A Structure–Activity Relationship Study of Benzylic Modifications of 4-[1-(1-Naphthyl)ethyl]-1*H*-imidazoles on α_1- and α_2-Adrenergic Receptors

Seoung-Soo Hong,[†] Karl J. Romstedt,[‡] Dennis R. Feller,[‡] Fu-Lian Hsu,[§] Thomas L. Cupps,[⊥] Robert A. Lyon,[⊥] and Duane D. Miller*,[∥]

Divisions of Medicinal Chemistry and Pharmacognosy and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210-1291, U.S. Army Chemical Research, Aberdeen Proving Ground, Maryland 21021, Procter and Gamble Company, Cincinnati, Ohio 45239-8707, and Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee, Memphis, Tennessee 38163

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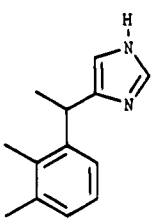
The naphthalene analog of medetomidine (**1**), 4-[1-(1-naphthyl)ethyl]-1*H*-imidazole (**2**), is a highly potent, selective α_2-adrenoceptor agonist. We have initiated a structure–activity relationship study of the replacement of the methyl group on the carbon bridge between the naphthalene and imidazole rings of **2** with a hydrogen, hydroxy, methoxy, carbonyl, or trifluoromethyl group and compared their biological activities with medetomidine **1** and the optical isomers of **2**. Analogs of **2** were antagonists of α_{2A}-adrenoceptor-mediated human platelet aggregation and agonists on α_1- and α_2-adrenoceptors in guinea pig ileum. The rank order and potencies of these analogs on platelets (α_{2A}-subtype) and guinea pig ileum (α_1-subtype) were nearly the same, whereas racemic and *S*-(+)-**2**, desmethyl, and hydroxy analogs were potent agonists on α_2-adrenoceptors in guinea pig ileum. With the exception of the desmethyl analog **5**, none of the other analogs were as potent as the parent drug **2** on α_{2A}- (human platelets), α_1- (guinea pig ileum), or α_2- (guinea pig ileum) adrenergic receptor systems. As with analog **2**, the desmethyl- and methoxy-substituted analogs retained a greater α_2/α_1-selectivity in both functional (agonist activity) and biochemical (receptor displacement) studies. Receptor binding studies indicate that *S*-(+)-**2** possessed greater affinity than the *R*-(−)-isomer on both α_1- and α_2-adrenoceptors in rat brain. In addition, *R*-(−)-**2** did not show agonist activity in α_2-adrenoceptors of guinea pig ileum and was 10-fold more potent than *S*-(+)-**2** as an antagonist of α_{2A}-adrenoceptors in human platelets. Thus, the nature of the substituent and the chirality at the carbon bridge between the naphthalene and imidazole rings play an important role in maintaining potent α_2-adrenoceptor activity and high α_2/α_1-selectivity within the 4-substituted imidazole class.

Introduction

α-Adrenergic agonists are divided into two major chemical classes, the phenethylamines and the imidazolines.[1–3] In contrast to imidazolines, the phenethylamines show significant activity differences between optical isomers and adhere to the Easson–Stedman hypothesis.[4] Recently, a new class of 4-substituted imidazole analogs has been studied for their selective interactions with α_2-adrenergic receptors. One of these imidazole derivatives, medetomidine (**1**),[5] is a selective and potent α_2-adrenergic agonist. Medetomidine is currently used in Scandinavian countries as a veterinary sedative–anesthetic drug with analgesic properties,[6–9] and clinical investigations are ongoing.[5,10] Our overall goal is to develop highly selective α_2-adrenoceptor agonists in the imidazole class of drugs.

Limited studies have been carried out with optical isomers of the 4-substituted imidazole class of adrenergic agents. Medetomidine (**1**) possesses a chiral center at the carbon bridge and has been resolved into two enantiomers.[11] The (+)-isomer of medetomidine was more potent than the (−)-isomer on α_2-adrenergic receptors. We also prepared the optical isomers (*S*-(+)-**2**, *R*-(−)-**2**) of a naphthyl analog, **2**, and evaluated the enantiomers for their α-adrenergic activities.[12] Like



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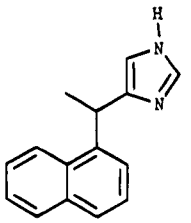

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medetomidine, there were qualitative and quantitative differences in biological activities of the optical isomers of naphthyl analog **2** in α_1- and α_2-adrenergic systems of guinea pig ileum and human platelets. Thus, stereochemistry at this carbon bridge position of medetomidine and analog **2** is an important factor for retention of potent and selective α_2-adrenergic receptor agonist activity.

