Synthesis and Cardiac Electrophysiological Activity of Aryl-Substituted Derivatives of the Class III Antiarrhythmic Agent Sematilide. Potential Class I/III Agents

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Twelve novel derivatives of the selective class III antiarrhythmic agent sematilide were prepared in an attempt to incorporate both class I and class III electrophysiological properties into a single molecule. Electrophysiological activity was determined by standard microelectrode techniques in canine cardiac Purkinje fibers. Initial assessment of class I efficacy was carried out in a ouabain-induced arrhythmia model in guinea pigs. All of the compounds prolonged action potential duration in Purkinje fibers (class III activity), and three were active against ouabain-induced arrhythmias (class I activity). Selected compounds were evaluated further in dogs for efficacy against arrhythmias occurring 24 h following coronary ligation (automatic arrhythmias) and induced by using programmed electrical stimulation techniques (reentrant arrhythmias). The most effective compounds from the series are **3g** and **-j**, which were effective in both canine models. Molecular modeling and structure–activity relationships are discussed.

A number of therapeutic approaches are available for the treatment of life-threatening arrhythmias. Due to the variety of pathophysiological conditions that may contribute to the development of arrhythmias no single agent is effective in all cases. Currently, the most widely prescribed agents are those that slow conduction in cardiac tissue, termed class I antiarrhythmic agents (Vaughan Williams classification).[1] These agents are effective in controlling premature ventricular contractions (PVC's) but are typically less effective when studied by using programmed electrical stimulation (PES) techniques.[2] PES is a technique used to determine and predict effective therapy for those patients at risk due to reentrant arrhythmias. We[3] and others[4] have described agents that selectively prolong action potential duration (increase refractoriness), termed Class III antiarrhythmic agents. Such agents have been shown to be effective against reentrant arrhythmias but are typically less effective against automatic arrhythmias (i.e., PVC's). In order to develop an agent that would be effective in a wider variety of arrhythmias, we sought to combine class I and class III effects in a single compound (class I/III agent).

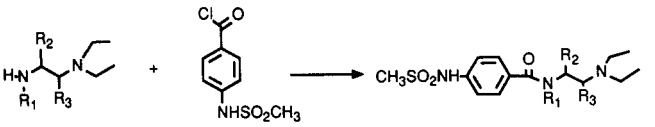
Our initial approach to the preparation of class I/III agents was to link the selective class III agent, sematilide (**1**),[3] with the class I agent lidocaine (**2**) at the amide nitrogen (Figure 1). We also investigated the effects on electrophysiological activity of substitution on the "class I aryl group" and position of the aryl group on the ethylenediamine chain.

Chemistry

The new compounds **3** were prepared by the general route outlined in Scheme I. Reaction of the appropriate *N,N*-diethyl-1,2-ethanediamine (**4**) with 4-[(methylsulfonyl)amino]benzoyl chloride (**5**)[5] provided the target compounds (Table I).

Some of the diamines **4** were previously known. The new diamines were prepared by standard routes. To prepare the *N*-aryl-*N'*,*N'*-diethyl-1,2-ethanediamines **4a–h**, the procedures of Lis[6] or Tenthorey[7] were used (Scheme II). Reaction of an excess of the appropriate aniline with 2-chloro-*N*,*N*-diethylethanamine gave **4**. Alternatively,

Scheme I



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sequential reaction of the aniline with chloroacetyl chloride and diethylamine gave **6**, which was reduced with lithium aluminum hydride. The 1-aryl-N^2,N^2-diethyl-1,2-ethanediamines **4i–j** were prepared by alkylation of diethylamine with the appropriate α-bromo ketone to give **7** followed by formation of the oxime **8** and reduction with lithium aluminum hydride (Scheme III). 1-Aryl-N^1,N^1-diethyl-1,2-ethanediamines **4k–l** were prepared by a modified Strecker reaction on an aromatic aldehyde to give the α-(diethylamino)acetonitrile **9** and subsequent reduction with lithium aluminum hydride (Scheme IV).

