Articles

Synthesis and Cardiac Electrophysiological Activity of *N*-Substituted-4-(1*H*-imidazol-1-yl)benzamides—New Selective Class III Agents

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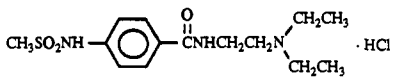
The synthesis and cardiac electrophysiological activity of 18 N-substituted imidazolylbenzamides or benzenesulfonamides are described. Compounds **6a,d,f–k** and 11 exhibited potency in the in vitro Purkinje fiber assay comparable to that of *N*-[2-(diethylamino)ethyl]-4-[(methylsulfonyl)amino]benzamide (1, sematilide), a potent selective class III agent which is undergoing clinical trials. These data indicate that the 1*H*-imidazol-1-yl moiety is a viable replacement for the methylsulfonylamino group for producing class III electrophysiological activity in the N-substituted benzamide series. *N*-[2-(Diethylamino)ethyl]-4-(1*H*-imidazol-1-yl)benzamide dihydrochloride (**6a**) was further studied in two in vivo models of reentrant arrhythmias and showed potency and efficacy comparable to those of 1.

Our group has been pursuing the development of compounds with class III electrophysiological activity (Vaughan Williams classification).[1] This type of agent prolongs action potential duration (and hence refractory period) in cardiac tissue with minimal effects on conduction. There are no selective class III agents on the market and compounds of this type should provide a useful alternative to the antiarrhythmic agents (predominately class I agents) currently available for clinical use.

We[2-4] and others[5-7] have been successful in using the (methylsulfonyl)amino moiety in a variety of structural classes to produce compounds with selective class III electrophysiological activity. Indeed, methylsulfonylation of the amino group in the class I drug procainamide affords the selective class III agent 1.[8] We were interested to learn



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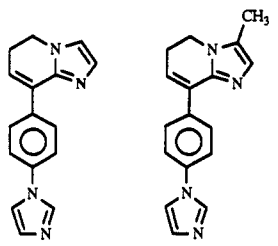
whether other functional groups could be used with N-substituted benzamides to give selective class III agents. In a series of 8-phenylimidazo[1,2-*a*]- and -[1,5-*a*]pyridines prepared as potential inotropic agents it was observed that substitution of the phenyl ring at the para position with a 1*H*-imidazol-1-yl moiety (e.g., **2** and **3**) produced com-



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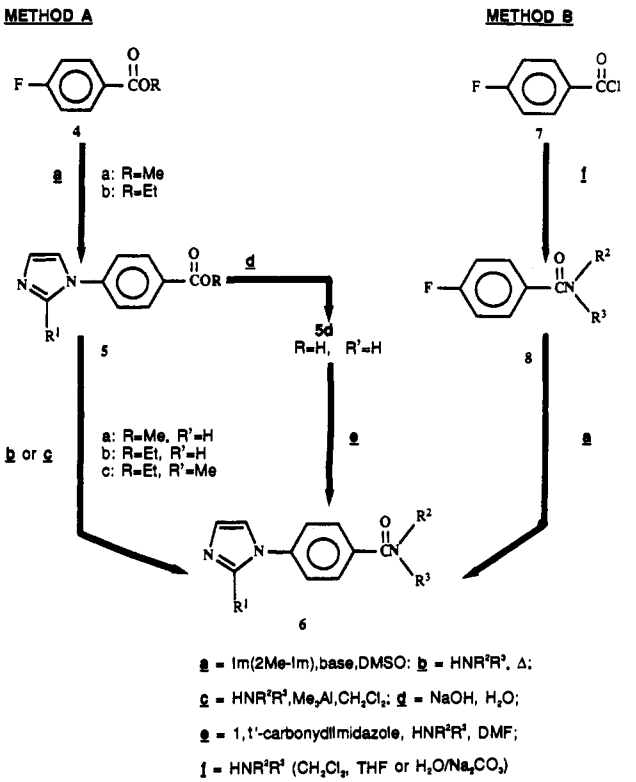
pounds with indications of class III electrophysiological activity.[9] On the basis of this observation, we prepared a series of 4-(1*H*-imidazol-1-yl)benzamides related to 1.

Scheme I



The synthesis and cardiac electrophysiological activity of these compounds are reported here.

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(3) Lis, R.; Morgan, T. K., Jr.; DeVita, R. J.; Davey, D. D.; Lumma, W. C., Jr.; Wohl, R. A.; Diamond, J.; Wong, S. S.; Sullivan, M. E. *J. Med. Chem.* **1987**, *30*, 696.
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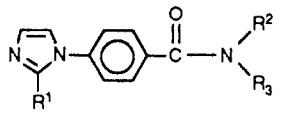
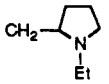
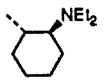
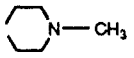
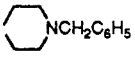
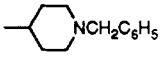
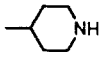
Table I. 4-(1*H*-Imidazol-1-yl)benzamides



	R^1	R^2	R^3	X	method	mp, °C	recryst solvent	elemental analysis
6a	H	H	$CH_2CH_2NEt_2$	2HCl	B	209–214	ethanol	C, H, N, Cl
6b	CH_3	H	$CH_2CH_2NEt_2$	$CH_3SO_3H{\cdot}0.75H_2O$	A	127–129	acetonitrile	C, H, N, S
6c	H	H	$CH_2CH_2NH_2$	$HCl{\cdot}H_2O$	A	244–248	methanol	C, H, N, Cl
6d	H	H	$CH_2CH_2NHCH_2C_6H_5$	HCl		209–212		C, H, N
6e	H	H	$CH_2CH_2N(CH_2C_6H_5)_2$	$0.45H_2O$	A	147–149		C, H, N[a]
6f	H	1-naph	$CH_2CH_2NEt_2$		B	182–184	acetone	C, H, N
6g	H	$CH_2C_6H_5$	$CH_2CH_2NEt_2$		B	94–95	ethyl acetate/hexane	C, H, N
6h	H	H	$CH_2CH_2CH_2NEt_2$	2HCl	B	212–214	2-propanol/methanol	C, H, N
6i	H	H		$TsOH{\cdot}0.6H_2O$	B	106–108	ethyl acetate/methanol	C, H, N, S[b]
6j	H	H		$HCl{\cdot}H_2O$	A	157–162	acetone/methanol	C, H, N, Cl
6k	H			$2HCl{\cdot}0.75H_2O$	B	236–239	ethanol	C, H, N, Cl
6l	H			$2CH_3SO_3H$	A	214–217	diethyl ether/ethanol	C, H, N
6m	H					114–119	acetonitrile	C, H, N
6n	H	H		$0.25H_2O$	A	171–173	methylene chloride/hexane	C, H, N
6o	H	H				129–130	acetonitrile	C, H, N

[a] H: calcd, 6.48; found, 6.04. [b] S: calcd, 6.66; found, 7.07.

