations between the binding affinities of the antagonists and their functional potencies in tissue preparations are in good agreement.[7,8] The reasons behind this apparent discrepancy are presently not well-understood. The current pharmacological evidence cannot account for the behavior of human prostate as a function of α_{1a} and the rat prostate as α_{1L} adrenoceptors.[17−19] It appears that the discrepancies in the binding affinities and functional potencies are due to some specific biophysical properties of certain compounds that are sensitive to differences in the conditions of the assays and do not support the existence of α_{1L} receptors.[20]

Compounds **(+)-15** and **(+)-18** show suboptimal pharmacokinetic profiles with 20% oral bioavailability in rats but less than 10% oral bioavailability in dogs.

Conclusion

In an effort to optimize pharmacokinetic parameters, we were able to replace the dihydropyridine moiety with a dihydropyrimidine template. A number of dihydropyrimidines showed good binding affinity (<1 nM) and selectivity (>300-fold) for α_{1a} receptor over α_{1b}, α_{1d}, and α_2 receptors. Most of the compounds displayed negligible affinity for rat L-type calcium channel. A number of modifications on the dihydropyrimidine template, linker chain, and piperidine or piperazine side chains are tolerated as is the case for dihydropyrimidinones. Some of the dihydropyrimidines, unlike the dihydropyrimidi-

Table 5. Summary of the in Vitro and in Vivo Properties of **(+)-14**, **(+)-15**, and **(+)-18**

assay	antagonist/agonist	**(+)-14**	**(+)-15**	**(+)-18**
K_i α_{1a} (nM)	[^{3}H]prazosin	0.4	0.1	0.6
$\alpha_{1b,1d}/\alpha_{1a}$	[^{3}H]prazosin	>100	>1000	>300
$\alpha_{2a,b,c}/\alpha_{1a}$	[^{3}H]rauwolscine	>180	>400	>100
Ca^{2+}/α_{1a}	[^{3}H]nitrendipine	$>10^5$	$>10^5$	>11000
K_i human prostate (nM)	[^{3}H]prazosin	0.33	ND[b]	ND
K_i human aorta (nM)	[^{3}H]prazosin	110	ND	ND
K_i rat prostate (nM)	[^{3}H]prazosin	0.97	ND	ND
K_b rat prostate (nM)	phenylephrine	60	27	7
rat *F*, $t_{1/2}$ (h)[a]		ND	17%,[c] 4.7	21%,[d] 2.1
dog *F*, $t_{1/2}$ (h)[a]		ND	8%,[e] 0.5	<10%,[f] 4.0

[a] Radioreceptor assay. [b] Not determined. [c] iv: 1 mg/kg dose, AUC = 35 μmol min/L. po: 3 mg/kg dose, AUC = 21 μmol min/L. [d] iv: 1 mg/kg dose, AUC = 5 μmol min/L. po: 3 mg/kg dose, AUC = 4 μmol min/L. [e] iv: 1 mg/kg dose, AUC = 11 μmol min/L. po: 3 mg/kg dose, AUC = 8 μmol min/L (low plasma levels). [f] iv: 1 mg/kg dose. po: 3 mg/kg dose, low plasma levels.

nones, showed only weak potency to inhibit the phenylephrine-induced contraction of isolated rat prostate tissue. The reasons for such a discrepancy are not yet clear.

Experimental Section

For the description of analytical protocols and biological methods, please refer to ref 7.

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (7). To a solution of acetamidine hydrochloride (1.53 g, 16.2 mmol) in DMF (10 mL) were added a solution of potassium *tert*-butoxide (1.33 g, 11.8 mmol) in DMF (10 mL) and a solution of methyl 2-((3,4-difluorophenyl)-methylene)-3-oxobutanoate (2.6 g, 10.8 mmol) in DMF (10 mL) at 0 °C. After the mixture was stirred for 0.5 h at 0 °C, *p*-toluenesulfonic acid monohydrate (4.1 g, 21.5 mmol) was added. The mixture was heated at 100−120 °C for 2 h. The reaction mixture was cooled to room temperature, quenched with aqueous NaOH solution (2 N, 60 mL), and extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in 59% yield (1.8 g) as a yellow solid: ^{1}H NMR δ 1.98 (3H, s), 2.31 (3H, s), 3.59 (3H, s), 5.47 (1H, s), 7.03−7.05 (3H, m). Chiral HPLC resolution (Chiralcel OD 20 × 250 mm column; hexane:ethyl alcohol: diethylamine, 90:10:0.1; 9.0 mL/min; 10.9 and 12.2 min) afforded both **(+)-7** and **(−)-7**.

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pent-1-yl)-2,4-dimethylpyrimidine (9). A mixture of (±)-**8a** (0.67 g, 1.73 mmol), 4-methoxycarbonyl-4-phenylpiperidine (0.76 g, 3.47 mmol), potassium carbonate (0.96 g, 6.95 mmol), and sodium iodide (0.52 g, 3.47 mmol) in 1,4-dioxane (15 mL) was heated at reflux overnight. The solid was then filtered off and the solvent was evaporated. The residue was purified by flash chromatography over silica gel (4:1 ethyl acetate−2 M ammonia in methanol) to give the title compound in 78% yield (0.77 g) as a yellow oil: CIMS *m/e* = 568 (MH^+); ^{1}H NMR δ 1.23−1.28 (2H, m), 1.43−1.51 (2H, m), 1.77−2.13 (8H, m), 2.16 (3H, s), 2.28 (3H, s), 2.47−2.55 (2H, m), 2.74−2.81 (2H, m), 3.00−3.12 (1H, m), 3.22−3.38 (1H, m), 3.613 (3H, s), 3.615 (3H, s), 5.22 (1H, s), 6.99−7.35 (3H, m). Anal. ($C_{32}H_{39}F_2N_3O_4$·2HCl·2.3H_2O) C, H, N. Chiral HPLC resolution (Chiralcel OD 20 × 250 mm column; λ = 254 nm; hexane:isopropyl alcohol, 80:20; 9.0 mL/min; 17.5 and 38.7 min) afforded the pure enantiomers. **(+)-9** (HCl salt): mp 118−120 °C; $[\alpha]_D$ = 63.0 (22.5 mg/mL MeOH). **(−)-9** (HCl salt): mp 119−121 °C; $[\alpha]_D$ = − 62.3 (24 mg/mL MeOH).

