Registry No. 1, 83119-51-1; 2, 83119-48-6; 3, 83119-56-6; 4, 83119-55-5; 5, 83119-84-0; 6, 83119-44-2; 7, 83119-76-0; 8, 83120-46-1; 9, 83119-46-4; 10, 83119-81-7; 11, 83118-91-6; 12, 83119-10-2; 13, 83140-66-3; 14, 83120-36-9; 15, 83119-30-6; 16, 83119-79-3; 17, 83120-49-4; 18, 83119-38-4; d19, 83119-83-9; 20, 83119-12-4; 21, 83120-23-4; 22, 83119-53-3; 23, 83119-24-8; 24, 83118-92-7; 25, 83119-11-3; 26, 83118-97-2; 27, 83120-37-0; 28, 83119-31-7; 29, 83119-80-6; 30, 83120-50-7; 31, 83119-39-5; 32, 83119-85-1; 33, 83119-13-5; 34, 83120-24-5; 35, 90340-15-1; 36, 110638-64-7; 37, 83119-86-2; 38, 110638-65-8; 39, 83118-93-8; 40, 83119-34-0; 41, 83118-98-3; 42, 83120-38-1; 43, 83119-32-8; 44, 83140-69-6; 45, 83120-51-8; 46, 83119-74-8; 47, 83120-03-0; 48, 83119-14-6; 49, 83120-25-6; 50, 90340-16-2; 51, 83119-88-4; 52, 83119-87-3; 53, 83119-90-8; 54, 83120-42-7; 55, 83119-94-2; 56, 83119-97-5; 57, 83118-96-1; 58, 83119-35-1; 59, 83118-99-4; 60, 83120-39-2; 161, 83119-33-9; 62, 83120-00-7; 63, 83120-52-9; 64, 83119-75-9; 65, 83120-04-1; 66, 83119-15-7; 67, 83140-70-9; 68, 90340-17-3; 69, 83119-91-9; 70, 83120-43-8; 71, 83119-98-6; 72, 83119-95-3; 73, 83119-00-0; 74, 83119-36-2; 75, 83119-05-5; 76, 83120-40-5; 77, 83119-37-3; 78, 83120-01-8; 79, 83120-53-0; 80, 83140-68-5; 81, 83120-05-2; 82, 83119-16-8; 83, 83120-26-7; 84, 90340-18-4; 85, 83119-93-1; 86, 83120-45-0; 87, 83119-92-0; 88, 83120-44-9; 89, 83119-99-7; 90, 83119-96-4; 91, 83119-08-8; 92, 83119-65-7; 93, 83120-15-4; 94, 83120-41-6; 95, 83119-69-1; 96, 83120-02-9; 97, 83120-54-1; 98, 83120-07-4; 99, 83120-06-3; 100, 83120-27-8; 101, 90340-19-5; 102, 110638-66-9; $ClCH(Et)CO_2H$, 4170-24-5; $ClCH(Pr\text{-}i)Co_2H$, 921-08-4; $ClCH(Bu\text{-}i)CO_2H$, 29671-29-2; chloroacetic acid, 79-11-8; 2-chloropropionic acid, 598-78-7; 2-chloropentanoic acid, 6155-96-0; 2-chlorohexanoic acid, 29671-30-5; (cyclopentyl)chloroacetic acid, 110638-67-0; (cyclohexyl)chloroacetic acid, 35468-15-6; chloroacetone, 78-95-5; 3-chloro-2-butanone, 4091-39-8; 2-chlorocyclopentanone, 694-28-0; 2-chlorocyclohexanone, 822-87-7; acetaldehyde, 75-07-0; acetone, 67-64-1; propionaldehyde, 123-38-6; ethyl bromoacetate, 105-36-2; ethyl [(2-acetyl-6,7-dichlorobenzo[*b*]thien-5-yl)oxy]acetate, 83119-89-5.

Synthesis and Antiarrhythmic Activity of Novel 3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium Salts and Related Compounds.[1] 2

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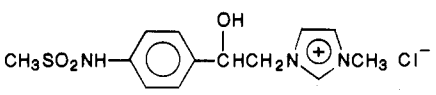
Berlex Laboratories, Inc., Cedar Knolls, New Jersey 07927. *Received May 26, 1987*

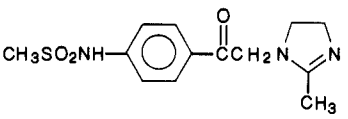
Novel analogues of the class III antiarrhythmic agent 1-[2-hydroxy-2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-3-methyl-1*H*-imidazolium chloride, 1 (CK-1649), were prepared and investigated for their class III electrophysiological activity on isolated canine cardiac Purkinje fibers and ventricular muscle tissue. Structure–activity relationships are discussed for a series of 11 compounds. One compound, *N*-[4-[1-hydroxy-2-(4,5-dihydro-2-methyl-1*H*-imidazol-1-yl)ethyl]phenyl]methanesulfonamide hydrochloride, **9**, was comparable in activity to **1** in vitro and prolonged the functional refractory period in anesthetized dogs when given intraduodenally. Unlike **1**, compound **9** was ineffective at preventing ventricular tachycardia induced by programmed electrical stimulation in anesthetized dogs 24 h after an acute myocardial infarction.

Antiarrhythmic agents that selectively prolong the action potential duration (APD) and concomitantly increase the refractory period (FRP) of heart cells without significant effects on cardiac conduction are termed class III antiarrhythmic agents in the Vaughan Williams classification.[2]

In a previous paper,[3] we reported the synthesis and class III antiarrhythmic activity of a new series of 3-alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium salts. One example from this series, **1** (CK-1649), possesses potent class III electrophysiological activity in vitro. Compound **1** also showed intraduodenal activity in anesthetized mongrel dogs (10 or 30 mg/kg) and was also effective in preventing ventricular tachycardia in



1



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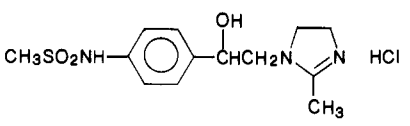
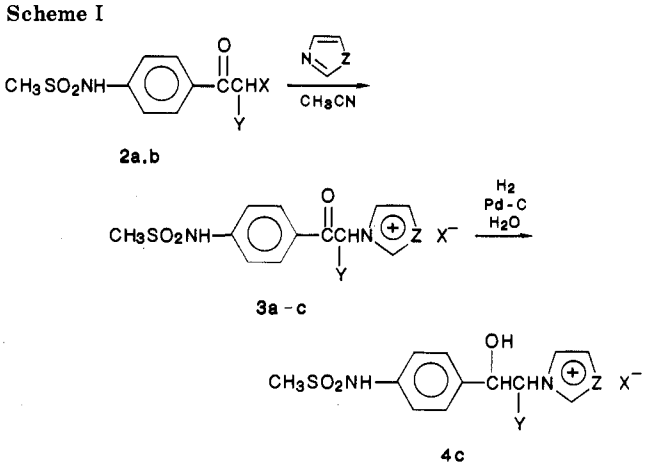


9

Scheme I



2a,b

3a-c

4c

a: X = Cl, Y = H, Z = S
b: X = Br, Y = CH_3, Z = NCH_3
c: X = Cl, Y = CH_3, Z = NCH_3

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§ Department of Pharmacology.

(1) A preliminary account of this work has appeared: Lis, R.; Morgan, T. K., Jr.; DeVita, R. J.; Davey D. D.; Lumma, W. C., Jr.; Wohl, R. A.; Wong, S. S.; Sullivan, M. E. 9th International Symposium on Medicinal Chemistry, West Berlin, Federal Republic of Germany, Sept 1986; European Federation for Medicinal Chemistry, 1986; SC 46.
(2) Vaughan Williams, E. M. In *Symposium on Cardiac Arrhythmias*; Sandoe, E., Flensted-Jansen, E., Olsen, K. H., Eds.; AB Astra, Sodertalje, Sweden, 1970; pp 449-472.