Chemistry

The compounds for pharmacological evaluation were prepared by one of the two methods outlined in Scheme I. In method A, the methyl or ethyl ester of 4-fluorobenzoic acid **4a,b** was reacted with the appropriate imidazole in dimethyl sulfoxide using potassium carbonate as base to give 4-(1*H*-imidazol-1-yl)benzoic acid esters **5a–c**. Ester **5** was then coupled with the required amine either by direct condensation at elevated temperature or by the method of Weinreb[10] which employs trimethylaluminum activation of the amine to yield 4-(1*H*-imidazol-1-yl)-benzamides **6**.[11] Alternately, basic hydrolysis of **5a** provided the corresponding benzoic acid **5d**, which was reacted with 1,1′-carbonyldiimidazole and then with the requisite amine to give **6l** and **6n**. In method B, 4-fluorobenzoyl chloride (**7**) was used to acylate the amine to provide 4-fluorobenzamides **8**. With the exception of *N*-[2-(diethylamino)ethyl]-4-fluorobenzamide (**8a**), which was isolated and characterized, the crude benzamides were used in the subsequent step. The fluoro substituents of **8** were replaced by reaction with imidazole in dimethyl sulfoxide as above using either potassium carbonate or sodium hydride as base to give **6**. Compounds **6d**, **6m**, and **6o** were prepared by hydrogenolysis of **6e**, **6l**, and **6n**, respectively, over palladium/carbon catalyst. The *N*-substituted-4-(1*H*-imidazol-1-yl)benzamides prepared for this study are listed in Table I.

In order to examine the effect of positional isomerism in the benzamide series on electrophysiological activity, we prepared two analogues of **6a**. Esterification of 4-(1*H*-imidazol-2-yl)benzoic acid[12] with methanol using boron trifluoride as catalyst gave methyl ester **9**. The ester was reacted with *N*,*N*-diethyl-1,2-ethanediamine via the Weinreb procedure to afford, after treatment with hydrochloric acid, *N*-[2-(diethylamino)ethyl]-4-(1*H*-imidazol-2-yl)benzamide dihydrochloride (**10**). Activation of 3-(1*H*-imidazol-1-yl)benzoic acid[12b] with 1,1′-carbonyldiimidazole followed by reaction with *N*,*N*-diethyl-1,2-ethanediamine then hydrochloric acid provided *N*-[2-(diethylamino)-ethyl]-3-(1*H*-imidazol-1-yl)benzamide dihydrochloride (**11**).

We also prepared the benzenesulfonamide analogue of compound **6k**. In a procedure analogous to method B, reaction of 4-fluorobenzenesulfonyl chloride with 1-methylpiperazine yielded 1-[(4-fluorophenyl)sulfonyl]-4-methylpiperazine (**12**). Reaction of **12** with imidazole in

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(8) Sematilide hydrochloride, CK-1752A.
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(10) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.
(11) (a) Lis, R.; Lumma, W. C., Jr.; Morgan, T. K., Jr.; Nickisch, K.; Wohl, R. A. U.S. Patent 4,804,662, 1989 [*Chem. Abstr.* **1989**, *110*, 231626*q*]. (b) Preliminary reports of our work were presented: Xth International Symposium on Medicinal Chemistry, Budapest, Hungary, August, 1988; Abstract P-116. 196th American Chemical Society National Meeting, Los Angeles, CA, September, 1988; MEDI 113.
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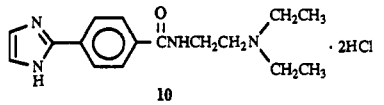

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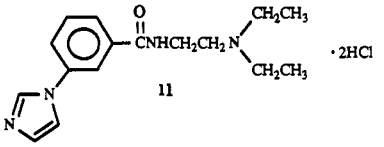

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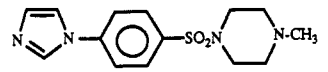

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dimethyl sulfoxide with sodium hydride as base yielded 1-[[4-(1*H*-imidazol-1-yl)phenyl]sulfonyl]-4-methylpiperazine (**13**).

Pharmacology

The electrophysiological characteristics of the new compounds were evaluated by using standard microelectrode techniques in isolated canine cardiac Purkinje fibers.[13] The effects of the compounds on action poential duration (APD) and the rate of rise of phase 0 ($\dot{V}_{max}$) of the action potential were determined simultaneously at a basic cycle length of 1 s. In Table II we report the percent change in APD at 95% repolarization ($\Delta\%APD_{95}$) at a concentration of 10 μM, the maximum observed percent change in APD_{95} (max $\Delta\%APD_{95}$) with the concentration at which the maximum occured, the percent change in $\dot{V}_{max}$ ($\Delta\%\dot{V}_{max}$) at 10 μM, and the maximum observed percent change in $\dot{V}_{max}$ (max $\Delta\%\dot{V}_{max}$) with the associated concentration. Decreases in $\dot{V}_{max}$ of <10% or increases in $\dot{V}_{max}$ were not considered biologically relevant and were classified as minimal (M). Also reported is the concentration (interpolated) of test compound which caused a 20% increase in APD_{95} ($C_{20}APD_{95}$). We have found that compounds which exhibit a $C_{20}APD_{95}$ at <10 μM usually are efficacious in vivo at reasonable doses (ca. 10 mg/kg iv or lower). The test compounds were compared to the selective class III agent 1. A compound was considered to have selective class III activity if it increased APD by 20% without causing a significant (≥10%) decrease in $\dot{V}_{max}$.

Due to good activity in the in vitro Purkinje fiber model and structural similarity to 1, compound **6a** was further studied in vivo and compared to the standard 1. Electrophysiological activity was assessed in anesthetized dogs after either intravenous or intraduodenal administration by using the extrastimulus conduction-interval technique of Carson and Dresel.[14] In this method, effects on functional refractory period (FRP, indicative of class III activity) and conduction time (CT, indicative of class I activity) were determined. Heart rate (HR) and blood pressure (BP) were also monitored. To be considered active in this model a compound must increase FRP or CT by ≥12%. After intravenous administration the duration of the drug effect was monitored and the half-life of the electrophysiological effect was determined. The intraduodenal model was used to obtain an indication of oral bioavailability.

Antiarrhythmic efficacy was studied in two canine models of programmed electrical stimulation (PES) induced arrhythmias. The PES technique is used in the clinical setting to assess the efficacy of antiarrhythmic drugs in patients. In the first model (AAI) anesthetized open chest dogs were studied in the PES protocol 24 h after an infarction was surgically produced by using the two-stage coronary occlusion method of Harris.[15] In the second model (AAII) conscious dogs were studied in the PES protocol 3–8 days after production of an infarct by using the occlusion/reperfusion method of Karagueuzian et al.[16] In each model, two control arrhythmias were induced prior to administration of the test compound. Sustained ventricular tachycardias were terminated by burst pacing; ventricular fibrillation was terminated by direct current countershock. To be considered effective in the efficacy models, the test compound had to prevent PES induction of an arrhythmia in at least two of three animals. The results of the in vivo studies are presented in Table III.

