1 H), 3.25 (dd, 1 H), 3.32 (d, 1 H), 3.46 (d, 1 H), 3.66 (d, 1 H), 3.86 (d, 1 H), 6.79 (t, 1 H), 6.95 (d, 2 H), 7.14–7.44 (m, 9 H), 7.63 (d, 2 H), 9.57 (s, 1 H), 10.03 (s, 1 H). Anal. ($C_{25}H_{28}N_4O_3S$) C, H, N, S.

***N*-[[[[4-Phenyl-1-(phenylmethyl)piperazin-2-yl]methyl]amino]phenyl]methanesulfonamide (22).** Borane–dimethyl sulfide complex (2.65 mL of a 10 M solution, 26.5 mmol) was added to **21** (4.1 g, 8.8 mmol) dissolved in THF (100 mL) under N_2. The solution was refluxed for 18 h and cooled to room temperature. Methanol (25 mL) was added dropwise followed by 2.0 N methanolic HCl (50 mL). The solution was refluxed for 5 h, and the solvent was removed in vacuo. The residue was dissolved in methanol (150 mL) and 50% aqueous NaOH was added to pH 8.5. Chromatography on silica (250 g) with EtOAc and recrystallization with EtOAc gave 2.4 g (60%) of **22** as a white solid: mp 155–156 °C; NMR (DMSO-d_6) δ 2.39 (br t, 1 H), 2.83 (s, 3 H), 2.83–3.03 (m, 4 H), 3.2–3.5 (m, 5 H), 4.13 (d, 1 H), 5.63 (br s, 1 H), 6.60 (d, 2 H), 6.80 (t, 1 H), 6.95 (m, 4 H), 7.20–7.43 (m, 7 H), 9.00 (s, 1 H). Anal. ($C_{25}H_{30}N_4O_2S$) C, H, N.

***N*-[4-[[(4-Phenylpiperazin-2-yl)methyl]amino]phenyl]methanesulfonamide 0.1-Hydrate (7j).** Reaction of **22** (1.90 g, 4.22 mmol) in a manner similar to **9a** gave 1.09 g (72%) of **7j** as an off-white solid: mp 190–193 °C; NMR ($CDCl_3$) δ 2.61 (dd, 1 H), 2.82 (td, 1 H), 2.93 (s, 3 H), 3.04 (td, 1 H), 3.11–3.35 (m, 4 H), 3.56 (m, 2 H), 4.18 (br s, 1 H), 6.08 (br, 1 H), 6.65 (d, 2 H), 6.91 (t, 1 H), 6.97 (d, 2 H), 7.12 (d, 2 H), 7.30 (m, 2 H). Anal. ($C_{18}H_{24}N_4O_2S \cdot 0.1H_2O$) C, H, N.

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Registry No. **2**, 58077-34-2; **3**, 15102-42-8; **4a**, 135036-19-0; **4b**, 138286-66-5; **4c**, 135036-27-0; **5**, 4554-16-9; **6**, 135036-22-5; **7a**, 135036-03-2; **7a**·HCl, 135036-12-3; **7b**, 135036-06-5; **7b**·HCl, 138286-70-1; **7c**, 135036-05-4; **7c**·2HCl, 135036-15-6; **7d**, 135036-04-3; **7d**·3HCl, 135036-14-5; **7e**, 135036-11-2; **7e**·HCl, 135036-18-9; **7f**, 138286-68-7; **7f**·HCl, 138286-71-2; **7g**, 135036-08-7; **7g**·$^3/_2$HCl, 138286-72-3; **7h**, 135036-01-0; **7h**·H_2SO_4, 135036-13-4; **7i**, 135036-07-6; **7i**·HCl, 135036-16-7; **7j**, 135036-02-1; **7k**, 138286-69-8; **8a**, 135036-20-3; **9a**, 138286-67-6; **9a**·HCl, 135036-56-5; **10**, 135036-53-2; **11a**, 135036-09-8; **11b**, 135036-10-1; **12**, 138286-73-4; **13**, 135036-34-9; **14**, 135036-35-0; **15**, 138286-74-5; **16**, 135036-37-2; **17**, 135036-38-3; **18**, 135036-39-4; **19**, 135063-15-9; **20**, 138286-75-6; **21**, 135036-40-7; **22**, 135036-41-8; methoxybenzene, 100-66-3; 1-fluoro-4-nitrobenzene, 350-46-9; *N*-(4-nitrophenyl)-2-propenamide, 7766-38-3; 1-(2-chlorophenyl)piperazine, 39512-50-0; 1-(3-chlorophenyl)piperazine, 6640-24-0; 1-(4-chlorophenyl)piperazine, 38212-33-8; 1-(*o*-anisyl)piperazine, 35386-24-4; 1-(*m*-anisyl)-piperazine, 16015-71-7; 1-(*p*-anisyl)piperazine, 38212-30-5; 1-(*o*-tolyl)piperazine, 39512-51-1; 1-(*m*-tolyl)piperazine, 41186-03-2; 1-(*p*-tolyl)piperazine, 39593-08-3; 1-(4-nitrophenyl)piperazine, 6269-89-2; 1-phenylpiperazine, 92-54-6; 1-(4-acetylphenyl)-piperazine, 51639-48-6.

Synthesis and α-Adrenergic Activities of 2- and 4-Substituted Imidazoline and Imidazole Analogues

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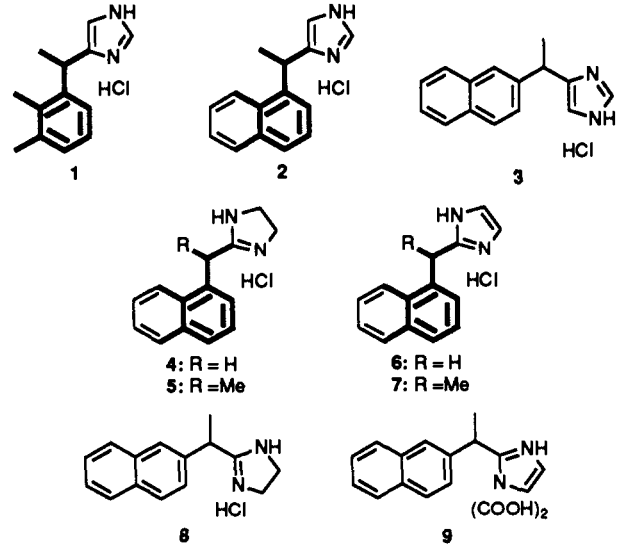
Seven analogues of medetomidine and naphazoline were synthesized and evaluated for their α_1 (aorta) and α_2 (platelet) activities. The analogues were composed of 2- and 4-substituted imidazoles and imidazolines attached through a methylene bridge to either the 1- or 2-naphthalene ring system. In general the 1-naphthalene analogues were the most potent inhibitors of epinephrine-induced platelet aggregation. Of considerable interest was the fact that the 1-naphthalene analogues (**2**, **5**–**7**) were partial agonists while the 2-naphthalene analogues (**3**, **8**, **9**) were antagonists in an α_1-adrenergic system (aorta). Thus, appropriately substituted naphthalene analogues of medetomidine and naphthazoline provide a spectrum of α_1-agonist, α_1-antagonist, and α_2-antagonist activity.

