Identification of a Dihydropyridine as a Potent α_{1a} Adrenoceptor-Selective Antagonist That Inhibits Phenylephrine-Induced Contraction of the Human Prostate

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Received February 3, 1998

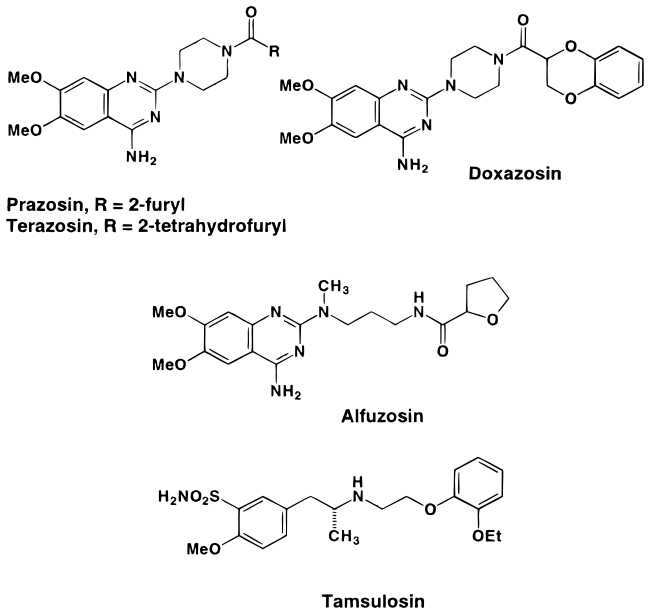
A number of novel dihydropyridine derivatives based upon 1,4-dihydro-3-(methoxycarbonyl)-2,6-dimethyl-4-(4-nitrophenyl)-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (**4**) have been synthesized and tested at cloned human α adrenoceptors as well as the rat L-type calcium channel. Within this compound series, 5-(aminocarbonyl)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)-3-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (**19**) displayed good binding affinity and selectivity for the α_{1a} adrenoceptor ($pK_i = 8.73$) and potently inhibited ($pA_2 = 9.23$) phenylephrine-induced contraction of the human prostate.

Introduction

Benign prostatic hyperplasia (BPH) is a progressive condition which is characterized by a nodular enlargement of prostatic tissue resulting in obstruction of the urethra.[1] This condition occurs in over 50% of the male population above age 60 and leads to a variety of urological symptoms including increased frequency in urination, nocturia, a poor urine stream, and hesitancy or delay in starting the urine flow. Several α_1 adrenoceptor antagonists of the quinazoline class such as prazosin, terazosin, doxazosin, and alfuzosin (Chart 1) are being used clinically for the treatment of BPH by relaxing the smooth muscle of the prostate.[2] However, these agents have been shown to cause significant side effects including dizziness, decreased blood pressure, nasal congestion, and impotence,[3] presumably as a result of their lack of selectivity for any one of the three α_1 adrenoceptor subtypes (α_{1a}, α_{1b}, and α_{1d}).[4] Tamsulosin,[5] a compound not belonging to the quinazoline class, is another α_1 antagonist indicated for BPH (Chart 1). Newer α_1 antagonists under development for treating BPH include **1** (Rec 15/2739),[6] **2** (SL 89.0591),[7] and **3** (KMD 3213)[8] (Chart 2).

With the cloning and characterization of the three human α_1 adrenoceptor subtypes, we were able to demonstrate that the α_{1a} subtype is the predominant receptor mediating smooth muscle contraction in human prostate.[9] This discovery suggested that an α_{1a}-selective antagonist will show better efficacy in the treatment of BPH with reduced side effects than nonselective α_1 antagonists. However, when we initiated these studies, no subtype-selective α_{1a} antagonists had been reported. Recently, reports from this laboratory revealed that compound **4** (SNAP 5089; Chart 2), a niguldipine analogue, is a selective α_{1a} antagonist which is relatively devoid of calcium channel activity.[10] We wanted to further explore the structure−activity relationship of this class of compounds at the α_{1a} adrenoceptor. In addition, **4** is difficult to handle due to the fact that it is very lipophilic and tends to adhere to tissues and container walls. Therefore, an analogue which is less lipophilic and will not adhere to tissues and container

Chart 1



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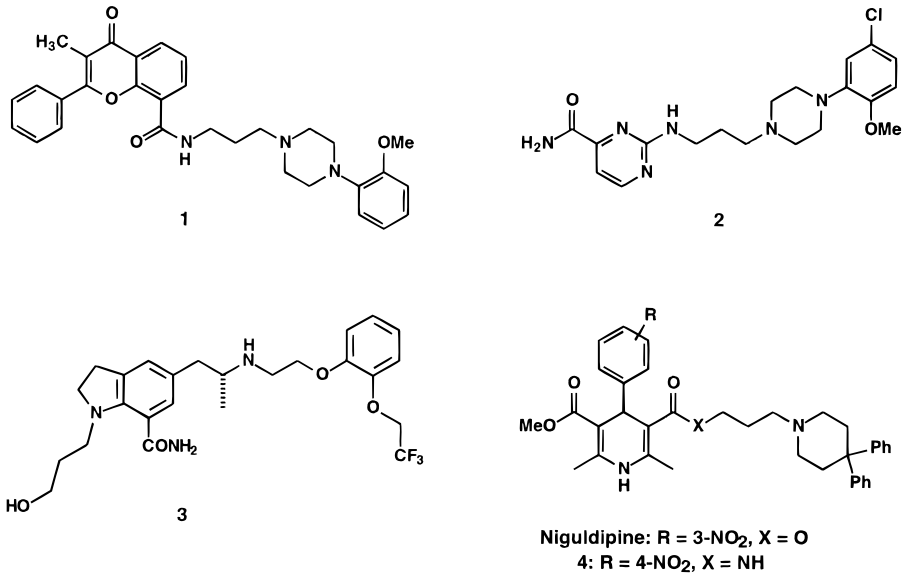
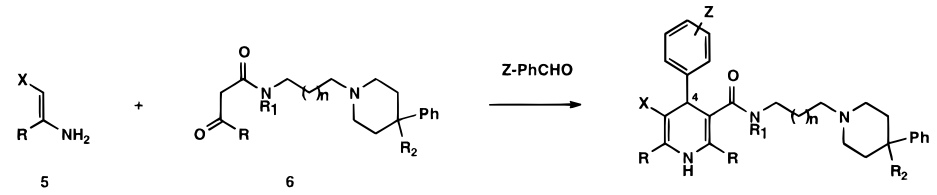
S0022-2623(98)00077-6 CCC: $15.00
Published on Web 06/16/1998

