Design and Synthesis of Novel α_{1a} Adrenoceptor-Selective Antagonists. 3. Approaches To Eliminate Opioid Agonist Metabolites by Using Substituted Phenylpiperazine Side Chains

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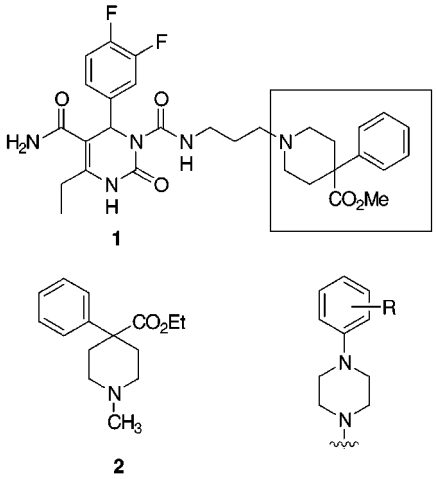
Dihydropyrimidinones, such as **1**, represent a novel class of α_{1a} adrenoceptor antagonists with potential for the treatment of benign prostatic hyperplasia (BPH) (see part 1 of this series). Analysis of the metabolites of **1** revealed that 4-methoxycarbonyl-4-phenylpiperidine is formed as the major metabolite and is an agonist at the μ-opioid receptor. To circumvent any potential liability resulting from the metabolite, we decided to identify alternate templates devoid of agonist activity at the μ-opioid receptor to replace the 4-methoxycarbonyl-4-phenylpiperidine moiety. The present study describes the synthesis and SAR of dihydropyrimidinones linked to substituted 4-phenylpiperazine containing side chains. Compound **(+)-38** was identified as a lead compound with a binding and functional profile comparable to that of **1**. The putative metabolite 2-carboxamidophenylpiperazine has negligible affinity for the μ-opioid receptor.

Introduction

Benign prostatic hyperplasia (BPH) is a progressive enlargement of the prostate resulting in a number of obstructive and irritative symptoms. The incidence of BPH increases with advancing age such that about 70% of males over the age of 70 manifest symptoms associated with BPH.[2] α_1 Adrenoceptor antagonists such as terazosin and doxazosin relax the smooth muscle in the prostate and lower urinary tract and are currently being used as treatments for BPH.[3,4] These clinical agents, while effective, have been associated with side effects such as orthostatic hypotension, dizziness, asthenia, and nasal congestion.[5] The side effect profile is presumably due to an inability of these antagonists to adequately discriminate between the α_1 receptors in the vascular and lower urinary tracts. The predominant α_1 receptor subtype in the prostate is α_{1a}, and functional studies reveal that α_{1a} receptors control the smooth muscle tone.[6] The data suggests that an α_{1a}-selective adrenoceptor antagonist will provide symptomatic relief without causing some of the aforementioned side effects.

Recently, we reported the discovery of dihydropyridines such as SNAP 5089 as a novel class of α_{1a}-selective antagonists.[7] Modifications in the dihydropyridine series led to dihydropyrimidinones as a second class of α_{1a}-selective antagonists, and **1** (i.e. SNAP 6201) was identified as a lead compound. It was found that 4-methoxycarbonyl-4-phenylpiperidine is formed via *N*-dealkylation as a major metabolite of **1** in rats and dogs.[8] 4-Methoxycarbonyl-4-phenylpiperidine which resembles the known opioid agonist meperidine[9] (**2**, Chart 1), was found to be an agonist at the μ-opioid receptor (IC_{50} = 3.0 μM). Meperidine is a controlled substance with narcotic and sedative properties.[10] In addition, the 4-methoxycarbonyl-4-phenylpiperidine was found to have long plasma half-life in rats and dogs (>12 h) which raised concerns regarding potential liabilities such as sedation or addiction that might be associated with the chronic administration of **1**. To circumvent this problem, a search was undertaken to find a suitable replacement for the 4-methoxycarbonyl-4-phenylpiperidine fragment. The goal was to obtain compounds which would maintain high binding affinity (<5 nM) and selectivity for the α_{1a} receptor (>300-fold over $\alpha_{1b,d}$ and $\alpha_{2a,b,c}$). The compound should exhibit good potency in a number of in vivo and in vivo functional assays. In addition, it was deemed essential that the metabolites of this compound should not be agonists at the μ-opioid receptor. The preceding paper describes the structure−activity relationship (SAR) in the dihydropyrimidinones

Chart 1



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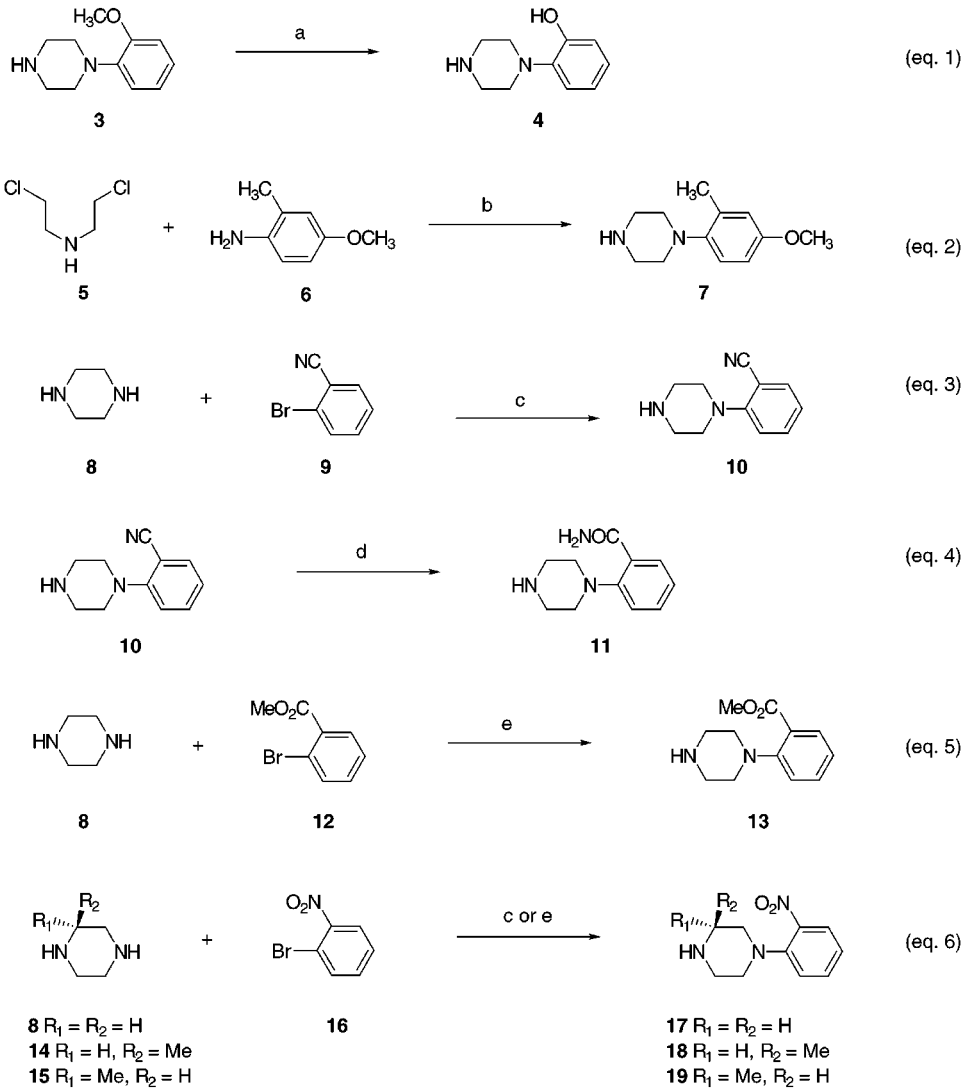
Scheme 1[a]



[a] (a) BBr_3, ref 11; (b) Na_2CO_3, *n*-BuOH, ref 11; (c) neat, 100 °C, ref 11; (d) concd H_2SO_4, 2 days, 73% yield; (e) K_2CO_3, dioxane, reflux, 10 h, 45−80% yield.

containing 4,4-disubstituted piperidine-containing side chains,[8] whereas the present study illustrates the synthesis and SAR of dihydropyrimidinones containing substituted 4-phenylpiperazines.