There are two major classes of drug that interact with adrenergic receptors.[1] It is known that phenethylamines adhere strictly to the Easson–Stedman hypothesis and show significant activity differences between optical isomers.[1-3] On the other hand, the imidazoline class of drugs does not follow the Easson–Stedman hypothesis and shows small differences between optical isomers. Recently, it has been reported that medetomidine (**1**)[4] is a new imidazole drug that possesses selective and potent α_2-adrenergic properties. Medetomidine has been reported to have an α_2/α_1 binding ratio of 5060 as compared to clonidine with a ratio of 969.[5] α_2-Adrenergic stimulation is known to mediate a variety of biological actions including hypertension, sedation, antianxiety, analgesia, hypothermia, decreased salivary secretions, and mydriasis.[6] Platelet aggregation induced by epinephrine is also an α_2-adrenergic mediated response[7] and it has recently been subclassified as an α_{2A}-adrenergic receptor system by Byland.[8]



To date, no reports of the action of medetomidine analogues on platelets have appeared. Accordingly, we

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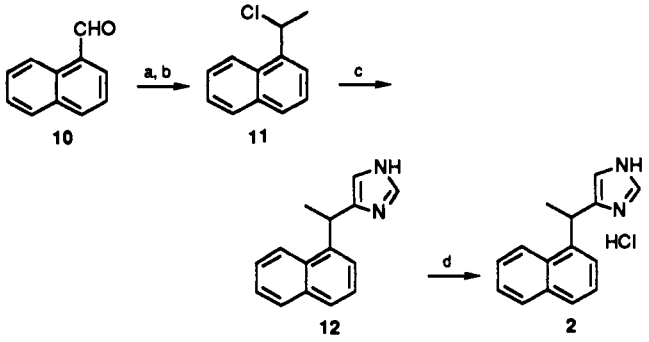
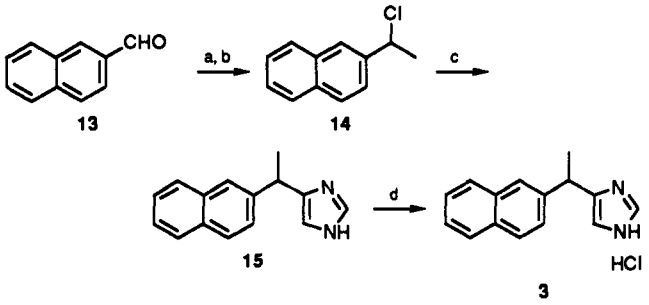
Scheme I[a]



[a] (a) MeMgI; (b) $SOCl_2$; (c) TMSI, $TiCl_4$; (d) dilute HCl.

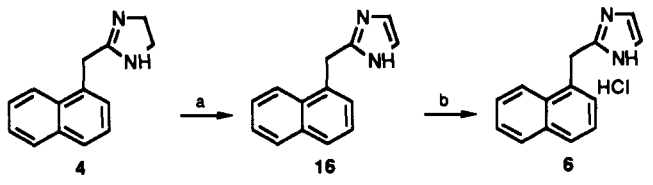
Scheme II[a]



[a] (a) MeMgI; (b) $SOCl_2$; (c) TMSI, $TiCl_4$; (d) dilute HCl.

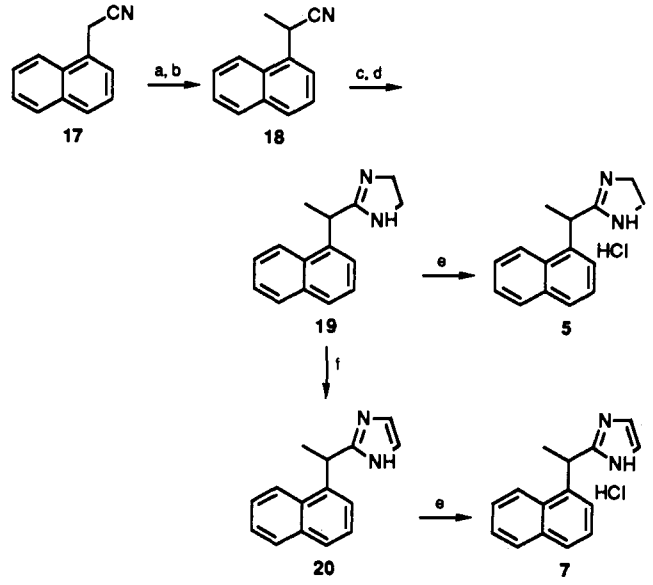
have designed a series of medetomidine analogues (**2**, **3**, **5**–**9**) to examine (1) the importance of an imidazole versus imidazoline ring system, (2) substitution of such ring systems at the 2 versus 4 position, and (3) replacement of the 2,3-dimethylphenyl ring system with a 1- or 2-naphthalenyl ring system on the biological activity in selected α_1- and α_2-adrenergic systems. The selection of the naphthalene ring system was due to its presence in the potent α-adrenergic stimulant naphazoline (**4**). Since the presence of a methyl group attached at the benzylic position of medetomidine is important for optimal α_2-adrenergic activity, we prepared a methyl-substituted analogue (**5**) to determine the effect on the α_2-adrenergic potency of naphazoline (**4**). Our studies also investigated the effect of 1 versus 2 substitution on the naphthalene ring for α-adrenergic activity (e.g., **2**, **5**–**7** versus **3**, **8**, and **9**). The profile of biological activity for these newly synthesized compounds was assessed in rat aorta and human platelets as representative α_1- and α_2-adrenergic systems, respectively.

Scheme III[a]



[a] (a) 10% Pd–C; (b) dilute HCl.