Chart 2



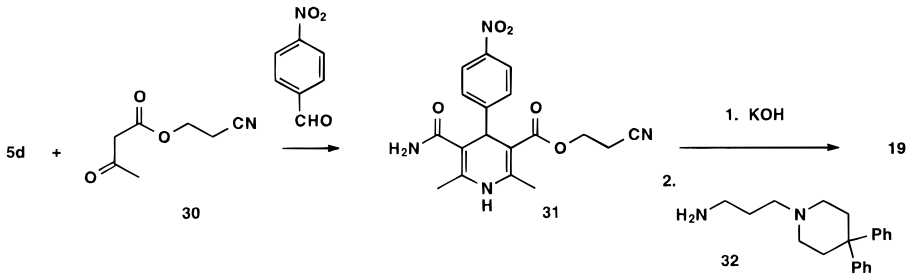
Scheme 1. Hantzsch Synthesis of Dihydropyridines **7**−**18** and **20**−**26**



5a, R = Me, X = CO_2Me
5b, R = Me, X = CN
5c,[16] R = Me, X = COMe
5d, R = Me, X = $CONH_2$
5e,[17] R = Me, X = CONHMe
5f,[17] R = Me, X = $CONMe_2$
5g,[18] R = Et, X = $CONH_2$
5h,[18] R = *i*Pr, X = $CONH_2$

6a, R = Me, R_1 = H, R_2 = Ph, n = 1
6b, R = Me, R_1 = R_2 = H, n = 1
6c, R = Et, R_1 = H, R_2 = Ph, n = 1
6d, R = *i*Pr, R_1 = H, R_2 = Ph, n = 1
6e, R = Me, R_1 = H, R_2 = Ph, n = 0
6f, R = Me, R_1 = H, R_2 = Ph, n = 2
6g, R = R_1 = Me, R_2 = Ph, n = 1

Scheme 2. Synthesis of Compound **19**

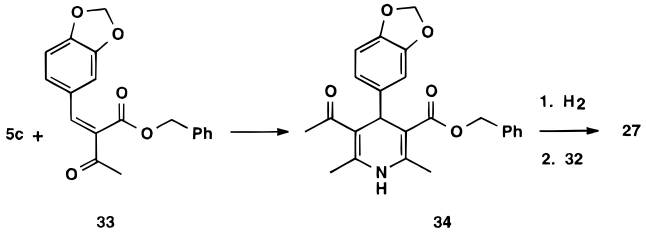


walls is needed for development. Herein we describe our initial results regarding the design and synthesis of analogues of **4**.[11]

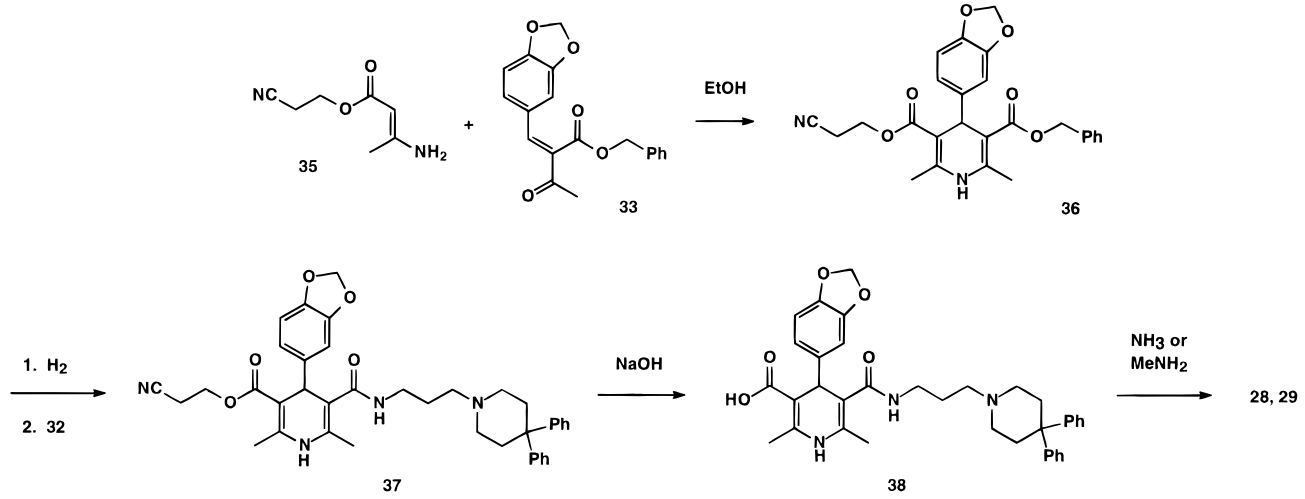
Synthesis

The compounds in this study were prepared by one of two methods. In the first method (Scheme 1), the dihydropyridine ring was assembled by the Hantzsch reaction[12] at the very last step of the synthesis. Hence, an appropriate enamine **5** was reacted with a benzaldehyde and a β-ketoamide **6** to provide compounds **7**−**18** and **20**−**26** (Tables 1−3). The β-ketoamides **6** used in this study were prepared[13] by reaction of the corresponding amines with either diketene or a Meldrum's acid derivative.[14] In the second method (Schemes 2−4), a double protection strategy[15] was used in which a dihydropyridine ring with an easily removable group at

Scheme 3. Synthesis of Compound **27**



Scheme 4. Synthesis of Compounds **28** and **29**

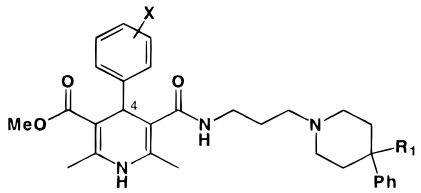


the C-3 and/or C-5 positions was assembled earlier in the synthesis. The removable group was subsequently replaced by the desired side chains to afford **19** and **27**−**29** (Table 4). This strategy allowed for flexibility in attaching different side chains to a common intermediate. For example, in the preparation of compound **19** (Scheme 2), enamine **5d** was reacted with *p*-nitrobenzaldehyde and acetoacetate **30**[19] to give dihydropyridine **31** which was then hydrolyzed and coupled with amine **32**[10] to afford **19**. Likewise, intermediate **34** (Scheme 3), which was obtained from the reaction of enamine **5c** and benzylidene **33**, was hydrogenolyzed and then coupled to amine **32** to provide **27**. In the preparation of compounds **28** and **29** (Scheme 4), enamine **35**[19] was reacted with benzylidene **33** to afford dihydropyridine **36**. Then the benzyloxy group, after hydrogenolysis, was replaced by amine **32**. Subsequently, the 2-cyanoethyl group was hydrolyzed, and the resulting acid **38** was treated with ammonia to give primary amide **28** or with methylamine to yield secondary amide **29**.

