Synthesis and Biological Studies of Novel 2-Aminoalkylethers as Potential Antiarrhythmic Agents for the Conversion of Atrial Fibrillation

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A series of 2-aminoalkylethers prepared as potential antiarrhythmic agents is described. The present compounds are mixed sodium and potassium ion channel blockers and exhibit antiarrhythmic activity in a rat model of ischemia-induced arrhythmias. Structure−activity studies led to the identification of three compounds **5**, **18**, and **26**, which were selected based on their particular in vivo electrophysiological properties, for studies in two canine atrial fibrillation (AF) models. The three compounds converted AF in both models, but only compound **26** was shown to be orally bioavailable. Resolution of the racemate **26** into its corresponding enantiomers **40** and **41** and subsequent biological testing of these enantiomers led to the selection of (1*S*,2*S*)-1-(1-naphthalenethoxy)-2-(3-ketopyrrolidinyl)cyclohexane monohydrochloride (**41**) as a potential atrial selective antiarrhythmic candidate for further development.

Atrial fibrillation (AF) is the most prevalent survivable arrhythmia in the Western world, with an incidence that increases significantly with age. Recent estimates, suggest that AF affects about 6% of individuals over age 65, and about 10% of those over the age of 80.[1] While AF is rarely fatal, it can impair cardiac function and is a major cause of stroke.[2,3]

Class Ia, Ic, and III antiarrhythmic drugs have been used to convert AF to sinus rhythm and prevent recurrence of the arrhythmia.[4] However, drug therapy is often limited by the adverse effects of these drugs, including the possibility of increased mortality and inadequate efficacy.[5−8] Conversion rates for Class I antiarrhythmics range between 50 and 90%.[4,9,10] Class III antiarrhythmics, more effective for terminating atrial flutter (FL) than AF, are generally regarded as less effective than Class I drugs for terminating AF.[4,10] Examples of Class III antiarrhythmic drugs include ibutilide, dofetilide, and sotalol. Conversion rates for these drugs range between 30 and 50% for the recent onset of AF,[10,11] but they are also associated with a risk of inducing the potentially fatal ventricular tachyarrhythmia commonly called Torsades de Pointes. For ibutilide, the risk of this ventricular arrhythmia is estimated at ∼4.4%, with ∼1.7% of patients requiring cardioversion for refractory ventricular arrhythmias.[12] Such events are particularly tragic in the case of AF, as this arrhythmia is rarely fatal in itself.

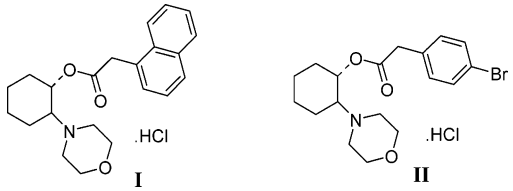

Figure 1. Structures of (1*R*,2*R*)/(1*S*,2*S*)-(2-morpholinyl)-1-cyclohexyl 1-naphthylacetate monohydrochloride (**I**) and (1*R*,2*R*)/(1*S*,2*S*)-(2-morpholinyl)-1-cyclohexyl 4-bromophenylacetate monohydrochloride (**II**).

The recent description of the ultra-rapid delayed rectifier potassium current (I_{Kur}) in animals[13] and man[14,15] hints that it may be possible to separate the pro- and antiarrhythmic actions of these drugs. I_{Kur} is abundant in the atria, but scarce in the ventricle. In addition, the transient outward current (I_{to1}) is an important current for repolarisation in the atria.[16,17] Blockade of currents that are predominantly found in the atria might prolong atrial action potentials without substantially influencing ventricular action potentials. A profile such as this might be effective for AF therapy, without the proarrhythmic risk associated with prolongation of ventricular action potentials.

Originally focused on ischemia-selective ventricular antiarrhythmics, our laboratory has developed a number of in vivo models of acute ischemia capable of detecting antiarrhythmic activity with sufficient precision and accuracy to serve as useful bioassays.[18] These models have been characterized using reference antiarrhythmic agents. As a result, we have chosen coronary occlusion in anaesthetized rats as a primary screen. The applicability of such a model for the screening of AF agents is based on the dependence of the rat ventricular action potential on early potassium currents (I_{to}, I_{Kur}) for repolarization, as in human atria. However, the efficacy of antiarrhythmic compounds in rat models have to be corroborated in a large animal experimental model of AF. AF has been produced in a number of different models by interventions that either induce atrial stretch (e.g., secondary to heart failure), heterogeneous atrial refractoriness (e.g., vagal stimulation), or other changes in electrophysiological substrate (e.g., pericarditis and rapid pacing). I_{to1}, I_{to2}, and both components of I_K are present in dog atrium, and the properties of two important repolarizing currents

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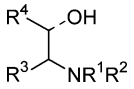
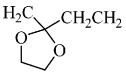
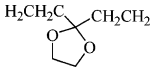
Table 1. Aminoalcohols **2**



cmpd	R^1	R^2	R^3	R^4	yield, %	^{13}C NMR ($CDCl_3$, ppm, APT)
2a[a]	$CH_2CH_2OCH_2CH_2$			$CH_2CH_2CH_2CH_2$	92	70.5 (−), 68.3 (−), 67.4 (+), 48.7 (+), 33.1 (+), 25.4 (+), 23.9 (+), 22.1 (+)
2b	$CH_2CH_2CH_2CH_2$			$CH_2CH_2CH_2CH_2$	87	70.4 (−), 64.8 (−), 47.4 (+), 33.1 (+), 25.1 (+), 24.2 (+), 24.0 (+), 21.1 (+)
2c	$CH_2CH_2OCH_2CH_2$			$CH_2CH_2CH_2$	70	75.0 (−), 74.5 (−), 67.5 (+), 52.5 (+), 35.5 (+), 28.5 (+), 21.5 (+)
2d	$CH_2CH_2OCH_3$	$CH_2CH_2OCH_3$		$CH_2CH_2CH_2CH_2$	77	72.0 (+), 69.5 (−), 67.8 (−), 58.7 (−), 50.0 (+), 33.0 (+), 25.5 (+), 24.2 (+), 23.3 (+)
2e[a]				$CH_2CH_2CH_2CH_2$	79	115.5 (+), 70.0 (−), 65.0 (−), 64.5 (+), 57.0 (+), 46.5 (+), 36.0 (+), 33.5 (+), 25.0 (+), 24.0 (+), 21.5 (+)
2f	$CH_2CH_2N(COCH_3)CH_2CH_2$			$CH_2CH_2CH_2CH_2$	87	168.5 (+), 70.0 (−), 68.2 (−), 48.3 (+), 47.7 (+), 46.5 (+), 41.6 (+), 32.9 (+), 25.1 (+), 23.6 (+), 22.0 (+), 21.0 (−)
2g				$CH_2CH_2CH_2CH_2$	90	107.0 (+), 70.0 (−), 69.0 (−), 64.0 (+), 46.0 (+), 36.0 (+), 33.0 (+), 26.0 (+), 24.0 (+), 22.0 (+)
2h[a]	$CH_2CH_2N(Boc)CH_2CH_2$			$CH_2CH_2CH_2CH_2$	100	154.6 (−), 79.6 (−), 70.4 (+), 68.4 (+), 48.2 (−), 33.1 (−), 32.7 (−), 28.3 (+), 25.3 (−), 23.9 (−), 22.3 (−)
2i[a]	$CH_2CH_2OCH_2CH_2$		H	n-C_4H_9	90	66.5 (+), 65.6 (−), 64.5 (+), 53.3 (+), 34.2 (+), 27.3 (+), 22.4 (+), 13.6 (−)
2j[a]	$CH_2SCH_2CH_2$			$CH_2CH_2CH_2CH_2$	47	71.0 (−), 69.0 (−), 55.0 (+), 53.0 (+), 33.0 (+), 31.0 (+), 26.0 (+), 25.0 (+), 23.0 (+)

[a] See Experimental Section.

(I_{to1} and I_K) previously described in human atrium are similar to those in dog atrium.[19] The canine sterile pericarditis[20] and vagal AF[21] models were selected as surrogates for clinical efficacy in conversion of atrial fibrillation/flutter (AF/FL) in man.

We hypothesized that potency and selectivity for AF could be achieved through a greater potency for early repolarizing potassium channels ($IC_{50} \leq 2\ \mu M$ for I_{Kur} and I_{to}) than sodium channels at 1 Hz ($IC_{50} > 10\ \mu M$ for the block of I_{Na}). This activity profile might provide selectivity for AF, because the block of sodium channels would be targeted to the rapidly activating fibrillating tissue, and the effects on repolarization would be targeted to the atria, as discussed above.

From our original program of ischemia-selective ventricular antiarrhythmics, two compounds, **I** and **II** (Figure 1) were shown to have the right attributes for selectively suppressing ischemia-induced arrhythmias in several species.[18,22−24] However, these two compounds, sensitive to ester hydrolysis, would limit their use solely to acute i.v. treatment of arrhythmias. We then designed new compounds to have increased chemical and possibly metabolic stability, by replacing the ester linkage by an ether linkage but with improved electrophysiological attributes compared to **I** and **II** (Table 3). The antiarrhythmic actions of these novel 2-aminoalkylethers were compared with known antiarrhythmic drugs such as quinidine (Class Ia), lidocaine (Class Ib), flecainide (Class Ic), and amiodarone (Class III; Figure 2).[10]

Chemistry. From the aminoalcohols **2a**−**j** (Table 1) and alcohols **3a**−**w** (Table 2) were prepared the antiarrhythmic aminoethers **4**−**53** (Table 3) by using general methods **A**−**G** and specific experimental procedures provided below.

Method A. Williamson ether synthesis,[25] condensing an activated form of aminoalcohol **2a**−**d** and **2f** with the alkoxide of an alcohol **3** in a polar solvent such as DMF (Scheme 1) provided the corresponding aminoethers **4**−**17** and **19**−**25** in moderate to low yields (Table 3). The stereochemical outcome of the ether coupling could be rationalized by a mechanism involving a double S_N2 displacement and an aziridinium ion intermediate (Scheme 2). That is, the neighboring nitrogen would displace the mesylate to give an aziridinium ion, which is subsequently attacked by the incoming sodium alkoxide. The lack of discrimination between the two aziridine carbons for attack by the alkoxide affords an ∼1:1 mixture of stereoisomers having *trans*-geometry.

Method B. Aminoethers **18**, **30**, **32**, **39**, **42**, **51**, and **52** or ketals of compounds **26**−**28**, **34**, **35**, **37**, **38**, **43**−**45**, **48**, and **53** were obtained from reaction of the appropriate activated form of aminoalcohol (**2**) and the sodium salt of alcohol (**3**) in moderate to high yields (Scheme 3) in ethylene glycol dimethyl ether (DME) instead of dimethylformamide (DMF), as previously described (Method A). Compounds **26**−**28**, **34**, **35**, **37**, **38**, **43**−**45**, and **48** were obtained by deprotecting the corresponding ketals by treatment with 6 M HCl in 2-butanone (Scheme 3), whereas compound **53** was prepared by subjection of the *N*-Boc derivative to trifluoroacetic acid.

Method C. This method was used to prepare *cis*-cyclohexylaminoethers **31** and **33** and acyclic aminoether **29**. Successive Swern oxidation[26] of aminoalcohol **2a** and reduction ($NaBH_4$,

Table 2. Alcohols **3**

	$RCHR^5(CH_2)_nOH$				
cmpd	R	R^5	*n*	yield, %	^1H NMR ($CDCl_3$, ppm)
3a	2-naphthyl	H	1		
3b	1-naphthyl	H	1		
3c	4-bromophenyl	H	1		
3d	2-naphthoxy	H	1		
3e	4-bromophenoxy	H	1		
3f	3,4-dimethoxyphenyl	H	1		
3g[a]	3-benzo[*b*]thiophenyl	H	1	92	7.80−7.20 (m, 4H, Ar), 7.00 (s, 1H, Ar), 3.80 (t, 2H, CH_2O), 3.00 (t, 2H, CH_2), 2.20 (s, 1H, OH)
3h[b]	4-benzo[*b*]thiophenyl	H	1	64	7.80−7.00 (m, 5H, Ar), 3.80 (t, 2H, CH_2O), 3.00 (t, 2H, CH_2), 2.20 (s, 1H, OH)
3i	3-bromophenyl	H	1		
3j	2-bromophenyl	H	1		
3k	3,4-dimethoxyphenyl	H	2		
3l[c]	3,4-dichlorophenyl	H	1	81	7.40−7.00 (m, 3H, Ar), 3.80 (t, 2H, CH_2O), 2.80 (t, 2H, CH_2), 1.80 (br s, 1H, OH)
3m[a]	2,4-dimethoxyphenyl	H	2	73	7.40−6.40 (m, 3H, Ar), 3.80 (s, 6H, 2 × CH_3O), 3.60 (m, 2H, CH_2O), 2.70 (t, 2H, CH_2), 1.80 (m, 2H, CH_2), 1.20 (m, 1H, OH)
3n[b]	4-benzo[*b*]furanyl	H	1	38	7.60−6.80 (m, 5H, Ar), 3.90 (t, 2H, CH_2O), 3.10 (t, 2H, CH_2), 2.10 (br s, 1H, OH)
3o[a]	4-bromophenyl	H	2	83	7.40−6.80 (q, 4H, Ar), 3.60−3.30 (m, 2H, CH_2O), 2.50 (t, 2H, CH_2), 1.80 (qt, 2H, CH_2), 1.20 (t, 1H, OH)
3p[a]	3,4-dimethoxyphenyl	H	3	47	7.05−6.60 (m, 3H, Ar), 3.70 (s, 6H, 2 × CH_3O), 3.45 (m, 2H, CH_2O), 2.24 (t, 2H, CH_2), 2.20 (s, 1H, OH), 1.50 (m, 4H, CH_2)
3q	2,4-dichlorophenyl	H	1		
3r[a]	2,6-dichlorophenyl	H	1	97	7.40−7.00 (m, 3H, Ar), 3.80 (t, 2H, CH_2O), 3.20 (t, 2H, CH_2), 2.10 (br s, 1H, OH)
3s[c]	2,4-dibromophenyl	H	1	29	7.70−7.10 (m, 3H, Ar), 3.90 (t, 2H, CH_2), 3.00 (t, 2H, CH_2), 1.40 (t, 1H, OH)
3t	2-(trifluoromethyl)phenyl	H	1		
3u[a]	phenyl	phenyl	1	86	7.40−7.20 (m, 10H, Ar), 4.30−4.10 (m, 3H, $CHCH_2O$), 2.20 (br s, 1H, OH)
3v[b]	4-bromonaphth-1-yl	H	1	48	8.29−7.17 (m, 6H, Ar), 3.92 (t, 2H, CH_2O), 3.26 (t, 2H, CH_2), 1.77 (br, s 1H, OH)
3w	cyclohexyl	H	2		

[a] Obtained from reduction ($LiAlH_4$ or B_2H_6) of the corresponding carboxylic acid. [b] See Supporting Information. [c] See Experimental Section.

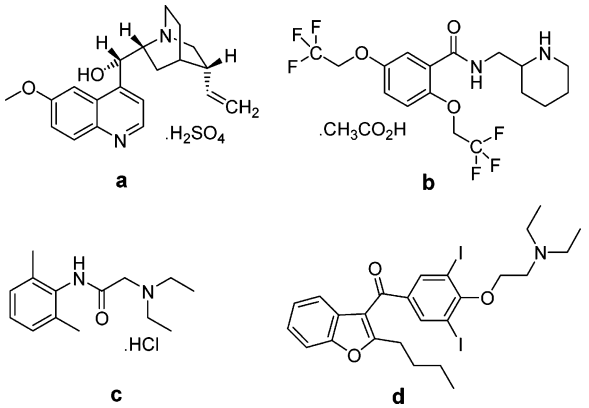


Figure 2. Structures of quinidine (**a**), flecainide (**b**), lidocaine (**c**), and amiodarone (**d**).

2-propanol) gave a *cis*/*trans*-mixture of 2-(4-morpholinyl)-cyclohexan-1-ol (Scheme 4). Subsequent esterification with a substituted phenylacetic acid mediated by *p*-TsOH·H_2O in toluene yielded a *cis*/*trans*-mixture of esters. The *cis*/*trans*-mixture was resolved by chromatography, and the *trans*-ester was identified by comparison with an authentic sample of the *trans*-ester obtained by direct esterification of **2a** with the same substituted phenylacetic acid.

Finally, compounds **31** and **33** were obtained by reduction ($NaBH_4$ and BF_3·Et_2O)[27] of the *cis*-ester precursor. Similarly, successive esterification of **2i** with 4-bromophenylacetic acid and reduction gave compound **29**.

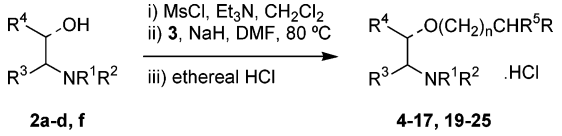
Method D. Cyclohexene oxide ring opening with **3b** in the presence of $Mg(ClO_4)_2$[28] followed by oxidation with pyridinium chlorochromate (PCC)[29] gave (2*R*/2*S*)-2-(1-naphthalenethoxy)-cyclohexan-1-one (Scheme 5). Subsequent enamine formation with **1e** in the presence of poly(4-vinylpyridine) (PVP) and hydrogenation on Pd/C yielded (1*R*,2*S*)/(1*S*,2*R*)-1-(1-naphthalenethoxy)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)cyclohexane as the major component. Identification of the minor *trans*-isomer was made by comparison with an authentic sample of the *trans*-isomer **32**. Successive purification of the *cis*-ketal by chromatography and treatment with 6 M HCl in 2-butanone gave aminoether **46**.

Method E. Reduction of compounds **26** and **28** with $NaBH_4$ in 2-propanol provided, respectively, compounds **50** and **47** (Scheme 3). Similarly, reduction of **46** gave aminoether **49** (Scheme 5).

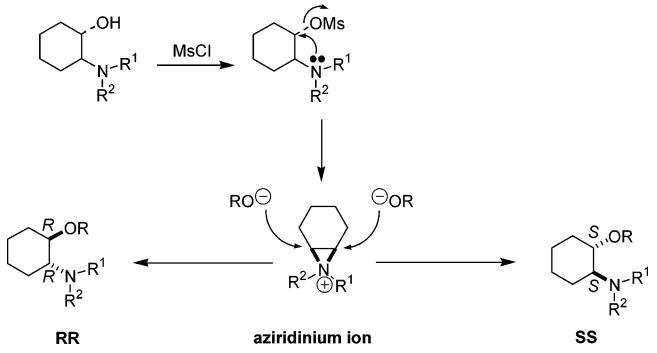
Method F. Successive reduction ($NaBH_4$, 2-propanol) of compound **26** and acetylation gave aminoether **36** (Scheme 3).

Method G. Resolution of (1*R*,2*R*)/(1*S*,2*S*)-1-(1-naphthalenethoxy)-2-(1,4-dioxa-7-azaspiro[4,4]non-7-yl)cyclohexane with di-*p*-toluoyl-D-tartaric acid in 2-butanone (Scheme 6) provided crystals that were recrystallized in a mixture of 2-butanone−MeOH. A single-crystal X-ray analysis allowed unambiguous assignment of the absolute configuration in (1*R*,2*R*)-1-(1-naphthalenethoxy)-2-(1,4-dioxa-7-azaspiro[4,4]non-7-yl)cyclohexane di-*p*-toluoyl-D-hemitartrate based on the connec-

Scheme 1. General Synthesis of *trans*-Aminoethers, Method A



Scheme 2. Proposed Mechanism Involving a Double S_N2 Displacement and an Aziridinium Ion Intermediate in Methods A and B



tivity.[30] Thus, this direct determination confirmed the postulated *trans* relative configuration of the aminoethers prepared via methods A or B. Recovery of the free amine and hydrolysis (6 M HCl, 2-butanone) of the ketal gave enantiomer **40**. Resolution of the mother liquor enriched in (1*S*,2*S*)-ketal using di-*p*-toluoyl-L-tartaric and subsequent ketal hydrolysis provided enantiomer **41**.

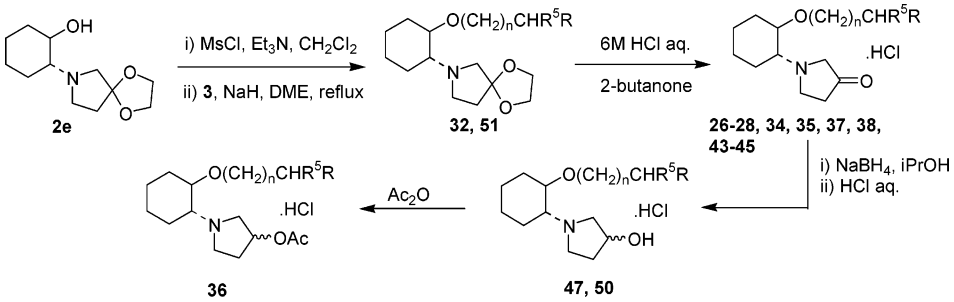
Preparation of Aminoalcohols 2. Aminoalcohols **2a**−**i** were prepared by typical S_N2 epoxide openings with the secondary amine of choice in the presence of water (Scheme 7), which, when R^3 and R^4 form a cycloalkyl ring, provide aminoalcohols **2a**−**h** with a *trans*-relationship relative to the cycloalkyl ring. Interestingly, it should be noted that, for the preparation of aminoalcohol **2j**, prior activation of the epoxide with a Lewis acid (i.e., $Mg(ClO_4)_2$)[28] was necessary to circumvent the weak basicity of thiazolidine.