Results and Discussion

Imidazol-1-ylbenzamides **6a,d,f–l,n** and 11 exhibited activity in the Purkinje fiber assay (prolongation of APD_{95}) comparable to or better than that of the standard 1. Compounds **6m**, **10**, and **13** were only weakly active ($C_{20}APD_{95}$ > 10 μM), while **6b,c,e,o** were essentially inactive ($C_{20}APD_{95}$ was not reached). All active compounds were selective class III agents (little or no effect on $\dot{V}_{max}$) except for **6f** and **6m**, which showed significant effects on $\dot{V}_{max}$ at higher (≥10 μM) concentrations.

A comparison of **6a** with **6b** and **10** indicates that there are strict requirements for substitution on the imidazole ring and position of attachment on the imidazole for class III electrophysiological activity. Compound **6b** with a methyl group at the 2-position on the imidazole ring is inactive. Attachment of the imidazole moiety to the benzene ring through the 2-carbon of the imidazole (as in **10**) results in very weak activity relative to **6a** (attachment through the imidazole nitrogen). In contrast, compound 11, with the 1*H*-imidazol-1-yl moiety attached at the meta position of the benzamide, exhibited comparable activity in the Purkinje fiber assay to **6a** (para attachment). This result was somewhat surprising to us since in the (methylsulfonyl)amino series the meta analog of 1 was essentially inactive [$C_{20}APD_{95}$ was not reached at concentrations up to 30 μM (two experiments) or 100 μM (one experiment)].[17] Substitution of SO_2 for C=O in the benzamide as in **6k** → **13** results in a ca. 10-fold decrease in activity. In general, a variety of aminoalkyl substituents on the benzamide nitrogen are well tolerated with the exception of **6c** (2-aminoethyl), **6e** [2-(dibenzylamino)ethyl], and **6o** (4-piperidinyl).

In the in vivo electrophysiology model, compound **6a** exhibited comparable, although slightly less potent, class III activity (increase in FRP) as the standard 1 after both intravenous and intraduodenal administration, which indicates that **6a** should be orally bioavailable. Both **6a** and 1 had minimal (≤5% change) effects on CT (increase in CT = class I activity) demonstrating the *selective* class III activity of the compounds. The half-life for the FRP increase of **6a**, determined in the intravenous study (>4 h), is approximately twice that of 1. As expected for class III agents in this model, both **6a** and 1 caused a moderate decrease in heart rate. The blood pressure effects of **6a** and 1 were not significantly different from control values at the doses studied.

Compound **6a** was equieffective as 1 in both the an-

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(17) Unpublished results, Berlex Laboratories.

Table II. Intracellular Electrophysiology in Canine Purkinje Fiber of (1*H*-Imidazolyl)benzamides

no.	N^a	concn range,[b] μM	Δ% APD_{95}[c] at 10 μM [range]	max Δ% APD_{95}[d] [range, concn]	$C_{20}APD_{95}$,[e] μM [range]	Δ% V_{max}[f] at 10 μM [range]	max Δ% V_{max}[g] [range, concn]
6a	3	0.1–100 (1) 0.1–30 (2)	34 [31–38]	56 [100 μM] 52.5 [52–53, 30 μM]	2.9 [2.2–3.4]	M [2–8]	M [100 μM] M [30 μM]
6b	4	1–100 (1) 0.1–30 (3)	4 [1–7]	16 [100 μM] 13 [30 μM]	NR	M [−15–2]	M [100 μM] M [−30–6, 30 μM]
6c	2	1–100 (1) 0.1–30 (1)	1 [0–2]	13 [100 μM] 10 [30 μM]	NR	M (1 expt)	M (1 expt)
6d	2	1–100 (1) 0.1–50 (1)	41 [33–49]	59 [100 μM] 41 [50 μM]	1.2 [1.1–1.4]	M [−8–(−1)]	−11 [100 μM] M [50 μM]
6e	2	0.1–30	6 [−2–14]	6.5 [−4–17, 30 μM]	NR	M [−2–13]	M [30 μM]
6f	4	0.1–30	28 [16–46]	39 [1 μM] 18 [1 μM] 46 [10 μM] 24 [1 μM]	0.4 [0.2–0.6] (3 expts) NR (1 expt)	−14 [−16–(−12)] (2 expts)	−31 [−36–(−27), 30 μM] (2 expts)
6g	2	0.1–30	65 [61–70]	65 [59–71, 30 μM]	0.5 [0.4–0.6]	M [−8–(−2)]	M [−11–(−6), 30 μM]
6h	4	0.1–30 (3) 1–30 (1)	40 [21–58]	48 [24–71, 30 μM]	3 [0.4–8.5]	NA	NA
6i	4	0.1–100	39 [29–50]	72 [44–94, 100 μM]	3 [2.2–4.5]	−13 [−22–(−7)]	−26 [−44–(−17), 100 μM] (3 expts) M [100 μM] (1 expt)
6j	6	1–100 (1) 0.1–30 (2) 0.1–100 (3)	60 [41–79]	85 [79–90, 100 μM] (2 expts)	1.2 [0.8–2.1]	M [−22–(−1)]	−46 [−100–(−12), 100 μM] (3 expts)
6k	4	0.1–10 (1) 0.1–30 (3)	32 [27–38]	31 [10 μM] 55 [45–62, 30 μM]	3.7 [3.2–4.9]	M [−8–11]	M [10 μM] M [30 μM]
6l	2	0.1–30	46 [44–49]	46 [44–49, 10 μM]	0.9 [0.7–1.0]	M [−7–2]	M [−14–(−1), 30 μM]
6m	4	0.1–30	17 [9–20]	28 [13–35, 30 μM]	10.5 [10.3–10.6,3] (3 expts) NR (1 expt)	M[−29–8]	−15 [−40–7, 30 μM]
6n	2	0.1–30	75 [65–84]	97 [84–110, 30 μM]	0.7 [0.3–1.0]	M [−6–3]	M [30 μM]
6o	2	0.1–30	5 [−1–10]	10 [2–17, 3 μM]	NR	M [−2–10]	M [30 μM]
10	4	0.1–100	7 [5–9]	31 [20–54, 100 μM]	65 [29–100]	M [−18–3] (3 expts)	−14 [−19–(−9), 100 μM], (3 expts)
11	4	0.1–30 (2) 0.1–100 (2)	27 [9–45]	60 [41–79, 30 μM] 50 [25–75, 100 μM]	4.0 [2.3–7.4] (3 expts) 36.6 (1 expt)	M [−13–(−1)] (3 expts)	M [−19–(−3), 100 μM] (2 expts) M [−4, 30 μM] (1 expt)
13	3	0.1–30 (1) 0.1–100 (2)	9 [2–15]	14 [30 μM] 24 [22–26, 100 μM]	NR (1 expt) 39 [21–57] (2 expts)	M [−23–3]	−23 [10 μM] (1 expt) M [100 μM] (2 expts)
1	18	*h*	31 [13–55]	51 [32–68, 30 μM][i] 65 [27–105, 100 μM][i]	4.4 [1.9–11]	M [−13–27][j]	M [−15–(−2), 30 μM][k] M [−17–22, 100 μM][l]