The specific objective of this work is to evaluate the influence of stereochemistry and structural modification at the carbon bridge between the naphthalene and imidazole rings of medetomidine analog **2** on pharmacological activity in selected α_2- and α_1-adrenoceptor systems. These chemical modifications were selected since the naphthyl analog **2**, like medetomidine,[11,12] is a potent, stereoselective α_2-adrenergic agonist and the

[†] Division of Medicinal Chemistry and Pharmacognosy, The Ohio State University.
[‡] Division of Pharmacology, The Ohio State University.
[§] U.S. Army Chemical Research.
[⊥] Procter and Gamble Co.
[∥] University of Tennessee.
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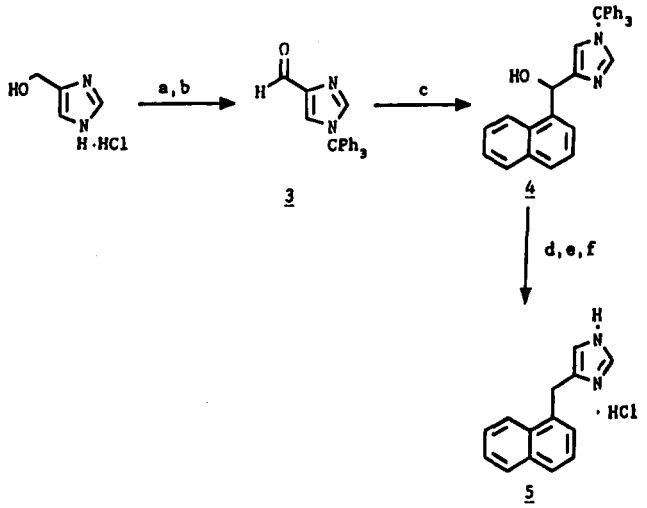
Scheme 1[a]



[a] (a) Ph_3CCl, Et_3N; (b) MnO_2; (c) Mg, 1-bromonaphthalene; (d) Et_3SiH, CF_3COOH; (e) 2 N HCl; (f) dilute HCl.

addition of a methyl group to the benzylic carbon atom of medetomidine (as in detomidine) enhanced its α_2-adrenergic agonist activity.[13] A variety of lipophilic and hydrophilic functional groups were placed at this position to better understand the optimal substitution at the benzylic carbon bridge for interaction with α_1- and α_2-adrenergic receptors. In this paper, we have examined the functional α-adrenoceptor activities and binding potencies of these drugs in human platelets, guinea pig ileum, and rat brain as representative α_1- and α_2-subtype systems.

Chemistry

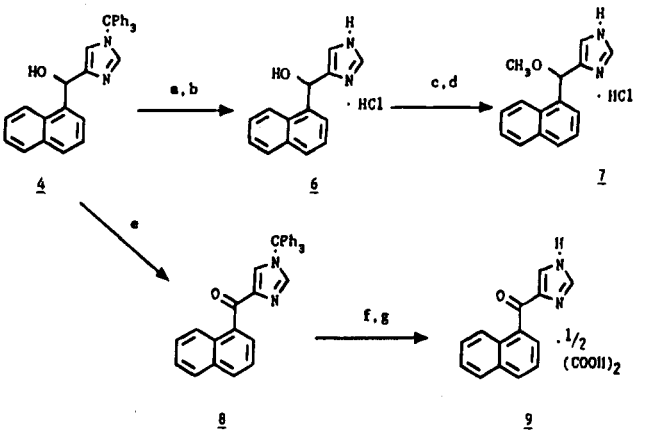
The synthesis of 4-[1-(1-naphthyl)ethyl]-1*H*-imidazole (**2**) was reported in a previous paper.[12,14] The synthesis of the 4-[(1-naphthyl)methyl]-1*H*-imidazole derivative **5** is shown in Scheme 1. 1-Bromonaphthalene was treated with magnesium turnings to form a Grignard reagent which was condensed with imidazolecarboxaldehyde[15] **3** to give alcohol **4** in 75% yield from the aldehyde. The hydroxy imidazole **4** was treated with triethylsilane and trifluoroacetic acid in CH_2Cl_2 to give the dehydroxylated and N-deprotected imidazole as a free base after sodium bicarbonate workup in 65% yield, which was treated with dilute HCl to give the HCl salt **5**.

Direct deprotection of **4** also gave the 4-[(1-naphthyl)-hydroxymethyl]-1*H*-imidazole derivative **6** (Scheme 2). Treatment of **4** with 2 N hydrochloric acid at refluxing temperature for 1 h followed by basic workup afforded the free base in 50% yield, which was converted to the HCl salt **6**.

For the synthesis of 4-[(1-naphthyl)methoxymethyl]-1*H*-imidazole derivative **7** (Scheme 2), in earlier attempts, treatment of imidazole **6**, as a free base, with thionyl chloride and methanol gave extensive decomposition. In addition, when the imidazole was treated with HCl gas or a concentrated HCl solution in CH_3OH, it did not provide the target compound. However, the imidazole hydrochloride salt **6** reacted with thionyl chloride in chloroform to give a chlorinated compound which was treated with methanol without further purification to give methoxy imidazole **7**.