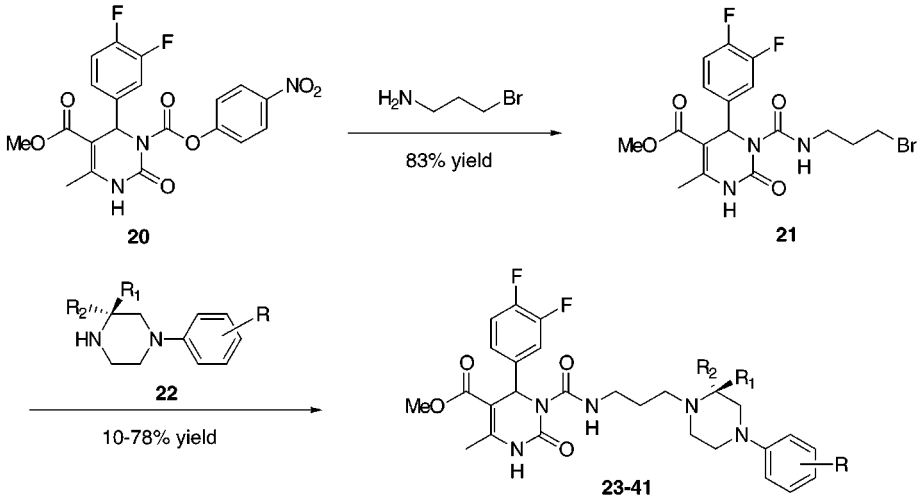
Chemistry

Some of the 4-phenylpiperazines used in the present study were purchased from commercial sources. The synthesis of other 4-phenylpiperazines was achieved by procedures depicted in Scheme 1.[11] Compound **4** was synthesized from the commercially available 2′-methoxyphenylpiperazine (**3**) (eq 1). The 2′-methyl-4′-methoxyphenylpiperazine (**7**) was synthesized by heating to reflux bis(2-chloroethyl)amine (**5**), 4′-methoxy-2′-methylaniline (**6**), and Na_2CO_3 in *n*-butyl alcohol for 2 days (eq 2). The 2′-cyanophenylpiperazine (**10**) was synthesized from piperazine and 2-bromobenzonitrile according to a known procedure[11] (eq 3) and was then converted into 2′-carboxamidophenylpiperazine (**11**) by treatment with concentrated sulfuric acid (eq 4). The phenylpiperazines **13**, **17**, **18**, and **19** were synthesized from **12** or **16** under identical reaction conditions as shown in eqs 5 and 6. The compounds **18** and **19** were synthesized from commercially available (*R*)- or (*S*)-2-methylpiperazines. The unsubstituted piperazine was used as a starting material for the synthesis of **13** and **17**.

The phenylpiperazines thus synthesized were then used to obtain the target compounds via parallel synthesis from common intermediate **21**, as depicted in Scheme 2. Compound **21**[12] was obtained by reaction of **20** with 3-aminopropyl bromide in THF at room temperature, followed by treatment with dilute hydrochloric acid in THF. Intermediate **21** was then heated in refluxing acetone with a number of 4-phenylpiperazines and K_2CO_3 to obtain the final products **23**−**41** in 20−78% yield. The (+) enantiomer of **20** was used as the starting material for the synthesis of the optically pure compounds shown in Table 2.

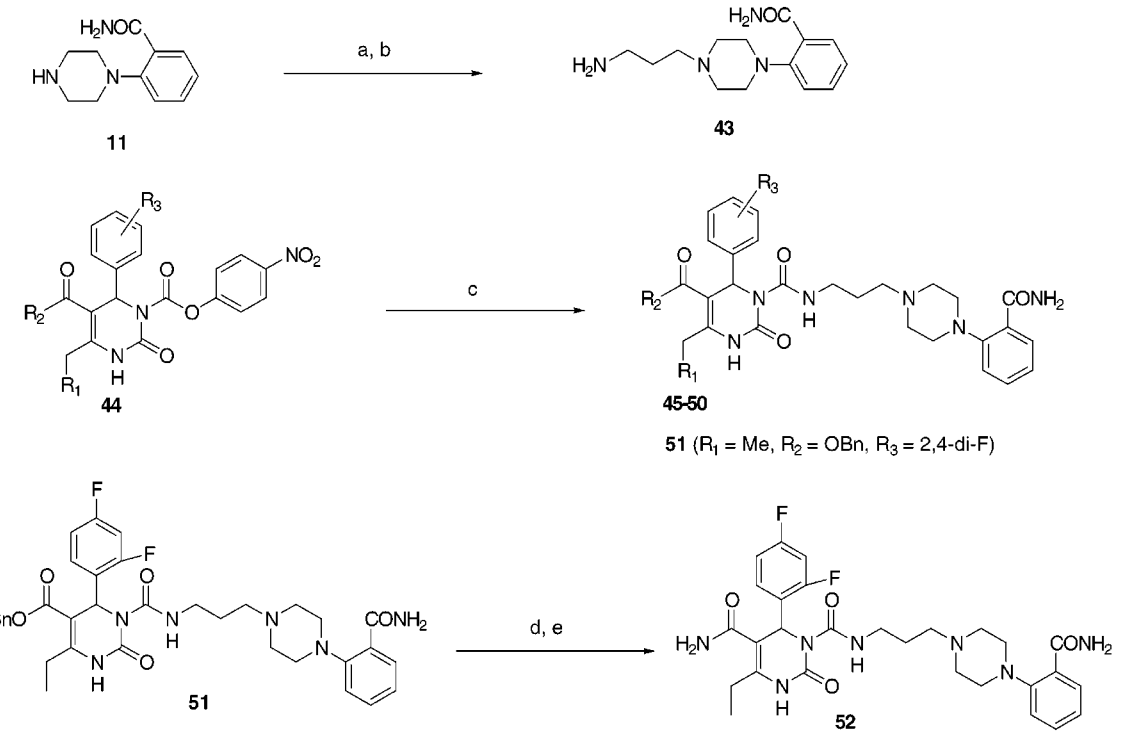
The compounds in Table 3 were synthesized by a modified procedure as shown in Scheme 3. Reaction of *N*-*tert*-butyloxycarbonyl-3-bromopropylamine with 2′-carboxamidophenylpiperazine (**11**) gave intermediate **42** which upon deprotection of the *tert*-butyloxy group with trifluoroacetic acid gave 1-(3-aminopropyl)-4-(2′-carboxamidophenyl)piperazine (**43**) in 78% yield. The amine

Scheme 2



For the description of R, R_1 and R_2, see Tables 1 and 2

Scheme 3[a]



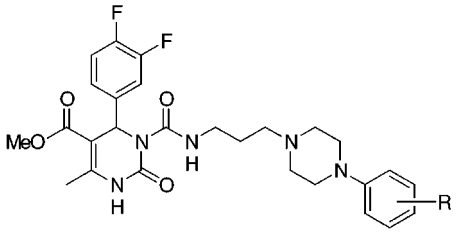
[a] (a) N-Boc-3-bromopropylamine, K_2CO_3, THF, reflux, 55% yield; (b) TFA, CH_2Cl_2, rt, 78% yield; (c) **43**, THF, rt, 49−93% yield; (d) H_2, Pd−C, 94% yield; (e) DMAP, EDC, NH_3, THF, 70% yield.

43 was then reacted with activated dihydropyrimidinones of general structure **44** to obtain compounds **45**−**50**. To synthesize compound **52** which contains a primary amide group at the C-5 position, 1-(3-aminopropyl)-4-(2′-carboxamidophenyl)piperazine (**43**) was treated with the activated dihydropyrimidinone **44** containing R_1 as a methyl, R_2 as an *O*-benzyl, and R_3 as a 2,4-difluoro group.[1] Benzyl ester **51** was converted to the carboxylic acid via hydrogenation and subsequently to the primary amide via treatment with ammonia in the presence of EDC.

Results and Discussion

The binding affinities of dihydropyrimidinones containing various 4-phenylpiperazines **23**−**41** are compared with that of **1** and terazosin in Table 1. Compounds containing phenylpiperazine side chains (except **25**, **26**, **29**, and **35**) show good binding affinities (<5 nM) for the α_{1a} receptor, although many of these compounds show high binding affinities for the α_{1b}, α_{1d}, and the α_2 adrenoceptors as well. Compounds containing either an electron-donating or an electron-withdrawing group in the *para* (**24**−**26** and **35**) or *meta* (**27**−**29**) position show inferior selectivity or binding profiles compared to **1**. The compounds containing a chloro substituent or electron-donating groups such as methyl, hydroxy, methoxy, and ethoxy (**30**−**34**) in the *ortho* position on the phenyl ring display high affinities for the α_{1a} receptor (<1 nM). These compounds, except for compound **33**, exhibit less than 300-fold selectivity for the α_{1a} receptor. It is

Table 1. Binding Affinity of 4-Substituted Phenylpiperazine-Containing Compounds at Recombinant Human α_1 and α_2 Adrenoceptors



compd	R	K_i (nM)[a,b] α_{1a}	α_{1b}	α_{1d}	fold selective of α_{1a} over $\alpha_{2a,b,c}$
terazosin		6.9	1.9	3.5	<10
1 (SNAP 6201)		0.2	260	340	>3200
23	H	0.2	7.5	21	>55
24	4-Cl	0.8	17	52	>65
25	4-OMe	14	410	480	>15
26	4-COMe	430	1300	1800	>2
27	3-Cl	0.7	8.4	37	>195
28	3-CF_3	4.9	43	120	>60
29	3-NO_2	12	150	340	>40
30	2-Me	0.3	17	9.8	>110
31	2-Cl	0.2	15	14	>190
32	2-OH	0.6	16	31	>65
33	2-OMe	0.1	18	31	>360
34	2-OEt	0.1	8.8	14	>210
35	2-Me, 4-OMe	16	510	610	>20
36	2-CN	0.1	15	12	>600

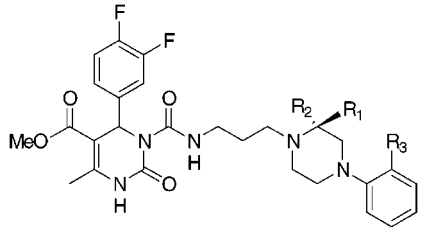
[a] K_i values obtained by displacement of [^{3}H]prazosin from cloned human receptors. [b] All K_i values are ±5% SE or less for $n > 2$. In cases where $n = 2$, both K_i values are within 2-fold of each other and the values shown are the average of the two experiments.

interesting to note that compound **35**, which possesses a methyl group in the *ortho* position and a methoxy group in the *para* position, shows a binding and selectivity profile similar to that of compound **25** containing a *p*-methoxy group rather than that of compound **30** which contains a methyl group in the *ortho* position. This observation clearly demonstrates the detrimental effect caused by an electron-donating group in the *para* position of the phenyl ring. The presence of the electron-withdrawing cyano group at the *ortho* position of the phenyl ring results in a compound (**36**) that has good binding affinity at the α_{1a} receptor but only modest selectivity over the other α_1 and α_2 adrenoceptors compared to **1**. It must be noted that the binding and selectivity profile of these compounds is significantly better than that of terazosin.