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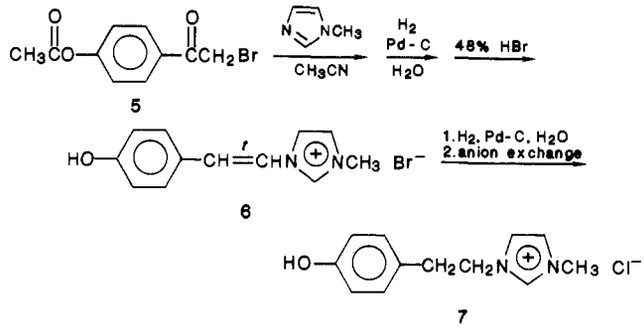
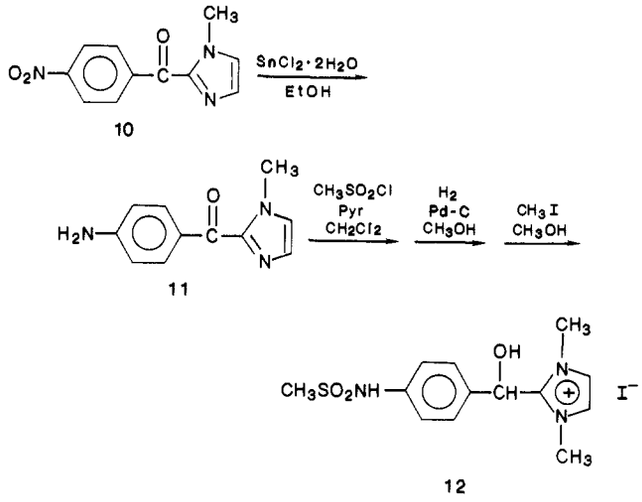
Scheme II



Scheme III



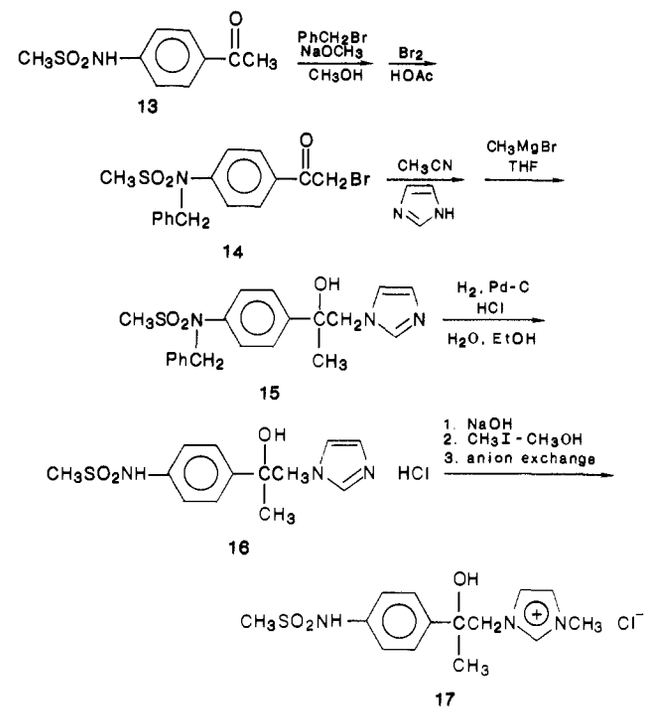
infarcted dogs (3, 10 mg/kg, iv). We have now prepared 11 additional derivatives to further expand and better understand structure–activity relationships in this series of selective class III agents.

Chemistry

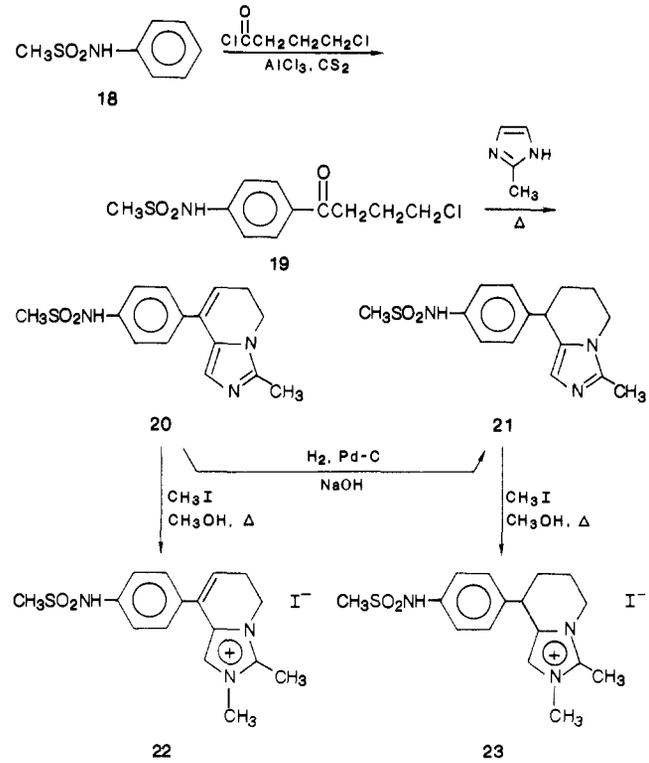
The synthetic routes to the target compounds **3a**,**c**, **4c**, **6–9**, **12**, **17**, **22**, and **23** are illustrated in Schemes I–V. The required haloacetophenone starting materials were obtained by a previously published procedure.[3] Treatment of chloroacetophenone **2a** with thiazole in refluxing acetonitrile afforded keto thiazolium salt **3a** (Scheme I). All attempts to reduce the ketone moiety of this compound either catalytically or chemically were unsuccessful. Reaction of bromopropiophenone **2b**[4] with 1-methylimidazole followed by anion exchange gave keto imidazolium salt **3c**. Catalytic hydrogenation[5] of **3c** provided hydroxy imidazolium salt **4c** as a 10:1 mixture of diastereomers.

The synthetic route to imidazolium salts **6** and **7** is depicted in Scheme II. Treatment of bromo ketone **5**[6] with 1-methylimidazole in refluxing acetonitrile gave the corresponding imidazolium salt, which could not be isolated in pure form. Catalytic reduction of this product afforded the labile hydroxy imidazolium salt, which could not be isolated. Dehydration and deacetylation were accomplished by treatment with 48% aqueous HBr and afforded imidazolium salt **6**. The 300-MHz NMR spectrum of **6** displayed the olefinic protons as doublets with J = 14.4 Hz, demonstrating the trans relationship. Reduction of **6** followed by anion exchange yielded imidazolium salt **7**.

Scheme IV



Scheme V



The preparation of **8** and **9** proceeded similarly to the synthesis of **3c** and **4c**. Compound **12** was prepared by the route outlined in Scheme III. Nitro imidazole **10**[7] was selectively reduced according to the method of Bellamy,[8] giving the corresponding amine (**11**) in 89% yield. Mesylation, reduction, and quaternization gave **12** in good overall yield.

(3) Lis, R.; Morgan, T. K., Jr.; DeVita, R. J.; Davey, D. D.; Lumma, W. C., Jr.; Wohl, R. A.; Diamond, J.; Wong, S. S.; Sullivan, M. E. *J. Med. Chem.* **1987**, *30*, 696.

(4) Uloth, R. H.; Kirk, J. R.; Gould, W. A.; Larsen, A. A. *J. Med. Chem.* **1966**, *9*, 88.

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(6) Rosenmund, K. W.; Pfroepffer, K. *Chem. Ber.* **1957**, *90*, 1922.

(7) Regel, E.; Buchel, K.-M. *Justus Liebigs Ann. Chem.* **1977**, 145.