[a] Number of experiments. [b] Concentration range studied (given for each experiment when varied). [c] Percent increase or decrease observed in action potential duration at 95% repolarization (APD_{95}) at a 10 μM concentration of the test compound. Lowest and highest experimental values given in brackets. [d] Maximum percent increase or decrease in APD_{95} observed for the test compound. Lowest and highest experimental values and concentration given in brackets. [e] Concentration (interpolated) of test compound which caused a 20% increase in APD_{95}. Lowest and highest values given in brackets. NR = not reached. [f] Percent change in $\dot{V}_{max}$ at a 10 μM concentration of the test compound. Decreases in $\dot{V}_{max}$ of <10% or increases in $\dot{V}_{max}$ were not considered to be significant and are classified as minimal (M). When $\dot{V}_{max}$ is not available for all experiments, the number of experiments is shown. Range given in brackets. NA = not available. [g] Maximum observed percent change in $\dot{V}_{max}$ and the concentration at which it was observed. Range and concentration given in brackets; when change is minimal (M) for all concentrations in the experiments, the range is not given. [h] Concentration ranges: 0.1–10 μM (four expts); 1–10 μM (two expts); 1–100 μM (one expt); 0.1–100 μM (eight expts), and 1–30 μM (three expts). [i] Nine expts. [j] Fourteen expts. [k] Five expts. [l] Six expts.

esthetized and conscious PES efficacy models. This result suggests that **6a** should be a clinically effective antiarrhythmic agent.

Conclusion

We have shown for a series of benzamide class III antiarrhythmic agents that the 4-(1*H*-imidazol-1-yl)moiety is a suitable replacement for the 4-[(methylsulfonyl)amino] group. Requirements for the imidazole moiety are specific since substitution of the 1*H*-imidazol-1-yl moiety at the two position by methyl (as in **6b**) or change in the imidazole attachment (i.e., 1*H*-imidazol-2-yl, as in **10**) results in compounds with little or no class III activity. Moving the substituent from the para to meta position on the benzene ring (as in **11**) maintained class III activity.

Compound **6a** exhibited activity comparable to the standard **1** (sematilide) in both in vitro and in vivo models and is an attractive candidate for clinical development.

Experimental Section

Melting points were taken on a Fisher-Johns or a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Berlex Analytical Section, Cedar Knolls, NJ; Galbraith Laboratories, Knoxville, TN; or Microlit Laboratories, Caldwell, NJ, and the results were within ±0.4% of the calculated values except where indicated. NMR spectra were recorded with either a Varian EM-360 (60 MHz) or a Varian XL-300 (300 MHz) spectrometer. Tetramethylsilane was used as the internal standard in all solvents except D_2O, where 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propanoic acid sodium salt was employed. IR spectra were obtained on either a Beckmann Acculab 2 or a Sargent Welch 3-300 spectrometer. All NMR and IR spectra were consistent with the assigned structures.

4-(1*H*-Imidazol-1-yl)benzoic Acid Methyl Ester (5a). A mixture of 101.6 g (0.65 mol) of 4-fluorobenzoic acid methyl ester (**4a**), 66.7 g (0.98 mol) of imidazole, and 182 g (1.31 mol) of potassium carbonate in 100 mL of dimethyl sulfoxide was heated at 120 °C for 3 h under a nitrogen atmosphere. The reaction mixture was then cooled and poured into 500 mL of cold water. The resulting precipitate was filtered. The precipitate was dissolved in methylene chloride, the aqueous layer was separated, and the methylene chloride solution was treated with charcoal and anhydrous sodium sulfate. After removal of the sodium sulfate and charcoal, the methylene chloride was evaporated to give a pale yellow solid, which was recrystallized from ethanol to give 52.1 g (40%) of **5a**: mp 126–128 °C; IR ($CHCl_3$) 1705

Table III. In Vivo Pharmacology of 6a and 1

In Vivo Electrophysiology

cmpd	n[a]	dose,[b] mg/kg	Δ%FRP[c]	$t_{1/2}$,[d] h	HR[e]
6a[f]	6	3 (iv)	+13 ± 1	>4	−18 ± 1
	2	10 (id)	+12 ± 4	ND	−15 ± 3
	2	30 (id)	+19 ± 4	ND	−29 ± 4
1[f]	5	3 (iv)	+19 ± 2	2	−23 ± 3
	4	10 (id)	+15 ± 5	ND	−17 ± 4
	1	30 (id)	+18	ND	−17

PES Efficacy Model

	anesthetized dog		conscious dog	
cmpd	no. effective/ no. tested[g]	effective dose,[h] mg/kg	no. effective/ no. tested[g]	effective dose,[h] mg/kg
6a	3/4	1 (1)	4/6	0.3 (3)
		10 (2)[i]		3 (1)[j]
1	4/5	0.3 (1)	8/9	0.3 (2)
		1 (2)		1 (5)
		3 (1)[i]		10 (1)[i]

[a] Number of experiments. [b] Dose tested in milligrams per kilogram; route of administration shown in parentheses: iv = intravenous, id = intraduodenal. [c] Percent change ± standard error from control value for the functional refractory period. [d] The half-life in hours of the electrophysiological effect. Determined from the time interval between the maximum effect on FRP and the corresponding half maximal value. ND = not determined. [e] Percent change ± standard error from control value for heart rate. [f] The effect of 6a and 1 on conduction time and blood pressure were not significantly different from control values after either intravenous or intraduodenal administration. [g] Number of animals in which sustained ventricular tachycardia or ventricular fibrillation was not inducible after drug administration over the number of animals tested. Test animals were inducible during two control periods prior to drug administration. [h] Effective dose of the test compound with the number of animals at which a given dose was effective shown in parentheses. [i] Not effective in one animal at 10 mg/kg. [j] Not effective in two animals at 3 mg/kg (one animal) and 10 mg/kg (one animal).

(carbonyl) cm^{-1}; NMR ($CDCl_3$) δ 3.97 (s, 3 H), 7.28 (m, 1 H), 7.37 (m, 1 H), 7.50 (d, 2 H), 7.97 (m, 1 H), 8.20 (d, 2 H). Anal. ($C_{11}H_{10}N_2O_2$) C, H, N.

4-(2-Methyl-1*H*-imidazol-1-yl)benzoic Acid Ethyl Ester (5c). The title compound was prepared from 4-fluorobenzoic acid ethyl ester (**4b**) and 2-methyl-1*H*-imidazole by the procedure used for compound **5a** above in 33% yield (not recrystallized): mp 67–70 °C; NMR ($CDCl_3$) δ 1.43 (t, 3 H), 2.41 (s, 3 H), 4.42 (quar, 2 H), 7.05 (m, 2 H), 7.39 (d, 2 H), 8.18 (d, 2 H). Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.