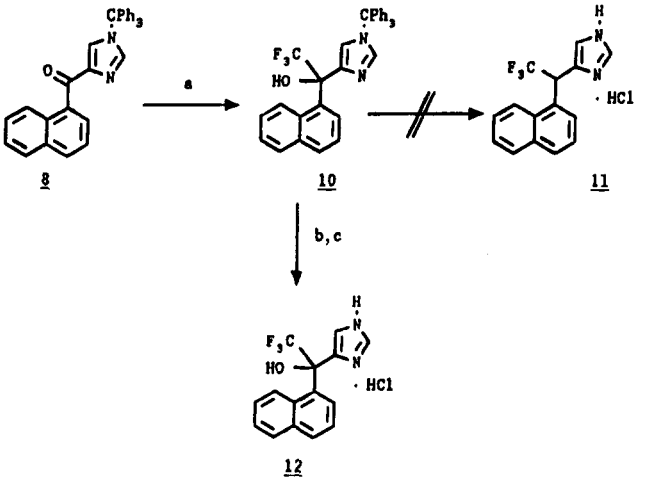
Synthesis of 4-[(1-naphthyl)carbonyl]imidazole derivatives **9** is outlined in Scheme 2. The imidazole

Scheme 2[a]



[a] (a) 2 N HCl; (b) dilute HCl; (c) $SOCl_2$; (d) CH_3OH; (e) MnO_2; (f) 2 N HCl; (g) $(COOH)_2 \cdot 2H_2O$.

Scheme 3[a]



[a] (a) TMS-CF_3, TBAF; (b) 2 N HCl; (c) dilute HCl.

alcohol **4** was treated with MnO_2 in methylene chloride to give oxidized imidazole **8** in 82% yield, which was further treated with 2 N hydrochloric acid followed by basic workup to give the free base in 54% yield which was converted to the oxalate salt **9**.

The synthesis of trifluoromethyl derivative **11** was initially attempted using a trifluoromethyl anion reagent as shown in Scheme 3. The imidazole ketone **8** was treated with TMS-CF_3[16] in dry THF in the presence of tetrabutylammonium fluoride to give **10** in 75% yield. Reduction of the tertiary alcohol geminal to the trifluoromethyl group in **10** has not been successful with various methods. A variety of synthetic reactions are presently being investigated toward the target **11**. The imidazole hydrochloride **12** was examined for its biological effects.

Biological Results and Discussion

Several reports[12,14,17,18] indicate that medetomidine (**1**), related imidazole derivatives, and naphthyl analog **2** are antagonists of α_{2A}-mediated platelet aggregation. Optical isomers of **2** and analogs of the parent drug **2** were tested for their abilities to antagonize epinephrine-induced primary wave aggregation in human platelets (Table 1). All analogs and optical isomers blocked aggregation in a concentration-dependent manner, giving a rank order of antagonist activity of *R*-(−)-**2** > **5** >

Table 1. Functional Effects of Medetomidine (1) and 4-Substituted Imidazole Analogs for α_1- and α_2-Adrenoceptor Activities in Human Platelets and Guinea Pig Ileum

		ileum[b]		
compound[c]	platelets[a] α_{2A} IC_{50}, μM	α_1 EC_{50}, nM	α_2 EC_{50}, nM	α_2-selectivity ratio[d]
1	3.4 ± 0.6	1165 (41%)	3 (71%)	388
2	9.1 ± 3.9	5793 (3%)	9 (73%)	643
S-(+)-**2**	12.3 ± 5.8	8273 (9%)	11 (84%)	752
R-(−)-**2**	1.3 ± 0.5	10 814 (25%)	na[e]	
5	3.0 ± 1.1	2113 (55%)	18 (34%)	117
6	61.9 ± 29.6	12 692 (28%)	375 (57%)	33.8
7	379.8 ± 63.7	nd[f]	32 992 (27%)	
9	580.4 ± 36.3	nd	nd	
12	>300[g]	nd	nd	

[a] IC_{50} = concentration (μM) of compound which inhibits epinephrine (10 μM)-induced aggregation in aspirin (1 mM)-treated human platelets. Data are given as the average ± SEM (n = 2–6). [b] Values are the EC_{50} for each compound, and the maximal responses are given in the parentheses. EC_{50} = concentration of compound which produces 50% of its maximal response. Maximal responses (E_{max}) were calculated relative to those of epinephrine and UK−14, 304 for α_1- and α_2-adrenergic effects, respectively. Data are given as the average ± SEM ($n \geq 3$). [c] Unless indicated otherwise, all compounds were used as racemates. [d] α_2-Selectivity ratio = $EC_{50}(\alpha_1)/EC_{50}(\alpha_2)$. [e] No activity at highest concentration (1 mM) used. [f] nd = not determined. [g] No inhibitory activity up to 300 μM.