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Table I. 3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium Salts and Related Compounds

compound[a]	yield, %	mp, °C (solv)[b]	formula	anal.[c]
3a	28	245–247 (A)	$[C_{12}H_{13}N_2O_3S_2]^+Cl^-$	C, H, N
3c	62	192–195	$[C_{14}H_{18}N_3O_3S]^+Cl^-\cdot 0.5H_2O$	C, H, N, S, Cl
4c[d]	41	204–207 (B)	$[C_{14}H_{20}N_3O_3S]^+Cl^-$	C, H, N, S, Cl
6	37	259–262 (C)	$[C_{12}H_{13}N_2O]^+Br^-\cdot 2H_2O$	C, H, N, Br
7	80	167–169 (D)	$[C_{12}H_{15}N_2O]^+Cl^-\cdot 0.15H_2O$	C, H, N, Cl
8	59	207–208 (E)	$C_{13}H_{17}N_3O_3S$	C, H, N
9	94	212–215 (D)	$C_{13}H_{19}N_3O_3S\cdot HCl$	C, H, N
12	89	*e*	$[C_{13}H_{18}N_3O_3S]^+I^-\cdot 0.5H_2O$	C, H, N, S, I
17	62	*e*	$[C_{14}H_{20}N_3O_3S]^+Cl^-\cdot 0.4C_3H_8O$	C, H, N, S, Cl
22	52	237–238 (D)	$[C_{16}H_{20}N_3O_2S]^+I^-$	C, H, N
23	74	187–188 (D)	$[C_{16}H_{22}N_3O_2S]^+I^-$	C, H, N

[a] All compounds are racemic. [b] Recrystallization solvent: A = 95% aqueous EtOH, B = CH_3CN–H_2O (1:1), C = H_2O, D = EtOH, and E = MeOH–EtOH (1:1). [c] Elemental analyses are within ±0.4% of the calculated values. [d] 10:1 mixture of diastereomers. [e] Isolated as a white foam.

Table II. Effects of Various 3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium Salts, Related Compounds, and the Standards Clofilium and Sotalol on Action Potential Characteristics of Isolated Canine Cardiac Purkinje Fibers and Refractory Period of Isolated Canine Cardiac Ventricular Muscle Tissue

	Purkinje fiber[a,b]			ventricular muscle tissue[b,c]		
compound[d]	*n*[e]	$C_{20}APD_{95}$,[f] μM	maxΔAPD_{95} (concn., μM)[g]	*n*[e]	$C_{20}FRP$,[h] μM	maxΔFRP (concn, μM)[i]
clofilium[j]	6	0.26 (0.08–0.82)[k]	39 ± 8% (10)	3	NR[l]	7 ± 9% (100)
sotalol[j]	6	14.4 (11.2–18.6)	48 ± 3% (100)	3	24.7 (3.7–162)	23 ± 4% (100)
1[j]	4	1.6 (1.3–1.9)	50 ± 5% (100)	8	5.9 (2.3–15.2)	31 ± 4% (100)
3a	3	3.1 (1.2–7.8)	80 ± 35% (100)	2	NR,[l] 10.0[m]	17%, 27% (100)
3c	2	3.0, 3.1	65%, 63% (100)	1	7.7[n]	22% (100)
4c[o]	2	4.2, 1.8	36%, 77% (100)	1	11.2	31% (100)
6	3	10.2 (4.5–23.4)	23% (10) 27% (100) 20% (10)	2	NR,[l] NR[l]	min[p]
7	2	6.2, 100	23% (10) 20% (100)	3	NR,[l,q] NR,[l,q] 50.1	7%, 11%, 24% (100)
8	2	1.3, 3.2	74%, 57% (100)	1	6.3	38% (100)
9	3	0.6 (0.1–3.0)	63 ± 8% (100)	2	1.1, 1.9	42%, 38% (100)
12	4	20.7 (2.3–190)	37 ± 11% (100)	1	NR[l]	17% (100)
17	4	1.5 (0.9–2.5)	71 ± 21% (100)	3	24.3 (11.7–49.0)	29 ± 6% (100)
22	4	2.8 (0.2–40)	38 ± 8% (100)	1	2.9	40% (100)
23	2	46.6, 23.5	27%, 30% (100)	1	NR[l]	min[p]

[a] The change in the rate of rise of phase 0 of the action potential (V_{max}) was less than 10% unless otherwise noted. [b] Dose range 0.1–100 μM unless otherwise noted. [c] The change in conduction time (CT) was less than 10% unless otherwise noted. [d] Compounds are racemic. [e] Number of experiments. [f] The concentration of drug that causes a 20% increase (+) or decrease (–) in APD_{95} (action potential duration at 95% repolarization) from control value, when $n > 2$, log mean and 90% confidence interval reported. [g] The maximum observed change in APD_{95} from control value and concentration when this occurred. [h] The concentration of drug that causes a 20% increase (+) or decrease (–) in the functional refractory period from control value, when $n > 2$, log mean and 90% confidence interval reported. [i] The maximum change from control in functional refractory period that was observed (frequency of 1.0 Hz) and the concentration at which this effect was observed. [j] Previously reported in ref 2. [k] Dose range 0.01–10 μM. [l] NR = never reached. [m] A 13% decrease in CT was observed at 100 μM. [n] A 24% decrease in CT was observed at 100 μM. [o] 10:1 mixture of diastereomers. [p] Minimal effects on FRP observed at the concentrations studied. [q] Variable effects on CT were observed over the dose range.

A different synthetic strategy was utilized for the preparation of compound **17** (Scheme IV). Acetophenone **13**[4] was protected and then brominated to give bromo ketone **14**. Displacement with imidazole followed by Grignard addition yielded tertiary alcohol **15**. The benzyl protecting group was absolutely necessary for adequate THF solubility in the Grignard reaction. Alcohol **15** was deprotected to give **16** in 85% yield. Remarkably, no hydrogenolysis of the tertiary benzylic alcohol moiety was observed under these conditions. Liberating the free base of **16** followed by quaternization and anion exchange gave **17** as an amorphous solid.

The preparation of analogues **22** and **23** is outlined in Scheme V. Friedel–Crafts acylation of *N*-phenylmethanesulfonamide (**18**) with 4-chlorobutyryl chloride provided an 85% yield of chloro ketone **19**. Heating **19** with 2-methylimidazole at 175 °C resulted in displacement of the chloride, followed by cyclization and dehydration giving **20**.[9] Treatment of **20** with methyl iodide in methanol provided imidazolium salt **22**. Catalytic hydrogenation of **20** in the presence of sodium hydroxide and subsequent treatment with methyl iodide in methanol yielded imidazolium salt **23** via **21**.

(9) Cf.: Davey, D. D. *J. Org. Chem.* **1987**, *52*, 1863.

Pharmacology

Screening for electrophysiological activity was carried out in two in vitro systems, an intracellular screen using canine cardiac Purkinje fibers and an extracellular screen using canine ventricular muscle tissue.

In the intracellular screen, the action potential characteristics of canine cardiac Purkinje fibers were recorded by using standard microelectrode recording techniques.[3] For a compound to be considered active as a class III agent in this model, it must prolong the action potential duration at 95% repolarization (APD_{95}) by at least 20% with minimal effects on the rate of rise of phase 0 of the action potential (V_{max}). In Table II, we report the concentration of drug that causes a 20% increase in APD_{95} (C_{20} APD_{95}), the maximum observed increase in APD_{95} (maxΔAPD_{95}), the effects on V_{max}, and the dose range studied.