Scheme IV[a]



[a] (a) NaH, $CO(OCH_3)_2$, then MeI; (b) NaOH, then concentrated HCl; (c) HCl gas, EtOH; (d) $(CH_2NH_2)_2$; (e) dilute HCl; (f) 10% Pd–C.

Chemistry

The synthesis of α-naphthyl 4-imidazole derivative **2** is outlined in Scheme I. 1-Naphthaldehyde (**10**) was treated with MeMgI in ether followed by $SOCl_2$ in toluene to give the crude chloro compound **11**[9] in 97% yield. Chloro compound **11** was treated with 1-(trimethylsilyl)imidazole in the presence of $TiCl_4$ in $CHCl_3$ to give 4-substituted imidazole **12** in 19.2% yield.[10] Treatment of the imidazole (**12**) with dilute HCl gave the desired imidazole hydrochloride **2**.

In Scheme II we show the synthesis of β-naphthyl-4-imidazole derivative **3**. β-Naphthyl 4-imidazole derivative **3** was synthesized starting with 2-naphthaldehyde (**13**) using the same conditions as reported for α-naphthyl analogue **2**. Treatment of aldehyde **13** with MeMgI in ether followed by $SOCl_2$ in toluene gave chloro compound **14**.[9] 1-(Trimethylsilyl)imidazole was allowed to react with

(1) Patil, P. N.; Miller, D. D.; Trendelenburg, U. Molecular Geometry And Adrenergic Drug Activity. *Pharmacol. Rev.* **1974**, *26*, 323–392.

(2) Miller, D. D.; Hamada, A.; Craig, E.; Christoph, G. G.; Gallucci, J. C.; Rice, P. J.; Banning, J. W.; Patil, P. N. Optically Active Catecholimidazolines: A Study Of Steric Interactions At α-Adrenoreceptors. *J. Med. Chem.* **1983**, *26*, 957–963.

(3) Ruffolo, R. R.; Rice, P. J.; Patil, P. N.; Hamada, A.; Miller, D. D. Differences In The Applicability Of The Easson–Stedman Hypothesis To The α_1- and α_2-Adrenergic Effects Of Phenethylamines And Imidazolines. *Eur. J. Pharmacol.* **1983**, *86*, 471–475.

(4) Scheinin, H.; Virtanen, R.; Macdonald, E.; Lammintausta, R.; Scheinin, M. Medetomidine-A Novel α_2-Adrenoceptor Agonist: A Review Of Its Pharmacodynamic Effects. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1989**, *13*, 635–651.

(5) Karjalalnen, A. J.; Virtanen, R. E.; Sevolalnen, E. J. UK Patent Application GB 2206880, 1988.

(6) Weinger, M. B.; Segal, I. S.; Maze, M. Dexmedetomidine, Acting Through Central Alpha-2 Adrenoceptors, Prevents Opiate-Induced Muscle Rigidity In The Rat. *Anesthesiology* **1989**, *71*, 242–249.

(7) Ruffolo, R. R., Jr.; Nichols, A. J.; Hieble, J. P. Functions Mediated by Adrenergic Receptors, In *The Alpha-2 Adrenergic Receptors*; Limbird, L. E., Ed.; Humana Press: Clifton, NJ, 1988, pp 187–280.

(8) Bylund, D. B. Subtypes Of α_2-Adrenoceptors: Pharmacological And Molecular Biological Evidence Converge. *Trends Pharmacol. Sci.* **1991**, *9*, 357–361.

(9) Berlinger, E.; Shieh, N. Relative Reactivities Of Polynuclear Aromatic Systems. The Solvolysis of α-Arylethylchlorides. *J. Am. Chem. Soc.* **1957**, *79*, 3849–3854.

(10) Karjalalnen, A. J.; Karkela, K. O. A. US Patent 4,443,466, 1984.

Table I. Adrenergic Activities Of Medetomidine (1) And Related Analogues In Rat Aorta and Human Platelets

	rat aorta (α_1)				human platelets (α_2)	
compd	EC_{50},[a] M [95% CL]	% maxima[b] ±SEM	K_B,[c] M (95% CL)	potency ratio[d]	IC_{50},[e] M [95% CL]	potency ratio[f]
1	3.1×10^{-7} [$(3.0–3.2) \times 10^{-7}$]	42 ± 7	-	1.0	3.3×10^{-6} [$(1.0–11) \times 10^{-6}$]	1.0
2	2.0×10^{-7} [$(0.87–5.3) \times 10^{-7}$]	27 ± 3	-	1.6	3.4×10^{-6} [$(2.3–5) \times 10^{-6}$]	0.97
3	-		6.8×10^{-8}	-	1.2×10^{-4} [$(0.92–1.6) \times 10^{-4}$]	0.028
4	1.2×10^{-8} [$(0.89–1.6) \times 10^{-8}$]	68 ± 2	-	25.8	1.1×10^{-6} [$(0.92–1.2) \times 10^{-6}$]	3.0
5	5.4×10^{-7} [$(2.4–12) \times 10^{-7}$]	62 ± 5	-	0.57	1.4×10^{-5} [$(0.77–2.5) \times 10^{-5}$]	0.24
6	2.0×10^{-7} [$(0.94–4.2) \times 10^{-7}$]	56 ± 6	-	1.6	3.4×10^{-5} [$(1–11) \times 10^{-5}$]	0.097
7	7.7×10^{-6} [$(2.8–21) \times 10^{-6}$]	40 ± 4	-	0.04	2.6×10^{-4} [$(1.1–6) \times 10^{-4}$]	0.013
8	-	-	2.6×10^{-7}	-	1.6×10^{-5} [$(0.74–3.3) \times 10^{-5}$]	0.21
9	-	-	1.5×10^{-6}	-	6.1×10^{-4} [$(4.9–7.4) \times 10^{-4}$]	0.0054

[a] EC_{50} = molar 50% effective concentration. Data expressed as the mean ±96% CL as given in parentheses. $N = 4$. [b] Data are expressed as the percent maximal analogue response relative to phenylephrine = 100%. [c] K_B = molar concentration of analogue which shifts concentration curve of phenylephrine to the right by 2-fold (0.3 log units). [d] Potency ratio = EC_{50}(medetomidine)/EC_{50}(analogue). [e] IC_{50} = molar 50% inhibitory concentration. Analogue concentration required to inhibit the epinephrine-induced aggregation response by 50%. N = 3–4. [f] Potency ratio = IC_{50}(medetomidine)/IC_{50}(analogue).

chloro compound **14** in the presence of $TiCl_4$ in $CHCl_3$, giving β-naphthyl 4-imidazole derivative **15** in 21% yield. Treatment of imidazole **15** with dilute HCl gave the desired imidazole hydrochloride.

