Design and Synthesis of Novel α_{1a} Adrenoceptor-Selective Dihydropyridine Antagonists for the Treatment of Benign Prostatic Hyperplasia

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We report the synthesis and evaluation of novel α_{1a} adrenoceptor subtype-selective antagonists. Systematic modification of the lipophilic 4,4-diphenylpiperidinyl moiety of the dihydropyridine derivatives **1** and **2** provided several highly selective and potent α_{1a} antagonists. From this series, we identified the 4-(methoxycarbonyl)-4-phenylpiperidine analogue SNAP 5540 (−) [(−)-**63**] for further characterization. When examined in an isolated human prostate tissue assay, this compound was found to have a K_i of 2.8 nM, in agreement with the cloned human receptor binding data (K_i = 2.42 nM). Further evaluation of the compound in isolated dog prostate tissue showed a K_i of 3.6 nM and confirmed it to be a potent antagonist (K_b = 1.6 nM). In vivo, this compound effectively blocked the phenylephrine-stimulated increase in intraurethral pressure (IUP) in mongrel dogs, at doses which did not significantly affect the arterial pressure (diastolic blood pressure, DBP), with a DBP K_b/IUP K_b ratio of 16. In addition, (−)-**63** also showed greater than 40 000-fold selectivity over the rat L-type calcium channel and 200-fold selectivity over several G protein-coupled receptors, including histamine and serotonin subtypes. These findings prove that α_{1a} adrenoceptor-subtype selective antagonists such as (−)-**63** may be developed as uroselective agents for an improved treatment of BPH over nonselective α_1 antagonists such as prazosin and terazosin, with fewer side effects.

Introduction

Benign prostatic hyperplasia (BPH), a urological disorder which is highly prevalent in the aging male population affecting over 50% of men above the age of 60, leads to a variety of symptoms including increased frequency of urination, poor stream of urine flow, dribbling, nocturia, hesitancy in starting urine flow, and large residual volumes.[1−3] The symptoms associated with BPH are due to urinary obstruction which results from a combination of two components: mechanical constriction of the urethra due to increased prostatic mass and a dynamic component attributable to increased noradrenergic tone in the hyperplastic prostate.

α_1 Adrenoceptor antagonists such as terazosin[4] and doxazosin[5] are proven to relieve the symptoms associated with BPH and are in clinical use.[3] These α_1 antagonists, however, also have side effects which include orthostatic hypotension, dizziness, impotence, and nasal congestion[6] that may be in part due to their inability to differentiate between the α_1 adrenoceptor subtypes present in the prostate and those involved in maintaining vascular tone.[7] We have demonstrated that the α_{1a} adrenoceptor subtype[8] is the predominant receptor present in the prostate smooth muscle.[9] We have further demonstrated in rat that selective α_{1a} antagonists have a lower propensity to induce orthostatic hypotension, an observation that lends credence to the notion that selective α_{1a} antagonists will provide an advance in therapy for the treatment of BPH.[10] Tamsulosin was recently introduced in the market as the first uroselective α_1 antagonist,[11] and new compounds such as KMD-3213 and RS-97078 were reported to be under development for the treatment of BPH[12,13] (Chart 1).

Recently, we reported the discovery of **1**[14] and **2**[15] as potent and selective α_{1a} antagonists, derived from the dihydropyridine calcium channel antagonist niguldipine. The purpose of this investigation was to identify a suitable substitute for the highly lipophilic phenyl group(s) of the 4,4-diphenylpiperidine moiety in **1** and **2** and to obtain several structurally divergent analogues with less lipophilicity than that of **1** (clog *P* 5.6)[15] and substantially better α_1 adrenoceptor subtype and α_2 adrenoceptor selectivity than that of **2** (α_{1a} K_i = 2.65 nM, α_{1b}/α_{1a} = 350-fold, α_{1d}/α_{1a} = 220-fold, $\alpha_{2a,b,c}/\alpha_{1a}$ > 96-fold). In addition, we also wanted to evaluate one or more of these very selective and potent α_{1a} antagonists in the in vivo dog model (a standard test for evaluating the efficacy of adrenergic BPH agents) to evaluate their uroselectivity and assess their potential orthostatic hypotensive liability in comparison to nonselective α_1 adrenoceptor antagonists.

Chemistry

Synthesis of initial target compounds was achieved by preparation of side chains and the dihydropyridinecarboxylic acids separately, followed by an amine−acid coupling reaction. Scheme 1 describes the synthesis of

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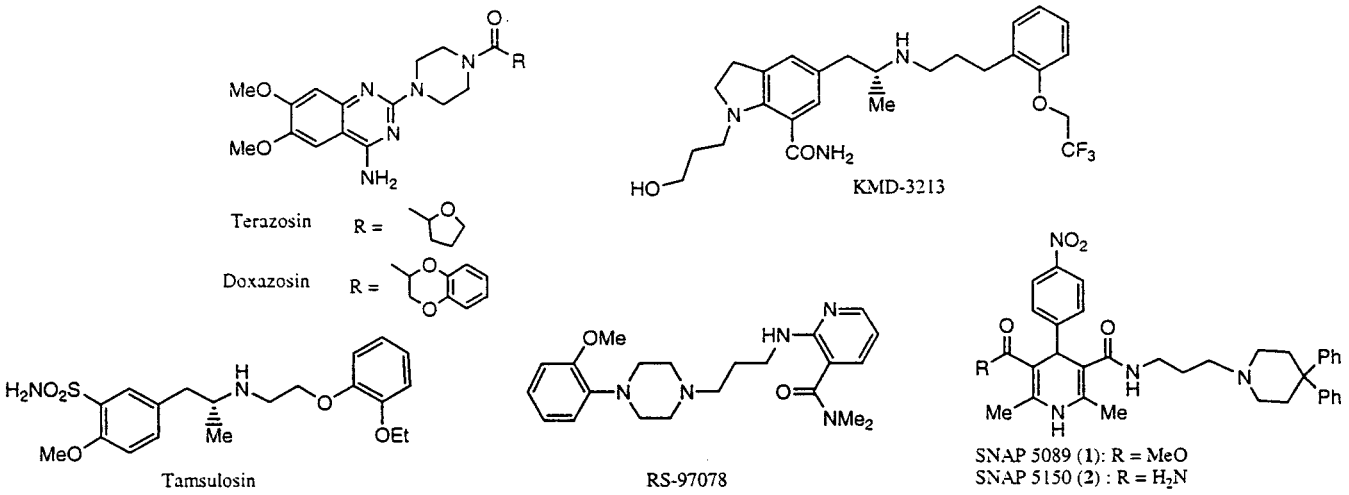
Chart 1



1-(3-aminopropyl)piperidine side chains. 4-Phenyl-4-methylpiperidine (**6**) was prepared by reaction of *N*-benzylpiperidone (**3**) with methyllithium followed by Friedel−Crafts reaction with benzene and subsequent hydrogenation. Piperidines **7**−**11** were obtained either from commercial sources or synthesized using literature methods. Two general synthetic methods were used to introduce the 3-aminopropyl group on the piperidine nitrogen: either by direct alkylation with 3-bromopropylamine or by reaction of piperidines with acrylonitrile followed by reduction of the 1-(2-cyanoethyl)piperidine intermediate **12**. 4-(*N*,*N*-Dimethylcarboxamido)-4-phenylpiperidine-, 4-(*N*,*N*-dimethylaminomethyl)-4-phenylpiperidine-, and 4-(2-cyanoethoxycarbonyl)-4-phenylpiperidine-substituted side chains **27**, **30**, and **32** were prepared from 4-phenyl-4-piperidinecarboxylic acid (**19**).

Scheme 2 describes the synthesis of a variety of dihydropyridine-5-carboxylic acid derivatives **42**−**45**, using a modified Hantzsch reaction.[16] Benzylidines (e.g., **36** and **37**) formed by reaction of 4-nitrobenzaldehyde (**33**) with acetoacetic esters or acetoacetamides (e.g., **34** and **35**) were treated with the enamines derived from 2-cyanoethyl acetoacetate or benzyl acetoacetate derivatives (e.g., **38** and **39**) to provide the dihydropyridine-5-carboxylic esters (e.g., **40** and **41**). Subsequently, the 2-cyanoethyl group was removed by hydrolysis in aqueous NaOH/acetone and the benzyl group by hydrogenation to provide the carboxylic acids **42**−**45**.

These dihydropyridinecarboxylic acids **42**−**45** were then coupled with 1-(3-aminopropyl)piperidines in the presence of EDC and DMAP to provide products **46**−**54**, **59**−**64**, **70**, and **71**. The 4-(2-cyanoethoxycarbonyl)-piperidine derivative **54** was hydrolyzed with aqueous NaOH/acetone to provide the carboxylic acid **55**. Independently, this acid was reacted with 2-methoxyethanol, ethylene glycol, and phenol to give the ester derivatives **56**, **57**, and **58**, respectively (Scheme 3).

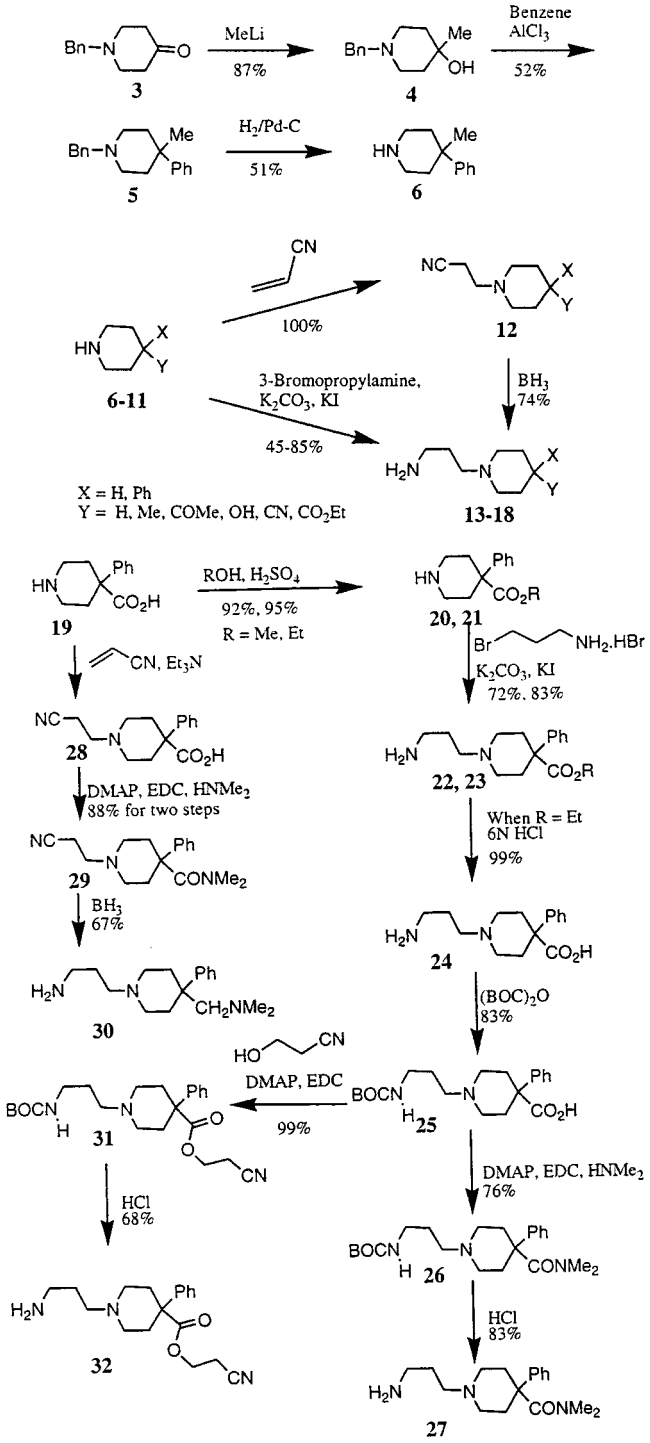
A similar approach, involving a 2-cyanoethyl protecting group on the dihydropyridine C-5 position, was utilized to synthesize the carboxylic acid **65**. This acid **65** was then independently coupled with ethylamine, methanol, ethanol, and ethylene glycol in the presence of EDC and DMAP to provide the amide **66** and ester derivatives **67**, **68**, and **69**, respectively (Scheme 4).

The 4-(3,4-methylenedioxyphenyl)dihydropyridine analogues **73** and **77** were obtained from the carboxylic acids **72** and **74**[15] using similar methods described earlier (Scheme 5). The enantiomers of compound **63** were obtained by chromatographically resolving the intermediate 5-(2-cyanoethoxycarbonyl)-2,6-dimethyl-4-(4-nitrophenyl)-5-(*N*-methylcarboxamido)-1,4-dihydropyridine (**40**) on a Chiralpak AS HPLC column. The individually resolved cyanoethyl esters **40** were converted to (+)-**63** and (−)-**63** using the reaction sequence described above.

Results and Discussion

Piperidine Modifications. Table 1 summarizes modifications of the piperidine 4-substituent of **2**. Molecules with a variety of substituents with varied physicochemical, electronic, and steric properties were synthesized and tested. Prazosin and **2** are included as references to compare the structure−activity relationships. Substitution of one of the piperidine 4-phenyl groups in **2** with a methyl (**46**) or an acetyl group (**47**) decreased the α_{1a} affinity by 30- and 10-fold, respectively. Similarly, a 4-hydroxy substituent (**48**) reduced the affinity by over 4-fold. However, a 4-cyano substitution (**49**) gave a good affinity of 2.88 nM at the α_{1a} adrenoceptor and selectivity over α_{1b} (370-fold) and α_{1d} (960-fold). The *N*,*N*-dimethylcarboxamide substituent (**50**) was not tolerated, and the α_{1a} affinity was reduced by over 100-fold. A *N*,*N*-dimethylaminomethyl group (**51**) reduced the affinity at α_{1a} by over 1000-fold (vs **2**), suggesting that a protonatable nitrogen at that site provides unfavorable interactions at the α_{1a} adrenoceptor. However, a methoxycarbonyl substituent (**52**) yielded improved α_{1a} affinity (0.84 nM) while significantly decreasing α_{1b} and α_{1d} affinity. Compound **52** had substantially improved selectivity for the α_{1a} adrenoceptor, to over 2700-fold over the other subtypes. We further extended our investigation on the size and electronic nature of the methyl group of the piperidine-carboxylic ester. Replacement of the methyl ester by an ethyl ester (**53**) resulted in >2-fold decrease in α_{1a} adrenoceptor affinity. Similarly, methoxyethyl and hydroxyethyl substituents (**56** and **57**) also reduced the α_{1a} affinity by more than 6- and 10-fold; however, all of these compounds showed more than 300-fold subtype

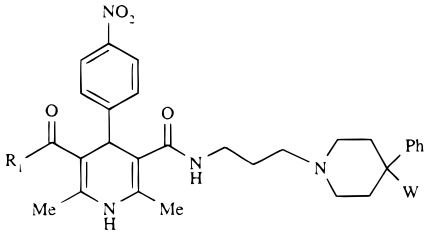
Scheme 1. Synthesis of Side Chains



selectivity. Substitution of the methyl ester in compound **52** with a phenyl ester (**58**) resulted in loss of both affinity and selectivity, perhaps due to increased steric interactions.

