Synthesis of Novel (Aryloxy)propanolamines and Related Compounds Possessing Both Class II and Class III Antiarrhythmic Activity

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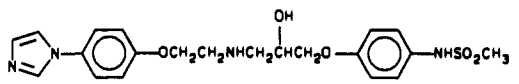
Several (aryloxy)propanolamines and related compounds (i.e. **5–13**, **16–18**, **20–24**, **27–33**, **35**, **37–39**, **41**, and **42**) were synthesized and investigated for their class III electrophysiological activity and class II (β-blocking) effects with use of in vitro and in vivo models. Structure–activity relationships are discussed for a series of 30 compounds. A number of these compounds prolonged the action potential duration at 95% repolarization of isolated canine cardiac Purkinje fibers by 20% ($C_{20}APD_{95}$) at concentrations of <1.0 μM, with no significant effects on cardiac conduction. β-Adrenergic receptor binding studies showed that some of these compounds were 2–20 times more potent for cardiac β_1 receptors than for β_2 receptors. In particular, compounds **32**, **41**, **1**, and especially (*S*)-**1** were found to be orally active class III agents in anesthetized mongrel dogs (1 or 3 mg/kg, id) and efficacious at suppressing programmed electrical stimulation induced arrythmias in halothane-anesthetized dogs. The profile of these compounds was similar to that found for sotalol. Compound (*S*)-**1**, which was more potent than sotalol in the PES study and equieffective in the halothane/epinephrine dog model, is being investigated further as a combined class III/II antiarrhythmic agent.

In a previous paper,[1] we reported the synthesis and pharmacological activity of a novel (aryloxy)propanolamine, **1**, and its enantiomers. Compound **1** was shown



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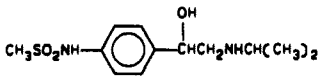
to possess both class II (β_1-selective) and class III electrophysiological activity and was effective at preventing arrhythmias in two models of antiarrhythmic efficacy. Reported herein is the conceptual approach that led to the design of this agent.

Reentrant arrhythmias are thought to be major contributors to sudden cardiac death (SCD).[2-4] Alleviation of reentrant arrhythmias has been demonstrated with class III antiarrhythmic agents.[2,5-8] Enhanced sympathetic activity may also lead to the development of reentrant arrhythmias.[9,10] Since β-blocking (class II)[11] agents reduce sympathetic activity, they may also be useful in offsetting reentrant arrhythmias and, hence, may have impact on reducing the occurrence of SCD. Thus, a combined class III/II agent would address *more than one* of the etiologies leading toward SCD and would show broader therapeutic application.

Sotalol, which was originally developed as a β-adrenergic blocking agent[12] for the treatment of hypertension and has subsequently been found to have class III electrophysiological activity,[13] can be considered as a standard class III/II agent. However, sotalol lacks potency as a class III



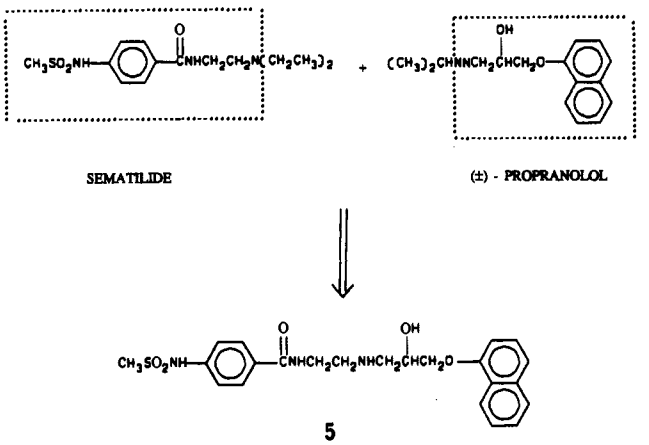
(±)-SOTALOL

agent and is a nonselective β-blocker. We felt that this was a major drawback and we wanted to design compounds that would possess *potent* class III activity and have a *balanced* amount of β-blocking effects (β_1-selective) without significantly affecting cardiac conduction.

Ideally, these compounds would be potentially useful against reentrant and catecholamine-dependent arrhythmias at doses below those causing β-blocker-mediated hypotension and cardiac depression.

We have reported that the combination of sematilide[5] (class III) and propranolol (class II) may provide additional

Scheme I



SEMATILIDE (±) - PROPRANOLOL

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therapeutic benefit over each drug alone in preventing programmed electrical stimulation induced reentrant

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‡ Pharmacology Department.

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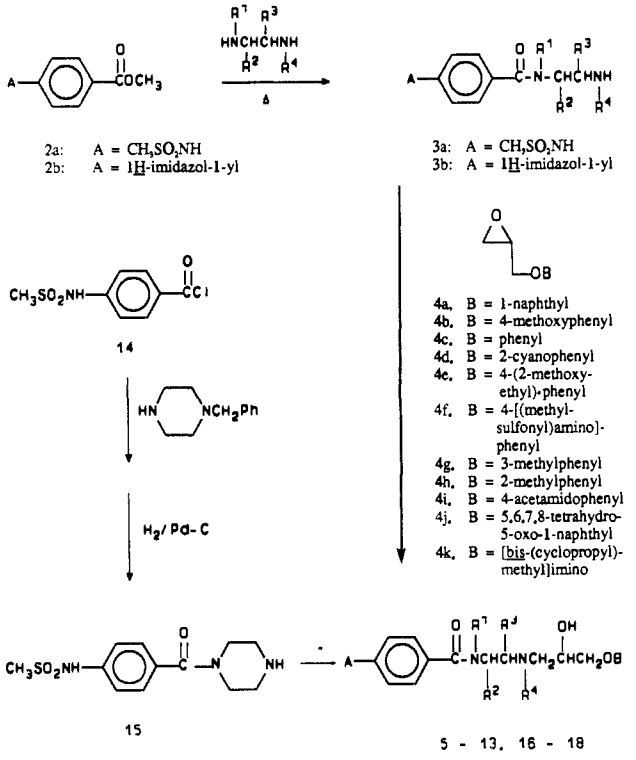
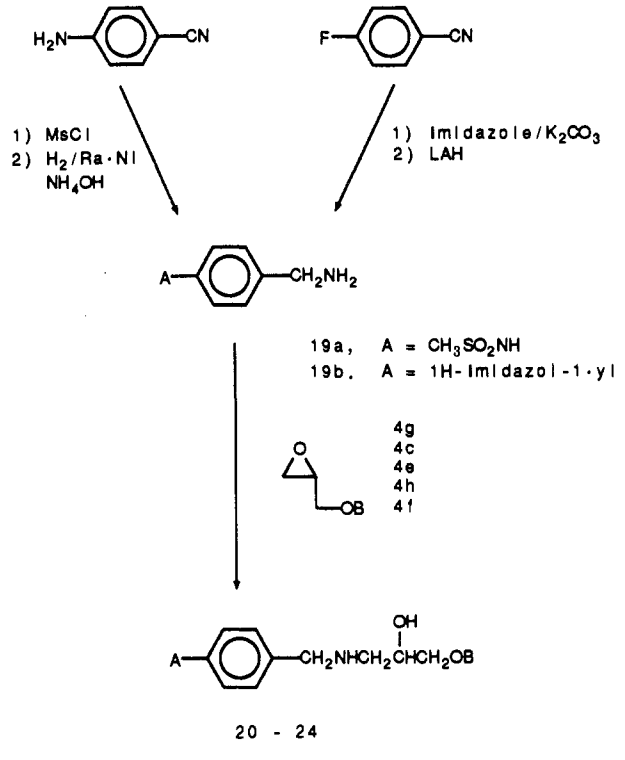
Scheme II



Structure Type I

Scheme III



Structure Type II

ventricular tachycardia (PES-VT) in dogs.[14] This synergism prompted us to combine the structures of these two drugs into one chemical entity.

Designing compounds with combined activity is not a new concept, and many accounts have appeared recently in the literature.[15-18] In most cases this has been done in order to give a balanced biological activity during the course of drug action.

The first compound synthesized as a combined class III/II agent was **5**. This hybrid was the result of combining sematilide and propranolol through a common basic nitrogen (Scheme I). Due to the inspiring results in vitro for **5**, in which potent class III electrophysiological activity and adequate β-receptor binding were found, we began a systematic investigation in preparing novel hybrid (class III/II) molecules.

The class III pharmacophores were chosen from in-house (unpublished) and published[19] structure–activity relationships. In general, a variety of substituents were well tolerated on the basic nitrogen moiety of the class III pharmacophore. The choice of the class II (β-blocking) portions were based on the extensive β-blocking literature[20] and with β-blockers such as propranolol, metoprolol, bunolol, bucindolol, atenolol, etc. Incorporation of β_1 selectivity into some of the target molecules was based on the work of Smith.[21]

By a systematic combination of class III and class II pharmacophores we have prepared 30 compounds as potential class III/II agents to further expand and better understand structure–activity relationships in this area.