Pharmacology

Primary evaluation for electrophysiological activity was carried out in canine cardiac Purkinje fibers. Standard

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(3) (a) Lumma, W. C., Jr.; Wohl, R. A.; Davey, D. D.; Argentieri, T. M.; DeVita, R. J.; Gomez, R. P.; Jain, V. K.; Marisca, A. J.; Morgan, T. K., Jr.; Reiser, H. J.; Sullivan, M. E.; Wiggins, J.; Wong, S. S. *J. Med. Chem.* **1987**, *30*, 755. (b) Lis, R.; Morgan, T. K., Jr.; Reiser, H. J.; Sullivan, M. E.; Wiggins, J.; Wong, S. S. *J. Med. Chem.* **1987**, *30*, 696. (c) Morgan, T. K., Jr.; Lis, R.; Marisca, A. J.; Argentieri, T. M.; Sullivan, M. E.; Wong, S. S. *J. Med. Chem.* **1987**, *30*, 2259.
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(5) Made by refluxing the sodium salt of the acid with thionyl chloride overnight. For an earlier preparation, see: Goldenberg, C.; Wandestrick, R.; Van Meerbeeck, C.; Descamps, M.; Richard, J.; Bauthier, J.; Charlier, R. *Eur. J. Med. Chem.* **1977**, *12*, 81.
(6) Lis, R.; Marisca, A. J. *Synth. Commun.* **1988**, *18*, 45.
(7) Tenthorey, P. A.; Block, A. J.; Ronfeld, R. A.; McMaster, P. D.; Byrnes, E. W. *J. Med. Chem.* **1981**, *24*, 798.

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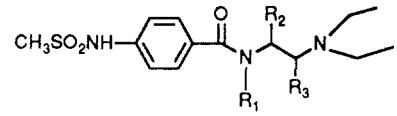
Table I. Aryl-Substituted Derivatives of *N*-[(Diethylamino)ethyl]-4-[(methylsulfonyl)amino]benzamide



no.	R_1	R_2	R_3	salt (mp, °C)	recrystn solvent	formula	anal.
3a	C_6H_5	H	H	HCl (133–136)	CH_3CN	$C_{20}H_{27}N_3O_3S$·HCl	C, H, N
3b	4-$(CH_3CH_2)C_6H_4$	H	H	HCl (84–90)		$C_{22}H_{31}N_3O_3S$·HCl	C, H, N
3c	4-ClC_6H_4	H	H	HCl (115–118)	CH_3CN	$C_{20}H_{26}ClN_3O_3S$·HCl·0.3CH_3CN	C, H, N, Cl, S
3d	4-$(CH_3O)C_6H_4$	H	H	fumarate (142–144)	EtOAc/MeOH	$C_{21}H_{29}N_3O_4S$·$C_4H_4O_4$·0.5H_2O	C, H, N, S
3e	4-$(CH_3SO_2NH)C_6H_4$	H	H	(80–88)		$C_{21}H_{30}N_4O_5S_2$·0.5H_2O	C, H, N, S
3f	2,6-$(CH_3)_2C_6H_3$	H	H	HCl (187–188.5)	CH_3CN/MeOH	$C_{22}H_{31}N_3O_3S$·HCl	C, H, N
3g	2,6-$[(CH_3)_2CH]_2C_6H_3$	H	H	HCl (244–245)	CH_3CN	$C_{26}H_{39}N_3O_3S$·HCl	C, H, N
3h	$C_{10}H_7$	H	H	HCl (177–180)	CH_3CN	$C_{24}H_{29}N_3O_3S$·HCl	C, H, N
3i	H	C_6H_5	H	HCl (180–183)	hexane	$C_{20}H_{27}N_3O_3S$·HCl·0.25H_2O	C, H, N, Cl, S
3j	H	$C_{10}H_7$	H	(183–185)	EtOAc/MeOH	$C_{24}H_{29}N_3O_3S$	C, H, N
3k	H	H	C_6H_5	(149–151)	EtOAc/Hex	$C_{20}H_{27}N_3O_3S$	C, H, N
3l	H	H	$C_{10}H_7$	HCl (217–220)	CH_3CN/MeOH	$C_{24}H_{29}N_3O_3S$·HCl	C, H, N