1 > **2** > *S*-(+)-**2** > **6** > **7** > **9** ≫ **12** (no activity). Desmethyl analog **5** and *R*-(−)-**2** were 3- and 7-fold more potent than racemic **2** at these α_{2A}-adrenergic receptor sites.

Optical isomers and selected analogs of **2** were also examined for their functional effects on α_1- and α_2-adrenergic receptors in guinea pig ileum (Table 1). The intrinsic activities (maximal drug effects) of analogs on these receptor systems differed from the standard agonists, epinephrine and UK-14,304. Whereas analog **2** and *S*-(+)-**2** exhibited a greatly reduced maximal response in the α_1-adrenergic receptor system of ileum (only 3% and 9% of the epinephrine maximum), the remaining analogs, *R*-(−)-**2**, and medetomidine elicited 25–55% of the maximal responses in this tissue. By comparison, these analogs and optical isomers produced responses which ranged from 27% to 84% of the UK-14,304 maximum for interaction with α_2-adrenergic receptors (Table 1). Furthermore, *R*-(−)-**2** shows no intrinsic activity and *S*-(+)-**2** shows enhanced α_2-agonist activity compared to the racemic **2**. Thus, medetomidine, **2**, its analogs, and optical isomers behave as partial α-adrenoceptor stimulants in guinea pig ileum. Other reports from our laboratory[14,19] demonstrate that 2-benzylimidazoline and 4-substituted imidazole analogs are partial agonists in vascular smooth muscle systems. In particular, our recent report[14] indicated that medetomidine (**1**) and the parent drug **2** were partial agonists relative to phenylephrine for contraction of rat thoracic aorta.

Medetomidine, all of the naphthyl analogs, and *S*-(+)-**2** were much more potent and selective for an interaction with α_2-adrenergic receptors in guinea pig ileum (Table 1). Whereas analogs **2**, **5**, and *S*-(+)-**2** exhibited slightly reduced α_2-adrenoceptor potencies (9, 18, and 11 nM) as compared with that of medetomidine (3 nM), their α_2/α_1-agonist selectivities were comparable in magnitude (643-, 117-, and 752-fold) to that of medetomidine (388-fold) in this tissue. The high α_2/α_1-selectivity of analog **5** may be related to its low efficacy (partial agonism) on the α_1-adrenoceptors in guinea pig ileum. Moreover, concentrations of medetomidine, related analogs, and optical isomers required for the antagonism of epinephrine-induced platelet aggregation were also at least a magnitude greater than those for α_2-adrenoceptor-mediated actions in ileum.

The receptor affinities of medetomidine and analogs and optical isomers of **2** were determined on α_1- and α_2-adrenergic receptor systems in membrane fractions of rat brain (Table 2). The rank order of receptor potencies for these compounds differed between these adrenergic receptor systems (**5** > **2** > *S*-(+)-**2** > *R*-(−)-**2** > **1** > **6** > **9** > **7** = **12** in α_1-adrenoceptors, and *S*-(+)-**2** > **2** > **1** > *R*-(−)-**2** > **5** > **7** ≥ **6** > **12** ≥ **9** in α_2-adrenoceptors). In addition to medetomidine (**1**), analogs **2** and **5** and optical isomers retained high receptor potency and α_2/α_1-selectivity in rat brain. There is some discrepancy between the experimentally determined potency ratios for functional agonist activity (Table 1) versus receptor binding affinities (Table 2) for these analogs and optical isomers. This may be due, in part, to the different tissues and species used for these experiments. Nevertheless, these data imply that the observed functional effects of these analogs in guinea pig ileum are mediated via an initial interaction with α_1- and α_2-adrenergic receptors.

Table 2. α_1- and α_2-Adrenoceptor Binding Affinities of Medetomidine and 4-Substituted Imidazole Analogs in Rat Brain Preparations

	binding, K_i, nM[c]		α_2-selectivity
compound[b]	α_1	α_2	ratio[d]
1	1102 ± 62	19 ± 7	58.0
2	310 ± 35	17 ± 4	18.2
S-(+)-**2**	461 ± 25	11 ± 3	41.9
R-(−)-**2**	536 ± 32	24 ± 3	22.3
5	188 ± 21	68 ± 26	2.7
6	9255 ± 193	8810 ± 1442	1.05
7	>50 000	8582 ± 461	>5.8
9	15 902 ± 800	31 754 ± 11 639	0.50
12	>50 000	>24 539 ± 2567	>2.0

[a] Membrane preparations were incubated with the radioligands for α_1- and α_2-adrenoceptors. Compounds were added in varying concentrations (1–100 000 nM). [b] Unless otherwise indicated, compounds were used as racemates. [c] K_i values were determined using the equation as follows: K_i (nM) = $IC_{50}/1 + [L]/K_D$ where IC_{50} = concentration (nM) of analog which reduces binding by 50%, [L] = concentration of radioligand, and K_D = equilibrium dissociation constant of the radioligand. Values are the average ± SEM (n = 3–9). [d] α_2-Selectivity ratio = $IC_{50}(\alpha_1)/IC_{50}(\alpha_2)$.