Chemistry

The synthetic routes to the target compounds **5–13**, **16–18**, **20–24**, **27–33**, **35**, **37–39**, **41**, and **42** are illustrated in Schemes II–V. The known benzoic acid methyl esters **2a**[5] and **2b**[22] were heated with diamines and yielded the corresponding amino benzamides **3a** and **3b**, respectively (Scheme II). Treatment of these compounds with the known racemic epoxides **4a–f**[23] provided the target compounds **5–13**. A statistical mixture of compounds (i.e. starting amine, monoalkylation product, and bisalkylation product) was generated in these reactions (TLC analysis). The product was isolated by either trituration or filtration and then recrystallized to obtain pure material.

Treating acid chloride **14**[5] with *N*-benzylpiperazine followed by hydrogenolysis (H_2/Pd–C) afforded benzoylpiperazine **15** in 85% overall yield (Scheme II). Reaction of **15** with racemic epoxides **4a**, **4c**, and **4e** gave the cor-

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(21) Smith, L. H. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 201.
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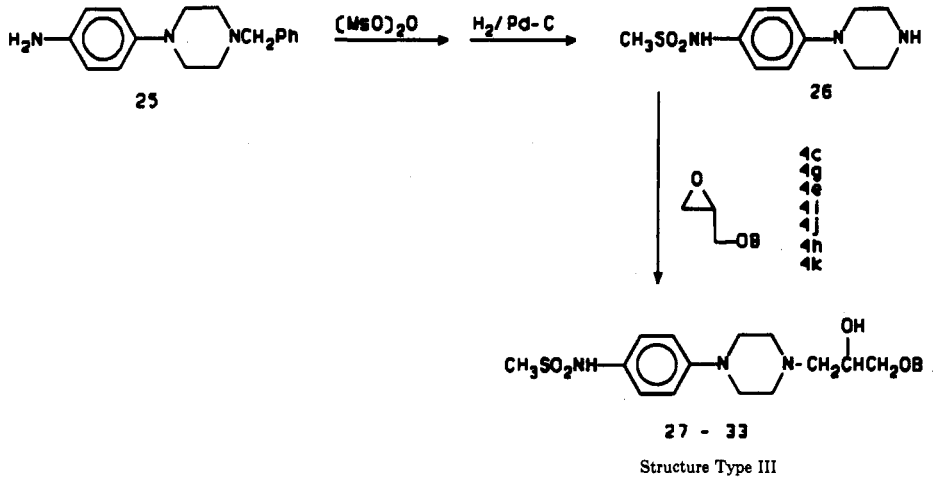
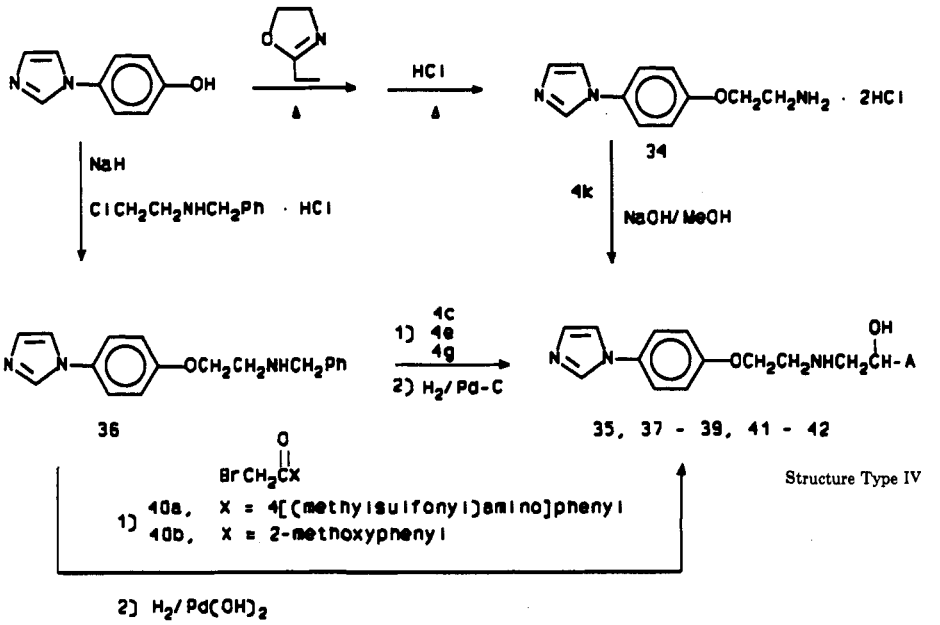
Scheme IV



Structure Type III

Scheme V



Structure Type IV

responding target compounds **16**, **17**, and **18** in good yield.

The synthetic routes to targets **20**–**24** are depicted in Scheme III. Mesylation of 4-aminobenzonitrile (MsCl/Pyr/CH_2Cl_2)[24] followed by reduction of the nitrile moiety (H_2/Ra-Ni/NH_4OH) afforded amine **19a** in 46% overall yield. This amine, in turn, was used to prepare target compounds **20**, **21**, and **22**. Preparation of the analogous imidazole compounds (i.e. **23** and **24**) followed a different route. Displacement of the fluoro group of 4-fluorobenzonitrile with imidazole[25] followed by reduction of the nitrile ($LiAlH_4$) gave amine **19b**. Formation of the trimethylsilyl (TMS) derivative of **19b** was accomplished in situ by treatment with hexamethyldisilazane in dimethyl sulfoxide. Epoxides **4f** and **4h** were then treated with this TMS derivative and gave target compounds **23** and **24**.

The phenylpiperazine compounds **27**–**33** were prepared by the chemistry summarized in Scheme IV. Mesylation of aniline **25**[26] ($(CH_3SO_2)_2O/CH_3CN$) followed by hydrogenolysis (H_2/Pd–C) afforded piperazine **26** in 65% overall yield. Reaction of **26** with epoxides **4c**, **4g**, **4e**, **4i**, **4j**, **4h**, and **4k** gave the target compounds **27**–**33**.

The synthesis of the remaining compounds is summarized in Scheme V. Ring opening of 2-ethyl-2-oxazoline with 4-(1*H*-imidazol-1-yl)phenol by the method of Fazio[27] followed by hydrolysis afforded amine **34** in 66% overall yield. Mixing amine **34** with epoxide **4k** gave amino alcohol **35** in 32% yield.

Target compounds **37**, **38**, and **39** were prepared by a modified procedure. Alkylation of 4-(1*H*-imidazol-1-yl)-phenol with *N*-benzyl-2-chloroethylamine hydrochloride[28] gave **36** in 68% isolated yield. Reaction of **36** with epoxides **4c**, **4e**, and **4g** followed by debenzylation (H_2/Pd–C) gave targets **37**, **38**, and **39**, respectively. Bisalkylation was eliminated by this method, but the overall yields were similar to those obtained when primary amine was utilized. Treating **36** with α-bromoacetophenones **40a**[29] and **40b**[30] and Hünigs base in acetonitrile followed by concurrent ketone reduction and debenzylation gave **41** and **42** in 31 and 14% yield, respectively. A summary of the prepared

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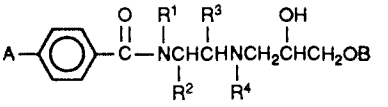
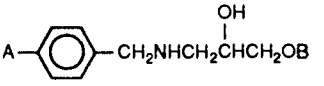
Table I. Physical Properties of Structural Type I