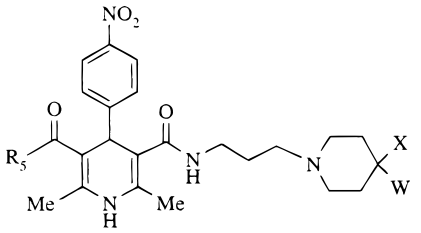
The data presented in Table 2 summarize the importance of the requirement of at least one phenyl group at the piperidine 4-position to maintain nanomolar affinity at the α_{1a} adrenoceptor. Whereas **59** and **60** show similar α_{1a} binding affinity of ~6 nM, removal of the phenyl group to give **61** and **62**, respectively, reduces the α_{1a} affinity by over 400-fold in each case. This supports the premise that at least one phenyl ring is necessary to maintain good α_{1a} affinity. From these

Table 1. Piperidine C-4 Modifications



			K_i (nM)		
compd	W	R_1	α_{1a}	α_{1b}	α_{1d}
prazosin			0.58	0.55	0.33
2	Ph	H_2N	1.87	330	600
46	Me	H_2N	63	530	1970
47	COMe	H_2N	27	5250	3770
48	OH	H_2N	7.7	1890	4680
49	CN	H_2N	2.88	1020	2770
50	$CONMe_2$	H_2N	460	24400	18600
51	CH_2NMe_2	MeNH	3770	45000	51300
52	CO_2Me	H_2N	0.84	2740	4520
53	CO_2Et	H_2N	2.19	2720	4990
56	$CO_2CH_2CH_2OMe$	H_2N	5.41	1570	3190
57	$CO_2CH_2CH_2OH$	H_2N	9.05	5500	11000
58	CO_2Ph	H_2N	5.98	156	585

Table 2. Piperidine C-4 Modifications

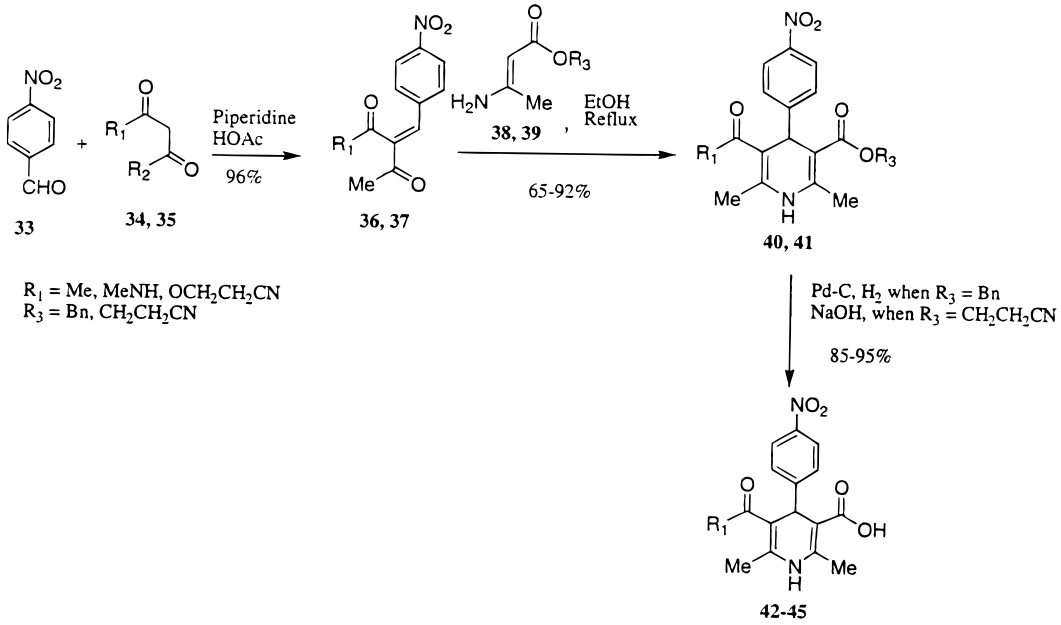


				K_i (nM)		
compd	W	R_5	X	α_{1a}	α_{1b}	α_{1d}
59	CO_2Et	MeNH	Ph	6.12	3920	5600
60	H	MeNH	Ph	6.17	215	630
61	CO_2Et	MeNH	H	2512	39500	45000
62	H	H_2N	H	4330	39500	30700

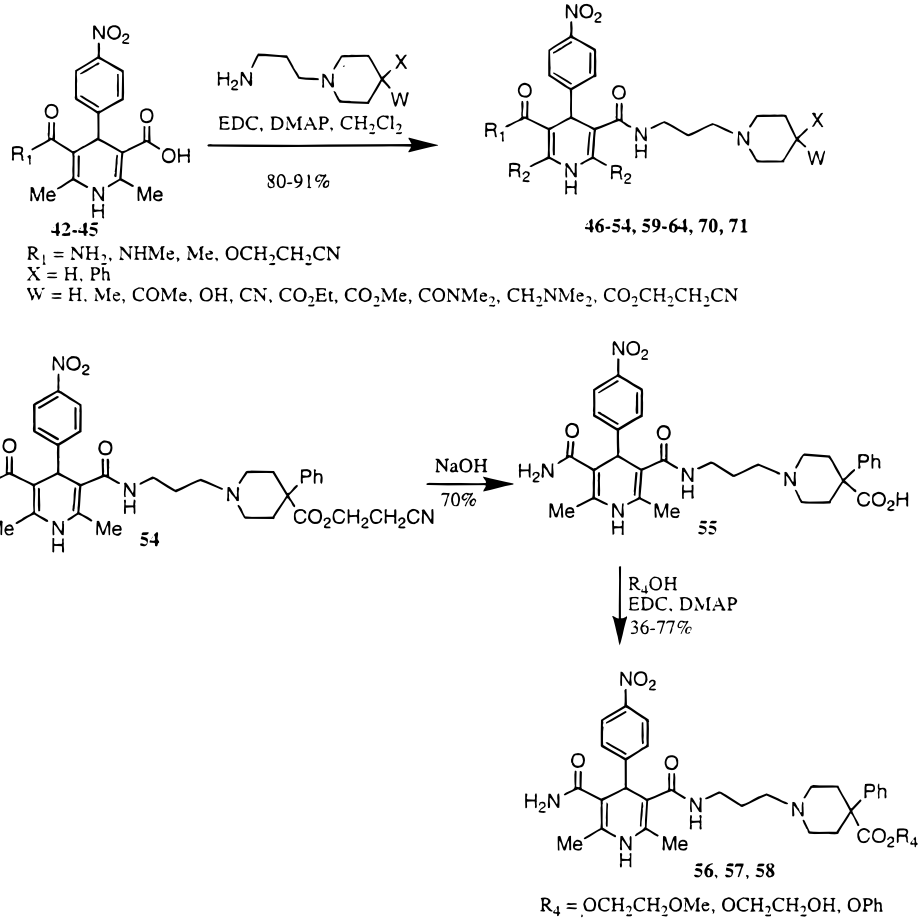
results we determined that the α_{1a} adrenoceptor affinity and selectivity could be significantly enhanced by substituting a 4-(alkoxycarbonyl)-4-phenylpiperidine for the 4,4-diphenylpiperidine moiety.

Dihydropyridine C-5 Modifications. In this part of the study (Table 3), we decided to modify the C-5 position of compound **52** while keeping the rest of the molecule intact. Substitution of the primary amide in compound **52** with methylamide (**63**) decreased the α_{1a} affinity by 3-fold; however, this compound showed greater than 1000-fold subtype selectivity. The ethylamide (**66**) showed a 6-fold lower affinity and less selectivity. Similarly, when the amide was converted into a methyl, ethyl, or 2-hydroxyethyl ester (**67**, **68**, and **69**, respectively), the affinity dropped by at least 3-fold, but all these compounds showed greater than 100-fold subtype selectivity. The carboxylic acid analogue of the amide **52** (**65**) was 70-fold weaker (K_i = 59 nM). Interestingly, the compound exhibited about 500-fold selectivity for α_{1a} over α_{1b} and α_{1d}. The 2-cyanoethyl ester intermediate (**64**) also showed <5 nM K_i for the α_{1a}. An acetyl substituent at the C-5 of the dihydropyridine (**70**) was found to be a good replacement for the

Scheme 2



Scheme 3

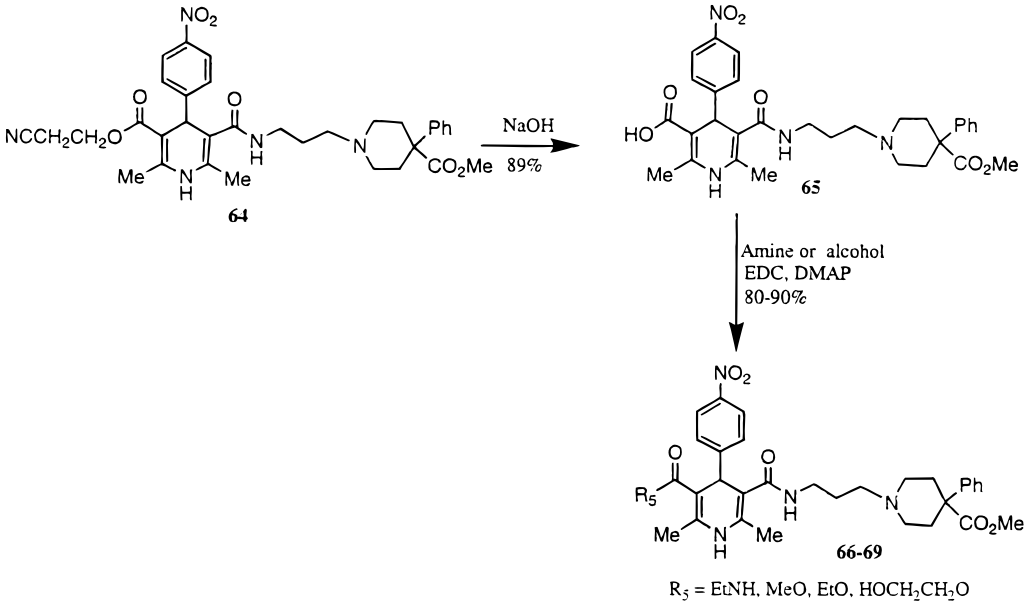


carboxamide group and showed over 450-fold selectivity over all other subtypes. The corresponding ethyl ester analogue (**71**) exhibited an improved affinity over compound **70** and showed >600-fold selectivity (Table 3).

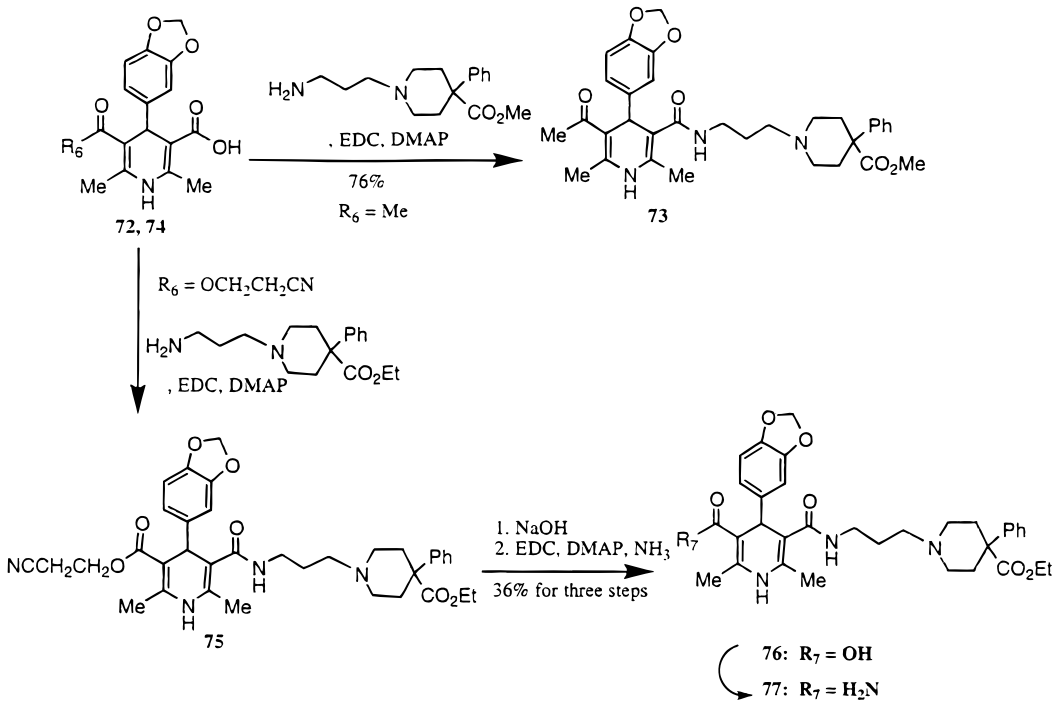
Dihydropyridine C-4 Phenyl Ring Substituent Modifications. In our previous studies,[15] we found that a 3,4-methylenedioxy group was a good substitute for the 4-nitro group. With a 4-(alkoxycarbonyl)-4-phenylpiperidine end group, the 4-(3,4-methylenedioxyphenyl)-dihydropyridines (e.g., **73** and **77**) showed 2−3 times weaker affinity at the α_{1a} adrenoceptor and less subtype selectivity than the corresponding 4-(4-nitrophenyl)-dihydropyridine analogues (Table 4).