Based on these observations, compounds **33** and **36** emerged as the compounds which show good binding affinity and a moderate selectivity for the α_{1a} receptor. It must be noted, however, that both compounds show relatively high binding affinities at the α_{1b} and α_{1d} subtypes as compared to **1**. Modifications based on compound **33** did not yield compounds with an improved selectivity profile, whereas the modifications based on compound **36** (Table 2) led to compounds that showed weak binding affinity for the α_{1b} and α_{1d} receptor subtypes while maintaining high binding affinity for the α_{1a} receptor.

It was initially thought that the presence of an *ortho*-substituted electron-withdrawing cyano group on the phenyl ring would decrease the basicity of the proximal piperazine nitrogen that might be essential for the high binding affinity and selectivity for the α_{1a} receptor. To

Table 2. Effect of *Ortho* Electron-Withdrawing Groups on the Binding Affinity and Selectivity at Recombinant Human α_1 and α_2 Adrenoceptors



compd	R_1	R_2	R_3	K_i (nM)[a] α_{1a}	α_{1b}	α_{1d}	fold selective of α_{1a} over $\alpha_{2a,b,c}$
1				0.21	260	340	>3200
23	H	H	H	0.20	7.5	21	>55
36	H	H	CN	0.10	15	12	>600
(+)-36	H	H	CN	0.08	15	15	>1300
37	H	H	CO_2Me	0.2	25	30	>85
38	H	H	$CONH_2$	0.26	135	310	>460
(+)-38	H	H	$CONH_2$	0.12	190	250	>3000
(+)-39	H	H	NO_2	0.01	23	32	>23000
(+)-40	H	Me	NO_2	0.05	13	28	>1600
(+)-41	Me	H	NO_2	0.02	49	34	>17000

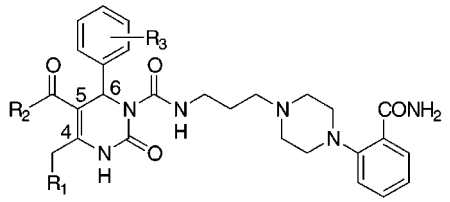
[a,b] Please see notes in Table 1.

test this hypothesis, a number of compounds containing different electron-withdrawing groups were synthesized, and the results are shown in Table 2.

Compound **(+)-36** does not show any improvement in the binding affinity and selectivity at the α_{1a} receptor compared to the racemic compound **36**. Replacement of the cyano group with a methoxycarbonyl group results in compound **37** which displays a similar α_1 binding profile as compound **36** but has significant cross-reactivity at the α_2 adrenoceptors. Compound **38** containing a primary amide group in the *ortho* position maintains the high affinity for the α_{1a} receptor but exhibits a much weaker binding affinity for the other α_1 and α_2 receptor subtypes. Compound **(+)-38**, the (+) enantiomer, shows a similar binding profile as the racemic compound **38**, an observation quite similar to the one discussed above for compounds **36** and **(+)-36**. More importantly, **(+)-38** exhibits a binding and selectivity profile for the α_{1a} receptor that is strikingly similar to that of **1**. If the presence of an electron-withdrawing group was crucial, then a stronger electron-withdrawing nitro group at the *ortho* position of the phenyl ring would be expected to improve the binding and selectivity profile. The compounds **39**−**41** containing a nitro group at the *ortho* position of the phenyl ring do indeed show high binding affinity and selectivity for the α_1 receptor. But, if this line of reasoning was correct, one would expect that the order of binding affinity and selectivity of these compounds would parallel the electron-withdrawing nature of the groups present on the phenylpiperazines (i.e. $NO_2 > CN > CO_2Me > CONH_2$). Clearly, the binding data is not consistent with such a hypothesis. These results indicate that the $CONH_2$ group contributes to the observed binding and selectivity profile of **(+)-38** not only because of the its electron-withdrawing nature but also in some other manner.

It is important to recognize that the selectivity exhibited by compounds **39**−**41** is due to an increased affinity for α_{1a} receptor and not due to a decrease in the binding affinity for the α_{1b} and α_{1d} receptor subtypes, as seen for **1**. The observed selectivity for **(+)-**

Table 3. Binding Affinities of Different Dihydropyrimidinones Containing 4-(2-Carboxamidophenyl)piperazine Side Chain at Recombinant Human α_1 and α_2 Adrenoceptors



compd	R_1	R_2	R_3	K_i (nM)[a,b] α_{1a}	α_{1b}	α_{1d}	fold selective of α_{1a} over $\alpha_{2a,b,c}$
(+)-38	H	OMe	3,4-di-F	0.1	190	250	>3000
45	H	OMe	3,4,5-tri-F	0.3	58	140	>430
(+)-46	OMe	OMe	3,4-di-F	0.1	100	140	>4500
47	OMe	OMe	2,4,5-tri-F	0.1	130	190	>660
(+)-48	Me	OMe	2,4-di-F	0.1	32	91	>1900
49	H	Me	3,4,5-tri-F	0.4	220	390	>160
50	H	Me	3,4-di-F	0.7	170	290	>70
(+)-52	Me	NH_2	2,4-di-F	1.3	720	1100	>600

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

38, in contrast, is mainly due to decreased binding affinity at the other receptor subtypes and not because of any enhancement in the binding affinity for the α_{1a} receptor. Therefore, it is possible that the unique binding profile of (2′-carboxamidophenyl)piperazine-containing compounds is due to unfavorable interactions with amino acid residues at the binding sites for α_{1b} and α_{1d} receptors rather than favorable interactions with amino acid residues at the α_{1a} receptor binding site.

The (2′-carboxamidophenyl)piperazine moiety which emerged as the optimal subunit was then coupled with a number of dihydropyrimidinones differing in the substituents on the dihydropyrimidinone template, to study the compatibility of the two subunits with each other. The results of this study are shown in Table 3. A change in the substitution pattern of the C-6 phenyl ring of dihydropyrimidinone from 3,4-difluoro in **(+)-38** to 3,4,5-trifluoro in **45** has a slightly deleterious effect on the selectivity for the α_{1a} receptor. When the C-4 group was changed from a methyl [**(+)-38**] to a methoxymethyl group (**46** and **47**) or an ethyl group (**48**), the compounds maintain high binding affinity at the α_{1a} but exhibit slightly lower selectivity over the other receptors. The nature of the group at the C-5 position has limited influence on the observed binding and selectivity profile of the compounds. Compound **(+)-38** is significantly better in terms of the selectivity for the α_{1a} receptor subtype over the α_2 receptor subtypes than the compounds containing methyl ketone (**49** and **50**). Compound **52**, which contains a primary amide group, however, maintains an excellent selectivity profile but lower binding affinity for the α_{1a} receptor.

On the basis of the results from Table 3, we conclude that although the presence of (2′-carboxamidophenyl)-piperazine subunit of the molecule is important, other parameters such as the nature of the linker (alkyl versus amide) and the substituents on the dihydropyrimidinone template play a subtle role in fine-tuning the observed binding and selectivity profile of these compounds.

In Vitro and in Vivo Experiments. As a representative example, compound **(+)-38** was chosen for further in vitro and in vivo evaluation. Compound **(+)-38** was counter-screened against a number of G-protein coupled receptors such as H_1, serotonin, and the rat L-type calcium channel receptor and showed >1000-fold selectivity for the α_{1a} receptor.[13−19] The 2-carboxamidophenylpiperazine was screened for cross-reactivity at the opioid receptors and showed much weaker binding affinity (45 μM) compared to the 4-carbomethoxy-4-phenylpiperidine (3 μM). Some results on **(+)-38** in a number of in vitro and in vivo assays are compared with those for our original lead compound **1**, and the results are summarized in Table 4. Compound **(+)-38** showed excellent selectivity for the rat prostate tissue which predominantly expresses α_{1a} subtype (K_b = 0.28 nM), compared to the rat aorta (K_b = 550 nM) which predominantly expresses the other subtypes. In the functional assay, **(+)-38** relaxed the phenylephrine-induced contraction of the rat prostate with AD_{50} = 22 μg/kg, and the duration of action was greater than 4 h, a profile quite similar to that of **1**.[2] The rat oral bioavailability and the plasma half-life of **(+)-38** were determined to be 13% and 2 h, respectively, which is similar to that of **1** (19% and 2.1 h, respectively). Compound **(+)-38** showed lower bioavailability but a similar plasma half-life in dogs (4% and 2.3 h, respectively) as compared to **1** (26% and 2.4 h, respectively).