***N*-[2-(Diethylamino)ethyl]-4-fluorobenzamide (8a).** To 9.0 g (57 mmol) of **7** in 160 mL of tetrahydrofuran cooled to 5 °C under a nitrogen atmosphere was added dropwise 6.6 g (57 mmol) of *N,N*-diethyl-1,2-ethanediamine in 15 mL of tetrahydrofuran. The reaction mixture was allowed to warm to ambient temperature and was stirred overnight. After this time the solvent was removed in vacuo and the residue was dissolved in 100 mL of water. The aqueous solution was taken to pH = 12 with aqueous sodium hydroxide solution and extracted with two 100-mL portions of methylene chloride. The solvent was evaporated and the residue was Kugelrohr distilled (120–130 °C at 0.05 mmHg). Redistillation provided 3.00 g (22%) of **8a**: bp 127–128 °C (0.12 mmHg); IR (neat) 1640 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 0.97 (t, 6 H), 2.50 (quar, 4 H), 2.54 (t, 2 H), 3.32 (dt, 2 H), 7.29 (dd, 2 H), 7.91 (dd, 2 H), 8.45 (t, 1 H). Anal. ($C_{13}H_{19}FN_2O$) C, H, N.

***N*-[2-(Diethylamino)ethyl]-4-(1*H*-imidazol-1-yl)benzamide Dihydrochloride (6a).** A mixture of 36.7 g (0.154 mol) of **8a**, 12.57 g (0.185 mol) of imidazole, and 42.6 g (0.308 mol) of potassium carbonate in 50 mL of dimethyl sulfoxide was heated at 125 °C for 44 h. The reaction mixture was cooled and poured into 500 mL of water. The aqueous mixture was extracted with three 200-mL portions of methylene chloride. The combined extracts were dried over anhydrous sodium sulfate. After filtration of the drying agent, the solvent was evaporated and the residue was dissolved in 100 mL of ethanol. The ethanolic solution was adjusted to pH = 1 with concentrated hydrochloric acid. Water was removed by azeotropic distillation with additional ethanol. The solution was cooled in an ice/water bath, and the resulting crystals were filtered to give 34 g (61%) of **6a**. Recrystallization (charcoal treatment) from ethanol provided **6a**: IR (Nujol) 1645 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 1.25 (t, 6 H), 3.19 (m, 4 H), 3.26 (m, 2 H), ca. 3.5 (br s, 1 H), 3.71 (dt, 2 H), 7.93 (s, 1 H), 7.97 (d, 2 H), 8.23 (d, 2 H), 8.39 (s, 1 H), 9.36 (t, 1 H), 9.82 (s, 1 H), 10.78 (br s, 1 H).

***N*-[2-(Diethylamino)ethyl]-4-(2-methyl-1*H*-imidazol-1-yl)benzamide Methanesulfonic Acid Salt (1:1) (6b).** The title compound was prepared from **5b** and *N,N*-diethyl-1,2-ethanediamine in 37% yield by a procedure similar to that for **6j** below: IR (KBr) 1640 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 1.22 (t, 6 H), 2.34 (s, 6 H, imidazole CH_3 and CH_3SO_3H) 3.15–3.30 (m, 6 H), 3.39 (br s, 1 H), 3.63 (dt, 2 H), 6.98 (s, 1 H), 7.38 (s, 1 H), 7.60 (d, 2 H), 8.00 (d, 2 H), 8.86 (t, 1 H).

***N*-(2-Aminoethyl)-4-(1*H*-imidazol-1-yl)benzamide Hydrochloride Monohydrate (6c).** A mixture of 2.0 g (9.2 mmol) of 4-(1*H*-imidazol-1-yl)benzoic acid ethyl ester (**5b**) and 9.0 g (0.15 mol) of 1,2-ethanediamine was heated at reflux for 24 h under a nitrogen atmosphere. The excess diamine was then removed in vacuo and the residue was dissolved in methanol. The methanolic solution was acidified to pH = 6.5 with concentrated hydrochloric acid, then the solvent was removed. The residue was triturated with ethanol and filtered to give 1.99 g of crude **6c** as an off-white solid. Recrystallization from methanol provided 1.29 g (49%) of **6c**: IR (KBr) 1650 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 3.02 (t, 2 H), 3.57 (dt, 2 H), 7.15 (s, 1 H), 7.82 (d, 2 H), 7.89 (s, 1 H), 8.10 (d, 2 H), ca. 8.22 (br s, 3 H), 8.42 (s, 1 H), 8.98 (t, 1 H).

4-(1*H*-Imidazol-1-yl)-*N*-[2-[(phenylmethyl)amino]ethyl]benzamide Hydrochloride (6d). A solution of 4.0 g (9.7 mmol) of **6e** in 25 mL of methanol and 7 mL of 1.35 M methanolic hydrogen chloride was hydrogenolyzed over 0.5 g of 10% palladium on carbon at 19 psi. At the completion of the reaction, the catalyst was filtered, and the solvent was evaporated. The residue was triturated with hot ethanol, filtered, and dried to afford 2.3 g (66%) of **6d**: IR (KBr) 1650 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 3.13 (t, 2 H), 3.65 (dt, 2 H), 4.21 (s, 2 H), 7.15 (s, 1 H), 7.42 (m, 3 H), 7.58 (m, 2 H), 7.81 (d, 2 H), 7.88 (s, 1 H), 8.06 (d, 2 H), 8.41 (s, 1 H), 8.97 (t, 1 H), 9.37 (br s, 2 H).

4-(1*H*-Imidazol-1-yl)-*N*-[2-[bis(phenylmethyl)amino]ethyl]benzamide (6e). A mixture of 4.23 g (21 mmol) of **5a** and 5.00 g (21 mmol) of *N,N*-bis(phenylmethyl)-1,2-ethanediamine in 10 mL of xylenes was heated at reflux for 36 h. On cooling a precipitate formed which was filtered and dried in vacuo to give 5.11 g (58%) of **6e**: IR (KBr) 1650 (amide I) cm^{-1}; NMR ($CDCl_3$) 2.73 (t, 2 H), 3.50 (dt, 2 H), 3.64 (s, 4 H), 6.48 (br t, 1 H), 7.24–7.42 (m, 12 H), 7.46 (d, 2 H), 7.72 (d, 2 H), 7.95 (s, 1 H).