Selection and Further Characterization of 63. The current investigation led to the identification of a variety of analogues of **1** and **2** with α_{1a} binding K_i of

Scheme 4



Scheme 5

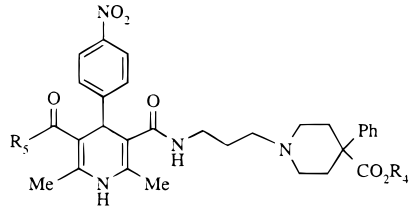


<4 nM and subtype selectivity of >400-fold. At this time, we decided to pick one of these new compounds which was structurally different from compounds **1** and **2**, viz., 1,4-dihydro-2,6-dimethyl-3-[*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido]-5-(*N*-methylcarboxamido)-4-(4-nitrophenyl)pyridine[SNAP 5540 (**63**)], with a 4-(methoxycarbonyl)-4-phenylpiperidine and a *N*-methylcarboxamide moiety, for further characterization. This compound, as a racemate, showed a 3.94 nM affinity at the human α_{1a} adrenoceptor and >1000-fold selectivity over α_{1b} and α_{1d} subtypes. In addition, the clog *P* of **63** was calculated to be 2.27, compared to the clog *P* of 5.6 for **1**.[15] Experimentally, **63** showed a log *D* value of 1.83 as against >3.75 for **1**. These results confirmed that **63** is less lipophilic than **1**. Resolution of the racemate and in vitro binding at the α_{1a} adrenoceptor showed the (−)-enantiomer to be 250-fold more potent (K_i = 2.42 nM) than its (+)-counterpart, with selectivity of 1512-fold over α_{1b} and 3599-fold over α_{1d} (Table 5). This represents a 5-fold improvement in subtype selectivity over that of **2**.

In in vitro assays using membrane preparations from human and dog prostate tissues, (−)-**63** inhibited [^{3}H]-prazosin/[^{125}I]HEAT binding with a K_i of 3.6 and 2.8 nM, respectively, in agreement with the binding affinity at the recombinant human α_{1a} receptor. Compound (−)-**63** was also found to be a competitive antagonist of the phenylephrine-induced contraction of isolated dog prostate tissue with a K_b of 1.6 nM (Table 6).

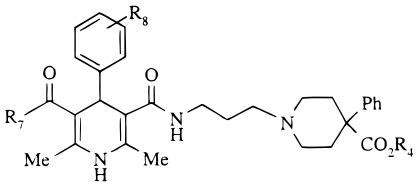
In vivo, (−)-**63** in the dog potently inhibited phenylephrine-stimulated intraurethral pressure (IUP) and demonstrated good selectivity versus phenylephrine-

Table 3. Dihydropyridine C-5 Modifications



compd	R_4	R_5	K_i (nM) α_{1a}	α_{1b}	α_{1d}
52	Me	H_2N	0.84	2740	4520
63 (SNAP 5540)	Me	MeNH	3.94	4920	7740
64	Me	$NCCH_2CH_2O$	4.79	520	750
65	Me	HO	59	29000	28800
66	Me	EtNH	4.82	3070	4820
67	Me	MeO	3.58	700	1140
68	Me	EtO	3.72	390	740
69	Me	$HOCH_2CH_2O$	3.66	1600	1850
70	Me	Me	2.57	1180	2240
71	Et	Me	1.90	1180	1920

Table 4. Dihydropyridine C-4 Phenyl Ring Substituent Modification



compd	R_7	R_8	R_4	K_i (nM) α_{1a}	α_{1b}	α_{1d}
73	Me	3,4-O-CH_2-O	Me	4.17	720	1750
77	H_2N	3,4-O-CH_2-O	Et	7.70	3410	4570
71	Me	4-NO_2	Me	2.57	1180	2240
53	H_2N	4-NO_2	Et	2.19	2270	4980

Table 5. Resolution of Compound **63**

compd	K_i (nM) α_{1a}	α_{1b}	α_{1d}
63	3.94	4920	7440
(−)-**63**	2.42	3660	8710
(+)-**63**	607	5170	8840

Table 6. Binding Affinities (K_i) and Antagonism of Phenylephrine-Induced Contractions (K_b) of (−)-**63** in Isolated Prostate Tissue

species	K_i (nM)	K_b (nM)
dog	3.6	1.6
human	2.8	ND

stimulated diastolic blood pressure (DBP) with a DBP/IUP K_b ratio of approximately 16 (IUP K_b = 4.6 μg/kg, DBP K_b = 73.8 μg/kg). In comparison, the subtype nonselective antagonist prazosin is equipotent for inhibiting phenylephrine responses of IUP and DBP (IUP K_b = 1 μg/kg, DBP K_b = 1.2 μg/kg) (Table 7). These results suggest the uroselectivity of (−)-**63** is by virtue of its potent and selective α_{1a} antagonist binding activity. This is a significant improvement over nonselective α adrenoceptor antagonists such as terazosin and prazosin, which influence urethral and blood pressure with similar potencies, thus limiting their therapeutic efficacy for the treatment of BPH.

Table 7. Effects of (−)-**63** and Prazosin on Inhibition of Phenylephrine-Stimulated Urethral and Arterial Pressure in Anesthetized Mongrel Dogs

compd	IUP K_b (μg/kg)	DBP K_b (μg/kg)	DBP/IUP ratio
(−)-**63**	4.6	74	16
prazosin	1.0	1.2	1

Table 8. Binding Affinity of (−)-**63** at Recombinant Human Receptors[a]

receptors	radioligand	K_i (nM)
α_{2a} adrenoceptor	[^{3}H]rauwolscine	760 ± 395
α_{2b} adrenoceptor	[^{3}H]rauwolscine	1281 ± 215
α_{2c} adrenoceptor	[^{3}H]rauwolscine	2244 ± 105
histamine-H_1	[^{3}H]pyrilamine	491 ± 88
histamine-H_2	[^{3}H]tiotidine	>10000
5HT-1A	[^{3}H]serotonin	427 ± 89
5HT-1B	[^{3}H]serotonin	2645 ± 985
5HT-1D	[^{3}H]serotonin	>5000
5HT-2A	[^{3}H]serotonin	>30000

[a] Data shown are the mean ± SEM of three independent experiments.

Besides its α_{1a} adrenoceptor selectivity, (−)-**63** was devoid of the potent calcium channel activity generally associated with dihydropyridines (rat L-type Ca^{2+} channel K_i = >100 000 nM). This compound also showed greater than 200-fold selectivity over other human G protein-coupled receptors including α_{2a}, α_{2b}, and α_{2c} adrenoceptors, histamine-H_1 and -H_2 receptors, and 5HT-1A, -1B, -1D, and -2A receptors (Table 8). Ongoing evaluation of (−)-**63** for its pharmacokinetic and safety profile will be reported in due course.

Summary

Structural modification of **1** and **2** and in vitro evaluation of resultant analogues at the cloned human α adrenoceptors resulted in the identification of many potent and selective α_{1a} adrenoceptor antagonists. Compound **63** was selected for further characterization due to its structural diversity and lower lipophilicity. The (−)-enantiomer of **63** was 250-fold more potent than the (+)-enantiomer. Compound (−)-**63** exibited a human α_{1a} K_i of 2.42 nM and selectivities of 1512- and 3599-fold over α_{1b} and α_{1d} adrenoceptors, respectively. In vitro, (−)-**63** showed binding affinities for α_{1a} adrenoceptors in dog and human prostate tissues comparable to that seen with the cloned human receptor, and functional assay in dog confirmed this compound to be a potent and selective α_{1a} antagonist. In vivo, (−)-**63** showed a 16-fold separation between IUP and DBP. These findings suggest that such a selective compound should provide a significant improvement over the nonselective α_1 antagonists currently used for the treatment of BPH.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded on a QE Plus 300-MHz spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Reactions were monitored by TLC on silica gel plates (Merck type 60 F_{254}), and flash column chromatography was done on silica gel (Merck type 60 for column chromatography, 230−400 mesh) in the solvent systems indicated. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Abbreviations: EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP, 4-(*N*,*N*-dimethylamino)pyridine. The yields reported are of the isolated purified compounds and are not optimized.

Preparation of Side Chains. 3-(Aminopropyl)-4-methyl-4-phenylpiperidine (13). (a) 1-Benzyl-4-methylpiperidin-4-ol (4). To a solution of 1-benzyl-4-piperidone (**3**) (5.00 mL, 27.0 mmol) in anhydrous ether at −78 °C under argon was added methyllithium (1.4 M in Et_2O, 54.0 mL). Stirring was continued at −78 °C for 1.5 h. Ether (200 mL) and water (40 mL) were added, and the two phases were separated. The aqueous solution was extracted with Et_2O (3 × 50 mL). The combined organic solutions were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc to EtOAc−MeOH, 9:1) to give 4.81 g (87%) of colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 3 H), 1.56 (dt, J = 13, 3 Hz, 2 H), 1.65 (td, J = 10, 4 Hz, 2 H), 2.35 (td, J = 10, 3 Hz, 2 H), 2.53 (m, 2 H), 7.24 (m, 1 H), 7.29 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.44, 39.37, 50.39, 63.80, 68.50, 127.56, 128.80, 129.80, 139.17.

(b) 1-Benzyl-4-methyl-4-phenylpiperidine (5). Compound **4** (4.81 g, 23.4 mmol) was added to a suspension of $AlCl_3$ (15.62 g, 117 mmol) in benzene (100 mL) at room temperature under argon. The mixture was stirred at reflux for 24 h, then cooled, and poured cautiously into ice water (100 g of ice plus 50 mL of water). The aqueous phase was adjusted to pH 11−12 by addition of 6 N aqueous NaOH at 0 °C and extracted with EtOAc (3 × 100 mL). The combined organic solutions were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, hexanes−Et_2O, 19:1 to 9:1, followed by hexanes−EtOAc, 3:1) to give 3.23 g (52%) of brown oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.80 (m, 2 H), 2.17 (m, 2 H), 2.44 (m, 2 H), 2.55 (m, 2 H), 3.50 (s, 2 H), 7.25 (m, 1 H), 7.35 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.82, 37.65, 50.95, 54.93, 64.08, 126.19, 126.51, 127.59, 128.83, 128.95, 129.05, 129.89, 139.24.

(c) 4-Methyl-4-phenylpiperidine (6). Freshly prepared methanolic formic acid solution (4.4 wt %, 70 mL) was added to **5** (3.23 g, 12.2 mmol). To the resulting solution was added palladium on carbon (10% Pd, 2.00 g). The mixture was stirred at room temperature for 24 h. The solid was filtered out and washed with MeOH (30 mL), H_2O (15 mL), CH_2Cl_2 (30 mL), and MeOH (15 mL). The combined filtrate and washings were concentrated, and the residue was dissolved in CH_2Cl_2 (50 mL) and H_2O (10 mL). The aqueous phase was adjusted to pH 11 by addition of 1 N aqueous NaOH. The organic phase was separated, dried over $MgSO_4$, and concentrated. The residual oil was purified by flash chromatography (SiO_2, $CHCl_3$−MeOH−2 M NH_3 in MeOH, 100:4:0 to 100:20:10) to afford 1.20 g of 1-benzyl-4-methyl-4-phenylpiperidine and 1.10 g (51%, 82% based on recovered starting material) of 4-methyl-4-phenylpiperidine: ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3 H), 1.71 (m, 2 H), 2.06 (m, 2 H), 2.82 (m, 3 H), 2.94 (m, 2 H), 7.19 (m, 1 H), 7.32 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.22, 38.54, 43.44, 47.74, 126.31, 127.43, 129.01, 149.73.

(d) 3-(Aminopropyl)-4-methyl-4-phenylpiperidine (13). 4-Methyl-4-phenylpiperidine (1.00 g, 5.70 mmol), 3-bromopropylamine hydrobromide (1.87 g, 8.55 mmol), and potassium carbonate (1.97 g, 14.2 mmol) were stirred in refluxing dioxane (20 mL) for 36 h. After removal of the solvent, water (50 mL) was added and the pH adjusted to 11−12 by addition of 1 N aqueous NaOH. The mixture was extracted with CH_2Cl_2 (150 mL + 3 × 100 mL). The combined organic solutions were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, $CHCl_3$−MeOH−2 M NH_3 in MeOH, 100:20:10) to give 241 mg (18%) of colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 3 H), 1.61 (quint, J = 7 Hz, 2 H), 1.75 (m, 2 H), 2.10 (m, 2 H), 2.33 (t, J = 7 Hz, 2 H), 2.40 (m, 2 H), 2.45 (m, 2 H), 2.72 (t, J = 6 Hz, 2 H), 3.02 (br s, 2 H), 7.14 (m, 1 H), 7.30 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.28, 36.78, 37.64, 41.51, 50.96, 57.51, 126.16, 126.40, 128.91, 149.20.

4-Acetyl-1-(3-aminopropyl)-4-phenylpiperidine (14). 4-Acetyl-4-phenylpiperidine (**7**; 1.53 g, 7.50 mmol), 3-bromopropylamine hydrobromide (1.64 g, 7.50 mmol), and potassium carbonate (1.24 g, 9.00 mmol) were stirred in refluxing 1,4-dioxane (50 mL) for 12 h. After removal of dioxane, water (50 mL) was added and the pH was adjusted to 11−12 by addition of 1 N aqueous NaOH. The mixture was extracted with CH_2Cl_2 (100 mL + 3 × 50 mL). The combined organic solutions were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (EtOAc−MeOH−Et_3N, 100:40:20) to give 780 mg (40%) of colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.56 (quint, J = 7 Hz, 2 H), 1.84 (s, 3 H), 1.98 (m, 2 H), 2.15 (br t, J = 12 Hz, 2 H), 2.29 (t, J = 7 Hz, 2 H), 2.41 (br d, J = 12 Hz, 2 H), 2.66 (t, J = 7 Hz, 4 H), 7.18−7.30 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.28, 31.11, 33.43, 41.47, 51.62, 55.31, 57.19, 77.32, 77.74, 78.17, 126.95, 127.69, 129.44, 142.25, 210.15.