The objective of this work was to evaluate the role of structural modification at the carbon bridge between the naphthalene and imidazoline rings of analog **2** on the profile of α_2/α_1-selectivity in selected pharmacological systems. In each adrenergic receptor system, replacement of the methyl group of **2** with other substituents (hydroxy, methoxy, carbonyl, or trifluoromethyl groups) reduced interactions at both α_1- and α_2-adrenoceptor sites and lowered the α_2/α_1-selectivity ratio. We found

that replacement of the methyl group of analog **2** with these different substituents produced compounds which were >42- and >500-fold less potent as α_2-agonists and α_2-receptor binding agents than **2**, respectively. As an exception, desmethyl analog **5**, which possessed a hydrogen atom in place of the methyl group of **2**, retained comparable potencies and α_2/α_1-adrenoceptor selectivity (guinea pig ileum and rat brain) to those of the parent analog **2**. Analog **5** was 117- and 2.7-fold more selective for α_2- versus α_1-agonist activity on guinea pig ileum (Table 1) and receptor binding potency on rat brain (Table 2), respectively. Although considerably less potent than the parent drug **2**, substitution of a methoxy group, as in analog **7**, also retained a 33- and >5-fold α_2/α_1-selectivity for agonist and receptor binding activities in these systems, respectively (Tables 1 and 2).

Considerably greater concentrations of **2** and its analogs were required to interact with α_{2A}- (human platelets) and α_1- (guinea pig ileum) adrenoceptors than that observed on α_2-adrenoceptors in guinea pig ileum. Since 2-benzyl-substituted imidazoline and 4-substituted imidazole analogs are known to exhibit α_{2A}-antagonist activity in human platelets and contractile effects in smooth muscle vasculature,[12,14,17,18] the observed concentration-dependent inhibitory actions and stimulatory actions of **2**, its analogs, and medetomidine in these systems were expected (Table 1). Our results show that the functional activity and rank order of medetomidine and related analogs (**2**, **5**, and **6**) in human platelets (α_{2A}-subtype) and ileum (α_1-subtype) were nearly identical and differed significantly from those in electrically stimulated ileum (α_2-subtype) (Table 1). In addition, whereas desmethyl analog **5** was about 3-fold more potent than **2** as an α_{2A}-antagonist and α_1-agonist in platelets and guinea pig ileum, respectively, this analog was 2-fold less potent than **2** as an α_2-agonist in guinea pig ileum (Tables 1 and 2). Moreover, the enantiomers of analog **2** exhibited a stereoselective interaction (*R*-(−)-isomer > *S*-(+)-isomer) for the blockade of α_{2A}-adrenoceptor actions in human platelets, and a qualitative difference in activity was observed on α_2-adrenergic receptors in guinea pig ileum. Thus, carbon bridge-modified analogs of **2** provide useful probes for studying interactions with α_1- and α_2-adrenergic receptors.

A methyl group added to the carbon bridge of detomidine gave rise to a compound (medetomidine) with an increased α_2-adrenoceptor activity.[19] Likewise, substitution of a methyl group on the carbon bridge of desmethyl analog **5**, to give the parent drug **2**, increased the functional (α_2-agonist) and receptor binding affinity (rat brain) to α_2-adrenoceptors. In addition, we have also observed that chirality at the carbon bridge of analog **2** was important for differentiation of interactions with α_1- and α_2-adrenergic receptors.[12] On the basis of these findings, we conclude that the substituent at the carbon bridge between the naphthalene and imidazole rings plays a critical role for obtaining analogs possessing potent and selective interactions with α_2-adrenergic receptor sites within this newly emerging chemical class of 4-substituted imidazoles.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The NMR spectra were obtained on either an IBM AF-250 FTNMR spectrometer (250 MHz) or an IBM AF-270 FTNMR spectrometer (270 MHz) and are reported in parts per million. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, interpretation, and coupling constant (Hz). Analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Analytical results for elements indicated were within ±0.4% of the theoretical values.

4-[(1-Naphthyl)hydroxymethyl]-*N*-(triphenylmethyl)-imidazole (4). Dry magnesium turnings (312 mg, 12.82 mmol) were covered with 34 mL of dry tetrahydrofuran, and 1-bromonaphthalene (2.57 g, 12.42 mmol) was added under an argon atmosphere. After the addition was complete, the reaction mixture was refluxed for about 1 h until the magnesium turnings were consumed. The reaction mixture was cooled to about 40–45 °C, and then, a solution of imidazolecarboxaldehyde **3** (1.4 g, 4.14 mmol) in 20 mL of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to attain room temperature, stirred for an additional 30 min, cooled in an ice–water bath, and treated with 20 mL of 2 N HCl with agitation. The stirring was continued for an additional 15 min, and the mixture was then extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (1 × 30 mL), dried over sodium sulfate, and evaporated under reduced pressure to give yellow solids. The solids were collected and washed with ethyl acetate (1 × 10 mL) to give 1.45 g (75% from the aldehyde) of **4** as a white solid: mp 154–155 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 8.18 (s, 1H), 7.86–6.93 (m, 23H), 6.73 (s, 1H), 6.10 (s, 1H). Anal. ($C_{33}H_{26}N_2O$) C, H, N.

