assay was terminated by rapid filtration over Whatman GF/C filters using a Brandel cell harvester (Gaithersburg, MD). The filters were quickly washed three times with 4 mL of ice-cold buffer and filters counted in a gamma counter. The data were analyzed using the Ligand program.[19] The K_d ± SE values were determined by analysis of two independent experiments with each data point being determined in triplicate.

Binding of [^{125}I]-7-IHPP-Fsk to Human Red Blood Cell Membranes. The membrane suspension was prepared as described above, diluted with ice-cold 50 mM Tris·HCl buffer, centrifuged at 20000*g* for 10 min and resuspended in 50 mM Tris·HCl buffer, pH 7.5, at a protein concentration of 10 μg/mL. The incubations were carried out at room temperature for 60 min in 12 mm × 75 mm glass test tubes in a total volume of 0.4 mL 50 mM Tris·HCl buffer, 5 mM $MgCl_2$, pH 7.4. The membranes (10 μg/tube) were incubated with a tracer amount of [^{125}I]-7-IHPP-Fsk, about 30 000 dpm, and forskolin derivatives at concentrations ranging from 1.28 nM to 20 μM. In some experiments the derivatives were tested at concentrations up to 100 μM. The assay was terminated by rapid filtration over Whatman GF/C filters using a Brandel cell harvester (Gaithersburg, MD). The filters were quickly washed three times with 4 mL of ice-cold buffer and filters counted in a gamma counter. The data were analyzed using the Ligand program. The K_d ± SE values were determined by analysis of two independent experiments with each data point being determined in triplicate.

Irreversible Loss of Binding Sites. The irreversible effects of the alkylating derivatives 19–22 were tested on [^{125}I]-6-IHPP-Fsk binding to bovine brain membranes or [^{125}I]-7-IHPP-Fsk binding to human erythrocyte membranes as described previously.[11] Membranes were incubated with either no additions (control) or 20 μM of forskolin or the indicated alkylating derivatives in 1 mL of buffer used for binding experiments for 30 min at room temperature. The membranes were then washed seven times with 50 mL of buffer. Membranes were resuspended in buffer, and the binding was determined as described above with a tracer amount of label, about 30 000 dpm/assay. Specific binding was determined as the difference between total binding and nonspecific binding determined in the presence of 100 μM forskolin.

Acknowledgment. We would like to acknowledge many helpful discussions with Dr. Kenner Rice, NIDDK, NIH, Bethesda, MD, and Dr. Radhakrishnan Iyer, Division of Biochemistry and Biophysics, FDA, Bethesda, MD. We would also like to thank Dr. Lawrence Philips, Division of Biochemistry and Biophysics, FDA, Bethesda, MD, for ^{1}H NMR spectra and Noel Whitaker, NIDDK, NIH, Bethesda, MD, for mass spectral data. We would also like to thank Dr. Ian Simpson, NIDDK, NIH, Bethesda, MD, for kindly supplying us with the human erythrocyte membranes.

Registry No. 1 (isomer 1), 136378-26-2; 1 (isomer 2), 136378-27-3; **2**, 135159-49-8; **3**, 135159-50-1; **4**, 136327-79-2; **5**, 136327-80-5; **6**, 136327-81-6; **7**, 136327-82-7; **8**, 136327-83-8; **9**, 136327-84-9; **10**, 136327-85-0; 11, 132523-83-2; 11-^{125}I, 135159-45-4; **12**, 136327-86-1; **13**, 136327-87-2; **14**, 136327-88-3; **15**, 136327-89-4; **15**-^{125}I, 136327-96-3; **16**, 136327-90-7; 17, 136327-91-8; **18**, 136327-92-9; **19**, 136327-93-0; **20**, 136327-94-1; 21, 136357-51-2; **22**, 136327-95-2; adenylyl cyclase, 9012-42-4.

Supplementary Material Available: NMR data for compounds **4–7**, **9**, **10**, **12–14**, and **16–18** (3 pages). Ordering information is given on any current masthead page.

Synthesis and Selective Class III Antiarrhythmic Activity of Novel *N*-Heteroaralkyl-Substituted 1-(Aryloxy)-2-propanolamine and Related Propylamine Derivatives

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The synthesis and biological evaluation of a series of novel 1-(aryloxy)-2-propanolamines and several related deshydroxy analogues are described. Compounds **4–29** were prepared and investigated for their class III electrophysiological activity in isolated canine Purkinje fibers and in anesthetized open-chest dogs. None of these compounds showed any class I activity. On the basis of the in vitro data, structure–activity relationships for the series are discussed. Two compounds, *N*-[4-[2-hydroxy-3-[methyl(2-quinolinylmethyl)amino]propoxy]phenyl]methanesulfonamide (**12**, WAY-123,223) and *N*-[2-[[methyl[3-[4-[(methylsulfonyl)amino]phenoxy]propyl]amino]methyl]-6-quinolinyl]-methanesulfonamide (**24**, WAY-125,971) were identified and characterized as potent and specific class III antiarrhythmic agents in vitro and in vivo. Compound **12** was found to be orally bioavailable, to produce large increases of ventricular fibrillation threshold (VFT), and, in some instances, to restore sinus rhythm from ventricular fibrillation in anesthetized open-chest dogs at a dose of 5 mg/kg (iv). The enantiomers of **12** (i.e., **13** and **14**) were synthesized and were found to exhibit similar electrophysiological effects in the Purkinje fiber screen. Compound **24**, a propylamine analogue with potency and efficacy comparable to those of UK-68798 (**2**) and E-4031 (**3**), was studied in voltage-clamp experiments (isolated cat myocytes) and was found to be a potent and specific blocker of the delayed rectifier potassium current (I_K).

Cardiovascular diseases are responsible for the deaths of over 1 million people annually in the United States.[1] Statistics indicate that sudden cardiac death (SCD) resulting from ventricular tachycardia (VT) and/or ventricular fibrillation (VF) plays a major role in 40–60% of these deaths.[2,3] Most of these life-threatening ventricular

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(1) Kaplan, H. R. Advances in Antiarrhythmic Drug Therapy: Changing Concepts. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1986**, *45*, 2184–2185.

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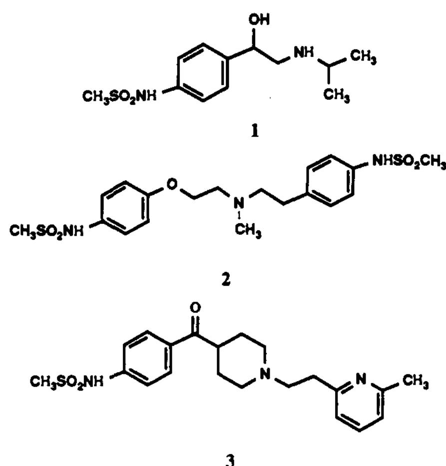
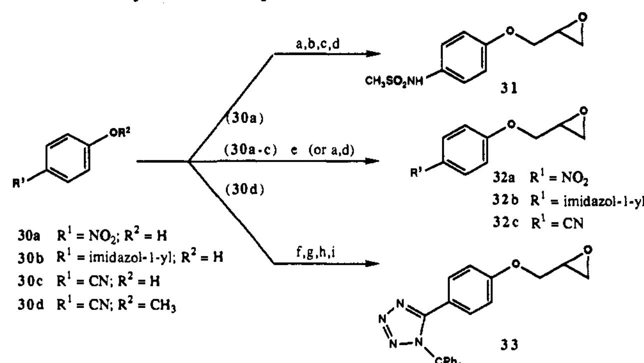
Chart I



Scheme I. Synthesis of Epoxides[a]



[a] Reagents: (a) NaH, $BrCH_2CH{=}CH_2$, DMF; (b) $SnCl_2{\cdot}H_2O$, HCl, 55 °C; (c) CH_3SO_2Cl, pyridine; (d) *m*-CPBA, CH_2Cl_2; (e) NaH, epibromohydrin, DMF; (f) NaN_3, Bu_3SnCl, xylenes, Δ; (g) $(Ph)_3CCl$, Et_3N, DMF, Δ; (h) PrSH, NaH, DMF, Δ; (i) NaH, epibromohydrin, DMF.

arrhythmias occur in patients suffering from coronary artery disease or from congestive heart failure. These patients constitute most of the population at risk for SCD and their long-term prophylactic treatment is the most challenging goal of antiarrhythmic therapy.[4,5]

Cardiac arrhythmias result from abnormalities of either impulse generation, impulse conduction, or a combination of both.[6] Several different mechanisms underlie each type of abnormality.[7] Considering the variety of arrhythmogenic processes, it is not surprising that antiarrhythmic drugs can act via several different mechanisms. According to the Vaughan Williams classification,[8] class I agents block the fast Na^+ channel. As a result, the maximum rate of depolarization ($\dot{V}_{max}$) of the transmembrane potential is depressed and this effect, in turn, decreases the velocity of propagation of cardiac impulse. Class I agents also delay the voltage-dependent recovery from inactivation of the Na^+ channels and thus prolong cardiac refractoriness. A plethora of compounds in this class are currently marketed worldwide.[9] These agents, although very effective in reducing the frequency of premature ventricular contractions (PVC), are poorly effective in controlling life-threatening VT and VF. Furthermore, class I agents suffer from serious side effects, chiefly among them proarrhythmia and negative inotropism, although gastrointestinal and central nervous system effects are also frequent.[10-12] The general concern about the unfavorable risk–benefit ratio in using class I agents has found new support in the results of the Cardiac Arrhythmia Suppression Trial (CAST)[13] which showed an increase in mortality over the control group in patients who survived myocardial infarction and were treated with flecainide and encainide, two potent class IC agents.[14]

Class II agents (β-blockers) antagonize the effects of catecholamines on cardiac tissue. Several multicenter clinical trials have shown convincingly that treatment with β-blockers reduces the incidence of SCD in patients who have survived a myocardial infarction.[15] However, the negative inotropic and chronotropic properties of β-blockers severely restrict their usage in the patient population at risk for SCD.

Class III antiarrhythmic agents, by definition, homogeneously prolong the transmembrane action potential duration (APD) and, consequently, refractoriness, without affecting cardiac conduction. APD prolongation can result from a block of outward K^+ current or from an increase of the inward current. Recently developed class III agents prolong repolarization by blocking outward K^+ current.[16]

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(7) Hoffman, B. F.; Rosen, M. R. Cellular Mechanisms for Cardiac Arrhythmias. *Circ. Res.* **1981**, *49*, 1–15.

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(14) Class I agents have been further classified into subgroups IA, IB, and IC, depending on whether the APD is prolonged, shortened, or unchanged, respectively. See: Muhiddin, K. A.; Turner, P. Is There an Ideal Antiarrhythmic Drug? A review—with particular reference on Class I agents. *Postgrad. Med. J.* **1985**, *61*, 665–678.

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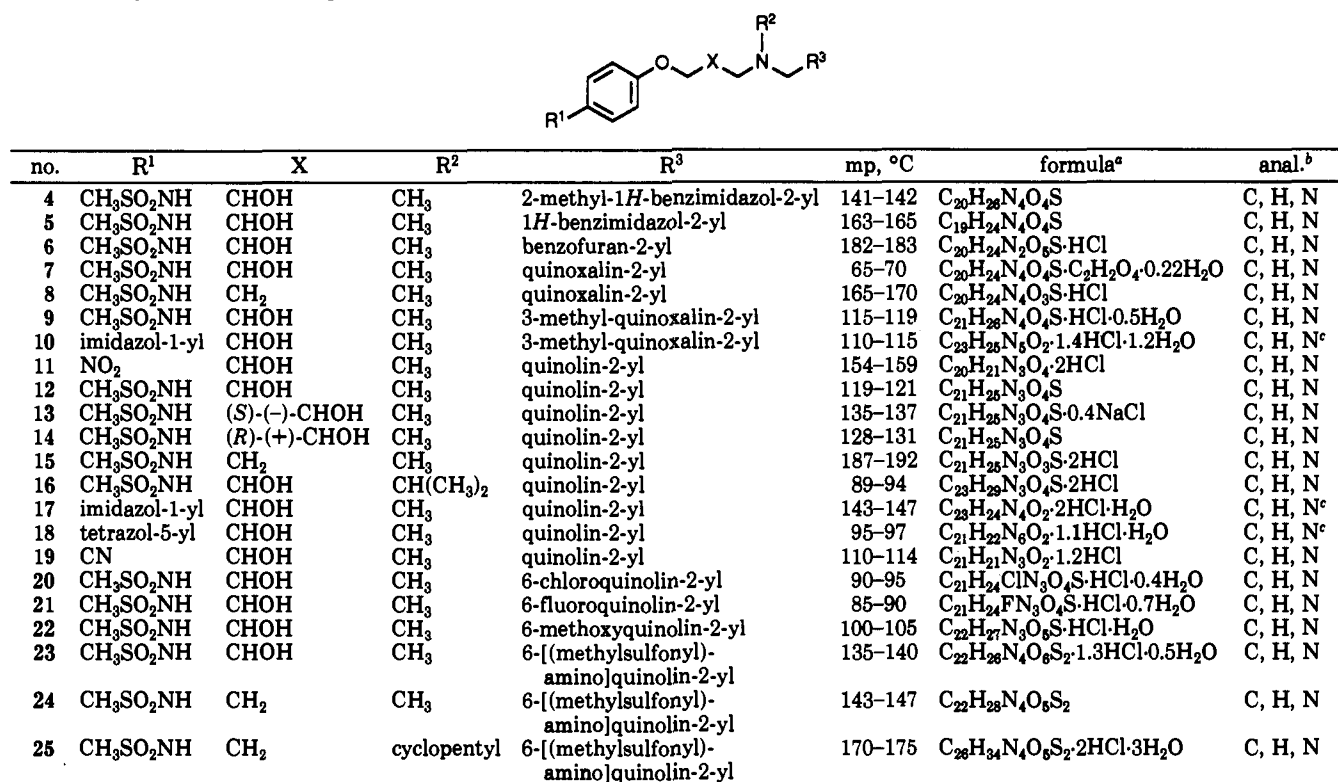
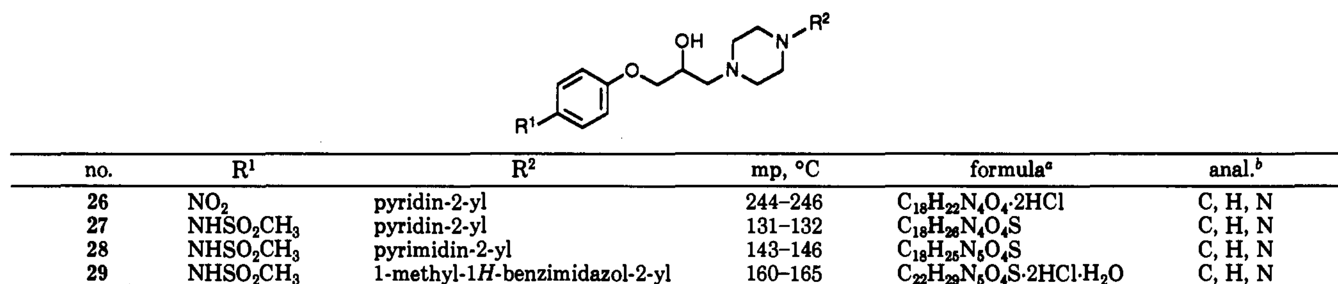
Table I. Physical Data for Compounds of Structure Type A



no.	R^1	X	R^2	R^3	mp, °C	formula[a]	anal.[b]
4	CH_3SO_2NH	CHOH	CH_3	2-methyl-1*H*-benzimidazol-2-yl	141–142	$C_{20}H_{26}N_4O_4S$	C, H, N
5	CH_3SO_2NH	CHOH	CH_3	1*H*-benzimidazol-2-yl	163–165	$C_{19}H_{24}N_4O_4S$	C, H, N
6	CH_3SO_2NH	CHOH	CH_3	benzofuran-2-yl	182–183	$C_{20}H_{24}N_2O_5S\cdot HCl$	C, H, N
7	CH_3SO_2NH	CHOH	CH_3	quinoxalin-2-yl	65–70	$C_{20}H_{24}N_4O_4S\cdot C_2H_2O_4\cdot 0.22H_2O$	C, H, N
8	CH_3SO_2NH	CH_2	CH_3	quinoxalin-2-yl	165–170	$C_{20}H_{24}N_4O_3S\cdot HCl$	C, H, N
9	CH_3SO_2NH	CHOH	CH_3	3-methyl-quinoxalin-2-yl	115–119	$C_{21}H_{26}N_4O_4S\cdot HCl\cdot 0.5H_2O$	C, H, N
10	imidazol-1-yl	CHOH	CH_3	3-methyl-quinoxalin-2-yl	110–115	$C_{23}H_{25}N_5O_2\cdot 1.4HCl\cdot 1.2H_2O$	C, H, N[c]
11	NO_2	CHOH	CH_3	quinolin-2-yl	154–159	$C_{20}H_{21}N_3O_4\cdot 2HCl$	C, H, N
12	CH_3SO_2NH	CHOH	CH_3	quinolin-2-yl	119–121	$C_{21}H_{25}N_3O_4S$	C, H, N
13	CH_3SO_2NH	(*S*)-(−)-CHOH	CH_3	quinolin-2-yl	135–137	$C_{21}H_{25}N_3O_4S\cdot 0.4NaCl$	C, H, N
14	CH_3SO_2NH	(*R*)-(+)-CHOH	CH_3	quinolin-2-yl	128–131	$C_{21}H_{25}N_3O_4S$	C, H, N
15	CH_3SO_2NH	CH_2	CH_3	quinolin-2-yl	187–192	$C_{21}H_{25}N_3O_3S\cdot 2HCl$	C, H, N
16	CH_3SO_2NH	CHOH	$CH(CH_3)_2$	quinolin-2-yl	89–94	$C_{23}H_{29}N_3O_4S\cdot 2HCl$	C, H, N
17	imidazol-1-yl	CHOH	CH_3	quinolin-2-yl	143–147	$C_{23}H_{24}N_4O_2\cdot 2HCl\cdot H_2O$	C, H, N[c]
18	tetrazol-5-yl	CHOH	CH_3	quinolin-2-yl	95–97	$C_{21}H_{22}N_6O_2\cdot 1.1HCl\cdot H_2O$	C, H, N[c]
19	CN	CHOH	CH_3	quinolin-2-yl	110–114	$C_{21}H_{21}N_3O_2\cdot 1.2HCl$	C, H, N
20	CH_3SO_2NH	CHOH	CH_3	6-chloroquinolin-2-yl	90–95	$C_{21}H_{24}ClN_3O_4S\cdot HCl\cdot 0.4H_2O$	C, H, N
21	CH_3SO_2NH	CHOH	CH_3	6-fluoroquinolin-2-yl	85–90	$C_{21}H_{24}FN_3O_4S\cdot HCl\cdot 0.7H_2O$	C, H, N
22	CH_3SO_2NH	CHOH	CH_3	6-methoxyquinolin-2-yl	100–105	$C_{22}H_{27}N_3O_5S\cdot HCl\cdot H_2O$	C, H, N
23	CH_3SO_2NH	CHOH	CH_3	6-[(methylsulfonyl)-amino]quinolin-2-yl	135–140	$C_{22}H_{26}N_4O_6S_2\cdot 1.3HCl\cdot 0.5H_2O$	C, H, N
24	CH_3SO_2NH	CH_2	CH_3	6-[(methylsulfonyl)-amino]quinolin-2-yl	143–147	$C_{22}H_{28}N_4O_5S_2$	C, H, N
25	CH_3SO_2NH	CH_2	cyclopentyl	6-[(methylsulfonyl)-amino]quinolin-2-yl	170–175	$C_{26}H_{34}N_4O_5S_2\cdot 2HCl\cdot 3H_2O$	C, H, N

[a] Structures of compounds confirmed by NMR, IR, and MS. [b] Analytical results are within ±0.4% of the theoretical value unless otherwise noted. [c] 10, H, N: calcd, 6.10, 14.71; found, 6.64, 14.22. 17, N: calcd, 11.69; found, 10.81. 18, N: calcd, 18.73; found, 17.92.

Table II. Physical Data for Compounds of Structure Type B



no.	R^1	R^2	mp, °C	formula[a]	anal.[b]
26	NO_2	pyridin-2-yl	244–246	$C_{18}H_{22}N_4O_4\cdot 2HCl$	C, H, N
27	$NHSO_2CH_3$	pyridin-2-yl	131–132	$C_{18}H_{26}N_4O_4S$	C, H, N
28	$NHSO_2CH_3$	pyrimidin-2-yl	143–146	$C_{18}H_{25}N_5O_4S$	C, H, N
29	$NHSO_2CH_3$	1-methyl-1*H*-benzimidazol-2-yl	160–165	$C_{22}H_{29}N_5O_4S\cdot 2HCl\cdot H_2O$	C, H, N

[a] Structures of compounds confirmed by NMR, IR, and MS. [b] Analytical results are within ±0.4% of theoretical value unless otherwise noted.