Aminoalcohol **2e** required the preparation of amine **1e** (Scheme 8). 3-Hydroxypyrrolidinol **1a** was N-protected by carbamoylation with benzylchloroformate to give **1b**, and Swern oxidation[26] to **1c** followed by ketalisation with ethylene glycol provided **1d**, which was then hydrogenolyzed to give **1e**.

Preparation of Alcohols 3. Reduction of the commercially available carboxylic acids or cinnamic acids with $LiAlH_4$ provided, respectively, alcohols **3g**, **3l**, **3p**, **3r**, and **3u** and **3m** and **3o**. Alcohols **3h** and **3n** were, respectively, accessible from 4-keto-4,5,6,7-tetrahydrothianaphthene in three steps[31] and 1,3-cyclohexanedione in four steps.[32−34] Alcohol **3s** was obtained in seven steps from 2,4-dibromoaniline.[35] 2,4-Dibromoaniline was reacted with potassium nitrite and then potassium cyanide in the presence of copper(I) cyanide to provide 2,4-dibromobenzonitrile.[36] Subsequent reduction to the aldehyde with diisobutylaluminum hydride (DIBAL) followed by reduction with $NaBH_4$ provided 2,4-dibromobenzyl alcohol. Further activation through the mesylate, reaction with potassium cyanide, and basic hydrolysis provided 2,4-dibromophenylacetic acid, which was then reduced with borane to the desired 2,4-dibromophenethyl alcohol **3s**. Finally, **3v** was obtained via alkylation of 1,4-dibromonaphthalene with ethylene oxide in the presence of *n*-BuLi.[37]

Biological. The compounds were evaluated for antiarrhythmic activity against ischemia-induced arrhythmias and for convulsive activity in rats (Table 4).[18] In the ischemia-induced arrhythmia model, the dose producing a 25% reduction in systemic blood pressure ($D_{25}BP$) was monitored to reflect undesired hemeodynamic effects. In addition, the arrhythmia scores (AS)[38] at infusion rates of 1.0, 2.0, and 4.0 μmol/kg/min were listed to aid in the evaluation of compounds with similar ED_{50}. Compounds for which the antiarrhythmic activity could not be estimated or the threshold for convulsion was low were not studied further. The other compounds were evaluated for their electrophysiological effects in vivo in electrical stimulation studies in the rat and for toxicity (MTD) in mice (Table 5). Putative ion channel blocking actions were assessed in terms of changes in the ECG and electrical stimulation variables. An increase of the PR interval of the ECG and of the current threshold for induction of an extrasystole (iT) were used as indicators of sodium channel blocking actions, and a lengthened QT interval was used as an indicator of potassium channel

Scheme 3. General Synthesis of *trans*-Aminoethers, Methods B, E, and F



Scheme 4. General Synthesis of *cis*-Aminoethers, Method C

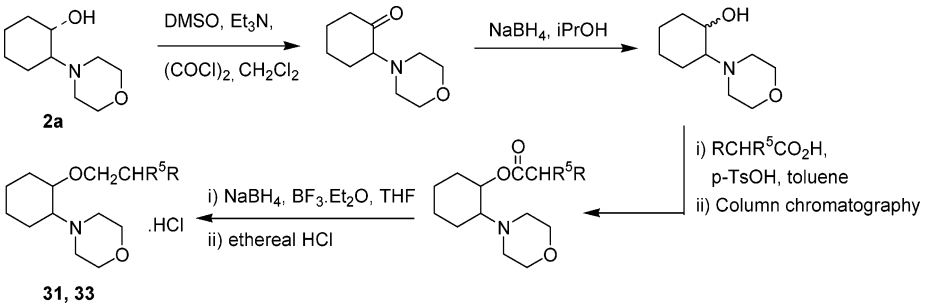
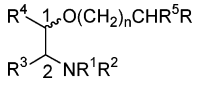


Table 3. Aminoethers **4**−**36**



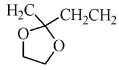
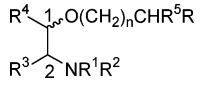
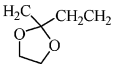
cmpd	R^1	R^2	R^3	R^4	rel./abs. conf. C_1-C_2	*n*	R^5	R	method	yield,[b] %	formula	elem. anal.
4	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	2-naphthyl	A[a]	31	$C_{22}H_{29}NO_2$·HCl	H, N; C: calcd, 70.29; found, 69.57
5	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	1-naphthyl	A	15	$C_{22}H_{29}NO_2$·HCl	H, N; C: calcd, 70.29; found, 69.78
6	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	4-bromophenyl	A	16	$C_{18}H_{26}NO_2Br$·HCl	C, H, N
7	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	2-naphthoxy	A	13	$C_{22}H_{29}NO_3$·HCl	C, H, N
8	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	4-bromo-phenoxy	A	44	$C_{18}H_{26}NO_3Br$·HCl	C, H, N
9	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	3,4-dimethoxy-phenyl	A	29	$C_{20}H_{31}NO_4$·HCl	H, N; C: calcd, 62.24; found, 61.69
10	$CH_2CH_2CH_2CH_2$		$(CH_2)_4$		trans	1	H	1-naphthyl	A	15	$C_{22}H_{29}NO$·HCl	C, H, N
11	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	3-benzo[b]thio-phenyl	A	15	$C_{20}H_{26}NO_2S$·HCl	H, N; C: calcd, 62.89; found, 60.87
12	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	4-benzo[b]thio-phenyl	A	15	$C_{20}H_{26}NO_2S$·HCl	H, N; C: calcd, 62.89; found, 62.53
13	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	3-bromophenyl	A	6	$C_{18}H_{26}NO_2Br$·HCl	C, H, N
14	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	2-bromophenyl	A	9	$C_{18}H_{26}NO_2Br$·HCl·$^1/_3$EtOH	C, H; N: calcd, 3.40; found, 4.01
15	CH_2CH_2-OCH_3	CH_2CH_2-OCH_3	$(CH_2)_4$		trans	1	H	2-naphthyl	A	9	$C_{24}H_{35}NO_3$·HCl	HPLC: 92.6%; CE: 94.2%[c]
16	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	2	H	3,4-dimethoxy-phenyl	A	5	$C_{21}H_{33}NO_4$·HCl	H, N; C: calcd, 63.06; found, 62.45
17	$CH_2CH_2OCH_2CH_2$		$(CH_2)_3$		trans	1	H	2-naphthyl	A	4	$C_{21}H_{27}NO_2$·HCl	H, N; C: calcd, 69.69; found, 69.23
18	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	3,4-dichloro-phenyl	B[a]	62	$C_{18}H_{25}NO_2Cl_2$·HCl	C, H, N
19	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	2	H	2,4-dimethoxy-phenyl	A	15	$C_{21}H_{33}NO_4$·HCl	H, N; C: calcd, 63.06; found, 62.52
20	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	4-benzo[b]-furanyl	A	8	$C_{20}H_{27}NO_3$·HCl	H, N; C: calcd, 65.65; found, 64.50
21	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	2	H	4-bromophenyl	A	10	$C_{19}H_{28}NO_2Br$·HCl	H, N; C: calcd, 54.49; found, 54.94
22	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	3	H	3,4-dimethoxy-phenyl	A	18	$C_{22}H_{35}NO_4$·HCl	C, H, N
23	$CH_2CH_2N(COCH_3)$-CH_2CH_2		$(CH_2)_4$		trans	1	H	2-naphthyl	A	25	$C_{24}H_{32}N_2O_2$·HCl·H_2O	H, N; C: calcd, 63.63; found, 62.93
24	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	2,4-dichloro-phenyl	A	13	$C_{18}H_{25}NO_2Cl_2$·HCl	C, H, N
25	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	2,6-dichloro-phenyl	A	9	$C_{18}H_{24}NO_2Cl_2$·HCl	C, H, N
26	$CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	H	1-naphthyl	B[a]	57	$C_{22}H_{27}NO_2$·HCl	C, H, N
27	$CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	H	3-benzo[*b*]thio-phenyl	B	14	$C_{20}H_{25}NO_2S$·HCl	C, H, N
28	$CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	H	2-bromophenyl	B	38	$C_{18}H_{24}NO_2Br$·HCl	C, H, N
29	$CH_2CH_2OCH_2CH_2$		H	*n*-C_4H_9		1	H	4-bromophenyl	C[a]	16	$C_{18}H_{28}NO_2Br$·HCl	C, H, N
30	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	2,4-dibromo-phenyl	B[a]	31	$C_{18}H_{25}NO_2Br_2$·HCl	C, H, N
31	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		cis	1	H	4-bromophenyl	C	53	$C_{18}H_{26}NO_2Br$·HCl	C, H, N
32			$(CH_2)_4$		trans	1	H	1-naphthyl	B[a]	49	$C_{24}H_{31}NO_3$·HCl	H, N; C: calcd, 68.97; found, 68.49
33	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		cis	1	H	2-(trifluoro-methyl)phenyl	C[a]	38	$C_{19}H_{26}F_3NO_2$·HCl	C, H, N
34	$CH_2COCH_2CH_2$		$(CH_2)_4$		trans	2	H	cyclohexyl	B	35	$C_{19}H_{33}NO_2$·HCl	C, H, N
35	$CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	H	2,4-dibromo-phenyl	B	19	$C_{18}H_{23}NO_2Br_2$·HCl	C, H, N
36	$CH_2CH(OCOCH_3)$-CH_2CH_2		$(CH_2)_4$		trans	1	H	1-naphthyl	F[a]	65	$C_{24}H_{31}NO_3$·HCl	H, N; C: calcd, 68.97; found, 67.52

Table 3. (Continued) Aminoethers **37**−**53**



cmpd	R^1 R^2	R^3 R^4	rel./abs. conf. C_1-C_2	*n*	R^5	R	method	yield,[b] %	formula	elem. anal.
37	$CH_2COCH_2CH_2$	$(CH_2)_4$	trans	1	H	4-bromophenyl	B	20	$C_{18}H_{24}NO_2Br$·HCl	C, H, N
38	$CH_2COCH_2CH_2$	$(CH_2)_4$	trans	1	H	3,4-dimethoxyphenyl	B	56	$C_{20}H_{29}NO_4$·HCl	H, N; C: calcd, 62.57; found, 60.32
39	$CH_2CH_2OCH_2CH_2$	$(CH_2)_4$	trans	1	H	2-(trifluoromethyl)phenyl	B	71	$C_{19}H_{26}F_3NO_2$·HCl	C, H, N
40	$CH_2COCH_2CH_2$	$(CH_2)_4$	1*R*,2*R*	1	H	1-naphthyl	G[a]	30	$C_{22}H_{27}NO_2$·HCl	C, H, N
41	$CH_2COCH_2CH_2$	$(CH_2)_4$	1*S*,2*S*	1	H	1-naphthyl	G[a]	37	$C_{22}H_{27}NO_2$·HCl	C, H, N
42	$CH_2SCH_2CH_2$	$(CH_2)_4$	trans	1	H	2,6-dichlorophenyl	B[a]	39	$C_{17}H_{23}NOSCl_2$·HCl	C, H, N
43	$CH_2COCH_2CH_2$	$(CH_2)_4$	trans	1	phenyl	phenyl	B	39	$C_{24}H_{29}NO_2$·HCl	C, H, N
44	$CH_2COCH_2CH_2$	$(CH_2)_4$	trans	1	H	2-(trifluoromethyl)phenyl	B	19	$C_{19}H_{24}F_3NO_2$·HCl	C, H, N
45	$CH_2COCH_2CH_2$	$(CH_2)_4$	trans	1	H	4-bromonaphth-1-yl	B[a]	21	$C_{22}H_{26}NO_2Br$·HCl	C, H, N
46	$CH_2COCH_2CH_2$	$(CH_2)_4$	cis	1	H	1-naphthyl	D[a]	59	$C_{22}H_{27}NO_2$·HCl	C, H, N
47	$CH_2CHOHCH_2CH_2$	$(CH_2)_4$	trans	1	H	2-bromophenyl	E	62	$C_{18}H_{26}NO_2Br$·HCl	HPLC: 99.1%; CE: 98.7%[a]
48	$CH_2CH_2COCH_2CH_2$	$(CH_2)_4$	trans	1	H	1-naphthyl	B	17	$C_{23}H_{29}NO_2$·HCl·H_2O	H, N; C: calcd, 68.05; found, 69.35
49	$CH_2CHOHCH_2CH_2$	$(CH_2)_4$	cis	1	H	1-naphthyl	E	57	$C_{22}H_{29}NO_2$·HCl	HPLC: 96.7%; CE: 98.7%[a]
50	$CH_2CHOHCH_2CH_2$	$(CH_2)_4$	trans	1	H	1-naphthyl	E[a]	79	$C_{22}H_{29}NO_2$·HCl	HPLC: 98.9%; CE: 98.9% [a]
51		$(CH_2)_4$	trans	1	H	3,4-dimethoxyphenyl	B	87	$C_{22}H_{33}NO_5$·HCl	HPLC: 84.2%; CE: 98.5%[a]
52	$CH_2CH_2CH_2CH_2$	$(CH_2)_4$	trans	1	H	3,4-dimethoxyphenyl	B	27	$C_{20}H_{31}NO_3$·HCl	H, N; C: calcd, 64.94; found, 63.04
53	$CH_2CH_2NHCH_2CH_2$	$(CH_2)_4$	trans	1	H	3,4-dimethoxyphenyl	B[a]	37	$C_{20}H_{33}N_2O_3Cl$·HCl	HPLC: 97.2%; CE: 95.3%[a]

[a] See Experimental Section. [b] Overall yield from aminoalcohol **2** (methods A−D).

blocking action. Some of the compounds tested with promising antiarrhythmic actions and a range of apparent (in vivo) sodium and potassium channel blocking actions were further evaluated on cloned human heart sodium (Nav1.5) and potassium (hKv1.5) channels and on cloned rat potassium channels (Kv4.2 and Kv2.1) expressed in HEK cells (Table 6). Voltage-dependent potassium channels of the supergene family for calcium and sodium channels[39] have regions of homology in the pore and voltage-sensing regions around the S4−S6 transmembrane domains. Two important currents involved in controlling the rat ventricle action potential duration are I_{to} (transient outward) and I_{Kur} (ultrarapid delayed rectifier) currents. Kv4 class genes encode for the rapidly recovering I_{to}. The I_{Kur} current appears to correlate with the product of the hKv1.5 gene,[15] although the role of the relatively noninactivating Kv2.1 in this current is still unclear. Concentration−response curves of selected compounds blocking actions were assessed on Nav1.5 sodium, hKv1.5, Kv4.2, and Kv2.1 potassium ion channels.

The efficacy for conversion of AF of the same group of compounds was evaluated in two canine AF models (Table 7). The vagal model[21] is a method in which continuous vagal stimulation is combined with a burst of rapid atrial pacing to induce AF in otherwise normal canine hearts. Additionally, the effects of these compounds on the atrial and ventricular effective refractory period (ERP) were assessed (Figure 4). The canine sterile pericarditis AF model was also used.[20] This canine model is prepared by dusting surgically exposed atria with talcum powder, allowing the animal to recover, and then "burst" pacing the atria over a period of days after recovery. AF is inducible two days after surgery, however, by the fourth day after surgical preparation, sustainable FL is the predominant inducible rhythm.

Finally, a pharmacokinetic study of the selected compounds was performed in rats (Table 8).

Results and Discussion

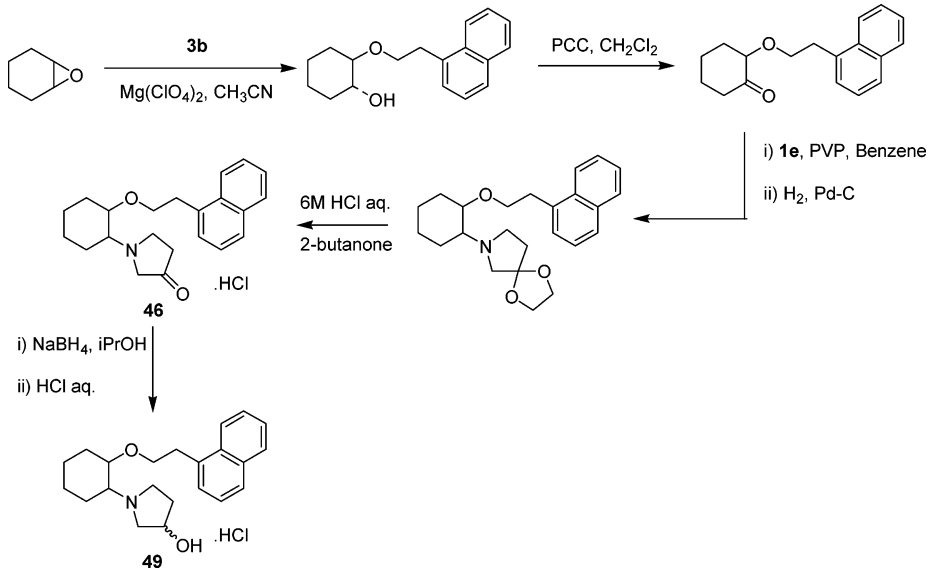
The antiarrhythmic activity in ischemia-induced arrhythmias and the threshold for convulsions in the rat for aminoethers **4**−**53** are described in Table 4.

Most of the compounds tested in this focused library exhibited some antiarrhythmic activity in the ischemia-induced arrhythmia model, with ED_{50} values ranging from 0.4 μmol/kg/min for the most potent to 8.0 μmol/kg/min for the least potent. The safety of the compounds was then assessed by comparing the potency against arrhythmias (ED_{50}) with that for hemeodynamic effects ($D_{25}BP$) in the same anaesthetized rat model (when available) and with the threshold dose for convulsions in conscious rats (cumulative convulsive dose).

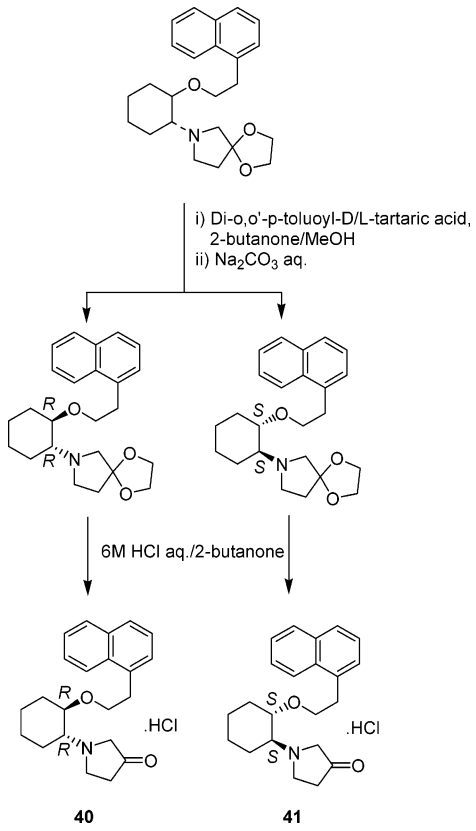
The following compounds were the most active aminoethers when tested intravenously ($ED_{50} \leq 1.0$ μmol/kg/min): **4**, **5**, **10**−**12**, **14**, **26**, **39**, and **47**−**50**.

However, **26** showed the best separation between antiarrhythmic efficacy ($ED_{50} = 0.43$ μmol/kg/min) and threshold dose for convulsions (cumulative dose = 225 μmol/kg). Another compound of interest **53** had the highest threshold for convul-

Scheme 5. Synthesis of *cis*-Aminoethers **46** and **49**, Methods D and E



Scheme 6. Method for the Resolution of (1*R*,2*R*)/(1*S*,2*S*)-1-(1,4-Dioxa-7-azaspiro[4,4]non-7-yl)-2-(1-naphthalenethoxy)cyclohexane with Di-*p*-toluoyl-D/L-tartaric Acid and Preparation of Enantiomers **40** and **41**

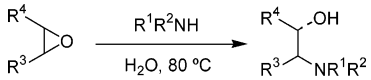


sions (392 μmol/kg) and was also efficacious in the ischemia-induced arrhythmia model (ED_{50} = 1.6 μmol/kg/min).

In comparison, quinidine, flecainide, lidocaine, and amiodarone showed poor separation between doses showing antiarrhythmic protection relative to side effects (Table 4).

Electrophysiological effects in electrically induced arrhythmias in the rat and maximum tolerated dose in mice are described in Table 5. D_{25} for the PR interval and D_{25} for the current threshold for induction of a systole (iT) are comparable throughout the series. Potency values for effects on PR interval

Scheme 7. General Synthesis of Aminoalcohols **2**



2a-i

and iT range from D_{25}PR = 1.1 μmol/kg/min and D_{25}iT = 0.8 μmol/kg/min for the most potent **10** to D_{25}PR = 23−26 μmol/kg/min and D_{25}iT = 25 μmol/kg/min for the least potent pair **40** and **41**.

All compounds lengthened the QT interval and prolonged ERP in the rat as shown in Table 5. Compounds **9** and **18** were most potent in this regard, with a D_{25} of 0.8, 1.0, and 0.5 and 1.4, 1.4, and 1.7 μmol/kg/min, respectively. The same compounds (**9** and **18**) showed a relatively weak effect on iT, with a D_{25} of 8.0 and 6.4 μmol/kg/min, respectively. All compounds were more potent in their effect on ERP than on the PR interval of the ECG.

Quinidine and flecainide decreased the systemic BP at the same low doses as they produce changes in ECG parameters, Flecainide was particularly toxic (LD_{50} = 20 μmol/kg) and lidocaine lacked potency in that model (Table 5).

Electrical stimulation studies uncovered compounds with unique electrophysiological characteristics.