In the extracellular screen, conduction interval curves were determined on isolated pieces of ventricular muscle tissue. This in vitro method was developed at Berlex and

Table III. In Vivo Test Results for Clofilium, Sotalol, and Selected Imidazolium Salts

	intraduodenal activity					antiarrhythmic efficacy (PES model)					
compound[a]	n[b]	active dose,[c] mg/kg, id	HR[d]	BP[e]	FRP[f]	n[b]	number effective	dose range, mg/kg, iv	mean effective dose,[g] mg/kg, iv	HR[d]	BP[e]
clofilium[h]	3	10	−18 ± 7	−4 ± 8	22 ± 1	10	7	0.1–10	0.63 ± 0.40	−12 ± 7	2 ± 5
sotalol[h]	7	10	−11 ± 1	8 ± 8	16 ± 2	10	3	0.1–30	1.4 ± 0.8	−23 ± 14	−23 ± 21
1[i,h]	3	10	−10 ± 4	5 ± 3	21 ± 2	3	2	0.3–10	6.5 ± 3.5	−23 ± 6	0 ± 0
9	2	10	−23 ± 7	2 ± 2	22 ± 4	8	2	0.3–30	2.0 ± 1.0	−21 ± 5	−1 ± 7

[a] All compounds are racemic. [b] Number of experiments. [c] FRP > 12% from control. [d] Percent change in heart rate at active or effective dose (mean ± SEM). [e] Percent change in blood pressure at active or effective dose (mean ± SEM). [f] Percent change of left ventricular functional refractory period. [g] Mean ± SE. [h] Previously reported in ref 2. [i] Tested as the iodide salt.

is an adaptation of the method of Carson and Dresel used in whole animals.[3] An active compound in the extracellular screen must prolong the functional refractory period (FRP) by 20% with minimal effects on conduction time (CT). In Table II, we report the concentration of drug that causes a 20% increase in FRP (C_{20} FRP), the maximum observed increase in FRP (maxΔFRP), the effects on CT, and the dose range studied.

Changes in V_{max} or CT of ≤10% from control were considered minimal. The majority of the compounds tested showed little effect on either of these parameters (selective class III). Some compounds showed variable or significant changes (>10% from control) at high doses (i.e., 100 μM) in V_{max} or CT and are reported in Table II.

Duplicate experiments were performed in canine cardiac Purkinje fibers in order to assess electrophysiological activity. Ventricular muscle tissue was used as a secondary in vitro screen.

The methods for evaluating intraduodenal activity and antiarrhythmic efficacy in a programmed electrical stimulation (PES) model have been reported.[3] These results are listed in Table III.

For a compound to be considered intraduodenally active, it must have prolonged the cardiac functional refractory period (FRP) by at least 12% in two of three animals.

Once a compound was considered intraduodenally active, it was then examined for efficacy in a programmed electrical stimulation (PES) model.[3] In this model, mongrel dogs were subjected to ligation of the left anterior descending coronary artery according to the method of Harris.[3] After a 24-h recovery period, the animals were anesthetized and their chests reopened, and recording and stimulating electrodes were attached to the myocardium. Before administration of the test compound, the animals were subjected to a PES protocol to induce either sustained ventricular tachycardia (SVT) or ventricular fibrillation (VF). SVT was terminated by burst pacing, and VF was terminated by DC cardioversion. After demonstrating the reproducibility of the induced arrhythmia, the test compound was administered and the stimulation protocol was repeated. A compound was considered effective if SVT or VF could not be reinduced in two of three animals. The results of the PES efficacy studies are listed in Table III.

Results and Discussion

The in vitro electrophysiological effects of the target compounds are reported in Table II. Clofilium, sotalol, and 1 (CK-1649) were also tested for comparison.

Compound **12**, in which the imidazolium moiety is attached at the 2-position to the benzylic carbon atom, was significantly less active than compound 1 in the Purkinje fiber screen (Table II). This suggests that activity may be sensitive to the distance between the center of the aromatic ring and the center of the imidazolium moiety. This concept is also consistent with our previous findings.[3]

The conformationally restricted analogues **22** and **23**, which may be viewed as 5-substituted imidazolium salts, were also prepared. Unsaturated analogue **22** exhibited greater potency than the saturated analogue **23** and was comparable in activity to compound 1.

Despite the chemical similarities between phenol (pK_a = 11.0) and methanesulfonanilide (pK_a = 9.9),[4] analogues **6** and **7** were less potent than 1 in both screens. Other compounds, such as a thiazolium salt (**3a**) or methyl group branching on the connecting chain (**3c**, **4c**, and **17**), showed comparable activity to 1 in the Purkinje fiber screen.

Of particular interest is the replacement of the imidazolium moiety with an imidazoline group. This afforded active analogues **8** and **9**.

To determine potential β-blocking activity, imidazoline **9** was examined for its ability to displace the β-receptor antagonist [^{3}H]dihydroalprenolol ([^{3}H]DHA) from canine cardiac tissue. A 39% displacement of [^{3}H]DHA observed at 10 mM (mean from at least six experiments) clearly demonstrated that imidazoline **9**, like 1, has little affinity for β-receptors.

Imidazoline **9** was therefore selected for further studies in in vivo models. The intraduodenal activity of **9** was similar to that of clofilium, sotalol, and 1 (Table III). Despite potent in vitro activity and the ability to increase FRP in vivo, imidazoline **9** was ineffective at preventing ventricular tachycardia induced by programmed electrical stimulation (PES) (Table III). Sotalol was also ineffective in this PES model. Interestingly, only the quaternary compounds (i.e., clofilium and 1) were efficacious in this PES model.

Conclusions

Various analogues of 3-alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium salts have been shown to possess potent class III electrophysiological activity in vitro. Compound **9** also showed activity by increasing FRP in anesthetized mongrel dogs at 10 mg/kg id but was ineffective at preventing ventricular tachycardia induced by programmed electrical stimulation in anesthetized mongrel dogs 24 h after an acute myocardial infarction.

Experimental Section

Chemistry. Proton nuclear magnetic resonance (NMR) spectra were taken at either 60 MHz (Varian EM-360) or 300 MHz (Varian XL-300) as indicated. Chemical shifts are reported in parts per million (δ) downfield from an internal standard of tetramethylsilane (TMS) for $CDCl_3$ and DMSO-d_6. Infrared (IR) spectra were recorded on a Sargent-Welch 3-300 or a Beckman Acculab 2 spectrophotometer as a KBr pellet, as a Nujol mull, or in $CHCl_3$ solution as indicated. Elemental analyses were performed by the analytical department of Berlex laboratories, Inc., or Microlit Laboratories, Inc., Caldwell, NJ. Melting points were obtained on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Woelm silica gel (63–200 mesh) and Fisher alumina (neutral, activity III) were used for column chromatography.

3-[2-[4-[(Methylsulfonyl)amino]phenyl]-2-oxoethyl]thiazolium Chloride (3a). A mixture of *N*-[4-(2-chloro-1-oxoethyl)phenyl]methanesulfonamide (**2a**)[3] (8.6 g, 34.9 mmol) and thiazole (3.0 g, 35.2 mmol) in 100 mL of acetonitrile was heated at reflux for 17 h and then cooled to room temperature. The solid was collected, washed with 50 mL of acetonitrile, and recrystallized from 95% ethanol. Drying at 80 °C (0.05 mm) for 5 h afforded 3.3 g (28%) of **3a** as an off-white solid: mp 245–247 °C dec; IR (Nujol) 3410, 1675, 1610, 1515, 1340, 1310, 1250, 1240, 1180, 1150, 985, 925, and 850 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 3.15 (s, 3), 6.41 (s, 2), 7.41 (d, 2, J = 8.8 Hz), 8.02 (d, 2, J = 8.8 Hz), 8.39 (m, 1), 8.51 (m, 1), 10.25 (s, 1), 10.66 (s, 1). Anal. [$(C_{12}H_{13}N_2O_3S_2)^+Cl^-$] C, H, N.