The synthesis of imidazole hydrochloride **6** is outlined in Scheme III. The oxidation of naphazoline (**4**) to imidazole **16** was achieved by a new and mild oxidation method using Pd–C developed in our laboratory.[11] Treatment of imidazoline **4** with 10% Pd–C in refluxing toluene gave imidazole **16** in 83% yield, which was converted to hydrochloride salt **6** by treatment with dilute HCl in MeOH.

The synthesis of α-naphthyl 2-imidazole derivatives **5** and **7** is outlined in Scheme IV. α-Naphthylacetonitrile (**17**) was treated with dimethyl carbonate in the presence of NaH in the mixture of DMF and toluene; then MeI was added to give the methyl cyanoacetate derivative, which was in turn hydrolyzed with NaOH in aqueous ethanol and then decarboxylated, giving nitrile **18**[12] in 77% yield. Treatment of nitrile **18** with HCl gas in the presence of ethanol gave the imidate, which was then treated with ethylenediamine to give 2-substituted imidazoline **19** in 53% yield. Treatment of imidazoline **19** with dilute HCl gave the desired imidazoline hydrochloride **5**. The oxidation of imidazoline **19** to corresponding imidazole **20** was achieved in 89% yield by the same method outlined in Scheme III using 10% Pd–C in refluxing toluene. Imidazole **20** was converted to the hydrochloride salt **7** by treatment with dilute HCl.

The synthesis of the β-naphthyl 2-imidazole derivatives **8** and **9** was achieved via a different synthetic route as outlined in Scheme V. We could not obtain the nitrile derivative **21**[13] from 2-naphthylacetonitrile in good yield

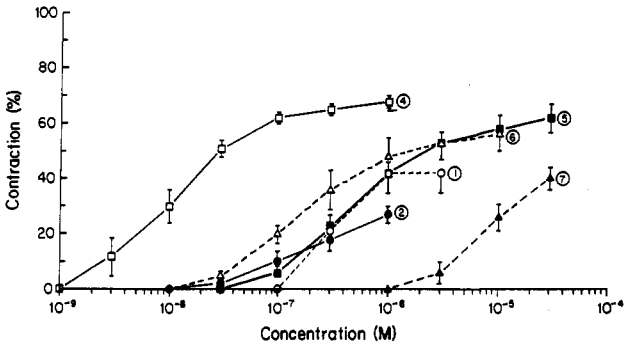


Figure 1. Dose–response curve of 1–7 on rat aorta.

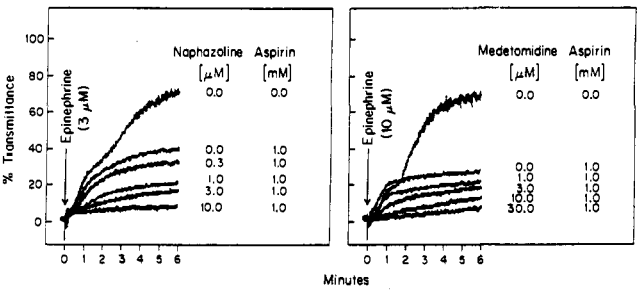
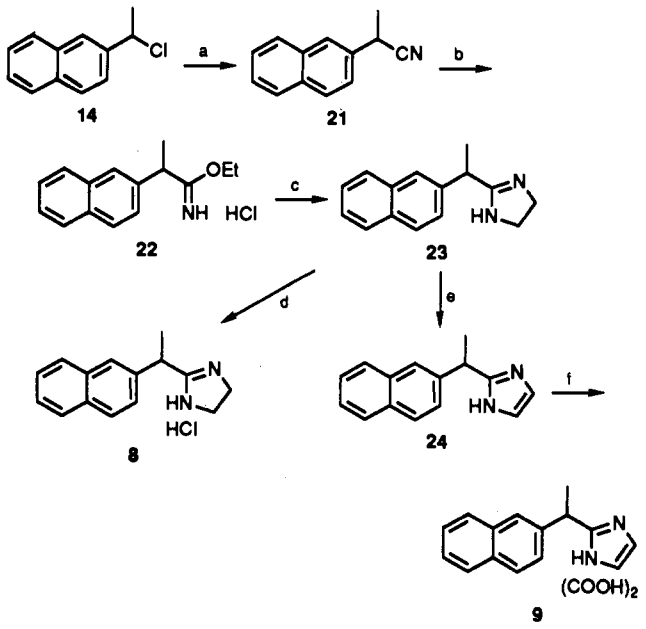


Figure 2. Dose–response curve of the inhibition by medetomidine (1) and naphazoline (4) on the platelet aggregation induced by epinephreine.

using the same synthetic method outlined in Scheme IV. However, treatment of **14** with NaCN in DMF at room temperature to 40 °C gave crude nitrile compound **21** with some impurities which were difficult to separate. Without any further purification, crude nitrile **21** was treated with HCl gas in the presence of ethanol in benzene to give imidate **22** in 65% yield, which was then treated with ethylenediamine in CH_2Cl_2 to yield imidazoline derivative **23**. Treatment of imidazoline **23** with dilute HCl gave imidazoline hydrochloride salt **8**. The oxidation of imidazoline **23** to corresponding imidazole **24** was achieved in 84% by the same method outlined in Scheme III using 10% Pd–C in refluxing toluene. Treatment of imidazole **24** with oxalic acid gave imidazole oxalic acid salt **9**.

(11) Amemiya, Y.; Hsu, F-L.; Miller, D. D. Dehydrogenation Of Imidazolines To Imidazoles With Pd-Carbon. *Synth. Commun.* **1990**, *20*, 2483–2489.
(12) Trehan, I. R.; Bala, K.; Singh, J. B. Synthesis Of 13-Aza-3-desoyx-11-methyl-18-nor-equilenin and 13-Aza-3-desoxy-18-nor-equilenin. *Indian J. Chem. Sect. B* **1979**, *18B*, 295–297.
(13) Harusawa, S.; Nakamura, S.; Yagi, S.; Kurihara, T.; Hamada, Y.; Shioiri, T. A New Synthesis Of Some Non-steroidal Anti-inflammatory Agents Via Cyanophosphates. *Synth. Commun.* **1984**, *14*, 1365–1371.