As the recent literature suggests,[17] the class III agents are receiving increased attention as a useful new therapy for the treatment of life-threatening arrhythmias and promise to become the most accepted class of antiarrhythmic agents.

d-Sotalol (1, Chart I), a compound with class III antiarrhythmic activity possessing only about 10% of the β-blocking activity of the racemate,[18] has been shown to be clinically effective against malignant reentrant ventricular arrhythmias.[19] Other class III agents that have been studied clinically include sematilide,[20] amiodarone (Cordarone),[21] and clofilium.[22] Clearly, a new benchmark for

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(19) (a) Cobbe, S. M. Sotalol. In *Handbook of Experimental Pharmacology, Vol. 89: Antiarrhythmic Drugs*; Vaughan Williams, E. M., Ed.; Springer-Verlag: Berlin, 1989; pp 365–387. (b) Schwartz, J.; Croker, K.; Wynn, J.; Somberg, J. C. The Antiarrhythmic Effects of *d*-Sotalol. *Am. Heart J.* **1987**, *114*, 539–544.

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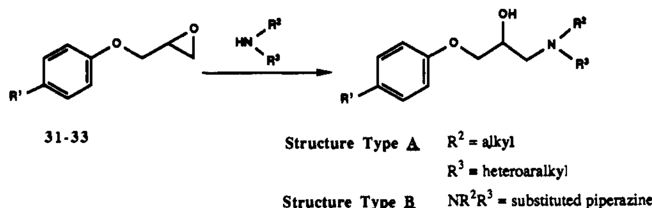
Scheme II. Synthesis of 1-(Aryloxy)-2-propanolamines 4–7, 9–12, 16–23, and 26–29



potency of class III agents has been set by two novel entries into the clinic: UK-68,798 (**2**)[23] and E-4031 (**3**).[24] These compounds, both in the early stages of development, have been shown to be 100–1000 times more potent than *d*-sotalol. Considering that most clinical arrhythmias are due to reentry,[25] one can speculate that a prolongation of refractoriness without depression of conduction would cause the reentrant impulse to encounter tissue that has not recovered from refractoriness, thereby terminating reentry. Thus, our goal was to develop selective class III agents devoid of any effects on cardiac conduction (class I effect) or β-blockade (class II effect). A class III effect can result from an increase of inward currents or from a decrease of outward, repolarizing currents.[26] More specifically, our goal was to develop a selective class III antiarrhythmic agent that prolongs repolarization by inhibiting a specific outward current, the delayed rectifier K^+ current (I_K).

In this paper, we wish to report the results of our investigation of a novel series of *N*-heteroaralkyl(aryloxy)propanolamines and corresponding propylamine derivatives[27] that are selective and potent class III antiarrhythmic agents. Our objective initially was to synthesize phenethanolamines and phenoxyalkanolamines, the basic building blocks of β-receptor blockers, and down-modulate the β-blocking property by transforming the nitrogen atom to a tertiary or quaternary species. Such changes at the nitrogen atom, in general, diminish β-blockade.[28] A recent

(22) (a) Steinberg, M. I.; Smallwood, J. K. Clofilium and Other Class III Agents. In *Handbook of Experimental Pharmacology, Vol. 89: Antiarrhythmic Drugs*; Vaughan Williams, E. M., Ed.; Springer-Verlag: Berlin, 1989; pp 389–412. (b) Steinberg, M. I.; Malloy, B. B. Clofilium, A New Antifibrillatory Agent That Selectively Increases Cellular Refractoriness. *Life Sci.* **1979**, *25*, 1397–1406.

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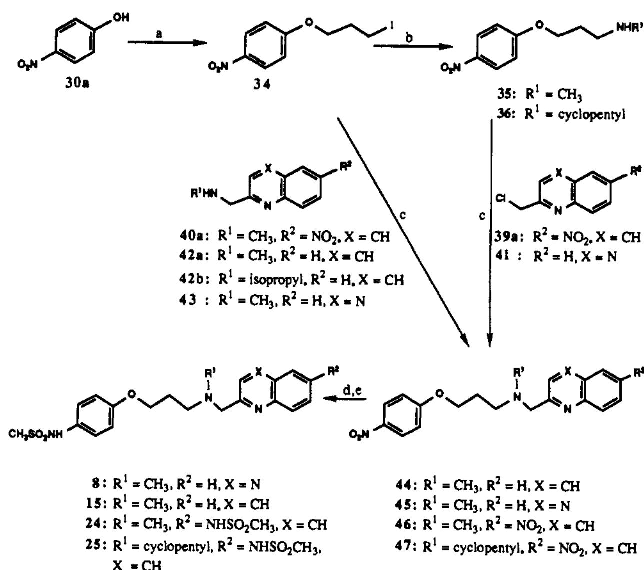
(26) Siegal, M. S.; Spinelli, W. Drug-Induced Early After Depolarizations in Isolated Tissues. In *Cardiac Electrophysiology: A Textbook*; Rosen, M. R., Janse, M. J., Wit, A. L., Eds.; Futura Publishing Co.: Mount Kisco, NY, 1990; pp 371–386.

(27) Others have recently reported several related N-heteroaralkyl-substituted phenethylamine derivatives, see: Cross, P. E.; Noel, T. G.; Arrowsmith, J. E.; Dickinson, R. P. *N*-Heterocycle Methyl-2-Phenylethylamine Derivatives as Antiarrhythmic and Inotropic Agents. European Patent Application 281,254 A-1, 1988.

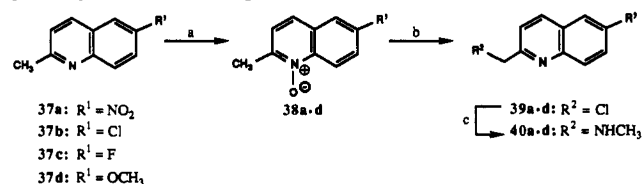
(28) Paterson, E.; Stetson, P.; Lucchesi, B. R. Plasma and Myocardial Tissue Concentrations of UM-272 (*N,N*-Dimethylpropranolol) After Oral Administration. *J. Pharmacol. Exp. Ther.* **1980**, *214*, 449–453.

Scheme III. Synthesis of 1-(Aryloxy)propylamines 8, 15, 24, and 25[a]



[a] Reagents: (a) $ICH_2CH_2CH_2OH$, DEAD, Ph_3P, THF; (b) NH_2R^1, EtOH; (c) K_2CO_3; AcCN/EtOH, Δ; (d) PtO_2, H_2 (1 atm), EtOH; (e) CH_3SO_2Cl, pyridine.

Scheme IV. Synthesis of 6-Substituted [(Methylamino)methyl]quinolines[a]



[a] Reagents: (a) *m*-CPBA, $C_2H_4Cl_2$, Δ; (b) TsCl, $C_2H_4Cl_2$, Δ; (c) NH_2CH_3, EtOH.

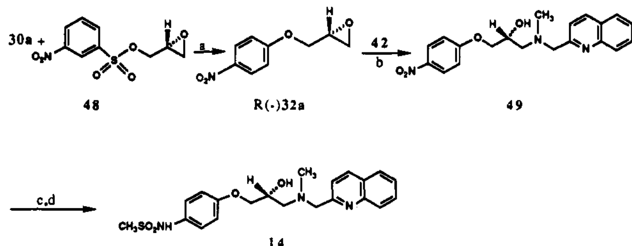
report describes the synthesis of several *secondary* (aryloxy)alkanolamines designed specifically as class II/III antiarrhythmic agents.[29] A series of (aryloxy)propanolamines and related (aryloxy)propylamines of structure type A and B was synthesized and evaluated as selective class III antiarrhythmic agents and are shown in Tables I and II, respectively.

Chemistry

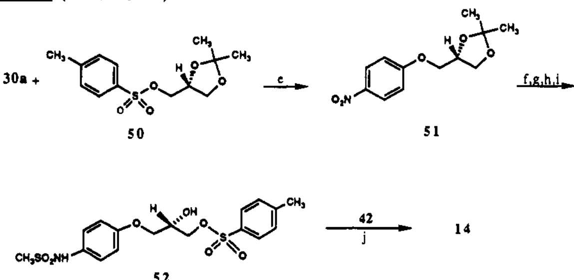
The synthetic routes toward target compounds **4–29** are illustrated in Schemes I–V. Racemic epoxides **32a–c** (Scheme I) were readily obtained by treating the corresponding 4-substituted phenols **30a–c** with sodium hydride and epibromohydrin in dimethylformamide. 4-[(Methylsulfonyl)amino]-substituted epoxide **31** was synthesized in a four-step sequence starting with **30a**. Alkylation with allyl bromide followed by stannous chloride reduction of the nitro group, mesylation of the resulting aniline, and epoxidation of the olefin gave **31**. 4-Tetrazolyl-substituted epoxide **33** was obtained in four steps from 4-cyanoanisole (**30d**). Cyclization with sodium azide/tributyltin chloride,

(29) Morgan, T. K.; Lis, R.; Lumma, W. C.; Wohl, R. A.; Nickisch, K.; Phillips, G. B.; Lind, J. M.; Lampe, J. W.; DiMeo, S. V.; Reiser, J.; Argentieri, T. M.; Sullivan, M. E.; Cantor, E. Synthesis and Pharmacological Studies of *N*-[4-[2-Hydroxy-3-[[2-[4-(1*H*-imidazol-1-yl)phenoxy]ethyl]amino]propoxy]-phenyl]methanesulfonamide, a Novel Antiarrhythmic Agent with Class II and Class III Activities. *J. Med. Chem.* **1990**, *33*, 1087–1090.

Scheme V. Synthesis of Optically Active 1-(Aryloxy)-2-propanolamines **13** and **14**[a]



Method B (illustrated for 14)



[a] Reagents: (a) NaH, DMF; (b) **42**, AcCN, Δ; (c) Pd/C, H_2 (50 psi), EtOH; (d) CH_3SO_2Cl, CH_3SO_2OH, H_2O; (e) NaH, DMF, Δ; (f) Pd/C, H_2 (50 psi), EtOH; (g) CH_3SO_2Cl, pyridine, CH_2Cl_2; (h) 90% HOAc, Δ; (i) TsCl, pyridine; (j) toluene, Δ.

followed by tritylation with triphenylmethyl chloride, yielded the protected tetrazolyl anisole. Demethylation with propanethiol/sodium hydride and alkylation of the resulting phenol with epibromohydrin yielded epoxide **33**.

Racemic 1-(aryloxy)-2-propanolamines were readily prepared (Scheme II) by treatment of epoxides **31–33** with the appropriate secondary amine to afford N-alkylated analogues (structure type A). Treatment of the epoxide with a suitably substituted piperazine affords piperazine analogues **26–29** (structure type B).[30] Deshydroxy analogues **8**, **15**, **24**, and **25** could be synthesized via either of two pathways as shown in Scheme III. Treatment of iodide **34** (obtained from Mitsunobu reaction between phenol **30a** and iodopropanol) with heteroaralkylamines **40a**, **42a**, or **43** afforded tertiary amines **44–46**. Alternatively, treatment of **34** with suitable primary amines afforded **35** and **36**. Subsequent treatment with chloromethyl compounds **39a** or **41** also generated products **45–47** in comparable yield. Reduction of the nitro group (or groups as in **46** and **47**) with platinum oxide followed by mesylation (or dimesylation) afforded the target compounds. It is imperative that the reduction be conducted at 1 atm of hydrogen using platinum oxide. All palladium-catalyzed reductions at higher hydrogen pressures resulted in decomposition of nitro compounds **44–47**.

The *N*-heteroaralkyl-substituted methylamines required to prepare compounds **4–15** and **17–19** were obtained from the corresponding chloromethyl compounds by treatment with ethanolic or aqueous methylamine. The 6-substituted-2-[(methylamino)methyl]quinolines needed for targets **20–24** were prepared as shown in Scheme IV. Treatment of 2-methylquinoline derivatives **37a–d** with 3-chloroperoxybenzoic acid afforded *N*-oxides **38a–d** nearly quantitatively. Conversion of the *N*-oxides to chloromethyl analogues **39a–d** was accomplished with *p*-toluenesulfonyl chloride in refluxing dichloroethane.[31] Subsequent treatment with ethanolic methylamine afforded **40a–d**.

To explore the possibility of enantioselectivity at the receptor level, it was deemed necessary to prepare optically pure 1-aryloxy-2-propanolamine enantiomers. Two efficient pathways for the synthesis of **14** are shown in Scheme V. (2*R*)-(−)-Glycidyl 3-nitrobenzenesulfonate (**48**)[32] (method A) was reacted with sodium 4-nitrophenoxide to give *R*-(−)-**32a**,[33] which is then treated with 2-[(methylamino)methyl]quinoline **42** to afford **49**. Catalytic reduction of the nitro group (5% Pd/C, H_2) followed by mesylation with methanesulfonyl chloride affords optically pure **14**. The *S*-(−)-enantiomer (**13**) was prepared in an analogous sequence starting from the appropriate enantiomeric glycidyl derivative. Alternatively (method B), treatment of (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol toluene-4-sulfonate (**50**)[34] with sodium 4-nitrophenoxide gives optically active acetonide **51**. Catalytic reduction of the nitro group (5% Pd/C, H_2), mesylation of the resulting aniline with methanesulfonyl chloride, diol deprotection with 90% acetic acid, and selective monotosylation afforded optically active **52**. Displacement of the tosylate group with 2-[(methylamino)methyl]quinoline gave **14**. This synthetic sequence is quite general and has been utilized to synthesize several optically pure aryloxypropanolamines.[34,35]

Pharmacology

Compounds were first evaluated using standard microelectrode techniques in canine Purkinje fibers at concentrations of 1 or 3 μM. The effects on the action potential were studied during stimulation at cycle lengths of 1000 ms (simulating "normal" heart rate) and 300 ms (simulating tachycardia). Compounds that decreased maximum diastolic potential, depressed the plateau phase of the action potential, or prolonged APD only at more repolarized voltages (−60 to −80 mV) producing a "triangular" profile of the action potential are not included in the results. The results of these in vitro studies are shown in Table III. Previous experience has shown that compounds producing a prolongation of APD_{-60mV} of 20% or more at a cycle length of 300 ms have good efficacy when tested in vivo following iv administration. Previous experience has also shown that alterations of $\dot{V}_{max}$ of about 10% or less are of little biological significance and are probably due to random variability in a small sample.

Selected compounds which showed promising class III activity in vitro were further tested in the open-chest pentobarbital-anesthetized dog. The prolongation of the atrial and ventricular effective refractory period (AERP and VERP) during pacing at a basic cycle length of stim-

(30) Butera, J. A.; Bagli, J. F. Aryloxypropane Substituted Piperazine Derivatives with Antiarrhythmic and Antifibrillatory Activity. U.S. Patent 4,994,459, 1991.

(31) Kataoka, H. Halomethylquinolines. Japan. Patent 17,465, 1961.

(32) Both enantiomers are commercially available from Aldrich Chemical Co.

(33) This compound can also be prepared by the reaction of (*R*)-glycidol with 4-fluoronitrobenzene, see ref 29.

(34) Both enantiomers are commercially available from Fluka Chemie AG or they can be conveniently prepared from the corresponding α,β-isopropylidine glycerol; see: (a) Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. Synthesis of (*R*)- and (*S*)-Epichlorohydrin. *J. Org. Chem.* **1978**, *43*, 4876–4878. (b) Jung, M. E.; Shaw, T. J. Total Synthesis of (*R*)-Glycerol Acetonide and the Antiepileptic and Hypotensive Drug (−)-γ-Amino-β-hydroxybutyric Acid (GABOB): Use of Vitamin C as a Chiral Starting Material. *J. Am. Chem. Soc.* **1980**, *102*, 6304–6311.

(35) Shetty, H. U.; Murthy, S. S.; Nelson, W. L. Stereospecific Synthesis of Specifically Deuterated Metoprolol Enantiomers from Chiral Starting Materials. *J. Labelled Comp. Radiopharm.* **1989**, *10*, 1215–1226.

Table III. Effects of Compounds 4-29 and Related Reference Compounds on the Transmembrane Potential of Canine Purkinje Fibers Paced at BCL = 300 and 1000 ms[a]

no.	concn, μM	BCL[b] = 300 ms			BCL[b] = 1000 ms		
		n	APD_{-60mV}[c]	$\dot{V}_{max}$[d]	n	APD_{-60mV}[c]	$\dot{V}_{max}$[d]
4	3.0	2	12 ± 2	4 ± 3	2	19 ± 9	7 ± 1
5	3.0	2	3 ± 1	-11 ± 12	2	14 ± 2	1 ± 1
6	3.0	3	16 ± 1	16 ± 10	3	47 ± 5	4 ± 3
7	3.0	2	8 ± 14	6 ± 1	2	26 ± 14	1 ± 5
8	3.0	2	27 ± 0	-14 ± 9	2	62 ± 13	-16 ± 12
9	3.0	2	11 ± 5	3 ± 8	2	17 ± 8	7 ± 6
10	3.0	2	24 ± 7	10 ± 5	2	69 ± 6	13 ± 11
11	3.0	2	27 ± 7	-10 ± 0	2	63 ± 21	0 ± 2
12	0.3	3	8 ± 2	5 ± 4	3	19 ± 3	-2 ± 5
	1.0	3	19 ± 1	15 ± 11	3	43 ± 8	6 ± 8
	3.0	3	27 ± 4	-9 ± 3	3	62 ± 10	-7 ± 6
13	0.3	2	13 ± 0	-4 ± 9	2	22 ± 8	9 ± 0
	1.0	2	14 ± 1	-3 ± 15	2	40 ± 10	0 ± 8
	3.0	5	27 ± 4	0 ± 9	5	54 ± 11	-5 ± 8
14	0.3	3	12 ± 2	-4 ± 7	3	25 ± 2	9 ± 16
	1.0	3	22 ± 5	-9 ± 5	3	48 ± 6	6 ± 14
	3.0	3	27 ± 7	-1 ± 7	3	70 ± 7	4 ± 12
15	3.0	2	22 ± 5	3 ± 2	2	45 ± 3	5 ± 1
16	3.0	2	30 ± 8	-11 ± 3	3	49 ± 3	-10 ± 2
17	3.0	3	10 ± 1	-11 ± 9	4	39 ± 9	-15 ± 7
18	3.0	2	4 ± 2	4 ± 5	2	11 ± 6	-10 ± 13
19	3.0	1[e]	0	8	2	41 ± 19	19 ± 16
20	3.0	3	29 ± 8	-2 ± 8	3	65 ± 16	0 ± 4
21	0.3	2	12 ± 0	3 ± 13	2	31 ± 13	3 ± 4
	1.0	2	19 ± 1	4 ± 21	3	50 ± 12	5 ± 6
	3.0	2	22 ± 3	8 ± 22	3	55 ± 14	11 ± 8
22	3.0	2	16 ± 6	-6 ± 7	2	54 ± 24	0 ± 17
23	0.3	3	13 ± 5	-2 ± 12	3	42 ± 4	-12 ± 3
	1.0	3	17 ± 1	-4 ± 9	3	55 ± 3	-10 ± 6
	3.0	4	18 ± 2	-1 ± 7	4	66 ± 3	-6 ± 5
24	0.01	7	15 ± 1	-1 ± 4	7	36 ± 3	-1 ± 5
	0.03	7	17 ± 2	-9 ± 5	7	56 ± 5	-8 ± 3
	0.10	7	22 ± 2	-14 ± 8	7	73 ± 6	-12 ± 4
25	0.10	1[e]	13	8	2	30 ± 3	7 ± 10
26	3.0	2	15 ± 8	-19 ± 4	3	29 ± 6	8 ± 5
27	3.0	3	24 ± 4	12 ± 5	3	53 ± 2	9 ± 4
28	3.0	2	15 ± 1	-12 ± 1	2	23 ± 1	-17 ± 1
29	3.0	2	21 ± 1	-9 ± 6	3	83 ± 6	-3 ± 7
1 (*dl*-sotalol)	30	4	18 ± 1	-12 ± 8	4	56 ± 8	2 ± 8
	300	4	36 ± 2	-20 ± 4	4	86 ± 11	-10 ± 5
2 (UK-68798)	0.01	4	22 ± 5	4 ± 1	4	37 ± 4	4 ± 5
	0.03	4	30 ± 5	7 ± 9	5	67 ± 14	2 ± 4
	0.10	4	29 ± 6	5 ± 9	5	85 ± 16	5 ± 8
3 (E-4031)	0.01	4	11 ± 3	8 ± 7	4	27 ± 6	12 ± 7
	0.03	3	21 ± 7	8 ± 10	3	53 ± 14	7 ± 8
	0.10	4	24 ± 3	-3 ± 2	4	54 ± 5	2 ± 7

[a] Data reported as percent change from predrug state ($\bar{x}$ ± SE). [b] BCL: basic cycle length of stimulation. [c] APD_{-60mV}: repolarization time to -60 mV. [d] $\dot{V}_{max}$: maximum rate of rise of the upstroke of the transmembrane potential. [e] Unable to pace one of two fibers at the shorter cycle length.

ulation (BCL) = 300 ms is indicative of class III effect, while the lack of effect on epicardial conduction times (ACT and VCT) indicates a lack of class I activity. In these experiments, heart rate, arterial pressure, and the lead II ECG were also monitored. Selected compounds were further studied in naive conscious dogs. A final cumulative dose of 20 mg/kg was injected iv over a 30-45-min period. Compounds that showed no behavioral side effects were further evaluated for oral activity. The bioavailability and duration of action of certain key compounds were studied by intragastric administration in conscious instrumented dogs. The duration of effects on VERP, hemodynamics, and ECG parameters were monitored and the half-life of class III effect was estimated. Alternatively, the oral bioavailability was estimated by injecting the compound in the duodenum of anesthetized dogs.