3-Methyl-1-[1-methyl-2-[4-[(methylsulfonyl)amino]phenyl]-2-oxoethyl]-1*H*-imidazolium Chloride 0.5-Hydrate (3c). A mixture of *N*-[4-(2-Bromo-1-oxopropyl)phenyl]methanesulfonamide (**2b**)[4] (4.6 g, 15.0 mmol) and 1-methylimidazole (1.3 g, 15.7 mmol) in 100 mL of acetonitrile was refluxed for 17 h and then cooled to room temperature. The solid was filtered, washed with 50 mL of acetonitrile, and air-dried for 5 h to give 5.6 g of a solid. This product was dissolved in water and passed through 36 g of chloride ion exchange resin (Bio-Rad, AG1-XS, 20–50 mesh). Concentration gave 3.3 g (62%) of **3c** as white crystals: mp 192–195 °C; IR (KBr) 3450, 1690, 1340, 1160, 970, and 910 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 1.76 (d, 3, J = 7.3 Hz), 3.16 (s, 3), 3.34 (s, ca. 1), 3.93 (s, 3), 6.60 (q, 1, J = 7.3 Hz); 7.39 (d, 2, J = 8.7 Hz), 7.78 (m, 1), 7.90 (m, 1), 8.07 (d, 2, J = 8.7 Hz), 9.42 (s, 1), 10.70 (br s, 1). Anal. [$(C_{14}H_{18}N_3O_3S)^+Cl^-\cdot 0.5H_2O$] C, H, N, S, Cl.

1-[2-Hydroxy-1-methyl-2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-3-methyl-1*H*-imidazolium Chloride (4c). A mixture of **3c** (22.1 g, 62.6 mmol) in 400 mL of distilled water containing 1.2 g of palladium on activated carbon was hydrogenated at ca. 50 psi for 17 h at room temperature. The catalyst was collected by filtration and the filtrate concentrated in vacuo, giving a solid. Recrystallization (two times) from CH_3CN–MeOH (1:1) afforded 8.8 g (41%) of **4c** as a 10:1 mixture of diastereomers: mp 204–207 °C; IR (KBr) 3260 (br), 1315, 1135, and 945 cm^{-1}; NMR (300 MHz, DMSO-d_6, major diastereomer) δ 1.33 (d, 3, J = 6.9 Hz), 2.97 (s, 3), 3.84 (s, 3), 4.71 (m, 1), 4.83 (t, 1, J = 4.4 Hz), 6.12 (d, 1, J = 4.4 Hz), 7.19 (d, 2, J = 8.7 Hz), 7.26 (d, 2, J = 8.7 Hz), 7.69 (m, 1), 7.99 (m, 1), 9.20 (s, 1), 9.85 (br s, 1). Anal. [$(C_{14}H_{20}N_3O_3S)^+Cl^-$] C, H, N, S, Cl.

(*E*)-1-[2-(4-Hydroxyphenyl)ethenyl]-3-methyl-1*H*-imidazolium Bromide Dihydrate (6). To a room temperature solution of **5**[6] (9.3 g, 36.2 mmol) in 70 mL of acetonitrile under nitrogen was added 1-methylimidazole (3.0 mL, 38.0 mmol). The mixture was refluxed for 4 h, then cooled to room temperature, and concentrated in vacuo. The residue was taken up in 100 mL of water and extracted withy methylene chloride (3 × 75 mL). The aqueous layer was then concentrated in vacuo to give 11.8 g of a green foam. This crude product was dissolved in 150 mL of distilled water containing 1.2 g of 10% palladium on activated carbon. The mixture was hydrogenated at ca. 50 psi for 22 h at room temperature. The catalyst was collected by filtration through 15 g of Celite and washed with 100 mL of water. The filtrate was treated with 2.0 mL of 48% aqueous HBr and heated to ca. 55 °C for 1.5 h. Concentration in vacuo afforded a solid, which was recrystallized from water, giving 4.2 g (37%) of **6** as white crystals: mp 259–262 °C; IR (Nujol) 3500–3000 (br), 2700, 1600, 1285, 1180, 940, and 745 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 3.34 (s, ca. 4), 3.91 (s, 3), 6.83 (d, 2, J = 8.2 Hz), 7.28 (d, 1, J = 14.4 Hz), 7.39 (d, 2, J = 8.2 Hz), 7.73 (d, 1, J = 14.4 Hz), 7.85 (s, 1), 8.17 (s, 1), 9.38 (s, 1), 9.85 (s, 1). Anal. [$(C_{12}H_{13}N_2O)^+Br^-\cdot 2H_2O$] C, H, N, Br.

1-[2-(4-Hydroxyphenyl)ethyl]-3-methyl-1*H*-imidazolium Chloride 0.15-Hydrate (7). A mixture of **6** (2.1 g, 6.6 mmol) in 50 mL of distilled water containing 30 mg of 10% palladium on activated carbon was hydrogenated for 14 h at room temperature. The catalyst was collected by filtration through Celite and washed with 20 mL of distilled water. The filtrate was concentrated in vacuo and the residue passed through 100 g of chloride ion exchange resin (Bio-Rad, AG1-X8, 20–50 mesh). Concentration gave a solid, which was recrystallized from absolute ethanol and afforded 1.3 g (80%) of **7** as white crystals: mp 167–169 °C; IR (Nujol) 3080 (br), 1610, 1570, 1510, 1170, 840, and 720 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 2.99 (t, 2, J = 7.2 Hz), 3.82 (s, 3), 4.35 (t, 2, J = 7.2 Hz), 6.69 (d, 2, J = 8.5 Hz), 6.98 (d, 2, J = 8.5 Hz), 7.67 (s, 1), 7.70 (s, 1), 9.04 (s, 1), 9.38 (s, 1). Anal. [$(C_{12}H_{15}N_2O)^+Cl^-\cdot 0.15H_2O$] C, H, N, Cl.

***N*-[4-[2-(4,5-Dihydro-2-methyl-1*H*-imidazol-1-yl)-1-oxoethyl]phenyl]methanesulfonamide (8).** To a 0 °C mixture of 2-methyl-2-imidazoline (34.0 g, 400.0 mmol) in 200 mL of acetonitrile under nitrogen was added *N*-[4-(2-chloro-1-oxoethyl)-phenyl]methanesulfonamide[3] (20.0 g, 80.0 mmol) in one portion. The mixture was stirred for 2 h at 0 °C, then slowly warmed to room temperature, and stirred for an additional 17 h. This solution was chromatographed directly on 1.2 kg of alumina. Gradient elution with methylene chloride–methanol (93:7 to 4:1) provided 14.0 g (59%) of **8** as yellow crystals, which were recrystallized from ethanol–methanol (1:1): mp 207–208 °C; IR (Nujol) 2580 (br), 1650, 1620, 1500, 975, and 845 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 2.05 (s, 3), 2.72 (s, 3), 3.60–3.80 (m, 5), 4.96 (s, 2), 6.91 (d, 2, J = 8.9 Hz), 7.69 (d, 2, J = 8.9 Hz). Anal. ($C_{13}H_{17}N_3O_3S$) C, H, N.

***N*-[4-[1-Hydroxy-2-(4,5-dihydro-2-methyl-1*H*-imidazol-1-yl)ethyl]phenyl]methanesulfonamide Hydrochloride (9).** Ketone **8** (8.1 g, 27.5 mmol) was dissolved in 1 N aqueous HCl (26.1 mL, 26.1 mmol) and then concentrated in vacuo to afford 6.2 g (72%) of **8** as the hydrochloride salt. This salt was dissolved in 150 mL of distilled water and 60 mg of 10% palladium on activated carbon added. The mixture was hydrogenated at ca. 40 psi for 24 h at room temperature. The catalyst was collected by filtration through 10 g of Celite and washed with 100 mL of distilled water. The filtrate was concentrated in vacuo to give white crystals. Recrystallization from absolute ethanol afforded 5.9 g (94%) of **9**: mp 212–215 °C; IR (Nujol) 3300 (br), 1590, 1330, 1300, 1150, 1065, 960, 845, and 770 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 2.11 (s, 3), 2.96 (s, 3), 3.36 (br s, 2), 3.45 (dd, 1, J = 3.9, 14.3 Hz), 3.54 (dd, 1, J = 8.2, 14.3 Hz), 3.72–4.07 (m, 2), 4.86 (d, 1, J = 3.9 Hz), 5.98 (br s, 1), 7.22 (d, 2, J = 8.4 Hz), 7.40 (d, 2, J = 8.4 Hz), ca. 10.0 (br s, 2). Anal. ($C_{13}H_{19}N_3O_3S\cdot HCl$) C, H, N.