Scheme V[a]



[a] (a) NaCN; (b) HCl gas, EtOH; (c) $(CH_2NH_2)_2$; (d) dilute HCl; (e) 10% Pd–C; (f) $(COOH)_2 \cdot 2H_2O$.

Biological Results and Discussion

Substituted imidazoline and imidazole analogues were tested for α_1- and α_2-adrenoceptor activities on rat aorta and human platelets (Figures 1 and 2 and Table I). In aorta, the percentage of agonist response shown in Table I was calculated from the maximal response to the reference agonist phenylephrine. Figure 1 shows the concentration effect curves of the agonist analogues tested on rat aorta. Medetomidine (1) was a partial agonist with the maximal response of 42% and EC_{50} value of 3.1×10^{-7} M. The stimulation of aorta was completely blocked by the selective α_1-blocker prazosin (not shown). At 10^{-6} M, medetomidine analogue 2 shifted the dose–response curve of phenylephrine to the right with a reduction of the maximal response to 27% with an EC_{50} value of 2.0×10^{-7} M. The dissociation constant of 2 as a blocker was 3.0×10^{-7} M, a value close to the EC_{50} of the parent drug 1. Similarly, at 10^{-6} M, analogue 3 was a blocker of phenylephrine-induced contractions of aorta with a dissociation constant of 6.1×10^{-8} M.

Naphazoline (4) and analogues 5–7 were α_1-adrenoceptor agonists. On the basis of EC_{50} values, naphazoline (4) was the most potent molecule ($EC_{50} = 1.2 \times 10^{-8}$ M) and 7 was the least potent ($EC_{50} = 7.7 \times 10^{-6}$ M). With the exception of 6, the concentration–response curves of these compounds were significantly shifted to the right by prazosin. The K_B values of prazosin ranged from 1.1×10^{-10} M to 7.6×10^{-11} M, showing a competitive interaction with α_1-adrenoceptors. The response of drug 7 was completely blocked by 10^{-8} M prazosin. The most interesting and consistent structure–activity relationship in this series of compounds was the fact that 2-substituted naphthalene analogues 3, 8, and 9 were antagonists on α_1-adrenergic receptors, whereas the 2-substituted naphthalene analogues 2, 5–7 [each has a chemical structure in common with 1 (see highlighted portions of structure)] were all partial agonists in this same α_1-adrenergic (aorta) system (Table I).

Epinephrine activates platelet function, giving primary aggregation in aspirin-treated platelet preparations. Each of the medetomidine and naphazoline analogues were concentration-dependent inhibitors of human platelet aggregation induced by epinephrine. Figure 2 illustrates the actions of two parent molecules, medetomidine (1) and naphazoline (4), as inhibitors of epinephrine-induced aggregation in aspirin-treated platelets. In this regard, medetomidine (1) and analogue 2 were equiactive (IC_{50} $3.3–3.4 \times 10^{-6}$ M) with the greatest inhibitory activity, while 9 was the least potent inhibitor of platelet aggregation (Table I).

These results indicate that replacement of the catechol moiety of catecholimidazolines with a naphthalene ring does not abolish the α_1-adrenoceptor activity although the potency was decreased.[14-16] Introduction of either a double bond in the imidazoline ring or a methyl group in the carbon bridge reduced the α-adrenergic activity, which agrees with earlier reports.[17-19] The imidazoline or imidazole ring link to the 2-position of the naphthalene (3, 8, and 9) ring gave α_1-adrenoceptor antagonist activity while these same rings linked to the 1-position of naphthalene (2, 5–7) produced partial agonists in this adrenergic system.

The α_1- and α_2-adrenoceptor activities indicate that medetomidine (1), analogues 2 and 5, and naphazoline (4) were moderately potent vasoconstrictors, whereas 1, 2, and 4 were the most potent inhibitors of platelet aggregation (Table I). Relative to medetomidine and naphazoline, only analogue 2 appears to retain comparable affinity for an interaction with platelet α_2-adrenoreceptors (similar to the affinity of clonidine and epinephrine which induce platelet aggregation with EC_{50} values of 3.3×10^{-5} and 2.6×10^{-6} M, respectively[20]) and has low maximal contraction of aorta (α_1), and this compound is serving as a substance for further investigations.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared data were collected on a Beckman 4230 or Analect RFX-40 spectrophotometer. The NMR spectra were recorded on an IBM AF-250 spectrometer or an IBM-270 spectrometer and 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),

(14) Ruffolo, R. R.; Dillard, R. D.; Yaden, E. L.; Waddell, J. E. Receptor Interactions Of Imidazolines. II. Affinities And Efficacies Of Hydroxy-Substituted Tolazoline Derivatives In Rat Aorta. *J. Pharmacol. Exp. Ther.* **1979**, *211*, 74–79.

(15) Ruffolo, R. R.; Rosing, E. L.; Waddell, J. E. Receptor Interactions Of Imidazolines. I. Affinity And Efficacy For Alpha Adrenergic Receptors In Rat Aorta. *J. Pharmacol. Exp. Ther.* **1979**, *209*, 429–436.

(16) Ruffolo, R. R.; Waddell, J. E.; Yaden, E. L.; Dillard, R. D. Receptor Interactions Of Imidazolines. VI. Significance Of Carbon Bridge Separating Phenyl And Imidazoline Rings Of Tolazoline-like Alpha-Adrenergic Imidazolines. *J. Pharmacol. Exp. Ther.* **1980**, *214*, 535.

(17) Lamba-Kanwal, V. K.; Hamada, A.; Adejare, A.; Clark, M. T.; Miller, D. D.; Patil, P. N. Activation Of Alpha-1 Adrenoceptors Of Rat Aorta By Analogs Of Imidazolines. *J. Pharmacol. Exp. Ther.* **1988**, *245*, 793.

(18) Rice, P. J.; Hamada, A.; Miller, D. D.; Patil, P. N. Asymmetric Catecholimidazolines And Catecholamidines: Affinity and Efficacy Relationships At The Alpha Adrenoceptor In Rat Aorta. *J. Pharmacol. Exp. Ther.* **1987**, *242*, 121–130.

(19) Miller, D. D.; Hamada, A.; Clark, M. T.; Adejare, A.; Patil, P. N.; Shams, G.; Romstedt, K. J.; Kim, S. U.; Intrasuksri, U.; McKenzie, J. L.; Feller, D. R. Synthesis And α_2-Adrenoceptor Effects Of Substituted Catecholimidazoline and Catecholimidazole Analogues Human Platelets. *J. Med. Chem.* **1990**, *33*, 1138–1144.