Compound **5** displayed good potency (ED_{50} = 0.8 μmol/kg/min) and a steep dose response curve (Hill coefficient, H = 3, Figure 3A) against ischemia-induced arrhythmias in the rat. It produced little effect on systemic arterial BP or ECG intervals when infused at a rate equal to the antiarrhythmic ED_{50}. At this dose, it did not significantly alter (<10% increase) the current threshold for capture (iT) or ventricular ERP measured during electrical stimulation. Compound **5** affected indicators of block of both sodium and potassium channels when infused at a rate producing full protection (AS = 0 at 4.0 μmol/kg/min) against ischemia-induced arrhythmias in the rat. At this dose, indicators of possible channel blockade included a reduction in BP (−15%) accompanied by significant (+40%) QT interval prolongation and less marked (+10%) PR interval prolongation. Commensurate with these effects, the infusion rate producing a 25% change (D_{25}) in iT was 0.9 μmol/kg/min, and the D_{25} for ERP was 1.3 μmol/kg/min.

In conscious rats compound **5** caused convulsions when infused at a rate of 16 μmol/kg/min (cumulative dose = 93

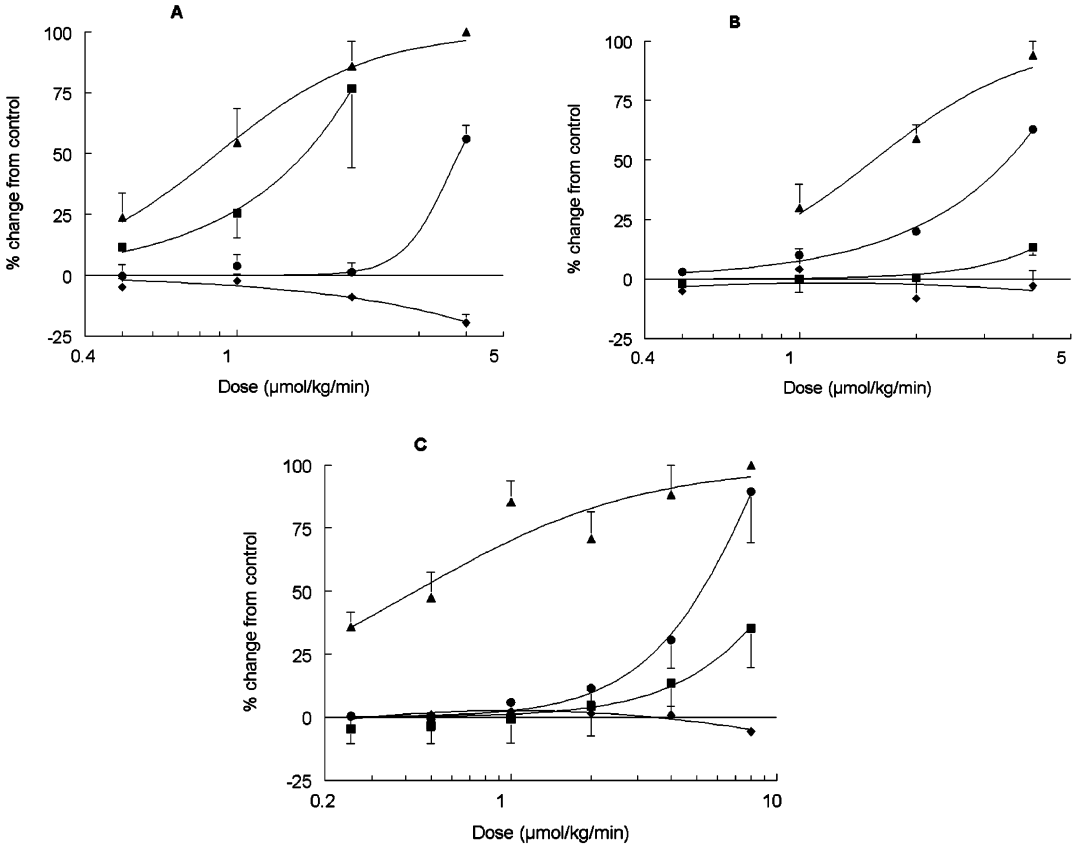
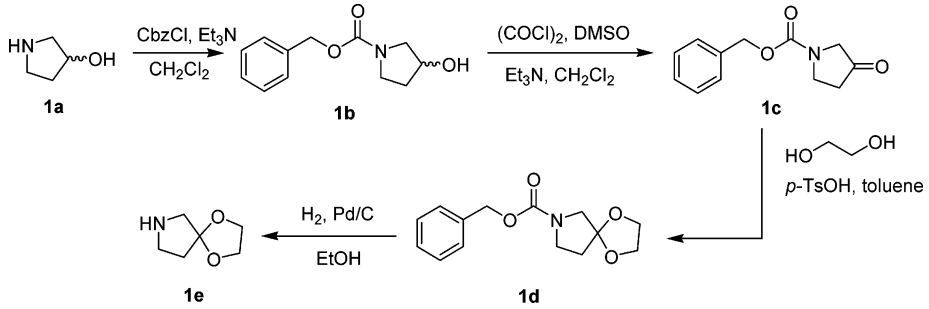


Figure 3. Antiarrhythmic activity (▲), iT or current threshold for induction of an extrasystole (■), arterial BP (◆), and QT interval (●) expressed as the % change from control following an incremental i.v. infusion in μmol/kg/min ± SD for compounds **5** (A), **18** (B), and **26** (C).

Scheme 8. Synthetic Pathway for the Preparation of 1,4-Dioxa-7-azaspiro[4.4]nonane **1e**



μmol/kg). In mice, the maximum tolerated dose was 42 μmol/kg i.v. Compound **5** is an example of a compound with apparent combined sodium and potassium channel blocking actions, with partial ischemia selectivity.

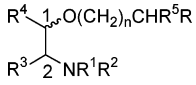
18 displayed good potency (ED_{50} = 1.5 μmol/kg/min) and a fairly steep dose response curve (H = 2.3, Figure 3B) against ischemia-induced arrhythmias in the rat. It produced no effect on BP or PR intervals, but did widen the QT interval when infused at a rate equal to the antiarrhythmic ED_{50}. At this dose, it had no effect on iT, but did increase ERP (20%) measured during electrical stimulation, an effect likely resulting from the blockade of cardiac potassium channels.

Compound **18** potently and selectively produced signs of blockade of the potassium channel when infused at a rate giving full protection (AS = 0.3 at 4.0 μmol/kg/min) against ischemia-induced arrhythmias in the rat. At this dose, there was no reduction in BP or increases in PR intervals, however, QT intervals were significantly prolonged (~50%). In keeping with these effects, the infusion rate producing a 25% change (D_{25}) in iT was 6.4 μmol/kg/min and the D_{25} for ERP was 1.7 μmol/kg/min (Table 5). In conscious rats, compound **18** caused convulsions at an infusion rate of 16 μmol/kg/min (cumulative dose = 118 μmol/kg). In mice, the maximum tolerated dose was 228 μmol/kg i.v. This compound is an example of a compound with apparently more potent potassium channel than sodium channel blocking actions.

Finally, **26** is an example of a compound with potent potassium channel blocking actions combined to sodium channel blocking properties, the latter being elicited under ischemic conditions. Compound **26** also displayed good potency (ED_{50} = 0.4 μmol/kg/min) and a reasonable dose response curve (H = 1, Figure 3C) against ischemia-induced arrhythmias in the rat, but had no effects on BP or any ECG intervals prior to ischemia when infused at a rate equal to the ED_{50}. At this infusion rate, it also did not affect iT or ERP measured during electrical stimulation protocols in anaesthetized rats.

Compound **26** showed signs of preferential potassium channel block when infused at a rate giving full protection (AS = 0.7 at 4.0 μmol/kg/min) against ischemia-induced arrhythmias in the rat. At this dose, there were only minor reductions in BP

Table 4. Convulsion Threshold (CNS Toxicity) and Antiarrhythmic Activity (Ischemia-Induced Arrhythmia) in the Rat



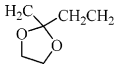
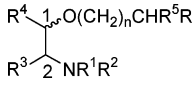
											antiarrhythmic act.			
											arrh. score[d]			
cmpd	R^1	R^2	R^3	R^4	rel/abs conf. C_1-C_2	*n*	R^5	R	cum. conv.[a]	D_{25} BP[b]	ED_{50}[c]	0	1.0	2.0	4.0
4	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	2-naphthyl	85	8.0	0.8	5.7	3.0	1.3	0.5
5	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	1-naphthyl	93	ne[g]	0.8	4.9	2.6	0.8	0
6	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	4-bromo-phenyl	91	ne	2.5	5.0	nd[h]	3.0	2.3
7	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	2-naphthoxy	62	6.9	ne	6.0	2.0	2.0	nd
8	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	4-bromo-phenoxy	83	ne	2.5	4.8	nd	3.7	1.3
9	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	3,4-dimethoxy-phenyl	113	ne	1.5	4.8	4.7	1.0	2.0
10	$CH_2CH_2CH_2CH_2$			$(CH_2)_4$	trans	1	H	1-naphthyl	nd	2.0	0.9	5.8	2.6	0	nd
11	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	3-benzo[*b*]-thiophenyl	65	4.0	0.8	5.0	1.0	1.0	0
12	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	4-benzo[*b*]-thiophenyl	54	ne	0.7	6.3	2.7	1.0	nd
13	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	3-bromo-phenyl	131	7.8	1.9	6.0	3.7	3.7	1.0
14	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	2-bromo-phenyl	125	8.0	1.0	6.3	2.8	1.5	1.5
15	CH_2CH_2-OCH_3	CH_2CH_2-OCH_3		$(CH_2)_4$	trans	1	H	2-naphthyl	83	2.8	3.0	6.3	3.7	3.3	7.0
16	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	2	H	3,4-dimethoxy-phenyl	109	8.9	1.5	6.0	3.3	2.3	0.7
17	$CH_2CH_2OCH_2CH_2$			$CH_2CH_2CH_2$	trans	1	H	2-naphthyl	187	ne	1.5	6.3	3.0	3.0	1.7
18	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	3,4-dichloro-phenyl	118	ne	1.5	6.0	4.0	2.3	0.3
19	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	2	H	2,4-dimethoxy-phenyl	94	4.8	1.2	7.0	3.7	1.0	0
20	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	4-benzo[*b*]-furanyl	nd	ne	1.4	5.0	4.3	0.3	1.7
21	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	2	H	4-bromo-phenyl	143	ne	3.5	5.0	nd	4.3	2.7
22	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	3	H	3,4-dimethoxy-phenyl	67	ne	1.5	6.0	4.0	1.7	1.3
23	$CH_2CH_2N(COCH_3)$-CH_2CH_2			$(CH_2)_4$	trans	1	H	2-naphthyl	67	6.0	ne	4.8	3.1	5.0	1.0
24	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	2,4-dichloro-phenyl	94	7.4	2.1	6.3	5.7	3.0	1.3
25	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	2,6-dichloro-phenyl	86	5.4	1.2	7.0	4.3	2.0	0
26	$CH_2COCH_2CH_2$			$(CH_2)_4$	trans	1	H	1-naphthyl	225	10	0.4	5.3	0.8	1.7	0.7
27	$CH_2COCH_2CH_2$			$(CH_2)_4$	trans	1	H	3-benzo[*b*]-thiophenyl	203	5.0	ne	5.6	2.8	0.7	0
28	$CH_2COCH_2CH_2$			$(CH_2)_4$	trans	1	H	2-bromo-phenyl	155	6.9	ne	4.3	3.0	4.0	0.7
29	$CH_2CH_2OCH_2CH_2$		H	*n*-C_4H_9		1	H	4-bromo-phenyl	193	ne	ne	6.0	nd	3.0	4.3
30	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	2,4-dibromo-phenyl	123	ne	ne	6.0	nd	2.3	2.0
31	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	cis	1	H	4-bromo-phenyl	67	ne	2.0	4.3	4.0	3.3	1.0
32				$(CH_2)_4$	trans	1	H	1-naphthyl	41[e]	ne	nd	nd	nd	nd	nd
33	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	cis	1	H	2-(trifluoro-methyl)phenyl	102	3.1	1.4	6.3	3.3	3.0	0.7
34	$CH_2COCH_2CH_2$			$(CH_2)_4$	trans	2	H	cyclohexyl	300	5.3	ne	4.3	nd	2.7	4.0
35	$CH_2COCH_2CH_2$			$(CH_2)_4$	trans	1	H	2,4-dibromo-phenyl	246	ne	ne	6.3	5.0	4.3	3.7
36	$CH_2CH(OCOCH_3)$-CH_2CH_2			$(CH_2)_4$	trans	1	H	1-naphthyl	65	ne	1.4	7.0	4.0	1.7	0
37	$CH_2COCH_2CH_2$			$(CH_2)_4$	trans	1	H	4-bromo-phenyl	161	ne	8.0	6.3	nd	4.7	3.3
38	$CH_2COCH_2CH_2$			$(CH_2)_4$	trans	1	H	3,4-dimethoxy-phenyl	235	ne	4.5	7.0	nd	5.0	2.7
39	$CH_2CH_2OCH_2CH_2$			$(CH_2)_4$	trans	1	H	2-(trifluoro-methyl)phenyl	134	ne	1.0	7.0	3.0	2.3	1.3
40	$CH_2COCH_2CH_2$			$(CH_2)_4$	1*R*,2*R*	1	H	1-naphthyl	193	3.4	1.2	6.5	2.0	3.3	0.7

Table 4. (Continued)



cmpd	R^1	R^2	R^3	R^4	rel/abs conf. C_1-C_2	*n*	R^5	R	cum. conv.[a]	antiarrhythmic act. D_{25} BP[b]	ED_{50}[c]	arrh. score[d] 0	1.0	2.0	4.0
41	$CH_2COCH_2CH_2$		$(CH_2)_4$		1*S*,2*S*	1	H	1-naphthyl	150	ne	1.9	6.0	3.7	3.0	1.3
42	$CH_2SCH_2CH_2$		$(CH_2)_4$		trans	1	H	2,6-dichloro-phenyl	331	ne	6.5	7.0	nd	5.7	5.7
43	$CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	phenyl	phenyl	155	ne	2.5	6.0	3.7	3.3	2.0
44	$CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	H	2-(trifluoro-methyl)phenyl	225	ne	2.7	6.3	nd	3.7	2.0
45	$CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	H	4-bromo-naphth-1-yl	246	8.0	2.8	6.0	nd	4.3	1.3
46	$CH_2COCH_2CH_2$		$(CH_2)_4$		cis	1	H	1-naphthyl	145	7.0	1.6	5.3	nd	3.0	0
47	$CH_2CHOHCH_2CH_2$		$(CH_2)_4$		trans	1	H	2-bromo-phenyl	67	ne	0.4	5.5	1.0	1.7	0
48	$CH_2CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	H	1-naphthyl	75	ne	0.9	6.3	3.3	0	nd
49	$CH_2CHOHCH_2CH_2$		$(CH_2)_4$		cis	1	H	1-naphthyl	70[f]	ne	0.4	6.0	2.0	1.7	nd
50	$CH_2CHOHCH_2CH_2$		$(CH_2)_4$		trans	1	H	1-naphthyl	67	ne	0.8	4.0	2.0	1.3	nd
51			$(CH_2)_4$		trans	1	H	3,4-dimethoxy-phenyl	91	ne	1.6	6.5	3.7	2.0	0
52	$CH_2CH_2CH_2CH_2$		$(CH_2)_4$		trans	1	H	3,4-dimethoxy-phenyl	118	ne	1.3	5.7	3.7	2.3	nd
53	$CH_2CH_2NHCH_2CH_2$		$(CH_2)_4$		trans	1	H	3,4-dimethoxy-phenyl	392	ne	1.6	6.3	3.3	2.7	2.0
quinidine									317	3.0	4.0	4.3	5.2	3.2	2.8
flecainide[i]									113	2.5	ne		4.3	3.7	3.7
lidocaine									190	5.9	4.5		3.6	4.8	3.8
amiodarone									ne	4.0[j]	ne	5.7	nd	nd	4.3

[a] Cumulative convulsion dose, μmol/kg i.v. [b] Lowest dose (*D*) producing a 25% change in BP from the predrug value (D_{25}BP), expressed in μmol/kg/min i.v. The precision of estimates (SEM/mean) × 100 is 38%. [c] Dose (*D*) required to provide 50% of maximum protection, expressed in μmol/kg/min i.v. The precision of estimates (SEM/mean) × 100 is 52%. [d] See Experimental Section for scoring system. [e] Paralyzed. [f] Died. [g] Not estimable. [h] Not done. [i] Doses for antiarrhythmic score are 0.75, 1.5, and 3.0 μmol/kg/min i.v. [j] Dose (*D*) producing a 10% change in BP from the predrug value (D_{10}BP), expressed in μmol/kg/min i.v.

and slight increases in PR intervals, however, QT intervals were significantly prolonged (20−40%). The infusion rate producing a 25% change (D_{25}) in iT was 5 μmol/kg/min and the D_{25} for ERP was 1.6 μmol/kg/min (Table 5). In conscious rats, compound **26** caused convulsions when infused at a rate of 32 μmol/kg/min (cumulative dose = 225 μmol/kg). In mice, the maximum tolerated dose was 227 μmol/kg i.v.

The blocking actions of compounds **5**, **18**, and **26** on cloned sodium and potassium channels were studied on transfected HEK cells (Table 6). Compound **5** inhibited sodium (IC_{50}Nav1.5 = 4.0 μM) and potassium (IC_{50}s for hKv1.5, rKv4.2, and rKv2.1 were 1.3, 17, and 3.2 μM, respectively) currents in a similar way as observed in vivo (vide supra), supporting the concept of compound **5** being a combined sodium and potassium channel blocker. Compounds **18** and **26** showed a preference for potassium currents (IC_{50}s for hKv1.5, rKv4.2, and rKv2.1 were 3.6, 11, and 2.4 and 4.3, 8.9, and 2.8 μM, respectively) as opposed to sodium current (IC_{50}Nav1.5 of 15 and 25 μM, respectively). These results agreed with in vivo electrophysiological data and suggest compounds **18** and **26** as compounds with relatively more potent potassium channel than sodium channel blocking actions. This sets the two compounds apart from other comparable reference antiarrhymthic agents (Table 6), quinidine, flecainide, and lidocaine, which are all more potent sodium than potassium channel blocking agents. In addition, neither flecainide nor lidocaine have therapeutically signifinant action on Kv1.5 channels, an important atria-selective potassium channel target.

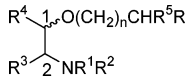
Compounds **5**, **18**, and **26**, characterized by a range of potassium channel versus sodium channel blocking actions, were then studied in the vagal and sterile pericarditis canine AF models to elucidate which relative balance of channel blockade was the most appropriate for termination of AF.

Canine Models of Atrial Fibrillation. None of the compounds **5**, **18**, and **26** reduced BP or heart rate at the median dose for termination of vagal AF. The heart rate response to vagal nerve stimulation was similar in all groups and was not influenced by any of the compounds tested. Vagal nerve stimulation at 60% of the voltage required to produce asystole (10 ± 1 V) produced a 1.3 ± 0.1 s pause.

All drugs tested were effective, but the efficacy for terminating AF was slightly greater for **18** than for **5** and **26** (Table 7). The dose required to terminate AF depended on the drug tested (Table 7). At effective doses, all of the drugs tested prolonged atrial ERP (Figure 4). In all cases, ERP was reduced during vagal nerve stimulation and none of the compounds had a significant effect on ERP of the ventricle (Figure 4).