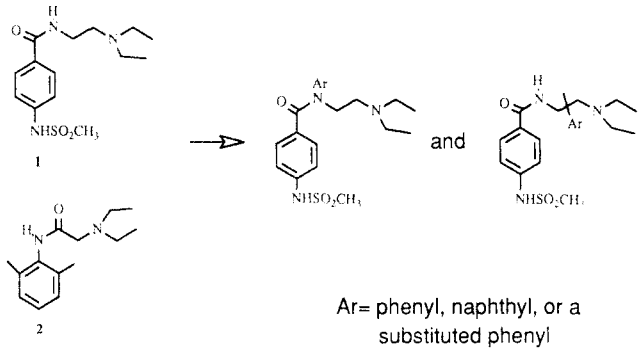


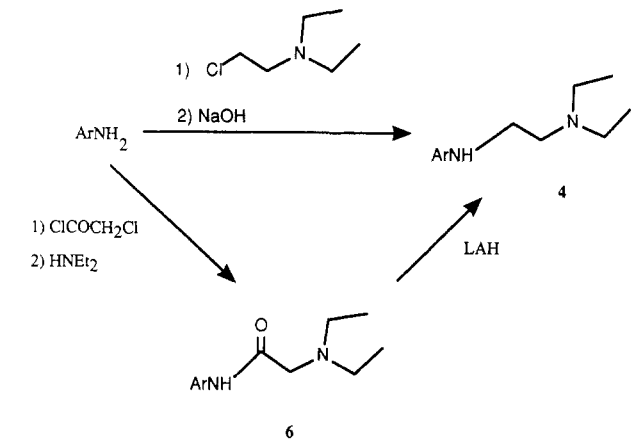
Figure 1. Approach to potential class I/III agents.

microelectrode techniques were used to determine the effects on action potential duration (APD) and the rate of depolarization ($\dot{V}_{max}$).[8] In Table II, we report the percent change from control of the action potential duration at 95% repolarization (% ΔAPD_{95}) and the percent change from control for $\dot{V}_{max}$ (% $\Delta\dot{V}_{max}$) at a number of concentrations for the test compounds. Shown for comparison are the selective class III agent sematilide (1) and the class I agents quinidine, lidocaine, and flecainide.

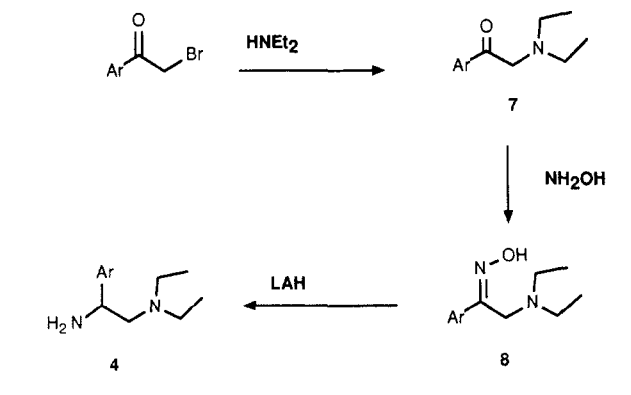
Compounds that increased APD_{95} by at least 20% over control at concentrations ≤10 μM were considered to show good activity as class III agents. Those compounds that increased APD_{95} by 10–19% at concentration ≤10 μM were designated as moderately active. If APD_{95} was increased ≤10%, the compound was considered to be inactive. We have found that compounds which prolonged APD_{95} by at least 20% at concentrations ≤10 μM generally show efficacy in the PES canine model at reasonable doses (<10 mg/kg). Decreases in $\dot{V}_{max}$ of 20% were considered indicative of class I activity.