Biological Methods

Stably transfected cloned human α adrenoceptors were used in this study. The displacement of [^{3}H]-prazosin from the α_{1a}, α_{1b}, and α_{1d} receptors[9] and the displacement of [^{3}H]rauwolscine from the α_{2a}, α_{2b}, and α_{2c} receptors[20] were used to calculate the binding affinities (pK_i) of the test compounds (average SEM < 0.07). The incubation time for radioligand binding assays was 30 min.[21] Antagonism at α_1 receptors was established by measuring changes in intracellular calcium ion concentrations in the absence and presence of norepinephrine. The affinities at the L-type calcium channel were determined from the displacement of [^{3}H]-nitrendipine from rat brain homogenate.[22] This assay was necessary to ensure weak calcium channel activity for our compounds since many dihydropyridines are well-known as calcium channel inhibitors. For prostate contraction studies, fresh human prostatic tissue was obtained from male patients aged 50−80 years undergoing prostatectomy for BPH. The contractile response induced by phenylephrine was determined as described elsewhere.[9] The antagonist dissociation constant (pA_2) was determined by Schild analysis.

Table 1. Modifications at C-4 of the Dihydropyridine Ring and at the Piperidine Ring



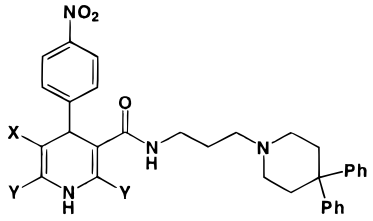
			pK_i						
compd	X	R_1	α_{1a}	α_{1b}	α_{1d}	α_{2a}	α_{2b}	α_{2c}	Ca
terazosin			8.16	8.71	8.46	6.26	7.51	6.65	
4	4-NO_2	Ph	9.46	6.66	6.27	5.92	6.10	6.43	6.27
7	4-Cl	Ph	8.75	6.91	6.35	5.67	5.64	6.00	<6
8	4-CN	Ph	8.74	6.82	6.42	6.12	5.90	6.06	<6
9	4-OMe	Ph	8.15	6.69	6.31	5.66	5.82	5.94	<6
10	4-Me	Ph	8.86	6.57	6.50	5.89	6.04	6.38	<6
11	3,4-OCH_2O	Ph	8.95	6.65	6.52	5.95	6.06	6.24	<6
12	3,4-Cl_2	Ph	8.73	6.94	6.49	6.04	5.90	6.80	<6
13	3-OMe-4-NO_2	Ph	8.83	6.79	6.50	6.20	6.24	6.40	<6
14	3,4-benzo	Ph	7.44	6.86	6.13	5.80	6.05	6.20	6.43
15	4-NO_2	H	9.64	7.87	7.18	6.56	6.66	7.09	<6
16	4-Cl-3-NO_2	H	9.28	7.38	6.90	6.96	7.04	7.32	<6

Results and Discussion

In an attempt to study the structure−activity relationship of analogues of **4** at the α_{1a} adrenoceptor, we modified each substituent on the dihydropyridine ring in a systematic manner. First, the phenyl group at the C-4 position of the dihydropyridine ring (compounds **7**−**14**, Table 1) was modified. The substituents on the phenyl group were chosen to include those with electron-donating and electron-withdrawing properties as well as with different steric demands. The results indicated that while α_{1a} antagonist affinity was maintained with a range of substituents, only the 4-methyl and 3,4-methylenedioxy compounds (**10** and **11**) maintained the affinity ($K_i \sim 1$ nM) and selectivity (>200-fold) of **4**. It is well-known that meta-substituents on dihydropyridines tend to favor calcium channel affinity while para-substituents abolish or greatly reduce affinity.[23] Therefore, it is interesting to note that compounds **11**−**13** showed only weak affinity ($K_i > 1$ μM) at the rat L-type calcium channel even though the phenyl groups of these compounds were meta,para-disubstituted.

In this series, when one phenyl group was removed from the 4-position of the piperidine ring (compounds

Table 2. Modifications at C-2, C-3, and C-6 of the Dihydropyridine Ring



			pK_i						
compd	X	Y	α_{1a}	α_{1b}	α_{1d}	α_{2a}	α_{2b}	α_{2c}	Ca
17	CN	Me	7.25	6.78	6.36	6.20	6.08	6.32	<6
18	COMe	Me	8.93	6.58	6.29	6.22	6.36	6.43	<6
19	$CONH_2$	Me	8.73	6.48	6.22	6.43	6.38	6.49	<6
(+)-**19**	$CONH_2$	Me	7.68	6.35	6.40	6.52	6.39	6.52	
(−)-**19**	$CONH_2$	Me	9.00	6.44	6.65	6.82	6.55	6.78	
20	CONHMe	Me	8.35	6.31	6.12	6.40	6.03	6.49	<6
21	$CONMe_2$	Me	7.23	5.93	5.77	6.02	5.74	6.09	<6
22	$CONH_2$	Et	8.97	6.61	6.33	6.45	6.59	6.72	
23	$CONH_2$	*i*-Pr	7.27	6.79	6.46	6.17	6.42	6.37	

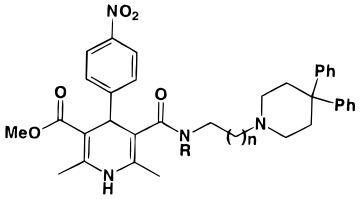
15 and **16**, Table 1), affinity at the α_{1a} receptor was maintained. Unfortunately, the affinity at the other α receptors was increased resulting in significantly lower selectivity for the α_{1a} receptor. It is plausible that the aromatic group on the piperidine ring of these two compounds enjoys more rotational freedom than those of the diarylpiperidine analogues (**4**, **7**−**14**) such that more desirable conformations may be achieved for a better fit in most of the α receptors. In addition, despite the presence of a *m*-nitro substituent on compound **16**, the affinity at the rat L-type calcium channel was greatly diminished.

Next, we replaced the methyl ester of **4** with other functional groups (compounds **17**−**21**, Table 2). Only ketone **18** and amide **19** were comparable to **4** in affinity and selectivity. Apparently, the carbonyl oxygen is playing a role in binding to the α_{1a} receptor because nitrile **17** showed relatively weak affinity. It is noteworthy that the (−)-enantiomer of **19** (obtained by chiral HPLC resolution of the racemate, see Experimental Section) displayed higher affinity than the racemate although there was no overall gain in selectivity. Moreover, substituting the primary amide with a methyl group as in compound **20** slightly reduced the binding affinity at the α_{1a} receptor. Further substituting the amide group with a second methyl produced a compound (**21**) with low affinity. Therefore, the binding pocket appears not to be compatible with tertiary amides which are more sterically demanding than secondary amides and esters.

We replaced the methyl groups at the C-2 and C-6 positions of the dihydropyridine ring with bulkier alkyl substituents including ethyl and isopropyl (compounds **22** and **23**, Table 2). The ethyl group, but not the isopropyl, was well-tolerated by the α_{1a} receptor. Hence, it is possible that the larger alkyl groups disrupt the desirable orientation of the secondary amide linker, leading to improper fit of the receptor site. Alternatively, the isopropyl groups are simply too bulky to be accommodated by the receptor pocket.