1-(5-Chloropent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (8a). To a suspension of NaH (90 mg, 60% dispersion in mineral oil, 2.25 mmol) in THF (7 mL) was added a solution of **7** (0.6 g, 2.14 mmol) in THF (8 mL) at 0 °C. After 20 min, 1-bromo-5-chloropentane (1 mL, 7.59 mmol) was added. The reaction mixture was then refluxed overnight. After removal of the solvent, the residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in 75% yield (0.614 g) as a yellow oil: ^{1}H NMR δ 1.42−1.75 (6H, m), 2.17 (3H, s), 2.28 (3H, s), 3.05−3.45 (2H, m), 3.49 (2H, t, *J* = 5.9 Hz), 3.63 (3H, s), 5.23 (1H, s), 7.01−7.15 (3H, m).

1-(5-Bromopent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (8b). To a suspension of NaH (310 mg, 60% dispersion in mineral oil, 7.75 mmol) in THF (10 mL) was added a solution of **7** (2.0 g, 7.14 mmol) and HMPA (1.28 g, 7.14 mmol) in THF (15 mL) at 0 °C. After 15 min, 1,5-dibromopentane (3.9 mL, 28.56 mmol) was added. The mixture was heated at reflux for 30 min before it was filtered. The filtrate was concentrated and the residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in 64% yield (1.95 g) as a yellow oil: ^{1}H NMR δ 1.39−1.69 (4H, m), 1.81−1.96 (2H, m), 2.17 (3H, s), 2.29 (3H, s), 3.09 (1H, m), 3.31 (1H, m), 3.36 (2H, t, *J* = 6.6 Hz), 3.62 (3H, s), 5.22 (1H, s), 7.01−7.23 (3H, m). **(+)-8b** was similarly prepared from **(−)-7**.

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(5-(4-phenylpiperidin-1-yl)pent-1-yl)pyrimidine (10). The procedure similar to the one described for the synthesis of **9** was used from **8a** (0.2 g, 0.52 mmol) and 4-phenylpiperidine (0.12 g, 0.75 mmol): 24% yield (0.062 g), yellow oil; CIMS *m/e* = 510 (MH^+); ^{1}H NMR δ 1.2−1.35 (2H, m), 1.44−1.90 (7H, m), 1.9−2.1 (2H, m), 2.16 (3H, s), 2.28 (3H, s), 2.3−2.55 (4H, m), 2.95−3.40 (4H, m), 3.61 (3H, s), 5.22 (1H, s), 6.95−7.30 (3H, m). Hydrochloride salt: yellow solid; mp 130−136 °C. Anal. ($C_{30}H_{37}F_2N_3O_2$·2HCl·1.2H_2O·0.6$CHCl_3$) C, H, N.

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-(2-methoxyphenyl)piperidin-1-yl)pent-1-yl)-2,4-dimethylpyrimidine (12). The procedure similar to the one described for the synthesis of **9** was used from **8b** (0.1 g, 0.23 mmol) and 4-(2-methoxyphenyl)piperidine hydrochloride (65 mg, 0.29 mmol): 48% yield (0.06 g), yellow oil; CIMS *m/e* = 540 (MH^+); ^{1}H NMR δ 1.28 (2H, m), 1.48−1.76 (6H, m), 1.98−2.02 (4H, m), 2.17 (3H, s), 2.27 (2H, m), 2.28 (3H, s), 2.96−3.12 (4H, m), 3.35 (1H, m), 3.62 (3H, s), 3.79 (3H, s), 5.24 (1H, s), 6.82 (1H, d, *J* = 8.0 Hz), 6.88 (1H, m), 7.00−7.18 (5H, m). Hydrochloride salt: white solid; mp 85−88 °C. Anal. ($C_{31}H_{39}F_2N_3O_3$·2HCl·2H_2O·0.9$CHCl_3$) C, H, N.

1-(5-(4-Cyano-4-phenylpiperidin-1-yl)pent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (13). The procedure similar to the one described for the synthesis of **9** was used from **8b** (30 mg, 0.07 mmol) and 4-cyano-4-phenylpiperidine hydrochloride (30 mg, 0.13 mmol): 59% yield (0.02 g), yellow oil; CIMS *m/e* = 535 (MH^+); ^{1}H NMR δ 1.22−1.32 (2H, m), 1.47−1.52 (2H, m), 1.60 (1H, m), 1.80 (1H, m), 2.00−2.08 (4H, m), 2.17 (3H, s), 2.28 (3H, s), 2.36−2.43 (4H, m), 2.94 (2H, m), 3.05 (1H, m), 3.35 (1H, m), 3.62 (3H, s), 5.24 (1H, s), 7.01−7.15 (3H, m), 7.29−7.39 (4H, m), 7.45 (1H, m). Hydrochloride salt: white solid; mp 89−93 °C. Anal. ($C_{31}H_{36}F_2N_4O_2$·2HCl·0.8CH_2Cl_2) C, H, N.