Table 4. Summary of the in Vitro and in Vivo Properties of **(+)-38** and **1**

assay	antagonist/agonist	**(+)-38**	**1**
K_i α_{1a} (nM)	[^{3}H]prazosin	0.1	0.2
$\alpha_{1b,1d}/\alpha_{1a}$	[^{3}H]prazosin	>1000	>1000
$\alpha_{2a,b,c}/\alpha_{1a}$	[^{3}H]rauwolscine	>1000	>1000
K_b rat prostate (nM)	phenylephrine	0.3	0.4[a]
K_b rat aorta (nM)	phenylephrine	550	>1000
AD_{50} rat (μg/kg)	phenylephrine	22	20
duration of action rat (h)	phenylephrine	>4 h	>4
opioid K_i (μM)	[^{3}H]DAMGO	>30	4
rat F, $t_{1/2}$ (h)		13%,[b] 2.0	15%,[c] 2.0
dog F, $t_{1/2}$ (h)		4%,[d] 2.4	26%,[c] 2.5

[a] K_b = 0.3 nM, when A-61603 was used as an agonist. [b] iv: 3 mg/kg dose, AUC = 88.4 μmol min/L. po: 10 mg/kg dose, AUC = 39.0 μmol min/L. [c] Reference 2. [d] iv: 1 mg/kg dose, AUC = 30 μmol min/L. po: 4 mg/kg dose, AUC = 30 μmol min/L.

Conclusion

We initiated this study to find a suitable replacement for the 4-methoxycarbonyl-4-phenylpiperidine moiety which was deemed to be a potential liability due to its agonist activity at the opioid receptors. It was essential that the compounds have good binding affinity and selectivity for the α_{1a} receptor. We were successful in identifying compounds containing a 4-phenylpiperazine devoid of agonist activity at the μ-opioid receptor. Judicious alterations of the steric and electronic nature of the substituents on the phenyl ring of the 4-phenylpiperazines led to the identification of 2-carboxamidophenylpiperazine moiety as a preferred side chain subunit having a much weaker binding affinity at the opioid receptors (45 μM). Compound **(+)-38** was identified as an antagonist with good binding affinity and selectivity for the α_{1a} receptor (K_i = 0.1 nM, >1500-fold over α_{1b} and α_{1d}). The compound showed good potency in the in situ rat prostate assay model (AD_{50} = 22 μg/kg) and excellent selectivity for the prostate tissue (K_b = 0.28 nM in rat prostate versus K_b = 550 nM in rat aorta).

Experimental Section

For the description of analytical protocols and biological methods, please refer to the Experimental Section of ref 2.

Synthesis of Piperazines. Compounds **4**, **7**, and **10** were synthesized according to the known procedure.[11]

1-(2-Carboxamidophenyl)piperazine (4). Concentrated sulfuric acid (15 mL) was added to 1-(2-cyanophenyl)piperazine (1.5 g, 8.0 mmol) placed in a round-bottom flask and the resulting slurry was stirred at room temperature for 48 h. The reaction mixture was poured on crushed ice very slowly and then basified (pH = 9) with 50% solution of NaOH. The aqueous layer was extracted several times with EtOAc, dried over K_2CO_3, and filtered and the solvent was evaporated. 1-(2-Carboxamidophenyl)piperazine was obtained as an off-white solid (1.2 g, 73%). It was used in the next step without further purification: mass spectrum 206 (M + 1, 100%); ^{1}H NMR δ 3.06−3.29 (m, 8 H), 6.14 (br, 1 H), 7.20−7.28 (m, 2 H), 7.47 (dt, J = 1.6 Hz, J = 6.0 Hz, 1 H), 8.16 (dd, J = 1.7 Hz, J = 9.6 Hz, 1 H), 9.45 (br, 1 H). Combustion analysis was obtained on its hydrochloride salt. Anal. ($C_{11}H_{17}N_3OCl\cdot 0.3CHCl_3$) C, H, N.

1-(2-Nitrophenyl)piperazine (17). A heterogeneous reaction mixture containing 2-bromonitrobenzene (2.02 g, 10.0 mmol) and piperazine (4.3 g, 50.0 mmol) was heated at 100 °C for 10 h. The orange-red solid was extracted with ethyl acetate and washed thoroughly with 3 N NaOH solution followed by brine. The organic layer was separated, dried over Na_2SO_4, and filtered and the solvent was removed in vacuo. The resulting red oil was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield 1-(2-nitrophenyl)piperazine as an orange-red oil (1.90 g, 92%): ^{1}H NMR ($CDCl_3$) δ 1.77 (br s, 1 H), 2.97 (br s, 8 H), 6.98 (t, J = 7.5 Hz, 1 H), 7.09 (d, J = 8.4 Hz, 1 H), 7.42 (dt, J = 1.5 Hz, J = 8.7 Hz, 1 H), 7.72 (dd, J = 1.5 Hz, J = 7.2 Hz, 1 H). It was characterized as a hydrochloride salt. Anal. ($C_{10}H_{14}N_3ClO_2\cdot 0.1CHCl_3$) C, H, N.

***(R)*-(−)-3-Methyl-1-(2-nitrophenyl)piperazine (18).** To a solution of 2-bromonitrobenzene (0.4 g, 2.0 mmol) in 1,4-dioxane (10 mL) were added (*R*)-(+)-2-methylpiperazine (0.25 g, 0.25 mmol) and powdered K_2CO_3 (7.5 mmol, 0.8 g) and the resulting suspension was heated at reflux for 10 h. After the suspension was cooled, it was filtered through a sintered glass funnel and the solvent was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield (*R*)-(−)-3-methyl-1-(2-nitrophenyl)piperazine as an orange-red oil (0.26 g, 78%): ^{1}H NMR ($CDCl_3$) δ 1.04 (d, J = 6.3 Hz, 3 H), 1.52 (br s, 1 H), 2.47 (dt, J = 1.5 Hz, J = 9.9 Hz, 1 H), 2.80−2.92 (m, 1 H), 2.97−3.13 (br m, 5 H), 7.01 (t, J = 7.5 Hz, 1 H), 7.13 (d, J = 8.1 Hz, 1 H), 7.46 (dt, J = 1.5 Hz, J = 8.7 Hz, 1 H), 7.74 (dd, J = 1.5 Hz, J = 7.2 Hz, 1 H). Anal. ($C_{11}H_{16}N_3ClO_2\cdot 0.05CHCl_3$) C, H, N.

***(S)*-(+)-3-Methyl-1-(2-nitrophenyl)piperazine (19).** To a solution of 2-bromonitrobenzene (0.6 g, 3.0 mmol) in 1,4-dioxane (15 mL) were added (*S*)-(+)-2-methylpiperazine (0.5 g, 0.5 mmol) and powdered K_2CO_3 (15.0 mmol, 1.5 g) and the resulting suspension was heated at reflux for 10 h. After the suspension was cooled, it was filtered through a sintered glass funnel and the solvent was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield (*S*)-(+)-3-methyl-1-(2-nitrophenyl)piperazine as an orange oil (0.53 g, 80%): ^{1}H NMR ($CDCl_3$) same as described for compound **18**. It was characterized as a hydrochloride salt, mp = 170−172 °C. Anal. ($C_{11}H_{16}N_3ClO_2\cdot 0.05CHCl_3$) C, H, N.

Synthesis of 1-(3-Aminopropyl)-4-(2-carboxamidophenyl)piperazine (43). A solution of *N*-*tert*-butyloxypropylamine (0.63 mg, 2.68 mmol), potassium carbonate (1.35 g, 9.76 mmol), and 4-(2′-carboxamidophenyl)piperazine (0.5 g, 2.44 mmol) in 25 mL of 1,4-dioxane was heated to reflux for 12 h. The solution was allowed to cool to room temperature and then the solid was filtered off. The solvent was removed in vaccuo and the resulting oil was purified by column chromatography on silica gel using EtOAc as an eluent. The resulting thick oil was then dissolved in CH_2Cl_2 (15 mL) and trifluoroacetic acid (5 mL) was added to the solution in a dropwise manner at room temperature with stirring. The solvent was removed in vaccuo after 1 h, the resulting residue was dissolved in 3:1 mixture of chloroform and isopropyl alcohol (25 mL), and then the solution was basified to pH 8 by addition of 10% NaOH. The aqueous layer was separated and extracted with the 3:1 $CHCl_3$/IPA solution (4 × 25 mL). The organic extracts were combined and dried over Na_2SO_4 and the solution was filtered. The solvent was removed in vaccuo to obtain 1-(3-aminopropyl)-4-(2-carboxamindophenyl)piperazine as an oil (0.35 g, 55% yield over two steps).

Procedure for the Synthesis of (+)-1-(3-Bromopropylcarbamoyl)-6-(3,4-difluorophenyl)-4-methyl-2-oxo-1,6-tetrahydropyrimidine-5-carboxylic Acid Methyl Ester (21). To a well-stirred solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (4.1 g, 9.1 mmol) in 20 mL of THF was added 5 mL of 10% aqueous solution of HCl at room temperature and the resulting solution was stirred overnight. THF was removed in vacuo and the resulting residue was extracted with EtOAc (3 × 20 mL), washed with brine (10 mL), and then dried over Na_2SO_4. The solvent was removed in vacuo to obtain (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-oxo-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine as a viscous oil (3.8 g) which was dissolved in 20 mL of THF. To this solution were added 3-bromopropylamine hydrobromide (2.33 g, 10.8 g) and $NaHCO_3$ (1.81 g, 21.5 mmol) and the resulting suspension was stirred at room temperature overnight. THF was removed in vacuo and the resulting residue was dissolved in 10 mL of water and then extracted with EtOAc (3 × 20 mL). The EtOAc extracts were combined, dried over Na_2SO_4, and filtered and the solvent was removed to obtain (+)-1-(3-bromopropylcarbamoyl)-6-(3,4-difluorophenyl)-4-methyl-2-oxo-1,6-tetrahydropyrimidine-5-carboxylic acid methyl ester (3.28 g, 83%): ^{1}H NMR δ 2.05−2.15 (m, 2 H), 2.43 (s, 3 H), 3.40−3.56 (m, 4 H), 3.72 (s, 3 H), 6.69 (s, 1 H), 7.08−7.27 (m, 3 H), 7.57 (br s, 1 H), 8.84 (br t, 1 H). Anal. ($C_{17}H_{18}N_3O_4F_2Br$) C, H, N.