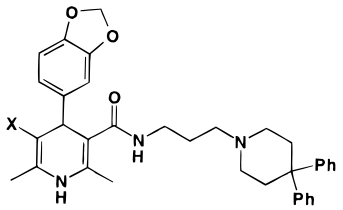
We also studied the consequence of modifying the linker chain between the piperidine and dihydropyridine rings. According to the data in Table 3, it appears that

Table 3. Modifications of the Linker Chain



			pK_i						
compd	R	*n*	α_{1a}	α_{1b}	α_{1d}	α_{2a}	α_{2b}	α_{2c}	Ca
24	H	1	8.06	7.11	5.94	6.35	6.29	6.61	<6
4	H	2	9.46	6.66	6.27	5.92	6.10	6.43	6.27
25	H	3	7.83	6.87	6.48	6.19	6.43	6.55	<6
26	Me	2	7.69	6.62	6.30	6.17	6.31	6.61	<6

Table 4. Modifications at C-3 of the Dihydropyridine Ring



		pK_i						
compd	X	α_{1a}	α_{1b}	α_{1d}	α_{2a}	α_{2b}	α_{2c}	Ca
27	COMe	8.05	6.42	6.34	6.02	6.42	6.39	<6
28	$CONH_2$	8.06	5.93	5.94	6.30	6.69	6.14	<6
29	CONHMe	7.79	5.75	5.82	5.68	6.24	5.99	
38	CO_2H	6.50	6.01	5.76	5.93	6.70	6.11	

the propyl linker chain of **4** is the optimal length and that further substitution on the amide nitrogen adversely affects binding affinity.

Since the 3,4-methylenedioxy group on the C-4 phenyl ring appeared to be a good substitute for the nitro group (compound **11** versus **4**, Table 1), several additional analogues (**27**−**29** and **38**) with 3,4-methylenedioxy substitution were prepared and tested (Table 4). Comparison of **11**, **27**−**29**, and **38** reveals that only the methoxycarbonyl substituent on the dihydropyridine ring is tolerated when the phenyl group has 3,4-methylenedioxy. This is in contrast to the tolerance of acetyl (**18**), carboxamide (**19**), and methylcarboxamide (**20**) as well as methoxycarbonyl (**4**) when the phenyl ring has a 4-nitro group.

Unlike **4** which is an ester, amide **19** does not adhere to tissues or container walls presumably because of its reduced lipophilicity as estimated by c Log P (4.3, BioByte Corp.) and R_f (0.23) on silica gel TLC plates ($CHCl_3$/MeOH/NH_3, 50:9:1) versus 5.6 and 0.55, respectively, for **4**. Nonetheless, **19** maintains good affinity and selectivity for the α_{1a} adrenoceptor. In order to determine whether an α_{1a}-selective antagonist would be effective in inhibiting agonist-induced smooth muscle contraction of the prostate, **19** was assayed using human prostatic tissue in the presence of phenylephrine according to published procedures.[9] Indeed, **19** showed a potency (pA_2) of 9.23 in the assay, which is comparable to the binding affinity (pK_i = 8.73) at the cloned human α_{1a} adrenoceptor and greater than the potency of nonselective terazosin (pA_2 = 8.48).

Recently, the α_1 adrenoceptor subtype in the human prostate has been claimed by others to be of the α_{1L}

subtype.[24,25] This classification remains highly controversial in light of no evidence for additional genes encoding α_1 adrenoceptors and of in vitro pharmacological evidence which indicates that the α_{1L} subtype displays an affinity profile toward selective α_{1a} antagonists similar to that of the recombinant α_{1a} adrenoceptor.[26] In this regard, the close agreement between the pK_i and pA_2 of **19** suggests that this antagonist does not differentiate between the α_{1a} and α_{1L} subtypes. Alternatively, this compound does not differentiate between the binding state of the cloned α_{1a} adrenoceptor and that of the native receptor in human prostate. Moreover, the findings that both **4** and **19** show weak hypotensive activity in vivo[27,28] are inconsistent with the notion that these antagonists bind with high affinity to the α_{1L} adrenoceptor which was originally described to be the predominant α_1 receptors in vascular tissue preparations.[29] Thus, the pharmacodynamic profile of **19**, by virtue of its α_{1a} selectivity with high in vitro potency in inhibiting human prostate contraction and low hypotensive activity, suggests that this compound, or its active enantiomer (−)-**19**, has the desired uroselectivity of a potential drug candidate for the treatment of BPH.

Conclusion

A number of analogues of **4** have been synthesized and tested at cloned human α adrenoceptors as well as the rat L-type calcium channel. The methyl and methylenedioxy groups are good replacements for the nitro moiety because they still give compounds with high affinity and selectivity for the α_{1a} adrenoceptor. The amide side chain containing the diphenylpiperidine group appears to be essential for high affinity (<2 nM) and selectivity (>150-fold) for the α_{1a} adrenoceptor. The methyl ester may be replaced by an acetyl or amide group. Alkyl groups larger than ethyl at the C-2 and C-6 positions of the dihydropyridine ring lead to compounds of lower affinity. However, combining these new features does not necessarily yield compounds with affinity profiles comparable to that of **4**. Finally, **19** displayed a potency (pA_2) of 9.23 in inhibiting phenylephrine-induced contraction of the human prostate smooth muscle, suggesting that this compound (or preferrably its (−)-enantiomer) may be effective for treating the symptoms of BPH. Further developments in this compound series will be reported in due course.

Experimental Section

Melting points (uncorrected) were determined on a Mel-Temp apparatus in open capillary tubes. Unless otherwise indicated, $CDCl_3$ was used as solvent for ^{1}H NMR spectra which were recorded on a GE QE Plus 300-MHz spectrometer. Mass spectra were obtained by Oneida Research Services, Inc. Elemental analyses were performed at Robertson Microlit Laboratories, Inc.

4-(4-Chlorophenyl)-1,4-dihydro-5-(methoxycarbonyl)-2,6-dimethyl-3-((3-(4,4-diphenylpiperidin-1-yl)propyl)-aminocarbonyl)pyridine (7). *N*-(3-(4,4-Diphenylpiperidin-1-yl)propyl)acetoacetamide[10] (**6a**; 200 mg, 0.53 mmol) was mixed with methyl 3-aminocrotonate (61 mg, 0.53 mmol) and 4-chlorobenzaldehyde (74 mg, 0.53 mmol) in 2-propanol (5 mL). The mixture was heated at reflux for 3 days, and the resulting precipitate, after cooling to room temperature, was filtered off to give an almost white solid (134 mg). It was recrystallized twice from chloroform/hexane to afford white crystals (99 mg, 31% yield): mp 240−242 °C; ^{1}H NMR δ 7.30−7.12 (m, 14H), 6.55 (t, 1H), 5.44 (s, 1H), 4.81 (s, 1H), 3.56 (s, 3H), 3.34 (m, 1H), 3.20 (m, 1H), 2.45−2.30 (m, 8H), 2.30 (s, 3H), 2.25−2.10 (m, 2H), 2.16 (s, 3H), 1.54 (m, 2H); ^{13}C NMR (75 MHz) δ 169.0, 168.5, 146.2, 145.8, 136.2, 132.8, 129.4, 129.2, 129.0, 127.7, 126.4, 109.6, 101.5, 57.6, 51.5, 51.1, 45.1, 41.3, 39.6, 36.8, 26.0, 20.6, 18.8; FTIR (NaCl) 1685, 1677, 1618, 1611, 1508, 1498, 1490, 1225 cm^{-1}; CIMS *m/e* = 598 (MH^+). Anal. ($C_{36}H_{40}ClN_3O_3 \cdot {}^1/_2H_2O$) C, H, N.