Further assessment of class I activity was carried out by using a ouabain-induced arrhythmia model in anesthetized guinea pigs.[9] Ten minutes after the intravenous administration of the test compound, ouabain was administered intravenously as a bolus (40 μg/kg) followed immediately by a constant intravenous infusion of ouabain (10 μg/kg/min) until an arrhythmia occurred. Reported in Table III is the percent change in mean time to the first arrhythmia for the drug-treated group relative to vehicle control value. Compounds that increased the time to first arrhythmia by ≥25% at 10 mg/kg were designated as having good activity, and those that increased time to first arrhythmia by 10–24% at 10 mg/kg were considered moderately active in this model. Compounds that caused <10% increase in time to first arrhythmia at 10 mg/kg were judged to be inactive. For comparative purposes, the

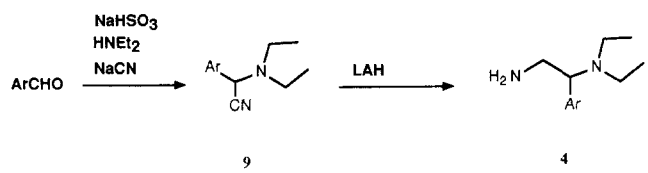
Scheme II



Scheme III



Scheme IV



(8) Davis, L. D.; Temte, J. V. *Circ. Res.* **1969**, *24*, 639.
(9) Model based on the following: (a) Kujime, K.; Natelson, B. H. *J. Pharm. Exp. Ther.* **1984**, *229*, 113. (b) Benharkate, M.; Plassard, G.; Legeai, J.; Worcel, M. *Arzneim.-Forsch.* **1986**, *36*, 1761.

Table II. In Vitro Electrophysiology in Canine Purkinje Fibers

compound	n^a	concn, μM	% Δ APD_{95}[b]	% Δ $\dot{V}_{max}$[c]
3a	2	0.1	4 ± 6	−4 ± 4
	4	1	18 ± 4	−3 ± 7
	4	10	52 ± 8	−12 ± 8
	1	30	38	−20
	2	100	45 ± 13	−39 ± 1
3b	4	0.1	12 ± 3	5 ± 4
	4	1	51 ± 10	8 ± 6
	4	10	70 ± 8	4 ± 8
	4	30	62 ± 12	−6 ± 7
3c	4 (2)	0.1	9 ± 5	3 ± 1
	4 (2)	1	34 ± 7	2 ± 4
	4 (2)	10	64 ± 16	−8 ± 6
	4 (2)	30	60 ± 8	−20 ± 15
3d	4 (3)	0.1	8 ± 3	0 ± 1
	4 (3)	1	35 ± 5	−3 ± 2
	4 (3)	10	82 ± 5	−3 ± 1
	3	30	66 ± 5	−8 ± 4
3e	2	0.1	7 ± 8	−4 ± 2
	2	1	10 ± 6	−2 ± 4
	2	10	30 ± 4	−3 ± 3
	2	30	40 ± 2	−6 ± 4
3f	3	0.1	7 ± 8	−4 ± 2
	4	1	10 ± 6	−2 ± 4
	4	10	30 ± 4	−3 ± 3
	4	100	40 ± 2	−6 ± 4
3g	4	1	21 ± 9	1 ± 3
	4	10	22 ± 11	−11 ± 3
	3	100	−4 ± 10	−67 ± 9
3h	2	0.1	10 ± 3	2 ± 3
	4	1	51 ± 10	−5 ± 4
	4	10	64 ± 10	−13 ± 4
	1	30	37	−16
	3	100	26 ± 9	−42 ± 4
3i	2 (1)	0.1	4 ± 3	6
	4 (3)	1	21 ± 8	−2 ± 3
	4 (3)	10	−2 ± 3	−13 ± 3
	2 (1)	30	−12 ± 13	−34
	2	100	−20 ± 0	−76 ± 16
3j	4	0.1	14 ± 5	−3 ± 3
	4	1	10 ± 3	−20 ± 5
	2	10	−14 ± 4	−74 ± 1
3k	2 (1)	0.1	11 ± 5	−4
	2 (1)	1	40 ± 20	−4
	1	10	46	−12
	1	30	52	−15
3l	6 (3)	0.1	4 ± 3	1 ± 3
	6 (4)	1	29 ± 7	−2 ± 4
	6 (4)	10	34 ± 14	−4 ± 7
	5	30	29 ± 15	−7 ± 4
sematilide (1)	12	0.1	0 ± 1	2 ± 3
	18 (14)	1	6 ± 1	0 ± 3
	3	3	14 ± 5	
	23 (18)	10	33 ± 2	0 ± 3
	9	30	51 ± 4	
	9 (6)	100	66 ± 7	0 ± 6
quinidine	4	0.1	2 ± 1	0 ± 1
	4	1	4 ± 3	−1 ± 1
	5	10	−4 ± 7	−8 ± 2
	3	30	−17 ± 7	−23 ± 3
	2	100	−14 ± 10	−75 ± 23
flecainide	3	0.1	−3 ± 2	2 ± 6
	8	1	−15 ± 2	−6 ± 2
	3	3	−35 ± 6	−11 ± 3
	7	10	−47 ± 3	−30 ± 2
lidocaine	2	1	−7 ± 0	2 ± 2
	3	10	−25 ± 2	1 ± 6
	2	100	−40 ± 8	−4 ± 16