An identical procedure was used for the synthesis of 1-(3-bromopropylcarbamoyl)-6-(3,4-difluorophenyl)-4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic acid methyl ester starting from racemic 6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)-carbonyl]pyrimidine.

General Procedure for the Synthesis of Compounds 23−42. To a solution of either racemic or the (+) enantiomer of 1-(3-bromopropylcarbamoyl)-6-(3,4-difluorophenyl)-4-methyl-2-oxo-1,6-dihydropyrimidine-5-carboxylic acid methyl ester (43 mg, 0.1 mmol) in 10 mL of anhydrous acetone was added the amine (0.15 mmol) followed by $NaHCO_3$ (41 mg, 0.3 mmol) and KI (16 mg, 0.1 mmol). The resulting suspension was heated to reflux for 10 h and then cooled to room temperature. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel with EtOAc followed by 10% MeOH in EtOAc. The product was characterized by ^{1}H NMR before converting it into a hydrochloride salt. The product thus obtained was then dissolved in 2 mL of either chloroform, acetone, or EtOAc. Then 0.5 mL of HCl in Et_2O (1 M) was added at room temperature. The solvent was removed in vacuo and the hydrochloride salt was characterized by combustion analysis.

1,2,3,6-Tetrahydro-1-{*N*-[[4-phenylpiperazin-1-yl]-propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (23). The amine used was 4-phenylpiperazine: ^{1}H NMR δ 1.68−1.74 (m, 2 H), 2.32 (s, 3 H), 2.32−2.39 (m, 2 H), 2.51−2.58 (m, 4 H), 3.12−3.20 (m, 4 H), 3.26−3.36 (m, 2 H), 3.64 (s, 3 H), 6.63 (s, 1 H), 6.80−7.23 (m, 9 H), 8.76 (t, J = 3.9 Hz, 1 H). It was characterized as a dihydrochloride salt, mp = 85−90 °C. Anal. ($C_{27}H_{33}N_5F_2Cl_2O_4\cdot 1.7CH_3OH$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(4′-chlorophenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (24). The amine used was 4-(4′-chlorophenyl)-

piperazine: ^{1}H NMR δ 1.73−1.79 (m, 2 H), 2.40 (s, 3 H), 2.41−2.46 (m, 2 H), 2.51 (br s, 4 H), 3.15 (br s, 4 H), 3.34−3.40 (m, 2 H), 3.71 (s, 3 H), 6.70 (s, 1 H), 6.82 (d, J = 7.2 Hz, 2 H), 7.07−7.20 (m, 4 H), 7.19 (d, J = 7.2 Hz, 2 H), 8.82 (t, J = 3.9 Hz, 1 H). It was characterized as a dihydrochloride salt, mp = 76−81 °C. Anal. ($C_{27}H_{32}N_5F_2Cl_3O_4$·1.5$H_2O$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(4′-methoxyphenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (25). The amine used was 4-(4′-methoxyphenyl)piperazine: ^{1}H NMR δ 1.68−1.82 (m, 2 H), 2.41 (s, 3 H), 2.41−2.47 (m, 2 H), 2.60−2.65 (m, 4 H), 3.01−3.14 (m, 4 H), 3.35−3.43 (m, 2 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 6.70 (s, 1 H), 6.81−7.18 (m, 8 H), 8.83 (t, J = 3.9 Hz, 1 H). It was characterized as its dihydrochloride salt (hygroscopic). Anal. ($C_{28}H_{35}N_5F_2Cl_2O_5$·0.25$CHCl_3$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(4′-acetoxyphenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (26). The amine used was 4-(4′-acetoxyphenyl)piperazine: ^{1}H NMR δ 1.73−1.78 (m, 2 H), 2.41 (s, 3 H), 2.41−2.47 (m, 2 H), 2.52 (s, 3 H), 2.54−2.58 (m, 4 H), 3.33−3.59 (m, 6 H), 3.72 (s, 3 H), 6.70 (s, 1 H), 6.85 (d, J = 9.0 Hz, 2 H), 7.05−7.20 (m, 4 H), 7.86 (d, J = 9.0 Hz, 2 H), 8.85 (t, J = 3.9 Hz, 1 H). It was characterized as a dihydrochloride salt. Anal. ($C_{29}H_{35}N_5F_2Cl_2O_5$·0.5$CHCl_3$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(3′-chlorophenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (27). The amine used was 4-(3′-chlorophenyl)-piperazine: ^{1}H NMR δ 1.74−1.78 (m, 2 H), 2.41 (s, 3 H), 2.41−2.48 (m, 2 H), 2.54−2.59 (m, 4 H), 3.11−3.25 (m, 4 H), 3.32−3.40 (m, 2 H), 3.72 (s, 3 H), 6.71 (s, 1 H), 6.77−7.21 (m, 8 H), 8.84 (t, J = 3.9 Hz, 1 H). It was characterized as its dihydrochloride salt, mp = 120−124 °C. Anal. ($C_{27}H_{32}N_5F_2Cl_3O_4$·0.2$CCl_4$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(3′-trfluoromethylphenyl)-piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (28). The amine used was 4-(3′-trifluoromethylphenyl)piperazine: ^{1}H NMR δ 1.74−1.80 (m, 2 H), 2.41 (s, 3 H), 2.41−2.49 (m, 2 H), 2.56−2.63 (m, 4 H), 3.21−3.27 (m, 4 H), 3.36−3.45 (m, 2 H), 3.72 (s, 3 H), 6.71 (s, 1 H), 7.04−7.38 (m, 8 H), 8.84 (t, J = 3.9 Hz, 1 H). It was characterized as a dihydrochloride salt. Anal. ($C_{28}H_{32}N_5F_5Cl_2O_4$·0.8 acetone) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(3′-nitrophenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (29). The amine used was 4-(3′-nitrophenyl)-piperazine: ^{1}H NMR δ 1.75−1.80 (m, 2 H), 2.41 (s, 3 H), 2.41−2.47 (m, 2 H), 2.57−2.61 (m, 4 H), 3.26−3.31 (m, 4 H), 3.38−3.44 (m, 2 H), 3.72 (s, 3 H), 6.70 (s, 1 H), 7.08−7.68 (m, 8 H), 8.81 (t, J = 3.9 Hz, 1 H). Anal. ($C_{27}H_{32}N_6F_2Cl_2O_6$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(2′-methylphenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (30). The amine used was 4-(2′-methylphenyl)piperazine: ^{1}H NMR δ 1.75−1.80 (m, 2 H), 2.29 (s, 3 H), 2.42 (s, 3 H), 2.41−2.48 (m, 2 H), 2.58−2.62 (m, 4 H), 2.91−2.97 (m, 4 H), 3.35−3.42 (m, 2 H), 3.72 (s, 3 H), 6.71 (s, 1 H), 6.97−7.26 (m, 8 H), 8.81 (t, J = 3.9 Hz, 1 H). It was characterized as a dihydrochloride salt, mp = 66−71 °C. Anal. ($C_{28}H_{35}N_5F_2Cl_2O_4$·1.75 acetone) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(2′-chlorophenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (31). The amine used was 4-(2′-chlorophenyl)-piperazine: ^{1}H NMR δ 1.79−1.84 (m, 2 H), 2.42 (s, 3 H), 2.49−2.54 (m, 2 H), 2.68 (br s, 4 H), 3.11 (br s, 4 H), 3.38−3.43 (m, 2 H), 3.72 (s, 3 H), 6.70 (s, 1 H), 6.81−7.34 (m, 8 H), 8.82 (t, J = 3.9 Hz, 1 H). It was characterized as a dihydrochloride salt, mp = 98−102 °C. Anal. ($C_{27}H_{32}N_5F_2Cl_3O_4$·0.5$CHCl_3$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(2′-hydroxyphenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (32). The amine used was 4-(2′-hydroxyphenyl)piperazine: colorless oil; ^{1}H NMR δ 1.72−1.78 (m, 2 H), 2.39 (s, 3 H), 2.40−2.44 (m, 2 H), 2.55−2.57 (m, 4 H), 2.85−2.88 (m, 4 H), 3.30−3.38 (m, 2 H), 3.68 (s, 3 H), 6.68 (s, 1 H), 6.79−7.18 (m, 9 H), 8.79 (t, J = 5.4 Hz, 1 H). It was characterized as a dihydrochloride salt, mp = 145−149 °C. Anal. ($C_{27}H_{33}N_5F_2Cl_2O_5$·0.15$CHCl_3$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(4′-methoxyphenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (33). The amine used was 4-(2′-methoxyphenyl)piperazine: ^{1}H NMR δ 1.62−1.76 (m, 2 H), 2.41 (s, 3 H), 2.45−2.58 (m, 6 H), 3.01−3.14 (m, 4 H), 3.35−3.43 (m, 2 H), 3.65 (s, 3 H), 3.77 (s, 3 H), 6.72 (s, 1 H), 6.69−7.02 (m, 8 H), 8.83 (t, J = 3.9 Hz, 1 H). It was characterized as its dihydrochloride salt, mp = 69−72 °C. Anal. ($C_{28}H_{35}N_5F_2Cl_2O_5$·0.25$CHCl_3$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(2′-ethoxyphenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (34). The amine used was 4-(2′-ethoxyphenyl)piperazine: ^{1}H NMR δ 1.45 (t, J = 6.9 Hz, 3 H), 1.73−1.82 (m, 2 H), 2.41 (s, 3 H), 2.41−2.47 (m, 2 H), 2.63 (br s, 4 H), 3.10 (br s, 4 H), 3.34−3.42 (m, 2 H), 3.72 (s, 3 H), 4.06 (q, J = 6.6 Hz, 2 H), 6.71 (s, 1 H), 6.83−7.17 (m, 8 H), 8.81 (t, J = 3.9 Hz, 1 H). It was characterized as a dihydrochloride salt, mp = 84−90 °C. Anal. ($C_{29}H_{32}N_5F_2Cl_2O_5$·2.0$H_2O$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(4′-methoxy-2′-methylphenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (35). The amine used was 4-(4′-methoxy-2′-methylphenyl)piperazine: yellow oil; ^{1}H NMR δ 1.71−1.76 (m, 2 H), 2.24 (s, 3 H), 2.38 (s, 3 H), 2.38−2.43 (m, 2 H), 2.54−2.59 (m, 4 H), 2.81−2.84 (m, 4 H), 3.29−3.37 (m, 2 H), 3.68 (s, 3 H), 3.72 (s, 3 H), 6.64 (d, J = 3.0 Hz, 1 H), 6.67 (s, 1 H), 6.71 (d, J = 2.7 Hz, 1 H), 6.92 (d, J = 8.4 Hz, 1 H), 7.00−7.23 (m, 3 H), 7.50 (br s, 1 H), 8.77 (t, J = 5.4 Hz, 1 H). It was characterized as a dihydrochloride salt, mp = 85−90 °C. Anal. ($C_{27}H_{33}N_5F_2Cl_2O_5$·0.2$CHCl_3$) C, H, N.