The following compounds were prepared in a similar fashion.

4-(4-Cyanophenyl)-1,4-dihydro-3-(methoxycarbonyl)-2,6-dimethyl-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)-aminocarbonyl)pyridine (8): 47% yield; pale-yellow crystals (MeOH/ether); mp 115−118 °C; ^{1}H NMR δ 7.46 (m, 2H), 7.36−7.16 (m, 12H), 6.95 (br, 1H), 5.38 (s, 1H), 4.94 (s, 1H), 3.54 (s, 3H), 3.40 (m, 1H), 3.20 (m, 1H), 2.50−2.20 (m, 10H), 2.31 (s, 3H), 2.15 (s, 3H), 1.60 (m, 2H); CIMS *m/e* = 589 (MH^+). Anal. ($C_{37}H_{40}N_4O_3$) C, H, N.

1,4-Dihydro-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2,6-dimethyl-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)-aminocarbonyl)pyridine (9): 31% yield; white crystals (EtOAc/hexane); mp 212−213 °C; ^{1}H NMR δ 7.14−7.30 (m, 12H), 6.75 (d, 2H, *J* = 8.4 Hz), 6.21 (br, 1H), 5.44 (s, 1H), 4.71 (s, 1H), 3.73 (s, 3H), 3.59 (s, 3H), 3.31 (m, 1H), 3.10 (m, 1H), 2.38 (m, 8H), 2.28 (s, 3H), 2.21 (s, 3H), 2.17 (m, 2H), 1.78 (m, 2H), 1.53 (m, 2H); CIMS *m/e* = 594 (MH^+). Anal. ($C_{37}H_{43}N_3O_4$) C, H, N.

1,4-Dihydro-3-(methoxycarbonyl)-2,6-dimethyl-4-(4-methylphenyl)-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)-aminocarbonyl)pyridine (10): 33% yield; white crystals (EtOAc/hexane); mp 234−235 °C; ^{1}H NMR δ 7.15−7.26 (m, 12H),7.02 (d, 2H, *J* = 8.0 Hz), 6.21 (br, 1H), 5.39 (s, 1H), 4.72 (s, 1H), 3.59 (s, 3H), 3.30 (m, 1H), 3.12 (m, 1H), 2.42 (br, 6H), 2.28 (s, 3H), 2.25 (s, 3H), 2.22 (s, 3H), 1.63 (br, 6H); FABMS *m/e* = 578 (MH^+). Anal. ($C_{37}H_{43}N_3O_3 \cdot {}^1/_2H_2O$) C, H, N.

1,4-Dihydro-3-(methoxycarbonyl)-2,6-dimethyl-4-(3,4-(methylenedioxy)phenyl)-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (11): 12% yield; yellow crystals (EtOAc/hexane); mp 197−200 °C; ^{1}H NMR δ 7.30−7.20 (m, 8H), 7.20−7.10 (m, 2H), 6.77 (d, 1H, *J* = 1.6 Hz), 6.73 (dd, 1H, *J* = 7.9, 1.7 Hz), 6.63 (d, 1H, *J* = 7.9 Hz), 6.29 (t, 1H), 5.86 (s, 2H), 5.56 (s, 1H), 4.70 (s, 1H), 3.59 (s, 3H), 3.33 (m, 1H), 3.16 (m, 1H), 2.50−2.30 (m, 8H), 2.27 (s, 3H), 2.20 (m, 2H), 2.18 (s, 3H), 1.55 (m, 2H); CIMS *m/e* = 608 (MH^+). Anal. ($C_{37}H_{41}N_3O_5$) C, H, N.

4-(3,4-Dichlorophenyl)-1,4-dihydro-3-(methoxycarbonyl)-2,6-dimethyl-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)-aminocarbonyl)pyridine (12): 23% yield; white crystals (EtOAc/hexane); mp 177−178 °C; ^{1}H NMR δ 7.09−7.31 (m, 13H), 6.88 (br, 1H), 5.56 (s, 1H), 4.87 (s, 1H), 3.54 (s, 3H), 3.45 (m, 1H), 3.19 (m, 1H), 2.22−2.37 (m, 10H), 2.31 (s, 3H), 2.11 (s, 3H), 1.55 (m, 2H); FABMS *m/e* = 632 (MH^+). Anal. ($C_{36}H_{39}Cl_2N_3O_3$) C, H, N.

1,4-Dihydro-3-(methoxycarbonyl)-4-(3-methoxy-4-nitrophenyl)-2,6-dimethyl-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (13): 5% yield; brown solid (EtOAc/hexane); mp 211−213 °C; ^{1}H NMR δ 7.67 (d, 1H, *J* = 8.4 Hz), 7.11−7.29 (m, 11H), 6.98 (d, 1H, *J* = 1.4 Hz), 6.84 (dd, 1H, *J* = 1.5, 8.4 Hz), 5.69 (s, 1H), 5.00 (s, 1H), 3.82 (s, 3H), 3.55 (s, 3H), 3.42 (m, 1H), 3.20 (m, 1H), 2.33 (s, 3H), 2.28 (br, 10H), 2.11 (s, 3H), 1.55 (br, 2H); FABMS *m/e* = 639 (MH^+). Anal. ($C_{37}H_{42}N_4O_6$) C, H, N.

1,4-Dihydro-3-(methoxycarbonyl)-2,6-dimethyl-4-(2-naphthyl)-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (14): 31% yield; white crystals (EtOAc/hexane); sublimed at room temperature; ^{1}H NMR δ 7.65−7.76 (m, 4H), 7.39−7.46 (m, 3H), 7.23−7.28 (m, 5H), 7.11−7.16 (m, 5H), 6.52 (br, 1H), 5.40 (s, 1H), 5.02 (s, 1H), 3.56 (s, 3H), 3.39 (m, 1H), 3.11 (m, 1H), 2.35 (s, 3H), 2.19 (s, 3H), 2.08 (m, 6H), 1.71 (m, 4H), 1.46 (m, 2H); FABMS *m/e* = 614 (MH^+). Anal. ($C_{40}H_{43}N_3O_3$) C, H, N.