***N*-[2-(Diethylamino)ethyl]-4-(1*H*-imidazol-1-yl)-4-(1-naphthalenyl)benzamide (6f).** Reaction of *N,N*-diethyl-*N'*-(1-naphthalenyl)-1,2-ethanediamine[18] in tetrahydrofuran with **7** in a manner similar to that described for **8a** afforded crude *N*-[2-(diethylamino)ethyl]-4-fluoro-*N*-(1-naphthalenyl)benzamide (**8f**) in 99% yield as a yellow oil [NMR ($CDCl_3$) δ 1.05 (t, 6 H), 2.65 (quar, 4 H), 2.85 (m, 1 H), 2.95 (m, 1 H), 3.65 (m, 1 H), 4.60 (m, 1 H), 6.70 (dd, 2 H), 7.30 (m, 3 H), 7.35 (t, 1 H), 7.55 (t, 1 H), 7.60 (t, 1 H), 7.80 (d, 1 H), 7.90 (d, 1 H), 8.05 (d, 1 H)]. The oil was used in the subsequent step without purification. Benzamide **8f** was reacted with imidazole in a manner similar to that used for the preparation of **5a** to give **6f**: IR (KBr) 1640 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 0.90 (t, 6 H), 2.43 (quar, 4 H), 2.67 (m, 2 H), 3.56 (m, 1 H), 4.33 (m, 1 H), 7.01 (s, 1 H), 7.32 (d, 2 H), 7.39 (d, 2 H), 7.43 (m, 2 H), 7.58 (t, 1 H), 7.64 (s, 1 H), 7.65 (t, 1 H), 7.83 (d, 1 H), 7.97 (d, 1 H), 8.04 (d, 1 H), 8.17 (s, 1 H).

***N*-[2-(Diethylamino)ethyl]-4-(1*H*-imidazol-1-yl)-*N*-(phenylmethyl)benzamide (6g).** Reaction of *N,N*-diethyl-*N'*-(phenylmethyl)-1,2-ethanediamine[19] in tetrahydrofuran with **7** using the same procedure as that used in the preparation of **8a**

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(19) Godefroi, E. F. *J. Org. Chem.* **1968**, *33*, 860.

provided crude *N*-[2-(diethylamino)ethyl]-4-fluoro-*N*-(phenylmethyl)benzamide (**8g**) in 99% yield as a yellow oil [NMR ($CDCl_3$, T = 50 °C) δ 1.00 (br, 2 H), 2.45 (br, 4 H), 2.55 (br, 2 H), 3.40 (br, 2 H), 4.60 (br, 2 H), 7.00 (t, 2 H), 7.30 (m, 5 H), 7.45 (dd, 2 H)]. Reaction of **8g** with imidazole under conditions used for the preparation of **5a** gave, after chromatography on silica gel [CH_3CN + NH_4OH (49 + 1)] and recrystallization from ethyl acetate, a 39% yield of **6g**: IR (KBr) 1625 (amide I) cm^{-1}; NMR (Me_2SO-d_6) 0.86 (t, 6 H), 2.35 (quar, 4 H), 2.55 (t, 2 H), 3.35 (t, 2 H), 4.65 (s, 2 H), 7.09 (s, 1 H), 7.30 (m, 5 H), 7.53 (d, 2 H), 7.64 (s, 1 H), 7.66 (d, 2 H), 8.17 (s, 1 H).

***N*-[3-(Diethylamino)propyl]-4-(1*H*-imidazol-1-yl)benzamide Dihydrochloride (6h).** Reaction of *N*,*N*-diethyl-1,3-propanediamine with **7** in a procedure similar to that used for the preparation of **8a** afforded crude *N*-[3-(diethylamino)-propyl]-4-fluorobenzamide (**8h**) in 97% yield as an oil [NMR ($CDCl_3$) δ 1.02 (t, 6 H), 1.75 (m, 2 H), 2.50 (m, 2 H), 2.54 (quar, 4 H), 3.52 (m, 2 H), 7.02 (t, 2 H), 7.75 (dd, 2 H), 8.70 (br s, 1 H)]. Further reaction of **8h** with imidazole using the procedure employed in the preparation of **5a** and chromatography on silica gel [CH_3CN + NH_4OH (19 + 1)] provided a 35% yield of free base. Treatment of the free base with a methanolic hydrogen chloride and recrystallization from 2-PrOH/MeOH gave **6h**: IR (KBr) 1645 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 1.24 (t, 6 H), 1.97 (m, 2 H), 3.11 (m, 6 H), 3.40 (m, 2 H), ca. 3.5 (br s, 1 H), 7.94 (s, 1 H), 7.99 (d, 2 H), 8.17 (d, 1 H), 8.39 (s, 1 H), 9.08 (t, 1 H), 9.81 (s, 1 H), 10.45 (br s, 1 H).

***N*-[(1-Ethylpyrrolidin-2-yl)methyl]-4-(1*H*-imidazol-1-yl)benzamide 4-Methylbenzenesulfonic Acid Salt (1:1) (6i).** To a solution of 4.6 mL (31.8 mmol) of 1-ethylpyrrolidine-2-methanamine and 3.85 g (35 mmol) of sodium carbonate in 50 mL of water cooled to 0 °C was added dropwise 3.76 mL (31.8 mmol) of **7**. After the addition was complete the reaction mixture was stirred for 30 min at 0 °C and then for 48 h at room temperature. The reaction mixture was extracted with two 100-mL portions of methylene chloride. The combined extracts were washed with 25 mL of saturated sodium carbonate solution and dried over anhydrous sodium sulfate. Removal of the drying agent and evaporation of the solvent yielded 5.85 g (74%) of crude *N*-[(1-ethylpyrrolidin-2-yl)methyl]-4-fluorobenzamide (**8i**) [NMR ($CDCl_3$) δ 1.13 (t, 3 H), 1.43–4.30 (m, 11 H), 6.75–7.60 (br, 1 H), 7.11 (dd, 2 H), 7.84 (dd, 2 H)]. Without further purification 5.8 g (23 mmol) of benzamide **8i** was reacted with imidazole in dimethyl sulfoxide with sodium hydride as base in a procedure similar to that used for **6k**. The crude product was chromatographed on silica gel [CH_3CN + NH_4OH (19 + 1)] then converted to the 4-methylbenzenesulfonic acid salt. Recrystallization of the salt from ethyl acetate/methanol afforded 1.5 g (13%) of **6i**: IR (Nujol) 1660 (amide I) cm^{-1}; NMR (D_2O) δ 1.39 (t, 3 H), 1.92–2.26 (m, 3 H), 2.35 (m, 1 H), 2.38 (s, 3 H, TsOH), 3.22 (m, 2 H), 3.61 (m, 1 H), 3.70–3.96 (m, 4 H), 7.23 (s, 1 H), 7.35 (d, 2 H), 7.63 (s, 1 H), 7.64 (d, 2 H), 7.68 (d, 2 H), 7.91 (d, 2 H), 8.23 (s, 1 H).