1-(3-Aminopropyl)-4-hydroxy-4-phenylpiperidine (15). To a solution of 4-hydroxy-4-phenylpiperidine (**8**; 3.11 g, 17.5 mmol) in EtOH (30 mL) was added acrylonitrile (2.89 mL, 43.8 mmol) dropwise at 0 °C. The mixture was stirred at room temperature for 1.5 h and then concentrated to afford 3.71 g of white solid, presumed to be 3-(4-hydroxy-4-phenylpiperidin-1-yl)propionitrile (**11**), which was used directly for the next reaction. To a solution of this white solid in THF (15 mL) at room temperature was added borane−tetrahydrofuran complex (1.0 M in THF, 56.3 mL, 56.3 mmol) dropwise. The mixture was stirred at reflux for 4.5 h and then cooled to room temperature. Aqueous HCl (6 N, 85 mL) was added, and the mixture was stirred at 50−70 °C for 2 h. The mixture was basified to pH 9−10 by addition of 6 N aqueous NaOH and extracted with EtOAc (75 mL) and CH_2Cl_2 (3 × 75 mL). The combined organic solutions were dried over $MgSO_4$ and concentrated. To a solution of the residue in CH_2Cl_2 (75 mL) was added HCl in Et_2O (1.0 M, 38 mL). After removal of the solvents, the residue was triturated with Et_2O (185 mL). The resulting white solid was collected by filtration and washed with Et_2O. Water (50 mL) was added to this solid, and the mixture was basified to pH 10−11 by addition of 1 N aqueous NaOH and extracted with CH_2Cl_2 (150 mL + 2 × 75 mL). The combined CH_2Cl_2 solutions were dried over $MgSO_4$ and concentrated to give 3.12 g (76%) of **15** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.65 (quint, J = 7 Hz, 2 H), 1.73 (dd, J = 13, 1 Hz, 2 H), 2.13 (td, J = 13, 4 Hz, 2 H), 2.42 (m, 4 H), 2.72 (t, J = 7 Hz, 2 H), 2.80 (m, 2 H), 7.23 (t, J = 7 Hz, 1 H), 7.33 (t, J = 7 Hz, 2 H), 7.49 (d, J = 7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.16, 39.11, 41.49, 50.26, 57.28, 71.70, 125.20, 127.53, 128.91, 149.19.

1-(3-Aminopropyl)-4-cyano-4-phenylpiperidine (16). 4-Cyano-4-phenylpiperidine hydrochloride (**9**; 5.01 g, 22.5 mmol) was added to water (100 mL), and the solution was basified to pH 10−11 by addition of 6 N aqueous NaOH. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic solutions were dried over $MgSO_4$ and concentrated. To the residue were added 3-bromopropylamine hydrobromide (4.92 g, 22.5 mmol), anhydrous K_2CO_3 (3.42 g, 24.8 mmol), and 1,4-dioxane (100 mL). The mixture was stirred at reflux for 24 h under a $CaSO_4$ drying tube. The solvent was removed, and the product was purified by flash chromatography (SiO_2, $CHCl_3$−MeOH−2 M NH_3 in MeOH, 100:8:4 to 100:20:8) to give 3.23 g (59%) of colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.64 (quint, J = 7 Hz, 2 H), 1.80 (s, 2 H), 2.07 (m, 4 H), 2.41 (m, 2 H), 2.48 (t, J = 7 Hz, 2 H), 2.74 (t, J = 7 Hz, 2 H), 3.01 (br d, J = 12 Hz, 2 H), 7.25−7.38 (m, 3 H), 7.46 (dd, J = 7, 1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.92, 37.17, 41.33, 43.41, 51.46, 56.92, 122.67, 126.21, 128.69, 129.61, 140.75.

3-(4-(Ethoxycarbonyl)piperidin-1-yl)propylamine (17). A mixture of ethyl piperidine-4-carboxylate (**10**; 12.2 g, 0.0776 mmol), 3-bromopropylamine hydrobromide (25.4 g, 0.116 mol), potassium carbonate (26.95 g, 0.195 mol), and KI (6.48 g, 0.039 mol) in 1,4-dioxane (250 mL) was stirred and refluxed for 36 h. Dioxane was evaporated under vacuum; the residue was treated with ice-cold 6 N NaOH (400 mL), and extracted with CH_2Cl_2 (4 × 120 mL). Solvent was evaporated from the combined dried (K_2CO_3) CH_2Cl_2 extracts, and the residue was purified by column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (20:2:1) as the eluent to afford the product as a viscous oil (8.38 g, 42%): ^{1}H NMR ($CDCl_3$) δ 4.06 (q, J = 7 Hz, 2 H), 3.07−2.90 (br s, 2 H, NH_2), 2.90−2.70 (m,

4 H), 2.45−2.30 (m, 2 H), 2.30−2.10 (m, 1 H), 2.05−1.60 (m, 8 H), 1.18 (t, J = 7 Hz, 3 H).

3-(4-Phenylpiperidin-1-yl)propylamine (18). Prepared from 4-phenylpiperidine (**11**) as reported earlier.[15]

3-[4-(*N*,*N*-Dimethylcarboxamido)-4-phenylpiperidin-1-yl]propylamine (27). (a) 4-(Ethoxycarbonyl)-4-phenylpiperidine (20). To a stirred solution of H_2SO_4 (1.62 g, 16.56 mmol) in EtOH (200 mL) was added 4-phenyl-4-piperidinecarboxylic acid 4-methylbenzenesulfonate (**19**; 25 g, 66.23 mmol), and the mixture was stirred and refluxed for 12 h. Excess ethanol was evaporated at reduced pressure, and the residue was poured into a mixture of ice and aqueous 6 N NaOH. The pH was adjusted to 10−11 by adding more 6 N NaOH and extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and the solvent evaporated to afford the desired product as a colorless viscous oil; the ^{1}H NMR showed it to be pure (14.68 g, 95%), and it was used without any further purification: ^{1}H NMR ($CDCl_3$) δ 7.38−7.20 (m, 5 H), 4.09 (q, J = 7 Hz, 2 H), 3.07−3.02 (m, 2 H), 2.82−2.77 (m, 2 H), 2.55−2.50 (m, 2 H), 1.86−1.79 (m, 2 H), 1.16 (t, J = 7 Hz, 3 H).

(b) 3-(4-(Ethoxycarbonyl)-4-phenylpiperidin-1-yl)propylamine (22). A mixture of **20** (30.5 g, 0.131 mol), 3-bromopropylamine hydrobromide (42.93 g, 0.196 mol), potassium carbonate (36.14 g, 0.241 mol), and KI (10.8 g, 0.065 mol) in 1,4-dioxane (500 mL) was stirred and refluxed for 24 h. Dioxane was evaporated under vacuum; the residue was treated with ice-cold aqueous 6 N NaOH (400 mL) and extracted with CH_2Cl_2 (4 × 120 mL). Solvent was evaporated from the combined dried (K_2CO_3) CH_2Cl_2 extracts and the residue purified by column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (20:2:1) as the eluent to afford the product as a viscous oil (24.2 g, 83.3%): ^{1}H NMR ($CDCl_3$) δ 7.38−7.20 (m, 5 H), 4.06 (q, J = 7 Hz, 2 H), 3.17−2.95 (m, 4 H), 2.72−2.52 (m, 4 H), 2.30−2.10 (m, 2 H), 2.00−1.79 (m, 4 H), 1.13 (t, J = 7 Hz, 3 H).

(c) 1-(3-Aminopropyl)-4-phenylpiperidine-4-carboxylic Acid (24). A solution of **22** (2.0 g) in 6 N aqueous HCl (16 mL) was heated under reflux for 3 h. Solvent was evaporated and the residue dried under vacuum to leave the product as a white powder (2.04 g, 99%). The ^{1}H NMR showed this product to be pure, and it was used in the next step without any purification: ^{1}H NMR (D_2O) δ 7.42−7.20 (m, 5 H), 3.80−3.65 (m, 2 H), 3.35−3.20 (m, 2 H), 3.20−3.00 (m, 4 H), 2.90−2.74 (m, 2 H), 2.30−2.10 (m, 4 H).

(d) 1-[3-(*N*-*tert*-Butoxycarbonylamino)propyl]-4-phenylpiperidine-4-carboxylic Acid (25). To a well-stirred solution of **24** (2.04 g, 6.89 mmol) in aqueous 1 N NaOH (15 mL) at 0 °C was added a solution of di-*tert*-butyl dicarbonate (1.8 g, 8.26 mmol) in dioxane (10 mL), and the stirring was continued for 12 h while the mixture was allowed to warm to room temperature. The mixture was treated with water (100 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography on silica gel using $CHCl_3$−MeOH (30:1) as the eluent to give the product as a white solid (2.06 g, 83%): ^{1}H NMR (CD_3OD) δ 7.45−7.15 (m, 5 H), 4.60 (br s, 1 H, NH), 3.50−3.35 (m, 2 H), 3.16−2.94 (m, 6 H), 2.75−2.60 (m, 2 H), 2.00−1.80 (m, 4 H), 1.55 (s, 9 H).

(e) 1-*N*-(*tert*-Butoxycarbonyl)-3-[4-(*N*,*N*-dimethylcarboxamido)-4-phenylpiperidin-1-yl]propylamine (26). A mixture of **25** (0.7 g, 1.93 mmol), EDC (0.925 g, 4.83 mmol), DMAP (0.471 g, 3.86 mmol), and dimethylamine hydrochloride (0.315 g, 3.86 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 24 h. The mixture was diluted with more CH_2Cl_2 (150 mL), washed with aqueous ammonium chloride solution (3 × 50 mL), and dried ($MgSO_4$). Solvent was evaporated and the residue purified by column chromatography on silica gel using $CHCl_3$−MeOH (9:1) as the eluent to give the product as a colorless oil (0.57 g, 76%): ^{1}H NMR (CD_3OD) δ 7.35−7.16 (m, 5 H), 5.76 (br s, 1 H, NH), 3.24−3.15 (m, 2 H), 2.92−2.80 (m, 2 H), 2.80−2.50 (m, 4 H), 2.50−2.30 (m, 8 H), 2.12−1.95 (m, 2 H), 1.73−1.62 (m, 2 H), 1.40 (s, 9 H).

(f) 3-[4-(*N*,*N*-Dimethylcarboxamido)-4-phenylpiperidin-1-yl]propylamine (27). To a well-stirred solution of **26** (0.57 g, 1.46 mmol) in methanol (10 mL) at 0 °C was added aqueous 6 N HCl (10 mL), and the mixture was allowed to warm to room temperature. After 3 h solvent was evaporated, and the residue was dried under vacuum to leave the hydrochloride salt of the product as a white solid (0.44 g, 83%): ^{1}H NMR (CD_3OD) δ 7.42−7.20 (m, 5 H), 3.65−3.55 (m, 2 H), 3.30−3.15 (m, 4 H), 3.05−2.95 (m, 2 H), 2.95−2.82 (m, 2 H), 2.60−2.55 (br s, 6 H), 2.40−2.20 (m, 2 H), 2.20−2.05 (m, 2 H).

3-[4-(*N*,*N*-Dimethylaminomethyl)-4-phenylpiperidin-1-yl]propylamine (30). (a) 1-(2-Cyanoethyl)-4-phenylpiperidine-4-carboxylic Acid (28). To a solution of 4-phenyl-4-piperidinecarboxylic acid 4-methylbenzenesulfonate (**19**; 10 g, 26.5 mmol) and triethylamine (4 mL) in methanol (100 mL) was added acrylonitrile (4 mL) at room temperature, and the mixture was stirred for 4 h. Solvent and the excess acrylonitrile were evaporated, and the residue was dried to leave the product as a white powder (12.95 g) which was used in the next step without purification.

(b) 1-(2-Cyanoethyl)-4-(*N*,*N*-dimethylaminomethyl)-4-phenylpiperidine (29). Part of the product from the above reaction (3.51 g, 13.6 mmol) was mixed with EDC (5.21 g, 27.2 mmol) and DMAP (6.64 g, 54.4 mmol) in CH_2Cl_2 (150 mL), and the solution was stirred at room temperature for 2 h. To this was added dimethylamine hydrochloride (2.22 g, 27.2 mmol), and the stirring was continued for 12 h. The resulting mixture was washed with aqueous NH_4Cl solution (3 × 50 mL) and dried ($MgSO_4$). Solvent was evaporated from the CH_2Cl_2 solution and the product purified by flash column chromatography on silica gel using $CHCl_3$−MeOH (9:1) as the eluent to give the product **29** as a white powder (3.44 g, 88%): ^{1}H NMR ($CDCl_3$) δ 7.39−7.19 (m, 5 H), 2.92−2.75 (m, 4 H), 2.70 (t, J = 7 Hz, 2 H), 2.50−2.40 (m, 2 H), 2.47 (s, 6 H), 2.40−2.32 (m, 2 H), 2.05−1.86 (m, 2 H).

(c) 3-[4-(*N*,*N*-Dimethylaminomethyl)-4-phenylpiperidin-1-yl]propylamine (30). To a stirred solution of compound **29** (3.44 g, 12 mmol) in THF (100 mL) at room temperature was added a solution of borane in THF (1 M, 52 mL, 52 mmol), and the mixture was refluxed for 10 h. It was cooled to 0 °C, aqueous HCl (6 N, 25 mL) was added carefully, and the mixture was warmed to 40 °C. After 2 h, the pH of the mixture was adjusted to 11 by the addition of 6 N NaOH and extracted with dichloromethane (3 × 150 mL). The combined CH_2Cl_2 solution was dried (K_2CO_3) and the solvent evaporated. The product was purified by flash column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (25:4:1) as the eluent to afford the product as a white solid (2.23 g, 67%): ^{1}H NMR ($CDCl_3$) δ 7.35−7.10 (m, 5 H), 2.72−2.50 (m, 4 H), 2.36 (s, 2 H), 2.32−2.22 (m, 2 H), 2.22−2.05 (m, 2 H), 2.00−1.80 (m, 4 H), 1.88 (s, 6 H), 1.60−1.52 (m, 2 H).