1,4-Dihydro-3-(methoxycarbonyl)-2,6-dimethyl-4-(4-nitrophenyl)-5-((3-(4-phenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (15): 33% yield; yellow crystalline solid

(CH_2Cl_2/ether/hexane); ^1H NMR δ 8.07 (dt, 2H, J = 8.8, 1.9 Hz), 7.42 (dt, 2H, J = 8.8, 1.9 Hz), 7.30 (m, 2H), 7.19 (m, 3H), 7.00 (t, 1H, J = 4.5 Hz), 6.28 (br s, 1H), 5.00 (s, 1H), 3.53 (s, 3H), 3.43 (m, 1H), 3.23 (m, 1H), 2.98 (dm, 1H, J = 11.2 Hz), 2.80 (dm, 1H, J = 11.2 Hz), 2.32 (s, 3 H), 2.26−2.53 (m, 3H), 2.12 (s, 3 H), 1.42−2.10 (m, 8 H); CIMS m/e = 533 (MH^+). Hydrochloride salt: mp 159−160 °C. Anal. ($C_{30}H_{36}N_4O_5 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

4-(4-Chloro-3-nitrophenyl)-1,4-dihydro-3-(methoxycarbonyl)-2,6-dimethyl-5-((3-(4-phenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (16): 29% yield; yellow crystals (EtOAc); mp 191−192 °C; ^1H NMR δ 7.74 (d, 1H, J = 2.1 Hz), 7.44 (dd, 1H, J = 8.3, 2.1 Hz), 7.37 (d, 1H, J = 8.3 Hz), 7.33−7.15 (m, 5H), 6.97 (t, 1H), 5.47 (s, 1H), 4.97 (s, 1H), 3.55 (s, 3H), 3.45 (m, 1H), 3.25 (m, 1H), 3.00 (m, 1H), 2.85 (m, 1H), 2.55−2.37 (m, 3H), 2.34 (s, 3H), 2.17 (s, 3H), 2.00−1.40 (m, 8H); FABMS m/e = 567 (MH^+). Anal. ($C_{30}H_{35}ClN_4O_5$) C, H, N.

5-Cyano-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)-3-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)-pyridine (17): 2% yield; yellowish oil; ^1H NMR δ 8.21 (m, 2H), 7.50 (m, 2H), 7.0−7.2 (m, 10H), 5.71 (s, 1H), 4.8 (s, 1H), 3.0−3.6 (m, 2H), 2.18 (s, 3H), 2.11 (s, 3H), 1.40−2.80 (m, 12H). Hydrochloride salt: colorless crystals (MeOH/Et_2O); mp 252 °C dec. Anal. ($C_{35}H_{37}N_5O_3 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

5-Acetyl-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)-3-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)-pyridine (18): 18% yield; yellow solid (CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$−CD_3OD, 1:1) δ 8.03 (d, 2H, J = 8.7 Hz), 7.35 (d, 2H, J = 8.7 Hz), 7.23 (m, 8H), 7.10 (m, 2 H), 5.06 (br s, 1H), 3.19 (m, 2H), 2.46 (m, 8H), 2.33 (s, 3H), 2.22 (m, 2H), 2.10 (s, 3H), 2.02 (s, 3H), 1.60 (m, 2 H); CIMS m/e = 593 (MH^+). Hydrochloride salt: mp 173−174 °C. Anal. ($C_{36}H_{40}N_4O_4 \cdot HCl \cdot H_2O$) C, H, N.

5-(Aminocarbonyl)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)-3-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (19). A solution of 3-aminocrotonamide (3.87 g, 38.6 mmol), 4-nitrobenzaldehyde (5.83 g, 38.6 mmol), and 2-cyanoethyl acetoacetate[19] (3.00 g, 19.3 mmol) in EtOH (100 mL) was heated at reflux for 48 h. The reaction mixture was filtered and the filtrate concentrated to give a brown oil which was dissolved in $CHCl_3$ (with the addition of a small amount of acetone to obtain a homogeneous solution), washed twice with water, and dried over Na_2SO_4. After filtration and removal of solvent, the residue (**31**) was dissolved in MeOH and treated with 2 N KOH solution at 0 °C. The mixture was stirred at 0 °C for 0.5 h. After the MeOH was removed in vacuo, the aqueous layer was washed twice with EtOAc and then acidified with hydrochloric acid to pH 1. The solid precipitate was collected by filtration and washed with a small amount of cold water to give a yellow powder. A portion of the powder (150 mg, 0.473 mmol) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (90.6 mg, 0.473 mmol) in CH_2Cl_2 (15 mL) were stirred at room temperature for 20 min and then treated with a solution of 3-(4,4-diphenylpiperidin-1-yl)propylamine[10] (**32**; 139 mg, 0.473 mmol) in CH_2Cl_2 (2 mL). The mixture was heated at reflux overnight. Then it was washed twice with water and saturated brine. After drying with Na_2SO_4 and removal of solvent, a yellowish oil was obtained which was recrystallized from CH_2Cl_2/Et_2O. A yellowish powder (165 mg, 59% yield) was obtained: mp 212−215 °C; ^1H NMR δ 8.06 (d, 2H, J = 8.7 Hz), 7.43 (d, 2H, J = 8.7 Hz), 7.00−7.40 (m, 11H), 5.18 (s, 1H), 5.08 (br, 2H), 4.95 (s, 1H), 3.00−3.60 (m, 2H), 2.29 (s, 3H), 2.08 (s, 3H), 1.50−2.80 (m, 12H); CIMS m/e = 594 (MH^+). Anal. ($C_{35}H_{39}N_5O_4$) C, H, N.

(+)- and (−)-19. The enantiomers of **19** were separated on a chiral HPLC column as follows. Four fractions (16 mg each in 2 mL of EtOH) were injected into a Chiralpak AS column (20 × 25 mm; Daicel), which was eluted with EtOH−hexane−diethylamine (10:90:0.05) at a flow rate of 9.0 mL/min with UV detection at 300 nm. The retention times were 50 and 65 min for the (+)-isomer and (−)-isomer, respectively. Each enantiomer was obtained as a yellowish powder after recrystallization from Et_2O/CH_2Cl_2.

(+)-19: $[\alpha]_D$ = 91.2 (c 0.32, $CHCl_3$). Anal. ($C_{35}H_{39}N_5O_4$) C, H, N.

(−)-19: $[\alpha]_D$ = −90.0 (c 0.38, $CHCl_3$). Anal. ($C_{35}H_{39}N_5O_4$) C, H, N.

1,4-Dihydro-2,6-dimethyl-5-(methylaminocarbonyl)-4-(4-nitrophenyl)-3-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (20): 7% yield; yellowish powder (CH_2Cl_2/Et_2O); mp 134 °C; ^1H NMR δ 8.06 (d, 2H, J = 8.7 Hz), 7.42 (d, 2H, J = 8.7 Hz), 7.00−7.40 (m, 11H), 5.28 (br, 1H), 5.20 (s, 1H), 4.92 (s, 1H), 3.00−3.50 (m, 2 H), 2.69 (d, 3H, J = 4.8 Hz), 2.24 (s, 3H), 2.09 (s, 3H), 1.20−2.70 (m, 12H); CIMS m/e = 608 (MH^+). Anal. ($C_{36}H_{41}N_5O_4$) C, H, N.