(20) Ahn, C.; Hamada, A.; Miller, D. D.; Feller, D. R. Alpha-Adrenoceptor-Mediated Actions Of Optical Isomers and Desoxy Analogs Of Catecholimidazoline and Norepinephrine In Human Platelets. *Biochem. Pharmacol.* **1986**, *35*, 4095–4102.

integration, interpretation, and coupling constant (Hz). The mass spectra were obtained with a Kratos MS-25 RFA mass spectrometer or at The Ohio State University Chemical Instrument Center, with use of a VG70-2505 or a Kratos MS-30 mass spectrometer. All organic solvents were appropriately dried and/or purified prior to use.

4-[1-(1-Naphthyl)ethyl]imidazole Hydrochloride (2). To a solution of MeMgI in ether, which was prepared from 1.08 g (44.4 mmol) of Mg and 2.75 mL (44.2 mmol) of MeI in 100 mL of ether, was added a solution of 5.75 g (36.8 mmol) of 1-naphthaldehyde (10) in 10 mL of ether with cooling in an ice–water bath; then the resulting reaction mixture was stirred for 2 h at room temperature. To the reaction mixture was added 25 mL of 2 N HCl, and then the organic layer was separated from the aqueous layer. The organic layer was washed with 50 mL of brine and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave 6.20 g (97%) of the alcohol as a viscous oil. A solution of 6.34 g (36.8 mmol) of the alcohol and 5.37 mL (73.6 mmol) of thionyl chloride in 65 mL of toluene was refluxed for 4 h. The reaction mixture was evaporated in vacuo to give the residue as an oil. The residue was dissolved in 150 mL of ethyl acetate, washed successively with 50 mL of H_2O, 50 mL of saturated $NaHCO_3$, and 50 mL of brine, and dried over Na_2SO_4. The solvent was removed in vacuo to give 6.83 g (97%) of chloride 11 as an oil. To a solution of 7.9 mL (72.0 mmol) of $TiCl_4$ in 70 mL of chloroform was added a solution of 10.5 mL (71.6 mmol) of 1-(trimethylsilyl)imidazole (TMSI) in 70 mL of chloroform with cooling in an ice–water bath for 30 min. The resulting orange mixture was kept stirring for additional 30 min, and then a solution of 6.83 g (36.8 mmol) of chloride 11 in 35 mL of chloroform was added to the reaction mixture with cooling in an ice–water bath. The reaction mixture was kept stirring overnight. Water (150 mL) was added to the reaction mixture. The aqueous layer was washed with 3 × 100 mL of CH_2Cl_2, and then 150 mL of 2 N NaOH was added to make the aqueous layer basic. The aqueous layer was extracted with 3 × 100 mL of brine, dried over Na_2SO_4, and evaporated in vacuo to give a solid which was recrystallized from MeOH–CH_2Cl_2–hexane, yielding 1.56 g (19.6%) of the 4-imidazole derivative 12: mp 175.0–176.0 °C; ^{1}H NMR (CD_3OD, TMS) δ 8.16–7.25 (m, 7 H), 7.57 (s, 1 H), 6.74 (s, 1 H), 4.95 (q, J = 7.12 Hz, 1 H), and 1.72 (d, J = 7.12 Hz, 3 H). Anal. ($C_{15}H_{14}N_2$) C, H, N.

To a solution of 0.23 g (1.03 mmol) of imidazole 12 in 3 mL of MeOH was added 1.09 mL of 1 N HCl in MeOH. Evaporation of the solvent gave the solid, which was recrystallized from MeOH–ether to give 0.20 g (76%) of imidazole hydrochloride 2: mp 120.0–123.5 °C. Anal. ($C_{15}H_{15}ClN_2$) C, H, N.

4-[1-(2-Naphthyl)ethyl]imidazole Hydrochloride (3). To a solution of MeMgI in ether, which was prepared from 2.87 mL (46.1 mmol) of MeI and 1.13 g (46.5 mmol) of Mg in 60 mL of ether, was added a solution of 6.0 g (38.4 mmol) of 2-naphthaldehyde in 20 mL of ether with cooling in an ice–water bath, and the reaction mixture was kept stirring at room temperature overnight. To the reaction mixture was added 25 mL of 2 N HCl, and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with 2 × 50 mL of ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave the crude alcohol, which was recrystallized from EtOAc–hexane, giving 5.09 g (77%) of the alcohol: mp 72.0–73.0 °C. A solution of 2.43 g (14.1 mmol) of the alcohol and 3.08 mL (42.2 mmol) of thionyl chloride in 25 mL of toluene was refluxed for 4 h. The reaction mixture was evaporated in vacuo to give the residue as an oil. The residue was dissolved in 100 mL of ethyl acetate and washed successively with H_2O, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and evaporated in vacuo, giving 2.60 g (97.8%) of chloride 14, which can be recrystallized from toluene, giving needles: mp 64.0–65.0 °C. To a solution of 1.68 mL (15.3 mmol) of $TiCl_4$ in 14 mL of chloroform was added a solution of 2.05 mL (14.0 mmol) of TMSI in 7 mL of chloroform with cooling in an ice–water bath. The resulting orange mixture was kept stirring for 30 min, then a solution of 1.33 g (6.98 mmol) of chloride 14 in 7 mL of chloroform was added to the reaction mixture with cooling in an ice–water bath. The reaction mixture was kept stirring overnight. Water (100 mL) was added to the reaction mixture. The aqueous layer was washed with 3 × 50 mL of CH_2Cl_2, and then 35 mL of 2 N NaOH was added to make the aqueous layer basic. The basic aqueous layer was extracted with 3 × 50 mL of CH_2Cl_2. The combined organic layer was washed with 3 × 50 mL of brine, dried over Na_2SO_4, and evaporated in vacuo to give a solid which was recrystallized from CH_2Cl_2–hexane, yielding 0.33 g (21.2%) of 4-imidazole derivative 15: mp 156.0–157.0 °C; ^{1}H NMR (CD_3OD, TMS) δ 7.79–7.33 (m, 7 H), 7.66 (m, 7 H), 7.66 (s, 1 H), 6.83 (s, 1 H), 4.27 (q, J = 7.20 Hz, 1 H), and 1.68 (d, J = 7.20 Hz, 3 H). Anal. ($C_{15}H_{14}N_2$) C, H, N.