***trans*-*N*-[2-(Diethylamino)cyclohexyl]-4-(1*H*-imidazol-1-yl)benzamide Hydrochloride Monohydrate (6j).** To a solution of 6.91 g (40.6 mmol) of *N*,*N*-diethyl-1,2-cyclohexanediamine[20] in 90 mL of methylene chloride under a nitrogen atmosphere at room temperature was added dropwise 21 mL (42 mmol) of 2 M trimethylaluminium in toluene. The reaction mixture was then refluxed for 20 min. A solution of 9.0 g (44.5 mmol) of **5a** in 90 mL of methylene chloride was added to the mixture and refluxing continued for 6 days. After cooling, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and filtered through Celite. The mixture was adjusted to pH = 5.5, and the layers were separated. The aqueous layer was further extracted with four portions of methylene chloride to remove unreacted **5a**. The aqueous solution was taken to pH = 11 and extracted with four 100-mL portions of methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate. After removal of the drying agent, the solvent was stripped to provide an oil which was dissolved in methanol and treated with hydrochloric acid (pH = 6). The solvent was evaporated and the residue was recrystallized from acetone/methanol (95/5) to afford 6.7 g (two crops, 48%) of **6j**: IR (KBr) 1650 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 1.20–1.40 (m, 7 H), 1.50–1.80 (m, 3 H), 1.88 (br t, 2 H), 2.10 (br d, 1 H), 3.00 (m, 1 H), 3.20 (m, 1 H), 3.25–3.60 (m, 4 H), 4.35 (m, 1 H), 7.19 (s, 1 H), 7.86 (d, 2 H), 7.92 (s, 1 H), 8.15 (d, 2 H), 8.46 (s, 1 H), 8.61 (br s, 1 H), 8.80 (d, 1 H).

1-[4-(1*H*-Imidazol-1-yl)benzoyl]-4-methylpiperazine Dihydrochloride (6k). In a procedure similar to that used for the preparation of **5a**, 1-(4-fluorobenzoyl)-4-methylpiperazine (**8k**)[21] was reacted with imidazole and sodium hydride in dimethyl sulfoxide to give, after chromatography on silica gel [CH_2Cl_2 + MeOH (19 + 1)] and salt formation, a 64% yield of **6k**: IR (Nujol) 1620 (amide I) cm^{-1}; NMR (D_2O) δ 3.03 (s, 3 H), 3.31–3.73 (m, 8 H), 7.70 (s, 1 H), 7.77 (d, 2 H), 7.84 (d, 2 H), 7.98 (s, 1 H), 9.27 (s, 1 H).

1-[4-(1*H*-Imidazol-1-yl)benzoyl]-4-(phenylmethyl)-piperazine Methanesulfonic Acid Salt (1:2) (6l). To a solution of 18.8 g (0.1 mol) of **5d** in 200 mL of dimethylformamide under a nitrogen atmosphere at room temperature was added 16.2 g (0.1 mol) of 1,1′-carbonyldiimidazole. This mixture was stirred for 2 h then 17.7 g (0.101 mol) of 1-(phenylmethyl)piperazine was added. Stirring was continued overnight at room temperature. After this time the solvent was removed in vacuo and the residue was dissolved in 600 mL of methylene chloride. The methylene chloride solution was washed successively with two 200-mL portions of saturated sodium bicarbonate solution and two 200-mL portions of water and then dried over anhydrous magnesium sulfate. Removal of the drying agent, evaporation of the solvent, and recrystallizaton of the residue from hexane/ethyl acetate provided 29.15 g (84% yield) of the free base. A portion of the free base was treated with 2 equiv of methanesulfonic acid in ethanol and then recrystallized from diethyl ether/ethanol to give **6l**: IR (KRr) 1636 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 2.37 (s, 6 H, CH_3SO_3H), 2.80–4.20 (br m, 10 H, piperazine protons + CH_3SO_3H), 4.39 (s, 2), 7.50 (m, 3 H), 7.55 (m, 2 H), 7.74 (d, 2 H), 7.94 (d, 2 H), 7.95 (s, 1 H), 8.35 (s, 1 H), 9.73 (s, 1 H).

1-[4-(1*H*-Imidazol-1-yl)benzoyl]piperazine (6m). To a solution of 26.65 g (77 mmol) of **6l** (as free base) in 500 mL of ethanol was added 2 g of 10% palladium on charcoal as a slurry in 10 mL of water. The mixture was hydrogenolyzed at 50 psi and 50 °C. At the completion of the reaction the catalyst was filtered and the solvent was removed in vacuo. The residue was triturated with diethyl ether and then recrystallized from hexanes/ethyl acetate to yield 13.75 g (70% yield) of **6m**. A portion of this material was recrystallized from acetonitrile to provide an analytical sample of **6m**: IR (KBr) 1608 (amide I) cm^{-1}; NMR ($CDCl_3$) δ 1.76 (br s, 1 H), 2.90 (br m, 4 H), 3.43 (br s, 2 H), 3.76 (br s, 2 H), 7.23 (s, 1 H), 7.31 (s, 1 H), 7.45 (d, 2 H), 7.55 (d, 2 H), 7.89 (s, 1 H).

***N*-[1-(Phenylmethyl)piperidin-4-yl]-4-(1*H*-imidazol-1-yl)benzamide (6n).** In a manner similar to that used for the preparation of **6l**, 1-(phenylmethyl)piperdin-4-amine and **5d** were reacted to give **6n** in 83% yield after recrystallization from hexane/methylene chloride. A portion of this material was recrystallized again from hexane/methylene chloride to provide an analytical sample of **6n**: IR (KBr) 1637 (amide I) cm^{-1}; NMR ($CDCl_3$) δ 1.58 (quar of d, 2 H), 2.05 (d, 2 H), 2.20 (t, 2 H), 2.85 (d, 2 H), 3.53 (s, 2 H), 4.05 (m, 1 H), 6.10 (d, 2 H), 7.23–7.33 (m, 7 H), 7.45 (d, 2 H), 7.88 (d, 2 H), 7.91 (s, 1 H).

***N*-(Piperidin-4-yl)-4-(1*H*-imidazol-1-yl)benzamide (6o).** Compound **6n** was hydrogenolyzed by using the same conditions as for the preparation of **6m** to provide **6o** in 97% crude yield. Two recrystallizations from acetonitrile afforded an analytical sample of **6o**: IR (KBr) 1610 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 1.34–2.11 (m, 2 H), 1.75 (d, 2 H), 2.50 (br t, 2 H), 2.60–3.60 (br s, 1 H), 2.97 (d, 2 H), 3.75–3.91 (m, 1 H), 7.15 (s, 1 H), 7.78 (d, 2 H), 7.87 (s, 1 H), 8.00 (d, 2 H), 8.35 (d, 1 H), 8.39 (s, 1 H).