Antiarrhythmic efficacy was studied in a model of electrically induced VF in open-chest anesthetized dogs. The intensity of current necessary to produce an episode of sustained VF was measured under control conditions and after iv administration of compound. Experimental evidence suggest that local reentry in the vicinity of the stimulating electrode is responsible for the initiation of the arrhythmia.[36] Compounds producing a large increase of the current threshold necessary to induce fibrillation (VFT) have been shown to be effective against life-threatening ventricular arrhythmias caused by reentry.[37]

Finally, to elucidate the mechanism of action of the class III effects of certain compounds, we studied their effects on membrane currents in isolated cat myocytes. As stated, our goal was to develop a selective blocker of the delayed rectifier K^+ current (I_K). Such a compound should specifically block the tail current associated with deactivation of the delayed rectifier, without affecting other membrane currents, such as the inward rectifier K^+ (I_{K1}) or the Ca^{2+}

(36) Euler, D. E.; Moore, E. N. Continuous Fractionated Electrical Activity After Stimulation of the Ventricles During the Vulnerable Period: Evidence for Local Reentry. *Am. J. Cardiol.* 1980, *46*, 783-791.
(37) Moore, E. N.; Spear, J. F. Ventricular Fibrillation Threshold. *Arch. Intern. Med.* 1975, *135*, 446-453.

Table IV. Effects of Selected Compounds and Related Reference Compounds after Intravenous (iv) or Intraduodenal (id) Administration on Cardiac Electrophysiology (BCL = 300 ms) and Hemodynamics in Open-Chest Anesthetized Dogs

no.	dose, mg/kg	n	AERP[b]	ACT[c]	VERP[d]	VCT[e]	HR[f]	MBP[g]
12	5.0 (iv)	5	45 ± 8	-9 ± 3	21 ± 3	-2 ± 2	-18 ± 4	-9 ± 3
	10.0 (id)	5	31 ± 10	-4 ± 4	20 ± 6	1 ± 2	-15 ± 7	-5 ± 4
15	5.0 (iv)	2	52 ± 11	-6 ± 6	30 ± 4	1 ± 1	-23 ± 16	-11 ± 1
24	0.05 (iv)	3	53 ± 10	-5 ± 1	26 ± 3	-1 ± 3	-16 ± 8	4 ± 5
	0.25 (iv)	3	70 ± 15	-4 ± 0	36 ± 4	-3 ± 4	-26 ± 8	4 ± 6
26	5.0 (iv)	3	69 ± 7	16 ± 14	25 ± 3	-7 ± 9	-33 ± 1	-33 ± 9
1 (*dl*-sotalol)	2.5 (iv)	5	42 ± 4	-5 ± 5	19 ± 2	-1 ± 2	-27 ± 3	-16 ± 4
	5.0 (iv)	5	57 ± 6	-7 ± 5	25 ± 4	-1 ± 3	-28 ± 6	-17 ± 4
	10.0 (iv)	5	68 ± 8	-4 ± 6	30 ± 5	-4 ± 3	-39 ± 3	-29 ± 4
2 (UK-68798)	0.05 (iv)	5	46 ± 6	-4 ± 2	23 ± 2	-4 ± 1	-14 ± 1	1 ± 2
	0.25 (iv)	5	60 ± 10	-6 ± 1	25 ± 4	-5 ± 1	-21 ± 2	1 ± 4
	0.50 (iv)	5	65 ± 10	-9 ± 2	27 ± 6	-4 ± 1	-24 ± 2	-2 ± 6
3 (E-4031)	0.05 (iv)	5	28 ± 5	1 ± 5	18 ± 3	-3 ± 2	-10 ± 1	2 ± 3
	0.25 (iv)	5	38 ± 7	1 ± 4	23 ± 3	-2 ± 1	-25 ± 5	-11 ± 6
	0.50 (iv)	5	44 ± 8	1 ± 6	24 ± 3	-3 ± 1	-29 ± 4	-15 ± 7

[a] Data reported as percent change from predrug state ($\bar{x}$ ± SE). [b] AERP: atrial effective refractory period. [c] ACT: atrial conduction time. [d] VERP: ventricular effective refractory period. [e] VCT: ventricular conduction time. [f] HR: heart rate. [g] MBP: mean arterial pressure.

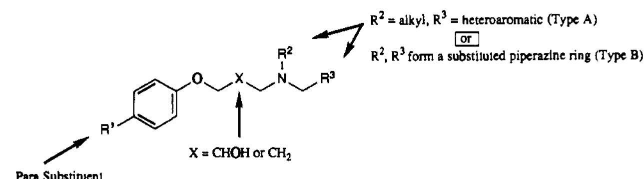


Figure 1. SAR study.

current flowing during plateau ($I_{Ca\text{-}L}$).

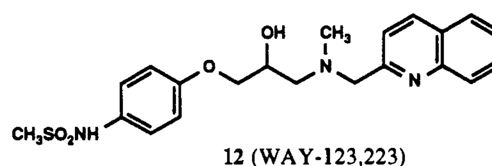
Results and Discussion

The electrophysiological effects of compounds 4–29 on the action potential in canine Purkinje fibers are shown in Table III. The class III standards sotalol (1), UK-68798 (2), and E-4031 (3) were also studied and the data are included for comparison. The key structural variations investigated in our SAR studies[38] are shown in Figure 1. As a starting point in the (aryloxy)propanolamine series (X = CHOH, structure type A), we chose to fix R^1 as methanesulfonamide, a structural feature common to most class III antiarrhythmic agents, and R^2 as a methyl group. The R^3 heteroaromatic substituent is varied in compounds 4–7, 9, and 12. The in vitro data suggest that the ideal substituent is a 2-quinolinyl group as seen in compound 12 (Chart II). In canine Purkinje fibers, compound 12 (3 μM) prolongs APD_{-60mV} by 27% at BCL = 300 ms and by 62% at BCL = 1000 ms, with no effect on $\dot{V}_{max}$. The response was dose dependent from 0.3 to 3.0 μM. As seen in Table III, the effects are similar to those observed with sotalol (1) at 300 μM and with UK-68798 (2) at 0.03 μM.

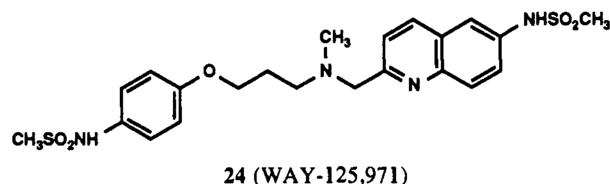
As expected, the ideal para substituent (R^1) was the methanesulfonamide group. Although nitro derivative 11 was equipotent with 12, substitution with imidazol-1-yl, tetrazol-5-yl, or cyano (i.e., 17, 18, or 19, respectively) resulted in less potent analogues. The corresponding trifluoromethylsulfonamide (R^1 = CF_3SO_2NH) and methylsulfonyl (R^1 = CH_3SO_2) derivatives were devoid of activity.[39] The comparable activity of isopropyl analogue 16 and methyl analogue 12 implies that the *size* of R^2 is not an important parameter for biological activity. Connecting R^2 and R^3 via a heteroaryl-substituted piperazine (structure type B) ring afforded analogues 26–29, which were slightly less potent than 12 in the Purkinje fiber screen.

(38) SAR discussion stems from in vitro results shown in Table III.
(39) Unpublished results.

Chart II



12 (WAY-123,223)



24 (WAY-125,971)

The effects of substitution onto the 6-position of the quinoline ring of compound 12 were studied and found to be relatively unimportant as seen by the comparable potencies of the 6-chloro-, 6-fluoro-, 6-methoxy-, and 6-[(methylsulfonyl)amino]quinolin-2-yl derivatives 20–23, respectively. As interest in *N*-[4-[2-hydroxy-3-[methyl(2-quinolinylmethyl)amino]propoxy]phenyl]methanesulfonamide (12) increased, it was deemed appropriate to investigate what, if any, effect the absolute configuration of the chiral carbon would have on class III activity. The *S* and *R* enantiomers (13 and 14, respectively) were examined and were found to have identical dose–response relationships with each other and with the racemate in the Purkinje fiber screen. These results show a lack of enantiomeric specificity at the receptor level.

The effects on biological activity was less predictable when altering the oxidation state of C-2 in the propyl tether (X = CHOH or CH_2). The deshydroxy derivative of 12, i.e. 15, was found to be essentially equipotent. In the corresponding pair of quinoxaline analogues (7, X = CHOH and 8, X = CH_2), there seems to be an increase in potency by a factor of 2 when the hydroxy group is removed. However, a dramatic 100-fold increase in potency is evident with bis-sulfonamide propylamine analogue 24 (which, at 0.03 μM, prolonged APD_{-60mV} by 18% at BCL = 300 ms and by 65% at BCL = 1000 ms) when compared to its (aryloxy)propanolamine counterpart, 23 (which possesses similar efficacy at 3.0 μM). As a result of the Purkinje fiber data, we chose to further evaluate (aryloxy)propanolamine 12 (or *R*-(+)-enantiomer 14) and (aryloxy)propylamine 24.

The effects of compound 12, its deshydroxy derivative 15, 24, and piperazine analogue 26 on in vivo cardiac

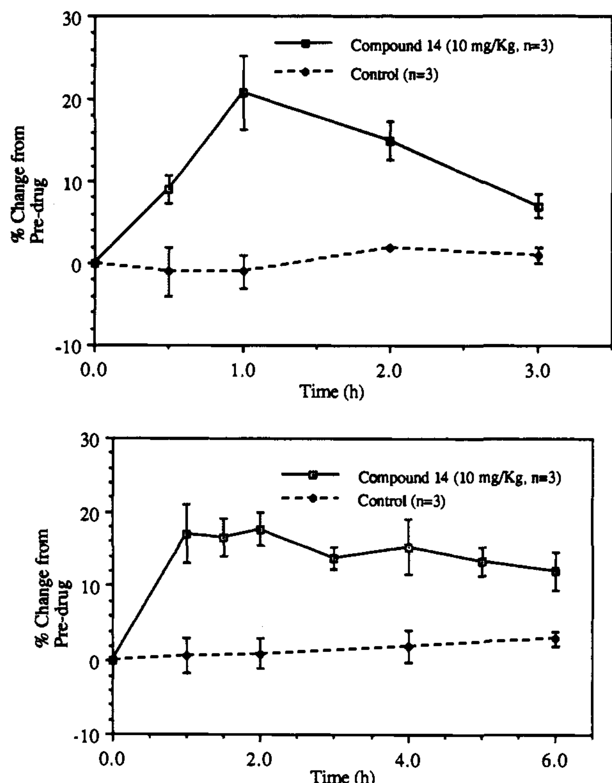


Figure 2. Effects of compound 14 administered iv (top) and ig (bottom) on VERP in conscious dogs.

Table V. Effects of Compound 12 on Ventricular Fibrillation Threshold (mA, $\bar{x} \pm$ SE)

	n	predrug	treatment
control	6	8.2 ± 1.2	7.8 ± 0.9
12 (5 mg/kg iv)	6	8.2 ± 1.6	25 ± 6.1[a]

[a] $p < 0.05$ vs predrug.

electrophysiology are shown in Table IV. Sotalol, UK-68798, and E-4031 were also studied, and the data are shown for comparison. Compound **12** prolongs AERP and VERP by 45% and 21% (respectively) at 5 mg/kg (iv) with no effect on atrial or ventricular conduction times and modest hemodynamic effects. Intraduodenal administration at 10 mg/kg produces a similar peak increase of VERP, thus showing oral bioavailability. Consistent with the in vitro results, deshydroxy analogue **15** was essentially equipotent with **12**. The effects of compound **14**, the R-(+) enantiomer of **12**, on VERP in conscious, instrumented dogs (iv and ig) are shown in Figure 2. Peak effects after iv and ig administration were similar and occurred 1 h after dosing. The increase in ventricular refractoriness after iv administration declined with a half-life of about 3 h; after ig administration, the increase in VERP was well-maintained for 6 h. The 100-fold increase in potency in vitro of **24** versus **12** is also evident in vivo. Compound **24**, which prolongs AERP and VERP by 53% and 26% (respectively) at 0.05 mg/kg (iv) with no effect on atrial or ventricular conduction times and no adverse hemodynamic effects, is equipotent in vitro and in vivo with UK-68798 and E-4031. Finally, examination of Table IV reveals that for all compounds the percentage increase of refractoriness, at the same dose, is much larger in the atrium than in the ventricle, suggesting potential high efficacy in atrial arrhythmias.

As a test for antiarrhythmic efficacy, compound **12** was shown to increase VFT by a factor of 3 (Table V) over control values in a model of electrically induced VF in open-chest anesthetized dogs. Previous studies have shown

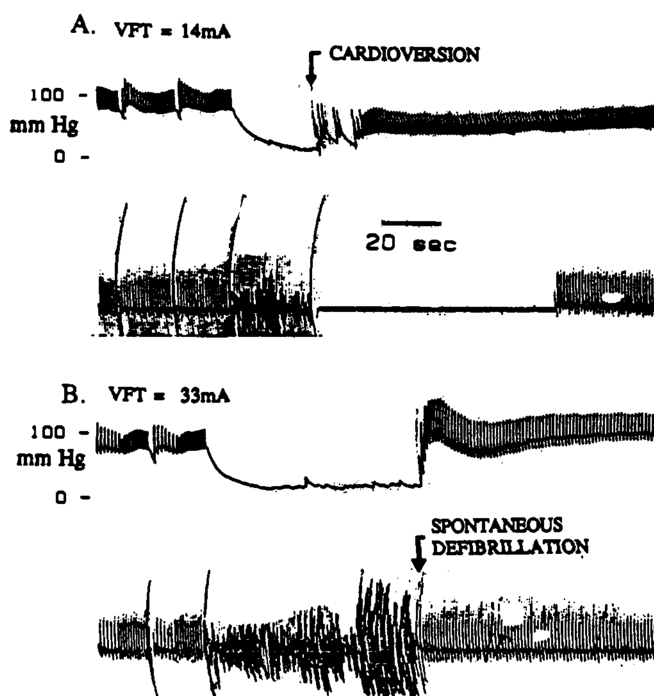


Figure 3. Restoration of sinus rhythm by compound 12 (5 mg/kg iv) in an open-chest dog. In part A, electrical stimulation during the vulnerable period causes ventricular fibrillation and hemodynamic collapse; electrical cardioversion restores normal sinus rate (bottom trace, ECG) and arterial pressure (top trace). In part B, compound 12 increases VFT and induces a return to sinus rhythm after a 30-s period of arrhythmia.

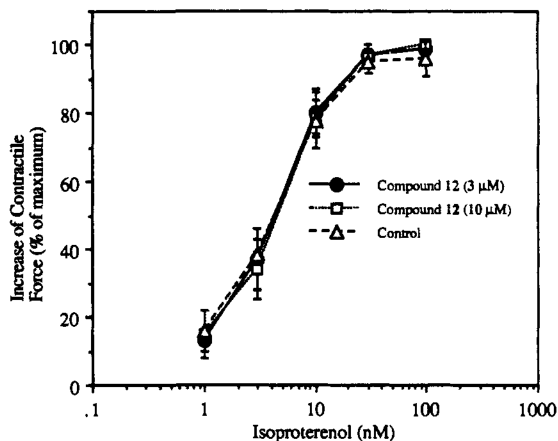


Figure 4. Lack of antagonism by compound 12 of isoproterenol-induced inotropy in guinea pig left atria (BCL = 330 ms).

that compounds producing large increases of VFT are effective against reentry induced arrhythmias.[36,37] In our studies we observed several cases of termination of VF and restoration of sinus rhythm without electrical countershock after treatment with compound **12**. Similar episodes of "spontaneous defibrillation" were never observed in vehicle-treated animals. Figure 3 illustrates one of several experiments in which we observed a spontaneous defibrillation caused by compound **12** (5 mg/kg, iv). In part A, an electrical pulse causes VF and hemodynamic collapse, while a subsequent electrical cardioversion restores normal sinus rate and arterial pressure. In part B, compound **12** increases VFT and induces spontaneous restoration of sinus rhythm after a 30-s period of arrhythmia.

As postulated earlier, (aryloxy)propanolamine **12** was indeed found to be inactive as a β_1-adrenergic blocker as seen in Figure 4, which shows a lack of antagonism by **12** of isoproterenol-induced inotropy in guinea pig left atria.

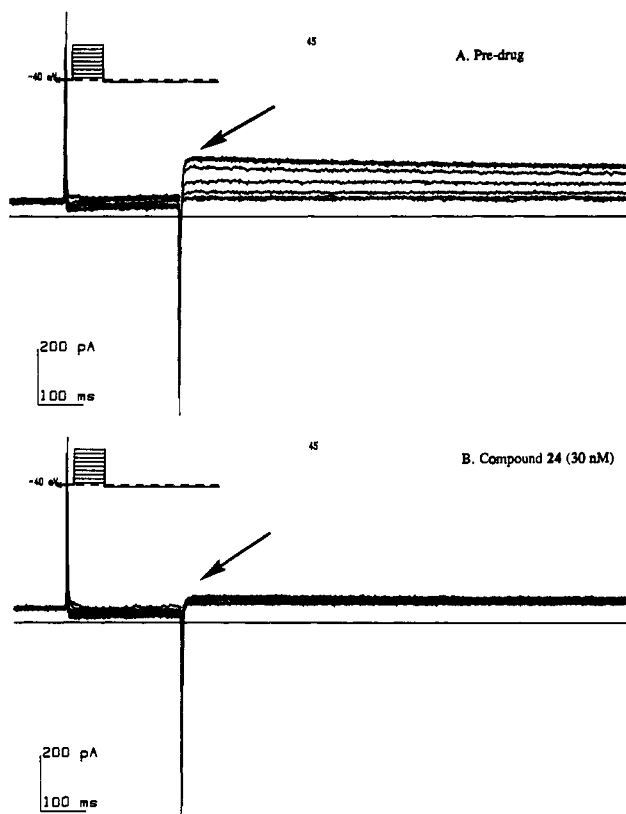


Figure 5. Effects of compound **24** (30 nM) on delayed rectifier potassium current (I_K). Compound **24** produces an almost complete block of the tail currents associated with the deactivation of I_K. The voltage protocol used is shown in the top left corner of each figure; nisoldipine (300 nM) is present in Tyrode's solution to block $I_{Ca\text{-}L}$.

Under the same experimental conditions, propranolol gave a pA_2 value of 8.5. This finding is consistent with early reports on lack of β-blockade associated with tertiary and quaternary (aryloxy)propanolamines.[28]

A series of voltage-clamp experiments using isolated cat myocytes were performed in an attempt to elucidate a mechanism of action for the observed class III effects. The most potent member of our series, (aryloxy)propylamine **24** was chosen as a representative example. As seen in Figure 5, compound **24** is a potent blocker of the delayed rectifier (I_K) potassium current. In predrug conditions (part A), repolarization to −45 mV after 250 ms long depolarization steps to more positive voltages (see insert for voltage protocol) produces a family of outward tail currents (arrow). These tail currents are due to the slow deactivation of I_K at −45 mV. In part B, compound **24** (30 nM) causes an almost complete block of the tails. The lack of effects of compound **24** on the inward rectifier potassium current (I_{K1}) is shown in Figure 6. During a slow depolarizing voltage ramp (5 mV/s), compound **24** (30 nM) reduces the outward current at voltages more positive than −30 mV (voltage threshold for the activation of I_K). However, no effect is observed at voltages more negative than −30 mV, where the contribution of I_{K1} to the steady-state relationship is predominant. In addition, compound **24** exerts no effect on the L-type Ca^{2+} current ($I_{Ca\text{-}L}$) as seen in Figure 7. After blocking K^+ conductance by adding 2 mM CsCl in Tyrode's solution and substituting Cs for K in the internal solution, voltage steps more positive than −45 mV activate $I_{Ca\text{-}L}$ (arrow). Compound **24** at 100 nM, a concentration that produces total block of I_K, does not affect $I_{Ca\text{-}L}$. In similar but separate experiments, nisoldipine (300 nM) completely blocked $I_{Ca\text{-}L}$ (data not shown). Compounds **12** and **14**, although less potent than compound **24**, were also effective in blocking I_K at concentrations similar to those that prolong APD in Purkinje fibers (data not shown). The results of these experiments in isolated myocytes are consistent with the hypothesis that compound **24** and its analogues prolong APD and cardiac refractoriness by selective blockade of the delayed rectifier potassium channel (I_K).