(+)-6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(5-(4,4-diphenylpiperidin-1-yl)pent-1-yl)pyrimidine ((+)-14). The procedure similar to the one described for the synthesis of **9** was used from **8b** (0.4 g, 0.93 mmol) and 4,4-diphenylpiperidine hydrochloride (0.33 g, 1.21 mmol): 35% yield (0.21 g), yellow oil; CIMS *m/z* 586 (MH^+); ^{1}H NMR δ 1.26 (2H, m), 1.44−1.65 (4H, m), 2.18 (3H, s), 2.20 (2H, m), 2.31 (3H, s), 2.47 (8H, m), 3.08 (1H, m), 3.32 (1H, m), 3.64 (3H, s), 5.24 (1H, s), 7.02−7.25 (13H, m). Chiral HPLC separation (Chiralcel OD 20 × 250 mm column; λ = 254 nm; hexane:isopropyl alcohol, 60:40; 9.0 mL/min; 17.5 min) gave the title enantiomer. Hydrochloride salt: pale yellow solid; mp 150−153 °C; $[\alpha]_D$ = 60.0 (2.95 mg/mL, MeOH). Anal. ($C_{36}H_{41}F_2N_3O_2$·2HCl·0.9$CHCl_3$) C, H, N.

(+)-6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(5-(4-(2-methylphenyl)-4-(4-methylphenyl)piperidin-1-yl)pent-1-yl)pyrimidine ((+)-15). The procedure similar to the one described for the synthesis of **9** was used from **(+)-8b** (0.18 g, 0.42 mmol) and 4,4-diphenylpiperidine hydrochloride (0.14 g, 0.46 mmol): 91% yield (0.24 g), yellow oil; CIMS *m/e* = 614 (MH^+); ^{1}H NMR δ 1.25 (2H, m), 1.4−1.65 (4H, m), 2.18 (3H, s), 2.19 (2H, m), 2.28 (3H, s), 2.29 (3H, s), 2.31 (3H, s), 2.45 (8H, m), 3.08 (1H, m), 3.30 (1H, m), 3.64 (3H, s), 5.24 (1H, s), 6.93−7.17 (11H, m). Hydrochloride salt: white solid; mp 158−161 °C; $[\alpha]_D$ = 72.7 (1.65 mg/mL, MeOH). Anal. ($C_{38}H_{45}F_2N_3O_2$·2HCl·2H_2O·0.8$CHCl_3$) C, H, N.

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-1-(5-(4-(2-methoxyphenyl)piperazin-1-yl)pent-1-yl)-2,4-dimethylpyrimidine (16). The procedure similar to the one described for the synthesis of **9** was used from **8b** (0.1 g, 0.233 mmol) and 4-(2-methoxyphenyl)piperazine (92 mg, 0.48 mmol): 55% yield (70 mg), yellow oil; CIMS *m/e* = 541 (MH^+); ^{1}H NMR δ 1.31 (2H, m), 1.50−1.62 (4H, m), 2.18 (3H, s), 2.29 (3H, s), 2.36 (2H, m), 2.61 (4H, m), 3.05 (5H, m), 3.32 (1H, m), 3.63 (3H, s), 3.83 (3H, s), 5.24 (1H, s), 6.84−7.21 (7H, m). Hydrochloride salt: white solid; mp 162−164 °C. Anal. ($C_{30}H_{38}F_2N_4O_3$·3HCl·0.6H_2O) C, H, N.

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-(5-(4-(2-methoxycarbonylphenyl)piperazin-1-yl)pent-1-yl)-2,4-dimethylpyrimidine (17). The procedure similar to the one described for the synthesis of **9** was used from **8b** (0.1 g, 0.23 mmol) and 4-(2-methoxycarbonylphenyl)piperazine (80 mg, 0.36 mmol): 44% yield (0.059 g), yellow oil; CIMS *m/e* = 569 (MH^+); ^{1}H NMR δ 1.22 (2H, m), 1.47−1.53 (4H, m), 2.17 (3H, s), 2.29 (3H, s), 2.35 (2H, m), 2.56 (4H, t, J = 4.7 Hz), 3.04 (4H, t, J = 4.7 Hz), 3.10 (1H, m), 3.35 (1H, m), 3.63 (3H, s), 3.85 (3H, s), 5.24 (1H, s), 6.93−7.08 (5H, m), 7.37 (1H, m), 7.68 (1H, m). Hydrochloride salt: white solid; mp 82−86 °C. Anal. ($C_{31}H_{38}F_2N_4O_4$·3HCl·0.7$CHCl_3$) C, H, N.

(+)-1-(5-(4-(2-Aminocarbonyl)phenylpiperazin-1-yl)-pent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine ((+)-18). The procedure similar to the one described for the synthesis of **9** was used from **8b** (1 g, 2.33 mmol) and 4-(2-aminocarbonylphenyl)-piperazine (0.65 g, 3.17 mmol): 98% yield (1.3 g), yellow oil; CIMS *m/e* = 554 (MH^+); ^{1}H NMR δ 1.24−1.32 (2H, m), 1.46−1.55 (4H, m), 1.85 (2H, m), 2.17 (3H, s), 2.28 (3H, s), 2.34 (2H, m), 2.56 (2H, m), 3.00 (4H, t, J = 4.7 Hz), 3.10 (1H, m), 3.32 (1H, m), 3.62 (3H, s), 5.23 (1H, s), 5.91 (1H, m), 7.00−7.23 (5H, m), 7.43 (1H, m), 8.10 (1H, m), 9.45 (1H, m). Chiral HPLC separation (Chiralcel OD 20 × 250 mm column; λ = 254 nm; hexane:ethyl alcohol, 85:15; 12 mL/min; 26.2 min) gave the title enantiomer which was converted to a hydrochloride salt: white solid; mp 167−168 °C; $[\alpha]_D$ = 121.5 (30 mg/mL MeOH). Anal. ($C_{30}H_{37}F_2N_5O_3$·2.5HCl·0.1Et_2O) C, H, N.

Benzyl 3-Oxo-2-(2,4-difluorobenzylidenyl)butanoate (20). A mixture of 2,4-difluorobenzaldehyde (7.1 g, 50 mmol), benzyl acetoacetate (12.48 g, 65 mmol), acetic acid (0.15 g, 2.5 mmol), piperidine (0.212 g, 2.5 mmol), and 2-propanol (300 mL) was stirred at room temperature for 2 days. After removal of the solvent, the residue was dissolved in ethyl acetate, washed with saturated $KHSO_4$, saturated $NaHCO_3$, and water, and then dried over Na_2SO_4. The solvent was evaporated, and the residue was flash-chromatographed over silica gel (1:5 ethyl acetate−hexane) to give the product in 91% yield (14.3 g) as a yellow solid: ^{1}H NMR δ 2.39 (3H, s), 5.26 (2H, s), 6.80 (2H, m), 7.15 (1H, m), 7.3−7.34 (5H, m), 7.63 (1H, s).