no.[a]	A	R^1	R^2	R^3	R^4	B	yield, %	mp, °C (solv)[b]	formula	anal.[c]
5	CH_3SO_2NH	H	H	H	H	1-naphthyl	22	168–171 (A)	$C_{23}H_{27}N_3O_5S$	CHN
6	CH_3SO_2NH	H	H	H	H	4-methoxyphenyl	20	160–162 (B)	$C_{20}H_{27}N_3O_6S$	CHN
7	CH_3SO_2NH	H	H	H	H	phenyl	16	162–163.5 (C)	$C_{19}H_{25}N_3O_5S$	CHN
8	CH_3SO_2NH	H	H	H	H	2-cyanophenyl	13	199–202 (C)	$C_{20}H_{24}N_4O_5S\cdot0.25H_2O$	CHNS
9	CH_3SO_2NH	H	$-(CH_2)_4-$		H	phenyl	17	166–170 (D)	$C_{23}H_{31}N_3O_5S\cdot0.5H_2O$	CHNS
10	imidazol-1-yl	H	H	H	H	4-(2-methoxyethyl)phenyl	11	120–122 (E)	$C_{24}H_{30}N_4O_4\cdot0.25H_2O$	CHN
11	imidazol-1-yl	H	H	H	H	4-methoxyphenyl	26	162–164 (F)	$C_{22}H_{26}N_4O_4$	CHN
12	imidazol-1-yl	H	H	H	H	1-naphthyl	21	118–122 (F)	$C_{25}H_{26}N_4O_3\cdot C_4H_4O_4\cdot0.5H_2O$	CHN
13	imidazol-1-yl	H	H	H	H	4-[(methylsulfonyl)amino]-phenyl	35	147–150 (G)	$C_{22}H_{27}N_5O_5S\cdot2HCl\cdot H_2O$	CHNSCl
16	CH_3SO_2NH	$-CH_2-$	H	H	$-CH_2-$	1-naphthyl	78	97–105	$C_{25}H_{29}N_3O_5S$	CHN
17	CH_3SO_2NH	$-CH_2-$	H	H	$-CH_2-$	phenyl	46	114–124 (H)	$C_{21}H_{27}N_3O_5S\cdot H_3PO_4\cdot 0.25H_2O$	CHNSP
18	CH_3SO_2NH	$-CH_2-$	H	H	$-CH_2-$	4-(2-methoxyethyl)phenyl	76	80–82 (F)	$C_{24}H_{33}N_3O_6S\cdot H_3PO_4\cdot H_2O$	CHNSP

[a] All compounds are racemic. [b] Recrystallization solvent: A = *i*-PrOH, B = 90% aqueous EtOH, C = CH_3CN/H_2O (1:1), D = CH_3CN, E = EtOAc, F = EtOH, G = CH_3CN/MeOH (1:1), H = MeOH. [c] Elemental analyses are within ±0.4% of the calculated values.

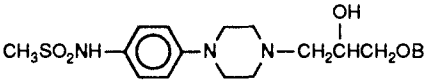
Table II. Physical Properties of Structural Type II



no.[a]	A	B	yield, %	mp, °C (solv)[b]	formula	anal.[c]
20	CH_3SO_2NH	3-methylphenyl	11	201–203 (A)	$C_{18}H_{24}N_2O_4S\cdot HCl$	CHN
21	CH_3SO_2NH	phenyl	22	205–207 (B)	$C_{17}H_{22}N_2O_4S\cdot HCl$	CHN
22	CH_3SO_2NH	4-(2-methoxyethyl)phenyl	8	202–204 (B)	$C_{20}H_{28}N_2O_5S\cdot HCl$	CHN
23	imidazol-1-yl	2-methylphenyl	63	202–204 (C)	$C_{20}H_{23}N_3O_2\cdot 2HCl$	CHN
24	imidazol-1-yl	4-[(methylsulfonyl)amino]phenyl	19	136–140 (B)	$C_{20}H_{24}N_4O_4S\cdot 0.5C_4H_4O_4\cdot H_2O$	CHNS

[a] All compounds are racemic. [b] Recrystallization solvent: A = MeOH, B = CH_3CN/MeOH (1:1), C = *i*-PrOH. [c] Elemental analyses are within ±0.4% of the calculated values.

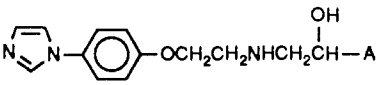
Table III. Physical Properties of Structural Type III



no.[a]	B	yield, %	mp, °C (solv)[b]	formula	anal.[c]
27	phenyl	33	180–181 (A)	$C_{20}H_{27}N_3O_4S\cdot 0.25H_2O$	CHNS
28	3-methylphenyl	81	190–194 (B)	$C_{21}H_{29}N_3O_4S\cdot 2HCl$	CHN
29	4-(2-methoxyethyl)phenyl	74	132–136 (B)	$C_{23}H_{33}N_3O_5S\cdot 2HCl\cdot 0.25H_2O$	CHNSCl
30	4-acetamidophenyl	53	220–223 (C)	$C_{22}H_{30}N_4O_5S\cdot HCl$	CHN
31	5,6,7,8-tetrahydro-5-oxo-1-naphthyl	48	205–210 (B)	$C_{24}H_{31}N_3O_5S\cdot 2HCl$	CHN
32	2-methylphenyl	69	190–196 (B)	$C_{21}H_{29}N_3O_4S\cdot HCl$	CHN
33	(dicyclopropylmethyl)imino	35	118–120 (D)	$C_{21}H_{32}N_4O_4S$	CHN

[a] All compounds are racemic. [b] Recrystallization solvent: A = MeOH, B = EtOH, C = 90% aqueous EtOH, D = EtOAc. [c] Elemental analyses are within ±0.4% of the calculated values.

Table IV. Physical Properties of Structural Type IV



no.[a]	A	yield, %	mp, °C (solv)[b]	formula	anal.[c]
35	[[(dicyclopropylmethyl)imino]oxy]methyl	32	173–174 (A)	$C_{21}H_{28}N_4O_3\cdot H_2SO_4\cdot 0.5H_2O$	CHNS
37	phenoxymethyl	31	92–96 (B)	$C_{20}H_{23}N_3O_3\cdot 0.3H_2O$	CHN
38	[[4-(2-methoxyethyl)phenyl]oxy]methyl	15	78–80 (C)	$C_{23}H_{29}N_3O_4\cdot 0.4H_2O$	CHN
39	(3-methylphenoxy)methyl	18	70–75 (D)	$C_{21}H_{25}N_3O_3\cdot 1.2H_3PO_4$	CHNP
41	4-[(methylsulfonyl)amino]phenyl	31	215–216 (D)	$C_{20}H_{24}N_4O_4S\cdot 2.2HCl\cdot 0.25H_2O$	CHNSCl
42	2-methoxyphenyl	14	*d*	$C_{20}H_{23}N_3O_3\cdot 1.75HCl\cdot 0.6H_2O\cdot 0.3C_2H_6O$	CHNCl

[a] All compounds are racemic. [b] Recrystallization solvent: A = *i*-PrOH, B = petroleum ether, C = EtOAc, D = EtOH. [c] Elemental analyses are within ±0.4% of the calculated values. [d] Isolated as a white foam.