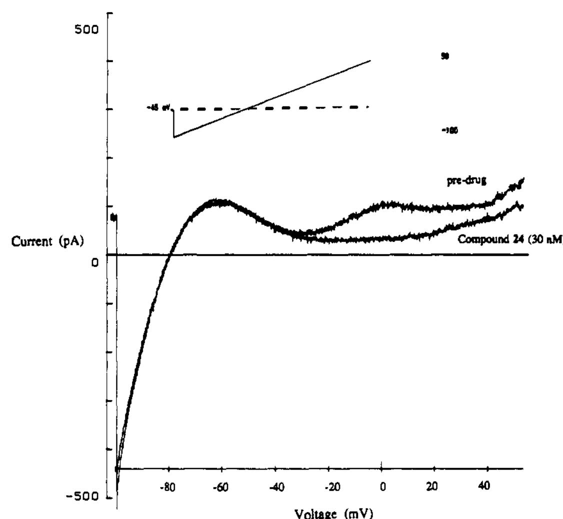


Figure 6. Effects of compound **24** (30 nM) on steady-state current–voltage relationship during a voltage ramp (voltage protocol shown above the current traces). Compound **24** reduces the outward current between −30 mV (threshold for I_K activation) and 50 mV. No effect is observed from −100 to −30 mV, a voltage range where the contribution of the inward rectifier is predominant.

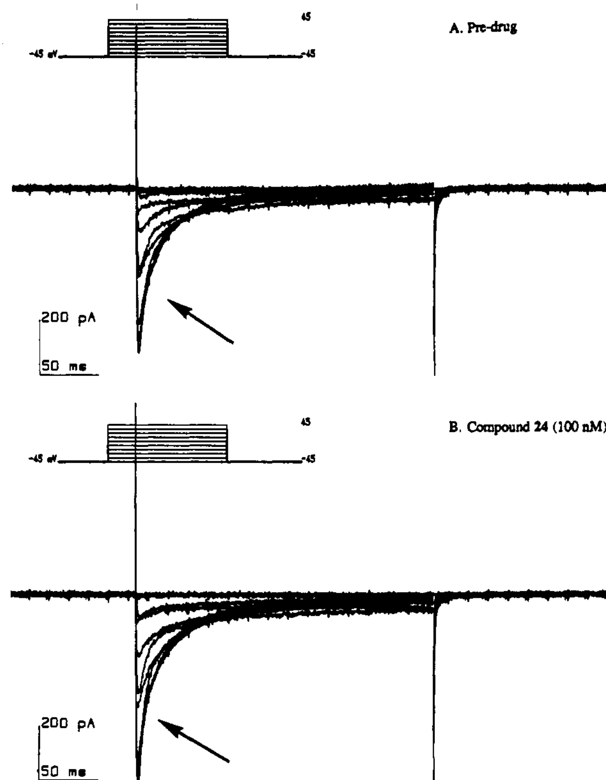


Figure 7. Lack of effects of compound **24** (100 nM) on calcium current ($I_{Ca\text{-}L}$). The voltage protocol used is shown in the top left corner of each figure.

Conclusions

We have investigated a series of (aryloxy)propanol-

amines and related (aryloxy)propylamine derivatives and have shown that several members possess potent class III electrophysiological activity and are devoid of class I activity in our in vitro (canine Purkinje fibers) and in vivo (open-chest dogs) tests. All selected compounds produced a proportionally larger prolongation of refractoriness in the atria than in the ventricles. *N*-[4-[2-Hydroxy-3-[methyl-(2-quinolinylmethyl)amino]propoxy]phenyl]methanesulfonamide (**12**, WAY-123,223), a potent and bioavailable (aryloxy)propanolamine, was found to significantly increase VFT and induce "spontaneous defibrillation" in anesthetized open-chest dogs. *N*-[2-[[Methyl[3-[4-[(methylsulfonyl)amino]phenoxy]propyl]amino]methyl]-6-quinolinyl]methanesulfonamide (**24**, WAY-125,971), a related deshydroxy derivative, was shown to be equipotent with UK-68798 and E-4031 in both in vitro and in vivo screens. Voltage-clamp studies of the mechanism of action of compound **24** in isolated myocytes show that it is a selective blocker of the delayed rectifier potassium channel (I_K) at concentrations similar to those prolonging APD. Compounds **12** and **24** both represent attractive candidates for clinical development as potent and selective class III antiarrhythmic agents.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Varian XL-200 or a Bruker AM-400 spectrometer using tetramethylsilane as an internal standard. The chemical shifts are reported in parts per million (δ) downfield from TMS and coupling constants are reported in hertz (Hz). Mass spectra were recorded on a Hewlett-Packard 5995A spectrometer or a Finnigan 8230 high-resolution instrument. The infrared spectra were recorded on a Perkin-Elmer 784 spectrophotometer. C, H, N combustion analyses were determined on either a Perkin-Elmer 240 or 2400 analyzer and all compounds are within ±0.4% of the theoretical value unless otherwise indicated. Organic extracts were dried over magnesium sulfate and were concentrated in vacuo with rotary evaporators. All products, unless otherwise noted, were purified by flash column chromatography using 230–400 mesh silica gel, by radial chromatography using precast silica gel rotors obtained from Analtech, Inc. (Newark, DE) or by HPLC using a Waters Prep 500 instrument with silica Prep-Pak cartridges. Thin-layer chromatography was performed on silica gel 60 F-254 (0.25 mm thickness) plates. Visualization was accomplished with UV light, I_2 vapor, and/or 10% phosphomolybdic acid in ethanol.

2-[[4-[(Methylsulfonyl)amino]phenoxy]methyl]oxirane (31). To a stirred solution of sodium 4-nitrophenoxide (30 g, 0.186 mol) in dimethylformamide (400 mL) was added allyl bromide (24 mL, 0.28 mol). The reaction mixture was stirred under N_2 at 25 °C for 48 h, diluted with water (300 mL), and extracted with ether (300 mL). The combined organic fraction was diluted with pentane (200 mL), washed with water, dried, and concentrated to afford 27.5 g (83%) of the allyl ether as an oil that was used without purification: ^{1}H NMR ($CDCl_3$) δ 8.19 (d, *J* = 8 Hz, 2 H, Ar*H*), 6.97 (d, *J* = 8 Hz, 2 H, Ar*H*), 6.17 (m, 1 H, C*H*=CH_2), 5.40 (m, 2 H, CH=CH_2), 4.65 (d, 2 H, *J* = 6 Hz, OCH_2).

To a stirred solution of the above allyl derivative (12.65 g, 70.67 mmol) in concentrated HCl (85 mL) at 0 °C was slowly added stannous chloride dihydrate (48 g, 212 mmol). Stirring continued for 20 min at 55 °C. The mixture was cooled (0 °C) and carefully neutralized with 50% aqueous NaOH. The mixture was extracted with ether and the organic phase was dried, decolorized (charcoal), and concentrated to afford 8.50 g (81%) of the aniline as a yellow oil which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.05 (m, 4 H, Ar*H*), 6.4 (m, 1 H, C*H*=CH_2), 5.70 (m, 2 H, CH=CH_2), 4.80 (d, 2 H, OCH_2).

Methanesulfonyl chloride (5.06 mL, 65.32 mmol) was added dropwise to a stirred solution of the above aniline (8.11 g, 54.43 mmol) in pyridine (80 mL) at 0 °C. The mixture was stirred for 72 h at ambient temperature and was then poured into ice water and extracted with diethyl ether. The organic phase was washed with cold 1 N HCl and then extracted with 1 N NaOH. The aqueous phase was acidified to afford 9.05 g (73%) of methanesulfonate as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.18 (d, *J* = 6.75 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.94 Hz, 2 H, Ar*H*), 6.63 (s, 1 H, N*H*SO_2CH_3), 6.00 (m, 1 H, OCH_2C*H*=CH_2), 5.40 and 5.30 (2 m, OCH_2CH=CH_2), 4.50 (m, OCH_2CH=CH_2), 2.94 (s, 3 H, $NHSO_2$CH_3). Anal. ($C_{10}H_{12}NO_3S$) C, H, N.

The above product (8.00 g, 35.24 mmol) in dichloromethane (120 mL) was treated with 3-chloroperoxybenzoic acid (12.16 g, 70.48 mmol) for 18 h at reflux. The mixture was cooled and filtered. Concentration afforded crude product which was purified by flash chromatography (1:1 hexane/ethyl acetate) to give 5.55 g (65%) of **31** as a white solid: mp 115–117 °C; ^{1}H NMR ($CDCl_3$) δ 7.17 (d, *J* = 6.87 Hz, 2 H, Ar*H*), 6.90 (d, *J* = 8.93 Hz, 2 H, Ar*H*), 6.40 (br s, 1 H, N*H*SO_2CH_3), 4.20 (dd, J_1 = 5.54 Hz, J_2 = 2.98 Hz, 1 H, OCH_2), 3.90 (dd, J_1 = 5.54 Hz, J_2 = 5.78 Hz, 1 H, OCH_2), 3.35 (m, 1 H, epoxide C*H*), 2.94 (s, 3 H, $NHSO_2$CH_3), 2.90 and 2.76 (2 m, 2 H, epoxide CH_2); MS *m/z* 243 (60), 164 (100). Anal. ($C_{10}H_{13}NO_4S$) C, H, N.

2-[(4-Nitrophenoxy)methyl]oxirane (32a).[40] To a solution of 1-(4-nitrophenoxy)-2,3-propene (19.25 g, 0.107 mol) in dichloromethane (300 mL) was added 3-chloroperoxybenzoic acid (24.13 g, 0.140 mol). The mixture was stirred for 48 h at room temperature, filtered, and concentrated. The residue was purified by flash chromatography to afford 11.75 g (56%) of product as an off-white solid: mp 64–66 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.95 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 4.36 and 3.98 (2 m, 2 H, OCH_2), 3.36 (m, 1 H, epoxide C*H*), 2.92 and 2.76 (2 m, 2 H, epoxide CH_2). Anal. ($C_9H_9NO_4$) C, H, N.

2-[[4-(1*H*-Imidazol-2-yl)phenoxy]methyl]oxirane (32b). To a stirred solution of 4-(imidazol-1-yl)phenol (5.00 g, 31.21 mmol) in dimethylformamide (70 mL) at 0 °C under N_2 was added NaH (1.50 g, 60%, 37.46 mmol) portionwise. After H_2 evolution ceased, epibromohydrin (2.94 mL, 34.34 mmol) was added dropwise. The mixture was stirred for 3 h at room temperature. Brine (150 mL) was added and the mixture was extracted with ethyl acetate. The organic phase was washed with 0.5 N NaOH and brine, dried, decolorized (charcoal), and concentrated to afford 5.15 g (76%) of **32b** of sufficient purity to use in the next step: mp 74–77 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (s, 1 H, imidazole *H*), 7.32 (d, *J* = 7.2 Hz, 2 H, Ar*H*), 7.20 (m, 2 H, imidazole *H*), 7.03 (d, *J* = 7.3 Hz, 2 H, Ar*H*), 4.30 and 3.98 (2 m, 2 H, OCH_2), 3.39 (m, 1 H, epoxide C*H*), 2.90 and 2.75 (2 m, 2 H, epoxide CH_2).

2-[(4-Cyanophenoxy)methyl]oxirane (32c). The method was exactly as for **32b**: yield 5.10 g (69%) from **30c**; mp 61–64 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, *J* = 8.43 Hz, 2 H, Ar*H*), 6.95 (d, *J* = 8.81 Hz, 2 H, Ar*H*), 4.30 and 3.94 (2 m, 2 H, OCH_2), 3.34 (m, 1 H, epoxide C*H*), 2.90 and 2.75 (2 m, 2 H, epoxide CH_2).

2-[[4-[1-(Triphenylmethyl)tetrazol-5-yl]phenoxy]methyl]oxirane (33). 4-Methoxybenzonitrile (10.00 g, 75.1 mmol), sodium azide (5.86 g, 90.1 mmol), and tributyltin chloride (24.4 mL, 90.1 mmol) were stirred in xylene (200 mL) at 120 °C under N_2 for 24 h. The mixture was cooled, diluted with 6 N HCl (200 mL), and stirred vigorously for 1 h under a stream of N_2. The heterogeneous mixture was filtered to afford the tetrazole as a white crystalline solid. The filtrate was extracted with ethyl acetate. The organic phase was dried and concentrated to afford additional product of sufficient purity to continue, combined yield 10.90 g (83%): mp 228–230 °C; ^{1}H NMR (DMSO-d_6) δ 7.96 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.14 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 3.80 (s, 3 H, OCH_3).

To the above tetrazole (11.34 g, 64.4 mmol) in dimethylformamide (250 mL) was added triethylamine (19.76 mL, 141.8 mmol) followed by triphenylmethyl chloride (19.76 g, 70.9 mmol). The mixture was stirred for 3 h at 70 °C under N_2, cooled, and poured into ice water (500 mL). The product was collected by filtration and recrystallized from acetone/dimethylformamide/water to afford 26.9 g (100%) of protected tetrazole as a white solid: mp 171–172 °C; ^{1}H NMR (DMSO-d_6) δ 8.18 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.30 (m, 9 H, Ar*H*), 7.15 (m, 6 H, Ar*H*), 6.98 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 3.80 (s, 3 H, OCH_3).

Sodium hydride (1.26 g, 80%, 41.84 mmol) was added portionwise to a stirred solution of propanethiol (3.79 mL, 41.84

(40) This epoxide is commercially available from Sigma Chemical Co.

mmol) in dimethylformamide (50 mL) at 0 °C under N_2. After 30 min, the above protected tetrazole (5.00 g, 11.95 mmol) was added and the resulting mixture was heated at 80 °C overnight. Water was added, and the mixture was extracted with ethyl acetate. The organic phase was diluted with hexane, washed with brine, dried, and concentrated to afford an oil which was purified by HPLC (3:1 hexane/ethyl acetate) to yield 2.05 g (42%) of phenol as a white crystalline solid: mp 188–190 °C; ^1H NMR (DMSO-d_6) δ 10.00 (s, 1 H, O*H*), 7.84 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 7.40 (m, 9 H, Ar*H*), 7.08 (m, 6 H, Ar*H*), 6.90 (d, *J* = 8.4 Hz, 2 H, Ar*H*).

The above phenol (5.00 g, 12.37 mmol) was converted to oxirane **33** in the same way as for **32b**: yield 3.31 g (58%); mp 159–164 °C; ^1H NMR ($CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 7.30 (m, 9 H, Ar*H*), 7.05 (m, 6 H, Ar*H*), 7.00 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 4.25 and 3.98 (2 m, 2 H, OCH_2), 3.38 (m, 1 H, epoxide C*H*), 2.90 and 2.75 (2 m, 2 H, epoxide CH_2).

General Methodology for the Synthesis of Racemic (Aryloxy)propanolamines. Procedure A. The required amine and epoxide are stirred in acetonitrile at reflux for 18–24 h. The solvents are removed and the crude product is purified by flash chromatography, HPLC, or recrystallized as indicated.

Procedure B. The required amine and epoxide are stirred in ethanol at 25 °C for 18–24 h. Purification follows as above.

Procedure C. The required amine and epoxide are stirred in ethanol at 40 °C for 18–24 h. Purification follows as above.

***N*-[4-[2-Hydroxy-3-[methyl[(1-methyl-1*H*-benzimidazol-2-yl)methyl]amino]propoxy]phenyl]methanesulfonamide (4).** *N*-Methyl-*o*-phenylenediamine dihydrochloride (5.00 g, 25.63 mmol) and chloroacetic acid (3.63 g, 38.44 mmol) were refluxed together in 2 N HCl (26 mL) for 18 h. The reaction mixture was cooled (0 °C) and basified with 1 N NaOH. The *N*-methyl-2-(chloromethyl)benzimidazole (2.80 g, 61%) was collected by vacuum filtration and used without further purification: ^1H NMR ($CDCl_3$) δ 7.72 (m, 1 H, Ar*H*), 7.30 (m, 3 H, Ar*H*), 4.82 (s, 2 H, CH_2Cl), 3.85 (s, 3 H, CH_3).

The above chloride (2.80 g, 15.50 mmol) was added portionwise to a stirred solution of ethanolic methylamine (50 mL, 33%) at 0 °C. After 45 min, the reaction mixture was diluted with water and extracted with dichloromethane. The organic phase was dried and concentrated to afford 2.37 g (87%) of *N*-methyl-2-[(methylamino)methyl]benzimidazole as a pale oil: ^1H NMR ($CDCl_3$) δ 7.72 (m, 1 H, Ar*H*), 7.28 (m, 3 H, Ar*H*), 4.00 (s, 2 H, CH_2NHCH_3), 3.00 (s, 3 H, NCH_3), 2.50 (s, 3 H, $NHCH_3$), 2.00 (br s, 1 H, $NHCH_3$).

The above amine (1.72 g, 9.86 mmol) was added to a solution of **31** (2.00 g, 8.22 mmol) in acetonitrile (20 mL) and the resulting mixture was stirred at reflux for 18 h (procedure A). Concentration afforded a residue which was purified by flash chromatography (10% methanol/dichloromethane). Trituration of the resulting foamy product with diethyl ether gave 1.08 g (31%) of **4** as a white solid: mp 141–142 °C; ^1H NMR (DMSO-d_6) δ 9.33 (s, 1 H, $NHSO_2CH_3$), 7.56 and 7.45 (2 m, 2 H, Ar*H*), 7.20 (m, 2 H, Ar*H*), 7.08 (d, *J* = 8.09 Hz, 2 H, Ar*H*), 6.73 (d, *J* = 8.05 Hz, 2 H, Ar*H*), 5.00 (br s, 1 H, O*H*), 3.94 (m, 1 H, C*H*OH), 3.82–3.70 (m, 7 H, OCH_2, imidazole CH_3, NCH_2-heterocycle), 2.88 (3 H, $NHSO_2CH_3$), 2.60–2.40 (m, 2 H, $CHOHCH_2N$), 2.23 (s, 3 H, NCH_3); IR (KBr) 3140, 1520, 1160 cm^{-1}; MS *m/z* 419 (MH^+, 20), 320 (60), 241 (100). Anal. ($C_{20}H_{26}O_4N_4S$) C, H, N.

***N*-[4-[3-[(1*H*-Benzimidazol-2-yl-methyl)methylamino]-2-hydroxypropoxy]phenyl]methanesulfonamide (5).** 2-(Chloromethyl)benzimidazole (3.00 g, 18.01 mmol) was dissolved in aqueous methylamine (50 mL, 40% in H_2O) at 10 °C under N_2. After 30 min, the reaction mixture was warmed to room temperature and stirred for 4 h. Water was added and the mixture extracted with dichloromethane. The organic phase was dried and concentrated to afford crude product which was purified by HPLC (gradient methanol/dichloromethane) to afford 0.650 g (22%) of 2-[(methylamino)methyl]benzimidazole: ^1H NMR ($CDCl_3$) δ 7.56 (m, 2 H, Ar*H*), 7.22 (m, 2 H, Ar*H*), 4.07 (s, 2 H, CH_2NHCH_3), 2.51 (s, 3 H, $NHCH_3$).