To a solution of 0.13 g (0.58 mmol) of imidazole 15 in 2 mL of MeOH was added 0.61 mL of 1 N HCl in MeOH. Evaporation of the solvent in vacuo gave the solid, which was recrystallized from MeOH–ether, yielding 0.138 g (91%) of imidazole hydrochloride 3: mp 173.0–174.0 °C: ^{1}H NMR (CD_3OD) δ 8.79 (d, J = 1.3 Hz, 1 H), 7.86–7.72 (m, 4 H), 7.49–7.33 (m, 4 H), 4.44 (q, J = 7.20 Hz, 1 H), and 1.76 (d, J = 7.20 Hz, 3 H). Anal. ($C_{15}H_{15}ClN_2$) C, H, N.

2-(1-Naphthylmethyl)imidazole Hydrochloride (6). A suspension of 1.00 g (4.76 mmol) of naphazoline (4) and 1.00 g of 10% Pd–C in 25 mL of toluene was refluxed under argon atmosphere for 9 days. Filtration of catalyst and evaporation of the filtrate in vacuo yielded 0.82 g (83%) of imidazole 16. To a solution of 0.82 g (3.94 mmol) of imidazole 16 in 10 mL of MeOH was added 4.13 mL of 1 N HCl in MeOH. Evaporation of the solvent in vacuo gave the crude solid which was recrystallized from MeOH–ether, yielding 0.84 g (87%) of imidazole hydrochloride 6: mp >260 °C; ^{1}H NMR (CD_3OD, TMS) δ 7.93–7.88 (m, 3 H), 7.59–7.42 (m, 6 H), and 4.82 (s, 2 H). Anal. ($C_{14}H_{13}ClN_2$) C, H, N.

2-[1-(1-Naphthyl)ethyl]imidazoline Hydrochloride (5). To a suspension of 5.02 g (126 mmol) of 60% NaH in 100 mL of toluene and 40 mL of DMF was added a solution of 20 g (120 mmol) of 1-naphthylacetonitrile in 100 mL of toluene at room temperature. After 1 h, 12 mL (142 mmol) of dimethyl carbonate was slowly added to the resulting reaction mixture, and the reaction mixture was kept stirring at room temperature overnight. Then 8.2 mL (132 mmol) of MeI was added to the reaction mixture at room temperature. After 2 h the reaction mixture was diluted with 200 mL of ethyl acetate and washed with 100 mL of H_2O and 2 × 100 mL of brine. The organic layer was dried over Na_2SO_4 and evaporated in vacuo to give 29.3 g of crude solid which was recrystallized from EtOAc–hexane, yielding 23.5 g (82%) of the product methyl 3-cyano-3-(1-naphthyl)propionate as needles: mp 112.0–113.0 °C. To a suspension of 11.0 g (46.1 mmol) of methyl 3-cyano-3-(1-naphthyl)propionate in 25 mL of EtOH was added 28 mL of 2 N NaOH at room temperature. After 4 h, 5.0 mL of concentrated HCl was carefully added to the reaction mixture and the resulting acidic mixture was refluxed for 3 h. After the evaporation of ethanol in vacuo and dilution with 50 mL of H_2O, the aqueous layer was extracted with 3 × 100 mL of ethyl acetate. The combined organic layer was washed successively with 100 mL of H_2O and 100 mL of brine and dried over Na_2SO_4. Evaporation of solvent in vacuo gave 6.45 g (77%) of methyl-substituted 1-naphthylacetonitrile 18 as an oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.91–7.79 (m, 3 H), 7.68–7.65 (1 H, m), 7.59–7.42 (m, 3 H), 4.57 (q, J = 7.20 Hz, 1 H), and 1.74 (d, J = 7.20 Hz, 3 H).

To a solution of 3.90 g (21.5 mmol) of nitrile 18 in 8 mL of benzene was added 1.89 mL (32.2 mmol) of EtOH, and an excess of HCl gas was passed into the solution with cooling in an ice–water bath. The resulting solution was stirred at room temperature for 1 h and then kept in a refrigerator overnight. The mixture was then poured into 200 mL of ether with cooling in an ice–water bath. After 1 h, decantation of ether gave the crude imidate as a gummy solid. To a solution of the crude imidate in 50 mL of CH_2Cl_2 was added a solution of 3.5 mL (52.4 mmol) of ethylenediamine in 30 mL of CH_2Cl_2 at room temperature, and the reaction mixture was kept stirring at room temperature overnight. The reaction mixture was diluted with 100 mL of saturated $NaHCO_3$ and extracted with 2 × 100 mL of CH_2Cl_2. The combined organic layer was washed with 50 mL of brine, dried over Na_2SO_4, and evaporated in vacuo to give 2.58 g (53%) of imidazoline 19 as an oil: ^{1}H NMR ($CDCl_3$, TMS) δ 8.17–8.13 (m, 1 H), 7.85–7.70 (m, 2 H), 7.53–7.38 (m, 4 H), 4.37 (q, J = 7.10 Hz, 1 H), 3.51 (br s, 4 H), and 1.69 (d, J = 7.10 Hz, 3 H). To a solution of 0.94 g (4.19 mmol) of imidazoline 19 in 10 mL of MeOH was added 2.20 mL of 2 N HCl in MeOH. Evaporation of the solvent in vacuo gave the crude solid which was recrystallized from

MeOH–ether, yielding 0.93 g (86%) of imidazoline hydrochloride **5**: mp 257.0–259.0 °C; ^{1}H NMR (CD_3OD, TMS): δ 8.03–7.87 (m, 3 H), 7.66–7.52 (m, 4 H), 4.92 (q, J = 7.0 Hz, 1 H), 3.94 (s, 4 H), and 1.78 (d, J = 7.20 Hz, 3 H). Anal. ($C_{15}H_{17}ClN_2$) C, H, N.

2-[1-(1-Naphthyl)ethyl]imidazole Hydrochloride (7). A suspension of 0.90 g of 10% Pd–C and 0.90 g (4.03 mmol) of imidazoline **19** in 20 mL of toluene was refluxed under argon for 9 days. Filtration of the catalyst and evaporation of the filtrate in vacuo yielded 0.80 g (89%) of imidazole derivative **20**. To a solution of 0.80 g (3.60 mmol) of imidazole **20** in 10 mL of MeOH was added 1.9 mL of 2 N HCl in MeOH. Evaporation of the solvent in vacuo gave the crude solid, which was recrystallized from MeOH–ether, yielding 0.56 g (60%) of imidazole hydrochloride **7**: mp 192.0–195.0 °C; ^{1}H NMR (CD_3OD, TMS) δ 7.32–7.29 (m, 1 H), 7.63–7.48 (m, 3 H), 8.04–7.89 (m, 3 H), 7.45 (s, 2 H), 5.43 (q, J = 7.20 Hz, 1 H), and 1.93 (d, J = 7.20 Hz, 3 H). Anal. ($C_{15}H_{15}ClN_2$) C, H, N.