(4-Aminophenyl)(1-methyl-1*H*-imidazol-2-yl)methanone (11). A slurry of (1-methyl-1*H*-imidazol-2-yl)(4-nitrophenyl)-methanone (**10**)[7] (60.0 g, 259.0 mmol) in 1.0 L of ethanol under nitrogen was heated to ca. 70 °C. Stannous chloride dihydrate[8] (292.6 g, 1.297 mol) was then added in three portions and the mixture stirred at ca. 70 °C for 1 h. The solution was then cooled to room temperature and concentrated in vacuo. The residue was poured into 1.5 L of water and the pH adjusted to 8.0 with 2 N aqueous NaOH. The mixture was then filtered and the filtrate concentrated in vacuo to give a solid, which was recrystallized from water and afforded 46.5 g (89%) of 11 as a yellow solid: mp 103–105 °C; IR ($CHCl_3$) 3500, 3410, 3000, 1620, 1595, 1400, 1270, 1160, 935, 905, and 840 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 3.09 (br s, 2), 4.03 (s, 3), 6.68 (d, 2, J = 8.3 Hz), 7.07 (s, 1), 7.22 (s, 1), 8.20 (d, 2, J = 8.3 Hz). Anal. ($C_{11}H_{11}N_3O$) C, H, N.

***N*-[4-[(1-Methyl-1*H*-imidazol-2-yl)carbonyl]phenyl]methanesulfonamide.** To a 0 °C solution of 11 (25.0 g, 124.0 mmol) in 600 mL of methylene chloride containing pyridine (20.0 mL, 248.0 mmol) was added methanesulfonyl chloride (19.2 mL, 248.0 mmol) dropwise via syringe. The mixture was stirred for 1 h at 0 °C and then at room temperature for 18 h. The solution was filtered, and the crystals were washed with methylene chloride (100 mL). The filtrate was washed with water (2 × 250 mL), dried (Na_2SO_4), and concentrated in vacuo to give crystals. Recrystallization from methanol–water (9:1) afforded 22.0 g (64%) of the title compound as an off-white solid: mp 198–200 °C; IR (Nujol) 3120, 1630, 1600, 1320, 1260, 1145, 910, and 855 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 3.13 (s, 3), 3.98 (s, 3), 7.19 (s, 1), 7.30 (d, 2, J = 8.9 Hz), 7.58 (s, 1), 8.27 (d, 2, J = 8.9 Hz), 10.35 (s, 1). Anal. ($C_{12}H_{13}N_3O_3S$) C, H, N.

***N*-[4-[Hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl]phenyl]methanesulfonamide.** A mixture of the previous compound (16.2 g, 58.0 mmol) in 1.0 L of methanol containing 1.6 g of 10% palladium on activated carbon was hydrogenated at room temperature and ca. 50 psi for 13.5 h. The catalyst was collected by filtration through 15 g of Celite and washed with 200 mL of methanol. The filtrate was concentrated in vacuo to give 15.3 g (94%) of the title compound as a white solid: mp 177–179 °C; IR (Nujol) 3120, 1610, 1320, 1150, 970, 815, and 770 cm^{-1}; NMR

(300 MHz, DMSO-d_6) δ 2.96 (s, 3), 3.50 (s, 3), 5.82 (d, 1, J = 4.0 Hz), 6.13 (d, 1, J = 4.0 Hz), 6.75 (s, 1), 7.04 (s, 1), 7.15 (d, 2, J = 8.5 Hz), 7.27 (d, 2, J = 8.5 Hz), 9.73 (s, 1). Anal. ($C_{12}H_{15}N_3O_3S$) C, H, N.

1,3-Dimethyl-2-[hydroxy[4-[(methylsulfonyl)amino]phenyl]methyl]-1*H*-imidazolium Iodide 0.5-Hydrate (12). A solution of the previous compound (12.3 g, 43.9 mmol) in 125 mL of methanol containing methyl iodide (16.4 mL, 263.0 mmol) was heated at ca. 50 °C for 36 h. The solution was cooled to room temperature and concentrated in vacuo. The residue was dissolved in 400 mL of water, washed with methylene chloride (4 × 75 mL), and then concentrated in vacuo to give 16.8 g (89%) of **12** as a white foam: mp 45–60 °C; IR (Nujol) 3400 (br), 2720, 1605, 1340, 1150, 965, and 720 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 3.01 (s, 3), 3.34 (s, ca. 1), 3.80 (s, 6), 6.41 (d, 1, J = 4.3 Hz), 6.99 (d, 1, J = 4.3 Hz), 7.25 (d, 2, J = 8.6 Hz), 7.32 (d, 2, J = 8.6 Hz), 7.71 (s, 2), 9.90 (s, 1). Anal. [$(C_{13}H_{18}N_3O_3S)^+I^-0.5H_2O$] C, H, N, S, I.

***N*-[4-(1-Oxoethyl)phenyl]-*N*-(phenylmethyl)methanesulfonamide.** *N*-[4-(1-Oxoethyl)phenyl]methanesulfonamide (**13**)[4] (5.0 g, 23.0 mmol) was suspended in 50 mL of methanol, sodium methoxide (1.5 g, 27.6 mmol) was added, and the mixture was stirred at room temperature for 30 min. Benzyl bromide (2.9 mL, 24.0 mmol) was then added via syringe and the mixture stirred at room temperature for 28 h. The solution was concentrated in vacuo and the residue dissolved in 50 mL of 1 N NaOH and extracted with methylene chloride (2 × 100 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo to give crystals, which were recrystallized from ether–methylene chloride (4:1) and gave 2.9 g (42%) of the title compound as a white crystalline solid: mp 117–119 °C; IR ($CHCl_3$) 3020, 1680, 1600, 1580, 1350, 1270, 1155, 1065, 960, and 870 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3), 2.98 (s, 3), 4.92 (s, 2), 7.26 (s, 5), 7.38 (d, 2, J = 8.7 Hz), 7.89 (d, 2, J = 8.7 Hz). Anal. ($C_{16}H_{17}NO_3S$) C, H, N.

***N*-[4-(2-Bromo-1-oxoethyl)phenyl]-*N*-(phenylmethyl)methanesulfonamide (14).** To a solution of the previous compound (70.0 g, 230.0 mmol) in 1.0 L of glacial acetic acid at room temperature was added bromine (11.9 mL, 230.0 mmol). The solution was stirred for 17 h at room temperature and then concentrated in vacuo. The residue was dissolved in 400 mL of water and 500 mL of methylene chloride, and the layers were separated. The organic layer was washed with 100 mL of saturated aqueous $Na_2S_2O_3$, 100 mL of 5% aqueous $NaHCO_3$, and 100 mL of water and then dried over Na_2SO_4. Concentration at reduced pressure gave a solid, which was recrystallized from ethanol to give 90.0 g of **14**[10] as a white solid: mp 90–95 °C; IR ($CHCl_3$) 3000, 1680, 1600, 1350, 1280, 1160, and 860 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 2.99 (s, 3), 4.38 (s, 2), 4.95 (s, 2), 7.27 (s, 5), 7.42 (d, 2, J = 8.8 Hz), 7.94 (d, 2, J = 8.8 Hz). Anal. ($C_{16}H_{16}BrNO_3S$) C, H, N, S, Br.