The above amine (0.993 g, 6.16 mmol) was treated with epoxide **31** (1.5 g, 6.16 mmol) according to procedure A: yield 1.32 g (53%) of **5**; mp 163–165 °C; ^1H NMR (DMSO-d_6) δ 9.33 (br s, 1 H, $NHSO_2CH_3$), 7.52 and 7.44 (2 m, 2 H, Ar*H*), 7.10 (d, *J* = 9.02 Hz, 2 H, Ar*H*), 7.09 (m, 2 H, Ar*H*), 6.98 (d, *J* = 9.00 Hz, 2 H, Ar*H*), 4.93 (br s, 1 H, O*H*), 3.95 (m, 2 H, OCH_2), 3.79 (s and m, 3 H, NCH_2-heterocycle and C*H*OH), 2.86 (s, 3 H, $NHSO_2CH_3$), 2.59 and 2.51 (m, 2 H, $CHOHCH_2N$), 2.27 (s, 3 H, $NHCH_3$); IR (KBr) 3300, 2900, 1505 cm^{-1}; MS *m/z* 405 (MH^+, 18), 131 (50), 91 (100). Anal. ($C_{19}H_{24}N_4O_4S$) C, H, N.

***N*-[4-[3-[(2-Benzofuranylmethyl)methylamino]-2-hydroxypropoxy]phenyl]methanesulfonamide Hydrochloride (6).** 2-(Chloromethyl)benzofuran (2.77 g, 16.63 mmol) was dissolved in aqueous methylamine (40 mL, 40 wt % in H_2O) at 10 °C under N_2. After 10 min, the reaction mixture was warmed to room temperature and stirring was continued for 72 h. The mixture was diluted with water and extracted with dichloromethane. The organic phase was dried and concentrated to afford crude product which was purified by flash column chromatography (10% methanol/dichloromethane) to afford 1.00 g (37%) of pure aminomethyl compound as a pale oil: ^1H NMR ($CDCl_3$) δ 7.48 (m, 2 H, Ar*H*), 7.21 (m, 2 H, Ar*H*), 6.56 (s, 1 H, Ar*H*), 3.89 (s, 2 H, CH_2NHCH_3), 2.47 (s, 3 H, $NHCH_3$).

The above amine (0.927 g, 6.16 mmol) was treated with epoxide **31** (1.40 g, 6.16 mmol) according to procedure A: yield 0.64 g (25%) of **6** as the hydrochloride salt; mp 182–183 °C; ^1H NMR (DMSO-d_6) δ 9.14 (s, 1 H, $NHSO_2CH_3$), 7.72 (d, *J* = 7.68 Hz, 1 H, Ar*H*), 7.61 (d, *J* = 6.39 Hz, 1 H, Ar*H*), 7.39 (m, 1 H, Ar*H*), 7.30 (m, 1 H, Ar*H*), 7.23 (s, 1 H, Ar*H*), 7.13 (d, *J* = 8.85 Hz, 2 H, Ar*H*), 6.88 (d, *J* = 8.93 Hz, 2 H, Ar*H*), 6.02 (br s, 1 H, O*H*), 4.65 (m, 2 H, OCH_2CHOH), 4.41 (m, 1 H, OCH_2CHOH), 3.91 (m, 2 H, NCH_2-heterocycle), 3.34 (s and m, 5 H, $CHOHCH_2N$ and $NHSO_2CH_3$), 2.87 (s, 3 H, NCH_3); IR (KBr) 3320, 3020, 1510 cm^{-1}; MS *m/z* 404 (M^+, 5), 174 (30), 131 (100). Anal. ($C_{20}H_{24}N_2O_5S\cdot HCl$) C, H, N.

***N*-[4-[2-Hydroxy-3-[methyl(2-quinoxalinylmethyl)amino]propoxy]phenyl]methanesulfonamide Ethanedioate (1:1) Salt (7).** To a stirring solution of 2-methylquinoxaline (20.0 g, 155 mmol) and benzoyl peroxide (3 g, 12 mmol) in carbon tetrachloride (800 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (22 g, 77 mmol). The resulting mixture was irradiated with a spotlight (200 W) for 1.5 h. The mixture was cooled, filtered, and concentrated to afford crude product which was purified by HPLC (hexane/ethyl acetate) to yield 14.0 g (40%) of monobromomethyl product as a grey solid [^1H NMR ($CDCl_3$) δ 9.00 (s, 1 H, Ar*H*), 8.10 (m, 2 H, Ar*H*), 7.80 (m, 2 H, Ar*H*), 4.72 (s, 2 H, $BrCH_2Ar$)] and 15.0 g (35%) of dibromomethyl product as a white solid [^1H NMR ($CDCl_3$) δ 9.39 (s, 1 H, Ar*H*), 8.15 (m, 2 H, Ar*H*), 7.90 (m, 2 H, Ar*H*), 6.76 (s, 1 H, Br_2CH-Ar)].

The 2-(bromomethyl)quinoxaline (3.0 g, 13.4 mmol) was added portionwise to a stirring solution of methylamine (30%) in ethanol (100 mL) at 0 °C. The reaction was stirred at 0 °C for 2 h, concentrated, and partitioned between 10% aqueous K_2CO_3 and ethyl acetate. The organic phase was dried, decolorized (charcoal), and concentrated. Purification was accomplished by eluting the sample through a short silica plug to yield 1.80 g (78%) of **43** as a brown oil: ^1H NMR ($CDCl_3$) δ 8.85 (s, 1 H, Ar*H*), 8.10 (m, 2 H, Ar*H*), 7.73 (m, 2 H, Ar*H*), 4.15 (s, 2 H, NCH_2Ar), 2.60 (s, 3 H, NCH_3).

Amine **43** (2.40 g, 13.86 mmol) was added to a stirred solution of **31** (3.38 g, 13.86 mmol) in ethanol (150 mL) and the mixture stirred at 25 °C for 18 h (procedure B). The mixture was concentrated and the resulting residue was partitioned between water and ethyl acetate. The organic phase was dried, decolorized (charcoal), and concentrated to give product which was treated with oxalic acid. Trituration with ether afforded 1.50 g (21%) of **7** as the oxalate salt: mp 65–70 °C; ^1H NMR (DMSO-d_6) δ 9.35 (s, 1 H, $NHSO_2CH_3$), 9.03 (s, 1 H, Ar*H*), 8.08 (m, 2 H, Ar*H*), 7.86 (m, 2 H, Ar*H*), 7.10 (d, *J* = 8.98 Hz, 2 H, Ar*H*), 6.82 (d, *J* = 9.01 Hz, 2 H, Ar*H*), 4.22 (m, 2 H, OCH_2CHOH), 4.12 (m, 1 H, OCH_2CHOH), 3.89 (m, 2 H, NCH_2-heterocycle), 2.86 (s and m, 5 H, $NHSO_2CH_3$ and $CHOHCH_2N$), 2.54 (s, 3 H, NCH_3); IR (KBr) 3200, 1620, 1500 cm^{-1}; MS *m/z* 417 (MH^+, 40), 186 (45), 144 (80), 44 (100), 23 (80). Anal. ($C_{20}H_{24}N_4O_4S\cdot C_2H_2O_4\cdot 0.22H_2O$) C, H, N.

***N*-[4-[2-Hydroxy-3-[methyl[(3-methyl-2-quinoxalinyl)methyl]amino]propoxy]phenyl]methanesulfonamide Hydrochloride (9).** To a stirring solution of 2,3-dimethylquinoxaline (12.94 g, 81.89 mmol) and benzoyl peroxide (1.97 g) in carbon tetrachloride (500 mL) was added *N*-bromosuccinimide (15.31 g, 86.0 mmol). The resulting mixture was heated at reflux and

irradiated with a spotlight (200 W). After 45 min, the mixture was cooled and filtered. The filtrate was concentrated and the crude product was purified by HPLC (3:1 hexane/ethyl acetate) to give 10.47 g (54%) of 3-methyl-2-(bromomethyl)quinoxaline: ^{1}H NMR ($CDCl_3$) δ 8.05 (m, 2 H, Ar*H*), 7.72 (m, 2 H, Ar*H*), 4.75 (s, 2 H, BrCH_2-heterocycle), 2.89 (s, 3 H, ArCH_3).

The 3-methyl-2-(bromomethyl)quinoxaline (9.25 g, 39.03 mmol) was added portionwise to stirring ethanolic methylamine (250 mL, 33%) at 0 °C. After 3 h, the mixture was concentrated. The residue was partitioned between 10% aqueous K_2CO_3 and ethyl acetate and the organic phase was dried and concentrated to yield 6.54 g (90%) of 3-methyl-2-[(methylamino)methyl]quinoxaline of sufficient purity for use in the next step.

The above amine (2.00 g, 10.69 mmol) and epoxide **31** (2.59 g, 10.69 mmol) were stirred together in ethanol (40 mL) at 40 °C under N_2 for 18 h (procedure C). The mixture was concentrated and the resulting crude product was purified by flash chromatography to give 4.32 g (94%) of (aryloxy)propanolamine. A 1.35-g portion was converted to the hydrochloride salt to give 1.20 g of **9**: mp 115–119 °C; ^{1}H NMR (DMSO-d_6) δ 9.43 (s, 1 H, N*H*SO_2CH_3), 8.05 (m, 2 H, Ar*H*), 7.84 (m, 2 H, Ar*H*), 7.13 (d, *J* = 7.06 Hz, 2 H, Ar*H*), 6.88 (m, 2 H, Ar*H*), 5.00 (m, 2 H, OCH_2CHOH), 4.50 (m, 1 H, OCH_2C*H*OH), 3.95 (m, 2 H, NCH_2-heterocycle), 3.50 (br m, 2 H, CHOHCH_2N), 3.14 (br s, 3 H, NCH_3), 2.87 (s, 3 H, $NHSO_2CH_3$), 2.71 (s, 3 H, CH_3Ar); IR (KBr) 3400 cm^{-1}; MS *m/z* 431 (MH$^+$, 50), 275 (100), 188 (60), 159 (64). Anal. ($C_{21}H_{26}N_4O_4S\cdot HCl\cdot 0.5H_2O$) C, H, N.

1-[4-(1*H*-Imidazol-1-yl)phenoxy]-3-[methyl[(3-methyl-2-quinoxalinyl)methyl]amino]-2-propanol Hydrochloride (10). 3-Methyl-2-[(methylamino)methyl]quinoxaline (1.36 g, 7.27 mmol) was treated with epoxide **32b** (1.57 g, 7.27 mmol) according to procedure C to yield 2.1 g (49%) of **10**. A small amount was converted to the hydrochloride salt: mp 110–115 °C; ^{1}H NMR (DMSO-d_6) δ 9.03 (s, 1 H, imidazole *H*), 8.06 (m, 2 H, Ar*H*), 7.97 (s, 1 H, imidazole *H*), 7.84 (m, 2 H, Ar*H*), 7.63 (d, *J* = 9.13 Hz, 2 H, Ar*H*), 7.55 (s, 1 H, imidazole *H*), 7.08 (d, *J* = 9.13 Hz, 2 H, Ar*H*), 6.08 (br s, 1 H, OH), 4.91 (m, 2 H, OCH_2CHOH), 4.50 (br m, 1 H, OCH_2C*H*OH), 4.06 (m, 2 H, NCH_2-heterocycle), 3.20 (br m, 2 H, CHOHCH_2N), 3.11 (br s, 3 H, NCH_3), 2.72 (s, 3 H, ArCH_3); IR (KBr) 3400, 1525 cm^{-1}; MS *m/z* 404 (MH$^+$, 100), 248 (72), 159 (55). Anal. Calcd for $C_{23}H_{25}N_5O_2\cdot 1.4HCl\cdot 1.2H_2O$): C, 58.01; H, 6.10; N, 14.71. Found: C, 57.72; H, 6.64; N, 14.22.

1-[Methyl(2-quinolinylmethyl)amino]-3-(4-nitrophenoxy)-2-propanol Dihydrochloride (11). 2-Chloromethylquinoline hydrochloride (3.00 g, 14.01 mmol) was suspended in aqueous methylamine (40 mL, 40 wt % in H_2O) at 10 °C under N_2. After 20 min, the reaction mixture was warmed to room temperature and stirred for 3 h. The mixture was diluted with water and extracted with dichloromethane. The organic extract was dried and concentrated to afford 2.22 g (92%) of 2-[(methylamino)methyl]quinoline of sufficient purity to carry on: ^{1}H NMR ($CDCl_3$) δ 8.08 (m, 2 H, Ar*H*), 7.78 (d, *J* = 8.11 Hz, 1 H, Ar*H*), 7.69 (m, 1 H, Ar*H*), 7.52 (d, *J* = 7.03 Hz, 1 H, Ar*H*), 7.44 (d, *J* = 8.72 Hz, 1 H, Ar*H*), 4.06 (s, 2 H, CH_2NHCH_3), 2.55 (s, 3 H, NHCH_3).

The above amine (3.17 g, 18.44 mmol) was treated with epoxide **32a** (3.00 g, 15.37 mmol) according to procedure A to give 2.0 g (30%) of **11** as a dihydrochloride: mp 157–159 °C; ^{1}H NMR (DMSO-d_6) δ 8.50 (d, *J* = 8.43 Hz, 1 H, Ar*H*), 8.17 (d, *J* = 9.28 Hz, 2 H, Ar*H*), 8.03 (m, 2 H, Ar*H*), 7.82 (m, 1 H, Ar*H*), 7.72 (d, *J* = 8.46 Hz, 1 H, Ar*H*), 7.67 (m, 1 H, Ar*H*), 7.07 (d, *J* = 9.26 Hz, 2 H, Ar*H*), 4.78 (m, 2 H, OCH_2CHOH), 4.50 (m, 1 H, OCH_2C*H*OH), 4.12 (m, 2 H, NCH_2-heterocycle), 3.40 (m, 2 H, CHOHCH_2N), 3.01 (s, 3 H, NCH_3); IR (KBr) 3260, 2580, 1590 cm^{-1}; MS *m/z* 368 (MH$^+$, 63), 185 (30), 143 (100). Anal. ($C_{20}H_{21}N_3O_4\cdot 2HCl$) C, H, N.

***N*-[4-[2-Hydroxy-3-[methyl(2-quinolinylmethyl)amino]propoxy]phenyl]methanesulfonamide (12).** 2-[(Methylamino)methyl]quinoline (3.14 g, 18.25 mmol) was treated with epoxide **31** (3.70 g, 15.21 mmol) according to procedure A to afford 3.10 g (49%) of **12** as an off-white solid: mp 119–121 °C; ^{1}H NMR (DMSO-d_6) δ 9.34 (s, 1 H, N*H*SO_2CH_3), 8.24 (d, *J* = 8.48 Hz, 1 H, Ar*H*), 7.94 (m, 2 H, Ar*H*), 7.72 (m, 1 H, Ar*H*), 7.61 (d, *J* = 8.52 Hz, 1 H, Ar*H*), 7.56 (m, 1 H, Ar*H*), 7.11 (d, *J* = 9.01 Hz, 2 H, Ar*H*), 6.84 (d, *J* = 8.93 Hz, 2 H, Ar*H*), 5.00 (br d, 1 H, O*H*), 3.96 (m, 2 H, OCH_2CHOH), 3.82 (m, 3 H, NCH_2-heterocycle and OCH_2C*H*OH), 2.87 (s, 3 H, $NHSO_2CH_3$), 2.61 (m, 2 H, CHOHCH_2N), 2.28 (s, 3 H, NCH_3); IR (KBr), 3450, 3180 cm^{-1}; MS *m/z* 416 (MH$^+$, 18), 275 (42), 188 (80), 144 (100). Anal. ($C_{21}H_{25}N_3O_4S$) C, H, N.

***N*-[4-[2-Hydroxy-3-[(Methylethyl)(2-quinolinylmethyl)amino]propoxy]phenyl]methanesulfonamide Dihydrochloride (16).** 2-(Chloromethyl)quinoline hydrochloride (5.00 g, 23.35 mmol) was added portionwise to a stirring solution of isopropylamine (9.95 mL, 116.8 mmol) in dimethoxyethane (20 mL) at 0 °C. The mixture was stirred at 45 °C overnight, diluted with water (50 mL), and extracted with ethyl acetate. The organic phase was dried and concentrated to afford a residue which was purified by HPLC to give 2.32 g (50%) of 2-[(isopropylamino)methyl]quinoline as an oil: ^{1}H NMR ($CDCl_3$) δ 8.05 (m, 2 H, Ar*H*), 7.70 (m, 2 H, Ar*H*), 7.45 (m, 2 H, Ar*H*), 4.08 (s, 2 H, NCH_2-heterocycle), 2.90 (m, 1 H, $(CH_3)_2$C*H*N), 1.20 (d, *J* = 7.2 Hz, 6 H, $(CH_3)_2$CHN).

The above amine (1.77 g, 7.28 mmol) was treated with epoxide **31** (1.76 g, 7.25 mmol) according to procedure A to afford 0.50 g (15%) of **16** after HPLC (10% methanol/dichloromethane): mp 89–94 °C; ^{1}H NMR (DMSO-d_6) δ 9.44 (s, 1 H, N*H*SO_2CH_3), 8.50 (d, *J* = 8.48 Hz, 1 H, Ar*H*), 8.04 (m, 2 H, Ar*H*), 7.83 (m, 1 H, Ar*H*), 7.73 (d, *J* = 8.52 Hz, 1 H, Ar*H*), 7.68 (m, 1 H, Ar*H*), 7.12 (d, *J* = 8.99 Hz, 2 H, Ar*H*), 6.83 (d, *J* = 8.94 Hz, 2 H, Ar*H*), 4.83 (m, 2 H, OCH_2CHOH), 4.32 (br m, 1 H, OCH_2C*H*OH), 3.91 (m, 2 H, NCH_2-heterocycle), 3.53 (m, 3 H, CHOHCH_2N and $(CH_3)_2$C*H*N), 2.86 (s, 3 H, $NHSO_2CH_3$), 1.38 (d, *J* = 6.2 Hz, 6 H, $(CH_3)_2$CHN); IR (KBr) 3420 cm^{-1}; MS *m/z* 444 (MH$^+$, 40), 303 (100). Anal. ($C_{23}H_{29}N_3O_4S\cdot 2HCl$) C, H, N.

1-[4-(1*H*-Imidazol-1-yl)phenoxy]-3-[methyl(2-quinolinylmethyl)amino]-2-propanol Dihydrochloride (17). 2-[(Methylamino)methyl]quinoline (2.39 g, 13.89 mmol) was treated with epoxide **32b** (2.00 g, 9.26 mmol) according to procedure B to afford 3.37 g (94%) of product. An aliquot was converted to hydrochloride salt **17**: mp 143–147 °C; ^{1}H NMR (DMSO-d_6) δ 9.70 (s, 1 H, imidazole *H*), 8.50 (d, *J* = 8.49 Hz, 1 H, Ar*H*), 8.22 (s, 1 H, imidazole *H*), 8.05 (d, *J* = 8.42 Hz, 2 H, Ar*H*), 7.90 (s, 1 H, Ar*H*), 7.84 (m, 2 H, Ar*H*), 7.69 (m, 3 H, Ar*H* and imidazole *H*), 7.10 (d, *J* = 8.57 Hz, 2 H, Ar*H*), 4.80 (m, 2 H, OCH_2CHOH), 4.52 (br m, 1 H, OCH_2C*H*OH), 4.07 (m, 2 H, NCH_2-heterocycle), 3.50 (m, CHOHCH_2N), 3.01 (s, 3 H, $NHSO_2CH_3$); IR (KBr) 3400, 3050 cm^{-1}; MS *m/z* 389 (MH$^+$, 55), 248 (82), 144 (100). Anal. Calcd for $C_{23}H_{24}N_4O_2\cdot 2HCl\cdot H_2O$: C, 57.62; H, 5.89; N, 11.69. Found: C, 57.30; H, 5.89; N, 10.81.

1-[Methyl(2-quinolinylmethyl)amino]-3-[4-(1*H*-tetrazol-5-yl)phenoxy]-2-propanol Hydrochloride (18). 2-[(Methylamino)methyl]quinoline (1.22 g, 7.13 mmol) was treated with epoxide **33** (3.29 g, 7.15 mmol) according to procedure A to afford 1.56 g (35%) of N-tritylated (aryloxy)propanolamine, which was stirred in saturated ethanolic HCl (50 mL) for 3 h. Upon addition of diethyl ether, **18** (0.35 g, 48%) precipitated as the hydrochloride salt: mp 95–97 °C; ^{1}H NMR (DMSO-d_6) δ 8.50 (d, *J* = 8.27 Hz, 1 H, Ar*H*), 8.01 (m, 4 H, Ar*H*), 7.82 (m, 1 H, Ar*H*), 7.73 (d, *J* = 8.47 Hz, 1 H, Ar*H*), 7.69 (m, 1 H, Ar*H*), 7.07 (d, *J* = 8.95 Hz, 2 H, Ar*H*), 4.79 (m, 2 H, OCH_2CHOH), 4.49 (br m, 1 H, OCH_2C*H*OH), 4.06 (m, 2 H, NCH_2-heterocycle), 3.40 (m, 2 H, CHOHCH_2N), 3.01 (s, 3 H, NCH_3); IR (KBr) 3400, 2700, 1610 cm^{-1}; MS *m/z* 391 (MH$^+$, 100), 143 (80), 91 (80). Anal. Calcd for $C_{21}H_{22}N_6O_2\cdot 1.1HCl\cdot H_2O$: C, 56.23; H, 5.64; N, 18.73. Found: C, 56.37; H, 5.44; N, 17.92.