4-(1*H*-Imidazol-2-yl)benzoic Acid Methyl Ester (9). To a solution of 28.75 g (0.15 mol) of 4-(1*H*-imidazol-2-yl)benzoic acid[12b] in 575 mL of methanol was added 38.5 mL (0.31 mol) of boron trifluoride etherate. This solution was refluxed for ca. 40 h, then the solvent was removed in vacuo. The residue was

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dissolved in 200 mL of water and then poured into 1 L of 5% aqueous sodium carbonate solution. The resulting beige precipitate was collected by filtration. The crude ester was dissolved in 1 L of methanol, treated twice with 1 g of charcoal, and recrystallized. Two crops (15 and 3.5 g) were collected to provide 18.5 g (60%) of **9**. Sublimation (180 °C at 0.1 mmHg) afforded an analytical sample of **9**: mp 232–235 °C; IR (KBr) 1705 cm^{-1}; NMR (MeSO-d_6) δ 3.33 (br s, 1 H), 3.75 (s, 3 H), 7.00 (s, 2 H), 7.80 (s, 4 H). Anal. ($C_{11}H_{10}N_2O_2$) C, H, N.

***N*-[2-(Diethylamino)ethyl]-4-(1*H*-imidazol-2-yl)benzamide Dihydrochloride (10).** To a solution of 50 mL (0.52 mol) of trimethylaluminum in 300 mL of chloroform cooled to 0 °C under a nitrogen atmosphere was added dropwise 6.25 g (0.054 mol) of *N,N*-diethyl-1,2-ethanediamine. After the addition was complete, the reaction mixture was stirred for 20 min at 0 °C and then for 1.5 h at ambient temperature. At this time 10 g (0.049 mol) of **9** was added and the reaction mixture was refluxed for 36 h. After this time the reaction mixture was cooled to room temperature and 6 N hydrochloric acid was added (pH = 2). The layers were separated and the aqueous layer was extracted with 200 mL of methylene chloride (discarded). The aqueous layer was taken to pH = 10 with 10% sodium hydroxide solution and then extracted with four 200-mL portions of methylene chloride. After drying over anhydrous potassium carbonate, the solvent was evaporated to give 2.5 g of crude product. During the extraction a solid precipitated and was collected by filtration. Thin-layer chromatography indicated that this material (9.5 g) was identical with the extracted material (total = 12 g, 85% yield). The crude material was recrystallized from ethyl acetate. A portion (3.4 g) of the free base was dissolved in 50 mL of ethanol and treated with excess concentrated hydrochloric acid (pH = 2). The solvent was stripped and the residue was dried at 90–110 °C (0.2 mmHg) for 16 h to afford **10**: mp 220–223 °C; IR (KBr) 1660 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 1.25 (t, 6 H), ca. 2.5–4.1 (br 1 H + H_2O), 3.20 (m, 4 H), 3.27 (m, 2 H), 3.70 (dt, 2 H), 7.83 (s, 2 H), 8.17 (d, 2 H), 8.37 (d, 2 H), 9.31 (t, 1 H), 10.66 (br s, 1 H). Anal. ($C_{16}H_{22}N_4O$·HCl·0.5H_2O) C, H, Cl, N.

***N*-[2-(Diethylamino)ethyl]-3-(1*H*-imidazol-1-yl)benzamide Dihydrochloride (11).** A mixture of 9.41 g (50 mmol) of 3-(1*H*-imidazol-1-yl) benzoic acid[12b] and 8.11 g (50 mmol) of 1,1′-carbonyldiimidazole was stirred at ambient temperature under a nitrogen atmosphere in 200 mL of methylene chloride for 2 h. To the reaction mixture was added 5.8 g (50 mmol) of *N,N*-diethyl-1,2-ethanediamine. Stirring was continued for 3.5 h, then the methylene chloride solution was washed with two 150-mL portions of water and two 150-mL portions of saturated sodium carbonate solution and dried over anhydrous magnesium sulfate. Removal of the drying agent by filtration and concentration of the filtrate afforded 14.17 g of a yellow oil. The oil was dissolved in 200 mL of ethanol and 25 mL of 5 N hydrochloric acid was added. The solvent was evaporated and the residue was stripped with two additional 200-mL portions of ethanol. Recrystallization from diethyl ether/ethanol provided 11.38 g (63%) of **11**: mp 175–180 °C; IR (KBr) 1655 (amide I) cm^{-1}; NMR (Me_2SO-d_6) δ 1.26 (t, 6), 3.20 (m, 4 H), 3.29 (t, 2 H), 3.47 (br s, 1 H + H_2O), 3.71 (dt, 2 H), 7.62 (t, 1 H), 7.92 (d, 1 H), 8.01 (dd, 1 H), 8.09 (d, 1 H), 8.47 (s, 1 H), 8.55 (s, 1 H), 9.45 (t, 1 H), 9.83 (s, 1 H), 10.48 (br s, 1 H). Anal. ($C_{16}H_{22}N_4O$·2HCl·0.25H_2O) C, H, Cl, N.

1-[(4-Fluorophenyl)sulfonyl]-4-methylpiperazine Hydrochloride (12). To a solution of 8.0 g (41 mmol) of 4-fluorobenzenesulfonyl chloride in 50 mL of methylene chloride cooled to 0 °C was added dropwise a solution of 4.55 mL (41 mmol) of 1-methylpiperazine in 25 mL of methylene chloride. After the addition was complete, the solution was stirred for 30 min at 0 °C and then for 20 h at room temperature. The resulting precipitate was filtered and dried in vacuo to yield 9.07 g (74%) of **12**: mp 237–240 °C; NMR (Me_2SO-d_6) δ 2.73 (s, 3 H), 2.92–3.62 (m, 8 H), 7.51 (dd, 2 H), 7.87 (dd, 2 H). Anal. ($C_{11}H_{15}FN_2O_2S$·HCl·0.1H_2O) C, H, N.

1-[[4-(1*H*-Imidazol-1-yl)phenyl]benzenesulfonyl]-4-methylpiperazine (13). In a procedure similar to that used for the preparation of **6k** the free base of **12** [from 5.32 g (18 mmol) of **12**] was reacted with imidazole in dimethyl sulfoxide with sodium hydride as base to provide 4.16 g (75%) of **13** after recrystallization from diethyl ether/ethyl acetate: mp 177–179 °C; NMR (Me_2SO-d_6) δ 2.14 (s, 3 H), 2.36 (br t, 4 H), 2.92 (br t, 4 H), 7.17 (s, 1 H), 7.86 (d, 2 H), 7.92 (s, 1 H), 7.95 (d, 2 H), 8.50 (s, 1 H). Anal. ($C_{14}H_{18}N_4O_2S$) C, H, N.

Pharmacology. The experimental protocols describing the intracellular electrophysiological studies in canine Purkinje fibers,[4] the in vivo conduction interval studies in anesthetized dogs (intraduodenal administration),[4] and the PES efficacy studies in anesthetized dogs (AAI)[3] have been reported previously. The method used for the conduction interval studies in anesthetized dogs (intravenous administration) was that of Carson and Dresel[14] and is essentially the same as the intraduodenal study listed above. The PES studies in conscious dogs were done according to Karagueuzian et al.[16]

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