(+)- and (±)-1,2,36-Tetrahydro-1-{*N*-[[4-(2-cyanophenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (36 and 37). The amine used was 4-(2′-cyanophenyl)piperazine. The product was analyzed as its dihydrochloride salt (hygroscopic): $[\alpha]_D$ = + 51.8 (c = 0.2, MeOH) for **37(+)**; mass spectrum 553 (M + 1, 18%); ^{1}H NMR δ 1.72−1.78 (m, 2 H), 2.38 (s, 3 H), 2.39−2.47 (m, 2 H), 2.54−2.64 (m, 4 H), 3.17−3.39 (m, 6 H), 3.67 (s, 3 H), 6.66 (s, 1 H), 6.93−7.19 (m, 4 H), 7.42−7.52 (m, 3 H), 7.78 (dd, J = 1.2 Hz, J = 7.8 Hz, 1 H), 8.78 (br t, 1 H). Anal. ($C_{28}H_{32}N_6F_2Cl_2O_4$·0.4$CHCl_3$) C, H, N.

1,2,3,6-Tetrahydro-1-{*N*-[[4-(2′-carbomethoxyphenyl)-piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (38). The amine used was 4-(2′-carbomethoxyphenyl)piperazine: ^{1}H NMR δ 1.75−1.80 (m, 2 H), 2.42 (s, 3 H), 2.41−2.49 (m, 2 H), 2.58−2.64 (m, 4 H), 3.02−3.10 (m, 4 H), 3.35−3.41 (m, 2 H), 3.72 (s, 3 H), 3.88 (s, 3 H), 6.70 (s, 1 H), 7.09−7.18 (m, 6 H), 7.41 (dt, J = 0.9 Hz, J = 8.1 Hz, 1 H), 7.72 (dd, J = 1.5 Hz, J = 7.5 Hz, 1 H), 8.82 (t, J = 3.9 Hz, 1 H). It was characterized as a dihydrochloride salt. Anal. ($C_{29}H_{35}N_5F_2Cl_2O_6$·0.18$CHCl_3$) C, H, N.

(+)- and (±)-1,2,36-Tetrahydro-1-{*N*-[[4-(2-carboxamidophenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (38). The amine used was 4-(2′-carboxamidophenyl)piperazine, 84% yield. Combustion analysis was obtained on its hydrochloride salt, mp = 190−193 °C; $[\alpha]_D$ = +98.8 (c = 0.31, MeOH); ^{1}H NMR δ 1.65−1.75 (m, 2 H), 2.41 (s, 3 H), 2.39−2.41 (m, 1 H), 2.45−2.58 (m, 2 H), 2.97 (br t, J = 4.5 Hz, 4 H), 3.31−3.37 (m, 1 H), 3.66 (s, 3 H), 6.55 (br d, J = 4.5 Hz, 1 H), 6.65 (s, 1 H), 6.99−7.19 (m, 5 H), 7.39 (t, J = 8.7 Hz, 1 H), 8.10 (dd, J = 1.5 Hz, J = 9.3 Hz, 1 H), 8.84 (br t, 1 H), 9.52 (br d, J = 4.5 Hz, 1 H). Anal. ($C_{28}H_{34}N_6F_2Cl_2O_5$·0.35EtOAc) C, H, N.

(+)-1,2,3,6-Tetrahydro-1-{*N*-[[4-(2-nitrophenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine [(+)-39]. The amine used was 4-(2′-nitrophenyl)piperazine, 29% yield. The product was analyzed as its hydrochloride salt, mp = 133−136 °C; $[\alpha]_D$ = + 56.7 (c = 0.11, MeOH); ^{1}H NMR δ 1.75−1.80 (m, 2 H), 2.42 (s, 3 H), 2.41−2.49 (m, 2 H), 2.57−2.62 (m, 4 H), 3.02−3.10 (m, 4 H), 3.29−3.51 (m, 2 H), 3.72 (s, 3 H), 6.71 (s, 1 H), 6.94 (br s, 1 H), 7.09−7.18 (m, 5 H), 7.47 (dt, J = 0.9 Hz, J = 8.4

Hz, 1 H), 7.75 (dd, J = 1.5 Hz, J = 8.1 Hz, 1 H), 8.82 (t, J = 3.9 Hz, 1 H). Anal. ($C_{27}H_{31}N_6F_2ClO_6 \cdot 0.20CH_2Cl_2$) C, H, N.

(+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{*N*-[[2(*R*)-methyl-4-(2-nitrophenyl)piperazin-1-yl]-propyl]carboxamido}-6-(3,4-difluorophenyl)pyrimidine [(+)-40]. The amine used was 2(*R*)-methyl-4-(2′-carboxamidophenyl)piperazine (0.02 g, 14% yield). The product was analyzed as its hydrochloride salt, mp = 135−138 °C; $[\alpha]_D$ = + 63.5 (c = 0.2, MeOH); ^{1}H NMR δ 1.04 (d, J = 6.0 Hz, 3 H), 1.63−1.78 (m, 2 H), 2.33−2.49 (m, 3 H), 2.42 (s, 3 H), 2.55−2.92 (m, 5 H), 3.00−3.10 (m, 3 H), 3.33−3.39 (m, 2 H), 3.72 (s, 3 H), 6.70 (s, 1 H), 6.99−7.17 (m, 6 H), 7.46 (dt, J = 0.9 Hz, J = 8.1 Hz, 1 H), 7.74 (dd, J = 1.5 Hz, J = 8.1 Hz, 1 H), 8.81 (t, J = 3.9 Hz, 1 H). Anal. ($C_{28}H_{33}N_6F_2ClO_6 \cdot 1.0CHCl_3$) C, H, N.

(+)-1,2,3,6-Tetrahydro-1-{*N*-[[2(*S*)-methyl-4-(2-nitrophenyl)piperazin-1-yl]propyl]carboxamido}-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine [(+)-41]. The amine used was 2(*S*)-methyl-4-(2′-carboxamidophenyl)piperazine, 10% yield. The product was analyzed as its hydrochloride salt, mp = 150−153 °C; $[\alpha]_D$ = + 58.3 (c = 0.3, MeOH); ^{1}H NMR δ 1.04 (d, J = 6.0 Hz, 3 H), 1.71−1.78 (m, 2 H), 2.33−2.49 (m, 3 H), 2.42 (s, 3 H), 2.55−2.92 (m, 5 H), 3.00−3.10 (m, 3 H), 3.34−3.42 (m, 2 H), 3.72 (s, 3 H), 6.71 (s, 1 H), 7.01−7.32 (m, 6 H), 7.46 (dt, J = 0.7 Hz, J = 8.4 Hz, 1 H), 7.74 (dd, J = 1.5 Hz, J = 8.4 Hz, 1 H), 8.82 (t, J = 3.9 Hz, 1 H). Anal. ($C_{28}H_{33}N_6F_2ClO_6 \cdot 0.20CH_2Cl_2$) C, H, N.