Table V. In Vitro Pharmacology

	Purkinje fiber[a,b]			β-receptor binding:[c]		β selectivity				
compound[d]	n[e]	$C_{20}APD_{95}$,[f] μM	maxΔAPD_{95} (concn, μM)[g]	n[e]	IC_{50}, μM	n[e]	β_1 IC_{50}, μm	n[e]	β_2 IC_{50}, μM	β_1/β_2
propranolol	4[h]	(–) 1.0, (–) 3.5 (–) NR,[i] (–) 2.5	NA[j]	6	0.012 ± 0.005	3	0.018 ± 0.004	3	0.017 ± 0.003	0.9
sematilide	18	4.4 (1.9–11.0)	33 ± 2% (10), 65 ± 8% (100)	3	7000 ± 3000					
sotalol	6	14.4 (11.2–18.6)	48 ± 3% (100)	6	7.2 ± 1.5	3	8.9 ± 4.5	3	5.2 ± 0.3	0.6
5	2	1.1, 0.3	40% 48% (10)	4	0.15 ± 0.02					
6	2	0.6, 0.3	86%, 86% (10)	3	43.8 ± 16.4					
7	2	7.1, 5.3	24%, 26% (30)	3	3.9 ± 3.0					
8	2	23.7,[k] 9.0	23%, 31% (30)	3	2.9 ± 1.2					
9	4	4.6, 0.3, 5.3, 2.9	24%, 45%, 21%, 29% (10)	3	192 ± 164					
10	3	1.4,[l] 1.2, <1.0	70%, 54% (100), 60% (10)	4	12.4 ± 5.1					
11	2	6.6, 2.5	30%, 47% (30)	3	61.4 ± 8.6					
12	4	1.8, 0.2, 0.2, 1.7	57% (100), 37% (1), 69% (30), 32% (10)	3	0.42 ± 0.07					
13	2	5.8, 5.0	58%, 49% (100)	4	227 ± 67					
16	2	0.5, 0.4	55% (100), 44% (10)	5	30.9 ± 7.9					
17	2	<1.0, 0.9[l]	88%, 50% (10)	3	12.2 ± 6.2					
18	4	NR,[i] 7.7, 1.4, <1.0	13% (100), 22%, 47%, 56% (10)	6	360 ± 172					
20	2	<1.0, 0.3[m]	44% (10), 34% (1)	4	0.99 ± 0.56	3	2.4 ± 0.2	3	4.4 ± 0.9	1.8
21	2	<1.0, 0.4[n]	36%, 40% (10)	6	2.9 ± 1.6					
22	2	0.5, 0.3	41%, 57% (10)	3	25.8 ± 17.0	3	7.3 ± 3.2	3	46.0 ± 6.0	6.3
23	2	0.3, 0.3[o]	65% (10), 64% (30)	4	0.78 ± 0.25	3	0.8 ± 0.3	3	1.2 ± 0.4	1.5
24	2	0.7, 1.8	67%, 54% (30)			3	33.1 ± 1.8	3	26 ± 2% @100	>3.0
27	4	1.2, 0.4, 2.7, 0.2	36%, 50%, 33% (10), 52% (1)	4	15.8 ± 2.0					
28	2	<1.0, 0.4[p]	55%, 31% (10)	3	15.7 ± 5.5	3	19.2 ± 5.2	3	49.3 ± 14.4	2.6
29	4	<1.0, 0.6,[q] nR,[i,r] 3.2	41% (1), 76%, 2%, 31% (10)	3	109 ± 44					
30	2	42.0,[s] 19.0	34%, 39% (100)	3	293 ± 27					
31	2	1.5, 1.9	48% (10), 48% (100)	3	8.4 ± 2.9					
32	4	2.1, <1.0,[t] 0.2, 4.5	31%, 26%, 53%, 22% (10)	3	2.3 ± 1.3	4	3.3 ± 1.4	7	6.6 ± 2.7	2.0
33	2	8.0, 3.4	41%, 45% (30)	4	15.7 ± 5.9					
35	2	1.5, 0.5	41%, 87% (10)	3	0.30 ± 0.09					
37	2	8.8,[u] 8.3[v]	21%, 21% (10)	3	0.04 ± 0.01	3	0.04 ± 0.01	3	0.28 ± 0.11	7.0
38	4	1.8, 3.0,[w] 1.9,[x] 14.8[l]	73% (30), 89%, 42%, 52% (100)	3	0.27 ± 0.04	3	0.27 ± 0.02	3	4.5 ± 1.3	16.7
39	4	0.7,[y] 2.5,[z] 1.0, 10.0	23% (1), 31% (30), 35%, 20% (10)	4	0.09 ± 0.02	3	0.27 ± 0.08	3	0.51 ± 0.06	1.9
41	4	<1.0, 0.1, 0.1, 0.2	134% (100), 108%, 133%, 155% (10)	4	3.6 ± 1.7	3	5.1 ± 2.0	3	5.7 ± 0.6	1.1
42	4	3.4,[aa] NR,[i,z] 10.4, 8.1	26% (10), 16%, 33%, 27% (30)	4	3.7 ± 2.0					
1	6	0.4 (0.1–3.5)	92 ± 19% (30)			10	2.4 ± 0.3	9	46.5 ± 9.2	19.4
(*S*)-1	4	0.4, 1.5, 1.8, 0.4[bb]	73%, 57%, 44%, 70% (30)			5	1.6 ± 0.4	6	50 ± 4% @100	62.5
(*R*)-1	4	0.4, 1.6, 1.6, 0.5	73%, 42%, 55%, 71% (30)			5	37.5 ± 7.6	6	41 ± 2% @100	>2.7

[a] The change in the rate of rise of phase 0 of the action potential (V_{max}) was less than 10% unless otherwise noted (basic cycle length = 1000 ms). [b] Concentration range 0.1–100 μM. [c] IC_{50} values represent the concentration that is effective in displacing [^{3}H]dihydroalprenolol from canine ventricular tissue and are expressed as mean ± SEM. [d] Compounds are racemic unless otherwise noted. [e] Number of experiments. [f] The concentration of drug that causes a 20% increase (+) in APD_{95} (action potential duration at 95% repolarization) from control value, when $n > 4$, log mean and 90% confidence interval reported. [g] The maximum observed change in APD_{95} from control value and concentration when this occurred. [h] A 20% decrease in V_{max} observed at 14 μM for $N = 4$. [i] NR = never reached. [j] NA = not applicable. [k] A 16% increase in V_{max} observed at 10 μM. [l] A 27% decrease in V_{max} observed at 100 μM. [m] A 16% decrease in V_{max} observed at 1 μM. [n] A 20% decrease in V_{max} observed at 100 μM. [o] A 16% decrease in V_{max} observed at 30 μM. [p] A 20% decrease in V_{max} observed at 100 μM. [q] A 25% decrease in V_{max} observed at 100 μM. [r] A 25% increase in V_{max} observed at 1 μM. [s] A 31% decrease in V_{max} observed at 1 μM. [t] A 21% decrease in V_{max} observed at 100 μM. [u] A 23% decrease in V_{max} observed at 30 μM. [v] A 27% decrease in V_{max} observed at 30 μM. [w] A 58% decrease in V_{max} observed at 100 μM. [x] A 31% decrease in V_{max} observed at 100 μM. [y] A 26% decrease in V_{max} observed at 30 μM. [z] A 24% decrease in V_{max} observed at 30 μM. [aa] A 63% decrease in V_{max} observed at 30 μM. [bb] A 16% decrease in V_{max} observed in 10 μM.

compounds is listed in Tables I–IV.

Pharmacology

Screening for class III electrophysiological activity was carried out in canine cardiac Purkinje fibers using standard microelectrode techniques.[31] For a compound to have been considered active as a class III agent in this screen, it must have prolonged the action potential duration at 95% repolarization (APD_{95}) by at least 20% and had minimal effects on the rate of rise of phase 0 of the action potential (V_{max}). In Table V, we report the concentration of drug that causes a 20% increase in APD_{95} ($C_{20}APD_{95}$), the maximum observed increase in APD_{95} (max ΔAPD_{95}), the effects on V_{max}, and the concentration range studied. Changes in V_{max} of ≤10% from control were considered minimal (no class I activity).

To determine potential β-blocking activity, compounds were examined for their ability to displace the β-receptor antagonist [^{3}H]dihydroalprenolol ([^{3}H]DHA) from canine cardiac tissue.[8] β-receptor selectivity was determined in a similar assay using canine cardiac tissue (β_1) in which β_2 receptors were blocked with zinterol and canine lung tissue (β_2) in which β_1 receptors were blocked by metoprolol.[1] These results are also listed in Table V.

The method of evaluating antiarrhythmic activity after intraduodenal administration has been reported.[8] For a compound to have been considered active it must have prolonged the cardiac functional refractory period (FRP) by at least 12% in two of three animals. In Table VI, we report the number of studies with increases in FRP ≥ 12% over control over the total number of experiments, the active dose, and the percent change in heart rate (HR), blood pressure (BP), and FRP at the active dose.

Some of the compounds that were active by intraduodenal administration were then examined for efficacy in a PES model.[1] In this model, concious mongrel dogs were studied 3–8 days after an occlusion/reperfusion-induced infarction according to the method of Karagueuzian et al.[32] Selective class III agents are efficacious in this model, whereas β-blockers, in general, are not. The num-

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Table VI. Intraduodenal Activity

compound[a]	no. active[b]/ no. tested	active dose,[c] mg/kg, id	HR[d]	BP[e]	FRP[f]
sotalol	6/7	10 (5), 30 (1)	−10 ± 1	9 ± 4	17 ± 2
5	0/2	NA[g]	NA[g]	NA[g]	NA[g]
6	0/2	NA[g]	NA[g]	NA[g]	NA[g]
7	0/2	NA[g]	NA[g]	NA[g]	NA[g]
9	2/2	30 (2)	−19 ± 1	17 ± 7	15 ± 1
11	2/2	22 (1), 30 (1)	−35 ± 9	−1 ± 6	24 ± 5
12	2/2	30 (2)	−15 ± 4	16 ± 8	13 ± 1
13	1/2	30 (1)	−18	30	14
16	2/2	10 (1), 30 (1)	−25 ± 7	5 ± 10	19 ± 0
21	0/2	NA[g]	NA[g]	NA[g]	NA[g]
27	1/4	30 (1)	−7	−17	14
28	2/2	10 (2)	−21 ± 3	13 ± 6	17 ± 3
29	3/3	10 (2), 30 (1)	−12 ± 6	9 ± 4	15 ± 1
31	1/2	10 (1)	−1	18	12
32	2/2	10 (2)	−11 ± 3	11 ± 20	13 ± 1
33	1/2	30 (1)	−17	17	15
35	2/3	10 (2)	−18 ± 3	2 ± 14	20 ± 6
37	0/1	NA[g]	NA[g]	NA[g]	NA[g]
41	2/2	10 (2)	−18 ± 4	17 ± 13	24 ± 1
1	4/4	1.0 (1), 10 (3)	−16 ± 3	3 ± 5	27 ± 5

[a] All compounds are racemic. [b] Number of animals that had increased left ventricular functional refractory period (FRP) by ≥12% from control over the number of animals tested. [c] Active dose of the test compound (FRP ≥ 12% from control) and the number of animals which this dose was active in parentheses. [d] Percent change in heart rate from control at active dose (mean ± SEM). [e] Percent change in blood pressure from control at active dose (mean ± SEM). [f] Percent change in FRP from control at active dose (mean ± SEM). [g] NA = not applicable.

ber of noninducible animals (either sustained ventricular tachycardia or ventricular fibrillation) over the total number of experiments, dose range, and effective dose and the effects on HR, BP, and FRP at the effective dose are reported for the test compounds in Table VII for this PES model.