The same compounds were effective in terminating episodes of AF/FL in the sterile pericarditis-induced AF model (Table 7). Compounds **5** and **18** terminated eight out of eight episodes of AF/FL after 8 μmol/kg and seven out of seven episodes after 10 μmol/kg, respectively. Compound **26** was slightly less potent and efficacious, terminating four out of five episodes of AF/FL at 14 μmol/kg. The efficacy of these compounds is likely

Table 5. Activities on BP, ECG Parameters (PR, QT_1, QT_2), and Electrical Stimulations (iT, ERP) in Electrically-Induced Arrhythmias in the Rat and Maximum Tolerated Dose (MTD) in Mice



									activities: D_{25}[a]						
cmpd	R^1	R^2	R^3	R^4	rel/abs conf. C_1-C_2	*n*	R^5	R	BP[b]	PR[c]	QT_1[d]	QT_2[d]	iT[e]	ERP[f]	MTD[g]
4	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	2-naphthyl	8.0	ne[h]	2.8	1.5	2.8	1.5	130
5	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	1-naphthyl	5.0	5.6	2.2	1.9	0.9	1.3	42
6	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	4-bromo-phenyl	16	32	3.1	2.8	5.8	4.0	103
8	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	4-bromo-phenoxy	11	15	2.5	1.8	4.0	1.8	nd[i]
9	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	3,4-dimethoxy-phenyl	21	21	0.8	1.0	8.0	0.5	97
10	$CH_2CH_2CH_2CH_2$		$(CH_2)_4$		trans	1	H	1-naphthyl	2.8	1.1	1.2	0.8	0.8	0.4	nd
11	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	3-benzo[*b*]-thiophenyl	5.2	7.1	1.4	1.2	2.0	0.7	52
12	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	4-benzo[*b*]-thiophenyl	5.4	4.6	1.5	1.7	1.9	0.8	38
13	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	3-bromo-phenyl	24	32	3.8	3.1	3.0	1.5	nd
14	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	2-bromo-phenyl	22	32	1.6	1.8	11	1.5	86
16	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	2	H	3,4-dimethoxy-phenyl	ne	11	2.8	4.1	3.0	1.5	112
17	$CH_2CH_2OCH_2CH_2$		$CH_2CH_2CH_2$		trans	1	H	2-naphthyl	23	45	2.5	2.5	3.3	2.5	nd
18	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	3,4-dichloro-phenyl	ne	ne	1.4	1.4	6.4	1.7	228
19	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	2	H	2,4-dimethoxy-phenyl	9.4	8.1	1.7	1.6	1.1	1.0	56
20	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	4-benzo[*b*]-furanyl	7.0	5.8	1.7	1.5	2.6	1.3	nd
21	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	2	H	4-bromo-phenyl	24	23	5.6	5.0	14	1.6	209
24	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	2,4-dichloro-phenyl	18	ne	3.5	4.1	7.4	3.6	nd
25	$CH_2CH_2OCH_2CH_2$		$(CH_2)_4$		trans	1	H	2,6-dichloro-phenyl	4.6	10	3.4	4.1	2.2	1.3	76
26	$CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	H	1-naphthyl	ne	16	4.4	2.4	5.0	1.6	227
27	$CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	H	3-benzo[*b*]-thiophenyl	12	24	4.0	3.3	3.4	3.0	nd
40	$CH_2COCH_2CH_2$		$(CH_2)_4$		1*R*,2*R*	1	H	1-naphthyl	7.6	26	2.8	2.6	25	2.9	nd
41	$CH_2COCH_2CH_2$		$(CH_2)_4$		1*S*,2*S*	1	H	1-naphthyl	ne	23	3.3	2.9	25	2.3	nd
42	$CH_2SCH_2CH_2$		$(CH_2)_4$		trans	1	H	2,6-dichloro-phenyl	25	2.3	10	11	10	5.4	nd
47	$CH_2CHOHCH_2CH_2$		$(CH_2)_4$		trans	1	H	2-bromo-phenyl	>16	2.4	0.75	0.7	1.0	0.8	nd
48	$CH_2CH_2COCH_2CH_2$		$(CH_2)_4$		trans	1	H	1-naphthyl	7.0	2.5	2.1	2.0	3.0	1.3	nd
quinidine									1.5	3.2	2.5	2.3	2.3	1.1	100
flecainide									1.7	2.8	ne	3.2	1.0	1.9	20
lidocaine									8.0	ne	ne	ne	11	6.9	64

[a] Corresponds to the lowest dose (*D*) required to produce a 25% change from the predrug value, expressed in μmol/kg/min i.v. [b] Arterial BP. The precision of estimates (SEM/mean) × 100 is 38%. [c] P−R interval. The precision of estimates (SEM/mean) × 100 is 23%. [d] QT_1 and QT_2 intervals. The precision of estimates (SEM/mean) × 100 are 23%. [e] Current threshold for induction of an extrasystole. The precision of estimates (SEM/mean) × 100 is 25%. [f] Effective refractory period. The precision of estimates (SEM/mean) × 100 is 21%. [g] Dose producing 50% lethalities in mice, expressed in μmol/kg i.v. [h] Not estimable. [i] Not done.

connected to their ability to prolong atrial refractoriness. The compounds were well tolerated, with no adverse cardiovascular events.

From those results, it was difficult to select one compound over the others because of their similar efficacy in both canine AF models. Thus, pharmacokinetics studies were carried out to evaluate the oral bioavailability and, hence, the clinical utility of compounds **5**, **18**, and **26**.

Pharmacokinetics Studies. In rats, compounds **5** and **18** had a very low absolute oral bioavailability, 4 and 7%, respectively, whereas the racemate **26** displayed a moderate plasma clearance, a high volume of distribution at steady-state, and a moderate to high bioavailability (58%, Table 8). Because the pharmacokinetics of single enantiomers can be stereospecific, and a superior pharmacokinetics of one enantiomer compared to the other or to the racemate cannot be excluded per se, the pharmacokinetics of the pure enantiomers (compounds **40** and **41**) of racemate **26** were examined. The mean plasma clearance following i.v. administration was moderate for enantiomer **41** (30.2 ± 5.2 mL/kg/min) and high for enantiomer **40** (59.3 ± 4.5 mL/kg/min). The mean volume of distribution at steady-state (Vd_{ss}) for racemate **26** and enantiomer **41** (4.5 ± 1.1 L/kg and 2.6 ± 0.9, respectively) was high, while that for enantiomer **40** (8.3 ± 4.6 L/kg) was even higher, indicating an extensive distribution into tissues. Absolute oral bioavailability was moderate to high for racemate **26** (58%) as well as for enantiomer **41** (32%), whereas

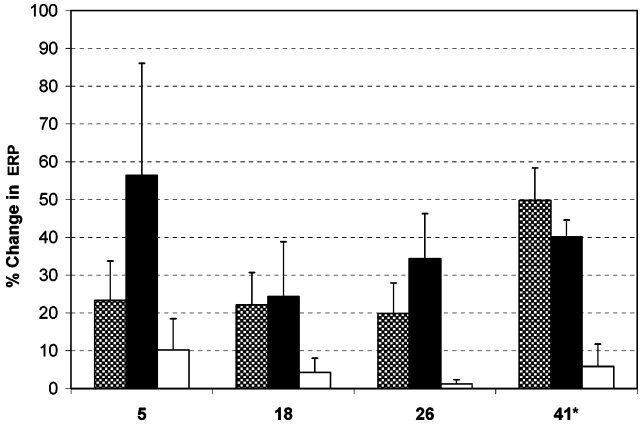


Figure 4. Atrial selectivity in the vagal AF canine model. The % change from control for right A-ERP without vagal stimulation (gray), right A-ERP with vagatonic stimulation (black), and left V-ERP (white) at the effective dose for compounds **5**, **18**, **26**, and **41**.* *Data are from the top dose 8 mg/kg. Values are shown as the mean ± SEM, $n = 4-6$.

Table 6. IC_{50} for Cloned Channels Expressed in HEK Cells for Compounds **5**, **18**, **26**, **40**, **41**, and Three Reference Compounds

	IC_{50}, μM			
cmpd	Nav1.5[a]	hKv1.5[a]	rKv4.2[b]	rKv2.1[b]
5	4.0	1.3	17	3.2
18	15	3.6	11	2.4
26	25	4.3	8.9	2.8
40	11	5.9	11	6.0
41	13	7.7	9.0	8.0
quinidine	6.9	7.3	2.2	nd[c]
flecainide	6.5	51	10.1	nd
lidocaine	108	2188	1210	nd

[a] Cloned human channel. The precision of estimates (SEM/mean) × 100 is 15% for Nav1.5 and 14% for Kv1.5. [b] Cloned rat channel. The precision of estimates (SEM/mean) × 100 is 7% for Kv4.2 and Kv2.1. [c] Not done.

Table 7. Efficacy in Conversion of AF/FL[a] in Canine AF Models by Compounds **5**, **18**, and **26**

	vagal AF model		sterile pericarditis AF model	
cmpd	efficacy[b]	mean dose[c]	efficacy[b]	mean dose[c]
5	5/6	16 ± 7	8/8	8 ± 2
18	6/6	17 ± 5	7/7	10 ± 3
26	4/6	20	4/5	14 ± 6

[a] FL stand for atrial flutter. [b] Efficacy expressed as [number of dogs that converted from AF or FL to normal sinus rhythm]/[number of treated dogs]. [c] Mean dose ± standard deviation for the converted dogs in μmol/kg i.v.

Table 8. Pharmacokinetic Parameters for Compounds **5**, **18**, **26**, **40**, and **41**

cmpd	iv dose,[a] mg/kg	$T_{1/2}$,[b] h	Vd_{ss},[c] L/kg	CL,[d] mL/kg/min	p.o. dose,[a] mg/kg	F,[e] %
5	12 (2)	6.5	29 ± 13	50.1 ± 7.0	24 (2)	4
18	12 (3)	4.5	19 ± 3	48.5 ± 6.8	24 (3)	7
26	17 (3)	6.3	4.5 ± 1.1	38.7 ± 8.1	34 (3)	58
40	17 (3)	3.8	8.3 ± 4.6	59.3 ± 4.5	34 (3)	6
41	17 (3)	1.0	2.6 ± 0.9	30.2 ± 5.2	34 (3)	32

[a] Number of animals in parentheses. [b] Half-life expressed as the harmonic mean. [c] Mean volume of distribution at steady-state ± standard deviation. [d] Mean plasma clearance ± standard deviation. [e] Absolute oral bioavailability.

enantiomer **40** showed a very low absolute oral bioavailability (6%). Assuming a blood to plasma ratio of about 0.9,[40] a hepatic blood flow of 60 ± 11 mL/kg/min, and solely hepatic metabolism, maximal achievable oral bioavailability of enantiomer **41** would be 44%. If this assumption holds true for enantiomer **40**, clearance would be in the range of hepatic blood flow and, therefore, would explain the very low oral bioavailability.

Atrial selectivity of enantiomer **41** in the vagal AF model was then examined (Figure 4). Preliminary results showed that compound **41** was atrial selective at the maximum dose of 8 mg/kg, but failed to convert AF at the same dose in the canine vagal model.

Structure−Activity Relationships. The ischemia-induced arrhythmias and threshold for convulsion rat data (Table 4) and electrically induced arrhythmias rat data (Table 5) suggested the following structure−activity relationships.

R^1 and R^2 Substituents. The presence of a pyrrolidinyl group in compound **10** provided the same antiarrhythmic protection as that observed with a morpholinyl group (compound **5**), but this substitution resulted in greater potency for PR interval widening and systemic arterial hypotension. Similarly, replacement of the 3-pyrrolidinone group in compound **26** with the 4-piperidone group (compound **48**) did not affect the antiarrhythmic activity but decreased the threshold for convulsion and D_{25}PR, indicative of potentially increased sodium channel block in the brain. Reduction of the 3-pyrrolidinone group (compound **26**) to 3-pyrrolidinol (compound **50**) increased CNS toxicity, and acetylation of the 3-pyrrolidinol (compound **36**) did not improve the safety toward the CNS nor did it affect antiarrhythmic actions.

Interestingly, replacement of the morpholinyl group in compound **9** by a 1,4-dioxa-7-azaspiro[4,4]non-7-yl or pyrrolidinyl groups (compound **51** and **52**, respectively) did not affect threshold for convulsions or antiarrhythmic actions. However, substitution with a 3-pyrrolidinone group (compound **38**) increased threshold for convulsion but significantly reduced antiarrhythmic protection. Replacement by a piperazinyl group (compound **53**) dramatically increased the therapeutic index, both thresholds for convulsions and antiarrhythmic potency increased by approximately 3-fold, relative to compound **38**.

In another series, replacement of the morpholinyl group of compound **4** with a bis(2-methoxyethyl)amino (compound **15**) or a *N*-acetylpiperazinyl group (compound **23**) resulted in a loss in antiarrhythmic activity. Yet in another series, replacement of the morpholinyl group of compound **25** with a thiazolidinyl group (compound **42**) increased the CNS safety but to the detriment of the antiarrhythmic efficacy.

R^3 and R^4 Substituents. Replacement of the cyclohexyl linker of compound **4** with a cyclopentyl linker (compound **17**) led to a less active compound and decreased sodium channel block (D_{25}PR) but greater safety in terms of reduced CNS toxicity and hemeodynamic effects (D_{25}BP).

Replacement of the cyclohexyl linker of compound **6** with an acyclic linker (compound **29**) resulted in a complete loss of antiarrhythmic activity. Switching from a *trans*-geometry in compounds **6**, **26**, **39**, and **50** to a *cis*-geometry (compounds **31**, **46**, **33**, and **49**, respectively) did not alter significantly the antiarrhythmic activity, but tended to slightly reduce the threshold dose for convulsions.

The influence of the absolute configuration was evaluated for enantiomers **40** and **41**. There were no significant differences in terms of antiarrhythmic activity or in vivo electrophysiological profile. In vitro electrophysiological studies in HEK cells (Table 6) of the two enantiomers **40** and **41** confirmed these findings. However, pharmacokinetics studies showed some stereospecificity with superior pharmacokinetics for enantiomer **41** (Table 8).

Homologation. The 3,4-dimethoxyphenethoxy substituent in **9** was homologated by increasing (analogues **16** and **22**) the number of methylene groups between the oxygen atom and the phenyl ring. Similarly, the 4-bromophenethoxy substituent in **6** was homologated by adding one methylene group (analogue **21**). In all cases, the analogues **16**, **22**, and **21** exhibited similar antiarrhythmic actions and a threshold dose for convulsions relative to that of **9** and **6**, respectively. Nevertheless, compounds **16** and **21** showed a concomitant slight increase in apparent sodium channel block (reduced D_{25}PR) and a slight decrease in apparent potassium channel block (increased D_{25}QT) relative to that of **9** and **6**, respectively.

The effect of introducing branching into the phenethoxy substituent was tested by examining the 2,2-diphenylethoxy derivative **43** and was found to result in reduced antiarrhythmic activity as compared to that of **26**.

The effect of introducing an oxygen atom between the phenyl ring and the ethoxy linker was evaluated by comparing analogues **7** (2-naphthoxy) and **8** (4-bromophenoxy) with **4** (2-naphthyl) and **6** (4-bromophenyl), respectively. Although the antiarrhythmic activity of **8** was comparable to that of **6**, all D_{25} values of **8** relative to **6** in electrical stimulation studies were reduced, which was indicative of an apparent increase of potency for sodium and potassium channel block, effects which were presumed to be deleterious to the safety of the compound.

R Substituent. Isosteric replacement of the 1-naphthyl group in **5** with the 4-benzo[*b*]thiophenyl or the 4-benzo[*b*]furanyl groups resulted in analogues **12** and **20**, respectively. The antiarrhythmic activities of **12** and **20** in ischemia- and electrically induced arrhythmias in the rat were comparable to **5**. Similarly, replacement of the 4-benzo[*b*]thiophenyl group in **12** with the isomeric 3-benzo[*b*]thiophenyl substituent resulted in analogue **11**, which exhibited identical antiarrhythmic properties as those of **12**. Comparison of the 3-benzo[*b*]thiophenyl analogue **27** with the 1-naphthyl analogue **26** led to the same observation, both compounds were equally efficacious against ischemia- and electrically induced arrhythmias.

Attachment at the 1-position of the naphthalene for **5** or at the 2-position for **4** did not have any significant changes in terms of antiarrhythmic protection. However, attachment to the 1-position (compound **5**) resulted in a slight increase in sodium channel block, as indicated by a reduced D_{25}iT, and was corroborated by a concomitant higher toxicity (LD_{50}) compared to **4**.

The effect of the nature of the substituents on the phenethoxy group was evaluated by comparing analogues **9** (3,4-dimethoxy), **14** (2-bromo), and **24** (2,4-dichloro) with **18** (3,4-dichloro), **39** (2-trifluoromethyl), and **30** (2,4-dibromo) in the morpholino ether series, respectively. In all cases, no significant changes in antiarrhythmic actions were observed. The same statement can be made when comparing analogues **28** (2-bromophenyl) and **44** (2-trifluoromethyl) in the 3-pyrrolidinone series.

The effect of the position of the substituents on the phenethoxy group was tested by examining derivatives **6** (4-bromo), **13** (3-bromo), and **14** (2-bromo), as well as derivatives **16** (3,4-dimethoxy) and **19** (2,4-dimethoxy), and derivatives **18** (3,4-dichloro), **24** (2,4-dichloro), and **25** (2,6-dichloro) in the morpholino ether series. The bromine derivatives did not differ from one another in terms of antiarrhythmic properties, whereas the 2,4-dimethoxy derivative seemed to be characterized by a slight increase in potency for indicators of channel blockade (sodium and potassium) accompanied by an increased toxicity (LD_{50}). Interestingly, the dichloro derivatives showed some in vivo electrophysiological differences. Within this series, the 3,4-disubstitution (compound **18**) had the most potassium blocking effects, whereas the 2,6-disubstitution (compound **25**) led to the most sodium blocking effects and most toxicity (LD_{50}) of these three dichloro derivatives. The 2,4-disubstituted derivative (compound **24**) combined both the sodium and the potassium blocking actions of **18** and **25**, respectively. In the 3-pyrrolidinone series, analogue **28** (2-bromo) and **37** (4-bromo) were both poor antiarrhythmics. Finally, bromination of the naphthyl ring in the 4-position (compound **45**) diminished antiarrhythmic activity compared to **26**, and substitution of the aromatic ring by an alicyclic ring (compound **34**) abolished all antiarrhythmic properties.

It is apparent from the structure−activity relationships that for a molecule to be active in our screening platform, it should have the following attributes: (1) an aromatic ring, (2) a basic nitrogen, and (3) a linker to connect the aromatic ring and the basic nitrogen in a "semirigid folded conformation". The necessity of an aromatic ring (1) is exemplified by compound **34**, which has an alicyclic ring instead of an aromatic ring and was inactive in the ischemia-induced arrhythmia model. Compound **42** illustrated the need of a basic nitrogen (2); the lone pair of the nitrogen is delocalized by the transannular effect of the sulfur, which was deleterious to antiarrhythmic activity. Finally, the prerequisite of a "semirigid folded conformation" was demonstrated by acyclic derivative **29**, which did not have any antiarrhythmic actions.

More specifically, a *trans*-configuration seemed to be preferred to a *cis*-configuration in terms of toxicity. All *cis*-isomers (**31**, **33**, **46**, and **49**) showed a slightly lower threshold dose for convulsions compared to their respective *trans*-isomers (**6**, **39**, **26**, and **50**).

The potency on sodium channel activity correlates well with the basicity of the nitrogen. For example, compound **10**, which has a pyrrolidine ring, was characterized by low D_{25} values for BP, PR interval, and iT, indicative of potent sodium channel block. The lone pair of the nitrogen in the morpholino group of analogue **5** is delocalized by the transannular and inductive effect of the oxygen atom, which results in a slightly lower pKa and a higher D_{25} value for the PR interval (Table 5). For analogue **26**, the lone pair of the nitrogen is even more delocalized by the ketone in 3-position, than in **5**, and resulted in increased D_{25} values for the PR interval and iT, compared to those of **5**.

However, the nature of prerequisites (1) and (2) have to be combined judiciously to design an effective and safe antiarrhythmic. For example, a combination of the 3-pyrrolidinone fragment with the naphthalene ring generated compound **26** which was potent (ED_{50} = 0.43 μmol/kg/min) and relatively safe (cumulative convulsive dose = 225 μmol/kg). However, on one hand, an increase of the pK_a and of the hydrophilic surrounding of the nitrogen, as in **50**, was deleterious to the safety (cumulative convulsive dose = 67 μmol/kg). On the other hand, replacement of the hydrophobic 1-naphthyl group by the more hydrophilic 3,4-dimethoxyphenyl group, as in **38**, was detrimental to the antiarryhthmic activity (ED_{50} = 4.5 μmol/kg/min).

In conclusion, the antiarrhythmic properties of a new class of antiarrhythmic agents has been described. Structure−activity studies in this aminoether series led to the identification of three compounds, **5**, **18**, and **26**, that exhibited novel and potentially promising antiarrhythmic properties in two AF canine models. Of these analogues, the racemate **26** was selected on the basis of its absolute oral bioavailability. The racemate **26** was subsequently resolved into its two enantiomers **40** and **41**, and

each one of them was profiled for their antiarrhythmic activity and pharmacokinetics. (1*S*,2*S*)-1-(1-Naphthalenethoxy)-2-(3-ketopyrrolidinyl)cyclohexane monohydrochloride (**41**) through a frequency dependent block of sodium channels (IC_{50}Nav1.5 > 10 μM at 1 Hz) and a concomitant block of rapid potassium channels (IC_{50} < 10 μM for Kv1.5, 2.1 and 4.2) can potentially convert AF episodes back to normal sinus rhythm and was chosen for further investigation.

Experimental Section

Melting points were determined on a Fisher−Johns apparatus and are uncorrected. NMR spectra were acquired in the indicated solvent on a Bruker AC-200, Varian XL-300, Bruker AV-300, or AV-400. Mass spectra were recorded for EI on a Kratos MS50, for FAB/LSIMS on a Kratos Concept IIHQ and for ES on a Micromass (Waters) Quattro (I) MS/MS, connected to a HP1090 Series 2 LC (Agilent), controlled by Masslynx version 3.3 software. Elemental analyses were performed on an Element Analyzer 1108 by D. & H. Malhow, University of Alberta, Edmonton, AB. Where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values. Whenever elemental analyses were not available, purity was determined by HPLC and capillary electrophoresis (CE). HPLC analyses were performed using a Gilson HPLC system (Gilson, Middleton, WI) with UV detection at 200 nm. A C_{18} column with 150 × 4.6 mm, 5 μ particle size was used. The mobile phase was delivered isocratically or as a gradient at a flow rate of 1 mL/min and consisted of a combination of phosphate buffer (low or high pH) and acetonitrile. Samples were prepared at ∼100 μg/mL in mobile phase, and 20 μL were injected into the HPLC. Purity was expressed in area %. CE analyses were performed using a P/ACE System MDQ (Beckman Coulter, Fullerton, CA). Uncoated silica capillaries with a 60 (50 to detector) cm length and a 75 μm internal diameter were used for chemical purity. The run buffer used was 100 mM sodium phosphate (pH 2.5). The separation voltage was either 23 or 25 kV (normal polarity), and the capillary cartridge temperature was maintained at 20 °C. Samples (∼0.5 mg/mL in water) were injected by pressure at 0.5 psi for 6 s. Detection was by UV at 200 or 213 nm. Purity was expressed in area %. Enantiomeric excess was determined by chiral CE using 5% highly sulfated γ-cylodextrin at 20 kV (reverse polarity) with a 30 (20 to detector) cm length and a 50 μm internal diameter capillary at 214 nm. IR was recorded on a Perkin-Elmer 983G spectrophotometer. Optical rotations were performed by F. Hoffman-La Roche, Ltd. (CH, Basel). Thin layer chromatography (TLC) was performed on E. Merck, TLC aluminum sheets 20 × 20 cm, silica gel 60 F_{254} plates, using UV_{254nm} and/or $KMnO_4$ as visualizing agents. Flash chromatography[41] was performed on E. M. Science silica gel 60 (70−230 mesh). Dry flash chromatography[42] was performed with Sigma silica gel type H. Chromatotron chromatography (Harisson Research, U.S.A.) was performed on 4 mm plate with E. M. Science silica gel 60P F_{254} with gypsum or aluminum oxide 60P F_{254} with gypsum (type E). Preparative HPLCs were performed on a Waters Delta Prep 4000 with a cartridge column (porasil, 10 μm, 125 Å, 40 mm × 100 mm). GC analyses were performed on a Hewlett-Packard HP 6890 equipped with 30 m × 0.25 mm × 0.25 μm capillary column HP-35 (crosslinked 35% PH ME siloxane) and a flame-ionization detector. Chemicals were purchased from Aldrich, Lancaster, or Acros. High-boiling solvents (DMF, DMSO) were Sure/Seal from Aldrich, and tetrahydrofuran (THF) and DME were distilled from sodium-benzophenone ketyl. Organic extracts were dried with Na_2SO_4 unless otherwise noted. All moisture-sensitive reactions were performed in dried glassware under a nitrogen or argon atmosphere.