1-{3-[4-(2-Carbamoylphenyl)piperazin-1-yl]propylcarbamoyl}-4-methyl-5-methoxycarbonyl-2-oxo-6-(3,4,5-trifluorophenyl)-1,2,3,6-tetrahydropyrimidine (45). (a) Methyl 1-{3-[4-(2-Carbamoylphenyl)piperazin-1-yl]propylcarbamoyl}-2-methoxy-4-methyl-6-(3,4,5-trifluorophenyl)-1,6-dihydropyrimidine-5-carboxylate. A solution of 1,6-dihydro-5-methoxycarbonyl-2-methoxy-1-(4-nitrophenyloxy)-carbonyl-6-(3,4,5-trifluorophenyl)-4-methylpyrimidine (15 mg, 0.031 mmol) and 2-[4-(3-aminopropyl)piperazin-1-yl]benzamide (12 mg, 0.047 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 2 days. The product was separated on a preparative TLC plate ($CHCl_3$/MeOH, 10:1) to get the title compound (13.5 mg, 63% yield): ^{1}H NMR ($CDCl_3$)δ 1.67−1.78 (m, 4 H), 2.40 (s, 3 H), 2.41−2.47 (m, 2 H), 2.50−2.65 (m, 2 H), 2.95−3.01 (m, 4 H), 3.33−3.45 (m, 2 H), 3.65 (s, 3 H), 3.94 (s, 3 H), 5.80 (br s, 1 H), 6.56 (s, 1 H), 6.72 (br s, 1 H), 6.88−6.93 (m, 2 H), 7.16−7.19 (m, 2 H), 7.43 (dd, J = 8.1 Hz, 1.8 Hz, 1 H), 8.11 (dd, J = 7.8 Hz, 1.5 Hz, 1 H), 9.37 (br s, 1 H).

(b) 1-{3-[4-(2-Carbamoylphenyl)piperazin-1-yl]propylcarbamoyl}-4-methyl-5-methoxycarbonyl-2-oxo-6-(3,4,5-trifluorophenyl)-1,2,3,6-tetrahydropyrimidine. A solution of methyl 1-{3-[4-(2-carbamoylphenyl)piperazin-1-yl]-propylcarbamoyl}-2-methoxy-4-methyl-6-(3,4,5-trifluorophenyl)-1,6-dihydropyrimidine-5-carboxylate (10 mg, 0.019 mmol) and HCl (6 N, 3 mL) in THF (3 mL) was stirred at room temperature for 12 h and the solvent was removed. The residue was dissolved in CH_2Cl_2 and washed with 1 N KOH solution. The organic layer was dried (Na_2SO_4) and concentrated to obtain the title compound (9.6 mg, 99% yield) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 1.61−1.90 (m, 6 H), 2.41 (s, 3 H), 2.60 (br s, 2 H), 3.00−3.03 (m, 2 H), 3.20−3.43 (m, 2 H), 3.55 (t, J = 6.6 Hz, 2 H), 3.69 (s, 3 H), 6.17 (br s, 1 H), 6.64 (s, 1 H), 6.92−7.00 (m, 2 H), 7.16−7.21 (m, 2 H), 7.43 (dd, J = 8.1 Hz, 1.8 Hz, 1 H), 7.85 (br s, 1 H), 8.11 (dd, J = 7.8 Hz, 1.5 Hz, 1 H), 8.81 (t, J = 5.4 Hz, H), 9.46 (br s, 1 H). Hydrochloride of the title compound was prepared with HCl in ether, mp = 203−207 °C. Anal. ($C_{29}H_{35}N_6F_3Cl_2O_6 \cdot 1.5C_6H_{12}$) C, H, N.

(+)-1,2,3,6-Tetrahydro-1-{*N*-[[4-(2-carboxamidophenyl)-piperazin-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine Hydrochloride (46). To a solution of (+)-1,6-dihydro-1-[*N*-(4-nitrophenoxy)carbonyl]-2-methoxyl-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine (212 mg, 0.43 mmol) in dichloromethane (20 mL) was added 1-(3-aminopropyl)-4-(2-carboxamidophenyl)piperazine (136 mg, 0.52 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h before concentrated to a residue. The residue was purified through column chromatography (chloroform/MeOH/2 N ammonia in MeOH = 100:12:6) to afford the desired product (227 mg, 88%), $[\alpha]_D$ = +124° (c = 0.75 in chloroform). The compound was converted to HCl salt by dissolving in 1 N HCl in ether followed by concentration to dryness: mp = 118−120 °C; ^{1}H NMR ($CDCl_3$) δ 1.69−1.76 (m, 4 H), 2.39−2.43 (m, 2 H), 2.53−2.60 (m, 2 H), 2.98−3.01 (m, 4 H), 3.30−3.44 (m, 2 H), 3.44 (s, 3 H), 3.67 (s, 3 H), 4.64 (s, 2 H), 6.64 (s, 1 H), 7.04−7.45 (m, 6 H), 7.69 (s, 1 H), 8.10−8.13 (d, J = 8 Hz, 1 H), 8.86 (t, 1 H, J = 7 Hz). Anal. ($C_{29}H_{36}F_2N_6Cl_2O_6 \cdot 0.3$ether$\cdot 0.6H_2O$) C, H, N.

1-{3-[4-(2-Carbamoylphenyl)piperazin-1-yl]propylcarbamoyl}-5-methoxycarbonyl-4-methoxymethyl-2-oxo-6-(2,4,5-trifluorophenyl)-1,2,3,6-tetrahydropyrimidine (47). (a) 1-{3-[4-(2-Carbamoylphenyl)pipirazin-1-yl]propylcarbamoyl}-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(2,4,5-trifluorophenyl)-1,6-dihydropyrimidine. A mixture of 2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(2,4,5-trifluorophenyl)-1,6-dihydropyrimidine (15 mg, 0.03 mmol) and 3-[4-(2-carbamoylphenyl)-piperazin-1-yl]propylamine (12 mg, 0.04 mmol) was stirred at room temperature for 2 days. The solvent was evaporated and the residue was separated on a preparative TLC plate ($CHCl_3$/MeOH, 10:1) to get the title compound (9 mg, 49% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.69−1.74 (m, 4 H), 2.42 (t, J = 6.9 Hz, 2H), 2.54−2.60 (m, 2 H), 2.98 (t, J = 4.5 Hz, 4 H), 3.31−3.40 (m, 2 H), 3.43 (s, 3 H), 3.65 (s, 3 H), 4.04 (s, 3 H), 4.55 (ABm, 2 H), 5.79 (br s, 1 H), 6.77 (s, 1 H), 6.79−6.87 (m, 1 H), 7.01−7.22 (m, 4 H), 7.43 (dt, J = 7.8 Hz, 1.5 Hz, 1 H), 8.11 (dd, J = 8.1 Hz, 1.5 Hz, 1 H), 9.38 (br s, 1 H).

(b) 1-{3-[4-(2-Carbamoylphenyl)piperazin-1-yl]propylcarbamoyl}-5-methoxycarbonyl-4-methoxymethyl-2-oxo-6-(2,4,5-trifluorophenyl)-1,2,3,6-tetrahydropyrimidine. A mixture of 1-{3-[4-(2-carbamoylphenyl)piperazin-1-yl]propylcarbamoyl}-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(2,4,5-trifluorophenyl)-1,6-dihydropyrimidine (9 mg, 0.014 mmol) in 3 mL of THF and aqueous HCl solution (6 N, 3 mL) was stirred at room temperature for 12 h. The reaction mixture was neutralized with KOH solution (1 N), separated, and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated to get the title compound (8 mg, 92% yield) as a white solid: ^{1}H NMR ($CDCl_3$)-δ 1.69−1.74 (m, 4 H), 2.42 (t, J = 6.9 Hz, 2H), 2.54−2.60 (m, 2 H), 2.98 (t, J = 4.5 Hz, 4 H), 3.31−3.40 (m, 2 H), 3.44 (s, 3 H), 3.64 (s, 3 H), 4.60 (s, 2 H), 5.80 (br s, 1 H), 6.58 (s, 1H), 6.79−6.89 (m, 1 H), 7.17−7.28 (m, 3 H), 7.40−7.46 (m, 1 H), 7.75 (br s, 1 H), 8.09−8.12 (m, 1 H), 8.89−8.93 (m, 1 H). 9.40 (br s, 1 H). Hydrochloride of the title compound was prepared with HCl in ether, mp = 210−215 °C. Anal. ($C_{28}H_{31}N_6F_3Cl_2O_5 \cdot 2.0C_6H_{12}$) C, H, N.

(+)-1,2,3,6-Tetrahydro-1-{*N*-[[4-(2-carboxamidophenyl)-4-phenylpiperazin-1-yl]propyl]carboxamido}-5-methoxycarbonyl-4-ethyl-6-(2,4-difluorophenyl)-2-oxopyrimidine Dihydrochloride (48). To a solution of (+)-1,2,3,6-tetrahydro-1-{*N*-[[4-(2-carboxamidophenyl)-4-phenylpiperazin-1-yl]propyl]carboxamido}-5-hydroxycarbonyl-4-ethyl-6-(2,4-difluorophenyl)-2-oxopyrimidine (200 mg, 0.356 mmol) in CH_2Cl_2 (10 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (137 mg, 0.71 mmol) and DMAP (87 mg, 0.71 mmol). The resulting mixture was stirred at room temperature for 4 h before MeOH (10 mL) was added. The reaction was stirred overnight and concentrated to a residue. The residue was purified by column chromatography (chloroform/MeOH/2 M ammonia in MeOH = 500:14:7) to afford the desired product (150 mg, 75%), $[\alpha]_D$ = +129 (c = 0.75 in chloroform). The compound was converted to HCl salt by dissolving in 1 N HCl in ether followed by concentration to dryness: mp = 160−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16−1.21 (t, J = 7 Hz, 3 H), 1.69−1.76 (m, 4 H), 2.36−2.43 (m, 2 H), 2.53−2.60 (m, 2 H), 2.70−2.80 (m, 2 H), 2.98−3.01 (m, 4 H), 3.22−3.38 (m, 2 H), 3.64 (s, 3 H), 6.66 (s, 1 H), 6.66−6.80 (m, 2 H), 7.18−7.22 (m, 2 H), 7.35−7.44 (m, 2 H), 8.10−8.13 (d, J = 8 Hz, 1 H), 8.86 (t, J = 7 Hz, 1 H). Anal. ($C_{29}H_{36}F_2N_6Cl_2O_5$) C, H, N.