4-[2-Hydroxy-3-[methyl(2-quinolinylmethyl)amino]propoxy]benzonitrile Hydrochloride (19). 2-[(Methylamino)methyl]quinoline (2.83 g, 16.5 mmol) was treated with epoxide **32c** (2.63 g, 16.5 mmol) according to procedure B to afford 1.2 g (22%) of product after column chromatography. An aliquot was converted to hydrochloride salt **19**: mp 110–114 °C; ^{1}H NMR (DMSO-d_6) δ 8.49 (d, *J* = 8.28 Hz, 1 H, Ar*H*), 8.03 (m, 2 H, Ar*H*), 7.87–7.60 (m, 5 H, Ar*H*), 7.03 (d, *J* = 9.00 Hz, 2 H, Ar*H*), 4.78 (m, 2 H, OCH_2CHOH), 4.50 (m, H, OCH_2C*H*OH), 4.07 (m, 2 H, NCH_2-heterocycle), 3.50–3.30 (m, 2 H, CHOHCH_2N), 3.00 (s, 3 H, CH_3); IR (KBr) 3220, 2220, 1600 cm^{-1}; MS *m/z* 348 (MH$^+$, 90), 143 (100), 44 (39). Anal. ($C_{21}H_{21}N_3O_2\cdot 1.2HCl$) C, H, N.

***N*-[4-[3-[[(6-Chloro-2-quinolinyl)methyl]methylamino]-2-hydroxypropoxy]phenyl]methanesulfonamide Hydrochloride (20).** To a stirring suspension of 6-chloro-2-methylquinoline (5.0 g, 28.14 mmol) in dichloroethane (150 mL) was

added 98% 3-chloroperoxybenzoic acid (4.8 g, 28.00 mmol). The mixture was stirred overnight at 40 °C and was then concentrated and partitioned between 10% aqueous K_2CO_3 and ethyl acetate. The organic phase was dried and concentrated to afford a crude solid which was purified by flash chromatography (5% methanol/dichloromethane) to give 1.85 g (34%) of pure *N*-oxide **38b**: ^{1}H NMR ($CDCl_3$) δ 8.70 (d, *J* = 9.20 Hz, 1 H, Ar*H*), 7.81 (d, *J* = 1.80 Hz, 1 H, Ar*H*), 7.67 (dd, J_1 = 8.90 Hz, J_2 = 1.8 Hz, 1 H, Ar*H*), 7.55 (d, *J* = 8.90 Hz, 1 H, Ar*H*), 7.37 (d, *J* = 8.80 Hz, 1 H, Ar*H*), 2.70 (s, 3 H, CH_3).

The above 6-chloro-2-methylquinoline *N*-oxide (1.73 g, 8.1 mmol) was added to a stirring solution of *p*-toluenesulfonyl chloride (1.7 g, 8.96 mmol) in dichloroethane (80 mL). The reaction mixture was heated to 100 °C overnight under N_2, cooled, concentrated, and partitioned between 10% aqueous K_2CO_3 and ethyl acetate. The organic phase was dried and concentrated to afford a solid which was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 0.93 g (52%) of **39b** as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 8.20–7.60 (m, 5 H, Ar*H*), 4.80 (s, 2 H, $ClCH_2$).

Chloromethyl compound **39b** (1.34 g, 6.32 mmol) was dissolved in ethanolic methylamine (30 mL, 33%) at 0 °C under N_2. After 10 min, the reaction was warmed to room temperature and stirring continued for 2 h. The mixture was concentrated and the residue partitioned between aqueous 10% K_2CO_3 and ethyl acetate. The organic phase was dried and concentrated to afford **40b** which was purified by flash chromatography (5% methanol/dichloromethane) to give 0.37 g (28%) of aminomethyl compound.

Amine **40b** (0.37 g, 1.78 mmol) was treated with epoxide **31** (0.43 g, 1.76 mmol) according to procedure B to yield 0.33 g (33%) of **20**, which was converted to the hydrochloride: mp 90–95 °C; ^{1}H NMR (DMSO-d_6) δ 10.09 (s, 1 H, +N*H*), 9.39 (s, 1 H, N*H*SO_2CH_3), 8.47 (d, *J* = 8.00 Hz, 1 H, Ar*H*), 8.20 (d, *J* = 1.62 Hz, 1 H, Ar*H*), 8.03 (d, *J* = 8.92 Hz, 1 H, Ar*H*), 7.84 (dd, J_1 = 9.02 Hz, J_2 = 2.40 Hz, 1 H, Ar*H*), 7.73 (d, *J* = 8.52 Hz, 1 H, Ar*H*), 7.12 (d, *J* = 9.00 Hz, 2 H, Ar*H*), 6.85 (d, *J* = 8.95 Hz, 2 H, Ar*H*), 6.00 (br s, 1 H, O*H*), 4.76 (m, 2 H, OCH_2CHOH), 4.41 (m, 1 H, C*H*OH), 3.92 (m, 2 H, NCH_2-heterocycle), 3.39 (m, 2 H, $CHOHCH_2NCH_3$), 2.99 (s, 3 H, NCH_3), 2.86 (s, 3 H, $NHSO_2CH_3$); IR (KBr) 3375, 3075 cm^{-1}; MS *m/z* 450 (MH^+, 100). Anal. ($C_{21}H_{24}ClN_3O_4S{\cdot}HCl{\cdot}0.4H_2O$) C, H, N.

***N*-[4-[3-[[(6-Fluoro-2-quinolinyl)methyl]methylamino]-2-hydroxypropoxy]phenyl]methanesulfonamide Hydrochloride (21).** By starting from 6-fluoro-2-methylquinoline, this compound was prepared in four steps using the same procedures (similar yields), as described for 6-chloro analogue **20**: mp 85–90 °C; ^{1}H NMR (DMSO-d_6) δ 10.00 (s, 1 H, +N*H*), 9.41 (s, 1 H, N*H*SO_2CH_3), 8.49 (d, *J* = 8.72 Hz, 1 H, Ar*H*), 8.09 (m, 1 H, Ar*H*), 7.87 (m, 1 H, Ar*H*), 7.76 (m, 2 H, Ar*H*), 7.13 (d, *J* = 8.92 Hz, 2 H, Ar*H*), 6.86 (d, *J* = 9.13 Hz, 2 H, Ar*H*), 6.00 (br s, 1 H, O*H*), 4.77 (m, 2 H, OCH_2CHOH), 4.41 (m, 1 H, C*H*OH), 3.92 (m, 2 H, NCH_2-heterocycle), 3.40 (m, 2 H, $CHOHCH_2NCH_3$), 2.99 (s, 3 H, $NHSO_2CH_3$), 2.87 (s, 3 H, NCH_3); IR (KBr) 3400, 3125 cm^{-1}; MS *m/z* 434 (MH^+, 30). Anal. ($C_{21}H_{24}FN_3O_4S{\cdot}HCl{\cdot}0.7H_2O$) C, H, N.

***N*-[4-[2-Hydroxy-3-[[(6-methoxy-2-quinolinyl)methyl]methylamino]propoxy]phenyl]methanesulfonamide Hydrochloride (22).** By starting from 6-methoxyquinaldine, this compound was prepared in four steps using the same procedures (similar yields) as described for 6-chloro analogue **20**: mp 100–105 °C; ^{1}H NMR (DMSO-d_6) δ 9.40 (s, 1 H, N*H*SO_2CH_3), 8.39 (d, *J* = 9.22 Hz, 1 H, Ar*H*), 7.92 (d, *J* = 8.90 Hz, 1 H, Ar*H*), 7.65 (d, *J* = 9.42 Hz, 1 H, Ar*H*), 7.43 (m, 2 H, Ar*H*), 7.12 (d, *J* = 9.01 Hz, 2 H, Ar*H*), 6.84 (d, *J* = 8.84 Hz, 1 H, Ar*H*), 5.95 (s, 1 H, O*H*), 4.67 (m, 2 H, OCH_2), 4.41 (m, 1 H, C*H*OH)O, 3.91 (m and s, 5 H, NCH_2-heterocycle and OCH_3), 3.40 (m, 2 H, $CHOHCH_2N$), 2.95 (br s, 3 H, NCH_3), 2.86 (s, 3 H, $NHSO_2CH_3$); IR (KBr) 3400, 3100 cm^{-1}; MS *m/z* 446 (MH^+, 20), 157 (25), 79 (100). Anal. ($C_{22}H_{27}N_3O_5S{\cdot}HCl{\cdot}H_2O$) C, H, N.

***N*-[2-[[[2-Hydroxy-3-[4-[(methylsulfonyl)amino]phenoxy]propyl]methylamino]methyl]-6-quinolinyl]methanesulfonamide Hydrochloride (23).** To a stirring solution of 2-methyl-6-nitroquinoline (10.0 g, 53.79 mmol) was added 98% 3-chloroperoxybenzoic acid (11.6 g, 66.10 mmol) in dichloromethane (150 mL). The mixture was stirred at 40 °C overnight. The precipitate was filtered and washed with 10% aqueous K_2CO_3 to afford 10.03 g (92%) of *N*-oxide **38a**: ^{1}H NMR ($CDCl_3$) δ 8.94 (d, *J* = 8.90 Hz, 1 H, Ar*H*), 8.80 (s, 1 H, Ar*H*), 8.49 (d, *J* = 9.22 Hz, 1 H, Ar*H*), 7.83 (d, *J* = 9.22 Hz, 1 H, Ar*H*), 7.52 (d, *J* = 9.10 Hz, 1 H, Ar*H*), 2.57 (s, 3 H, CH_3).

The above 2-methyl-6-nitroquinoline *N*-oxide (13.0 g, 63.72 mmol) was added to a stirring solution of *p*-toluenesulfonyl chloride (13.5 g, 70.81 mmol) in dichloroethane (200 mL). The reaction was stirred at 100 °C for 24 h and then at room temperature for 48 h. The reaction mixture was diluted with ethyl acetate and a solid precipitated and was filtered and recrystallized from acetone/water to afford 7.91 g (56%) of **39a**: ^{1}H NMR ($CDCl_3$) δ 8.80 (d, *J* = 1.8 Hz, Ar*H*), 8.46 (dd, J_1 = 10.64 Hz, J_2 = 1.8 Hz, 1 H, Ar*H*), 8.17 (d, *J* = 8.90 Hz, 1 H, Ar*H*), 7.80 (d, *J* = 9.22 Hz, 1 H, Ar*H*), 4.86 (s, 2 H, $ClCH_2$).

Chloromethyl compound **39a** (5.00 g, 22.47 mmol) was added to a saturated solution of methylamine in toluene (70 mL) at 0 °C. The mixture was slowly warmed to room temperature over 4 h and was then partitioned between 10% aqueous K_2CO_3 and ethyl acetate. The organic phase was dried, decolorized (charcoal), and concentrated to give 4.89 g (100%) of **40a** which was used directly in the next step.

The above amine **40a** (4.75 g, 21.89 mmol) was treated with epoxide **31** (5.32 g, 21.89 mmol) according to procedure C to yield 1.96 g (19%) of the 6-nitroquinolin-2-yl epoxide cleavage product after HPLC (10% methanol/ethyl acetate): ^{1}H NMR ($CDCl_3$) δ 8.75 (d, *J* = 2 Hz, 1 H, Ar-*H*), 8.45 (dd, J_1 = 9.6 Hz, J_2 = 2 Hz, 1 H, Ar*H*), 8.30 (d, *J* = 9.0 Hz, 1 H, ArH), 8.18 (d, *J* = 9.0 Hz, 1 H, Ar*H*), 7.64 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.15 (d, *J* = 7.3 Hz, 2 H, Ar*H*), 6.80 (d, *J* = 7.3 Hz, 2 H, Ar*H*), 4.25–3.80 (m, 5 H, OCH_2 and C*H*OH and NCH_2-heterocycle), 2.92 (s, 3 H, $NHSO_2CH_3$), 2.75 (br d, 2 H, $CHOHCH_2N$), 2.45 (s, 3 H, NCH_3).

The above 6-nitroquinolin-2-yl derivative (1.20 g, 2.61 mmol) and PtO_2 (0.120 g, 10% by wt) were suspended in ethanol (100 mL), and the flask was charged with H_2 (1 atm). After stirring for 6 h, the mixture was filtered through a pad of Solka-Floc and the filtrate was concentrated in vacuo to afford 1.00 g (89%) of amine as a pale oil, which was used directly in the next step: ^{1}H NMR (DMSO-d_6) δ 9.45 (br s, 1 H, N*H*SO_2CH_3), 7.93 (d, *J* = 7.8 Hz, 1 H, Ar*H*), 7.70 (d, *J* = 9 Hz, 1 H, Ar*H*), 7.41 (d, *J* = 9 Hz, 1 H, Ar*H*), 7.2 (m, 3 H, Ar*H*), 6.95 (m, 2 H, Ar*H*), 6.80 (s, 1 H, Ar*H*), 5.60 (br s, 2 H, NH_2), 5.10 (m, 1 H, O*H*), 4.15–3.65 (m, 5 H, OCH_2 and C*H*OH and NCH_2-heterocycle), 2.93 (s, 3 H, $NHSO_2CH_3$), 2.60 (m, 2 H, $CHCH_2N$), 2.35 (s, 3 H, NCH_3).

To the above amine (0.94 g, 2.19 mmol) in water (10 mL) at 0 °C was added methanesulfonic acid (0.14 mL, 2.19 mmol) and methanesulfonyl chloride (0.30 mL, 3.93 mmol). After stirring for 18 h at 25 °C the pH was adjusted to 6 with K_2CO_3 and an additional 0.30 mL of methanesulfonyl chloride was added. The mixture stirred for an additional 20 h and was then readjusted to pH 6 and recharged with 0.30 mL of methanesulfonyl chloride. Upon completion (TLC), the reaction mixture was diluted with 10% aqueous $NaHCO_3$ and extracted with 4:1 dichloromethane/2-propanol. The organic phase was dried, decolorized (charcoal), and concentrated to afford crude product which was purified by HPLC (5% methanol/ethyl acetate; 0.5% NH_4OH) to yield 0.34 g (31%) of **23** as an amorphous solid. This was converted to the hydrochloride salt by treatment with 1 N HCl/ether and ethanol to yield 0.25 g as a light yellow solid: mp 135–140 °C; ^{1}H NMR (DMSO-d_6) δ 10:31 (s, 1 H, N*H*SO_2CH_3), 10.04 (br s, 1 H, +N*H*), 9.40 (s, 1 H, N*H*SO_2CH_3), 8.43 (d, *J* = 8.34 Hz, 1 H, Ar*H*), 8.00 (d, *J* = 9.05 Hz, 1 H, Ar*H*), 7.77 (d, *J* = 2.42 Hz, 1 H, Ar*H*), 7.65 (dd, J_1 = 8.65 Hz, J_2 = 2.34 Hz, 2 H, Ar*H*), 7.11 (d, *J* = 9.02 Hz, 2 H, Ar*H*), 6.85 (d, *J* = 9.02 Hz, 2 H, Ar*H*), 5.97 (br s, 1 H, O*H*), 4.73 (m, 2 H, OCH_2CHOH), 4.41 (m, 1 H, C*H*OH), 3.91 (m, 2 H, NCH_2-heterocycle), 3.38 (m, 2 H, CH_2N), 3.11 (s, 3 H, $NHSO_2CH_3$), 2.97 (s, 3 H, NCH_3), 2.87 (s, 3 H, $NHSO_2CH_3$); IR (KBr) 3250, 2920 cm^{-1}; MS *m/z* 509 (MH^+, 10), 275 (90), 237 (90), 188 (100). Anal. ($C_{22}H_{28}N_4O_6S_2{\cdot}1.3HCl{\cdot}0.5H_2O$) C, H, N.

α-[(4-Nitrophenoxy)methyl]-4-(2-pyridinyl)-1-piperazineethanol Dihydrochloride (26). 1-(2-Pyridyl)piperazine (6.24 mL, 40.78 mmol) was treated with epoxide **32a** (4.00 g, 20.49 mmol) according to procedure A to give 6.10 g (69%) of **26** as the dihydrochloride: mp 244–246 °C; ^{1}H NMR (DMSO-d_6) δ 10.9 (br s, 2 H, +N*H*), 8.22 (d, *J* = 9.21 Hz, 2 H, Ar*H*), 8.12 (dd, J_1 = 1.2 Hz, J_2 = 5.4 Hz, 1 H, Ar*H*), 7.87 (m, 1

H, ArH), 7.21 (m, 1 H, ArH), 7.17 (d, J = 9.27 Hz, 2 H, ArH), 6.91 (t, J = 6.19 Hz, 1 H, ArH), 4.50–4.42 (m, 4 H, OCH_2CHOH), 4.15 (br d, 2 H, $CHOHCH_2N$), 3.89–3.15 (br m, 8 H, piperazine CH_2); IR (KBr) 3320, 1600–1500 cm^{-1}; MS m/z 358 (MH^+, 18), 107 (100). Anal. ($C_{18}H_{22}N_4O_4·2HCl$) C, H, N.

N-[4-[2-Hydroxy-3-[4-(2-pyridinyl)-1-piperazinyl]propoxy]phenyl]methanesulfonamide (27). 1-(2-Pyridyl)piperazine (2.50 mL, 16.44 mmol) was treated with epoxide **31** (2.00 g, 8.22 mmol) according to procedure A to give 2.19 g (66%) of **27**: mp 131–132 °C; ^1H NMR (DMSO-d_6) δ 9.33 (br s, 1 H, $NHSO_2CH_3$), 8.08 (m, 1 H, ArH), 7.50 (m, 1 H, ArH), 7.13 (d, J = 8.91 Hz, 2 H, ArH), 6.92 (d, J = 9.01 Hz, 2 H, ArH), 6.78 (d, J = 8.62 Hz, 1 H, ArH), 6.61 (m, 1 H, ArH), 4.89 (br d, J = 4.12 Hz, 1 H, OH), 3.95 (m, 2 H, OCH_2CHOH), 3.85 (m, 1 H, OCH_2CHOH), 3.44–3.30 (m, 10 H, piperazinyl CH_2N), 2.86 (s, 3 H, $NHSO_2CH_3$); IR (KBr) 3150, 2920, 1600 cm^{-1}; MS m/z 407 (MH^+, 40). Anal. ($C_{19}H_{26}N_4O_4S$) C, H, N.

N-[4-[2-Hydroxy-3-[4-(2-pyrimidinyl)-1-piperazinyl]propoxy]phenyl]methanesulfonamide (28). 1-(2-Pyrimidinyl)piperazine (1.65 g, 10.06 mmol) was treated with epoxide **32a** (1.31 g, 6.71 mmol) according to procedure A to give 1.57 g (62%) of the epoxide cleavage product which was used directly in the next step. A small amount was converted to hydrochloride salt: ^1H NMR (DMSO-d_6) δ 10.69 (br s, 2 H, HCl), 8.44 (d, J = 4.67 Hz, 2 H, ArH), 8.22 (d, J = 9.27 Hz, 2 H, ArH), 7.17 (d, J = 9.26 Hz, 2 H, ArH), 6.76 (m, 1 H, ArH), 4.85 (br m, 1 H, OH), 4.66 (m, 2 H, OCH_2CHOH), 4.49 (m, 1 H, OCH_2CHOH), 4.15 (br d, 2 H, CH_2N), 3.70–3.10 (br m, 8 H, piperazine CH_2); IR (KBr) 3300 cm^{-1}; MS m/z 359 (M^+, 60), 177 (100).

The above nitro-substituted (aryloxy)propanolamine (1.32 g, 3.68 mmol) was hydrogenated in a Parr reactor using 5% Pd/C (0.198 g, 15% by wt) in ethyl acetate (40 mL). After 5 h, the mixture was filtered through Solka-Floc and concentrated to afford 1.2 g (100%) of amine which was used directly in the next step: ^1H NMR ($CDCl_3$) δ 8.25 (d, J = 5.4 Hz, 2 H, ArH), 6.72 (d, J = 9.0 Hz, 2 H, ArH), 6.59 (d, J = 9.2 Hz, 2 H, ArH), 6.45 (m, 1 H, ArH), 4.10 (m, 1 H, CHOH), 3.90–3.50 (m, 9 H, OCH_2CHOH, NH_2, 4 piperzine CH_2), 2.80–2.40 (m, 6 H, CH_2N and 4 piperazine CH_2).