Chemistry. *N*-Benzyloxycarbonyl-3-pyrrolidinol (1b). To a cold (−60 °C) solution of **1a** (20.0 g, 225 mmol) and Et_3N (79 mL, 560 mmol) in CH_2Cl_2 (200 mL) was added dropwise a solution of benzyl chloroformate (34 mL, 225 mmol) in CH_2Cl_2 (80 mL). After the addition was completed within 45 min, the reaction mixture (a yellow suspension) was allowed to warm up to room temperature and was stirred under argon at room temperature overnight. The reaction mixture was then quenched with 1 M aq HCl (350 mL), and the organic layer was collected. The acidic aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL), and the combined organic layers were dried. Evaporation in vacuo of the solvent provided 59.6 g of pale yellow oil, which was further pumped under high vacuum for 15 min to yield 58.2 g (17% over theoretical yield) of **1b** suitable for the next step without any further purification. R_f 0.42 (EtOAc−*i*-$PrNH_2$, 98:2, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 5.10 (s, 2H), 4.40 (br s, 1H), 3.60−3.40 (m, 4H), 2.80 (d, J = 15 Hz, 1H), 2.00−1.90 (m, 2H); ^{13}C (50 MHz, APT, $CDCl_3$) δ 137.0 (+), 128.5 (−), 127.5 (−), 71.0 (−), 70.0 (−), 66.5 (+), 55.0 (+), 54.5 (+), 44.0 (+), 43.5 (+), 34.0 (+), 33.5 (+); IR (film) 3415 (broad), 1678 cm^{-1}.

***N*-Benzyloxycarbonyl-3-pyrrolidinone (1c).** To a chilled (−60 °C) solution of oxalyl chloride (23 mL, 258.6 mmol) in CH_2Cl_2 (400 mL) was added dropwise a solution of DMSO (36.7 mL, 517.3 mmol) in CH_2Cl_2 (20 mL) at such a rate to keep the temperature below −40 °C. The reaction mixture was then stirred at −60 °C for 15 min. Then a solution of **1b** (58.2 g, no more than 225.0 mmol) in CH_2Cl_2 (80 mL) was added dropwise, keeping the reaction mixture temperature below −50 °C. The reaction mixture was then stirred at −60 °C for 30 min before adding Et_3N (158.3 mL, 1125.0 mmol). The resulting mixture was allowed to warm up to room temperature and then washed with water (600 mL), 1 M aq HCl (580 mL), and water (400 mL). The organic layer was dried and concentrated in vacuo to leave 54.5 g of amber oil, which was further pumped under high vacuum with stirring at room temperature for 25 min to give 52 g (5.6% over theoretical yield) of **1c** suitable for the next step without any further purification. R_f 0.81 (EtOAc−*i*-$PrNH_2$, 98:2, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 5.20 (s, 2H), 3.90−3.80 (m, 4H), 2.60 (t, J = 7 Hz, 2H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 136.0 (+), 128.5 (−), 128.0 (−), 67.0 (+), 52.5 (+), 42.5 (+), 36.5 (+); IR (film) 1759, 1708 cm^{-1}.

7-Benzyloxycarbonyl-1,4-dioxa-7-azaspiro[4.4]nonane (1d). A mixture of **1c** (52 g, no more than 225.0 mmol) and ethylene glycol (18.8 mL, 337.4 mmol) in toluene (180 mL) with a catalytic amount of *p*-TsOH·H_2O (1.0 g, 5.4 mmol) was refluxed in a Dean−Stark apparatus for 16 h. The reaction mixture was then diluted with more toluene (250 mL) and washed with saturated aq $NaHCO_3$ (150 mL) and brine (2 × 150 mL). The combined aqueous layers were back-extracted with toluene (100 mL). The combined organic layers were dried and concentrated in vacuo to leave 79.6 g of dark oil. The crude product was dissolved in EtOH (500 mL), and running it through a bed of activated carbon (80 g) decolorized the resultant solution. The charcoal was washed with more EtOH (1000 mL) and toluene (500 mL). The filtrate was concentrated in vacuo and further pumped under high vacuum for 1 h to yield 63.2 g (6.8% over theoretical yield) of **1d** suitable for the next step without any further purification. R_f 0.78 (EtOAc−*i*-$PrNH_2$, 98:2, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 5.20 (s, 2H), 4.00 (s, 4H), 3.60−3.50 (m, 2H), 3.50−3.40 (m, 2H), 2.10−2.00 (m, 2H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 137.0 (+), 128.5 (−), 128.0 (−), 67.0 (+), 65.0 (+), 55.0 (+), 45.0 (+), 34.5 (+); IR (film) 1703 cm^{-1}.

1,4-Dioxa-7-azaspiro[4.4]nonane (1e). A mixture of **1d** (34.8 g, no more than 124.0 mmol) and 10% Pd−C (14.0 g) in EtOH (90 mL) was hydrogenolyzed (60 psi) in a Parr shaker apparatus at room temperature for 1.5 h. The catalyst was filtered off, the solvent was evaporated in vacuo, and the residue was pumped under high vacuum for 20 min to yield **1e** (15.9 g, quant. yield). R_f 0.14 (EtOAc−*i*-$PrNH_2$, 95:5, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.00 (s, 4H), 3.10 (t, J = 7 Hz, 2H), 2.90 (s, 2H), 2.00 (t, J = 7 Hz, 2H); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 64.5 (+), 55.0 (+), 45.5 (+), 37.0 (+); IR (film) 3292 cm^{-1}.

(1*R*,2*R*)/(1*S*,2*S*)-2-(1,4-Dioxa-7-azaspiro[4.4]non-7-yl)cyclohexan-1-ol (2e). A mixture of **1e** (23.5 g, no more than 182.0 mmol), cyclohexene oxide (23 mL, 220.0 mmol), and water (8 mL) was heated at 80 °C for 2 h. The reaction mixture was then partitioned between 40% aq NaOH (60 mL) and Et_2O (120 mL). The basic aqueous layer was extracted twice more with Et_2O (2 ×

120 mL). The combined organic extracts were dried and concentrated in vacuo. The residue was then heated under high vacuum at 50 °C for 1 h with stirring (to remove the excess of cyclohexene oxide) to yield 32.8 g of **2e** (79% yield). R_f 0.33 (EtOAc−*i*-$PrNH_2$, 98:2, v/v); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 115.5 (+), 70.0 (−), 65.0 (−), 64.5 (+), 57.0 (+), 46.5 (+), 36.0 (+), 33.5 (+), 25.0 (+), 24.0 (+), 21.5 (+); IR (film) 3457 cm^{-1}.

The aminoalcohol **2g** (Table 1) was prepared by following the procedure described above.

(1*R*,2*R*)/(1*S*,2*S*)-2-(4-Morpholinyl)cyclohexan-1-ol (2a). A mixture of cyclohexene oxide (206 mL, 2.0 mol) and morpholine (175 mL, 2.0 mol) in water (60 mL) was refluxed for 3.5 h. Morpholine (5.3 mL, 0.06 mol) was added to the reaction mixture, which was then further refluxed for 1.5 h to complete the reaction. The cooled reaction mixture was then partitioned between 40% aq NaOH (100 mL) and Et_2O (200 mL). The aqueous layer was separated from the organic layer and extracted twice more with Et_2O (2 × 100 mL). The combined organic extracts were dried and the solvent was evaporated in vacuo. Vacuum distillation yielded 342.0 g (92% yield) of **2a**. ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 70.5 (−), 68.3 (−), 67.4 (+), 48.7 (+), 33.1 (+), 25.4 (+), 24.0 (+), 22.1 (+).

(1*R*,2*R*)/(1*S*,2*S*)-2-[1-(4-t-Butyloxycarbonylpiperazinyl)]-cyclohexan-1-ol (2h). A mixture of cyclohexene oxide (6.0 g, 60.0 mmol) and *tert*-butyl 1-piperazinecarboxylate (3.8 g, 20.0 mmol) in water (3 mL) was refluxed for 16 h. The cooled reaction mixture was then partitioned between 5 M aq NaOH (20 mL) and Et_2O (50 mL). The aqueous layer was extracted twice more with Et_2O (2 × 50 mL), the combined organic extracts were dried, and the solvent was evaporated in vacuo. The excess of cyclohexene oxide was removed under high vacuum at 60 °C for 2.5 h to yield **2h** (6.8 g, no more than 20.0 mmol) suitable for the next step without any further purification. ^{13}C NMR (100 MHz, APT, $CDCl_3$) δ 154.6 (−), 79.6 (−), 70.4 (+), 68.4 (+), 48.2 (−), 33.1 (−), 32.7 (−), 28.3 (+), 25.3 (−), 23.9 (−), 22.3 (−); EIMS *m*/*z* (relative intensity) 284 (M^+, 18).

(2*R*)/(2*S*)-2-(4-Morpholinyl)hexan-1-ol (2i). A mixture of 1,2-epoxyhexane (12.4 g, 120.0 mmol) and morpholine (10.6 g, 120.0 mmol) in water (4 mL) was refluxed for 2 h. The cooled reaction mixture was then partitioned between 20% aq NaOH (50 mL) and Et_2O (60 mL). The aqueous layer was separated and extracted twice more with Et_2O (2 × 60 mL). The combined organic extracts were dried over potassium carbonate, and the solvent was evaporated in vacuo. Full vacuum distillation yielded 20.0 g (90% yield) of the title compound **2i** as a colorless oil. R_f 0.16 (EtOAc−hexanes, 1:4, v/v, + 0.5% v/v *i*-$PrNH_2$); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 66.5 (+), 65.6 (−), 64.5 (+), 53.3 (+), 34.2 (+), 27.3 (+), 22.4 (+), 13.6 (−).

The aminoalcohols **2b**−**d** and **2f** (Table 1) were prepared by using the procedures described above.

(1*R*,2*R*)/(1*S*,2*S*)-2-(3-Thiazolidinyl)cyclohexan-1-ol (2j). To $Mg(ClO_4)_2$ (12.9 g, 53.0 mmol) was added a solution of cyclohexene oxide (6.1 mL, 59.0 mmol) in CH_3CN (25 mL), and the resultant mixture was stirred at room temperature for 20 min. Then a solution of thiazolidine (5.2 g, 55.0 mmol) in CH_3CN was added and the reaction mixture was heated at 35 °C for 16 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between water (350 mL) and Et_2O (350 mL). The aqueous layer was separated and extracted once more with Et_2O (350 mL). The combined organic extracts were dried and concentrated in vacuo to provide the crude product. The crude aminoalcohol was purified by dry-column chromatography with a mixture of EtOAc−hexanes (1:1, v/v, + 0.5% v/v *i*-$PrNH_2$) as eluent to yield 4.8 g (47% yield) of **2j** suitable for the next step without further purification. ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 71.0 (−), 69.0 (−), 55.0 (+), 53.0 (+), 33.0 (+), 31.0 (+), 26.0 (+), 25.0 (+), 23.0 (+).

3,4-Dichlorophenethyl Alcohol (3l). To a solution of $LiAlH_4$ (7.8 g, 195.0 mmol) in Et_2O (435 mL) was added slowly as a powder, via a solid dropping funnel, 3,4-dichlorophenyl acetic acid (27.2 g, 130.0 mmol). When the addition was completed, the reaction mixture was refluxed for 12 h. The reaction was quenched by cautious addition of saturated aq Na_2SO_4 (20 mL), the resultant insoluble was then filtered off, and the filtrate was concentrated in vacuo to yield quantitatively **3l** (25.0 g). ^1H NMR (200 MHz, $CDCl_3$) δ 7.40−7.00 (m, 3H, Ar), 3.80 (t, 2H, OCH_2), 2.80 (t, 2H, CH_2), 1.80 (br s, 1H, OH).

Alcohols **3m**, **3o**,**p**, **3r**, and **3u** (Table 2) were prepared by using the procedure described above.

2,4-Dibromophenethyl Alcohol (3s). To a chilled (<0 °C) solution of 90% HNO_3 (67 mL) and water (33 mL) was added a solid mixture of 2,4-dibromoaniline (25.6 g, 100.0 mmol) and KNO_2 (9.2 g, 105.0 mmol) over an 80 min time period. The reaction mixture was stirred for another 20 min and then poured into ice water (500 mL). The resultant mixture was filtered and the cold filtrate was added slowly to a solution of CuCN (10.9 g, 120.0 mmol) and KCN (24.2 g, 360.0 mmol) in water (400 mL) at 70 °C. During the addition, the temperature of the reaction mixture was kept at 62−70 °C and the reaction mixture was always kept basic by adding 12 M aq KOH. The stirred reaction mixture was maintained at 70 °C for another 30 min and then was allowed to cool to room temperature. The aqueous layer was extracted with EtOAc (3 × 700 mL), the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated in vacuo. Purification by flash chromatography with hexanes and mixtures of EtOAc−hexanes (1:19, 1:9, v/v) yielded 17.9 g (69% yield) of 2,4-dibromobenzonitrile. R_f 0.10 (EtOAc−hexanes, 1:99, v/v); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 135.9 (−), 134.9 (−), 131.1 (−), 128.2 (+), 126.0 (+), 116.5 (+), 114.7 (+); IR (film) 2229 cm^{-1}; EIMS *m*/*z* (relative intensity) 263 (M^+, 48), 261 (M^+, 100), 259 (M^+, 50), 182 (45), 180 (48), 100 (77), 75 (43).

To a chilled (0 °C) solution of 2,4-dibromobenzonitrile (25.9 g, 93.0 mmol) in THF (140 mL) was added 1 M DIBAL solution in hexanes (98 mL) over a 30 min time period. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 20 h. A total of 300 mL of 1 M aq HCl was added to quench the reaction, and the organic solvents were evaporated under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL), the combined organic extracts were dried, and the solvent was evaporated in vacuo. The crude aldehyde was used for the next step without any further purification. R_f 0.53 (EtOAc−hexanes, 1:19, v/v).

To a chilled (0 °C) suspension of $NaBH_4$ (1.38 g, 36.0 mmol) in THF (50 mL) was added a solution of 2,4-dibromobenzaldehyde in THF (150 mL) over a 20 min time period. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 2.5 h before adding water (200 mL) and 10% aq HCl (4.8 mL) to quench the reaction. The organic solvents were evaporated under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were dried and the solvent was evaporated in vacuo. Purification by dry-column with hexanes and a mixture of EtOAc−hexanes (1:19, v/v) yielded 14.0 g (yield 56%, 2 steps) of 2,4-dibromobenzyl alcohol. R_f 0.30 (EtOAc−hexanes, 1:6, v/v); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 138.8 (+), 134.8 (−), 130.7 (−), 129.7 (−), 122.8 (+), 121.6 (+), 64.4 (+); IR (film) 3218 cm^{-1}.

To a chilled (0 °C) solution of 2,4-dibromobenzyl alcohol (3.84 g, 14.1 mmol) and Et_3N (1.58 g, 15.5 mmol) in THF (30 mL) was added dropwise neat CH_3SO_2Cl (1.81 g, 15.5 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 50 min. The reaction mixture was quenched with water (40 mL), and the organic solvents were evaporated under reduced pressure. The aqueous layer was extracted with EtOAc (3 × 40 mL), the combined organic extracts were dried over potassium carbonate, and the solvent was evaporated in vacuo.

A mixture of the crude 2,4-dibromobenzyl mesylate, KCN (2.0 g, 30.0 mmol) in DMF (30 mL), and water (10 mL) was stirred at room temperature for 3.5 h. The reaction mixture was extracted with EtOAc (1 × 30 mL and 2 × 15 mL), the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated in vacuo. The crude nitrile was used for the next step without any further purification. R_f 0.29 (EtOAc−hexanes, 1:9, v/v).

A mixture of crude 2,4-dibromophenyl acetonitrile, KOH (2.52 g, 39.0 mmol) in EtOH (10 mL), and water (10 mL) was refluxed

for 3 h. The organic solvent was evaporated under reduced pressure, and the aqueous layer was diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The pH of the aqueous layer was adjusted to pH 4 with 10% aq HCl, and the resultant aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated in vacuo to yield 3.1 g (53% yield, over 3 steps) of 2,4-dibromophenyl acetic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 2H, Ar), 7.40 (dd, 2H, Ar), 7.15 (d, 2H, Ar), 3.77 (s, 2H, CH_2); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 175.9 (+), 135.2 (−), 132.5 (−), 130.8 (−), 125.6 (+), 121.9 (+), 40.7 (+); EIMS *m/z* (relative intensity) 296 (M^+, 14), 294 (M^+, 28), 292 (M^+, 14).

To a chilled (0 °C) solution of 2,4-dibromophenyl acetic acid (2.93 g, 10.0 mmol) in THF (20 mL) was added a 1 M BH_3 solution in THF (13 mL). The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 16 h. The reaction was quenched with 1 M aq HCl, and the organic solvent was evaporated under reduced pressure. The aqueous layer was diluted with water to 60 mL and extracted with CH_2Cl_2 (2 × 80 mL). The combined organic extracts were dried and the solvent was evaporated in vacuo to yield 2.74 g (98% yield) of **3s**. R_f 0.58 (EtOAc−hexanes, 1:2, v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.10 (m, 3H, Ar), 3.90 (t, 2H, CH_2), 3.00 (t, 2H, CH_2), 1.40 (t, 1H, OH).

Method A. (1*R*,2*R*)/(1*S*,2*S*)-1-(2-Naphthalenethoxy)-2-(4-morpholinyl)cyclohexane Monohydrochloride (4). To a chilled (0 °C) solution of **2a** (6.0 g, 32.4 mmol) and Et_3N (6.8 mL, 48.0 mmol) in CH_2Cl_2 (100 mL) was added via cannula a solution of CH_3SO_2-Cl (3.1 mL, 40.0 mmol) in CH_2Cl_2 (50 mL). The addition was completed in 10 min, and the reaction mixture was stirred for 1 h at 0 °C and then at room temperature for 4 h. The CH_2Cl_2 mixture was washed with water (2 × 50 mL) and the combined aqueous washings were back-extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried and concentrated in vacuo to provide 8.5 g of the crude mesylate suitable for the next step without any further purification.

To NaH, 80% oil dispersion, previously washed with hexanes (3 × 20 mL, 1.24 g, 51.7 mmol) in DMF (50 mL) was added via cannula a solution of **3a** (6.8 g, 40.0 mmol) in DMF (50 mL). The resultant reaction mixture was stirred at room temperature for 30 min. Then the stirred reaction mixture was heated to 80 °C, while the solution of mesylate dissolved in DMF (50 mL) was rapidly (3 min) added via cannula. The reaction mixture was heated overnight at 80 °C and then cooled to room temperature. The resulting yellow solution was poured into ice water (800 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were back-washed with brine (300 mL) and dried. Evaporation of the solvent in vacuo provided 13.4 g of an amber oil that was dissolved in water (150 mL), and the pH of the solution was adjusted to pH 2 with 1 M aq HCl. The acidic aqueous solution was extracted with Et_2O (2 × 100 mL) and then basified to pH 10 with 50% aq NaOH. The basic aqueous solution was extracted with Et_2O (2 × 100 mL), and the combined organic layers were dried and concentrated in vacuo to leave 7.16 g of the crude title compound as a free base. The crude product was purified by flash chromatography with a mixture of EtOAc−$CHCl_3$ (1:1, v/v) as eluent to yield 4.37 g of the pure compound. The product was dissolved in Et_2O (80 mL) and converted to the HCl salt by treatment with ethereal HCl. The solvent was evaporated in vacuo, the residue was dissolved in the minimum amount of warm EtOH, and then addition of a large volume of Et_2O triggered crystallization. The crystals were collected to afford **4** (3.83 g, 31% yield); mp 158−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (br s, 1H, HN^+), 7.80−7.20 (m, 7H, Ar), 4.25−1.50 (m, 22H, aliph); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 135.9 (+), 133.3 (+), 132.1 (+), 128.2 (−), 127.5 (−), 127.3 (−), 127.2 (−), 126.7 (−), 126.1 (−), 125.5 (−), 77.2 (−), 69.6 (−), 68.1 (+), 63.7 (+), 63.0 (+), 53.4 (+), 47.8 (+), 36.4 (+), 30.3 (+), 26.6 (+), 24.4 (+), 23.1 (+); HRMS (EI) mass calcd for $C_{22}H_{29}NO_2$, 339.21982; found, 339.21992 (100%); Anal. ($C_{22}H_{30}$-NO_2Cl) H, N. Anal. Calcd for $C_{22}H_{30}NO_2Cl$: C, 70.29. Found: C, 69.57.