***N*-[4-[2-(1*H*-Imidazol-1-yl)-1-oxoethyl]phenyl]-*N*-(phenylmethyl)methanesulfonamide 0.25-Ethanolate.** To a 0 °C solution of **14**[10] (30.1 g, 72.2 mmol) in 300 mL of acetonitrile was added imidazole (26.8 g, 394.0 mmol) in one portion. The solution was stirred for 2 h at 0 °C, then slowly warmed to room temperature, and stirred for an additional 15 h. The solution was filtered and washed with 50 mL of acetonitrile and the filtrate concentrated in vacuo. The residue was dissolved in 400 mL of water and extracted with methylene chloride (2 × 350 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on 750 g of silica gel. Elution with methylene chloride–methanol (19:1) provided crystals. Recrystallization from ethanol afforded 18.7 g (68%) of the title compound as a yellow solid: mp 70–73 °C; IR ($CHCl_3$) 3000, 2970, 1700, 1600, 1500, 1250, 1155, and 855 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 3), 4.96 (s, 2), 5.33 (s, 2), 6.91 (s, 1), 7.14 (s, 1), 7.26 (s, 5), 7.45 (d, 2, J = 8.6 Hz), 7.50 (s, 1), 7.92 (d, 2, J = 8.6 Hz). Anal. ($C_{19}H_{19}N_3O_3S\cdot0.25C_2H_6O$) C, H, N, S.

***N*-[4-[1-Hydroxy-2-(1*H*-imidazol-1-yl)-1-methylethyl]phenyl]-*N*-(phenylmethyl)methanesulfonamide (15).** To a 0 °C solution of the previous compound (9.0 g, 23.6 mmol) in 250 mL of anhydrous tetrahydrofuran under nitrogen was added methylmagnesium bromide (11.8 mL, 3.1 M in ether, 36.6 mmol) dropwise via syringe. The solution was stirred for 30 min at 0 °C, then warmed to room temperature, and stirred for an additional 18 h. The reaction mixture was quenched by careful addition of saturated aqueous NH_4Cl (25 mL) and then concentrated in vacuo. The residue was dissolved in 50 mL of water and extracted with methylene chloride (3 × 100 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated at reduced pressure to give a solid. The solid was triturated with hot ethyl acetate–ethanol (9:1), filtered, and washed with ethyl acetate to give 7.0 g (77%) of **15** as white crystals: mp 169–171 °C; IR (Nujol) 3100 (br), 1500, 1320, 1225, 1140, and 860 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 1), 1.55 (s, 3), 2.95 (s, 3), 4.03 (d, 1, J = 14.2 Hz), 4.11 (d, 1, J = 14.2 Hz), 4.82 (d, 1, J = 14.4 Hz), 4.86 (d, 1, J = 14.4 Hz), 6.48 (s, 1), 6.88 (s, 1), 7.23 (d, 2, J = 8.6 Hz), 7.26 (s, 5), 7.30 (d, 2, J = 8.6 Hz), 7.60 (s, 1). Anal. ($C_{20}H_{23}N_3O_3S$) C, H, N.

***N*-[4-[1-Hydroxy-2-(1*H*-imidazol-1-yl)-1-methylethyl]phenyl]methanesulfonamide Hydrochloride 0.3-Hydrate 0.3-Ethanolate (16).** A mixture of **15** (3.2 g, 8.4 mmol), 8.4 mL of 1 N HCl (8.4 mmol), 20 mL of distilled water, and 7 mL of ethanol containing 3.0 g of 10% palladium on activated carbon was hydrogenated at 50 °C and ca. 50 psi for 22 h. The catalyst was collected by filtration through 10 g of Celite and washed with 50 mL of ethanol. Concentrating the filtrate in vacuo afforded 2.5 g (85%) of **16** as a white foam: mp 50–65 °C; IR (Nujol) 3300 (br), 2600 (br), 1620, 1510, 1330, 1150, 970, and 840 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 1.43 (s, 3), 2.97 (s, 3), 3.36 (br s, ca. 1) 4.35 (d, 1, J = 13.4 Hz), 4.46 (d, 1, J = 13.4 Hz), 5.90 (s, 1), 7.17 (d, 2, J = 8.5 Hz), 7.38 (d, 2, J = 8.5 Hz), 7.42 (s, 1), 7.55 (s, 1), 8.84 (s, 1), 9.78 (s, 1). Anal. ($C_{13}H_{17}N_3O_3S\cdot HCl\cdot0.3H_2O\cdot0.3C_2H_6O$) C, H, N, S, Cl.

1-[2-Hydroxy-2-methyl-2-[4-[(methylsulfonyl)amino]phenyl]ethyl]-3-methyl-1*H*-imidazolium Chloride 0.4-(2-Propanolate) (17). A solution of **16** (3.5 g, 10.0 mmol) in 50 mL of methanol was treated with 10.0 mL of 1 N aqueous NaOH solution (10.0 mmol). The mixture was concentrated in vacuo to give the free base. To a solution of this free base in 10 mL of methanol was added methyl iodide (2.8 mL, 44.8 mmol) via syringe. This solution was heated at ca. 50 °C for 48 h and then cooled to room temperature. The mixture was concentated in vacuo and the residue dissolved in 50 mL of water and washed with methylene chloride (2 × 25 mL). The aqueous layer was then concentrated in vacuo and passed through 200 g of chloride ion exchange resin (Bio-Rad, AG1-X8, 20–50 mesh). Concentration of the aqueous solution with 2-propanol gave 2.3 g (62%) of **17** as a white foam: mp 45–55 °C; IR (Nujol) 3300 (br), 1610, 1560, 1510, 965, and 840 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 1.43 (s, 3), 2.98 (s, 3), 3.84 (s, 3), 4.32 (d, 1, J = 13.7 Hz), 4.46 (d, 1, J = 13.7 Hz), 5.95 (s, 1), 7.19 (d, 2, J = 8.5 Hz), 7.41 (d, 2, J = 8.5 Hz), 7.44 (s, 1), 7.61 (s, 1), 8.97 (s, 1), 9.82 (s, 1). Anal. [$(C_{14}H_{20}N_3O_3S)^+Cl^-\cdot0.4C_3H_8O$] C, H, N, S, Cl.

***N*-[4-(4-Chloro-1-oxobutyl)phenyl]methanesulfonamide (19).** To a well-stirred solution of *N*-phenylmethanesulfonamide (**18**)[11] (20.0 g, 120.0 mmol) and 4-chlorobutyryl chloride (26.0 mL, 230.0 mmol) in 200 mL of carbon disulfide at 0 °C under nitrogen was added aluminum chloride (47.0 g, 350.0 mmol). The resultant mixture was warmed to room temperature and heated to reflux. After 5 h at reflux, the mixture was cooled to room temperature and the carbon disulfide decanted. The insoluble residue was cooled to −10 °C and quenched by adding 6 N HCl (400 mL). The resulting precipitate was collected and washed with water (100 mL). Drying to constant weight gave 28.0 g (85%) of **19** as a light yellow solid: mp 142–143 °C; IR (Nujol) 3220, 1655, 1595, and 1150 cm^{-1}; NMR (60 MHz, DMSO-d_6) δ 1.80–2.30 (m, 2), 3.08 (s, 3), 3.09 (t, 2), 3.73 (t, 2), 7.30 (d, 2), 7.92 (d, 2). Anal. ($C_{11}H_{14}ClNO_3S$) C, H, N.

5,6-Dihydro-3-methyl-8-[4-[(methylsulfonyl)amino]phenyl]imidazo[1,5-*a*]pyridine (20). A mixture of **19** (100 g, 360 mmol) and 2-methylimidazole (400 g, 488 mmol) was heated

(10) This product was found to contain ca. 7.5% of *N*-[4-(2,2-dibromo-1-oxoethyl)phenyl]-*N*-(phenylmethyl)methanesulfonamide based on C, H, N and NMR analyses.