1,4-Dihydro-2,6-dimethyl-3-(dimethylaminocarbonyl)-4-(4-nitrophenyl)-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)-aminocarbonyl)pyridine (21): 8% yield; yellowish powder (EtOAc/hexane); mp 135 °C; ^1H NMR δ 8.08 (d, 2H, J = 8.7 Hz), 7.39 (d, 2H, J = 8.7 Hz), 7.00−7.30 (m, 10H), 6.35 (br, 1H), 5.00 (s, 1H), 4.86 (s, 1H), 3.19 (m, 2H), 2.37 (br, 6H), 2.23 (s, 3 H), 1.77 (s, 3H), 1.20−3.00 (m, 12H), CIMS m/e = 622 (MH^+). Anal. ($C_{37}H_{43}N_5O_4 \cdot {}^1/_2H_2O$) C, H, N.

5-(Aminocarbonyl)-2,6-diethyl-1,4-dihydro-4-(4-nitrophenyl)-3-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (22): 5% yield; yellowish powder (CH_2Cl_2/Et_2O); mp 119−123 °C. Anal. ($C_{37}H_{43}N_5O_4 \cdot {}^3/_2H_2O$) C, H, N.

5-(Aminocarbonyl)-1,4-dihydro-2,6-diisopropyl-4-(4-nitrophenyl)-3-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (23): 7% yield; yellowish powder (CH_2Cl_2/Et_2O); mp 76−80 °C. Anal. ($C_{39}H_{47}N_5O_4 \cdot {}^1/_2H_2O$) C, H, N.

1,4-Dihydro-3-(methoxycarbonyl)-2,6-dimethyl-4-(4-nitrophenyl)-5-((2-(4,4-diphenylpiperidin-1-yl)ethyl)aminocarbonyl)pyridine (24): 37% yield; yellow solid; ^1H NMR δ 8.07 (d, 2H, J = 8.7 Hz), 7.47 (d, 2H, J = 8.7 Hz), 7.24−7.32 (m, 8H), 7.13−7.17 (m, 2H), 6.14 (t, 1H, J = 4.9 Hz), 5.69 (s, 1H), 4.94 (s, 1H), 3.57 (s, 3H), 3.24 (m, 2H), 2.40−2.42 (m, 8H), 2.32 (m, 2H), 2.31 (s, 3H), 2.29 (s, 3H). Hydrochloride salt: mp 170−171 °C. Anal. ($C_{35}H_{38}N_4O_5 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

1,4-Dihydro-3-(methoxycarbonyl)-2,6-dimethyl-4-(4-nitrophenyl)-5-((4-(4,4-diphenylpiperidin-1-yl)butyl)aminocarbonyl)pyridine (25): 31% yield; yellow solid; ^1H NMR δ 8.08 (d, 2H, J = 8.6 Hz), 7.41 (d, 2H, J = 8.6 Hz), 7.22−7.30 (m, 8H), 7.11−7.19 (m, 2H), 6.13 (s, 1H), 5.73 (m, 1H), 4.91 (s, 1H), 3.60 (s, 3H), 2.38−2.44 (m, 8H), 2.27 (s, 3H), 2.24 (m, 2H), 2.12 (s, 3H), 1.40 (m, 4H). Hydrochloride salt: mp 166−167 °C. Anal. ($C_{37}H_{42}N_4O_5 \cdot HCl \cdot {}^3/_4H_2O$) C, H, N.

1,4-Dihydro-3-(methoxycarbonyl)-2,6-dimethyl-4-(4-nitrophenyl)-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)methylaminocarbonyl)pyridine (26): light-yellow solid; ^1H NMR δ 8.07 (d, 2H, J = 8.4 Hz), 7.33 (d, 2H, J = 8.4 Hz), 7.24 (m, 8H), 7.12 (m, 2H), 6.39 (br, 1H), 4.89 (br s, 1H), 3.49 (s, 3H), 3.31 (br, 2H), 2.47 (br, 11H), 2.32 (br s, 3H), 2.21 (br, 2H), 1.70 (br s, 3H), 1.64 (br, 2H); CIMS m/e = 623 (MH^+). Hydrochloride salt: mp 179−180 °C. Anal. ($C_{37}H_{43}N_4O_5 \cdot HCl \cdot {}^1/_2H_2O$) C, H, N.

5-Acetyl-1,4-dihydro-2,6-dimethyl-4-(3,4-(methylenedioxy)phenyl)-3-((3-(4,4-diphenylpiperidin-1-yl)propyl)-aminocarbonyl)pyridine (27). To a well-stirred suspension of 10% Pd/C (3.0 g) in cold methanol (200 mL, 0 °C) under argon were added formic acid (8.8 mL) and **34** (6.0 g, 15.5 mmol). The mixture was stirred at room temperature for 15 min before the catalyst was removed by filtration. The filtrate was concentrated to give the carboxylic acid as a white powder (4.9 g, 85%). A portion (0.150 g, 0.495 mmol) was mixed with 4-(dimethylamino)pyridine (0.121 g, 1 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (0.190 g, 1 mmol), and 3-(4,4-diphenylpiperidin-1-yl)propylamine (**32**; 0.189 g, 0.644 mmol) in CH_2Cl_2 (40 mL) and stirred at room temperature for 12 h. Then the mixture was washed with saturated NH_4Cl solution (3 × 40 mL) and dried ($MgSO_4$). The residue obtained from evaporation of the solvent was flash-chromatographed over silica gel eluting with $CHCl_3$/MeOH/2

M NH_3 in MeOH (50:2:1) to afford the product as a white powder (0.210 g, 72% yield): mp 94−95 °C; ^{1}H NMR δ 7.35−7.10 (m, 10H), 6.90 (br t, 1H, NH), 6.71−6.66 (m, 3H), 5.84 (m, 2H), 5.60 (s, 1H, NH), 4.84 (s, 1H), 3.57−3.40 (m, 1H), 3.02−3.20 (m, 1H), 2.40−2.20 (m, 8H), 2.28 (s, 3 H), 2.05 (s, 3H), 2.00 (s, 3H), 1.52 (m, 2H). Anal. ($C_{37}H_{41}N_3O_4 \cdot {}^3/_{10}CH_2Cl_2 \cdot {}^9/_{10}H_2O$) C, H, N.