The aminoethers **5**−**17** and **19**−**25** (Table 3) were prepared by using the procedure described above, method A.

Method B. (1*R*,2*R*)/(1*S*,2*S*)-1-(3,4-Dichlorophenethoxy)-2-(4-morpholinyl)cyclohexane Monohydrochloride (18). To a chilled (0 °C) solution of **2a** (40.8 g, 220.0 mmol) and Et_3N (36.6 mL, 260.0 mmol) in CH_2Cl_2 (400 mL) was added dropwise a solution of CH_3SO_2Cl (20.5 mL, 260.0 mol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at 0 °C for 45 min and then at room temperature for 3 h. The reaction mixture was then washed with water (2 × 100 mL), and the combined washings were back-extracted with CH_2Cl_2 (100 mL). The combined organic extracts were dried and the solvent was evaporated in vacuo to yield the crude mesylate suitable for the next step without any further purification.

To NaH (6.0 g, 0.2 mol, 80% dispersion in oil) in DME (200 mL) was added a solution of **3l** (38.9 g, 0.2 mol) in DME (100 mL). The resulting mixture was stirred for 3 h at ambient temperature under an argon atmosphere.

The mesylate in DME (100 mL) was added quickly to the alkoxide and the resulting reaction mixture was refluxed for 16 h. To the cooled reaction mixture was added water (200 mL), and the organic solvent was evaporated in vacuo. The resulting aqueous solution was further diluted with water (200 mL) and the pH was adjusted to pH 1.5 with 10% aq HCl. The acidic aqueous layer was extracted with Et_2O (500 mL) to eliminate the unreacted **3l**. Further basification of the aqueous layer with 5 M aq NaOH to pH 5.7 followed by extraction with Et_2O provided the crude title compound as a free base contaminated with some remaining mesylate. The solvent of the organic extract at pH 5.7 was evaporated in vacuo, and the residue was then refluxed in a mixture of EtOH−water (1:1, v/v, 200 mL) in the presence of NaH (4.12 g, 0.1 mol) for 2 h to hydrolyze the remaining mesylate. The cooled reaction mixture was diluted with water (300 mL) and the organic solvent was evaporated in vacuo. The pH of the residual aqueous solution was adjusted to pH 5.7 with 6 M aq HCl followed by extraction with Et_2O (700 mL). The organic extract was concentrated in vacuo to yield the pure title compound as a free base. The residual product was then partitioned between 1 M aq HCl (300 mL) and CH_2Cl_2 (300 mL). The acidic aqueous solution was extracted twice more with CH_2Cl_2 (2 × 300 mL), the combined organic layers were dried, and the solvent was evaporated in vacuo. The residue was recrystallized from a mixture of EtOH−hexanes (3:7, v/v, 700 mL) to yield **18** (49.3 g, 62% yield); mp 175−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.75 (br s, 1H, HN^+), 7.50−7.00 (m, 3H, Ar), 4.50−1.00 (m, 22H, aliph); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 138.8 (+), 132.3 (+), 130.5 (−), 130.4 (−), 128.1 (−), 69.6 (−), 67.7 (+), 63.8 (+), 63.2 (+), 53.2 (+), 48.3 (+), 35.3 (+), 30.2 (+), 26.5 (+), 24.3 (+), 23.0 (+); HRMS (EI) mass calcd for $C_{18}H_{25}NO_2Cl_2$, 357.12622; found, 357.12624 (100%); Anal. ($C_{18}H_{26}NO_2Cl_3$) C, H, N.

The aminoethers **39**, **42**, **51**, and **52** (Table 3) were prepared by using the procedure described above, method B.

(1*R*,2*R*)/(1*S*,2*S*)-1-(1-Naphthalenethoxy)-2-[1,4-dioxa-7-azaspiro-[4.4]non-7-yl] cyclohexane Monohydrochloride (32) and (1*R*,2*R*)/(1*S*,2*S*)-1-(1-Naphthalenethoxy)-2-(3-ketopyrrolidinyl)cyclohexane Monohydrochloride (26). To a chilled (0 °C) solution of **2e** (27.5 g, 120.0 mmol) and Et_3N (15.9 g, 156.0 mmol) in CH_2Cl_2 (240 mL) was added dropwise CH_3SO_2Cl (18.2 g, 156.0 mmol). The reaction mixture was stirred at 0 °C for 45 min and then at room temperature for 3 h. The reaction mixture was then washed with 2 M aq $NaHCO_3$ (120 mL). The washing layer was collected and was back-extracted with CH_2Cl_2 (120 mL). The combined organic extracts were dried, the solvent was evaporated in vacuo, and the residue was pumped under high vacuum for 4 h to yield the crude mesylate suitable for the next step without any further purification.

To NaH (4.32 g, 144.0 mmol) suspended in DME (80 mL) was added a solution of **3b** (25.3 g, 144.0 mmol) in DME (80 mL). The resultant mixture was then stirred at room temperature for 4 h.

A solution of mesylate in DME (80 mL) was added quickly to the alkoxide and then the resultant mixture was heated to reflux under argon for 66 h. The cooled reaction mixture was quenched with water (200 mL), and the organic solvent was evaporated in vacuo. The remaining aqueous solution was diluted with water (500 mL) and acidified with 10% aq HCl to pH 0.5. The acidic aqueous layer was extracted with Et_2O (2 × 500 mL) to extract unreacted **3b**. The pH of the aqueous solution was adjusted to pH 6.5 with 5 M aq NaOH and then extracted with Et_2O (3 × 600 mL). The combined organic extracts were dried, the solvent was evaporated in vacuo, and the residue was pumped under high vacuum for 3.5 h to yield 35.8 g (75% yield) of (1*R*,2*R*)/(1*S*,2*S*)-1-(1-naphthalenethoxy)-2-[1,4-dioxa-7-azaspiro[4.4]non-7-yl]cyclohexane suitable for the next step without any further purification.

(1*R*,2*R*)/(1*S*,2*S*)-1-(1-Naphthalenethoxy)-2-[1,4-dioxa-7-azaspiro-[4.4]non-7-yl]cyclohexane (1.2 g, 3.14 mmol) in Et_2O (80 mL) was treated with ethereal HCl. The solvent was evaporated in vacuo, and the residue was taken up with Et_2O and triturated. The title compound **32** was precipitated from a mixture of CH_2Cl_2−Et_2O (0.85 g, 65% yield); mp 117−118 °C; ^{1}H NMR (300 MHz, free base, $CDCl_3$) δ 8.1−7.3 (m, 7 H, Ar), 3.9−1.1 (m, 23 H, aliph.); ^{13}C NMR (75 MHz, APT, free base, $CDCl_3$) δ 135.0 (+), 133.7 (+), 132.0 (+), 128.6 (−), 126.8 (−), 126.7 (−), 125.7 (−), 125.4 (−), 125.3 (−), 123.7 (−), 115.2 (+), 79.1 (−), 68.8 (+), 64,2 (+), 63.8 (−), 60.3 (−), 49.8 (+), 35.8 (+), 33.9 (+), 28.6 (+), 26.9 (+), 23.0 (+), 22.7 (+); HRMS (EI) mass calcd for $C_{24}H_{31}O_3N$, 381.23041; found, 381.23008 (21.4%); Anal. ($C_{24}H_{32}O_3$-NCl) H, N. Anal. Calcd for $C_{24}H_{32}O_3NCl$: C, 68.97. Found: C, 68.49.

A solution of (1*R*,2*R*)/(1*S*,2*S*)-1-(1-naphthalenethoxy)-2-[1,4-dioxa-7-azaspiro[4.4]non-7-yl]cyclohexane (13.7 g, 36.0 mmol) with 6 M aq HCl (50 mL) in 2-butanone (200 mL) was refluxed for 12 h. The butanone was evaporated in vacuo and the residual aqueous solution was diluted to 250 mL with water. The aqueous solution was extracted with Et_2O (2 × 200 mL) and then with CH_2-Cl_2 (2 × 200 mL). The pooled CH_2Cl_2 extracts were dried and the solvent was evaporated in vacuo. The residual oil was azeotropically dried with toluene. The sticky product was triturated in Et_2O (500 mL), the resultant solid was collected and solubilized in a small amount of CH_2Cl_2 (∼10 mL), and then addition of a large quantity of Et_2O (∼400 mL) triggered recrystallization. The solid was collected and dried under high vacuum for 3 h to yield **26** (9.3 g, 76% yield); mp 121−125 °C (decomposes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.80 (br s, 1H, HN^+), 8.20−7.20 (m, 7H, Ar), 4.00−1.00 (m, 20H, aliph); ^{13}C NMR (75 MHz, APT, free base, $CDCl_3$) δ 215.1 (+), 134.9 (+), 133.7 (+), 131.9 (+), 128.7 (−), 126.9 (−), 126.8 (−), 125.8 (−), 125.4 (−), 123.6 (−), 79.4 (−), 68.6 (+), 63.7 (−), 58.8 (+), 47.9 (+), 37.6 (+), 33.8 (+), 29.1 (+), 26.9 (+), 23.5 (+), 23.0 (+); HRMS (EI) mass calcd for $C_{22}H_{27}$-NO_2, 337.20419; found, 337.20471 (100%); Anal. ($C_{22}H_{27}NO_2Cl$) C, H, N.

The aminoethers **27**, **28**, **34**, **35**, **37**, **38**, **43**−**45**, and **48** (Table 3) were prepared by using the procedure described above, method B.

(1*R*,2*R*)/(1*S*,2*S*)-1-(2,4-Dibromophenethoxy)-2-(4-morpholinyl)-cyclohexane monohydrochloride (30). To a chilled (0 °C) solution of **2a** (1.0 g, 5.4 mmol) and Et_3N (0.63 g, 6.4 mmol) in CH_2Cl_2 (15 mL) was added dropwise neat CH_3SO_2Cl (0.7 g, 6.0 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 1.5 h. The reaction mixture was then washed with water (15 mL). The aqueous layer was collected and back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried and the solvent was evaporated in vacuo to yield the crude mesylate suitable for the next step without any further purification.

To NaH (0.12 g, 80% dispersion in mineral oil, 5.9 mmol) suspended in DME (2 mL) was added a solution of **3s** (1.1 g, 3.6 mmol) in DME (8 mL). The resultant mixture was then stirred at room temperature for 40 min.

A solution of mesylate in DME (10 mL) was added quickly to the alkoxide, and the resultant mixture was heated to 75−95 °C under argon for 20 h. The cooled reaction mixture was quenched with water (20 mL), and the organic solvent was evaporated in vacuo. The residual mixture was acidified with 1 M aq HCl (15 mL), and the resultant acidic aqueous layer was extracted with Et_2O (1 × 20 mL, 1 × 15 mL). The pH of the aqueous solution was adjusted to pH 5.5 with 5 M aq NaOH and then extracted with Et_2O (20 mL). The Et_2O extract was dried and the solvent was evaporated in vacuo. Purification by dry-column with hexanes and a mixture of EtOAc−hexanes (1:4, v/v, +0.5% v/v *i*-$PrNH_2$) yielded 0.69 g (43% yield) of the title compound as a free base.

A total of 1.22 g (2.74 mmol) of the free base was dissolved in CH_2Cl_2 (15 mL) and stirred with 0.5 M aq HCl (11 mL). The aqueous layer was separated and extracted twice more with CH_2-Cl_2 (2 × 10 mL). The combined organic layers were dried and concentrated in vacuo. Crystallization from a mixture of EtOH, acetone, and hexanes provided **30** (0.97 g, 31% yield over 2 steps). R_f 0.10 (EtOAc−hexanes, 1:9, v/v, + 0.5% v/v *i*-$PrNH_2$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.0 (br, s, 1H, NH^+), 7.65−7.12 (m, 3H, Ar), 4.48−1.05 (m, 22H, aliph); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 136.6 (+), 135.2 (−), 132.1 (−), 130.5 (−), 124.8 (+), 120.7 (+), 77.4 (−), 69.6 (−), 66.4 (+), 63.8 (+), 63.2 (+), 53.4 (+), 47.7 (+), 35.8 (+), 30.1 (+), 26.6 (+), 24.3 (+), 23.0 (+); IR (film) 3403, 2933, 2862, 1576, 1466, 1371, 1096, 727 cm^{-1}; HRMS (EI) mass calcd for $C_{18}H_{25}Br_2NO_2$, 445.02521; found, 445.02188 (69.5%); Anal. ($C_{18}H_{26}Br_2NO_2Cl$) C, H, N.

(1*R*,2*R*)/(1*S*,2*S*)-1-(2,6-Dichlorophenethoxy)-2-(3-thiazolidinyl)-cyclohexane Monohydrochloride (42). To a chilled (0 °C) solution of **2j** (3.2 g, 17.0 mmol) and Et_3N (3.1 mL, 22.0 mmol) in CH_2Cl_2 (30 mL) was added dropwise CH_3SO_2Cl (1.74 mL, 22.0 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at ambient temperature for 3 h. The reaction mixture was diluted with CH_2-Cl_2 (20 mL) and washed with water (2 × 30 mL). The combined washings were back-extracted with CH_2Cl_2 (25 mL), and the combined organic extracts were dried. Evaporation of the solvent in vacuo yielded the mesylate suitable for the next step without further purification.

To NaH, 80% oil dispersion (0.61 g, 20.3 mmol) in DME (30 mL), was added a solution of **3r** (3.9 g, 20.3 mmol) in DME (15 mL). The resultant mixture was stirred at room temperature under an argon atmosphere for 2 h.

The mesylate in DME (15 mL) was quickly added to the alkoxide, and the reaction mixture was refluxed for 40 h. The cooled reaction mixture was poured into water (100 mL), and the organic solvent was evaporated in vacuo. The residual aqueous solution was diluted with more water (100 mL), and the pH was adjusted to pH 1.5. The acidic aqueous solution was extracted with Et_2O (3 × 100 mL), the combined organic extracts were dried, and the solvent was removed in vacuo to provide the crude free base. Purification by dry-column chromatography with a mixture of EtOAc−hexanes (1:10, v/v, + 0.5% v/v *i*-$PrNH_2$) as eluent yielded 2.4 g (39% yield) of the title compound as free base. A total of 1.0 g (2.8 mmol) was converted to the HCl salt by treatment with ethereal HCl, and the resultant salt was recrystallized from a mixture of acetone−Et_2O to yield **42** (0.69 g, 62% yield, 24% over two steps). ^{1}H NMR (400 MHz, free base, $CDCl_3$) δ 8.60 (br s, 1H, HN^+), 7.30−7.00 (m, 3H, Ar), 4.60−1.00 (m, 20H, aliph); ^{13}C NMR (75 MHz, APT, free base, $CDCl_3$) δ 135.6 (+), 134.1 (+), 133.8 (+), 128.2 (−), 128.1 (−), 77.5 (−), 77.0 (−), 67.5 (−), 66.8 (−), 65.5 (+), 65.4 (+), 56.4 (+), 55.0 (+), 52.8 (+), 52.5 (+), 34.6 (+), 30.2 (+), 30.2 (+), 29.3 (+), 28.6 (+), 28.2 (+), 24.5 (+), 24.4 (+), 23.0 (+), 22.9 (+); HRMS (EI) mass calcd for $C_{17}H_{23}NOSCl_2$, 359.08774; found, 359.08707 (4.5%); Anal. ($C_{17}H_{24}$-$NOSCl_3$) C, H, N.

(1*R*,2*R*)/(1*S*,2*S*)-1-(3,4-Dimethoxyphenethoxy)-2-(1-piperazinyl)cyclohexane Dihydrochloride (53). To a chilled (0 °C) solution of **2h** (2.2 g, 7.7 mmol) and Et_3N (1.0 g, 10.0 mmol) in CH_2Cl_2 (18 mL) was added dropwise CH_3SO_2Cl (1.2 g, 10.0 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 3 h. The reaction mixture was then washed with 2 M aq $NaHCO_3$ (1:1, v/v, 14 mL). The aqueous layer was collected and back-extracted with CH_2Cl_2 (2 × 15 mL). The combined

organic extracts were dried and the solvent was evaporated in vacuo to yield the crude mesylate suitable for the next step without further purification.

To a mixture of NaH (280.0 mg, 80% dispersion in mineral oil, 9.2 mmol) and **3f** (1.68 g, 9.23 mmol) was slowly added DME (30 mL). The resultant mixture was then stirred at room temperature for 1.5 h.

A solution of mesylate in DME (20 mL) was quickly added to the alkoxide, and the resultant mixture was refluxed under argon for 3.5 h. The cooled reaction mixture was quenched with water (80 mL), and the organic solvent was evaporated in vacuo. The residual aqueous solution was acidified with 6 M aq HCl to pH 1 and extracted with Et_2O (2 × 90 mL). The aqueous layer was collected, basified to pH 11 with 5 M aq NaOH, and extracted with Et_2O (3 × 140 mL). The combined organic extracts were dried and the solvent was evaporated in vacuo to yield 2.37 g (89% yield) of (1*R*,2*R*)/(1*S*,2*S*)-1-(3,4-dimethoxyphenethoxy)-2-[1-(4-*t*-butyloxycarbonylpiperazinyl)]cyclohexane, which was then mixed with CF_3CO_2H (7.3 g, 63.3 mmol) in CH_2Cl_2 (6 mL) and stirred at room temperature for 19 h. The volatile compounds were evaporated in vacuo, and the residue was partitioned between 5 M aq NaOH (12 mL) and CH_2Cl_2 (60 mL). The aqueous layer was collected and extracted twice more with CH_2Cl_2 (2 × 60 mL), the combined organic extracts were dried, and the solvent was evaporated in vacuo. Purification by dry-column chromatography with a mixture of EtOAc−*i*-$PrNH_2$ (99.5:0.5, v/v) yielded 1.54 g (56% yield over two steps) of the title compound as a free base.

The free base (0.62 g, 1.6 mmol) in THF (16 mL) was mixed with ethereal HCl (100 mL). The solvents were evaporated in vacuo, and the residual oil was azeotropically dried with benzene and under high vacuum for 4 h to yield **53** (0.45 g, 37% yield over two steps). R_f 0.11 (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.82 (br s, 2H, HN^+), 9.64 (br s, 1H, HN^+), 6.88−6.78 (m, 3H, Ar), 3.87 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 3.77−0.86 (m, 22H, aliph); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 148.8 (+), 147.5 (+), 131.3 (+), 121.1 (−), 112.9 (−), 111.5 (−), 76.3 (−), 70.0 (−), 68.9 (+), 56.1 (−), 55.9 (−), 49.2 (+), 45.6 (+), 41.0 (+), 40.9 (+), 35.6 (+), 30.2 (+), 26.3 (+), 24.3 (+), 22.8 (+); LRMS (EI) *m*/*z* (relative intensity) 348 (M^+, 24), 306 (25), 183 (100), 166 (52), 125 (77); HPLC (Zorbax Extend C-18 150 × 4.6 mm; 25 mM phosphate buffer, pH 3 : ACN, 83:17) 97.2% ; CE 95.3%.

Method C. (1*R*)/(1*S*)-1-(4-Bromophenethoxy)-2-(4-morpholinyl)hexane Monohydrochloride (29). A mixture of **2i** (9.4 g, 50.0 mmol), 4-bromophenylacetic acid (13.0 g, 60.0 mmol), and *p*-TsOH·H_2O (50.0 mg) in toluene (60 mL) was refluxed for 16 h. After cooling to room temperature, the reaction mixture was washed with 2 M aq $NaHCO_3$ (40 mL) and the aqueous layer was back-extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried over potassium carbonate and the solvents were evaporated in vacuo. Purification by dry-column with mixtures of EtOAc−hexanes (1:9, 1.4, v/v, +0.5% v/v *i*-$PrNH_2$) yielded (1*R*)/(1*S*)-2-(4-morpholinyl)hex-1-yl 4-bromophenylacetate (18.5 g, 96% yield) as a pale yellow oil. R_f 0.33 (EtOAc−hexanes, 1:4, v/v, + 0.5% v/v *i*-$PrNH_2$); IR (film) 1734 cm^{-1}.

A mixture of (1*R*)/(1*S*)-2-(4-morpholinyl)hex-1-yl 4-bromophenylacetate (7.7 g, 20.0 mmol) and $NaBH_4$ (1.4 g, 36.0 mmol) in THF (60 mL) was refluxed for 40 min. BF_3·Et_2O (25.3 mL, 200.0 mmol) was added dropwise to the refluxing reaction mixture over a 1 h period. Heating was continued for another 1.2 h and then the reaction mixture was poured into ice water (150 mL). After stirring for 50 min, 5 M aq NaOH (ca. 38 mL) was added to adjust the pH to pH 6.5. The organic solvents were evaporated in vacuo, and Et_2O (200 mL) and then 5 M aq NaOH were added to adjust the pH to pH 8.1. The aqueous layer was separated and extracted once more with Et_2O (200 mL). The combined organic layers were dried and concentrated in vacuo. Purification by dry-column chromatography with a mixture of EtOAc−hexanes (1:9, v/v, +0.5% v/v *i*-$PrNH_2$) yielded 1.33 g (18% yield) of the title compound as a free base.