(4-(Methoxycarbonyl)-4-phenylpiperidin-1-yl)propylamine (23). (a) 4-(Methoxycarbonyl)-4-phenylpiperidine (21). To a stirred solution of H_2SO_4 (16 mL) in MeOH (400 mL) was added 4-phenyl-4-piperidinecarboxylic acid 4-methylbenzenesulfonate (**19**; 37.7 g, 0.1 mol), and the mixture was stirred and refluxed for 8 h. Excess methanol was evaporated at reduced pressure, and the residue was poured into a mixture of ice and 6 N NaOH. The pH was adjusted to 10−11 by adding more 6 N NaOH and extracted with CH_2Cl_2 (3 × 150 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and the solvent evaporated to leave the desired product as a viscous oil. The ^{1}H NMR showed it to be pure (20.2 g, 92%), and it was used without any further purification: ^{1}H NMR ($CDCl_3$) δ 7.38−7.20 (m, 5 H), 3.63 (s, 3 H), 3.08−3.01 (m, 2 H), 2.80−2.71 (m, 2 H), 2.55−2.50 (m, 2 H), 1.86−1.79 (m, 2 H).

(b) (4-(Methoxycarbonyl)-4-phenylpiperidin-1-yl)propylamine (23). A mixture of **21** (8.5 g, 0.039 mol), 3-bromopropylamine hydrobromide (12.7 g, 0.058 mol), K_2CO_3 (13.475 g, 0.0957 mol), and KI (3.24 g, 0.0195 mol) in 1,4-dioxane (200 mL) was stirred and refluxed for 24 h. Dioxane was evaporated under vacuum; the residue was treated with ice-cold 6 N NaOH (400 mL) and extracted with CH_2Cl_2 (4 × 120 mL). Solvent was evaporated from the

combined dried (K_2CO_3) CH_2Cl_2 extracts, and the residue was purified by column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (20:2:1) as the eluent to afford the product as a viscous oil (7.8 g, 72%): ^{1}H NMR ($CDCl_3$) δ 7.58−7.19 (m, 5 H), 5.26 (br s, 2 H, NH_2), 3.78 (s, 3 H), 2.98−2.60 (m, 4 H), 2.57−2.53 (m, 2 H), 2.43−2.39 (m, 2 H), 2.16−2.03 (m, 2 H), 1.98−1.92 (m, 2 H), 1.70−1.67 (m, 2 H).

3-[4-(2-Cyanoethoxycarbonyl)-4-phenylpiperidin-1-yl]-propylamine (32). (a) 1-*N*-(*tert*-Butoxycarbonyl)-3-[4-(2-cyanoethoxycarbonyl)-4-phenylpiperidin-1-yl]propylamine (31). A mixture of acid **25** (0.7 g, 1.93 mmol), EDC (0.925 g, 4.83 mmol), DMAP (0.59 g, 4.83 mmol), and 2-cyanoethanol (0.527 g, 7.72 mmol) in CH_2Cl_2 (15 mL) was refluxed for 16 h. The mixture was cooled to room temperature, diluted with more CH_2Cl_2 (150 mL), washed with aqueous NH_4-Cl solution (3 × 50 mL), and dried ($MgSO_4$). Solvent was evaporated, and the residue was purified by column chromatography on silica gel using $CHCl_3$−MeOH (9:1) as the eluent to give the product as a colorless oil (0.8 g, 99%): ^{1}H NMR (CD_3OD) δ 7.40−7.20 (m, 5 H), 5.50 (br s, 1 H, NH), 4.24 (t, J = 6.8 Hz, 2 H), 3.20−3.05 (m, 2 H), 2.92−2.80 (m, 2 H), 2.70−2.55 (m, 2 H), 2. 36 (t, J = 6.8 Hz, 2 H), 2.22−2.05 (m, 2 H), 2.05−1.95 (m, 2 H), 1.75−1.58 (m, 2 H), 1.37 (s, 9 H).

(b) 3-[4-(2-Cyanoethoxycarbonyl)-4-phenylpiperidin-1-yl]propylamine (32). To a well-stirred solution of compound **31** (0.8 g, 1.93 mmol) in methanol (10 mL) at 0 °C was added aqueous 6 N HCl (10 mL), and the mixture was allowed to warm to room temperature. After 3 h, the solvent was evaporated and the residue purified by column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (10:2:1) as the eluent to afford the product as a white solid (0.51 g, 68%): ^{1}H NMR (CD_3OD) δ 7.42−7.20 (m, 5 H), 4.22 (t, J = 6 Hz, 2 H), 3.08−2.75 (m, 4 H), 2.20−2.10 (m, 2 H), 2.10−1.90 (m, 2 H).

Preparation of Dihydropyridinecarboxylic Acids. 5-Carboxamido-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3-carboxylic Acid (42). Prepared by following the procedure described in Scheme 2; experimental described elsewhere.[15]

5-(*N*-Methylcarboxamido)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3-carboxylic Acid (43). (a) *N*1-Methyl-(*Z*)-2-acetyl-3-(4-nitrophenyl)-2-propenamide (36). A mixture of 4-nitrobenzaldehyde (**33**; 15.49 g, 10.24 mmol), *N*-methyl-2,4-dioxobutanamide (**34**; 11.8 g, 10.24 mmol), acetic acid (31 mg, 0.5 mmol), and piperidine (44 mg, 0.5 mmol) in 2-propanol (200 mL) was stirred at room temperature for 48 h. Solvent was evaporated, and the crude product was used in the next step without further purification.

(b) 3-(2-Cyanoethoxycarbonyl)-5-(*N*-methylcarboxamido)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine (40). A mixture of *N*1-methyl-(*Z*)-2-acetyl-3-(4-nitrophenyl)-2-propenamide (**36**; 8.5 g, 34.24 mmol) and 2-cyanoethyl 3-amino-2-butenoate (**38**; 5.8 g, 37.67 mmol) in ethanol (200 mL) was heated under reflux for 12 h. Solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica gel using chloroform−ethyl acetate (19:1) as the eluent (9.24 g, 70%).

(c) 5-(*N*-Methylcarboxamido)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3-carboxylic Acid (43). To a stirred solution of compound **40** (12.06 g, 31.37 mmol) in acetone (200 mL) at −5 to 0 °C was added aqueous NaOH (1 N, 94 mL, 94 mmol) dropwise, and the stirring was continued for 3 h. Then most of the acetone was evaporated under reduced pressure. The residue was treated with aqueous 1 N HCl to adjust the pH to 3−4. The yellow solid that formed was filtered, washed with cold water (20 mL), and dried (9.46 g, 91%).

5-Acetyl-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3-carboxylic Acid (44). Prepared using a similar procedure described above.

3-(2-Cyanoethoxycarbonyl)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-5-carboxylic Acid (45). (a) 2-Cyanoethyl 2-Acetyl-3-(4-nitrophenyl)-2-propenoate (37). A mixture of 4-nitrobenzaldehyde (**33**; 20 g, 13.23 mmol), 2-cyanoethyl 2,4-dioxobutanoate (**35**; 22.6 g, 14.55 mmol), acetic acid (396 mg, 6.6 mmol), and piperidine (563 mg, 6.6 mmol) in 2-propanol (200 mL) was stirred at room temperature for 48 h. The pale-yellow precipitate that formed was filtered and dried (35.7 g, 96%). The ^{1}H NMR showed this product to be a mixture of *Z* and *E* isomers.

3-(2-Cyanoethoxycarbonyl)-5-(benzyloxycarbonyl)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine (41). A mixture of **37** (30 g, 106 mmol) and benzyl 3-amino-2-butenoate (**39**; 23.21 g, 121 mmol) in ethanol (300 mL) was heated under reflux for 24 h. Solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica gel using chloroform−ethyl acetate (19:1) as the eluent (43 g, 88%).

(c) 3-(2-Cyanoethoxycarbonyl)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-5-carboxylic Acid (45). To a stirred solution of compound **41** (3.0 g, 6.55 mmol) in 4% formic acid in methanol (100 mL) at −5 to 0 °C was added 10% palladium on charcoal (1.8 g) carefully, and the stirring was continued until all the starting material disappeared as monitored by TLC (3 h). The catalyst was removed by filtration and washed with chloroform (200 mL). Solvents were evaporated from the combined filtrate to leave the product as a yellow solid (2.19 g, 90%).

Preparation of Final Products. 5-Carboxamido-1,4-dihydro-2,6-dimethyl-3-{*N*-[3-(4-methyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine Hydrochloride Hydrate (46). A mixture of 5-carboxamido-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3-carboxylic acid (**42**; 148 mg, 0.465 mmol), EDC (149 mg, 0.776 mmol, 1.67 equiv), and DMAP (69.5 mg, 0.569 mmol) in anhydrous CH_2Cl_2 (15 mL) was stirred at room temperature under argon for 1 h. A solution of 3-(aminopropyl)-4-methyl-4-phenylpiperidine (**13**; 120 mg, 0.517 mmol) in CH_2Cl_2 (5 mL) was injected, and stirring was continued at reflux for 6 h. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (120 mL), and washed with saturated aqueous NH_4Cl (3 × 35 mL). The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (SiO_2, $CHCl_3$−MeOH−2 M NH_3 in MeOH, 100:3:1.5 to 100:4:2) to afford 135 mg (54%) of **46** free base as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3 H), 1.57 (m, 4 H), 1.85 (m, 2 H), 2.03 (s, 3 H), 2.25 (s, 3 H), 2.31 (m, 6 H), 3.18 (m, 1 H), 3.39 (m, 1 H), 4.94 (s, 1 H), 5.41 (br s, 2 H), 5.54 (br s, 1 H), 7.22 (m, 5 H), 7.41 (d, J = 9 Hz, 2 H), 8.06 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.73, 19.70, 25.49, 36.47, 37.55, 40.21, 43.24, 50.64, 50.91, 58.11, 102.81, 108.49, 124.62, 126.15, 126.47, 128.71, 129.06, 135.33, 142.84, 147.31, 149.00, 153.25, 169.10, 170.78. To a solution of this product (132 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) and MeOH (1 mL) was added HCl in ether (1.0 M, 0.5 mL, 2.0 equiv). After removal of the solvents, the residue was dissolved in CH_2Cl_2 (4 mL) and MeOH (1 mL) and added dropwise to ether (30 mL) with swirling to give, after filtration, 110 mg of yellow solid: mp 178 °C dec. Anal. ($C_{30}H_{37}N_5O_4$·HCl·1.4H_2O) C, H, N.

3-{*N*-[3-(4-Acetyl-4-phenylpiperidin-1-yl)propyl]carboxamido}-5-carboxamido-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine Hydrochloride Sesquihydrate (47). Prepared from the acid **42** (200 mg, 0.63 mmol) and 4-acetyl-1-(3-aminopropyl)-4-phenylpiperidine (**14**; 197 mg, 0.756 mmol) using a similar procedure described earlier to afford 220 mg (62%) of **47** free base as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 2 H), 1.89 (s, 3 H), 2.18 (s, 3 H), 2.15−2.30 (m, 2 H), 2.24 (s, 3 H), 2.40−2.65 (m, 8 H), 2.91 (m, 2 H), 3.25 (m, 2 H), 3.37 (m, 1 H), 5.12 (s, 1 H), 5.75 (s, 1 H), 7.20−7.47 (m, 5 H), 7.51 (d, J = 9 Hz, 2 H), 8.06 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.58, 18.96, 24.26, 25.45, 30.94 (br), 37.32, 41.80, 50.29, 53.53 (br), 55.51, 103.34, 105.45, 123.87, 126.08, 127.90, 128.26, 129.35, 138.00, 139.50, 141.63, 146.62, 152.98, 168.66, 170.21, 208.57. To a solution of this product in CH_2Cl_2 (10 mL) was added HCl in ether (1.0 M, 0.5 mL, 1.3 equiv). After removal of the solvents, the residue was dissolved in CH_2Cl_2 (5 mL) and added dropwise to ether (30 mL) with swirling to give, after filtration, 190 mg of **47** hydrochloride sesquihy-

drate (yellow solid): mp 177 °C dec. Anal. ($C_{31}H_{37}N_5O_5$·HCl·1.5H_2O·0.1Et_2O) C, H, N.

5-Carboxamido-1,4-dihydro-3-{*N*-[3-(4-hydroxy-4-phenylpiperidin-1-yl)propyl]carboxamido}-2,6-dimethyl-4-(4-nitrophenyl)pyridine Hydrochloride Hydrate (48). Prepared from acid **42** (200 mg, 0.63 mmol) and 1-(3-aminopropyl)-4-hydroxy-4-phenylpiperidine (**15;** 177 mg, 0.756 mmol) and obtained 145 mg (43%) of **48** free base as a yellow solid: ^{1}H NMR (CD_3OD) δ 1.65 (m, 4 H), 2.05 (s, 3 H), 2.13 (m, 2 H), 2.14 (s, 3 H), 2.35 (m, 2 H), 2.52 (m, 2 H), 2.75 (m, 2 H), 3.19 (br t, J = 6 Hz, 2 H), 5.02 (s, 1 H), 7.19 (t, J = 6 Hz, 1 H), 7.30 (t, J = 6 Hz, 2 H), 7.44 (m, 4 H), 8.08 (dm, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, CD_3OD) δ 16.76, 17.26, 26.28, 37.74, 38.00, 43.51, 46.78, 56.35, 70.52, 103.45, 105.85, 123.83, 124.91, 127.07, 128.46, 128.92, 137.60, 140.79, 147.11, 148.96, 153.95, 171.22, 173.48. To a solution of this product in CH_2Cl_2 (10 mL) was added HCl in ether (1.0 M, 0.5 mL, 1.3 equiv). After removal of the solvents, the residue was dissolved in CH_2Cl_2 (5 mL) and added dropwise to ether (30 mL) with swirling to give, after filtration, 130 mg of **48** hydrochloride hydrate (yellow solid): mp 159 °C dec. Anal. ($C_{29}H_{35}N_5O_5$·HCl·1.9H_2O) C, H, N.