A second antiarrhythmic efficacy model was also utilized. In this study arrhythmias were induced by administration of epinephrine to halothane-anesthetized dogs according to the method of Mitsuhashi et al.[33] In this model, β-blockers are very effective while class III agents are ineffective. In Table VIII, we report the number of animals protected from arrhythmias over the total number of animals studied and at the dose that this occurred.

Results and Discussion

The in vitro electrophysiological effects (class III) and β-receptor binding and selectivity of the synthesized compounds are reported in Table V. Sotalol, propranolol, sematilide, **1**, (*R*)-**1**, and (*S*)-**1** were also tested for comparison. With the exception of **8** and **30**, all of the prepared compounds possess potent activity in the cardiac Purkinje fiber screen and are more potent than sotalol. To determine potential β-blocking activity, these compounds were examined for their ability to displace the β-receptor antagonist ([^{3}H]DHA) from canine cardiac tissue (Table V). Sotalol and propranolol were used as standards in this assay. The tertiary amine analogues (i.e. **16**–**18** and **27**–**33**) were, in general, less effective at displacing the β receptor [^{3}H]DHA than the secondary amines. This trend is consistent with the literature.[34]

Selective β_1-receptor affinity was then checked for those compounds that possessed both potent class III activity and β-receptor affinity that was greater than or equal to that found for sotalol ($C_{20}APD_{95}$ = 14.4 μM and IC_{50} = 7.2 μM, respectively). Potent class III activity and β_1 selectivity was found for compounds **20**, **32**, **37**, **38**, and **39**. This was also found previously for **1**.

The hemodynamic and electrophysiological effects of a number of target compounds were investigated following intraduodenal administration (Table VI). Of the compounds tested, only **9**, **11**–**13**, **16**, **28**, **29**, **31**–**33**, **35**, and **41** showed class III potency similar to sotalol. A number of these compounds were then selected for further studies using in vivo efficacy models.

A group of eight compounds (i.e. **12**, **28**, **32**, **33**, **35**, **39**, **41**, and **1**) were then evaluated for efficacy in a PES model in concious dogs (Table VII). Compounds were chosen for this screening based on their pharmacological profile (electrophysiology, β-receptor affinity, and activity after intraduodenal administration). This model is useful in determining efficacy in selective class III agents. All of the compounds tested in this model were comparable in potency to that of sotalol. No adverse hemodynamic or CNS effects were observed in this model for any of the compounds studied.

A second antiarrhythmic efficacy model was then utilized to determine if some of the prioritized compounds would protect against arrhythmia (Table VIII). β blockers are generally very effective in this halothane/epinephrine-treated dog model, whereas class III agents are not. This model is considered as an indirect assessment of β-blocking activity for our compounds. Compounds **28**, **32**, and **41** were not as effective as sotalol in this model. Compound **1** and (*S*)-**1**, however, were found to be equieffective as sotalol in this model. As expected, (*R*)-**1**, which has a low affinity for β receptors, was not effective in this model. Studies centered around (*S*)-**1**[1] as a combined class III/II antiarrhythmic agent are continuing.

Conclusions

We have shown that various (aryloxy)propanolamines possess potent class III antiarrhythmic and β-blocking activity both in vitro and in vivo. In particular, compounds **32**, **41**, **1**, and especially (*S*)-**1** were found to be orally active class III agents in anesthetized mongrel dogs (1 or 3 mg/kg, id) and efficacious at suppressing PES-induced reentrant ventricular tachyarrhythmias and epinephrine-induced arrhythmias in halothane-anesthetized dogs. The profile of these compounds was similar to that found for sotalol. Compound (*S*)-**1**, which was more potent than sotalol in the PES study and equieffective in the halothane/epinephrine dog model, is being investigated further as a combined class III/II antiarrhythmic agent.

Experimental Section

Chemistry. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz (Varian XL-300). Chemical shifts are reported in parts per million (δ) downfield from an internal standard of tetramethylsilane (Me_4Si) for $CDCl_3$ and Me_2SO-d_6 or sodium 3-(trimethylsilyl)propionate (TSP) for D_2O. Infrared (IR) spectra were taken on a Sargent-Welch 3-300 or a Beckman Acculab 2 spectrophotometer as a KBr pellet or as a Nujol mull as indicated. Elemental analyses were performed by the analytical department of Berlex Laboratories, Inc. or Microlit Laboratories Inc., Caldwell, NJ. Melting points were obtained on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Woelm silica gel (63–200 mesh) and Fisher alumina (neutral, activity III) were used for column chromatography. Compounds **1**, (*S*)-**1**, and (*R*)-**1** were synthesized previously.[1]

***N*-(2-Aminoethyl)-4-[(methylsulfonyl)amino]benzamide (3a).** A mixture of **2a**[5] (57 g, 0.25 mmol) and ethylenediamine (250 mL) was heated at reflux for 5 h. The mixture was concentrated in vacuo first with water and then with acetonitrile to azeotrope the excess ethylenediamine. The residue was then crystallized from 90% aqueous ethanol and gave 47 g (73%) of analytically pure **3a**: mp 184.5–186 °C; ^{1}H NMR (DMSO-d_6) δ 2.76 (t, 2 H), 2.93 (s, 3 H), 3.32 (q, 2 H), 5.35 (br s, 3 H), 7.12 (d, 2 H), 7.75 (d, 2 H), 8.23 (t, 1 H). Anal. ($C_{10}H_{15}N_3O_3S$) C, H, N.

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Table VII. Antiarrhythmic Efficacy (PES Model)

compound[a]	no. effective[b]/ no. tested	dose range, mg/kg, iv	effective dose,[c] mg/kg, iv	HR[d]	BP[e]	FRP[f]
sotalol	7/9	0.3 - 10	1.0 (3), 3.0 (3), 10 (1)	−6 ± 6	8 ± 3	14 ± 4
12	4/5	1.0 - 10	1.0 (2), 3.0 (1), 10 (1)	24 ± 13	−5 ± 4	6 ± 8
28	3/5	1.0 - 10	1.0 (2), 10 (1)	18 ± 12	−1 ± 2	13 ± 2
32	5/6	1.0 - 10	1.0 (4), 3.0 (1)	−3 ± 4	13 ± 8	8 ± 2
33	3/4	1.0 - 10	1.0 (3)	9 ± 9	8 ± 5	6 ± 3
35	2/3	1.0 - 10	1.0 (1), 10 (1)	−13 ± 1	−5 ± 12	3 ± 1
39	3/5	1.0 - 10	1.0 (1), 3.0 (1), 10 (1)	−12 ± 6	−4 ± 6	9 ± 5
41	7/8	0.1 - 10	0.3 (2), 1.0 (4), 10 (1)	1 ± 4	−4 ± 6	15 ± 6
1	8/8	0.3 - 3.0	0.3 (2), 1.0 (5), 3.0 (1)	9 ± 7	3 ± 3	13 ± 2
(*S*)-**1**	7/8	0.1 - 3.0	0.3 (6), 1.0 (1)	−2 ± 5	4 ± 6	5 ± 3

[a] All compounds are racemic unless otherwise noted. [b] Number of animals in which sustained ventricular tachycardia (SVT) or ventricular fibrillation (VF) was not inducible after drug administration over the number of animals tested (basic cycle length = 400 ms). [c] Effective dose of the test compound and the number of animals which this dose was effective in parentheses. [d] Percent change in heart rate from control at effective dose (mean ± SEM). [e] Percent change in blood pressure from control at effective dose (mean ± SEM). [f] Percent change in FRP from control at effective dose (mean ± SEM).

Table VIII. Epinephrine-Induced Arrhythmia Model

compound[a]	no. effective/no. tested (dose mg/kg, iv)[b]
sotalol	4/4 (1.0), 6/6 (3.0)
28	2/3 (1.0), 2/5 (3.0)
32	4/8 (1.0), 4/8 (3.0)
41	2/4 (0.3), 4/7 (1.0)
1	0/2 (0.3), 6/8 (1.0)
(*S*)-**1**	2/4 (0.3), 4/4 (1.0)
(*R*)-**1**	1/4 (1.0), 1/4 (3.0)

[a] All compounds are racemic unless otherwise noted. [b] Number of animals protected from arrhythmia over the total number of animals tested followed by dose in parentheses.