A total of 0.82 g (2.2 mmol) of the free base was dissolved in CH_2Cl_2 (35 mL) and stirred with 0.5 M aq HCl (10 mL). The aqueous layer was extracted twice more with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were dried and concentrated in vacuo. Crystallization from EtOH−hexanes provided **29** (0.78 g, 16% yield). R_f 0.29 (EtOAc−hexanes, 1:9, v/v, + 0.5% v/v *i*-$PrNH_2$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.7 (br s, 1H, HN^+), 7.34 (dd, 2H, Ar), 7.07 (dd, 2H, Ar), 4.23−1.26 (m, 21H, aliph), 0.82 (t, 3H, CH_3); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 138.1 (+), 131.2 (−), 130.7 (−), 119.9 (+), 74.3 (−), 68.4 (+), 63.5 (+), 63.3 (+), 61.2 (+), 53.5 (+), 52.5 (+), 35.6 (+), 30.7 (+), 25.7 (+), 22.6 (+), 13.8 (−); IR (HCl salt, film) 2925, 2858 cm^{-1}; HRMS (EI) mass cald for $C_{18}H_{28}BrNO_2$, 369.13034; found, 369.12901 (0.5%); Anal. ($C_{18}H_{29}BrNO_2Cl$) C, H, N.

(1*R*,2*S*)/(1*S*,2*R*)-1-[2-(Trifluoromethyl)phenethoxy]-2-(4-morpholinyl)cyclohexane Monohydrochloride (33). To a cooled (−60 °C) solution of CH_2Cl_2 (500 mL) and oxalyl chloride (20 mL, 230.0 mmol) was added dropwise at a rapid rate a solution of DMSO (34 mL, 480.0 mmol) in CH_2Cl_2 (50 mL). After 5 min of stirring, a solution of **2a** (37.0 g, 200.0 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 10 min while the temperature was maintained at −50 to −60 °C. After 15 min of stirring, Et_3N (140 mL) was added dropwise while keeping the temperature at or below −50 °C. Stirring was continued for 5 min, after which time the mixture was allowed to warm to room temperature and water (600 mL) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (500 mL). The combined organic extracts were dried and the solvent was evaporated in vacuo. High vacuum distillation yielded 35.1 g (96% yield) of (2*R*)/(2*S*)-2-(4-morpholinyl)cyclohexan-1-one.

To a chilled (0 °C) suspension of $NaBH_4$ (0.92 g, 24.0 mmol) in *i*-PrOH (42 mL) was added slowly a solution of (2*R*)/(2*S*)-2-(4-morpholinyl)cyclohexan-1-one (11.0 g, 60.0 mmol) in *i*-PrOH (42 mL). The reaction mixture was stirred for 10 min, and then the ice bath was removed and the reaction mixture was further stirred at room temperature for 30 min. Water (60 mL) was added and the organic solvent was evaporated under reduced pressure. The aqueous layer was extracted with EtOAc (4 × 50 mL), the combined organic extracts were dried, and the solvent was evaporated in vacuo to yield 11.1 g of a *cis*/*trans*-mixture of 2-(4-morpholinyl)cyclohexan-1-ol, suitable for use in the next step without further purification.

A mixture of the above material (7.4 g, 40.0 mmol), 2-(trifluoromethyl)phenylacetic acid (10.2 g, 49.0 mmol), and *p*-TsOH·H_2O (40.0 mg) in toluene (60 mL) was refluxed for 48 h in a Dean−Stark apparatus. After cooling to room temperature, the reaction mixture was washed with 2 M aq $NaHCO_3$ (40 mL), and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried and the solvent was evaporated in vacuo. The *cis*/*trans*-mixture was purified by dry-column chromatography with mixtures of EtOAc−hexanes (1:19, 1:9, 1:3.9, v/v, +0.5% v/v *i*-$PrNH_2$) to yield 3.19 g of (1*R*,2*S*)/(1*S*,2*R*)-2-(4-morpholinyl)cyclohex-1-yl 2-(trifluoromethyl)phenylacetate. R_f 0.26 (EtOAc−hexanes, 1:2, v/v, + 0.5% v/v *i*-$PrNH_2$).

To a mixture of (1*S*,2*R*)/(1*R*,2*S*)-2-(4-morpholinyl)cyclohex-1-yl 2-(trifluoromethyl)phenylacetate (1.64 g, 4.3 mmol) and $NaBH_4$ (0.33 g, 8.7 mmol) in THF (35 mL) under reflux was added a solution of BF_3·Et_2O (8.2 mL, 65.0 mmol) over 1.5 h. The reaction mixture was quenched by addition of water (~70 mL), the organic solvent was evaporated in vacuo, and the pH of the residual aqueous solution was adjusted to pH 9.6. The aqueous layer was extracted with Et_2O (2 × 70 mL), the combined organic extracts were dried, and the solvent was evaporated in vacuo. The residue was then partitioned between 0.5 M aq HCl (50 mL) and Et_2O (2 × 50 mL). The aqueous solution was basified to pH 5.9 and extracted with Et_2O (50 mL). The organic layer was collected and dried, and the solvent was evaporated in vacuo. The resultant free base was converted to the HCl salt by partition between 0.5 M aq HCl (10 mL) and CH_2Cl_2 (10 mL). The acidic aqueous solution was extracted once more with CH_2Cl_2 (10 mL), the combined organic extracts were dried, and the solvent was evaporated in vacuo. Recrystallization from a mixture of EtOH−hexanes yielded **33** (0.64 g, 38% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.39 (br s, 1H,

HN^+), 7.58−7.24 (m, 4H, Ar), 4.44−1.14 (m, 22H, aliph); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 137.3 (+), 131.7 (−), 131.3 (−), 128.6 (+), 126.4 (−), 126.2 (+), 125.8 (−), 72.5 (−), 67.6 (−), 67.5 (+), 63.8 (+), 63.3 (+), 50.5 (+), 49.3 (+), 32.6 (+), 27.3 (+), 24.6 (+), 20.7 (+), 18.6 (+); HRMS (EI) mass calcd for $C_{19}H_{26}F_3NO_2$, 357.19156; found, 357.19160 (11.7%); Anal. ($C_{19}H_{27}F_3NO_2Cl$) C, H, N.

Aminoether **31** (Table 3) was prepared using the procedure described above.

Method D. (1*R*,2*S*)/(1*S*,2*R*)-1-(1-Naphthalenethoxy)-2-(3-ketopyrrolidinyl) Cyclohexane Monohydrochloride (46). To a flask containing $Mg(ClO_4)_2$ (2.14 g, 0.95 mmol) vacuum flame-dried, cooled, and charged with argon was added via cannula a solution of **3b** (21.6 g, 125.0 mmol) in CH_3CN (15 mL). The resultant mixture was refluxed until all material had dissolved and then cyclohexene oxide (1.0 g, 10.0 mmol) was added over a period of 2.5 h. The reaction mixture was then refluxed for 16 h, cooled to room temperature, and partitioned between water (150 mL), saturated aq $NaHCO_3$, (50 mL) and Et_2O (100 mL). The aqueous layer was collected and extracted twice with Et_2O (2 × 100 mL). The combined Et_2O extracts were back-washed with brine (50 mL), dried, and concentrated in vacuo to yield 25.2 g of crude material, which solidified upon standing. The excess **3b** was recovered by successive recrystallizations in Et_2O−hexanes (1:1, v/v). The resultant mother liquor (7.5 g) obtained after three recrystallizations was purified by chromatography using a mixture of EtOAc−hexanes (1:5, v/v, +0.5% v/v *i*-$PrNH_2$) to provide 1.5 g (55% yield) of crude (1*R*,2*R*)/(1*S*,2*S*)-2-(1-naphthalenethoxy)cyclohexan-1-ol, which was used in the next step without further purification.

To a suspension of pyridinium chlorochromate or PCC (4. 8 g, 22.2 mmol) in CH_2Cl_2 (35 mL) was added at once a solution of (1*R*,2*R*)/(1*S*,2*S*)-2-(1-naphthalenethoxy)cyclohexan-1-ol (1.5 g, 5.5 mmol) in CH_2Cl_2 (5 mL). The resultant dark brown mixture was stirred at room temperature for 16 h and then filtered through a plug of silica gel topped with Na_2SO_4. The plug was further rinsed with Et_2O (3 × 40 mL) and the filtrate was concentrated in vacuo to yield 2.0 g of crude material. The crude material was applied to a dry column of silica gel and eluted with a mixture of EtOAc−hexanes (1:6, v/v, + 0.5% v/v *i*-$PrNH_2$) to yield 1.0 g of (2*R*/2*S*)-2-(1-naphthalenethoxy)cyclohexan-1-one (68% yield). ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 203.0 (+), 135.0 (+), 134.0 (+), 132.0 (+), 129.0 (−), 127.0 (−), 125.5 (−), 125.0 (−), 123.5 (−), 113.0 (−), 83.0 (−), 70.0 (+), 40.0 (+), 34.5 (+), 33.5 (+), 28.0 (+), 23.0 (+); IR (film) 1720 cm^{-1}.

(2*R*/2*S*)-2-(1-Naphthalenethoxy)cyclohexan-1-one (1.0 g, 3.7 mmol), **2e** (1.2 g, 9.3 mmol), and PVP (0.4 g) in benzene (10 mL) were refluxed in a Dean−Stark apparatus for 5 h. The cooled reaction mixture was then quickly transferred to a Parr shaker apparatus, Pd on activated carbon (0.2 g) was added, and the mixture was hydrogenated for 16 h. The catalyst was removed by filtration, the filtrate was concentrated in vacuo, and the resultant crude material (*cis*/*trans*, 87:13, area %/GC) was purified by dry-column chromatography with a mixture of EtOAc−hexanes (1:2, v/v, + 0.5% v/v *i*-$PrNH_2$) to provide 1.0 g (70% yield) of (1*R*,2*S*)/(1*S*,2*R*)-1-(1-naphthalenethoxy)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)cyclohexane, which was refluxed with 6 M aq HCl (20 mL) in 2-butanone (80 mL) for 16 h. The cooled reaction mixture was concentrated in vacuo, and the residue was diluted with water (90 mL). The aqueous solution was then extracted with Et_2O (2 × 50 mL) and CH_2Cl_2 (3 × 70 mL). The combined CH_2Cl_2 extracts were dried and the solvent was evaporated in vacuo. Trituration in Et_2O provided **46** (0.82 g, 84% yield); mp 176−178 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.53 (br s, 1H, HN^+), 8.06−7.32 (m, 7H, Ar), 4.05−1.16 (m, 20H, aliph); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 204.2 (+), 204.0 (+), 135.0 (+), 134.9 (+), 133.6 (+), 131.9 (+), 131.8 (+), 128.7 (−), 127.1 (−), 127.0 (−), 125.9 (−), 125.8 (−), 125.5 (−), 125.4 (−), 123.7 (−), 123.6 (−), 72.4 (−), 71.7 (−), 68.3 (+), 68.2 (+), 65.5 (−), 64.9 (−), 54.7 (+), 54.3 (+), 48.8 (+), 48.2 (+), 35.5 (+), 35.1 (+), 32.9 (+), 26.8 (+), 26.7 (+), 24.0 (+), 22.5 (+), 21.9 (+), 18.3 (+); Anal. ($C_{22}H_{28}NO_2Cl$) C, H, N.

Methods E and F. (1*R*,2*R*)/(1*S*,2*S*)-1-(1-Naphthalenethoxy)-2-(3-(*R*/*S*)-hydroxypyrrolidinyl)cyclohexane Monohydrochloride (50) and (1*R*,2*R*)/(1*S*,2*S*)-1-(1-Naphthalenethoxy)-2-(3-(*R*/*S*)-acetoxypyrrolidinyl)cyclohexane Monohydrochloride (36). To a solution of **26** (1.4 g, 3.7 mmol) in *i*-PrOH (30 mL) was added portion-wise at room-temperature $NaBH_4$ (0.5 g, 13.2 mmol). The resultant mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with 1 M aq HCl (∼2 mL) for 40 min and then concentrated in vacuo. The residue was taken up with CH_2Cl_2 (20 mL), the insoluble material was filtered and washed with CH_2Cl_2 (20 mL), and the combined filtrates were dried and split in two equal parts.

One part was treated with ethereal HCl (20 mL). The solvents were evaporated in vacuo and the residual oil was triturated in Et_2O (80 mL) to yield **50** (0.55 g, 79% yield) as a hygroscopic solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10−7.35 (m, 7H, Ar), 4.20−1.10 (m, 22H, aliph); ^{13}C NMR (75 MHz, APT, $CDCl_3$) δ 135.0 (+), 133.7 (+), 132.0 (+), 128.6 (−), 126.9 (−), 126.8 (−), 125.8 (−), 125.4 (−), 123.7 (−), 79.5 (−), 79.3 (−), 70.9 (−), 70.7 (−), 68.7 (+), 68.6 (+), 63.3 (−), 63.2 (−), 59.6 (+), 59.3 (+), 48.6 (+), 48.4 (+), 34.3 (+), 34.1 (+), 33.8 (+), 29.1 (+), 29.0 (+), 27.0 (+), 23.5 (+), 23.4 (+), 23.1 (+), 23.0 (+); HRMS (EI) mass calcd for $C_{22}H_{29}O_2N$, 339.21983; found, 339.21962 (100%); HPLC (Supelco ODP-50 150 × 4.6 mm, 5 μ; 50 mM phosphate buffer (pH 11)−acetonitrile (50:50)) 98.9% ; CE 98.9%.

Aminoethers **47** and **50** (Table 3) were prepared by using the procedure described above, method E.

The other part was concentrated in vacuo, taken up with Ac_2O (15 mL), and refluxed for 2 h. The excess Ac_2O was removed in vacuo, the residue was taken up with water (100 mL), and the pH was adjusted to pH 1 with 1 M aq HCl. The resultant acidic aqueous solution was extracted with Et_2O (2 × 30 mL), basified to pH 8, and extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts at pH 8 were dried, concentrated under reduced pressure to ∼20 mL volume, and then treated with ethereal HCl. The solvent was evaporated in vacuo, the resultant sticky material was redissolved in CH_2Cl_2 (5 mL) and addition of Et_2O triggered crystallization of **36** (0.5 g, 65% yield) as a hygroscopic solid. ^1H NMR (400 MHz, free base, $CDCl_3$) δ 8.10−7.35 (m, 7H, Ar), 5.10 (m, 1H, CH), 4.00−1.10 (m, 23H, aliph); ^{13}C NMR (75 MHz, APT, free base, $CDCl_3$) δ 170.7 (+), 134.9 (+), 133.6 (+), 131.9 (+), 128.5 (−), 126.7 (−), 126.6 (−), 125.6 (−), 125.3 (−), 125.2 (−), 123.6 (−), 79.6 (−), 79.2 (−), 73.9 (−), 73.7 (−), 68.8 (+), 68.7 (+), 63.5 (−), 63.4 (−), 56.9 (+), 56.8 (+), 49.4 (+), 49.0 (+), 33.8 (+), 33.7 (+), 31.3 (+), 31.2 (+), 28.9 (+), 27.3 (+), 26.9 (+), 23.3 (+), 23.2 (+), 22.9 (+), 21.1 (−), 21.0 (−); HRMS (EI) mass calcd for $C_{24}H_{31}O_3N$, 381.23041; found, 381.23117 (62.2%); Anal. ($C_{24}H_{32}O_3NCl$) H, N. Anal. Calcd for $C_{24}H_{32}O_3NCl$: C, 68.97. Found: C, 67.52.

Method G. (1*R*,2*R*)-1-(1-Naphthalenethoxy)-2-(3-ketopyrrolidinyl)cyclohexane Monohydrochloride (40) and (1*S*,2*S*)-1-(1-Naphthalenethoxy)-2-(3-ketopyrrolidinyl)cyclohexane Monohydrochloride (41). A warm solution of (1*R*,2*R*)/(1*S*,2*S*)-1-(1-naphthalenethoxy)-2-(1,4-dioxa-7-azaspiro[4,4]non-7-yl)cyclohexane (1.19 g, 3 mmol) in 2-butanone (15 mL) was mixed with a warm solution of di-*p*-toluoyl-D-tartaric acid (1.20 g, 3.1 mmol) in 2-butanone (20 mL). The mixture was allowed to cool down to room temperature and placed at −20 °C overnight. The resultant precipitate (ee 73.7%) was recrystallized from MeOH−butanone to yield (1*R*,2*R*)-1-(1-naphthalenethoxy)-2-(1,4-dioxa-7-azaspiro[4,4]non-7-yl)cyclohexane tartrate (0.73 g, ee ≥ 99%). The residual mother liquor was concentrated in vacuo, and the residue was partitioned between 10% aq NaOH and CH_2Cl_2. The combined organic extracts were dried and the solvent was evaporated in vacuo. The residue (0.61 g, 1.6 mmol) was dissolved in 2-butanone (8 mL) and mixed with a warm solution of di-*p*-toluoyl-L-tartaric acid (0.63 g, 1.2 mmol) in 2-butanone (10 mL). The mixture was allowed to cool down to room temperature overnight to yield (1*S*,2*S*)-1-(1-naphthalenethoxy)-2-(1,4-dioxa-7-azaspiro[4,4]non-7-yl)cyclohexane tartrate (0.89 g, ee 97.5%).

(1*R*,2*R*)-1-(1-naphthalenethoxy)-2-(1,4-dioxa-7-azaspiro[4,4]non-7-yl)cyclohexane tartrate was partitioned between 10% aq NaOH and CH_2Cl_2, the organic layer was collected, dried, and concentrated in vacuo to provide the corresponding free base. Treatment with 6 M aq HCl in 2-butanone as previously described for **26** provided **40** in 97% yield. R_f 0.5 (EtOAc−hexanes, 1:1, v/v, +1% v/v Et_3N); ee 96.5%; $[\alpha]_{589nm}$ −30.61° (1, EtOH); MS [ES; $(M^+ + H)$] 338.1 (100%); Anal. ($C_{22}H_{28}O_2NCl$) C, H, N. The same procedure was applied to the (1*S*,2*S*)-1-(1-naphthalenethoxy)-2-(1,4-dioxa-7-azaspiro[4,4]non-7-yl)cyclohexane tartrate to provide **41** in 98% yield. R_f 0.5 (EtOAc−hexanes, 1:1, v/v, +1% v/v Et_3N); ee 95.8%; $[\alpha]_{589nm}$ +30.32° (1, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.1 (br s, 1H, HN^+), 8.05−7.20 (m, 7H, Ar), 4.00−1.00 (m, 20H, aliph); ^{13}C NMR (75 MHz, APT, free base, $CDCl_3$) δ 215.2 (+), 135.0 (+), 133.8 (+), 132.0 (+), 128.8 (−), 127.0 (−), 126.8 (−), 125.8 (−), 125.4 (−), 123.6 (−), 79.4 (−), 68.7 (+), 63.7 (−), 58.9 (+), 48.0 (+), 37.7 (+), 33.8 (+), 29.1 (+), 26.9 (+), 23.6 (+), 23.1 (+); MS [ES; $(M^+ + H)$] 338.1 (100%); Anal. ($C_{22}H_{28}O_2NCl$) C, H, N.

Single-Crystal X-ray Analysis of (1*R*,2*R*)-1-(1-Naphthalenethoxy)-2-(1,4-dioxa-7-azaspiro[4,4]non-7-yl)cyclohexane as its Tartrate. Crystal Data. A clear needle crystal of $C_{44}H_{49}NO_{11}$ having approximate dimensions of 0.40 × 0.10 × 0.05 mm was mounted on a glass fiber. All measurements were made on an ADSC CCD area detector coupled with a Rigaku AFC7 diffractometer with graphite monochromated Mo Kα radiation. Cell constants and an orientation matrix for data collection corresponded to a orthorhombic cell with dimensions: a = 10.991(4) Å, b = 11.861(4) Å, c = 34.87(1) Å, V = 4545(2) Å^3.

For Z = 4 and FW = 767.87, the calculated density is 1.12 g/cm^3. Based on the systematic absences of h00, $h \pm 2n$; 0k0, $k \pm 2n$; and 00l, $l \pm 2n$ uniquely determine the space group to be: $P2_12_12_1$ (#19).

Crystallographic Measurements. The data were collected at a temperature of −100 ± 1 °C to a maximum 2θ value of 41.6°. Data were collected in 0.30° oscillations with 27.0 s exposures. A sweep of data was done using ω oscillations from −23.0 to 25.0° at χ = −90.0°. A second sweep was performed using ϕ oscillations from 0.0 to 189.0° at χ = −90.0°. The crystal-to-detector distance was 50.13 mm. The detector swing angle was −5.91°. Of the 21 987 reflections that were collected, 4718 were unique (R_{int} = 0.227, Friedels not merged); equivalent reflections were merged. Data were collected and processed using d*TREK.[43] Net intensities and sigmas were derived as follows: $F^2 = [\sum(P_i - mB_{ave})] \times$ Lp, where P_i is the value in counts of the ith pixel, m is the number of pixels in the integration area, B_{ave} is the background average, and Lp is the Lorentz and polarization factor. $B_{ave} = \sum(B_j)/n$, where n is the number of pixels in the background area and B_j is the value of the jth pixel in counts. $\sigma^2(F^2_{hkl}) = [(\sum P_i) + m((\sum(B_{ave} - B_j)^2)/(n - 1))]\cdot$Lp$\cdot$errmul + (erradd$\cdot F^2)^2$, where erradd = 0.04 and errmul = 2.50. The linear absorption coefficient, μ, for Mo Kα radiation is 0.8 cm^{-1}. An empirical absorption correction was applied that resulted in transmission factors ranging from 0.53 to 1.00. The data were corrected for Lorentz and polarization effects.