5-Carboxamido-3-{*N*-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]carboxamido}-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine Hydrochloride Sesquihydrate (49). Prepared from acid **42** (200 mg, 0.63 mmol) and 1-(3-aminopropyl)-4-cyano-4-phenylpiperidine (**16**; 184 mg, 0.756 mmol) as described earlier to afford 220 mg (64%) of **49** free base as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.59 (quint, J = 6 Hz, 2 H), 1.87 (qm, J = 12, 3 Hz, 2 H), 1.97 (m, 2 H), 2.07 (s, 3 H), 2.20 (s, 3 H), 2.35 (m, 4 H), 2.83 (br dd, J = 26, 12 Hz, 2 H), 3.25 (m, J = 6 Hz, 2 H), 4.91 (s, 1 H), 5.60 (s, 2 H), 6.10 (s, 1 H), 6.34 (t, J = 6 Hz, 1 H), 7.28−7.45 (m, 7 H), 8.01 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.69, 19.47, 26.64, 36.98, 39.33, 43.13, 51.20, 51.44, 57.05, 103.50, 107.41, 122.56, 124.58, 126.16, 128.76, 128.85, 129.70, 136.87, 140.44, 142.01, 147.24, 153.49, 169.14, 171.08. To a solution of this product (210 mg, 0.387 mmol) in CH_2Cl_2 (10 mL) was added HCl in ether (1.0 M, 0.5 mL, 1.3 equiv). After removal of the solvents, the residue was dissolved in CH_2Cl_2 (5 mL) and added dropwise to ether (30 mL) with swirling to give, after filtration, 200 mg of **49** hydrochloride sesquihydrate (yellow solid): mp 182 °C dec. Anal. ($C_{30}H_{34}N_6O_4$·HCl·1.5H_2O) C, H, N.

2,6-Dimethyl-1,4-dihydro-3-{*N*-[(4-(*N*,*N*-dimethylcarboxamido)-4-phenylpiperidin-1-yl)propyl]carboxamido}-5-carboxamido-4-(4-nitrophenyl)pyridine (50). Prepared from acid **42** (0.186 g, 0.585 mmol) and 3-(4-(*N*,*N*-dimethylaminocarbonyl)-4-phenylpiperidin-1-yl)propylamine hydrochloride (**27**; 0.212 g, 0.585 mmol) following a similar procedure described above to afford the product as a yellow powder (0.160 g, 47%): mp 142−143 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J = 8.6 Hz, 2 H), 7.40 (d, J = 8.6 Hz, 2 H), 7.40−7.15 (m, 6 H), 5.40 (br m, 2 H, NH2), 4.98 (s, 1 H), 3.46−3.15 (m, 2 H), 2.80−2.40 (m, 4 H), 2.40−2.20 (m, 2 H), 2.30 (s, 6 H), 2.05 (s, 6 H), 2.15−2.00 (m, 2 H), 1.95−1.80 (m, 2 H), 1.70−1.58 (m, 2 H). Anal. ($C_{32}H_{40}N_6O_5$·0.3$CHCl_3$) C, H, N.

3-{[(4-(*N*,*N*-Dimethylaminomethyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-5-(*N*-methylcarboxamido)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine (51). Prepared from 5-(*N*-methylcarboxamido)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3-carboxylic acid (**43**; 0.20 g, 0.60 mmol) and 3-(4-(*N*,*N*-dimethylaminomethyl)-4-phenylpiperidin-1-yl)propylamine (**30**; 0.200 g, 0.725 mmol) using a similar procedure described earlier to get the product as a yellow powder (0.230 g, 65%): mp 117−119 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 8.6 Hz, 2 H), 7.38 (d, J = 8.6 Hz, 2 H), 7.28−7.20 (m, 5 H), 7.05 (br t, 1 H), 5.32 (br s, H, NH), 5.05 (br s, 1 H, NH), 4.89 (s, 1 H), 3.50−3.35 (m, 1 H), 3.20−3.05 (m, 1 H), 2.66 (d, J = 5 Hz, 2 H), 2.40−2.32 (m, 2 H), 2.30−2.20 (m, 2 H), 2.31 (s, 2 H), 2.23 (s, 3 H), 2.03 (s, 3 H), 2.04−1.95 (m, 2 H), 1.92 (s, 6 H), 1.95−1.85 (m, 4 H), 1.70−1.58 (m, 2 H). Anal. ($C_{33}H_{44}N_6O_4$·0.75H_2O) C, H, N.

5-Carboxamido-1,4-dihydro-2,6-dimethyl-3-{*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine (52). Prepared from acid **42** (0.60 g, 1.89 mmol) and 3-(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propylamine (**23**; 0.679 g, 2.457 mmol): yield 0.730 g, 67%; mp 120−121 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 8.6 Hz, 2 H), 7.41 (d, J = 8.6 Hz, 2 H), 7.38−7.23 (m, 5 H), 6.85 (br t, 1 H), 5.22 (br s, H, NH), 5.15 (br s, 2 H, NH_2), 4.87 (s, 1 H), 3.60 (s, 3 H), 3.42−3.17 (m, 2 H), 2.80−2.62 (m, 2 H), 2.60−2.40 (m, 2 H), 2.40−2.20 (m, 2 H), 2.23 (s, 3 H), 2.04 (s, 3 H), 2.04−1.95 (m, 2 H), 1.95−1.85 (m, 2 H), 1.70−1.58 (m, 2 H). Anal. Calcd. for $C_{31}H_{37}N_5O_6$·0.7C_6H_{12}·1.05H_2O: C, 64.70; H, 7.33; N, 10.72. Found: C, 64.71; H, 7.25; N, 10.50.

5-Carboxamido-1,4-dihydro-2,6-dimethyl-3-{*N*-[(4-(ethoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine (53). Prepared from acid **42** (0.60 g, 1.89 mmol) and 3-(4-(ethoxycarbonyl)-4-phenylpiperidin-1-yl)propylamine (**22**; 0.714 g, 2.46 mmol): yield 0.660 g, 59.3%; mp 118−120 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 8.6 Hz, 2 H), 7.41 (d, J = 8.6 Hz, 2 H), 7.38−7.23 (m, 5 H), 6.85 (br t, 1 H), 5.28 (br s, 1 H, NH), 5.15 (br s, 2 H, NH_2), 4.87 (s, 1 H), 4.05 (q, J = 7.2 Hz, 2 H), 3.45−3.17 (m, 2 H), 2.80−2.62 (m, 2 H), 2.58−2.40 (m, 2 H), 2.40−2.20 (m, 2 H), 2.23 (s, 3 H), 2.03 (s, 3 H), 2.04−1.95 (m, 2 H), 1.90−1.65 (m, 2 H), 1.65−1.50 (m, 2 H), 1.12 (t, J = 7.1 Hz, 3 H). Anal. ($C_{32}H_{32}N_5O_6$·0.5C_6H_{12}·0.5H_2O) C, H, N.

5-Carboxamido-1,4-dihydro-2,6-dimethyl-3-{*N*-[(4-(2-methoxyethoxy)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine (56). (a) 5-Carboxamido-1,4-dihydro-2,6-dimethyl-3-{*N*-[(4-(2-cyanoethoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine (54). Prepared from acid **42** (0.415 g, 1.31 mmol) and 3-[4-(2-cyanoethoxycarbonyl)-4-phenylpiperidin-1-yl]propylamine (**32**; 0.508 g, 1.31 mmol) using a similar procedure described earlier: yield 0.487 g, 61%; mp 99−101 °C; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, J = 8.6 Hz, 2 H), 7.41 (d, J = 8.6 Hz, 2 H), 7.38−7.22 (m, 5 H), 6.80 (br t, 1 H), 5.40 (br s, 1 H, NH), 5.20 (br s, 2 H, NH_2), 4.85 (s, 1 H), 4.05 (m, 2 H), 3.40−3.15 (m, 2 H), 2.60 (t, J = 6 Hz, 2 H), 2.60−2.20 (m, 4 H), 2.23 (s, 3 H), 2.05 (s, 3 H), 1.90−1.75 (m, 4 H), 1.65−1.50 (m, 2 H). Anal. ($C_{33}H_{38}N_6O_6$·0.55C_6H_{12}) C, H, N.

(b) 5-Carboxamido-3-{*N*-[(4-carboxy-4-phenylpiperidin-1-yl)propyl]carboxamido}-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine (55). To a solution of **54** (0.394 g, 0.64 mmol) in dioxane (2 mL) at 0 °C was added aqueous 1 N NaOH (1.95 mL) slowly, and the mixture was allowed to warm to room temperature. After 1 h, the mixture was concentrated to half the volume, and the pH was adjusted carefully to 5−6. The yellow precipitate formed was filtered and dried (0.25 g, 70%): ^{1}H NMR (CD_3OD) δ 8.09 (d, J = 8.8 Hz, 2 H), 7.40 (d, J = 8.68 Hz, 2 H), 7.40−7.15 (m, 5 H), 4.86 (s, 1 H), 3.40−3.15 (m, 4 H), 3.05−2.90 (m, 2 H), 2.90−2.75 (m, 2 H), 2.70−2.55 (m, 2 H), 2.07 (br s, 6 H), 2.04−1.70 (m, 4 H).

(c) 5-Carboxamido-1,4-dihydro-2,6-dimethyl-3-{*N*-[(4-(2-methoxyethoxy)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine (56). A mixture of compound **55** (0.080 g, 0.142 mmol), EDC (0.0546 g, 0.284 mmol), DMAP (0.0347 g, 0.284 mmol), and 2-methoxyethanol (0.0324 g, 0.426 mmol) in CH_2Cl_2 (15 mL) was stirred and refluxed for 14 h and cooled. The reaction mixture was diluted to 50 mL with CH_2Cl_2, washed with saturated NH_4Cl solution (3 × 10 mL), and dried ($MgSO_4$). Solvent was evaporated from the CH_2Cl_2 solution, and the product was purified by flash column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (100:4:2) as the eluent to afford the product as a yellow powder (0.032 g, 36%): mp 79−80 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (d, J = 8.6 Hz, 2 H), 7.39 (d, J = 8.6 Hz, 2 H), 7.30−7.20 (m, 5 H), 7.15 (br s, 2 H, NH2), 7.00 (br t, 1 H, NH), 5.95 (br s, 1 H, NH), 4.66 (s, 1 H), 4.20 (br t, 2 H), 3.45 (br t, 2 H), 3.23 (s, 3 H), 3.25−3.05 (m, 2 H), 2.80−2.40 (m, 4 H), 2.40−2.20 (m, 2 H), 2.09 (s, 3 H), 1.98 (s, 3 H), 2.04−1.95 (m, 2 H), 1.90−1.65 (m, 2 H), 1.65−1.55 (m, 2 H). Anal. ($C_{33}H_{41}N_5O_7$) C, H, N.

5-Carboxamido-1,4-dihydro-2,6-dimethyl-3-{*N*-[(4-(2-hydroxyethoxy)-4-phenylpiperidin-1-yl)propyl]carboxa-

mido}-4-(4-nitrophenyl)pyridine (57). Prepared from **55** (0.055 g, 0.098 mmol), EDC (0.0375 g, 0.196 mmol), DMAP (0.024 g, 0.196 mmol), and ethylene glycol (0.0182 g, 0.294 mmol) using a similar procedure described earlier to afford the product as a yellow powder (0.038 g, 64%): mp 116−118 °C; ^{1}H NMR (CD_3OD) δ 8.02 (d, J = 8.6 Hz, 2 H), 7.36 (d, J = 8.6 Hz, 2 H), 7.30−7.20 (m, 5 H), 4.83 (s, 1 H), 4.15 (br t, 2 H), 3.65 (br t, 2 H), 3.25−3.05 (m, 2 H), 2.80−2.40 (m, 4 H), 2.40−2.20 (m, 2 H), 2.13 (s, 3 H), 2.00 (s, 3 H), 2.04−1.95 (m, 2 H), 1.90−1.65 (m, 2 H), 1.65−1.55 (m, 2 H). Anal. ($C_{32}H_{39}N_5O_7$·0.6$CHCl_3$) C, H, N.

5-Carboxamido-1,4-dihydro-2,6-dimethyl-3-{*N*-[(4-(phenoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine (58). Prepared from **55** (0.050 g, 0.098 mmol), EDC (0.0375 g, 0.196 mmol), DMAP (0.024 g, 0.196 mmol), and phenol (0.028 g, 0.294 mmol) using a similar procedure described earlier to afford the product as a yellow powder (0.048 g, 77%): mp 121−122 °C; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, J = 8.6 Hz, 2 H), 7.42 (d, J = 8.6 Hz, 2 H), 7.30−7.10 (m, 8 H), 6.95−6.80 (d, J = 7.5 Hz, 2 H), 6.75 (br t, 1 H, NH), 5.30 (br s, 1 H, NH), 5.18 (br s, 2 H, NH_2), 4.88 (s, 1 H), 3.45−3.05 (m, 2 H), 2.95−2.60 (m, 4 H), 2.40−2.15 (m, 4 H), 2.22 (s, 3 H), 2.06 (s, 3 H), 1.95−1.75 (m, 2 H), 1.75−1.55 (m, 2 H). Anal. ($C_{36}H_{39}N_5O_6$·0.35$CHCl_3$) C, H, N.

2,6-Dimethyl-1,4-dihydro-3-{*N*-[(4-(ethoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-5-(*N*-methylcarboxamido)-4-(4-nitrophenyl)pyridine (59). Prepared from carboxylic acid **43** (0.450 g, 1.36 mmol), EDC (0.520 g, 2.72 mmol), DMAP (0.286 g, 2.34 mmol), and 3-(4-(ethoxycarbonyl)-4-phenylpiperidin-1-yl)propylamine (**22**; 0.473 g, 1.63 mmol) in CH_2Cl_2 (75 mL) to afford the product as a yellow powder (0.60 g, 73%): mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 8.6 Hz, 2 H), 7.39 (d, J = 8.6 Hz, 2 H), 7.30−7.23 (m, 5 H), 6.78 (br t, 1 H), 5.36 (br s, 1 H, NH), 5.27 (s, 1 H), 4.84 (s, 1 H), 4.07 (q, J = 7.2 Hz, 2 H), 3.40−3.17 (m, 2 H), 2.80−2.62 (m, 2 H), 2.66 (d, J = 4.5 Hz, 3 H), 2.60−2.40 (m, 2 H), 2.40−2.20 (m, 2 H), 2.16 (s, 3 H), 2.04 (s, 3 H), 2.04−1.95 (m, 2 H), 1.95−1.85 (m, 2 H), 1.70−1.58 (m, 2 H), 1.16 (t, J = 7 Hz, 3 H). Anal. $C_{33}H_{41}N_5O_6$·0.075hexane·0.75H_2O) C, H, N.