In a similar manner as above, (±)-*trans*-*N*-(2-aminocyclohexyl)-4-[(methylsulfonyl)amino]benzamide hemihydrate was prepared: mp 166–170 °C; IR (KBr) 3350, 1625, 1609, 1325, and 1135 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.09–1.38 (m, 4 H), 1.68 (m, 2 H), 1.88 (m, 2 H), 2.68 (dt, 1 H), 2.93 (s, 3 H), 3.57 (m, 1 H), ca. 4.0 (br s, 3 H), 7.12 (d, 2 H), 7.77 (d, 2 H), 7.98 (d, 1 H). Anal. ($C_{14}H_{21}N_3O_3S$) C, H, N.

(±)-*N*-[2-[[2-Hydroxy-3-(1-naphthalenyloxy)propyl]amino]ethyl]-4-[(methylsulfonyl)amino]benzamide (5). A mixture of **3a** (10 g, 38.9 mmol) and (±)-[(1-naphthyloxy)methyl]oxirane (**4a**) (7.8 g, 40.0 mmol) in 90% aqueous methanol (700 mL) was heated at 50 °C for 18 h. The mixture was concentrated in vacuo and partitioned between ethyl acetate (500 mL) and water (500 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, yielding 13 g of a tacky white solid which was recrystallized from 2-propanol, giving analytically pure **5** (4.0 g, 22%): mp 168–171 °C; IR (Nujol) 3370, 3320, 3140, 1635, 1605, 1570, and 1500 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.7–2.9 (m, 4 H), 3.04 (s, 3 H), 3.37 (m, 2 H), 4.0–4.2 (m, 3 H), 6.2 (br s, 2 H), 7.00 (d, 1 H), 7.23 (d, 2 H), 7.4–7.6 (m, 4 H), 7.8–7.95 (m, 3 H), 8.24–8.4 (m, 2 H).

Compounds **6–9** were prepared in a similar manner.

***N*-(2-Aminoethyl)-4-(1*H*-imidazol-1-yl)benzamide Hydrochloride (3b).** A mixture of 4-(1*H*-imidazol-1-yl)benzoic acid methyl ester (**2b**)[22] (21 g, 97 mmol) and ethylenediamine (150 mL) was heated at reflux for 24 h. The excess ethylenediamine was then removed in vacuo and the residue triturated with water (200 mL) and filtered. This compound was dissolved in ethanol and treated with excess hydrochloric acid gas. The precipitate was collected and gave 17.6 g (34%) of **3b** as a white solid: mp 245–248 °C; IR (KBr) 3230, 1640, 1600, 1500, 1290, 1255, and 1050 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.02 (t, 2 H), 3.57 (q, 2 H), 7.15 (s, 1 H), 7.81 (s, 1 H), 7.88 (s, 1 H), 8.11 (d, 2 H), 8.42 (s, 1 H), 8.99 (t, 1 H), 7.95–8.80 (br s, 3 H). Anal. ($C_{12}H_{14}N_4O$·HCl) C, H, N.

(±)-*N*-[2-[[2-Hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl]amino]ethyl]-4-(1*H*-imidazol-1-yl)benzamide 0.25-Hydrate (10). A mixture of **3b** (10 g, 37.5 mmol), (±)-[[4-(2-methoxyethyl)phenoxy]methyl]oxirane (**4e**) (8.59 g, 41.2 mmol), sodium hydroxide (1.69 g, 42 mmol) in methanol (50 mL), and water (5 mL) was heated at ca. 60 °C for 17 h. After cooling to room temperature, the mixture was concentrated in vacuo and the residue triturated with methylene chloride and filtered. The filtrate was concentrated in vacuo and the residue chromatographed on alumina with 2% methanol in methylene chloride as eluent. Product fractions were collected and concentrated in vacuo to give an oil which crystallized upon standing. Recrystallization from ethyl acetate afforded analytically pure **10** (1.81 g, 11%): mp 120–122 °C; IR (KBr) 3260, 2930, 1660, 1610, 1510, 1300, 1240, 1120, 1095, 1065, and 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (t, 2 H), 2.90 (m, 2 H), 2.95 (t, 2 H), 3.59 (t, 3 H), 3.62 (m, 2 H), 3.78 (s, 3 H), 4.00 (m, 2 H), 4.15 (m, 1 H), 6.85 (d, 2 H), 6.90 (t, 1 H), 7.16 (d, 2 H), 7.28 (d, 2 H), 7.29 (s, 1 H), 7.35 (s, 1 H), 7.45 (d, 2 H), 7.93 (s, 1 H), 7.94 (d, 2 H).

Compounds **11–13** were prepared in a similar manner.

1-[4-[(Methylsulfonyl)amino]benzoyl]-4-(phenylmethyl)piperazine Hydrochloride 0.25-Hydrate. To a solution of 4-[(methylsulfonyl)amino]benzoyl chloride (**14**)[5] (33.15 g, 142 mmol) in tetrahydrofuran (THF) (400 mL) cooled to 0 °C was added a solution of 1-benzylpiperazine (25.0 g, 142 mmol) in THF (50 mL) dropwise via dropping funnel. The mixture was then warmed to room temperature and stirred for 3 h. The precipitate was collected and washed with ether and air-dried. Recrystallization from 95% aqueous ethanol afforded 51.5 g (88%) of the title compound as white crystals: mp 223–226 °C; IR (Nujol) 3120, 2440 (broad), 1610, 1240, 1160, and 845 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.06 (s, 3 H), 3.10–4.20 (m, 8 H), 4.33 (m, 2 H), 7.25 (d, 2 H), 7.44 (d, 2 H), 7.46 (br s, 3 H), 7.59 (br s, 2 H), 10.13 (s, 1 H), 11.10 (br s, 1 H). Anal. ($C_{19}H_{23}N_3O_3S$·HCl·0.25H_2O) C, H, N, S, Cl.

1-[4-[(Methylsulfonyl)amino]benzoyl]piperazine Hydrochloride (15). A mixture of the above compound (25.8 g, 63 mmol) in water (500 mL) was treated with 10% Pd–C (2.7 g) and hydrogenated at 50 psi at room temperature for 22 h. The catalyst was removed by filtration through Celite and the filtrate concentrated in vacuo to give **15** (19.6 g, 97%): mp 219–222 °C; IR (Nujol) 3180, 2600 (broad), 1610 (broad), 1235, 1155, and 850 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.06 (s, 3 H), 3.12 (m, 4 H), 3.71 (m, 4 H), 7.27 (d, 2 H), 7.44 (d, 2 H), 9.82 (br s, 3 H). Anal. ($C_{12}H_{17}N_3O_3S$·HCl) C, H, N.

(±)-1-[2-Hydroxy-3-(1-naphthylenyloxy)propyl]-4-[4-[(methylsulfonyl)amino]benzoyl]piperazine (16). Compound **15** (15.9 g, 50 mmol) was dissolved in water (100 mL), and 1 N sodium hydroxide was added until the pH was 8.5. The mixture was then concentrated in vacuo and the residue triturated with ethanol and filtered. The filtrate was then concentrated in vacuo to give 12.0 g of a white foam. This free base was dissolved in methanol (200 mL) and (±)-[(1-naphthyloxy)methyl]oxirane (**4a**) (7.9 g, 42 mmol) added at room temperature. The mixture was then heated at reflux for 46 h and then cooled to room temperature and concentrated in vacuo. The residue was chromatographed on silica gel (600 g) with 5% methanol in methylene chloride as eluent. This afforded **16** (15.9 g, 78%) as a crystalline solid: mp 97–105 °C; IR (Nujol) 3400 (broad), 1610, 1580, 1340, 1265, 1160, 970, and 780 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.40–2.70 (m, 6 H), 3.04 (s, 3 H), 3.28–3.76 (m, 4 H), 4.04–4.22 (m, 3 H), 5.04 (d, 1 H), 7.23 (d, 2 H), 7.37 (d, 2 H), 7.39–7.57 (m, 4 H), 7.86 (dd, 1 H), 8.24 (dd, 1 H), 10.43 (s, 1 H).

Compounds **17** and **18** were prepared in a similar manner.

***N*-(4-Cyanophenyl)methanesulfonamide.** This compound was prepared according to the literature[24] in 62% yield: mp 190–192 °C (lit.[24] mp 197.5 °C).