5-(Aminocarbonyl)-1,4-dihydro-2,6-dimethyl-4-(3,4-(methylenedioxy)phenyl)-3-((3-(4,4-diphenylpiperidin-1-yl)-propyl)aminocarbonyl)pyridine (28). A mixture of **38** (0.120 g, 0.202 mmol), 4-(dimethylamino)pyridine (0.049 g, 0.404 mmol), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (0.078 g, 0.404 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 2 h. To this was added 40% aqueous ammonia (0.085 g, 1.01 mmol), and stirring was continued for 12 h. It was washed with saturated NH_4Cl solution (3 × 15 mL) and dried ($MgSO_4$). The residue obtained from the evaporation of solvent was flash-chromatographed over silica gel eluting with $CHCl_3$/MeOH/2 M NH_3 in MeOH (50:2:1) to afford the product as a white powder (0.065 g, 54% yield): mp 125−127 °C; ^{1}H NMR δ 7.35−7.10 (m, 10H), 6.90 (br t, 1H, NH), 6.80−6.60 (m, 3H), 5.86 (m, 2H), 5.15 (s, 1H, NH), 5.05 (br s, 2H, NH_2), 4.63 (s, 1H), 3.57−3.40 (m, 1H), 3.20−3.02 (m, 1H), 2.40−2.10 (m, 8H), 2.26 (s, 3H), 2.08 (s, 3H), 1.52 (m, 2H). Anal. ($C_{36}H_{40}N_4O_4 \cdot {}^3/_{10}C_6H_{14} \cdot {}^9/_{10}H_2O$) C, H, N.

1,4-Dihydro-2,6-dimethyl-5-(methylaminocarbonyl)-4-(3,4-(methylenedioxy)phenyl)-3-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (29). A mixture of **38** (0.120 g, 0.202 mmol), 4-(dimethylamino)pyridine (0.087 g, 0.707 mmol), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (0.078 g, 0.404 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 2 h. To this was added methylamine hydrochloride (0.020 g, 0.303 mmol), and stirring was continued for 12 h. It was washed with saturated NH_4Cl solution (3 × 15 mL) and dried ($MgSO_4$). The residue obtained from the evaporation of solvent was flash-chromatographed over silica gel eluting with $CHCl_3$/MeOH/2 M NH_3 in MeOH (50:2:1) to afford the product as a white powder (0.065 g, 53% yield): mp 120−123 °C; ^{1}H NMR δ 7.35−7.10 (m, 10H), 6.90 (br t, 1H, NH), 6.80−6.60 (m, 3H), 5.85 (m, 2H), 5.40 (br s, 1H, NH), 5.03 (s, 1H, NH), 4.61 (s, 1H), 3.50−3.38 (m, 1H), 3.20−3.02 (m, 1H), 2.62 (d, 3H, J = 4.7 Hz), 2.40−2.05 (m, 8H), 2.22 (s, 3 H), 2.00 (s, 3H), 1.50 (m, 2H). Anal. ($C_{37}H_{42}N_4O_4 \cdot {}^1/_5C_6H_{14} \cdot {}^3/_5H_2O$) C, H, N.

Benzyl 2-(3,4-(Methylenedioxy)benzylidenyl)-3-oxobutyrate (33). A mixture of 3,4-(methylenedioxy)benzaldehyde (15.013 g, 0.1 mol), benzyl acetoacetate (20.18 g, 0.105 mol), piperidine (0.41 g, 476 μL, 4.8 mmol), and acetic acid (0.288 g, 274 μL, 4.8 mmol) in 2-propanol (500 mL) was stirred at room temperature for 48 h. The white solid, benzyl 2-((3,4-(methylenedioxy)phenyl)methylene)-3-oxobutyrate, formed was filtered, washed with 2-propanol (2 × 50 mL), and dried (29.84 g, 92%): mp 137−138 °C; ^{1}H NMR δ 7.59 (s, 1H), 7.35−7.26 (m, 5H), 6.78−6.93 (m, 3H), 6.00 (s, 2H), 5.26 (s, 1H), 2.37 (s, 3H).

5-Acetyl-3-(benzyloxycarbonyl)-1,4-dihydro-2,6-dimethyl-4-(3,4-(methylenedioxy)phenyl)pyridine (34). A mixture of **33** (18.7 g, 57.6 mmol) and 4-amino-3-penten-2-one (**5c**; 6.0 g, 60.5 mmol) in ethanol (200 mL) was refluxed for 12 h, and the solvent was evaporated off. The crude product was used without purification for the next step.

3-(Benzyloxycarbonyl)-5-((2-cyanoethoxy)carbonyl)-1,4-dihydro-2,6-dimethyl-4-(3,4-(methylenedioxy)phenyl)-pyridine (36). A mixture of **33** (8.0 g, 24.67 mmol) and 2-cyanoethyl 3-aminocrotonate[19] (**35**; 4.83 g, 28.36 mmol) in ethanol (250 mL) was refluxed for 24 h, and the solvent was evaporated off. The residue was purified by column chromatography on silica gel using $CHCl_3$/hexane as the eluent to give the desired product (5.49 g, 45%).

3-((2-Cyanoethoxy)carbonyl)-1,4-dihydro-2,6-dimethyl-4-(3,4-(methylenedioxy)phenyl)-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)aminocarbonyl)pyridine (37). To well-stirred cold methanol (100 mL) under argon was added carefully 10% Pd/C (2.0 g), followed by formic acid (4.4 mL) and **36** (4.5 g, 9.1 mmol). The mixture was stirred for 15 min. The catalyst was removed by filtration, and the solvent was evaporated to leave a white solid (2.8 g, 83%). A portion of the solid (1.50 g, 4.05 mmol), 4-(dimethylamino)pyridine (0.99 g, 8.1 mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (1.55 g, 8.1 mmol), and 3-(4,4-diphenylpiperidin-1-yl)propylamine (**32**; 1.55 g, 5.26 mmol) in CH_2Cl_2 (270 mL) were stirred at room temperature for 12 h. Then the mixture was washed with saturated NH_4Cl solution (3 × 50 mL) and dried ($MgSO_4$). The solvent was evaporated off, and the residue was purified by flash column chromatography on silica gel using $CHCl_3$/MeOH/2 M NH_3 in MeOH (50:2:1) as the eluent to afford the product as a white powder (2.30 g, 88%): mp 96−97 °C; ^{1}H NMR (CD_3OD) δ 7.25−7.10 (m, 10H), 6.64−6.71 (m, 2H), 6.50 (d, lH, J = 7.9 Hz), 5.74 (s, 2H), 4.81 (s, ^{1}H), 3.15−3.20 (m, 2H), 2.70−2.85 (m, 4H), 2.50−2.65 (m, 4H), 2.35−2.45 (m, 2H), 2.14 (s, 3H), 2.06 (s, 3H).

3-Carboxy-1,4-dihydro-2,6-dimethyl-4-(3,4-(methylenedioxy)phenyl)-5-((3-(4,4-diphenylpiperidin-1-yl)propyl)-aminocarbonyl)pyridine (38). To a stirred solution of **37** (2.20 g, 3.4 mmol) in acetone (10 mL) at 0 °C was added 1 N NaOH (10 mL) over 10 min. The mixture was stirred for 1 h before the acetone was evaporated and the resulting residue adjusted to pH 7 with 1 N HCl. The product precipitated out as a white solid which was filtered off, dried, and used without further purification (1.92 g, 95%).

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JM980077M