1,4-Dihydro-2,6-dimethyl-3-[[3-(4-phenylpiperidin-1-yl)propyl]aminocarbonyl]-5-*N*-methylcarboxamido)-4-(4-nitrophenyl)pyridine Hydrochloride Hemihydrate (60). Prepared from carboxylic acid **43** (0.205 g, 0.386 mmol), EDC (0.280 g, 1.45 mmol), DMAP (0.267 g, 2.19 mmol), and 3-(4-phenylpiperidin-1-yl)propylamine (**18**; 0.148 g, 0.535 mmol) in CH_2Cl_2 (40 mL) to afford the product as a yellow powder (0.140 g, 68%). The product was converted to the HCl salt by treatment with 1 N HCl in ether: mp 165−166 °C; ^{1}H NMR (CDCl3) δ 8.05 (d, J = 8.6 Hz, 2 H), 7.42 (d, J = 8.6 Hz, 2 H), 7.30−7.23 (m, 5 H), 6.95 (br t, 1 H), 5.45 (s, 1 H), 5.42 (br s, 1 H, NH), 4.94 (s, 1 H), 3.45−3.17 (m, 2 H), 3.00−2.95 (m, 1 H), 2.80−2.62 (m, 2 H), 2.68 (d, J = 4.5 Hz, 3 H), 2.60−2.40 (m, 2 H), 2.40−2.20 (m, 2 H), 2.24 (s, 3 H), 2.12 (s, 3 H), 2.04−1.95 (m, 2 H), 1.95−1.85 (m, 2 H), 1.70−1.58 (m, 2 H). Anal. ($C_{30}H_{38}N_5O_4Cl$·0.5H_2O) C, H, N.

1,4-Dihydro-2,6-dimethyl-3-{*N*-[(4-(ethoxycarbonyl)piperidin-1-yl)propyl]carboxamido}-5-(*N*-methylcarboxamido)-4-(4-nitrophenyl)pyridine (61). Prepared from carboxylic acid 43 (0.331 g, 1.0 mmol), EDC (0.383 g, 2.0 mmol), DMAP (0.183 g, 1.5 mmol), and amine 17 (0.257 g, 1.2 mmol) in CH_2Cl_2 (20 mL) to afford the product as a yellow powder (0.478 g, 91%): mp 119−121 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8.6 Hz, 2 H), 7.40 (d, J = 8.6 Hz, 2 H), 6.75 (br t, 1 H), 5.36 (br s, 1 H, NH), 4.84 (s, 1 H), 4.05 (q, J = 7.2 Hz, 2 H), 3.40−3.17 (m, 2 H), 3.05−3.00 (m, 1 H), 2.80−2.62 (m, 2 H), 2.66 (d, J = 4.5 Hz, 3 H), 2.60−2.40 (m, 2 H), 2.40−2.20 (m, 1 H), 2.15 (s, 3 H), 2.04 (s, 3 H), 2.04−1.95 (m, 2 H), 1.95−1.85 (m, 2 H), 1.70−1.58 (m, 2 H), 1.15 (t, J = 7.2 Hz, 3 H). Anal. ($C_{32}H_{39}N_5O_6$·0.3$C_4H_{10}O$·0.9H_2O) C, H, N.

5-Carboxamido-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)-3-{*N*-[3-(piperidin-1-yl)propyl]carboxamido}-pyridine (62). To a mixture of carboxylic acid **42** (212 mg, 0.668 mmol, 1.00 equiv), EDC (195 mg, 1.02 mmol, 1.52 equiv), and DMAP (91 mg, 0.74 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (3 mL) was added a solution of 1-(3-aminopropyl)piperidine[17] (115.9 mg, 0.815 mmol, 1.22 equiv) in CH_2Cl_2 (3.7 mL), and the mixture was stirred at room temperature under argon for 20 h. Aqueous NaOH (1 M, 50 mL) was added, and the mixture was extracted with CH_2Cl_2−2-propanol (3:1, 3 × 50 mL). The combined organic solutions were dried over Na_2SO_4 and concentrated to give 635.7 mg of dark-brown oil. This oil was purified by flash chromatography (SiO_2, Cl_3CCH_3−MeOH−methanolic ammonia (2 M), 70:15:15) to afford 385 mg of yellow oil. This yellow oil was further purified by HPLC with a 25- × 300-mm Waters NovaPak 6-μm SiO_2 radial compression column and UV detection at 252 nm. The column was eluted with the following gradient at 25 mL/min: initial conditions CH_2Cl_2/(CH_2Cl_2−MeOH−Et_2NH, 93.8:6:0.2), 50:50, duration 30 min, ramped to 13:87 over 30 min. The pure product was obtained as a yellow solid: 167.4 mg (56%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (br, 6 H), 1.59 (m, 2 H), 2.12 (s, 3 H), 2.20 (m, 6 H), 2.33 (s, 3 H), 3.20 (m, 1 H), 3.45 (m, J = 5.7 Hz, 1 H), 5.02 (s, 1 H), 5.40 (br s, 2 H), 7.48 (d, J = 8.7 Hz, 2 H), 8.13 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.83, 19.80, 24.57, 25.26, 26.30, 40.09, 43.21, 55.00, 58.55, 102.95, 108.31, 135.54, 142.81, 147.33, 153.30, 169.07, 170.74; mp 170 °C. Anal. ($C_{23}H_{31}N_5O_4$·0.1CH_2Cl_2) C, H, N.

1,4-Dihydro-2,6-dimethyl-3-{*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-5-(*N*-methylcarboxamido)-4-(4-nitrophenyl)pyridine (63). Prepared from acid **43** (0.4839 g, 1.46 mmol), EDC (0.560 g, 2.92 mmol), DMAP (0.267 g, 2.19 mmol), and amine **23** (0.444 g, 1.607 mmol) in CH_2Cl_2 (40 mL) to afford the product as a yellow powder (0.605 g, 70.3%): mp 122−123 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8.6 Hz, 2 H), 7.39 (d, J = 8.6 Hz, 2 H), 7.30−7.23 (m, 5 H), 6.75 (br t, 1 H), 5.36 (br s, 1 H, NH), 4.84 (s, 1 H), 3.59 (s, 3 H), 3.40−3.17 (m, 2 H), 2.80−2.62 (m, 2 H), 2.66 (d, J = 4.5 Hz, 3 H), 2.60−2.40 (m, 2 H), 2.40−2.20 (m, 2 H), 2.15 (s, 3 H), 2.04 (s, 3 H), 2.04−1.95 (m, 2 H), 1.95−1.85 (m, 2 H), 1.70−1.58 (m, 2 H). Anal. ($C_{32}H_{39}N_5O_6$·0.3$C_4H_{10}O$·0.9H_2O) C, H, N.

The (+)- and (−)-enantiomers of this compound were obtained by resolving the intermediate 3-(2-cyanoethoxycarbonyl)-5-(*N*-methylcarboxamido)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine (**40**) by HPLC on a Chiralpack AS column (20 × 250 mm, Daicel) using hexanes−ethyl acetate (80:20) as eluent under UV detection at 300 nm. These resolved intermediates were used to synthesize the final products using the experimental conditions described for the racemate. The first peak (t_R = 13.4 min) of the intermediate upon completion of the sequence of the reactions described above gave the (+)-enantiomer of **63**, $[\alpha]_D$ = +3.85 (c = 4.25, chloroform), and the second peak (t_R = 84 min) gave the (−)-enantiomer of **63**, $[\alpha]_D$ = −3.25 (c = 6.44, chloroform).

2,6-Dimethyl-1,4-dihydro-3-{*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-5-(2-cyanoethoxycarbonyl)-4-(4-nitrophenyl)pyridine (64). A mixture of 5-(2-cyanoethoxycarbonyl)-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3-carboxylic acid (**45**; 1.568 g, 4.22 mmol), EDC (1.62 g, 8.44 mmol), DMAP (1.03 g, 8.44 mmol), and 3-(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propylamine (**23**; 1.4 g, 5.06 mmol) in CH_2Cl_2 (300 mL) was stirred and refluxed for 12 h. The mixture was cooled to room temperature, diluted to 190 mL with CH_2Cl_2, washed with saturated NH_4Cl solution (3 × 140 mL), and dried ($MgSO_4$). Solvent was evaporated from the CH_2Cl_2 solution, and the product was purified by flash column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (100:4:2) as the eluent to afford the product as a yellow powder (1.76 g, 66%): mp 73−74 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 8.6 Hz, 2 H), 7.39 (d, J = 8.6 Hz, 2 H), 7.30−7.20 (m, 5 H), 6.80 (br t, 1 H, NH), 5.62 (br s, 1 H, NH), 4.91 (s, 1 H), 4.10 (q, J = 6.5 Hz, 2 H), 3.60 (s, 3 H), 3.42−3.15 (m, 2 H), 2.80−2.40 (m, 6 H), 2.40−2.20 (m, 2 H), 2.28 (s, 3 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 2.04−1.95 (m, 2 H), 1.90−1.65 (m, 2 H), 1.65−1.55 (m, 2 H). Anal. ($C_{33}H_{39}N_5O_7$·1.25H_2O·0.25CH_2Cl_2) C, H, N.

1,4-Dihydro-2,6-dimethyl-3-{*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine-5-carboxylic Acid (65). To a well-stirred solution of **64** (1.70 g, 2.70 mmol) in dioxane (15 mL) at 0 °C was added aqueous 1 N NaOH (5.4 mL), and the stirring was continued. After 30 min, aqueous 1 N HCl was added to the reaction mixture and the pH adjusted to 6−7. The yellow precipitate formed was filtered and dried under vacuum (1.35 g, 86%): mp 139−141 °C; ^{1}H NMR (CD_3OD) δ 8.03 (d, J = 8.6 Hz, 2 H), 7.43 (d, J = 8.6 Hz, 2 H), 7.30−7.20 (m, 5 H), 5.02 (s, 1 H), 3.60 (s, 3 H), 3.20−3.15 (m, 2 H), 3.00−2.80 (m, 2 H), 2.60−2.40 (m, 2 H), 2.40−2.20 (m, 4 H), 2.21 (s, 3 H), 2.04 (s, 3 H), 2.00−1.85 (m, 2 H), 1.70−1.60 (m, 2 H). Anal. ($C_{31}H_{37}N_4O_7$·0.4$CHCl_3$·1.6H_2O) C, H, N.

1,4-Dihydro-2,6-dimethyl-5-(*N*-ethylcarboxamido)-3-{*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)-propyl]carboxamido}-4-(4-nitrophenyl)pyridine (66). A mixture of carboxylic acid **65** (0.70 g, 1.222 mmol), EDC (0.469 g, 2.445 mmol), DMAP (0.299 g, 2.445 mmol), and 70% aqueous ethylamine (0.275 g, 4.277 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 14 h, diluted to 150 mL with CH_2Cl_2, washed with saturated NH_4Cl solution (3 × 40 mL), and dried ($MgSO_4$). Solvent was evaporated from the CH_2Cl_2 solution, and the product was purified by flash column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (100:4:2) as the eluent to afford the product as a yellow powder (0.36 g, 41.5%): mp 117−118 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8.6 Hz, 2 H), 7.40 (d, J = 8.6 Hz, 2 H), 7.30−7.20 (m, 5 H), 6.65 (br t, 1 H), 5.37 (s, 1 H), 5.35 (br t, 1 H, NH), 4.85 (s, 1 H), 3.59 (s, 3 H), 3.40−3.11 (m, 4 H), 2.80−2.40 (m, 4 H), 2.40−2.20 (m, 2 H), 2.12 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.04−1.95 (m, 2 H), 1.90−1.65 (m, 2 H), 1.65−1.55 (m, 2 H), 0.95 (t, J = 7.0 Hz, 3 H). Anal. ($C_{33}H_{41}N_5O_6$.0.25 C_6H_{12}·0.05CH_2Cl_2·0.25H_2O) C, H, N.

1,4-Dihydro-2,6-dimethyl-5-(methoxycarbonyl)-3-{*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]-carboxamido}-4-(4-nitrophenyl)pyridine (67). Prepared from acid **65** (0.10 g, 0.174 mmol), EDC (0.0666 g, 0.347 mmol), DMAP (0.0424 g, 0.347 mmol), and methanol (1 mL) in CH_2-Cl_2 (40 mL) using an analogous method to afford the product as a yellow powder (0.045 g, 44%): mp 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 8.6 Hz, 2 H), 7.36 (d, J = 8.6 Hz, 2 H), 7.30−7.20 (m, 5 H), 6.85 (br t, 1 H), 5.68 (br s, H, NH), 4.90 (s, 1 H), 3.60 (s, 3 H), 3.49 (s, 3 H), 3.40−3.15 (m, 2 H), 2.80−2.60 (m, 2 H), 2.60−2.40 (m, 2 H), 2.40−2.20 (m, 2 H), 2.24 (s, 3 H), 2.09 (s, 3 H), 2.04−1.95 (m, 2 H), 1.90−1.65 (m, 2 H), 1.65−1.55 (m, 2 H). Anal. ($C_{33}H_{38}N_4O_7$·0.2C_6H_{12}·0.4H_2O) C, H, N.

1,4-Dihydro-2,6-dimethyl-5-(ethoxycarbonyl)-3-{*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine (68). Prepared from acid **65** (0.10 g, 0.174 mmol), EDC (0.0666 g, 0.347 mmol), DMAP (0.0424 g, 0.347 mmol), and ethanol (1 mL) using a similar procedure described above to afford the product as a yellow powder (0.055 g, 53%): mp 73−75 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 8.6 Hz, 2 H), 7.37 (d, J = 8.6 Hz, 2 H), 7.30−7.20 (m, 5 H), 6.75 (br t, 1 H, NH), 5.76 (br s, 1 H, NH), 4.91 (s, 1 H), 3.95 (q, J = 7 Hz, 2 H), 3.60 (s, 3 H), 3.42−3.15 (m, 2 H), 2.80−2.40 (m, 4 H), 2.40−2.20 (m, 2 H), 2.24 (s, 3 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 2.04−1.95 (m, 2 H), 1.90−1.65 (m, 2 H), 1.65−1.55 (m, 2 H), 1.09 (t, J = 7 Hz, 2 H). Anal. ($C_{33}H_{40}N_4O_7$·0.25C_6H_{12}·0.5H_2O) C, H, N.