(11) Marvel, C. S.; Melfrick, M. D.; Belsley, J. P. *J. Am. Chem. Soc.* **1929**, *51*, 1272.

to ca. 175 °C under argon for 22 h. After cooling to room temperature, the reaction mixture was dissolved in methylene chloride (1 L) and washed with 10% aqueous $KHCO_3$ (2 × 1 L) and water (2 × 1 L). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (500 g) with methanol–methylene chloride (1:9) as eluent and afforded 19 g (17%) of **20**. Recrystallization from ethanol gave **20** as an off-white solid: mp 235–237 °C; IR (Nujol) 3100, 1600, 1545, 1510, and 1310 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 2.32 (s, 3), 2.57 (q, 2), 3.02 (s, 3), 3.94 (t, 2), 5.84 (t, 1), 6.70 (s, 1), 7.24 (d, 2), 7.44 (d, 2), 9.90 (s, 1). Anal. ($C_{15}H_{17}N_3O_2S$) C, H, N.

3-Methyl-8-[4-[(methylsulfonyl)amino]phenyl]-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine (21). A 500-mL Parr bottle was charged with **20** (5.0 g, 16.5 mmol), 2.0 g of 10% palladium on activated carbon, and 100 mL of 1 N NaOH. The mixture was hydrogenated at ca. 50 psi for 16 h at room temperature. The catalyst was collected by filtration, neutralized by using solid NH_4Cl, and extracted with methylene chloride (2 × 100 mL). Drying the organic extracts (Na_2SO_4) and concentrating at reduced pressure gave 5.0 g of **21** as a gummy solid. Recrystallization from ethyl acetate gave 4.6 g (92%) of **21** as a white solid: mp 206–207 °C; IR (Nujol) 1505, 1460, 1340, and 1155 cm^{-1}; NMR (300 MHz, DMSO-d_6) 1.80–2.05 (m, 4), 2.34 (s, 3), 2.97 (s, 3), 3.75 (m, 1), 3.96 (m, 2), 6.09 (s, 1), 7.15 (d, 2), 7.17 (d, 2), 9.68 (s, 1). Anal. ($C_{15}H_{19}N_3O_2S$) C, H, N.

5,6-Dihydro-2,3-dimethyl-8-[4-[(methylsulfonyl)amino]phenyl]imidazo[1,5-*a*]pyridinium Iodide (22). A mixture of **20** (6.0 g, 19.8 mmol) and methyl iodide (13.0 mL, 208.8 mmol) in 50 mL of methanol was heated in a pressure bottle for 20 h at ca. 60 °C. After cooling to room temperature, the solution was concentrated at reduced pressure and the resulting solid (6.2 g) slurried in ethanol. Recrystallization from ethanol afforded 4.6 g (52%) of **22** as a white solid: mp 237–238 °C; IR (Nujol) 2940, 1605, 1595, 1505, 1340, and 1170 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 2.64 (s, 3), 2.72 (q, 2), 3.04 (s, 3), 3.75 (s, 3), 4.20 (t, 2), 6.30 (t, 1), 7.28 (d, 2), 7.45 (d, 2), 7.61 (s, 1), 9.95 (s, 1). Anal. [($C_{16}H_{20}N_3O_2S$)$^+I^-$] C, H, N.

2,3-Dimethyl-8-[4-[(methylsulfonyl)amino]phenyl]-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridinium Iodide (23). A mixture of **21** (6.0 g, 19.6 mmol) and methyl iodide (15.0 mL, 240.9 mmol) in 100 mL of methanol was heated in a pressure bottle for 20 h at ca. 60 °C. After cooling to room temperature, the solution was concentrated at reduced pressure and the resulting solid (9.2 g) slurried in ethanol. Recrystallization from ethanol afforded 6.5 g (74%) of **23** as a white solid: mp 187–188 °C; IR (Nujol) 3090, 1510, 1330, and 1155 cm^{-1}; NMR (300 MHz, DMSO-d_6) δ 1.80–2.10 (m, 4), 2.56 (s, 3), 3.00 (s, 3), 3.69 (s, 3), 3.99–4.30 (m, 3), 7.04 (s, 1), 7.20 (d, 2), 7.25 (d, 2), 9.76 (s, 1). Anal. [($C_{16}H_{22}N_3O_2S$)$^+I^-$] C, H, N.

Pharmacology. Intracellular and extracellular elecrophysiological profiles, intradueodenal bioavailability, antiarrhythmic efficacy (PES model) and β-adrenergic receptor binding studies were performed according to previously established procedures.[3] Samples of sotalol and clofilium were prepared by in-house synthesis.

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Registry No. **2a**, 64488-52-4; **2b**, 5317-90-8; **3a**, 110698-54-9; **3c**, 110698-73-2; **4c** (isomer 1), 110698-74-3; **4c** (isomer 2), 110698-75-4; **5**, 41104-10-3; **6**, 110698-55-0; **7**, 110698-56-1; **8**, 110698-57-2; **8**·HCl, 110698-58-3; **9**, 110698-59-4; **10**, 30148-20-0; **11**, 110698-60-7; **12**, 110698-61-8; **13**, 5317-89-5; **14**, 110698-62-9; **15**, 110698-63-0; **16**, 110698-64-1; **17**, 110698-76-5; **18**, 1197-22-4; **19**, 108060-61-3; **20**, 108060-52-2; **21**, 108060-55-5; **22**, 110698-65-2; **23**, 110698-66-3; thiazole, 288-47-1; 1-methylimidazole, 616-47-7; 1-[2-[4-(acetyloxy)phenyl]-2-oxoethyl]-3-methyl-1*H*-imidazolium bromide, 110698-67-4; 2-methyl-2-imidazoline, 534-26-9; *N*-[4-[(1-methyl-1*H*-imidazol-2-yl)carbonyl]phenyl]methanesulfonamide, 110698-68-5; *N*-[4-[hydroxy(1-methyl-1*H*-imidazol-2-yl)-methyl]phenyl]methanesulfonamide, 110698-69-6; *N*-[4-(1-oxoethyl)phenyl]-*N*-(phenylmethyl)methanesulfonamide, 110698-70-9; *N*-[4-[2-(1*H*-imidazol-1-yl)-1-oxoethyl]phenyl]-*N*-(phenylmethyl)methanesulfonamide, 110698-71-0; imidazole, 288-32-4; 4-chlorobutyryl chloride, 4635-59-0; 2-methylimidazole, 693-98-1; *N*-[4-(2,2-dibromo-1-oxoethyl)phenyl]-*N*-(phenylmethyl)-methanesulfonamide, 110698-72-1; *N*-[4-[1-hydroxy-2-(4,5-dihydro-2-methyl-1*H*-imidazol-1-yl)ethyl]phenyl]methanesulfonamide, 111323-42-3.

Design and Synthesis of Peptide Derivatives of a 3-Deoxy-D-*manno*-2-octulosonic Acid (KDO) Analogue as Novel Antibacterial Agents Acting upon Lipopolysaccharide Biosynthesis

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On the basis of the knowledge that the amino acid **3** (8-amino-2,6-anhydro-3,8-dideoxy-D-*glycero*-D-*talo*-octonic acid) is a potent inhibitor of 3-deoxy-*manno*-octulosonate cytidylyltransferase, attempts were made to design derivatives that would act as antibacterials against Gram-negative bacteria by inhibiting lipopolysaccharide biosynthesis. Compound **3** and the derivatives **15** and **16** containing an additional amino acid were not lethal to bacteria. However, compounds **17–22**, which contain a N-terminally linked dipeptide, exhibited good antibacterial activity in vitro on testing against strains of the Gram-negative bacteria *Escherichia coli* and *Salmonella typhimurium*. They have no activity against Gram-positive bacteria such as *Staphylococcus aureus*.

Since the outer membrane of Gram-negative bacteria is important both to pathogenesis and resistance to existing antimicrobial agents,[1,2] the rational design of inhibitors of its biosynthesis should produce novel agents effective only against Gram-negative bacteria.[3] The outer leaflet of this membrane contains lipopolysaccharide[4] (LPS), which provides an attractive target, since it contains components unique to Gram-negative bacteria. Among these is the sugar 3-deoxy-D-*manno*-2-octulosonic acid[5] (KDO, 1),

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