2-[1-(2-Naphthyl)ethyl]imidazoline Hydrochloride (8). To a solution of 2.74 g (14.4 mmol) of chloride **14** in 55 mL of DMF was added 2.82 g (57.5 mmol) of NaCN at room temperature. The reaction mixture was stirred at 40 °C for 2 days, and then 2 N HCl (50 mL) was carefully added, and the mixture was diluted with 150 mL of H_2O and extracted with 3 × 100 mL of ethyl acetate. The combined organic layer was washed with 3 × 100 mL of brine and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave 1.72 g of the crude oil containing the desired product **21**. To a solution of 1.72 g of crude nitrile **21** in 3.5 mL of benzene was added 0.83 mL of EtOH, and an excess of HCl gas was passed into the solution with cooling in an ice–water bath. The resulting solution was stirred at room temperature for 1 h, and then kept in a refrigerator overnight. The mixture was then poured into 100 mL of ether with cooling in an ice–water bath. The resulting precipitate was filtered, washed with ether, and dried to yielded 1.38 g (65%) of imido ester hydrochloride **22**: mp 123.0–124.0 °C. To a solution of 1.38 g (5.23 mmol) of imidate **22** in 15 mL of CH_2Cl_2 was added a solution of 0.84 mL (12.6 mmol) of ethylenediamine in 5 mL of CH_2Cl_2 with cooling in an ice–water bath. The reaction mixture was stirred at room temperature overnight and then refluxed for 3 h. The reaction mixture was diluted with 50 mL of saturated $NaHCO_3$ and extracted with 2 × 50 mL of CH_2Cl_2. The combined organic layer was washed with 2 × 50 mL of brine, dried over Na_2SO_4, and evaporated in vacuo to yield a crude solid, which was recrystallized from EtOAc–hexane, giving 1.10 g (94%) of imidazoline **23**: mp 99.0–100.0 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 7.84–7.41 (m, 4 H), 3.83 (q, J = 7.20 Hz, 1 H), 3.58 (br, s, 4 H), and 1.64 (d, J = 7.20 Hz, 3 H). To a solution of 0.60 g (2.67 mmol) of the imidazoline (**23**) in 5 mL of MeOH was added 2.8 mL of 1 N HCl in MeOH. Evaporation of the solvent in vacuo gave a crude solid which was recrystallized from MeOH–ether, yielding 0.66 g (94%) of imidazoline hydrochloride **8**: mp 178.0–180.0 °C; ^{1}H NMR (CD_3OD) δ 7.93–7.86 (m, 4 H), 7.55–7.42 (m, 3 H), 4.28 (q, J = 7.26 Hz, 1 H), 3.93 (s, 4 H), and 1.72 (d, J = 7.26 Hz, 3 H). Anal. ($C_{15}H_{17}ClN_2$) C, H, N.

2-[1-(2-Naphthyl)ethyl]imidazoline Oxalic Acid (9). A suspension of 1.10 g of 10% Pd–C and 1.10 g (4.90 mmol) of imidazoline **23** in 30 mL of toluene was refluxed under an argon atmosphere for 9 days. Filtration of the catalyst and evaporation of the filtrate yielded 0.92 g (84%) of imidazole **24**. To a solution of 0.34 g (1.53 mmol) of imidazole **24** in 10 mL of MeOH was added 0.202 g (1.60 mmol) of oxalic acid dihydrate. Evaporation of the solvent in vacuo and recrystallization of the residue from MeOH–ether gave 0.39 g (82.2%) of imidazole oxalic acid **9**: mp 155.0–156.0 °C; ^{1}H NMR (CD_3OD) δ 7.91–7.34 (m, 7 H), 7.44 (s, 2 H), 4.75 (q, J = 7.26 Hz, 1 H), 1.87 (d, J = 7.26 Hz, 3 H). Anal. ($C_{17}H_{16}N_2O_4$) C, H, N.

Pharmacological Tests. Rat Aorta. Male albino rats (300–350 g) were used to obtain thoracic aorta after exposure to dry ice. Aortic strips were suspended in 10-mL organ baths containing physiological salt solutions maintained at 37 °C and continuously bubbled with a 5% CO_2–95% O_2 mixture.[17] Aortic strips were preincubated for 60 min with prazosin (10^{-8} M) before construction of the concentration–response curve for each drug. Matched control strips without the blocking drug were used and the shifts in the concentration–response curve were analyzed for the determination of the dissociation constant K_B value for the antagonist. A maximal response to phenylephrine in the tissue was 100% and the percentage of response for each drug was adjusted from this value.

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.[19] Aspirin (1 mM) was routinely added to platelet preparations 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.[19]

Data Analyses. Difference among mean values were evaluated by the Student's "t" test using the 5% level of significance. Analysis of concentration–response data and K_B or IC_{50} values of prazosin drugs in aorta and platelets, respectively, was performed using a computerized method.[21]

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Registry No. **2**, 137967-81-8; **3**, 137967-82-9; **4**, 550-99-2; **5**, 137967-83-0; **6**, 131548-86-2; **7**, 131548-87-3; **8**, 137967-84-1; **9**, 137967-86-3; **10**, 66-77-3; **11**, 62094-18-2; **11** alcohol, 1517-72-2; **12**, 137967-87-4; **13**, 66-99-9; **14**, 58464-06-5; **14** alcohol, 7228-47-9; **15**, 137967-88-5; **16**, 1019-21-2; **17**, 132-75-2; **18**, 24168-42-1; **18** imidale, 137967-91-0; **19**, 131548-80-6; **20**, 131548-85-1; **21**, 22250-78-8; **22**, 137967-89-6; **23**, 137967-90-9; **24**, 137967-85-2; methyl 3-cyano-3-(1-naphthyl)propionate, 137967-92-1.

(21) Tallarida, R. J.; Murray, R. B. In *Manual of Pharmacologic Calculations with Computer Programs, Second Edition*; Springer-Verlag, New York, 1987; p 53.