1,4-Dihydro-2,6-dimethyl-5-(2-hydroxyethoxycarbonyl)-3-{*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine (69). Prepared from acid **65** (0.10 g, 0.174 mmol), EDC (0.0666 g, 0.347 mmol), DMAP (0.0424 g, 0.347 mmol), and ethylene glycol (1 mL) using a similar procedure described above to afford the product as a yellow powder (0.052 g, 48%): mp 90−91 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8.6 Hz, 2 H), 7.41 (d, J = 8.6 Hz, 2 H), 7.30−7.20 (m, 5 H), 6.95 (br t, 1 H, NH), 5.75 (br s, 1 H, NH), 4.99 (s, 1 H), 4.10−4.0 (br t, 2 H), 3.75−3.60 (br t, 2 H), 3.60 (s, 3 H), 3.42−3.15 (m, 2 H), 2.80−2.40 (m, 6 H), 2.40−2.20 (m, 2 H), 2.28 (s, 3 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 2.04−1.95 (m, 2 H), 1.90−1.65 (m, 2 H), 1.65−1.55 (m, 2 H). Anal. ($C_{33}H_{40}N_4O_8$·0.8H_2O) C, H, N.

5-Acetyl-1,4-dihydro-2,6-dimethyl-3-{*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine (70). Prepared from 5-acetyl-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3-carboxylic acid (**44**; 0.70 g, 2.21 mmol), EDC (0.849 g, 4.43 mmol), DMAP (0.541 g, 4.43 mmol), and 3-(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propylamine (**23**; 0.732 g, 2.65 mmol) using a similar procedure described earlier to afford the product as a yellow powder (0.880 g, 70%): mp 94−95 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 8.6 Hz, 2 H), 7.35 (d, J = 8.6 Hz, 2 H), 7.30−7.20 (m, 5 H), 6.85 (br t, 1 H, NH), 5.52 (br s, 1 H, NH), 5.05 (s, 1 H), 3.59 (s, 3 H), 3.45−3.17 (m, 2 H), 2.80−2.40 (m, 4 H), 2.40−2.20 (m, 2 H), 2.26 (s, 3 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 2.04−1.95 (m, 2 H), 1.90−1.65 (m, 2 H), 1.65−1.55 (m, 2 H). Anal. ($C_{32}H_{38}N_4O_6$·0.4H_2O) C, H, N.

5-Acetyl-1,4-dihydro-2,6-dimethyl-3-{*N*-[(4-(ethoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(4-nitrophenyl)pyridine (71). Prepared from 5-acetyl-1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3-carboxylic acid (**44**; 0.70 g, 2.21 mmol), EDC (0.849 g, 4.43 mmol), DMAP (0.541 g, 4.43 mmol), and 3-(4-ethoxycarbonyl-4-phenylpiperidin-1-yl)propylamine (**22**; 0.770 g, 2.65 mmol) using a similar procedure described above to afford the product as a yellow powder (0.890 g, 68.4%): mp 87−88 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 8.6 Hz, 2 H), 7.35 (d, J = 8.6 Hz, 2 H), 7.35−7.20 (m, 5 H), 6.85 (br t, 1 H, NH), 5.62 (br s, 1 H, NH), 5.05 (s, 1 H), 4.06 (q, J = 7.2 Hz, 2 H), 3.45−3.17 (m, 2 H), 2.80−2.40 (m, 4 H), 2.40−2.20 (m, 2 H), 2.26 (s, 3 H), 2.05 (s, 6 H), 2.04−1.95 (m, 2 H), 1.90−1.65 (m, 2 H), 1.65−1.50 (m, 2 H), 1.12 (t, J = 7.1 Hz, 3 H). Anal. ($C_{33}H_{40}N_4O_6$·0.6H_2O) C, H, N.

2,6-Dimethyl-1,4-dihydro-3-{*N*-[(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-5-acetyl-4-(3,4-methylenedioxyphenyl)pyridine (73). Prepared from 5-acetyl-1,4-dihydro-2,6-dimethyl-4-(3,4-methylenedioxyphenyl)-pyridine-3-carboxylic acid[15] (**72**; 0.150 g, 0.495 mmol), EDC (0.190 g, 1 mmol), DMAP (0.121 g, 1 mmol), and 3-(4-(methoxycarbonyl)-4-phenylpiperidin-1-yl)propylamine (**23**; 0.64 g, 0.594 mmol) to afford the product as a white powder (0.220 g, 76%): mp 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.20 (m, 5 H), 6.70−6.60 (m, 3 H), 6.58 (br t, 1 H, NH), 5.86 (s, 2 H), 5.85 (br s, 1 H, NH), 4.80 (s, 1 H), 3.60 (s, 3 H), 3.45−3.10 (m, 2 H), 2.80−2.65 (m, 1 H), 2.60−2.38 (m, 3 H), 2.35−2.20 (m, 2 H), 2.24 (s, 3 H), 2.06 (s, 3 H), 2.05−1.95 (m, 2 H), 2.00 (s, 3 H), 1.90−1.75 (m, 2 H), 1.60−1.55 (m, 2 H). Anal. ($C_{33}H_{39}N_3O_6$·0.5H_2O·0.1CH_2Cl_2) C, H, N.

2,6-Dimethyl-1,4-dihydro-3-{*N*-[3-(4-(ethoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-5-carboxamido-4-(3,4-methylenedioxyphenyl)pyridine (77). (a) 5-(2-Cyanoethoxycarbonyl)-2,6-dimethyl-1,4-dihydro-3-{*N*-[3-(4(ethoxycarbonyl)4-phenylpiperidin-1-yl)propyl]-carboxamido}-4-(3,4-methylenedioxyphenyl)pyridine (75). Prepared from 5-(2-cyanoethoxycarbonyl)-1,4-dihydro-2,6-dimethyl-4-(3,4-methylenedioxyphenyl)pyridine-3-carboxylic acid[15] (**74**; 1.50 g, 4.05 mmol), EDC (1.55 g, 8.10 mmol), DMAP (0.99 g, 8.1 mmol), and 3-(4-(ethoxycarbonyl)-4-phenylpiperidin-1-yl)propylamine (**22**; 1.41 g, 4.86 mmol) to afford the product as a white powder (2.17 g, 83%): mp 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.18 (m, 5 H), 6.80−6.60 (m, 3 H), 6.28 (br t, 1 H, NH), 5.86 (s, 2 H), 5.45 (br s, 1 H, NH), 4.62 (s, 1 H), 4.20−4.00 (m, 4 H), 3.40−3.10 (m, 2 H), 2.80−2.60 (m, 2 H), 2.60−2.40 (m, 4 H), 2.35−2.20 (m, 2 H), 2.25 (s, 3 H), 2.14 (s, 3 H), 2.05−1.95 (m, 2 H), 1.90−1.75 (m, 2 H), 1.60−1.55 (m, 2 H), 1.14 (t, J = 7 Hz, 3 H). Anal. ($C_{36}H_{42}N_4O_7$·0.9H_2O·0.3hexane) C, H, N.

(b) 2,6-Dimethyl-1,4-dihydro-3-{*N*-[3-(4-(ethoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-4-(3,4-methylenedioxyphenyl)pyridine-5-carboxylic Acid (76). To a stirred solution of compound **75** (2.10 g, 3.26 mmol) in acetone (15 mL) at −5 to 0 °C was added an aqueous solution of NaOH (1 N, 9.8 mL, 9.8 mmol) dropwise, and the stirring was continued for 3 h. Then most of the acetone was evaporated under reduced pressure. The residue was treated with

1 N HCl and the pH adjusted to 3−4. The white solid that formed was filtered, washed with cold water (2 mL), and dried (1.75 g, 91%): mp 118−120 °C; ^{1}H NMR (CD_3OD) δ 7.38−7.20 (m, 5 H), 6.75−6.55 (m, 3 H), 4.60 (s, 1 H), 4.08 (q, J = 7 Hz, 2 H), 3.20−3.10 (m, 2 H), 3.05−2.90 (m, 2 H), 2.60−2.35 (m, 6 H), 2.22 (s, 3 H), 2.10−1.95 (m, 2 H), 2.05 (s, 3 H), 1.85−1.60 (m, 2 H), 1.13 (t, J = 7 Hz, 3 H). Anal. ($C_{33}H_{39}N_3O_7 \cdot 2.0H_2O \cdot 0.4NaCl$) C, H, N.

(c) 2,6-Dimethyl-1,4-dihydro-3-{*N*-[3-(4-(ethoxycarbonyl)-4-phenylpiperidin-1-yl)propyl]carboxamido}-5-carboxamido-4-(3,4-methylenedioxyphenyl)pyridine (77). A mixture of compound **76** (0.120 g, 0.2 mmol), EDC (0.78 g, 0.4 mmol), and DMAP (0.050 g, 0.4 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 2 h; to this was introduced 40% aqueous ammonia (0.2 mL), and the stirring was continued for 14 h. The mixture was washed with saturated aqueous NH_4Cl solution (3 × 20 mL) and dried ($MgSO_4$). Solvent was evaporated from the CH_2Cl_2 solution and the product purified by flash column chromatography on silica gel using $CHCl_3$−MeOH−2 M NH_3 in MeOH (100:4:2) as the eluent to afford the product as a yellow powder (0.056 g, 47%): mp 100−103 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.20 (m, 5 H), 6.80−6.60 (m, 3 H), 5.80 (dd, 2 H), 5.20−5.17 (m, 2 H), 4.60 (s, 1 H), 4.08 (q, J = 7 Hz, 2 H), 3.50−3.30 (m, 1 H), 3.30−3.10 (m, 1 H), 2.80−2.40 (m, 4 H), 2.35−2.20 (m, 2 H), 2.23 (s, 3 H), 2.20−1.95 (m, 2 H), 1.98 (s, 3 H), 1.80−1.60 (m, 2 H), 1.60−1.50 (m, 2 H), 1.13 (t, J = 7 Hz, 3 H). Anal. ($C_{33}H_{40}N_4O_6 \cdot 0.6H_2O$) C, H, N.

Biological Methods. 1. Binding Assays: Equilibrium competition binding assays were performed in membrane preparations from cell lines expressing the recombinant human, rat, and dog α_{1a}, α_{1b}, and α_{1d} adrenoceptors using [^{3}H]-prazosin as the ligand as described elsewhere.[14,15] The affinities at the L-type calcium channel were determined from the displacement of [^{3}H]nitrendipine from rat brain membrane preparations.[18] Binding affinities (K_i) at the human α_{2a}, α_{2b}, α_{2c} adrenoceptors, histamine-H_1 and -H_2 receptors, and 5HT-1A, -1B, -1D, and -2A receptors were determined by radioligand competition binding assays in membrane preparations of cells expressing the human recombinant receptors, as described elsewhere.[19−24] All K_i values are ±5% or less, with $n \geq 2$.

2. [^{3}H]Prazosin/[^{125}I]HEAT Binding in Human and Dog Prostate Membranes: Competition binding assays in human prostate membrane preparations were performed using [^{3}H]-prazosin and assays in dog prostate membranes using [^{125}I]-HEAT as described previously.[25]

3. Functional α_1 Antagonism in Isolated Dog Prostate Tissue: Dog prostates were cut into 6−8 pieces longitudinally along the urethra opening and stored in ice-cold oxygenated Krebs solution (NaCl, 118 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM; KH_2PO_4, 1.2 mM; $MgSO_4$, 1.2 mM; $NaHCO_3$, 2.0 mM; dextrose, 11 mM) before use, overnight if necessary. Excess lipid material and connective tissue were carefully removed, and tissue segments were attached to glass tissue holders with 4.0 surgical silk and placed in a 5-mL jacketed tissue bath containing Krebs buffer at 37 °C, bubbled with 5% CO_2/95% O_2. The tissues were connected to a Statharn-Gould force transducer, 2 g of tension was applied, and the tissues were allowed to equilibrate for 1 h. Contractions were recorded on a Hewlett-Packard 7700 series strip chart recorder. After a single priming dose of 10 μM phenylephrine (the tissue was washed every 10 min for 1 h), a cumulative concentration−response curve to phenylephrine was generated; the tissues were washed every 10 min for 1 h. Vehicle or antagonist was added to the bath and allowed to incubate for 1 h; then another cumulative concentration−response curve to phenylephrine was generated. EC_{50} values were calculated for each group using GraphPad Inplot software. K_b values were calculated as follows: $K_b = B/(x - 1)$, where B is the concentration of antagonist used and x is the ratio of EC_{50} values in the presence and absence of antagonist.

4. In Vivo Functional Assay: Male purpose bred mongrel dogs (9−14 kg) were anesthetized with pentobarbital sodium (35 mg/kg iv, plus 4−5 mg/kg/h iv infusion). The dogs were intubated and ventilated with room air using a Harvard instruments positive displacement, large animal ventilator. Polyethylene catheters were placed in the aorta via the femoral artery and vena cava via the femoral veins (two catheters, one in each vein) for the measurement of arterial pressure and the administration of drugs, respectively. A Millar microtip pressure transducer was advanced into the urethra via the bladder dome and positioned so that the tip of the transducer was in the prostatic urethra. The position of the catheter was verified by gently squeezing the prostate and noting the large change in urethral pressure. The catheter was held in position by ligatures at the bladder dome, bladder neck, and distal urethra.

5. Determination of Potency and Selectivity: Phenylephrine, an α_1 adrenergic agonist, was administered intravenously (0.1−300 μg/kg, bolus) in order to construct control dose−response curves for changes in intraurethral pressure (IUP) and diastolic blood pressure (DBP). Inhibition of phenylephrine dose−response curves by successive doses of antagonist (30, 100, 300 μg/kg iv) was determined for both IUP and DBP. The potency is given as the K_b (μg/kg) as determined by the method of Arunlaksana and Schild.[26] The relative selectivity was calculated as the ratio of DBP and IUP K_b values.

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