6-(2,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (21). To a solution of acetamidine hydrochloride (2.84 g, 30 mmol) in DMF (20 mL) were added a solution of potassium *tert*-butoxide (2.46 g, 21.8 mmol) in DMF (20 mL) and a solution of **19** (2.84 g, 20 mmol) in DMF (20 mL) at 0 °C. After the mixture was stirred for 0.5 h at 0 °C, *p*-toluenesulfonic acid monohydrate (7.6 g, 39.8 mmol) was added. The mixture was heated at 100−120 °C for 2 h. The reaction mixture was cooled to room temperature, quenched with 2 N NaOH solution (100 mL), and extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in 49% yield (2.74 g) as a yellow solid: ^{1}H NMR δ 1.93 (3H, s), 2.33 (3H, s), 3.55 (3H, s), 5.75 (1H, s), 6.75 (2H, m), 7.23 (1H, m).

5-Benzyloxycarbonyl-6-(2,4-difluorophenyl)-1,6-dihydro-2,4-dimethylpyrimidine (22). To a stirred solution of acetamidine hydrochloride (2.84 g, 30 mmol) in DMF (20 mL) were added a solution of potassium *tert*-butoxide (2.46 g, 22 mmol) in DMF (20 mL) and a solution of **20** (6.32 g, 20 mmol) in DMF (20 mL) at 0 °C. After the mixture was stirred for 15 min at 0 °C, *p*-toluenesulfonic acid monohydrate (7.6 g, 40 mmol) was added. The mixture was heated at 100−110 °C for 2 h. After cooling, the reaction mixture was quenched with 2 N aqueous NaOH solution and extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography over silica gel (20:1 ethyl acetate−2 M ammonia in methanol) to give the product in 42% yield (1.5 g) as an off-white solid: ^{1}H NMR δ 1.71 (3H, s), 2.20 (3H, s), 4.90 (1H, d, J = 12.5 Hz), 5.04 (1H, d, J = 12.5 Hz), 5.75 (1H, s), 6.64−6.71 (2H, m), 7.04−7.22 (6H, m).

1-(5-Bromopent-1-yl)-6-(2,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (23). To a suspension of NaH (0.405 g, 60% dispersion in mineral oil, 10.1 mmol) in THF (20 mL) was added a solution of **21** (2.7 g, 9.64 mmol) in THF (10 mL) at 0 °C. After 20 min, 1-bromo-5-chloropentane (3.8 mL, d 1.408, 28.8 mmol) was added. The reaction mixture was then refluxed overnight. After the removal of the solvent, the residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in 79% yield (2.91 g) as a yellow oil: ^{1}H NMR δ 1.25−1.75 (6H, m), 1.86 (3H, s), 2.21 (3H, s), 3.0 (1H, m), 3.2 (1H, m), 3.37 (2H, t, J = 7.6 Hz), 3.43 (3H, s), 5.50 (1H, s), 6.60 (2H, m), 7.25 (1H, m).

5-Benzyloxycarbonyl-1-(5-bromopent-1-yl)-6-(2,4-difluorophenyl)-1,6-dihydro-2,4-dimethylpyrimidine (24). To a suspension of NaH (123 mg, 60% dispersion in mineral oil) in THF (5 mL) was added a solution of **22** (1.0 g, 2.8 mmol) and HMPA (0.5 g, 2.8 mmol) in THF (5 mL) at 0 °C. After 15 min, 1,5-dibromopentane (1.53 mL, 11.2 mmol) was added. The reaction mixture was then refluxed for 30 min. The solid was filtered off. After the removal of the solvent, the residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in 78% yield (1.1 g) as a yellow oil: ^{1}H NMR δ 1.40−1.90 (6H, m), 2.10 (3H, s), 2.37 (3H, s), 3.10 (1H, m), 3.25 (1H, m), 3.35 (2H, t, J = 6.6 Hz), 4.94 (1H, d, J = 12.4 Hz), 5.10 (1H, d, J = 12.4 Hz), 5.63 (1H, s), 6.64−6.79 (2H, m), 7.10−7.36 (6H, m).

6-(2,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pent-1-yl)-2,4-dimethylpyrimidine (25). The procedure similar to the one described for the synthesis of **9** was used from **23** (0.4 g, 1.04 mmol) and 4-methoxycarbonyl-4-phenylpiperidine (0.45 g, 2.05 mmol): 25% yield (0.15 g), yellow oil; CIMS *m/e* = 568 (MH^+); ^{1}H NMR δ 1.27 (2H, m), 1.45−1.75 (4H, m), 1.92−2.11 (4H, m), 2.09 (3H, s), 2.23 (2H, m), 2.34 (3H, s), 2.51 (2H, m), 2.81 (2H, m), 3.05 (1H, m), 3.30 (1H, m), 3.56 (3H, s), 3.61 (3H, s), 5.61 (1H, s), 6.71−6.78 (2H, m), 7.20−7.38 (6H, m). Hydrochloride salt: pale yellow solid; mp 128−132 °C. Anal. ($C_{32}H_{39}F_2N_3O_4$·2HCl·H_2O·$CHCl_3$) C, H, N.