The material was very weakly diffracting, resulting in only a small fraction of observed reflections with very poor statistics. The structure was solved by direct methods[44] and expanded using Fourier techniques.[45] The nonhydrogen atoms were refined isotropically. Hydrogen atoms were included in fixed positions. The final cycle of full-matrix least-squares refinement[46] on F^2 was based on 4718 observed reflections and 189 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of $R1 = \sum||F_o| - |F_c||/\sum|F_o| = 0.386$ and $wR2 = [\sum(w(F_o^2 - F_c^2)^2)/\sum w(F_o^2)^2]^{1/2} = 0.663$. The standard deviation of an observation of unit weight[47] was 1.16. The weighting scheme was based on counting statistics. Plots of $\sum w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, $\sin\theta/\lambda$, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.61 and −0.41 e$^-$/Å^3, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[48] Anomalous dispersion effects were included in F_{calc},[49] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[50] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[51] All calculations were performed using the teXsan[52] crystallographic software package of Molecular Structure Corporation and SHELXL-97.[53] Experimental details and final positional and thermal parameters are listed at the end of the Supporting Information (Tables 1−4).

Biology. The following studies were performed with male Sprague−Dawley rats weighing 250−350 g unless otherwise specified. The protocols were approved by Animal Care Committee of the University of British Columbia.

Test for Convulsive Activity. A serious toxicity produced by several Class I antiarrhythmic drugs is CNS toxicity. To test for CNS toxicity, a method was developed to assess the convulsive activity of compounds. The maximum acutely tolerated dose in conscious rats was assessed using an ascending continuous infusion regimen. Under pentobarbitone anaesthesia (65 mg/kg i.p.), rats were implanted with venous and arterial cannulae as well as ECG electrodes. Wound sites were infiltrated with bupivacaine and the animals were allowed to recover for 1 day before the drug was infused at a starting dose of 2 μmol/kg/min. The infusion rate was doubled every 5 min until (a) severe symptoms occurred, (b) the rat died, or (c) a maximum infusion rate of 64 μmol/kg/min was attained. Drug effects were assessed in terms of the dose that caused changes in breathing patterns, pupil dilation, exophthalmos, piloerection, paralysis, tremors, twitches, ataxia, loss of righting reflex, and convulsions as well as BP and an ECG. At the first sign of convulsions, an overdose of pentobarbitone was given to euthanize the animal.

Ischemia-Induced Arrhythmias. Regional ischemia was induced by occlusion of the left anterior descending coronary artery as previously described.[54,55] Briefly, rats were anaesthetized with pentobarbital (65 mg/kg, i.p.) and a jugular vein and carotid artery were cannulated. Rats were intubated, via a tracheotomy, and ventilated with oxygen at 60 breaths/min and 10 mL/kg. The chest was opened and a polypropylene suture was loosely placed around the left anterior descending coronary artery. Thereafter, the chest was closed and the air evacuated from the chest.

Animals were allowed to recover for fifteen minutes before test compound or vehicle was infused continuously starting 5 min prior to occlusion. Monitoring continued for 20 min after occlusion to cover the first phase (5−10 min after occlusion) of ischemia-induced arrhythmias.[56] ECG and BP measurements were taken at baseline and at 1 min prior to occlusion.

At the end of 20 min, the heart was excised and the size of the occluded zone was measured by perfusing the heart with cardiogreen dye (0.5 mg/mL). The occluded zone size was calculated as a percentage of total ventricular mass. Animals were excluded if the occluded zone size was <25% or >50% of the total ventricular mass. All experiments were performed in a blinded fashion using a random block design.

Electrical Stimulation Studies. Haemodynamic, electrocardiographic (ECG), and electrophysiological variables were measured as previously described.[57] Briefly, rats were anaesthetized with pentobarbital (65 mg/kg i.p.) and a jugular vein and carotid artery were cannulated. The trachea was intubated, and the rats were ventilated with oxygen at 60 breaths/min and a stroke volume of 10 mL/kg. A lead II ECG was recorded from subcutaneous pin electrodes. Mean BP, heart rate, and ECG intervals (PR and QT) were recorded via a customized Labview software.

Electrical stimulation of normal hearts in situ was facilitated by two fine Teflon coated silver wires inserted transthoracically into the apical wall of the left ventricle. Insertion was accomplished by passing electrodes via a transthoracic needle (27 gauge) into the left ventricle. Hearts were stimulated using square wave pulses of 0.5 ms duration at a rate of 7.5 Hz delivered from a custom built stimulator. The variables measured included threshold currents for capture (iT-μA) and ERP-ms. All determinations were made in duplicate.

The value of iT was found by determining the lowest current required to capture the ventricle. ERP was determined at a cycle length of 133 ms (7.5 Hz) using a stimulus strength twice iT. Hearts were paced for 10 beats after which an extrastimulus was introduced. The coupling interval was systematically increased from a starting value of 20 ms. ERP was defined as the shortest coupling interval that failed to produce a response.[58] Drugs were infused in a dose-doubling regime. Each dose was administered for 5 min, variables were measured during the last 2 min of infusion, and the infusion rate was doubled to give the next dose.

We have previously found[54,59−61] that such ECG and electrical stimulation studies give functional in vivo estimates of the ion channel (sodium and potassium) blocking actions of drugs. These data are consistent with data obtained in vitro in isolated rat cardiac myocytes.

Precision of estimates (SEM/mean) × 100 for the variables measured in Table 4 (D_{25}BP, ED_{50}), and in Table 5 (D_{25}BP, D_{25}PR, $D_{25}QT_1$, $D_{25}QT_2$, D_{25}iT, D_{25}ERP) were calculated as described by Barrett et al.[23] Dose−response curves for BP, ECG, as well as electrical stimulation variables were plotted using a best-fit algorithm (usually an exponential) for individual animals. From these curves the lowest dose (D) required to produce a 25% change from predrug value ($D_{25\%}$) was interpolated. These values were pooled as appropriate for calculation of the mean.

Dose−response curves for antiarrhythmic actions were plotted using an arrhythmia score (AS) because the alternative data, such as quantal data incidence of ventricular tachycardia or fibrillation, are less precise.[38] The Lambeth conventions recommend that such scores be used to summarize data.[62] The AS used summarizes an animal's arrhythmic history as a single normally (Gaussian) distributed variable (score A),[38] which takes into account the occurrence, severity, and duration of arrhythmias.

The antiarrhythmic response for each dose (AS_{test}) was expressed as the percent protection ($\%P_{test}$) relative to the ArS in the control group ($AS_{control}$) according to eq 1.

$$\%P_{test} = 100 - 100 \times (AS_{test}/AS_{control}) \quad (1)$$

By expressing data in this way, the antiarrhythmic effect of the drug is easily seen as an increase in the percent protection. The dose−response data was then fit to a logistic function (eq 2) using Slide Write version 2.

$$\%P = \text{maximum} \times D^h/(D^h + {ED_{50}}^h) \quad (2)$$

In eq 2, D is the infused dose in μmol/kg/min, h is the slope factor, and ED_{50} is the dose required to provide 50% of maximum protection. The baseline was defined as the occurrence of arrhythmias in controls (i.e., 0% protection, AS = 5.7), while the maximum response was defined as 100% protection (i.e., AS = 0, which corresponds to complete abolition of arrhythmias).

Maximum Tolerated Dose in Mice. The mice (female CD-1, approximately 25−30 g) were preweighed and injected intravenously by the tail vein with a constant injection volume of 0.05 mL/10 g of body weight, injected over 30 s. A heating lamp was used to warm the mice and help dilate the vein prior to injection in the lateral tail vein using a 1 mL syringe and a 27 G needle. An initial dose was injected into two mice; if both died, then the initial dose was diluted by 10× and the experiment was repeated. Doses were doubled ($n = 2$) until mortality of both mice was observed. The dose at which half of the mice would be expected to die is calculated as the LD_{50}.

Electrophysiology. Cell Culture. Stable cell lines defrosted from frozen stocks and expressing specific ion channels (Nav1.5, hKv1.5, rKv2.1, and rKv4.2) were used in all experiments. To establish stable human embryonic kidney (HEK) cell lines expressing a specific ion channel, transiently transfected cells are maintained under high antibiotic selection (G418). After 2−3 weeks, cells are tested to evaluate their current levels. Once a stable line has been established, it can be further selected to obtain a monoclonal cell line, if required. The chosen cells are then kept and passaged for electrophysiological recording. The cells were grown in minimal essential medium (MEM, Canadian Life Technologies, Bramalea, ON) at 37 °C in an air/5% CO_2 incubator. The media contained 10% bovine serum and 0.5 mg/mL G418 (Geneticin, Sigma-Aldrich, Ont Ca). On the day before recording, cells were washed with MEM, treated with trypsin/EGTA for 1 min, and plated on 25 mm coverslips.

Solutions. For whole-cell (W/C) recordings, the control pipet was filled with KCl, 130; EGTA, 5; $MgCl_2$, 1; HEPES, 10; Na_2-ATP, 4; GTP, 0.1 (all in mM), adjusted to pH 7.2 with KOH. The control bath solution contained (in mM) NaCl, 135; KCl, 5; sodium acetate, 2.8; $MgCl_2$, 1; HEPES, 10; $CaCl_2$, 1, and was adjusted to pH 7.4 with NaOH. Studies were performed using concentrations ranging from 0.5 to 100 μM.

Recordings. Coverslips containing cells are removed from the incubator before experiments and placed in a superfusion chamber (volume 250 μL) containing the control bath solution at 25 °C. W/C recordings were made via the patch-clamp technique,[63] using an Axopatch 200B amplifier (Axon Instruments, CA). Patch electrodes were pulled from thin-walled borosilicate glass (World Precision Instruments, FL) on a horizontal micropipette puller, fire-polished, and filled with appropriate solutions. Electrodes have resistances of 1.5−3.0 mΩ when filled with control filling solution. Analog capacity compensation and 75−85% series resistance compensation were used in all W/C measurements. If necessary, leak subtraction was applied to data. Leak amplitude must be less than peak outward current or the preparation is discarded. Membrane potentials were corrected, where appropriate, for junctional potentials that arise between the pipet and bath solution. Data were filtered at 5 to 10 kHz before digitization and stored on a microcomputer for later analysis using the pClamp6 software (Axon Instruments, Foster City, CA). Pipettes are routinely fire-polished to reduce electrode capacitance and improve seal resistance.

Experimental protocols used to evaluate the properties of a cloned ion-channel (hKv1.5, rKv2.1, rKv4.2, and Nav1.5 sodium channels) and the potency of a compound on the channel are as follows.

Potassium Channel (hKv1.5, rKv2.1 and rKv4.2), Cycle Protocol. (Used for washing in/out drugs and eliciting cumulative concentration−response curves.) Cells are depolarized at 1 Hz from the holding potential of −80 mV to a voltage of +60 mV for 200 ms to fully open the channel. After control recording (200 pulses for Kv1.5, 100 pulses for Kv2.1 and 4.2) when a stable current level is reached, one concentration of drug is washed in. In the presence of the drug, the recording is maintained for 100 pulses or until the current level is stable. After the concentration−response curve is complete, the solution is returned to control to observe washout.

Sodium Channel, Cycle Protocol. (Used for washing in/out drugs and eliciting concentration−response curves.) Cells are depolarized at 1 Hz from the holding potential of −100 mV to a voltage of −30 mV for 10 ms to fully open the channel. After 50 pulses in control (usually 80−100 traces), when the peak current is stable, the drug can be washed in. In the presence of the drug, at least 100 pulses are recorded or until the current is stable. When the drug effect is stable, the concentration can be increased in a half-log manner, and after several concentrations have been tested, the control solution can be used to test for reversibility of drug actions.

Data Analysis. The concentration−response curve for changes in peak current (sodium channel), steady-state current (hKv1.5, rKv2.1), and integrated current (rKv4.2) produced by a certain compound were computer-fitted to the Hill equation:

$$f = 1/[1 + (IC_{50}/[D]^n)]$$

where f is the fractional current block ($f = 1 - I_{drug}/I_{control}$) at drug concentration [D], IC_{50} is the concentration producing half-maximal inhibition, and n is the Hill coefficient.

Canine Vagal-Induced AF Model. Mongrel dogs of either sex weighing 15−49 kg were anaesthetized with morphine (2 mg/kg im initially, followed by 0.5 mg/kg i.v. every 2 h) and α-chloralose

(120 mg/kg i.v. followed by an infusion of 29.25 mg/kg/h). Dogs were ventilated mechanically with room air supplemented with oxygen via an endotracheal tube at 20 to 25 breaths/min with a tidal volume obtained from a nomogram. Arterial blood gases were measured and kept in the physiological range (SaO_2 > 90%, pH 7.30−7.45). Catheters were inserted into the femoral artery for BP recording and blood gas measurement and into both femoral veins for drug administration and venous sampling. Catheters were kept patent with heparinized 0.9% saline solution. Body temperature was maintained at 37−40 °C with a heating blanket.

The heart was exposed via a medial thoracotomy, and a pericardial cradle was created. Three bipolar stainless steel, Teflon-coated electrodes were inserted into the right atria for recording and stimulation, and one was inserted into the left atrial appendage for recording. A programmable stimulator (Digital Cardiovascular Instruments, Berkeley, CA) was used to stimulate the right atrium with 2 ms, twice diastolic threshold pulses. Two stainless steel, Teflon-coated electrodes were inserted into the left ventricle, one for recording and the other for stimulation. A ventricular demand pacemaker (GBM 5880, Medtronics Minneapolis, MN) was used to stimulate the ventricles at 90 beats/min when (particularly during vagal-AF) the ventricular rate became excessively slow. A P23 ID transducer, electrophysiological amplifier (Bloom Associates, Flying Hills, PA) and paper recorder (Astromed MT-95000, Toronto, ON, Canada) were used to record ECG leads II and III, atrial and ventricular electrograms, BP, and stimulation artefacts. The vagi were isolated in the neck, doubly ligated, and divided, and electrodes were inserted in each nerve (see below). To block changes in β-adrenergic effects on the heart, nadolol was administered at an initial dose of 0.5 mg/kg i.v., followed by 0.25 mg/kg i.v. every 2 h.

Drug effects to terminate sustained AF maintained during continuous vagal nerve stimulation were assessed. Unipolar hook electrodes (stainless steel insulated with Teflon coating except for the distal 1−2 cm) were inserted via a 21 gauge needle within and parallel to the shaft of each nerve. In most experiments, unipolar stimuli were applied with a stimulator (model DS-9F, Grass Instruments, Quincy, MA) set to deliver 0.1 ms square-wave pulses at 10 Hz and a voltage 60% of that required to produce asystole. In some experiments, bipolar stimulation was used. The voltage required to produce asystole ranged between 3 and 20 V. Under control conditions, a short burst of rapid atrial pacing (10 Hz, four times diastolic threshold) was delivered to induce AF, which was ordinarily sustained for more than 20 min. The vagal stimulation voltage was adjusted under control conditions and then readjusted after each treatment to maintain the same bradycardic effect. AF was defined as rapid (>500 beats/min under control conditions), irregular atrial rhythm with varying electrogram morphology.

A diastolic threshold current was determined at a basic cycle length of 300 ms by increasing the current 0.1 mA incrementally until stable capture was obtained. For subsequent protocols, current was set to twice diastolic threshold. Atrial and ventricular ERP was measured with the extrastimulus method over a range of S1S2 intervals at a basic cycle length of 300 ms. A premature extrastimulus S2 was introduced every 15 basic stimuli. The S1S2 interval was increased in 5 ms increments until capture occurred, with the longest S1S2 interval consistently failing to produce a propagated response defining ERP. Diastolic threshold and ERP were determined in duplicate and averaged to give a single value. These values were generally within a 5 ms range. The interval between the stimulus artifact and the peak of the local electrogram was measured as an index of conduction velocity.

The stimulus voltage−heart rate relationship for vagal nerve stimulation was determined under control conditions in most experiments. The vagi were stimulated as described above with various voltages to determine the voltage, which caused asystole (defined as a sinus pause greater than 3 s). The response to vagal nerve stimulation was confirmed under each experimental condition, and the voltage was adjusted to maintain the heart rate response to vagal nerve stimulation constant. In cases in which it was not possible to produce asystole, vagal nerve stimulation was adjusted to a voltage that allowed two 20 min episodes of vagal-AF to be maintained under control conditions (see below).

All drugs were administered i.v. via an infusion pump, with drug solutions prepared freshly on the day of the experiment. Vagal stimulation parameters were defined under control conditions as described above, and maintenance of AF during 20 min of vagal nerve stimulation under control conditions was verified. After the termination of AF, the diastolic threshold and ERP of the atrium and ventricle were determined. Subsequently, these variables were reassessed in the atrium under vagal nerve stimulation.

Canine Sterile Pericarditis-Induced AF Model. FL or AF was induced 2−4 days after creation of sterile pericarditis in 22 adult mongrel dogs weighing 19−25 kg. In all instances, the AF or FL lasted longer than 10 min. All studies were performed in accordance with guidelines specified by The Case Western Reserve University Animal Care and Use Committee, the American Heart Association Policy on Research Animal Use, and the Public Health Service Policy on Use of Laboratory Animals.

The canine sterile pericarditis model was created as previously described.[20]At the time of surgery, a pair of stainless steel wire electrodes coated with FEP polymer except for the tip (O Flexon, Davis and Geck) were sutured on the right atrial appendage, Bachman's bundle, and the posteroinferior left atrium close to the proximal portion of the coronary sinus. The distance between each electrode of each pair was approximately 5 mm. These wire electrodes were brought out through the chest wall and exteriorized posteriorly in the interscapular region for subsequent use. At the completion of the surgery, the dogs were given antibiotics and analgesics and then were allowed to recover. Postoperative care included administration of antibiotics and analgesics.

In all dogs, beginning on postoperative day 2, induction of stable AF/FL was attempted in the conscious, nonsedated state to confirm the inducibility and the stability of AF/FL and to test the efficacy of the compounds. Atrial pacing was performed through the electrodes sutured during the initial surgery.

For the induction of AF/FL, one of two previously described methods was used: (1) introduction of one or two premature atrial beats after a train of eight paced atrial beats at a cycle length of 400, 300, 200, or 150 ms or (2) rapid atrial pacing for periods of 1−10 s at rates incrementally faster by 10−50 beats/min than the spontaneous sinus rate until FL was induced or there was a loss of 1:1 atrial capture. Atrial pacing was performed from either the right atrial appendage electrodes or the posteroinferior left atrial electrodes. All pacing was performed using stimuli of twice the threshold for each basic drive train with a modified Medtronic 5325 programmable, battery-powered stimulator with a pulse width of 1.8 ms. (1) ERPs were measured from three sites, right atrial appendage (RAA), posterior left atrium (PLA), and Bachmann's bundle (BB), at two basic cycle lengths 200 and 400 ms. (2) Pace induce A-Fib or AFL. This was attempted for 1 h. If no arrhythmia was induced, no further study was done on that day. (3) If induced, AF must have been sustained for 10 min. Then a waiting period was allowed for spontaneous termination or 20 min, whichever came first. (4) AF was then reinduced and 5 min was allowed before starting drug infusion. (5) Drug was then infused as a bolus over 5 min. (6) If AF terminated with the first dose, then a blood sample was taken and ERP measurements were repeated. (7) A period of 5 min was allowed for the drug to terminate AF. If there was no termination, then the second dose was given over 5 min. (8) After termination and ERPs were measured, a second attempt to reinduce AF was tried for a period of 10 min. (9) If reinduced and sustained for 10 min, a blood sample was taken and the study was repeated from (3) above. (10) If no reinduction could be obtained, the study was terminated.

Pharmacokinetics. The jugular vein of male Wistar rats were cannulated 2 days before drug administration. Single intravenous doses (12 or 17 mg/kg, bolus) and oral doses (24 or 34 mg/kg, gavage) of compounds of interest were administered to fasted rats. Blood samples were taken at 5, 15, and 30 min and 1, 2, 4, 8, and 24 h post dose. Typically, to each plasma sample (100 μL) was added the internal standard in 1 M perchloric acid (100 μL) for

protein precipitation. After centrifugation, the supernatant was transferred to another tube and 1 M aq ammonium formate (350 μL) was added. The resultant solution was subjected to the on-line solid-phase extraction narrow bore HPLC-MS/MS analysis. The sample was trapped on a 20 × 2 mm Superspher RP-18 trapping column and washed for 2 min with 5 mM ammonium formate pH 3.6 buffer. The analyte and the internal standard were then transferred to the analytical column (Superspher RP-18 125 × 2 mm) where separation takes place with an eluent mixed from A (CH_3CN−MeOH−AcOH, 50:50:1) and B (5 mM NH_4OAc with 1% AcOH) in a 9/1 ratio. After elution, the trapping column as well as the analytical column were washed carefully. Detection was performed on an API III triple quadrupole mass spectrophotometer in selected reaction monitoring mode with collision energy of ∼20 eV. Calibration graphs were constructed for all tested compounds from 5 to 100 ng/mL, with an accuracy of approximately 15% over the entire concentration range. Pharmacokinetic parameters were determined by noncompartmental analysis using WinNonLin Pro 1.5.

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Supporting Information Available: Experimental procedures for compounds **2a**,**b**, **2f**, **2g**, **3h**, **3n**, **3v**, **5**−**17**, **19**−**25**, **27**, **28**, **31**, **34**, **35**, **37**−**39**, **43**−**45**, **47**−**49**, **51**, and **52** and a crystallographic information file for compound (1*R*,2*R*)-1-(1-naphthalenethoxy)-2-(1,4-dioxa-7-azaspiro[4,4]non-7-yl)cyclohexane di-*p*-toluoyl-D-hemitartrate. This material is available free of charge via the Internet at http://pubs.acs.org.

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