[a] Number of experiments. Numbers in parentheses are the number of experiments in which $\dot{V}_{max}$ data were obtained when different from the total number of experiments. [b] Percent change (mean ± SEM) from control value for the action potential duration at 95% repolarization (APD_{95}) at the designated concentration off the test compound. [c] Percent change (mean ± SEM) from control value for $\dot{V}_{max}$ at the designated concentration of the test compound.

Table III. Effect of Compounds on Ouabain-Induced Arrhythmia in Guinea Pigs

compound	dose, mg/kg	% Δ[a]
3a	10	−9 ± 1
3b	10	20 ± 2
3c	10	18 ± 2
3d	10	15 ± 1
3e	10	22 ± 1
3f	10	−8 ± 1
3g	3	22 ± 1
3h	3	8 ± 1
	10	−25 ± 3
3i	10	61 ± 5
3j	3	70 ± 4
3k	10	−13 ± 1
3l	10	0 ± 1
quinidine	10	28 ± 2
flecainide	3	51 ± 3
lidocaine	10	30 ± 1

[a] Percent change in the mean time to first arrhythmia (n = 4–6) from control (n = 3–4).

results of the class I agents quinidine, lidocaine, and flecainide are also shown.

Three compounds (**3g**, **-h**, and **-j**) were selected for further evaluation in two conscious canine arrhythmia models (Table IV). In the first model, dogs were studied by utilizing PES techniques 3–8 days after undergoing an occlusion/reperfusion infarction according to the method of Karagueuzian.[10] Two control arrhythmias were induced prior to drug administration. Ventricular fibrillation (VF) was terminated by DC countershock, and sustained ventricular tachycardia (SVT) was terminated by burst pacing. After drug administration reinduction of arrhythmia was attempted. A drug was considered effective in the model if SVT or VF could not be induced in 50% of the test animals. Class III agents are typically effective in this model while class I agents are less effective. The second model employed the method of Harris.[11] Animals were studied 24 h after being infarcted by a two-stage occlusion technique. At this time the dog is highly ectopic (>75% ectopy). For a compound to be considered effective in this model it must have decreased ectopy by >30% in at least half of the animals studied. This model is highly selective for class I agents, while class III agents are typically ineffective in this model. The new compounds were compared to the selective class III agent sematilide and the class I agents quinidine and flecainide.