4-[(1-Naphthyl)methyl]-1*H*-imidazole Hydrochloride (5). A stirred solution of **4** (0.7 g, 1.5 mmol) in 20 mL of methylene chloride was treated with triethylsilane (1.4 g, 12 mmol) and trifluoroacetic acid (5.47 g, 48 mmol). The resulting clear solution was stirred at room temperature overnight, and 20 mL of water was then added. The reaction mixture was made basic with solid sodium bicarbonate. The organic layer was separated, washed with water (1 × 10 mL), dried over sodium sulfate, and concentrated under reduced pressure to give an oil which was crystallized from methylene chloride to give 0.20 g (65%) of the free base as a peach-colored solid. A solution of this free base (0.53 g, 2.54 mmol) in 5 mL of methanol was treated with 2.7 mL of 1 N HCl in methanol. Evaporation of the solvent under reduced pressure gave a red-orange solid which was recrystallized from methanol/diethyl ether to give 0.37 g (60%) of **5** as a white solid: mp 205–206 °C; ^{1}H NMR (CD_3OD) δ 8.78 (d, 1H, J = 1.3 Hz), 7.54–7.42 (m, 7H), 7.19 (d, 1H, J = 1.3 Hz), 4.55 (s, 2H). Anal. ($C_{14}H_{13}ClN_2$) C, H, N.

4-[(1-Naphthyl)hydroxymethyl]-1*H*-imidazole Hydrochloride (6). A suspension of **4** (1 g, 2.14 mmol) in 20 mL of 2 N HCl was refluxed for 1 h. After the mixture was cooled to room temperature, 20 mL of methylene chloride were added to dissolve precipitated materials (triphenylmethyl alcohol). The organic layer was discarded. The water layer was made basic with saturated sodium bicarbonate solution and extracted with methylene chloride (2 × 20 mL). The organic layers were washed with brine (1 × 20 mL), dried over sodium sulfate, and concentrated under reduced pressure to give 0.24 g (50%) of the free base as a white solid. A solution of this free base (0.65 g, 2.9 mmol) in 5 mL of methanol was treated with 3 mL of 1 N HCl in methanol. The mixture was concentrated under reduced pressure to give an oil which was crystallized from methanol/diethyl ether to give 0.43 g (57%) of **6** as a white solid: mp 162–165 °C; ^{1}H NMR (CD_3OD) δ 8.83 (s, 1H), 8.1–7.48 (m, 7H), 7.17 (s, 1H), 6.63 (s, 1H). Anal. ($C_{14}H_{13}ClN_2O$) C, H, N.

4-[(1-Naphthyl)methoxymethyl]-1*H*-imidazole Hydrochloride (7). A suspension of **6** (0.93 g, 3.57 mmol) in 10 mL of chloroform was treated dropwise with 1.1 mL of thionyl chloride (14.8 mmol) at room temperature. The resulting mixture was refluxed overnight and then the solvent removed under reduced pressure to give a solid. The solid was dissolved in 20 mL of methanol and refluxed for 5 h. The resulting solution was stirred an additional 1 h at room temperature,

and the solvent was removed under reduced pressure to give a solid which was recrystallized from methanol/ethyl acetate to give 0.73 g (75%) of **7** as light yellow crystals: mp >260 °C dec; ^{1}H NMR (CD_3OD) δ 8.87 (d, 1H, J = 1.3 Hz), 7.97–7.12 (m, 7H), 7.11 (d, 1H, J = 1.3 Hz), 6.16 (s, 1H), 3.46 (s, 3H). Anal. ($C_{15}H_{15}ClN_2O$) C, H, N.

4-[(1-Naphthyl)carbonyl]-*N*-(triphenylmethyl)imidazole (8). Activated manganese oxide (9.21 g, 105.88 mmol) was added to a solution of **4** (4.94 g, 10.59 mmol) in 100 mL of methylene chloride. The reaction mixture was refluxed for 4 h, cooled to room temperature, and filtered through a Celite pad, and the solids were washed with methylene chloride (1 × 20 mL). The combined filtrate and washing was evaporated under reduced pressure to give 4.04 g (82%) of **8** as a white solid: mp 159–161 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 8.32–7.12 (m, 21H), 7.94 (d, 1H, J = 8.2 Hz), 7.63 (d, 1H, J = 1.4 Hz), 7.53 (d, 1H, J = 1.4 Hz). Anal. ($C_{33}H_{24}N_2O$) C, H, N.