5-Benzyloxycarbonyl-6-(2,4-difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pent-1-yl)-2,4-dimethylpyrimidine (26). The procedure similar to the one described for the synthesis of **9** was used from **23** (1.62 g, 3.2 mmol) and 4-methoxycarbonyl-4-phenylpiperidine (1.4 g, 6.4 mmol): 66% yield (1.36 g), yellow oil; ^{1}H NMR δ 1.25 (2H, m), 1.46−1.70 (4H, m), 1.90−2.07 (4H, m), 2.08 (3H, s), 2.23 (2H, m), 2.36 (3H, s), 2.51 (2H, m), 2.81 (2H, m), 3.05 (1H, m), 3.25 (1H, m), 3.61 (3H, s), 4.93 (1H, d, J = 12.5 Hz), 5.09 (1H, d, J = 12.5 Hz), 5.63 (1H, s), 6.62 (1H, m), 6.78 (1H, m), 7.10−7.36 (11H, m).

5-Carboxy-6-(2,4-difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pent-1-yl)-2,4-dimethylpyrimidine (27). A solution of **26** (0.36 g, 0.56 mmol) in methanol (20 mL) was subjected to hydrogenation with a H_2 balloon in the presence of 5% palladium on carbon (36 mg). The reaction was carried out at room temperature for 30 min. The catalyst was then filtered off and the solvent was removed in vacuo to give the product in quantitative yield (0.31 g) as an off-white solid: ^{1}H NMR δ 1.30 (2H, m), 1.52 (3H, m), 2.05−2.28 (4H, m), 2.55 (2H, m), 2.93 (2H, m), 2.24 (3H, s), 2.32 (3H, s), 3.30 (1H, m), 3.55 (1H, m), 3.60 (3H, s), 5.95 (1H, s), 6.96 (2H, m, 7.20−7.45 (6H, m).

5-Aminocarbonyl-6-(2,4-difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pent-1-yl)-2,4-dimethylpyrimidine (28). A mixture of **27** (0.2 g, 0.36 mmol), 4,4-dimethylaminopyridine (0.26 g, 2.12 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.13 g, 0.66 mmol), and CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. After the addition of ammonium chloride (0.06 g, 1.08 mmol), the mixture was stirred at room temperature for 3 days. To the mixture was added another 25 mL of CH_2Cl_2 and it was washed with saturated NH_4Cl solution.

After removal of the solvent, the residue was separated by silica gel TLC plate (5:1 ethyl acetate−2 M ammonia in methanol) to give the title compound in 7.5% yield (0.015 g) as a yellow oil: CIMS *m/e* = 553 (MH^+); ^{1}H NMR δ 1.20 (4H, m), 1.45 (3H, m), 1.65 (1H, m), 1.92 (2H, m), 2.15 (5H, m), 2.25−2.31 (5H, m), 2.55 (2H, m), 2.80 (2H, m), 3.02 (1H, m), 3.28 (1H, m), 3.61 (3H, s), 5.37 (1H, s), 6.80 (2H, m), 7.20−7.34 (6H, m). Hydrochloride salt: pale yellow solid; mp 77−80 °C. Anal. ($C_{31}H_{38}F_2N_4O_3\cdot 2HCl\cdot H_2O\cdot 0.2CHCl_3\cdot 2Et_2O$) C, H, N.

6-(2,4-Difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pent-1-yl)-2,4-dimethyl-5-methylaminocarbonylpyrimidine (29). A mixture of **15** (0.244 g, 0.44 mmol), 4-dimethylaminopyridine (0.26 g, 2.12 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.13 g, 0.66 mmol), and CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. After the addition of methylamine hydrogen chloride (0.09 g, 1.32 mmol), the mixture was stirred at room temperature overnight. To the mixture was added another 25 mL of CH_2Cl_2 and it was washed with saturated NH_4Cl solution. After removal of the solvent, the residue was flash-chramotographed over silica gel (5:1 ethyl acetate−2 M ammonia in methanol) to give the title compound in 22% yield (0.055 g) as a yellow oil: CIMS *m/e* = 567 (MH^+); ^{1}H NMR δ 1.25 (2H, m), 1.45 (3H, m),1.65 (1H, m), 1.92−2.05 (4H, m), 2.07 (3H, s), 2.14 (3H, s), 2.24 (2H, m), 2.50 (2H, m), 2.73 (5H, m), 3.02 (1H, m), 3.24 (1H, m), 3.61 (3H, s), 5.37 (1H,s), 5.58 (1H, s), 6.76 (2H, m), 7.20−7.34 (6H, m). Hydrochloride salt: pale yellow solid; mp 152−155 °C. Anal. ($C_{32}H_{40}F_2N_4O_3\cdot 2HCl\cdot 1.6H_2O\cdot 0.8CHCl_3$) C, H, N.

1-(4-Bromobut-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (33). To a suspension of NaH (50 mg, 60% dispersion in mineral oil) in THF (7 mL) was added a solution of **7** (0.32 g, 1.14 mmol) and HMPA (0.205 g, 1.14 mmol) in THF (8 mL) at 0 °C. After 15 min, 1,4-dibromobutane (0.47 mL, 4.0 mmol) was added. The reaction mixture was then refluxed for 10 min. The solid was filtered off. After removal of the solvent, the residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in 44% yield (0.2 g) as a yellow oil: ^{1}H NMR δ 1.71−1.81 (4H, m), 2.17 (3H, s), 2.28 (3H, s), 3.12 (1H, m), 3.36 (3H, m), 3.62 (3H, s), 5.22 (1H, s), 7.00−7.08 (3H, m).

1-(5-Bromo-4(*S*)-methylpent-1-yl)-6(*R*,*S*)-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (34). To a suspension of NaH (47 mg, 60% dispersion in mineral oil) in THF (3 mL) was added a solution of **7** (0.3 g, 1.07 mmol) and HMPA (0.193 g, 1.07 mmol) in THF (4 mL) at 0 °C. After 10 min, a solution of **31** (0.86 g, 3.53 mmol) in THF (5 mL) was added. The reaction mixture was then refluxed for 10 min. The solid which formed was filtered off. After removal of the solvent, the residue was flash-chromatographed over silica gel (20:1 ethyl acetate−2 M ammonia in methanol) to give the product in 36% yield (0.169 g) as a yellow oil: ^{1}H NMR δ 0.97 (3H, d, *J* = 6.5 Hz), 1.22 (1H, m), 1.35−1.80 (5H, m), 2.18 (3H, s), 2.29 (3H, s), 3.10 (1H, m), 3.30 (2H, m), 3.63 (3H, s), 5.23 (1H, s), 6.95−7.18 (3H, m).