(±)-1,2,3,6-Tetrahydro-1-{*N*-[[4-(2-carboxamidophenyl)-piperazin-1-yl]propyl]carboxamido}-5-acetyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methylpyrimidine Dihydrochloride (49). To a solution of (±)-1,2,3,6-tetrahydro-1-[*N*-(4-nitrophenoxy)carbonyl]-5-acetyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methylpyrimidine (45 mg, 0.10 mmol) in methylene chloride (10 mL) was added 1-(3-aminopropyl)-4-(2-carboxamindophenyl)piperazine (26 mg, 0.10 mmol). The resulting mixture was stirred at room temperature for 1 h before concentrated to a residue. The residue was purified through a preparative TLC plate to yield 60 mg (93%) of the desired product. The compound was converted to HCl salt by dissolving in 1 N HCl in ether followed by concentration to dryness: mp = 235−240 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74−1.82 (m, 2 H), 2.22 (s, 3 H), 2.42 (s, 3 H), 2.40−2.50 (m, 2 H), 2.58−2.68 (m, 4 H), 2.98−3.06 (m, 4 H), 3.36−3.42 (m, 4 H), 6.73 (s, 1 H), 6.92−6.99 (m, 2 H), 7.16−7.22 (m, 2 H), 7.40−7.45 (m, 1 H), 8.08−8.11 (d, J = 8 Hz, 1 H), 8.42 (br s, 1 H), 8.77−8.79 (t, J = 7 Hz, 1 H). Anal. ($C_{28}H_{33}F_3N_6Cl_2O_4 \cdot 0.4H_2O$) C, H, N.

(±)-1,2,3,6-Tetrahydro-1-{*N*-[[4-(2-carboxamidophenyl)-piperazin-1-yl]propyl]carboxamido}-5-acetyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine Dihydrochloride (50). To a solution of (±)-1,2,3,6-tetrahydro-1-[*N*-(4-nitrophenoxy)carbonyl]-5-acetyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine (44.5 mg, 0.100 mmol) in methylene chloride (10 mL) was added 1-(3-aminopropyl)-4-(2-carboxamindophenyl)-piperazine (26 mg, 0.10 mmol). The resulting mixture was stirred at room temperature for 1 h before concentrated to a residue. The residue was purified through a preparative TLC plate to yield 52 mg (83%) of the desired product. The compound was converted to HCl salt by dissolving in 1 N HCl in ether followed by concentration to dryness: mp = 235−240 °C; ^{1}H NMR ($CDCl_3$) δ 1.74−1.82 (m, 2 H), 2.20 (s, 3 H), 2.42 (s, 3 H), 2.40−2.50 (m, 2 H), 2.58−2.68 (m, 4 H), 2.98−3.06 (m, 4 H), 3.36−3.42 (m, 4 H), 6.74 (s, 1 H), 7.02−7.09 (m, 2 H), 7.12−7.22 (m, 3 H), 7.40−7.45 (t, J = 7 Hz, 1 H), 8.00 (br s, 1 H), 8.09−8.12 (d, J = 8 Hz, 1 H), 8.77−8.79 (t, J = 7 Hz, 1 H), 9.44−9.50 (m, 1 H). Anal. ($C_{28}H_{34}F_2N_6Cl_2O_4 \cdot 0.3Et_2O$) C, H, N.

(+)-1,2,3,6-Tetrahydro-1-{*N*-[[4-(2-carboxamidophenyl)-4-phenylpiperazin-1-yl]propyl]carboxamido}-5-carboxamido-4-ethyl-6-(2,4-difluorophenyl)-2-oxopyrimidine Dihydrochloride (52). (a) (+)-1,2,3,6-Tetrahydro-5-benzyloxycarbonyl-1-{*N*-[[4-(2-carboxamidophenyl)-4-phenylpiperazin-1-yl]propyl]carboxamido}-4-ethyl-6-(2,4-difluorophenyl)-2-oxopyrimidine. To a solution of (+)-1,6-dihydro-5-benzyloxycarbonyl-4-ethyl-6-(2,4-difluorophenyl)-2-methoxy-1-[*N*-(4-nitrophenoxy)carbonyl]pyrimidine (400 mg, 0.727 mmol) in CH_2Cl_2 (15 mL) was added 1-(3-aminopropyl)-4-(2-carboxamidophenyl)piperazine (229 mg, 0.873 mmol). The resulting mixture was stirred over 2 h before concentrated to a residue. The residue was purified through column chromatography (chloroform/MeOH/2 N ammonia in MeOH = 1000:18:9) to afford the desired product (427 mg, 89%): $[\alpha]_D = +108$ (c = 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.14−1.20 (t, J = 7 Hz, 3 H), 1.65−1.68 (m, 4 H), 2.35−2.40 (m, 2 H), 2.53−2.60 (m, 3 H), 2.68−2.80 (m, 2 H), 2.96−3.00 (m, 3 H), 3.20−3.36 (m, 2 H), 5.05 (ABq, J = 12 Hz, J = 2.3 Hz, 2 H), 6.63 (s, 1 H), 6.64−6.67 (m, 1 H), 7.16−7.30 (m, 9 H), 7.42 (t, J = 8 Hz, 1 H), 8.11−8.14 (d, J = 8 Hz, 1 H), 8.85 (t, J = 5.4 Hz, 1 H), 9.47−9.51 (m, 1 H).

(b) (+)-1,2,3,6-Tetrahydro-1-{*N*-[[4-(2-carboxamidophenyl)-4-phenylpiperazin-1-yl]propyl]carboxamido}-4-ethyl-6-(2,4-difluorophenyl)-5-hydroxycarbonyl-2-oxopyrimidine. To a solution of (+)-1,2,3,6-tetrahydro-5-benzyloxycarbonyl-1-{*N*-[[4-(2-carboxamidophenyl)-4-phenylpiperazin-1-yl]propyl]carboxamido}-4-ethyl-6-(2,4-difluorophenyl)-2-oxopyrimidine (426 mg, 0.65 mmol) in MeOH (100 mL) was added Pd/C (85 mg, 10%) carefully. The resulting mixture was left under hydrogen (80 psi) overnight. The mixture was filtered through Celite and concentrated to afford the desired product as a white solid (340 mg, 94%) which was used in the next step without further purification.

(c) (+)-1,2,3,6-Tetrahydro-1-{*N*-[[4-(2-carboxamidophenyl)-4-phenylpiperazin-1-yl]propyl]carboxamido}-5-carboxamido-4-ethyl-6-(2,4-difluorophenyl)-2-oxopyrimidine Dihydrochloride. To a solution of (+)-1,2,3,6-tetrahydro-1-{*N*-[[4-(2-carboxamidophenyl)-4-phenylpiperazin-1-yl]-propyl]carboxamido}-5-hydroxycarbonyl-4-ethyl-6-(2,4-difluorophenyl)-2-oxopyrimidine (340 mg, 0.607 mmol) in CH_2Cl_2 were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (233 mg, 1.21 mmol) and 4-methylmorpholine (122 mg, 1.21 mmol). The resulting mixture was stirred at room temperature for 4 h before ammonium hydroxide (1 mL, 40 wt %) was added. The reaction mixture was stirred overnight before quenched with NH_4Cl (aqueous, 50 mL). The mixture was extracted with CH_2Cl_2 (30 mL × 3), and the organic layers were combined, dried over $MgSO_4$, and concentrated. The residue was purified through column chromatography (chloroform/MeOH/2 N ammonia in MeOH = 500:16:8) to afford the desired product (240 mg, 70%), $[\alpha] = +138$ (c = 0.75 in chloroform). The compound was converted to HCl salt by dissolving in 1 N HCl in ether followed by concentration to dryness: mp = 178−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16−1.21 (t, J = 7 Hz, 3 H), 1.65−1.68 (m, 4 H), 2.35−2.40 (m, 2 H), 2.53−2.60 (m, 3 H), 2.63−2.70 (m, 2 H), 2.98−3.01 (m, 3 H), 3.20−3.40 (m, 2 H), 6.57 (s, 1 H), 6.74−6.80 (m, 2 H), 7.14−7.19 (m, 2 H), 7.36−7.39 (m, 2 H), 8.08−8.11 (d, J = 8 Hz, 1 H), 8.89 (t, J = 5 Hz, 1 H), 9.45−9.47 (d, J = 5 Hz, 1 H). Anal. ($C_{28}H_{35}F_2N_7Cl_2O_4 \cdot 2.0H_2O$) C, H, N.

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