4-[(1-Naphthyl)carbonyl]-1*H*-imidazole Oxalate (9). A suspension of **8** (1 g, 2.15 mmol) in 20 mL of 2 N HCl was refluxed for 1 h. After cooling to room temperature, the precipitated materials were removed by filtration. The water layer was made basic with solid sodium bicarbonate and extracted with methylene chloride (2 × 20 mL). The organic layers were washed with brine (2 × 20 mL), dried over sodium sulfate, and concentrated under reduced pressure to give 0.26 g (54%) of the free base as a white solid. A solution of the free base (0.25 g, 1.12 mmol) in 5 mL of methanol was treated with a solution of oxalic acid dihydrate (0.15 g, 1.18 mmol) in 5 mL of methanol. The mixture was concentrated under reduced pressure to give a solid which was recrystallized from methanol to give 0.24 g (82%) of **9** as white crystals: mp 218–221 °C; ^{1}H NMR (CD_3OD) δ 8.26 (s, 1H), 8.20–7.51 (m, 5H), 8.09 (d, 1H, J = 8.3 Hz), 7.83 (dd, 1H, J = 7.1 and 1.2 Hz), 7.7 (s, 1H). Anal. ($C_{14}H_{10}N_2O \cdot {}^1/_2H_2C_2O_4$) C, H, N.

4-[(1-Naphthyl)(trifluoromethyl)hydroxymethyl]-*N*-(triphenylmethyl)imidazole (10). A solution of **8** (1 g, 2.15 mmol) and TMS-CF_3 (0.86 mL, 6.02 mmol) in 10 mL of dry tetrahydrofuran was cooled in an ice–water bath for 30 min, and tetrabutylammonium fluoride (4.3 g, 16.58 mmol) was added under an argon atmosphere. An orange color developed instantaneously, and the reaction mixture was brought to room temperature and stirred overnight. The reaction mixture was treated with 30 mL of water and stirred for 30 min and then extracted with methylene chloride (2 × 50 mL). The organic extracts were washed with water (1 × 50 mL) and brine (1 × 50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to give a solid which was recrystallized from methylene chloride/hexane to give 0.86 g (75%) of **10** as a white solid: mp 231–232 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 8.13 (d, 1H, J = 8.7 Hz), 7.81–6.94 (m, 21H), 7.49 (d, 1H, J = 1.3 Hz), 6.34 (d, 1H, J = 1.3 Hz), 5.3 (s, 1H). Anal. ($C_{34}H_{25}F_3N_2O$) C, H, N.

4-[(1-Naphthyl)(trifluoromethyl)hydroxymethyl]-1*H*-imidazole Hydrochloride (12). A solution of **10** (0.7 g, 1.31 mmol) in 30 mL of methylene chloride was treated with triethylsilane (1.24 g, 41.92 mmol) and trifluoroacetic acid (4.74 g, 41.92 mmol). The reaction mixture was stirred overnight, and 20 mL of water was then added. The solution was basified by adding solid sodium bicarbonate and extracted with methylene chloride (3 × 20 mL). The extracts were washed with water (2 × 20 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to give a solid which was recrystallized from methanol to give 0.35 g (97%) of the free base as a white solid. A solution of the free base (0.46 g, 1.6 mmol) in 5 mL of methanol was treated with 1.7 mL of 1 N HCl in methanol. Evaporation of the solvent under reduced pressure gave an oil which was crystallized from methanol/diethyl ether to give 0.36 g (68%) of **12** as a white solid: mp 258–260 °C dec; ^{1}H NMR (CD_3OD) δ 8.94 (d, 1H, J = 1.3 Hz), 8.10 (d, 1H, J = 8.5 Hz), 8.01 (d, 1H, J = 8.3 Hz); 7.94–7.34 (m, 5H), 7.28 (d, 1H, J = 1.3 Hz); ^{13}C NMR BB (CD_3OD) δ 126.13 (q, J_{CF_3} = 287.4 Hz), 77.34 (q, J_{C-CF_3} = 30.0 Hz), 136.54, 136.11, 134.63, 132.46, 132.35, 131.69, 130.36, 127.35, 127.28, 126.91, 126.86, 125.48, 120.07; ^{19}F NMR ($CFCl_3$ = 0 ppm, external reference) δ −74.77. Anal. ($C_{15}H_{12}ClF_3N_2O$) C, H, N.