***N*-[4-(Aminomethyl)phenyl]methanesulfonamide Hydrochloride (19a).** A suspension of the above compound (45 g, 229 mmol) in methanol (450 mL) was saturated with ammonia gas and then Raney nickel catalyst (4 g) was added. The mixture was hydrogenated at ca. 50 psi for 2 h and then filtered. The filtrate was concentrated in vacuo, the residue taken up in ethyl acetate/methanol (9:1) and then treated with hydrochloric acid gas. The resulting precipitate was collected and gave 40 g (74%) of **19a**: mp 255–257 °C; IR (KBr) 3000 (broad), 1610, 1340, 1160, 990, and 970 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.01 (s, 3 H), 3.96 (s, 2 H), 7.24 (d, 2 H), 7.48 (d, 2 H), 8.25 (br s, 3 H), 9.9 (br s, 1 H). Anal. ($C_8H_{12}N_2O_2S$·HCl) C, H, N.

(±)-*N*-[4-[[[2-Hydroxy-3-(3-methylphenoxy)propyl]amino]methyl]phenyl]methanesulfonamide Hydrochloride (20). To a solution of **19a** (15 g, 63.4 mmol) in 1 N potassium hydroxide (63.3 mL) and methanol (50 mL) warmed to 50 °C was added (±)-[(3-methylphenoxy)methyl]oxirane (**4g**) (10.41 g, 63.4 mmol) in one portion. The mixture was stirred at 50 °C for 3.5 h and then cooled to room temperature and concentrated in vacuo. The residue was then dissolved in methanol and treated with hydrochloric acid gas. The precipitate was collected and air-dried to give 2.79 g (11%) of **20** as a white crystalline solid: mp 201–203 °C; IR (KBr) 3400, 3270, 2960, 2800, 1600, 1230, 1150, 1000, and 780 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.27 (s, 3 H), 2.85–3.15 (m, 2 H), 3.02 (s, 3 H), 3.93 (s, 2 H), 4.14 (s, 2 H), 4.23 (br s, 1 H), 5.90 (br s, 1 H), 6.74 (m, 3 H), 7.19 (m, 1 H), 7.24 (d, 2 H), 7.53 (d, 2 H), ca. 9.3 (br s, 2 H), 9.97 (s, 1 H).

Compounds **21** and **22** were prepared in a similar manner.

4-(1*H*-Imidazol-1-yl)benzonitrile. This compound was prepared according to the literature[25] in 82% yield: mp 146–149 °C (lit.[25] mp 151–152 °C).

1-[4-(Aminomethyl)phenyl]-1*H*-imidazole. A suspension of the above compound (10 g, 59 mmol) in dry dioxane (300 mL) was treated with lithium aluminum hydride (4.5 g, 118 mmol) heated at reflux under nitrogen for 18 h and then cooled at room temperature. The reaction was quenched by careful addition of water (4.5 mL) and then 4 N sodium hydroxide (4.5 mL) and additional water (13 mL). A white solid formed after stirring for 40 min. The solid was collected by filtration through Celite and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel (200 g) with 2% ammonium hydroxide in acetonitrile as eluent. The product fractions were collected and evaporated to give 1.85 g (18%) of **19b**.

(±)-1-[[[4-(1*H*-Imidazol-1-yl)phenyl]methyl]amino]-3-(2-methylphenoxy)-2-propanol Dihydrochloride (23). To a solution of **19b** (1.74 g, 10.04 mmol) in dry dimethyl sulfoxide (20 mL) was added hexamethyldisilazane (2.44 mL, 11.55 mmol). The solution was stirred for 0.5 h at room temperature and then treated with (±)-[(2-methylphenoxy)methyl]oxirane (**4h**) (1.73 g, 10.54 mmol) in dry dimethyl sulfoxide (10 mL). The mixture was then heated at 60 °C for 24 h and then cooled to room temperature. The mixture was poured into water (200 mL) and extracted with methylene chloride (3 × 75 mL). The organic extracts were then combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (120 g) with 2% ammonium hydroxide in acetonitrile as eluent. The product fractions were combined, and the solvent was removed. The residue was taken up in 2-propanol and treated with hydrochloric acid gas. The precipitate was collected and afforded 2.60 g (63%) of **23** as a yellow solid: mp 202–204 °C; IR (KBr) 3350, 2380, 1595, 1545, 1250, and 1060 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.11 (s, 3 H), 3.0 (m, 1 H), 3.2 (m, 1 H), 3.5 (br s, 2 H), 3.97 (m, 2 H), 4.32 (m, 2 H), 6.66 (t, 1 H), 6.72 (d, 1 H), 7.13 (m, 2 H), 7.90 (s, 4 H), 7.93 (s, 1 H), 8.33 (s, 1 H), 9.5 (br s, 1 H), 9.78 (s, 1 H), 9.88 (br s, 1 H).

Compound **24** was prepared in a similar manner.

***N*-[4-[4-(Phenylmethyl)piperazin-1-yl]phenyl]methanesulfonamide 1.2-Hydrochloride.** Methanesulfonic anhydride (6.49 g, 37.0 mmol) was added at room temperature to a solution of **25**[26] (9.50 g, 35.5 mmol) in acetonitrile (100 mL) and stirred for 5 h. The solution was then concentrated in vacuo and saturated aqueous sodium bicarbonate solution (100 mL) was added to the residue. The mixture was extracted with methylene chloride (2 × 100 mL), and the organic extracts were then combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was taken up in methanol (200 mL) and acidified with hydrochloric acid gas until pH 1.0. Crystals were collected and air-dried to give 10.0 g (67%) of the title compound as white crystals: mp 252–255 °C; IR (KBr) 3400, 2540, 1336, and 1149 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.87 (s, 3 H), 3.03–3.25 (m, 4 H), 3.33 (d, 2 H), 3.63–3.81 (m, 2 H), 4.37 (d, 2 H), 6.96 (d, 2 H), 7.12 (d, 2 H), 7.47 (m, 3 H), 7.66 (m, 2 H), 9.37 (br s, 1 H), 11.38 (br s, 1 H). Anal. ($C_{18}H_{23}N_3O_2S$·1.2HCl) C, H, N, S, Cl.

***N*-(4-Piperazin-1-ylphenyl)methanesulfonamide Hydrochloride 0.1-Hydrate (26).** A mixture of the above compound (7.03 g, 18.2 mmol) and 10% Pd–C (350 mg) in water (200 mL) and ethanol (200 mL) was hydrogenated at ca. 50 psi at room temperature for 4 h. The catalyst was filtered through Celite and the filtrate concentrated in vacuo. The crystalline residue was then recrystallized from ethanol and gave 4.5 g (97%) of **26**: mp 240–242 °C; IR (KBr) 3400, 2480, 1319, and 1142 cm^{-1}; ^1H NMR (D_2O) δ 3.08 (s, 3 H), 3.48 (m, 8 H), 7.16 (d, 2 H), 7.31 (d, 2 H). Anal. ($C_{11}H_{17}N_3O_2S$·HCl·0.1H_2O) C, H, N, S, Cl.

(±)-*N*-[4-[4-(2-Hydroxy-3-phenoxypropyl)piperazin-1-yl]phenyl]methanesulfonamide 0.25-Hydrate (27). A mixture of **26** (22.1 g, 56.9 mmol), (±)-(phenoxymethyl)oxirane (**4c**) (8.55 g, 56.9 mmol), and sodium methoxide (3.07 g, 56.9 mmol) in 90% aqueous methanol (800 mL) was heated at 60 °C for 17 h and then cooled to room temperature. The white crystalline precipitate was collected and washed with water (100 mL) and then methanol (100 mL) and air-dried to give 7.65 g (33%) of **27**: mp 180–181 °C; IR (KBr) 1605, 1520, 1333, and 1163 cm^{-1}; ^1H NMR (DMSO-d_6, 100 °C) δ 2.57 (dd, 2 H), 2.6 (m, 4 H), 2.85 (s, 3 H), 3.0 (br s, 1 H), 3.12 (t, 4 H), 3.93 (m, 1), 3.97 (m, 2), 6.88 (m, 3), 6.94 (d, 2), 7.09 (d, 2 H), 7.25 (m, 2 H), 8.9 (br s, 1 H).

Compounds **28–33** were prepared in a similar manner.

***N*-[2-[4-(1*H*-Imidazol-1-yl)phenoxy]ethyl]propanamide Hemihydrate.** A mixture of 4-(1*H*-imidazol-1-yl)phenol (25.96 g, 162 mmol) and 2-ethyl-2-oxazoline (40 mL, 396 mmol) was heated at reflux for 4 h and then cooled to room temperature. The mixture was taken up in methylene chloride (50 mL) and washed with 4 N potassium hydroxide (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo to give a brown oil. The oil solidified upon petroleum ether trituration and was then recrystallized from ethyl acetate/hexanes to give analytically pure title compound (30.0 g, 72%): mp 72–75 °C; IR (Nujol) 1655, 1570, 1535, 1260, 1080, and 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, 3 H), 2.26 (q, 2 H), 3.70 (dt, 2 H), 4.08 (t, 2 H), 5.98 (br s, 1 H), 6.98 (d, 2 H), 7.19 (s, 1 H), 7.21 (s, 1 H), 7.31 (s, 1 H), 7.76 (s, 1 H). Anal. ($C_{14}H_{17}N_3O_2$·0.5H_2O) C, H, N.