Methanesulfonyl chloride (0.31 mL, 4.01 mmol) was added dropwise to a stirring solution of the above amine (1.20 g, 3.65 mmol) in pyridine (15 mL) at −30 °C under N_2. The reaction was stirred at 25 °C for 1.5 h. Ice water was added, and the resulting mixture was extracted with ethyl acetate. The organic phase was dried, decolorized (charcoal), and concentrated to afford a residue. Trituration followed by recrystallization from methanol/ethyl acetate/hexane afforded 0.65 g (44%) of analytically pure **28**: mp 143–146 °C; (DMSO-d_6) δ 9.35 (s, 1 H, CH_3SO_2NH), 8.35 (d, J = 4.77 Hz, 2 H, ArH), 7.15 (d, J = 8.72 Hz, 2 H, ArH), 6.93 (d, J = 8.72 Hz, 2 H, ArH), 6.61 (m, 1 H, ArH), 4.92 (m, 1 H, OH), 3.98 (m, 2 H, OCH_2CHOH), 3.87 (m, 1 H, OCH_2CHOH), 3.71 (m, 4 H, piperazine CH_2), 2.88 (s, 3 H, CH_3SO_2NH), 2.49 (m, 6 H, CH_2N and piperazine CH_2); IR (KBr) 3120 cm^{-1}; MS m/z 407 (M^+, 10), 177 (100). Anal. ($C_{18}H_{25}N_5O_4S$) C, H, N.

N-[4-[2-Hydroxy-3-[4-(1-methyl-1H-benzimidazol-2-yl)-1-piperazinyl]propoxy]phenyl]methanesulfonamide Dihydrochloride (29). 1-[2-(1-Methyl-1H-benzimidazolyl)]piperazine (1.16 g, 5.4 mmol) was treated with epoxide **31** (1.00 g, 4.10 mmol) according to procedure C to give 1.09 g (58%) of product which was converted to the dihydrochloride: mp 160–165 °C; ^1H NMR (DMSO-d_6) δ 9.43 (s, 1 H, $NHSO_2CH_3$), 7.65 (m, 1 H, ArH), 7.57 (m, 1 H, ArH), 7.37 (m, 2 H, ArH), 7.17 (d, J = 8.92 Hz, 2 H, ArH), 6.96 (d, J = 9.13 Hz, 2 H, ArH), 6.00 (br m, 1 H, CHOH), 4.47 (m, 1 H, CHOH), 4.10–3.25 (m and s, 15 H, OCH_2CHOH, NCH_2, piperazine CH_2 and NCH_3), 2.88 (s, 3 H, $NHSO_2CH_3$); IR (KBr) 3220, 2900, 1120 cm^{-1}; MS m/z 460 (MH^+, 100), 188 (95), 81 (54). Anal. ($C_{22}H_{29}N_5O_4S·2HCl·H_2O$) C, H, N.

Synthesis of Optically Active (Aryloxy)propanolamines: (−)-(S)-N-[4-[2-Hydroxy-3-[methyl(2-quinolinylmethyl)amino]propoxy]phenyl]methanesulfonamide (13). Method A. To a solution of sodium 4-nitrophenoxide (3.18 g, 15.43 mmol) in dimethylformamide (20 mL) at 0 °C was added (2S)-(+)-glycidyl 3-nitrobenzenesulfonate (4.00 g, 15.43 mmol). The mixture was stirred for 18 h under N_2 at 20 °C. The reaction mixture was diluted with brine (50 mL) and extracted with ethyl acetate. The combined organic phase was washed with cold 0.1 N NaOH, water, and brine. The extract was dried and concentrated to afford 3.0 g of product which was purified by flash column chromatography using 2:1 hexane/ethyl acetate to afford 2.49 g (83%) of epoxide S-(+)-**32a** as a white solid: mp 73–75 °C; ^1H NMR ($CDCl_3$) δ 8.20 (d, J = 9 Hz, 2 H, ArH), 7.00 (d, J = 9 Hz, 2 H, ArH), 4.39 and 4.00 (2 m, 2 H, OCH_2CH), 3.38 (m, 1 H, epoxide CH), 2.90 and 2.80 (2 m, 2 H, epoxide CH_2); $[\alpha]^{25}_D$ = +10.6° (methanol).

2-[(Methylamino)methyl]quinoline (4.47 g, 25.96 mmol) was treated with epoxide S-(+)-**32a** according to procedure A to give 5.01 g (63%) of S-**49** after HPLC (1:1 ethyl acetate/hexane): ^1H NMR ($CDCl_3$) 8.15 (m, 4 H, ArH), 7.75 (d, J = 8.0 Hz, 1 H, ArH), 7.70 (m, 1 H, ArH), 7.50 (m, 1 H, ArH), 7.40 (d, J = 8.0 Hz, 1 H, ArH), 6.90 (d, J = 9.6 Hz, 2 H, ArH), 5.12 (br s, 1 H, OH), 4.20–4.00 (m, 5 H, $OCH_2CHOHNCH_2$-heterocycle), 2.72 (m, 2 H, CH_2N), 2.50 (s, 3 H, NCH_3).

The above nitro compound (4.60 g, 12.51 mmol) was added to a suspension of 5% Pd/C (0.46 g) in ethanol (100 mL). The Parr vessel was charged with H_2 (50 psi) for 3 h. The mixture was filtered through Solka-Floc and the filtrate was concentrated to afford 4.0 g (95%) of amine that was used directly in the next step.

Methanesulfonyl chloride (1.08 mL, 13.95 mmol) was added dropwise to a solution of the above amine (3.93 g, 11.66 mmol) and pyridine (1.89 mL, 23.36 mmol) in dichloromethane (25 mL) at 0 °C under N_2. The reaction was stirred for 3 h at room temperature, concentrated, diluted with water, and extracted with ethyl acetate. The organic layer was dried and evaporated to afford product which was purified by HPLC (10% methanol/dichloromethane) to give 3.46 g (72%) of **13**: mp 135–137 °C; ^1H NMR (DMSO-d_6) δ 9.33 (s, 1 H, $NHSO_2CH_3$), 8.24 (d, J = 8.57 Hz, 1 H, ArH), 7.93 (m, 2 H, ArH), 7.72 (m, 1 H, ArH), 7.61 (d, J = 8.48 Hz, 1 H, ArH), 7.48 (m, 1 H, ArH), 7.11 (d, J = 8.92 Hz, 2 H, ArH), 6.83 (d, J = 8.94 Hz, 2 H, ArH), 4.96 (br s, 1 H, OH), 3.96 (m, 2 H, OCH_2CHOH), 3.81 (m, 3 H, NCH_2-heterocycle and CHOH), 2.86 (s, 3 H, $NHSO_2CH_3$), 2.48 (m, 2 H, $CHOHCH_2N$), 2.27 (s, 3 H, NCH_3); $[\alpha]^{25}_D$ = −15.96° (methanol); IR (KBr) 3450, 3180 cm^{-1}; MS m/z 416 (MH^+, 75), 237 (20), 185 (42), 143 (100). Anal. ($C_{21}H_{25}N_3O_4S·0.4NaCl$) C, H, N.

(+)-(R)-N-[4-[2-Hydroxy-3-[methyl(2-quinolinylmethyl)amino]propoxy]phenyl]methanesulfonamide (14). Method A. Compound R-(−)-**32a** was prepared in a way similar to that of the enantiomer: yield 6.35 g (77%) as a white solid; mp 75–76 °C; ^1H NMR ($CDCl_3$) δ 8.20 (d, J = 9 Hz, 2 H, ArH), 7.00 (d, J = 9 Hz, 2 H, ArH), 4.39 and 4.00 (2 m, 2 H, OCH_2), 3.38 (m, 1 H, epoxide CH), 2.90 and 2.79 (2 m, 2 H, epoxide CH_2); $[\alpha]^{25}_D$ = −11.0° (methanol).

2-[(Methylamino)methyl]quinoline (5.57 g, 32.41 mmol) was treated with epoxide R-(−)-**32a** according to procedure A to give 10.08 g (85%) of (R)-**49**, which was used directly in the next step: ^1H NMR ($CDCl_3$) δ 8.15 (m, 4 H, ArH), 7.80 (d, J = 7.8 Hz, 1 H, ArH), 7.72 (m, 1 H, ArH), 7.52 (m, 1 H, ArH), 7.41 (d, J = 8.4 Hz, 1 H, ArH), 6.90 (d, J = 9.6 Hz, 2 H, ArH), 5.13 (br s, 1 H, OH), 4.23–3.90 (m, 5 H, OCH_2CHOH and NCH_2-heterocycle), 2.78 (m, 2 H, CH_2N), 2.49 (s, 3 H, NCH_3).

The above nitro compound (10.00 g, 27.25 mmol) was added to a suspension of 5% Pd/C (1.00 g) in ethanol (200 mL). The Parr vessel was charged with H_2 (50 psi) and shaken for 18 h. The mixture was filtered through Solka-Floc and the filtrate was concentrated to give the amine which was purified by HPLC (10% methanol/ethyl acetate) to yield 5.96 g (65%) of product as an oil that was directly mesylated with methanesulfonyl chloride/methanesulfonic acid in water as in compound **23** to afford 5.40 g (74%) of 14: mp 128–131 °C; ^1H NMR ($CDCl_3$) δ 8.13 (d, J = 8.51 Hz, 1 H, ArH), 8.09 (d, J = 8.51 Hz, 1 H, ArH), 7.81 (d, J = 8.09 Hz, 1 H, ArH), 7.70 (m, 1 H, ArH), 7.53 (m, 1 H, ArH), 7.46 (d, J = 8.51 Hz, 1 H, ArH), 7.15 (d, J = 8.92 Hz, 2 H, ArH), 6.84 (d, J = 9.13 Hz, 2 H, ArH), 4.20 (m, 1 H, CHOH), 4.10–3.90 (m, 4 H, OCH_2 and NCH_2-heterocycle), 2.92 (s, 3 H, $NHSO_2CH_3$), 2.77 (m, 2 H, $CHOHCH_2N$), 2.51 (s, 3 H, NCH_3); $[\alpha]^{25}_D$ = +16.5° (methanol); IR (KBr) 3400, 3180, 2920 cm^{-1}; MS m/z 416 (MH^+, 18), 217 (42), 109 (32), 91 (100). Anal. ($C_{21}H_{25}N_3O_4S$) C, H, N.

Compound 14. Method B. To a stirring solution of sodium 4-nitrophenoxide (19.50 g, 190.1 mmol) in dimethylformamide (150 mL) was added optically active acetonide **50**[34] (26.0 g, 90.91 mmol) and the resulting mixture was stirred at 100 °C for 48 h under N_2. The solvent was concentrated to one-half volume, brine

(100 mL) was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with 2.5 N NaOH, dried, decolorized (charcoal), and concentrated to afford 19.68 g (86%) of **51** as an oil which was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 6.95 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 4.48 (m, 1 H, C*H*), 4.20–3.90 (m, 4 H, OCH_2, acetonide CH_2), 1.48 and 1.40 (2 s, 6 H, $(CH_3)_2$).

51 (19.60 g, 77.47 mmol) was added to a Parr vessel containing 5% Pd/C (1.90 g) and ethanol (200 mL) and the vessel was charged with H_2 (50 psi) for 6 h. The mixture was filtered through the Solka-Floc and the filtrate was concentrated to afford the crude aniline which was purified by HPLC (1:1 hexane/ethyl acetate) to yield 12.96 g (75%) as a pale oil: ^{1}H NMR ($CDCl_3$) δ 6.73 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 6.64 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 4.42 (m, 1 H, C*H*), 4.15–3.80 (m, 4 H, OCH_2 and acetonide-CH_2), 1.45 and 1.31 (2 s, 6 H, $(CH_3)_2$).

To the above aniline (13.00 g, 58.29 mmol) in dichloromethane (170 mL) at 0 °C was added pyridine (9.4 mL, 116.6 mmol) followed by methanesulfonyl chloride (5.41 mL, 69.96 mmol). The mixture was stirred at room temperature for 3 h and was then partitioned between aqueous 10% $NaHCO_3$/ethyl acetate. The organic phase was washed with brine, dried, decolorized (charcoal), and concentrated to afford a residue. Recrystallization from ethyl acetate/hexane afforded 14.61 g (83%) of the corresponding methanesulfonate as a tan solid: ^{1}H NMR ($CDCl_3$) δ 7.23 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 6.93 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 6.72 (br s, 1 H, $NHSO_2CH_3$), 4.45 (m, 1 H, C*H*), 4.20–3.80 (m, 4 H, OCH_2 and acetonide CH_2), 2.96 (s, 3 H, $NHSO_2CH_3$), 1.47 and 1.41 (2 s, 6 H, $(CH_3)_2$).

The above acetonide (14.56 g, 48.4 mmol) was stirred in 90% acetic acid/water (150 mL) for 1 h at 100 °C. The mixture was cooled and concentrated to afford a residue which was triturated with ethyl acetate/ether to give 11.50 g (91%) of deprotected diol which was used directly in the next step: ^{1}H NMR (DMSO-d_6) δ 9.30 (s, 1 H, $NHSO_2CH_3$), 7.15 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 6.90 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 4.70 (br s, 2 H, OH), 4.00–3.60 (m, 3 H, OCH_2CHOH), 3.40 (m, 2 H, $CHOHCH_2OH$), 2.87 (s, 3 H, $NHSO_2CH_3$).

The above diol (10.99 g, 42.11 mmol) was dissolved in pyridine (160 mL) at 0 °C under N_2 and to it was added *p*-toluenesulfonyl chloride (7.88 g, 41.27 mmol). The mixture was stirred at room temperature overnight, diluted with ethyl acetate (200 mL), and washed with 1.0 N HCl (1.5 L). The organic phase was dried, decolorized (charcoal), and concentrated to afford 13.58 g (78%) of the primary monotosylate as an oil which was used directly in the next step: ^{1}H NMR (DMSO-d_6) δ 7.76 (d, *J* = 7.8 Hz, 2 H, Ar*H*), 7.30 (d, *J* = 9 Hz, 2 H, Ar*H*), 7.15 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 6.80 (d, *J* = 9.3 Hz, 2 H, Ar*H*), 4.25–3.85 (m, 5 H, $OCH_2CHOHCH_2OSO_2$), 2.93 (s, 3 H, $NHSO_2CH_3$), 2.40 (s, 3 H, $ArCH_3$).

The above tosylate (13.40 g, 32.29 mmol) was refluxed in toluene (200 mL) containing 2-[(methylamino)methyl]quinoline (8.89 g, 51.66 mmol) overnight under N_2. The mixture was partitioned between aqueous 10% $NaHCO_3$ and 4:1 dichloromethane/2-propanol. The organic phase was dried and concentrated to afford crude product which was purified by HPLC (10% methanol/dichloromethane) to yield 6.0 g (45%) of **14** which was identical to that obtained from method A.

1-(4-Nitrophenoxy)-3-iodopropane (34). To a stirring solution of 4-nitrophenol (10.0 g, 71.94 mmol) in tetrahydrofuran (100 mL) at 0 °C was added triphenylphosphine (22.6 g, 86.33 mmol), 3-iodopropanol (16.73 g, 89.93 mmol), and diethyl azodicarboxylate (14.3 mL, 86.33 mmol). The resulting mixture was stirred at 25 °C overnight. The mixture was partitioned between brine and ethyl acetate. The organic phase was dried and concentrated. The residue was triturated with 8:1 ether/ethyl acetate to induce the precipitation of 22 g of triphenylphosphine oxide which was separated by filtration. The filtate was preabsorbed onto silica gel and flash chromatographed (5:1 hexane/ethyl acetate) to afford 17.5 g (79%) of white solid: mp 68–73 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.96 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 4.15 (t, *J* = 5.8 Hz, 2 H, OCH_2), 3.37 (t, *J* = 7.0 Hz, 2 H, CH_2I), 2.31 (m, 2 H, $CH_2CH_2CH_2I$).

2-[[*N*-[3-(4-Nitrophenoxy)propyl]methylamino]methyl]quinoxaline (45). To a stirred suspension of 2-[(methylamino)methyl]quinoxaline (**43**, 1.10 g, 6.35 mmol) and K_2CO_3 (0.88 g, 6.35 mmol) in 2:1 acetonitrile/ethanol (40 mL) was added iodide **34** (1.95 g, 6.35 mmol). The resulting mixture was heated at 85 °C overnight, concentrated, and partitioned between ethyl acetate and 10% aqueous K_2CO_3. The organic phase was dried, decolorized (charcoal), and concentrated to afford 1.86 g (83%) of **45** as a yellow semisolid which was of sufficient purity to use in the next step: ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 1 H, Ar*H*), 8.10 (d, *J* = 9.4 Hz, 2 H, Ar*H*), 8.0 (m, 2 H, Ar*H*), 7.72 (m, 2 H, Ar*H*), 6.76 (d, *J* = 9.8 Hz, 2 H, Ar*H*), 4.09 (t, *J* = 5.4 Hz, 2 H, OCH_2), 2.67 (t, *J* = 5.2 Hz, 2 H, CH_2N), 2.41 (s, 3 H, CH_3N), 2.05 (m, 2 H, $OCH_2CH_2CH_2N$).

***N*-[4-[3-[Methyl(2-quinoxalinylmethyl)amino]propoxy]phenyl]methanesulfonamide Hydrochloride (8).** A mixture of **45** (1.75 g, 4.97 mmol) and PtO_2 (0.14 g, 0.62 mmol) in ethanol (170 mL) was charged with H_2 (1 atm). After 30 min the mixture was filtered through Solka-Floc and concentrated to afford crude amine which was purified by HPLC (1:5 hexane/ethyl acetate) to yield 1.18 g (74%) of amine as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1 H, Ar*H*), 8.07 (m, 2 H, Ar*H*), 7.73 (m, 2 H, Ar*H*), 6.70 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.02 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 3.95 (t, *J* = 6 Hz, 2 H, OCH_2), 3.89 (s, 2 H, NCH_2-heterocycle), 3.40 (br s, 2 H, NH_2), 2.68 (t, *J* = 6.6 Hz, 2 H, CH_2N), 2.33 (s, 3 H, NCH_3), 1.99 (m, 2 H, $OCH_2CH_2CH_2N$).

The above amine (0.93 g, 2.89 mmol) was mesylated with methanesulfonyl chloride/pyridine in dichloromethane as in compound **13** to afford 0.93 g (80%) of **8** as a yellow oil (one spot by TLC). The compound was treated with ethanolic HCl/ether to afford 0.75 g of the hydrochloride salt as a grey powder: mp 165–170 °C; ^{1}H NMR (DMSO-d_6) δ 9.42 (s, 1 H, $NHSO_2CH_3$), 9.20 (s, 1 H, Ar*H*), 8.16 (m, 2 H, Ar*H*), 7.95 (m, 2 H, Ar*H*), 7.14 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 6.87 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 4.84 (m, 2 H, NCH_2-heterocycle), 4.05 (t, *J* = 6 Hz, 2 H, OCH_2), 3.40 (m, 2 H, $OCH_2CH_2CH_2N$), 2.93 (s, 3 H, NCH_3), 2.87 (s, 3 H, $NHSO_2CH_3$), 2.26 (m, 2 H, $OCH_2CH_2CH_2N$); IR (KBr) 3400, 3020, 2900, 2500 cm^{-1}; MS *m/z* 400 (M^+, 5), 257 (80), 144 (100). Anal. ($C_{20}H_{24}N_4O_3S{\cdot}HCl$) C, H, N.

2-[[*N*-[3-(4-Nitrophenoxy)propyl]methylamino]methyl]quinoline (44). To a stirred suspension of 2-[(methylamino)methyl]quinoline (3.67 g, 21.35 mmol), NaI (2.78 g, 18.56 mmol), and K_2CO_3 (3.08 g, 138.21 mmol) in acetonitrile (80 mL) was added 1-(4-nitrophenoxy)-3-chloropropane (4.00 g, 18.56 mmol). The mixture was stirred at 80 °C overnight, concentrated, and partitioned between aqueous 10% K_2CO_3 and ethyl acetate. The organic phase was washed with brine, dried, and concentrated to afford an oil. The product was purified by HPLC (10% methanol/dichloromethane) to afford 2.34 g (36%) of **44** as an oil: ^{1}H NMR ($CDCl_3$) δ 8.2–7.9 (m, 4 H, Ar*H*), 7.7 (m, 2 H, Ar*H*), 7.5 (d, *J* = 6 Hz, 2 H, Ar*H*), 6.8 (d, *J* = 6.2 Hz, 2 H, Ar*H*), 4.1 (t, *J* = 4.8 Hz, 2 H, OCH_2), 3.8 (s, 2 H, NCH_2-heterocycle), 2.62 (t, *J* = 4 Hz, 2 H, CH_2N), 2.35 (s, 3 H, NCH_3), 2.0 (m, 2 H, $OCH_2CH_2CH_2N$).