1-(5-Bromo-4(*R*)-methylpent-1-yl)-6(*R*,*S*)-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (35). Prepared in 32% yield from **7** and **32** according to the procedure described for **34**: ^{1}H NMR δ 0.99 (3H, d, *J* = 6.6 Hz), 1.40−1.80 (4H, m), 2.20 (3H, s), 2.31 (3H, s), 3.12 (1H, m), 3.33 (3H, m), 3.65 (3H, s), 5.26 (1H, s), 7.00−7.20 (3H, m).

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(4-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)but-1-yl)-2,4-dimethylpyrimidine (36). The procedure similar to the one described for the synthesis of **9** was used from **33** (0.21 g, 0.51 mmol) and 4-methoxycarbonyl-4-phenylpiperidine (0.22 g, 1.02 mmol): 63% yield (0.18 g), yellow oil; CIMS *m/e* = 554 (MH^+); ^{1}H NMR δ 1.46−1.58 (4H, m), 1.92−2.0 (4H, m), 2.23 (2H, m), 2.15 (3H, s), 2.27 (3H, s), 2.5 (2H, m), 2.73 (2H, m), 3.08 (1H, m), 3.30 (1H, m), 3.613 (3H, s), 3.59 (3H, s), 5.22 (1H, s), 6.98−7.31 (8H, m). Hydrochloride salt: pale yellow solid; mp 178−181 °C. Anal. ($C_{31}H_{37}F_2N_3O_4\cdot 2HCl\cdot 1.6H_2O\cdot 0.8CHCl_3$) C, H, N.

(+)-1-(5-(4-(2-Aminocarbonyl)phenylpiperazin-1-yl)-4(*R*)-methylpent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine ((+)-41). The procedure similar to the one described for the synthesis of **9** was used from **35** (0.3 g, 0.68 mmol) and 4-(2-aminocarbonylphenyl)piperazine (0.2 g, 0.96 mmol): 52% yield (0.2 g), yellow oil. Chiral HPLC separation (Chiralcel OD 20 × 250 mm column; λ = 254 nm; hexane:ethyl alcohol:diethylamine, 85:15:0.1; 9.0 mL/min; 15.6 min) gave the title enantiomer: CIMS *m/e* = 568 (MH^+); ^{1}H NMR δ 0.89 (3 H, d, *J* = 6.6 Hz), 1.05 (1H, m), 1.40 (1H, m), 1.62 (3H, m), 2.15 (2H, m), 2.22 (3H, s), 2.32 (3H, s), 2.54 (4H, m), 3.02 (2H, m), 3.12 (1H, m), 3.35 (1H, m), 3.68 (3H, s), 5.28 (1H, s), 5.85 (1H, m), 7.04−7.24 (5H, m), 7.46 (1H, m), 8.16 (1H, m), 9.55 (1H, m). Hydrochloride salt: pale yellow solid; mp 158−162 °C; $[\alpha]_D$ = 43.9 (2.05 mg/mL, MeOH). Anal. ($C_{31}H_{39}F_2N_5O_3\cdot 3HCl\cdot H_2O\cdot 1.1CH_2Cl_2$) C, H, N.

(+)-1-(5-(4-(2-Aminocarbonyl)phenylpiperazin-1-yl)-4(*S*)-methylpent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine ((+)-40). The procedure similar to the one described for the synthesis of **9** was used from **34** (0.25 g, 0.56 mmol) and 4-(2-aminocarbonylphenyl)piperazine (0.17 g, 0.83 mmol): 63% yield (0.2 g), yellow oil. Chiral HPLC separation (Chiralcel OD 20 × 250 mm column; λ = 254 nm; hexane:ethyl alcohol:diethylamine, 85:15:0.1; 9.0 mL/min; 27.5 min) gave the title enantiomer: CIMS *m/e* = 568 (MH^+); ^{1}H NMR δ 0.90 (3H, d, *J* = 6.6 Hz), 1.05 (1H, m), 1.40−1.65 (4H, m), 2.15 (2H, m), 2.21 (3H, s), 2.32 (3H, s), 2.54 (4H, m), 3.02 (2H, m), 3.12 (1H, m), 3.35 (1H, m), 3.64 (3H, s), 5.28 (1H, s), 5.90 (1H, m), 7.04−7.24 (5H, m), 7.46 (1H, m), 8.14 (1H, m), 9.55 (1H, m). Hydrochloride salt: pale yellow solid; mp 155−158 °C; $[\alpha]_D$ = 64.7 (2.75 mg/mL, MeOH). Anal. ($C_{31}H_{39}F_2N_5O_3\cdot 3HCl\cdot H_2O\cdot 0.6Et_2O$) C, H, N.

(+)-6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-4(*S*)-methylpent-1-yl)-2,4-dimethylpyrimidine ((+)-37). The procedure similar to the one described for the synthesis of **9** was used from **35** (3.50 g, 7.9 mmol) and 4-methoxycarbonyl-4-phenylpiperidine (3.50 g, 15.7 mmol): 44% yield (2.0 g). Chiral HPLC separation (Chiralcel OD 20 × 250 mm column; λ = 254 nm; hexane:isopropyl alcohol:diethylamine, 90:10:0.1; 12.0 mL/min; 11.3 min) afforded the title enantiomer: CIMS *m/e* = 582 (MH^+); ^{1}H NMR δ 1.03 (3H, m), 1.22 (1H, m), 1.56 (1H, m), 1.77 (2H, m), 2.05−2.30 (7H, m), 2.39 (3H, s), 2.49 (3H, s), 2.73 (2H, m), 2.90 (2H, m), 3.27 (1H, m), 3.48 (1H, m), 3.81 (3H, s), 5.44 (1H, s), 7.20−7.52 (8H, m). Hydrochloride salt: light yellow solid; mp 133−134 °C; $[\alpha]_D$ = 137.6 (11 mg/mL, MeOH). Anal. ($C_{33}H_{41}F_2N_3O_4\cdot 2HCl\cdot 1/2H_2O$) C, H, N.