Pharmacological Tests. Human Platelets. Blood was collected from normal volunteers who were free of medication for 10 days prior to testing. All aggregation studies were conducted using platelet-rich plasma.[18] Aspirin (1 mM) was routinely added to platelet preparations to block prostaglandin biosynthesis in order to examine the effect of drugs on the primary wave aggregation response to epinephrine. Various concentrations of inhibitors were added 1 min prior to activation of platelets by epinephrine, and IC_{50} values for each compound were determined as described previously.[17]

Guinea Pig Ileum. α_2-Adrenoceptor functional testing was performed as previously described with some modifications.[20] Male Hartley–Felt guinea pigs (ca. 300 g; Charles River Laboratories) were individually housed and afforded free access to food and water throughout the duration of the study. Guinea pigs were anesthetized with carbon dioxide prior to sacrifice by cervical dislocation, and ileum was removed beginning 20 cm from the ileocecal junction. The ileal lumens were washed, cut into 2 cm segments, suspended in 15 mL muscle baths, and perfused with a Kreb's solution containing 2.5 mM $CaCl_2$, 118.5 mM NaCl, 4.74 mM KCl, 1.2 mM $MgSO_4$, 1.18 mM KH_2PO_4, 25 mM $NaHCO_3$, 10 mM glucose, and 10 mM HEPES at 37 °C. The buffer also contained desipramine (0.1 μM) to block neuronal uptake, normetanephrine (1.0 μM) to block extraneuronal uptake, propranolol (1.0 μM) to block β-receptor-mediated relaxation, and Ca_2EDTA (23 μM). Ileal segments were continually gassed with 5% carbon dioxide and 95% oxygen. Once suspended, ileal segments were equilibrated for 75 min under a resting tension of 1.0 g. Following equilibration, two doses of acetylcholine (1.0 μM) were given 15 min apart, and the segments were washed and equilibrated for another 60 min. Cholinergic nerves were electrically stimulated supramaximally at a duration of 0.5 ms and a frequency of 0.1 Hz using a Harvard dual impedance stimulator connected to two parallel platinum electrodes placed on either side of the ileal segment. Ileal contractions were recorded isometrically using Grass FT03 force transducers and monitored through a Grass physiograph (Model 7E). When the stimulation-induced contractions had become constant, the α_2-adrenoceptor-selective agonist UK-14,304 was added to each bath in a cumulative dosing schedule (1–1000 nM) as a control drug. Following a 45 min equilibration period, test compounds were administered using a similar cumulative dosing schedule (1–100 000 nM).

α_1-Adrenoceptor contractile responses were also monitored in segments of isolated guinea pig ileum as previously described.[21,22] In these studies, atropine (1.0 μM) was added to the buffer to eliminate cholinergic-induced contraction. Following equilibration, nonstimulated ileal segments were dosed twice with 100 μM epinephrine and allowed to equilibrate for 60 min prior to a noncumulative epinephrine control dose response (1–100 000 nM). Each drug dose was followed by at least three washes and a 5 min time period before the next dose. Test compounds were administered using a similar noncumulative dosing schedule 45 min after the last epinephrine dose. Drug-induced contractions were recorded as described above.

Each compound was tested in at least three baths on three separate days, and EC_{50} and E_{max} values were calculated using the computer program Allfit. UK-14,304 was the generous gift of Pfizer, Inc.

Radioligand Binding Studies. Radioligand binding studies were performed as previously described.[23] In brief, frozen rat brains were obtained from Pel-Freez Biologicals (Rogers, AR) and stored at −70 °C until used. Frontal cortices were removed and homogenized in an ice-cold buffer containing 50 mM Tris-HCl (pH 7.7 at room temperature), 10 mM $MgSO_4$, and 0.5 mM Na_2EDTA and then centrifuged at 14 000 rpm for 20 min. Following resuspension in buffer, homogenates were preincubated at 37 °C for 30 min and centrifuged again at 14 000 rpm for 20 min. Following a final wash in ice-cold buffer, pellets were stored at −70 °C until used.

All radioligand binding assays were performed in triplicate in borosilicate glass tubes in a final volume of 2.0 mL to which frontal cortical membranes were added last. α_1-Receptors were labeled using 0.2 nM [^{3}H]prazosin (76 Ci/mmol; NEN) with 2

mg/mL wet wt frontal cortical membranes. α_2-Receptors were labeled using 2.0 nM [^{3}H]rauwolscine (76 Ci/mmol; NEN) with 12 mg/mL wet wt frontal cortical membranes. Phentolamine (10 μM) was used to determine specific binding in both α_1 and α_2 assays. Assays were performed in a buffer containing 50 mM Tris-HCl (pH 7.4 at 37 °C), 10 mM $MgSO_4$, 0.5 mM Na_2-EDTA, 10 μM pargyline, and 0.1% ascorbic acid. Competition experiments were performed using 11 concentrations of test compound (10^{-10}–10^{-5} M). Samples were incubated at 37 °C for 30 min and then filtered (Whatman GF-B filters presoaked in 0.1% poly(ethyleneimine)) and washed with 10 mL of ice-cold assay buffer. Individual filters were inserted into scintillation vials and equilibrated for 4 h with 5 mL of aqueous scintillant (EcoScint, National Diagnostics) prior to counting (Beckman LS 6000; 55% efficiency). Competition data were analyzed using the EBDA program[24] to obtain K_i values.

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