***N*-[4-[3-[Methyl(2-quinolinylmethyl)amino]propoxy]phenyl]methanesulfonamide (15).** A mixture of **44** (1.97 g, 5.61 mmol) and 5% Pd/C (0.197 g) in ethyl acetate (40 mL) in a Parr reactor was charged with H_2 (50 psi) and left overnight. The mixture was then filtered through Solka-Floc and concentrated to afford 1.86 g (100%) of amine which was used directly in the next step. ^{1}H NMR ($CDCl_3$) δ 8.1 (m, 2 H, Ar*H*), 7.8–7.4 (m, 4 H, Ar*H*), 6.70 (m, 4 H, Ar*H*), 3.95 (t, *J* = 4.8 Hz, 2 H, OCH_2), 3.84 (s, 2 H, NCH_2-Heterocycle), 3.38 (br s, 2 H, NH_2), 2.64 (t, *J* = 4.8 Hz, 2 H, CH_2N), 2.31 (s, 3 H, NCH_3), 1.97 (m, 2 H, $OCH_2CH_2CH_2N$).

The above amine (1.43 g, 4.45 mmol) was mesylated as in compound **28** to afford the crude product which was converted to a dihydrochloride salt by treatment with ethanolic HCl to yield 0.70 g (33%) of **15** as an off-white solid: mp 187–192 °C; ^{1}H NMR (DMSO-d_6) δ 9.44 (br s, 1 H, $NHSO_2CH_3$), 8.52 (d, *J* = 8.51 Hz, 1 H, Ar*H*), 8.05 (m, 2 H, Ar*H*), 7.83 (m, 2 H, Ar*H*), 7.69 (m, 1 H, Ar*H*), 7.13 (d, *J* = 8.92 Hz, 2 H, Ar*H*), 6.85 (d, *J* = 9.13 Hz, 2 H, Ar*H*), 5.30 (br s, 2 H, +N*H*), 4.73 (s, 2 H, NCH_2-heterocycle), 4.04 (t, *J* = 6.02 Hz, 2 H, OCH_2), 3.37 (m, 2 H, CH_2N), 2.91 (s, 3 H, NCH_3), 2.87 (s, 3 H, $NHSO_2CH_3$), 2.27 (m, $OCH_2CH_2CH_2N$); IR (KBr) 3400, 3040, 2500, 1960 cm^{-1}; MS *m/z* 400 (MH^+, 100), 143 (42), 79 (51). Anal. ($C_{21}H_{25}N_3O_3S{\cdot}2HCl$) C, H, N.

***N*-[3-(4-Nitrophenoxy)propyl]methylamine Hydrochloride (35).** Iodide **34** (4.76 g, 15.50 mmol) was added por-

tionwise to a stirring solution of methylamine (33%) in ethanol (100 mL) at 0 °C. The mixture stirred at room temperature for 4 h and was then concentrated. The residue was partitioned between ethyl acetate and aqueous 10% K_2CO_3. The organic phase was dried, decolorized, and concentrated to afford an oil which was treated with ethanolic HCl to yield 2.5 g of hydrochloride salt which was used without purification: mp 135–137 °C; ^{1}H NMR (DMSO-d_6) δ 9.15 (br s, 2 H, +NH_2), 8.20 (d, J = 9.0 Hz, 2 H, ArH), 7.15 (d, J = 9 Hz, 2 H, ArH), 4.20 (t, J = 7.2 Hz, 2 H, OCH_2), 3.00 (m, 2 H, CH_2N), 2.51 (s, 3 H, NCH_3), 2.15 (m, 2 H, $OCH_2CH_2CH_2N$).

***N*-Methyl-6-nitro-*N*-[(4-nitrophenoxy)propyl]-2-quinolinemethanamine (46).** Amine **35** (3.08 g, 12.49 mmol), chloride **39a** (2.78 g, 12.49 mmol), and K_2CO_3 (3.45 g, 25.0 mmol) were stirred in 2:1 acetonitrile/ethanol (120 mL) at reflux for 18 h. The mixture was concentrated and the residue was partitioned between 10% aqueous K_2CO_3 and 4:1 dichloromethane/2-propanol. The organic phase was dried, decolorized (charcoal), and concentrated to afford crude product which was purified by column chromatography (1:2 hexane/ethyl acetate) to yield 2.63 g (53%) of **46** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.70 (d, J = 2.4 Hz, 1 H, ArH), 8.43 (dd, J_1 = 9.8 Hz, J_2 = 2.4 Hz, 1 H, ArH), 8.15 (m, 3 H, ArH), 7.70 (d, J = 9.0 Hz, 1 H, ArH), 6.92 (m, 3 H, ArH), 4.12 (t, J = 6.6 Hz, 2 H, OCH_2), 3.85 (s, 2 H, NCH_2-heterocycle), 2.64 (t, J = 6.6 Hz, 2 H, CH_2N), 2.36 (s, 3 H, NCH_3), 2.02 (m, 2 H, $OCH_2CH_2CH_2N$).

***N*-[2-[[Methyl[3-[4-[(methylsulfonyl)amino]phenoxy]propyl]amino]methyl]-6-quinolinyl]methanesulfonamide (24).** Dinitro derivative **46** (2.60 g, 6.57 mmol) was dissolved in ethanol (170 mL) containing PtO_2 (0.39 g). The mixture was charged with H_2 (1 atm), stirred for 4 h, and filtered through a pad of Solka-Floc. The filtrate was concentrated to afford 2.18 g (99%) of the diamino compound as a yellow oil that was used directly without purification: ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2 H, ArH), 7.45 (d, J = 7.8 Hz, 1 H, ArH), 7.12 (dd, J_1 = 7.6 Hz, J_2 = 2.4 Hz, 1 H, ArH), 6.87 (d, J = 2.4 Hz, 1 H, ArH), 6.70 (m, 4 H, ArH), 3.95 (t, J = 6.6 Hz, 2 H, OCH_2), 3.75 (s, 2 H, NCH_2-heterocycle), 2.60 (t, J = 7.0 Hz, 2 H, CH_2N), 2.30 (s, 3 H, NCH_3), 1.95 (m, 2 H, $OCH_2CH_2CH_2N$).

Methanesulfonyl chloride (2.55 mL, 32.96 mmol) was added dropwise to a stirred solution of the above diamine (4.05 g, 12.05 mmol) in pyridine (100 mL) at 0 °C under N_2. The resulting mixture was stirred at room temperature for 6 h, diluted with ice water containing $NaHCO_3$, and extracted with 4:1 dichloromethane/2-propanol. The organic phase was dried, decolorized (charcoal), and concentrated to give crude product that was purified by HPLC (10% dichloromethane/methanol) to yield 3.80 g (64%) of **24** as a white solid: mp 143–147 °C; ^{1}H NMR (DMSO-d_6) δ 10.20 and 9.32 (2 br s, 2 H, $NHSO_2CH_3$), 8.17 (d, J = 8.51 Hz, 1 H, ArH), 7.92 (d, J = 8.92 Hz, 1 H, ArH), 7.67 (d, J = 2.49 Hz, 1 H, ArH), 7.55 (m, 2 H, ArH), 7.12 (d, J = 8.92 Hz, 2 H, ArH), 6.85 (d, J = 9.13 Hz, 2 H, ArH), 3.99 (t, J = 6.43 Hz, 2 H, OCH_2), 3.74 (s, 2 H, NCH_2-heterocycle), 3.07 and 2.87 (2 s, 6 H, $NHSO_2CH_3$), 2.55 (m, 2 H, CH_2N), 2.21 (s, 3 H, NCH_3), 1.91 (m, 2 H, $OCH_2CH_2CH_2N$); IR (KBr) 3420, 3240, 2920 cm^{-1}; MS m/z 493 (MH^+, 10), 259 (100), 237 (46), 188 (29). Anal. ($C_{22}H_{28}N_4O_5S_2$) C, H, N.

***N*-[3-(4-Nitrophenoxy)propyl]cyclopentylamine Hydrochloride (36).** 1-(4-Nitrophenoxy)-3-chloropropane (6.0 g, 28.0 mmol) was added portionwise to a stirred solution of cyclopentylamine (13.8 mL, 140 mmol) in 2:1 acetonitrile/ethanol (120 mL) containing K_2CO_3 (7.5 g, 57 mmol) and NaI (0.21 g, 1.4 mmol). The mixture was stirred at 60 °C for 24 h and then concentrated to afford a residue which was partitioned between ethyl acetate/10% aqueous K_2CO_3. The organic phase was dried, decolorized (charcoal), and concentrated to afford an oil which was converted to the hydrochloride (5.31 g, 63%) and used directly in the next step: mp 195–197 °C; ^{1}H NMR (DMSO-d_6) δ 9.20 (br s, 2 H, +NH), 8.20 (d, J = 7.8 Hz, 2 H, ArH), 7.14 (d, J = 7.8 Hz, 2 H, ArH), 4.23 (t, J = 6.2 Hz, 2 H, OCH_2), 3.43 (m, 1 H, NCH), 3.05 (t, J = 6.4 Hz, 2 H, CH_2N), 2.18 (m, 2 H, $OCH_2CH_2CH_2N$), 2.00–1.40 (m, 8 H, cyclopentyl CH_2).

***N*-Cyclopentyl-6-nitro-*N*-[(4-nitrophenoxy)propyl]-2-quinolinemethanamine (47).** Amine **36** (1.30 g, 4.3 mmol), chloride **39a** (0.90 g, 4.1 mmol), K_2CO_3 (1.22 g, 8.8 mmol), and NaI (0.12 g, 0.8 mmol) were stirred in 2:1 acetonitrile/ethanol (100 mL) at 60 °C for 24 h. The mixture was worked up exactly as for compound **46** to yield 1.2 g (62%) of **47** as a brown solid: mp 100–102 °C; ^{1}H NMR (DMSO-d_6) δ 8.87 (d, J = 2.4 Hz, 1 H, ArH), 8.48 (d, J = 8.4 Hz, 1 H, ArH), 8.37 (dd, J_1 = 2.7 Hz, J_2 = 9.3 Hz, 1 H, ArH), 8.10 (d, J = 9.0 Hz, 1 H, ArH), 8.00 (d, J = 9.1 Hz, 2 H, ArH), 7.76 (d, J = 8.4 Hz, 1 H, ArH), 6.85 (d, J = 9.3 Hz, 2 H, ArH), 3.99 (t, J = 6.0 Hz, 2 H, OCH_2), 3.88 (s, 2 H, NCH_2-heterocycle), 3.18 (m, 1 H, NCH), 2.68 (t, J = 6.0 Hz, 2 H, CH_2N), 1.85–1.40 (m, 10 H, $OCH_2CH_2CH_2N$ and cyclopentyl CH_2).

***N*-[2-[[Cyclopentyl[3-[4-[(methylsulfonyl)amino]phenoxy]propyl]amino]methyl]-6-quinolinyl]methanesulfonamide Dihydrochloride (25).** Dinitro derivative **47** (1.18 g, 2.60 mmol) was dissolved in 2:1 ethanol/ethyl acetate (48 mL) containing PtO_2 (0.17 g). The mixture was charged with H_2 (1 atm), stirred for 3 h, and filtered through a pad of Solka-Floc. The filtrate was concentrated to afford crude product which was purified by radial chromatography (10% methanol/dichloromethane) to yield 0.50 g (49%) of diamine as a yellow oil: ^{1}H NMR (DMSO-d_6) δ 7.85 (d, J = 6.0 Hz, 1 H, ArH), 7.64 (d, J = 6.0 Hz, 1 H, ArH), 7.40 (d, J = 6.0 Hz, 1 H, ArH), 7.13 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1 H, ArH), 6.78 (d, J = 1.2 Hz, 1 H, ArH), 6.55 (d, J = 7.2 Hz, 2 H, ArH), 6.48 (d, J = 7.2 Hz, 2 H, ArH), 5.45 and 4.70 (2 br s, 4 H, NH_2), 3.78 (m, 4 H, OCH_2 and NCH_2-heterocycle), 3.10 (m, 1 H, CHN), 2.63 (m, 2 H, CH_2N), 1.80–1.25 (m, 10 H, $OCH_2CH_2CH_3N$ and cyclopentyl CH_2).

Methanesulfonyl chloride (0.28 mL, 3.60 mmol) was added dropwise to a stirred solution of the above diamine (0.50 g, 1.28 mmol) in pyridine (12 mL) at 0 °C under N_2. The reaction was worked up with the method described for **24** to afford an oil which was converted to 0.30 g (42%) of dihydrochloride: mp 170–175 °C; ^{1}H NMR (DMSO-d_6) δ 10.31 and 9.38 (2 s, 2 H, $NHSO_2CH_3$), 8.43 (d, J = 8.30 Hz, 1 H, ArH), 8.00 (d, J = 9.13 Hz, 1 H, ArH), 7.78 (d, J = 2.08 Hz, 1 H, ArH), 7.74 (d, J = 8.72 Hz, 1 H, ArH), 7.65 (m, 1 H, ArH), 7.11 (d, J = 8.72 Hz, 2 H, ArH), 6.76 (d, J = 8.72 Hz, 2 H, ArH), 3.96 (t, J = 5.81 Hz, 2 H, OCH_2), 3.87 (m, 1 H, CHN), 3.60–3.20 (m, 2 H, NCH_2-heterocycle and H_2O), 3.12 and 2.86 (2 s, 6 H, $NHSO_2CH_3$), 2.25–1.50 (m, 10 H, $OCH_2CH_2CH_2N$ and cyclopentyl CH_2); IR (KBr) 3410 cm^{-1}; MS m/z 547 (MH^+, 22), 307 (19), 154 (100), 136 (80). Anal. ($C_{26}H_{34}N_4O_5S_2 \cdot 2HCl \cdot 3H_2O$) C, H, N.

In Vitro Pharmacology: A. Intracellular Voltage Recordings. The methods employed have been described.[41] Briefly, Purkinje fiber bundles were harvested from mongrel dogs anesthetized with pentobarbital. The fibers were superfused at 37.5–38.0 °C with Tyrode's solution containing (in mM): 138 NaCl, 4 KCl, 2 $CaCl_2$, 24 $NaHCO_3$, 0.5 $MgCl_2$, 1.8 $NaHPO_4$, 5.5 dextrose. The Tyrode's solution was equilibrated with 95% O_2–5% CO_2; the pH was 7.3–7.4. The fiber bundles were stimulated with square wave current pulses 2.0 ms in duration and at 2 times threshold. The preparations were allowed to equilibrate at least 1 h or until the action potential parameters had reached steady-state before initiating drug superfusion. In each fiber, action potentials were recorded from four to six sites during control and after drug. The action potential parameters were then averaged to provide mean values for the experimental intervention in each fiber. Because action potential parameters can vary significantly in different locations of the fiber bundle, all impalements were made in the same location to minimize variability. When the same impalement was maintained throughout the experiment the results were identical to those obtained from multiple impalements. Each compound was superfused for 45–60 min before the measurements of the action potential were taken; this time interval was sufficient to reach steady state of effects with each concentration of compound.

B. Voltage-Clamp Experiments. Single ventricular myocytes were isolated from cat hearts by enzymatic disaggregation.[42] Ionic

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currents were measured under voltage-clamp conditions using the "perforated-patch" technique.[43] In brief, fire-polished microelectrodes were filled with the following solution (in mM): 120 potassium aspartate, 20 KCl, 5 NaCl, 5 Hepes, 1 $MgCl_2$, 0.05 EGTA. The pH was adjusted to 7.4 with KOH. Nystatin, previously dissolved in dimethyl sulfoxide (5 mg in 0.1 mL DMSO), was diluted in the electrode-filling solution to a final concentration of 100 μg/mL. A few minutes after the formation of a high-resistance seal between the microelectrode and the cell membrane, nystatin forms small pores which allow the passage of small monovalent ions but prevent the movement of larger molecules. Thus, the nystatin-produced pores allow electrical continuity between the cell cytoplasm and the inside of the patch microelectrode while reducing the dialysis of the cytoplasmic constituents. For studies of K^+ currents, the cells were superfused with standard Tyrode's solution (same composition as the solution used for voltage recordings in Purkinje fibers) containing nisoldipine (300 nM) to block the Ca^{2+} current ($I_{Ca\text{-}L}$). For studies of $I_{Ca\text{-}L}$, the external Tyrode's solution contained CsCl (2 mM); for these studies the internal solution had the following composition (in mM): 20 CsCl, 120 Cs_2SO_4, 5 NaCl, 1 $MgCl_2$, 0.05 EGTA, 5 Hepes. The pH was adjusted with CsOH to 7.4. Cs was added to the external solution and substituted for K in the internal solution to block K^+ currents. All studies were conducted at 36–37 °C using myocytes that were quiescent, rod-shaped, free of blebs, and with clear regular striations.

C. β-Adrenergic Antagonism Studies. Adult mongrel cats weighing between 1.6 and 2.5 kg were anesthetized with pentobarbital. The left atria were mounted in tissue baths and superfused with Krebs–Henseleit solution of the following composition (in mM): 118 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 1.2 KH_2PO_4, 1.2 $MgSO_4 \cdot 7H_2O$, 20 $NaHCO_3$, 11 glucose. The solution was equilibrated with 95% O_2–5% CO_2 (pH = 7.4, T = 32–34 °C).

The lower atrium was fixed to the tissue bath while the atrial appendage was connected to a force-displacement transducer. The tissues were paced at BCL = 330 ms using square wave current pulses 2 ms in duration and 1.5 times threshold intensity. Basal tension was set at about 200 mg after establishing a force–tension relationship for each preparation. After a stabilization period lasting about 1 h, concentrations of isoproterenol were introduced in a cumulative fashion every 5–10 min. After establishing a concentration–response relationship for isoproterenol, the tissue was superfused with drug-free Tyrode's solution until contractility returned to predrug levels. The concentration–response study was then repeated in the presence of the compound under study. The stability of the preparation was examined in previous preliminary experiments: following the stabilization period, untreated preparations showed a modest decrease of developed tension (−17 ± 4%: n = 5) over a 2-h period. Thus, the preparation used in these studies was stable over the duration of the experiment.

In Vivo Pharmacology. The method used to measure atrial and ventricular refractoriness has been already reported.[44] Briefly, mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg iv supplemented with 5 mg/kg per h). Epicardial electrodes were sutured on the free wall of the lower right atrium and near the base of the right ventricle. Each electrode set contained a linear array of electrodes consisting of one bipolar stimulating electrode and two bipolar recording electrodes embedded in a rigid acrylic matrix. Each electrode array was oriented to be parallel to the epicardial fiber axis. Atrial and ventricular refractory periods (AERP and VERP) were determined by introducing an extrastimulus (S_2) every eight paced beats (S_1) at BCL = 300 ms. Both S_1 and S_2 were of identical duration (2 ms) and intensity (twice threshold). The S_1–S_2 interval was gradually decreased until the extrastimulus failed to induce a propagated response. This interval was considered to define the effective refractory period. Atrial and ventricular conduction times (ACT and VCT) were measured as the time interval between the two electrograms recorded at the proximal and distal sites of the recording electrode array.

Ventricular fibrillation threshold (VFT) was studied in a surgical preparation similar to the one used to measure refractoriness. Ventricular fibrillation was induced via a ventricular bipolar electrode during atrial pacing (BCL = 300 ms). Trains of square wave current pulses (pulse duration: 4 ms) lasting 200 ms with a pulse frequency of 50 Hz were delivered to the right ventricle every 12 paced beats. The beginning of the train of pulses was timed to initiate ca. 50 ms after the peak of the R wave of the electrocardiogram. The smallest current intensity producing sustained ventricular fibrillation was defined as VFT. When VF was induced, the heart was promptly defibrillated by a capacitor-discharge direct-current defibrillator. Control studies show that 15–30 min after an episode of VF followed by prompt cardioversion, arterial pressure and ECG parameters recover to control values. Drug was administered 30 min after the control VFT determination by iv injection. A first determination of VFT was performed 15 min after the end of dosing and the dog was promptly defibrillated. As soon as arterial pressure and ECG parameters had recovered, a second VFT determination was performed. This time, defibrillation was withheld in order to observe an eventual drug-induced cardioversion.

Effective refractory periods in the conscious dog were measured using the same methods as in the anesthetized dogs. Under pentobarbital anesthesia and using sterile techniques, bipolar electrodes were sutured to the ventricular epicardium to measure refractoriness; two more electrodes used to record the ECG were implanted subcutaneously. A catheter was implanted in the superior vena cava by advancing it through the azygos vein; the leads from the electrodes and the catheter were exteriorized in the interscapular area. The dogs were studied 2 weeks after surgery while resting unsedated in a sling.

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