(+)-1-(5-(4-Cyano-4-phenylpiperidin-1-yl)-4(*S*)-methylpent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine ((+)-38). The procedure similar to the one described for the synthesis of **9** was used from **34** (0.23 g, 0.515 mmol) and 4-cyano-4-phenylpiperidine hydrochloride (0.23 g, 1.0 mmol): 32% yield (0.09 g), yellow oil. Chiral HPLC separation (Chiralcel OD 20 × 250 mm column; λ = 254 nm; hexane:isopropyl alcohol:diethylamine, 80:20:0.1; 12.0 mL/min; 15.9 min) gave the title enantiomer: CIMS *m/e* = 549 (MH^+); $[\alpha]_D$ = 142.8 (6 mg/mL, MeOH); ^{1}H NMR δ 0.89 (3H, d, *J* = 6.6 Hz), 1.03−1.75 (7H, m), 2.09 (4H, m), 2.21 (3H, s), 2.31 (3H, s), 2.45 (2H, m), 2.90 (2H, m), 3.10 (1H, m), 3.35 (1H, m), 3.64 (3H, s), 5.28 (1H, s), 7.02−7.49 (8H, m). Hydrochloride salt: light yellow solid; mp 140−141 °C. Anal. ($C_{32}H_{38}F_2N_4O_2\cdot 2HCl\cdot 0.7CHCl_3$) C, H, N.

(+)-1-(5-(4-Cyano-4-phenylpiperidin-1-yl)-4(*R*)-methylpent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine ((+)-39). The procedure similar to the one described for the synthesis of **9** was used from **35** (0.3 g, 0.68 mmol) and 4-cyano-4-phenylpiperidine hydrochloride (0.3 g, 1.35 mmol): 54% yield (0.2 g), yellow oil. Chiral HPLC separation (Chiralcel OD 20 × 250 mm column; λ = 254 nm; hexane:ethyl alcohol:diethylamine, 85:15:0.1; 9.0

mL/min; 18.9 min) gave the title enantiomer: CIMS *m/e* = 549 (MH^+); $[\alpha]_D$ = 169.9 (9.5 mg/mL MeOH); ^{1}H NMR δ 0.89 (3H, d, *J* = 6.6 Hz), 1.05 (1H, m), 1.40 (1H, m), 1.55−1.67 (4H, m), 2.09 (4H, m), 2.20 (1H, m), 2.21 (3H, s), 2.31 (3H, s), 2.45 (2H, m), 2.90 (2H, m), 3.10 (1H, m), 3.35 (1H, m), 3.64 (3H, s), 5.28 (1H, s), 7.02−7.20 (3H, m), 7.35−7.49 (5H, m). Hydrochloride salt: pale yellow solid; mp 171−172 °C. Anal. ($C_{32}H_{38}F_2N_4O_2$·2HCl·0.1$CHCl_3$) C, H, N.

1-(3-Bromomethylbenzyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (42). To a suspension of NaH (31 mg, 60% dispersion in mineral oil) in THF (5 mL) was added a solution of **7** (0.3 g, 1.07 mmol) and HMPA (0.193 g, 1.07 mmol) in THF (5 mL) at 0 °C. After 15 min, α,α′-dibromo-*m*-xylene (0.99 g, 3.75 mmol) was added. The reaction mixture was then refluxed for 15 min. The solid was filtered off. After the removal of the solvent, the residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in 91% yield (0.45 g) as a yellow oil: ^{1}H NMR δ 2.19 (3H, s), 2.36 (3H, s), 3.55 (3H, s), 4.18 (1H, d, *J* = 16.4 Hz), 4.45 (2H, s), 4.63 (1H, d, *J* = 16.5 Hz), 5.12 (1H, s), 6.99−7.34 (7H, m).

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)methylbenzyl)-2,4-dimethylpyrimidine (43). A mixture of **42** (0.45 g, 0.97 mmol), 4-methoxycarbonyl-4-phenylpiperidine (0.42 g, 1.9 mmol), potassium carbonate (0.67 g, 4.86 mmol), sodium iodide (0.14 g, 0.97 mmol), and 1,4-dioxane (10 mL) was refluxed overnight. The solid was then filtered off and the solvent was evaporated. The residue was purified by flash chromatography over silica gel (20:1 ethyl acetate−2 M ammonia in methanol) to give the title compound in 17% yield (0.1 g) as a yellow oil: CIMS *m/e* = 602 (MH^+); ^{1}H NMR δ 1.68−1.85 (2H, m), 1.95 (2H, m), 2.13 (2H, m), 2.19 (3H, s), 2.34 (3H, s), 2.49 (2H, m), 2.75 (2H, m), 3.43 (2H, s), 3.52 (3H, s), 3.62 (3H, s), 4.18 (1H, d, *J* = 16.7 Hz), 4.61 (1H, d, *J* = 16.7 Hz), 5.13 (1H, s), 6.99−7.36 (12H, m). Hydrochloride salt: off-white solid; mp 181−183 °C. Anal. ($C_{35}H_{37}F_2N_3O_4$·2HCl·H_2O) C, H, N.