2-[4-(1*H*-Imidazol-1-yl)phenoxy]ethanamine Dihydrochloride Hemihydrate (34). A solution of the above compound (18.2 g, 70.2 mmol) and 6 N aqueous hydrochloric acid (30 mL) was heated at 130 °C for 3.5 h and then cooled to room temperature. The mixture was then concentrated in vacuo and then triturated with 2-propanol (80 mL). The solid was collected and then dissolved in hot methanol (125 mL) and 2-propanol (105 mL) and then slowly cooled to room temperature. The crystals were collected and air-dried to give 17.9 g (92%) of **34** as light brown needles: mp 242–245 °C; IR (Nujol) 1610, 1560, 1510, 1260, 1190, 1070, 1020, and 830 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.22 (m, 2 H), 4.30 (t, 2 H), 7.23 (d, 2 H), 7.89 (s, 1 H), 8.23 (s, 1 H), 8.43 (br s, 4 H), 9.65 (s, 1 H). Anal. ($C_{11}H_{13}N_3O$·2HCl·0.5H_2O) C, H, N, Cl.

Dicyclopropanemethanone (±)-*O*-[2-Hydroxy-3-[[2-[4-(1*H*-imidazol-1-yl)phenoxy]ethyl]amino]propyl]oxime Sulfuric Acid Salt (1:1) Hemihydrate (35). Epoxide **4k** (3.14 g, 17.3 mmol) was dissolved in methanol (60 mL) followed by **34** (4.58 g, 16.1 mmol) and 2 N sodium hydroxide (20 mL) and the resulting solution heated at 60 °C for 22 h. The solution was concentrated in vacuo and the residue chromatographed on silica gel (90 g) first with 10% methanol in methylene chloride and then with 20% methanol in methylene chloride as eluent. Product fractions were collected and the solvent removed to give 2.59 g of an oil. The oil was dissolved in methanol (20 mL), and concentrated sulfuric acid (0.35 mL) was added. Addition of 2-propanol afforded crystals of **35** (2.56 g, 32%): mp 173–174 °C; IR (KBr) 2100–3700, 1610, 1540, and 1505 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.59 (m, 4 H), 0.8–1.1 (m, 5 H), 2.30 (m, 1 H), 2.98 (m, 1 H), 3.20 (d, 1 H), 3.42 (br t, 2 H), 3.88 (dd, 1 H), 3.97 (dd, 1 H), 4.10 (br s, 1 H), 4.34 (br t, 2 H), 5.88 (br s, 1 H), 7.10 (s, 1 H), 7.11 (d, 2 H), 7.60 (d, 2 H), 7.66 (s, 1 H), 8.15 (s, 1 H), 8.9 (br s, 3 H).

2-[4-(1*H*-Imidazol-1-yl)phenoxy]-*N*-(phenylmethyl)-ethanamine Dihydrochloride (36). To a suspension of sodium hydride (39.5 g, 823 mmol) in dry dimethylformamide (500 mL) cooled to 0 °C was added portionwise 4-(1*H*-imidazol-1-yl)phenol (37.32 g, 233 mmol). The reaction was then stirred until gas evolution ceased and then *N*-benzyl-2-chloroethylamine hydrochloride[27] (60.22 g, 292 mmol) was added portionwise. After the addition the mixture was heated at 65 °C for 3 h and then cooled to room temperature and carefully treated with water (20 mL). The mixture was then concentrated in vacuo and the residue chromatographed on silica gel (800 g) with 2% methanol in methylene chloride as eluent. The product fractions were collected, and the solvent was evaporated to give 46.4 g (68%) of **36** as the free base. The dihydrochloride could be prepared by treatment with ethanolic hydrochloric acid: mp 215–218 °C; IR (Nujol) 3400, 1500, 1240, and 1050 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.32 (br s, 3 H), 4.24 (s, 2 H), 4.42 (t, 2 H), 7.22 (d, 2 H), 7.43 (m, 3 H), 7.63 (m, 2 H), 7.76 (m, 3 H), 8.15 (s, 1 H). Anal. ($C_{18}H_{19}N_3O\cdot 2HCl$) C, H, N.

(±)-1-[[2-[4-(1*H*-Imidazol-1-yl)phenoxy]ethyl]amino]-3-phenoxy-2-propanol 0.3-Hydrate (37). A mixture of **36** (6.99 g, 23.9 mmol) and (±)-(phenoxymethyl)oxirane (**4c**) (3.6 g, 23.9 mmol) in methanol (20 mL) was heated at 60 °C overnight and then cooled to room temperature. The mixture was concentrated in vacuo and the residue chromatographed on silica gel (400 g) with 20% acetone in petroleum ether as eluent. Collection of the product fractions and removal of the solvent gave 6.0 g of oil. The oil was dissolved in methanol (25 mL) and 10% Pd–C catalyst added (0.8 g) and the resulting mixture hydrogenated at ca. 50 psi for 48 h at room temperature. The mixture was filtered and the filtrate concentrated in vacuo to give an oil which was triturated with petroleum ether to give crystals of **37** (2.6 g, 31%): mp 92–96 °C; IR (Nujol) 1595, 1520, 1500, 1310, 1265, 1250, 1160, 835, and 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (br s, 2 H), 2.93 (m, 2 H), 3.10 (t, 2 H), 4.00 (d, 2 H), 4.13 (t, 3 H), 6.89–6.99 (m, 5 H), 7.18 (m, 2 H), 7.27 (m, 4 H), 7.75 (s, 1 H).

Compounds **38** and **39** were prepared in a similar manner.

(±)-*N*-[4-[1-Hydroxy-2-[[2-[4-(1*H*-imidazol-1-yl)phenoxy]ethyl]amino]ethyl]phenyl]methanesulfonamide 2.2-Hydrochloride 0.25-Hydrate (41). To a stirred solution of **36** (4.8 g, 16 mmol) and *N*,*N*-diisopropylethylamine (2.8 mL, 16 mmol) in acetonitrile (10 mL) cooled to 0 °C was added *N*-[4-(2-bromo-1-oxoethyl)phenyl]methanesulfonamide (**40a**)[29] (4.67 g, 16 mmol) portionwise. The mixture was then slowly warmed to room temperature and stirred for 17 h and then concentrated in vacuo. The residue was taken up in 6 N sodium hydroxide (25 mL) and washed with ether (2 × 50 mL). The aqueous layer was then adjusted to pH 7.5 with 1 N hydrochloric acid and extracted with methylene chloride (3 × 50 mL), combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was then taken up in 1 N hydrochloric acid (30 mL) and $Pd(OH)_2$ on carbon (0.6 g) was added and the mixture hydrogenated at ca. 50 psi for 8 h at room temperature. The reaction mixture was filtered and the pH of the filtrate adjusted to 8.0 with 1 N sodium hydroxide and then extracted with methylene chloride (3 × 50 mL). Concentration of the organic layers afforded a brown oil which was then treated with ethanolic hydrochloric acid. Crystals formed from the cooled solution and were collected, giving **41** (2.45 g, 31%): mp 215–216 °C; IR (Nujol) 3420, 1510, 1330, 1250, 1150, and 830 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.98 (s, 3 H), 3.21 (m, 2 H), 3.44 (m, 3 H), 4.42 (t, 2 H), 5.03 (d, 1 H), 6.24 (br s, 1 H), 7.23 (d, 4 H), 7.37 (d, 2 H), 7.76 (d, 2 H), 7.87 (s, 1 H), 8.21 (s, 1 H), 9.12 (br s, 1 H), 9.50 (br s, 1 H), 9.60 (s, 1 H), 9.84 (s, 1 H).

Compound **42** was prepared in a similar manner.

Pharmacology. Intracellular electrophysiological profiles in canine cardiac Purkinje fibers, intraduodenal bioavailability, and β-receptor binding studies were performed according to previously established procedures.[8] The β_1/β_2 receptor binding studies, antiarrhythmic efficacy (PES model), and epinephrine-induced arrhythmia model used in this investigation have also been published.[1]

Acknowledgment. We thank Mr. Edward B. Saxton and Ms. Janet Forst of our Medicinal Chemistry Department for synthesis of some of the compounds. Appreciation is also given to Drs. William C. Lumma, Jr., Thomas M. Argentieri, and Elinor H. Cantor for their collaboration during the course of this investigation.

Supplementary Material Available: Table listing the elemental analyses of the compounds (4 pages). Ordering information is given on any current masthead page.