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (46). To a solution of 2-methoxyacetamidine hydrochloride (1.4 g, 11.2 mmol) in DMF (6 mL) were added a solution of potassium *tert*-butoxide (0.69 g, 6.1 mmol) in DMF (6 mL) and a solution of **5** (1.4 g, 5.8 mmol) in DMF (6 mL) at 0 °C. After the mixture was stirred for 0.5 h at 0 °C, *p*-toluenesulfonic acid monohydrate (2.2 g, 11.6 mmol) was added. The mixture was heated at 100−120 °C for 2.5 h. The mixture was cooled to room temperature, quenched with 2 N NaOH solution (30 mL), and extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in 44% yield (0.8 g) as a yellow oil: ^{1}H NMR δ 2.38 (3H, s), 3.39 (3H, s), 3.63 (3H, s), 4.06 (2H, q, *J* = 12.4 Hz), 5.57 (1H, s), 6.89 (1H, b), 7.04−7.15 (3H, m).

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-2-methylpyrimidine (47). To a stirred solution of acetamidine hydrochloride (0.71 g, 7.5 mmol.) in DMF (5 mL) were added a solution of potassium *tert*-butoxide (0.61 g, 5.5 mmol) in DMF (5 mL) and a solution of **29** (1.35 g, 5 mmol) in DMF (5 mL) at 0 °C. After the mixture was stirred for 15 min at 0 °C, *p*-toluenesulfonic acid monohydrate (1.9 g, 10 mmol) was added. The mixture was heated at 100−110 °C for 2 h. After cooling, the reaction mixture was quenched with 2 N aqueous NaOH solution and extracted with ether. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was flash-chromatographed over silica gel (ethyl acetate) to give the product in 23% yield (0.352 g) as an off-white solid: ^{1}H NMR δ 2.01 (3H, s), 3.41 (3H, s), 3.57 (3H, s), 4.59 (1H, d, *J* = 16.2 Hz), 4.64 (1H, d, *J* = 16.2 Hz), 5.46 (1H, s), 6.98−7.06 (3H, m).

1-(5-Bromopent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (48). To a suspension of NaH (0.11 g, 60% dispersion in mineral oil, 2.8 mmol) in THF (20 mL) was added a solution of **46** (0.8 g, 2.6 mmol) in THF (5 mL) at 0 °C. After 20 min, 1,5-dibromopentane (0.7 mL, 5.2 mmol) was added. The mixture was then refluxed overnight. After the removal of solvent, the residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in quantitative yield (1.2 g) as a yellow oil: ^{1}H NMR δ 1.43−1.94 (6H, m), 2.34 (3H, s), 3.15 (1H, m), 3.34 (3H, s), 3.42 (2H, t, *J* = 6.6 Hz), 3.69 (3H, s), 3.65−3.75 (1H, m), 4.05 (1H, d, *J* = 12.9 Hz), 4.30 (1H, d, *J* = 12.8 Hz), 5.31 (1H, s), 7.0−7.09 (3H, m).

1-(5-Bromopent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-2-methylpyrimidine (49). To a suspension of NaH (0.12 g, 60% oil dispersion, 3 mmol) in THF (5 mL) was added a solution of **47** (0.8 g, 2.58 mmol) in THF (5 mL) at 0 °C. After 20 min, 1,5-dibromopentane (1.18 mL, 7.74 mmol) was added. The mixture was then refluxed for 3 h. After the removal of the solvent, the residue was purified by flash chromatography over silica gel (ethyl acetate) to give the product in 78% yield (0.92 g) as a yellow oil: ^{1}H NMR δ 1.41−1.85 (6H, m), 2.23 (3H, s), 3.05 (1H, m), 3.35 (1H, m), 3.40 (3H, s), 3.48 (2H, t, *J* = 6.3 Hz), 3.63 (3H, s), 4.42 (1H, d, *J* = 12.4 Hz), 4.48 (1H, d, *J* = 12.4 Hz), 5.25 (1H, s), 7.01−7.08 (3H, m).

1-(5-(4-Cyano-4-phenylpiperidin-1-yl)pent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (50). The procedure similar to the one described for the synthesis of **9** was used from **48** (0.15 g, 0.33 mmol) and 4-cyano-4-phenylpiperidine hydrochloride (0.15 g, 0.67 mmol): 44% yield (0.08 g), yellow oil; CIMS *m/e* = 565 (MH^+); ^{1}H NMR δ 1.31−1.37 (2H, m), 1.52−1.75 (4H, m), 2.03−2.13 (4H, m), 2.34 (3H, s), 2.40−2.51 (4H, m), 3.00−3.04 (2H, m), 3.14 (1H, m), 3.34 (3H, s), 3.68 (3H, s), 3.70 (1H,m), 4.05 (1H, d, *J* = 12.9 Hz), 4.32 (1H, d, *J* = 12.9 Hz), 5.32 (1H, s), 7.05−7.19 (3H, m), 7.33−7.52 (5H, m). HCl salt: off-white solid; mp 98−101 °C; $[\alpha]_D$ = 190.5 (55 mg/mL CH_2Cl_2). The (+) enantiomer was obtained by chiral HPLC separation (column: Chiralcel OD 20 × 250 mm; 2-propanol: hexane:diethylamine, 10:90:0.1). Anal. ($C_{32}H_{38}F_2N_4O_3$·2HCl·1.1$CHCl_3$) C, H, N.

1-(5-(4-Cyano-4-phenylpiperidin-1-yl)pent-1-yl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-2-methylpyrimidine (51). Prepared from **49** and 4-cyano-4-phenylpiperidine hydrochloride according to the procedure described for **9** as a yellow oil (29% yield): CIMS *m/e* = 565 (MH^+); ^{1}H NMR δ 1.34−1.37 (2H, m), 1.58−1.63 (4H, m), 2.12−2.26 (4H, m), 2.35 (3H, s), 2.55−2.64 (4H, m), 3.15−3.21 (3H, m), 3.40 (1H, m), 3.44 (3H, s), 3.68 (3H, s), 4.46 (1H, d, *J* = 12.5 Hz), 4.56 (1H, d, *J* = 12.5 Hz), 5.32 (1H, s), 7.08−7.53 (8H, m). Hydrochloride salt: yellow solid; mp 98−100 °C. Anal. ($C_{32}H_{38}F_2N_4O_3$·2HCl·$CHCl_3$) C, H, N.

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