Discussion

All of the new compounds with the exception of **3j** exhibited good class III electrophysiological activity in the Purkinje fiber assay; **3j** showed moderate activity. In fact, **3b–d**, **-f–i**, **-k**, and **-l** were more potent than the selective class III agent **1**. In contrast to compounds in this series, quinidine, a class Ia agent, did not increase APD_{95} in Purkinje fibers. Compounds **3a**, **-c**, and **-g–j** also showed class I electrophysiological activity; however, class I activity was usually observed at higher concentrations than the class III effect. Compound **3j**, which had moderate class III activity, was the most potent compound in producing class I effects. For some compounds (**3g–j**), which were potent class I agents at higher concentrations, the APD_{95} was significantly reduced from the maximum value observed at lower concentrations. This biphasic response of APD_{95} has been noted in other series[3c] with both class III

(10) Karagueuzian, H. S.; Fenoglio, J. J., Jr.; Weiss, M. B.; Wit, A. L. *Circ. Res.* **1979**, *44*, 833.
(11) Harris, A. S. *Circulation* **1950**, *1*, 1318.

Table IV. In Vivo Antiarrhythmic Efficacy of Selected Compounds

	PES model			Harris model		
compound	n	no. effective	effective dose, mg/kg[a]	n	no. effective	effective dose, mg/kg[a]
sematilide	6	5	1 (5)	10	0	
quinidine	10[b]	5	1 (2), 3 (1), 10 (2)	7[c]	3	10 (3)
flecainide	8	2	1 (2)	10[d]	8	1 (4), 2.5 (1), 5 (3)
3g	5	4	1 (4)	4	2	10 (2)
3h	4	2	1 (1), 3 (1)	4	0	
3j	7	4	1 (2), 3 (1), 6 (1)	3	3	2 (2), 4 (1)

[a] Number of animals in which a given dose was effective is shown in parentheses. For animals in which the drug was ineffective a cumulative dose of 10 mg/kg was given unless otherwise specified. [b] Not effective in 3 animals at 20 mg/kg. [c] Not effective in 4 animals at 15 mg/kg. [d] Not effective in 2 animals at 5 mg/kg.

Table V. Relationship of the N–C–C–N Dihedral Angle of Models of **3h**, **-j**, and **-l** and Their Respective Calculated Relative Energies

	model of **3h**		model of **3j**		model of **3l**	
N–C–C–N dihedral angle (deg)	calcd energy, kcal/mol	relative energy, kcal/mol	calcd energy, kcal/mol	relative energy, kcal/mol	calcd energy, kcal/mol	relative energy, kcal/mol
0	37.5	0	15.0	0	28.6	0
60	33.6	−3.9	12.1	−2.9	26.7	−1.9
120	34.9	−2.6	15.1	0.1	29.6	1.0
180	31.7	−5.8	7.6	−7.4	27.3	−1.3
240	34.8	−2.7	12.7	−2.3	31.0	2.4
300	34.1	−3.4	11.1	−3.9	22.9	−5.7
360	37.5	0	15.0	0	28.6	0

and class I activity and for fixed concentrations of the standard **1** in the presence of increasing concentrations of class I agents.[12] Thus, in Purkinje fibers, increasing class I activity can blunt class III electrophysiological activity.

The ouabain-induced arrhythmia model in guinea pigs gives a more direct indication of potential class I activity in an intact animal. Compounds **3g**, **-i**, and **-j** were the most effective in this model, and compounds **3b–e** showed moderate activity. Compound **3j** was as effective as the potent class I agent flecainide; **3g** and **3i** were more potent than lidocaine or quinidine but less potent than flecainide. There is not a direct correlation between class I electrophysiological activity in Purkinje fibers and efficacy in the ouabain model. This may be due to the fact that the electrophysiological assay focuses on only one part of the cardiac conducting system (i.e., Purkinje fibers) while the composite effects of the drug on the whole myocardium are seen in the ouabain model.

Variation of substituents on the phenyl ring for the N-substituted series (**3a–h**) had little effect on class III electrophysiological activity in Purkinje fibers and class I activity in the guinea pig with the exception of the more lipophilic compound **3g**, which shows class I activity. In contrast, a comparison among the phenyl compounds **3a**, **-i**, and **-k** and the naphthalenyl compounds **3h**, **-j**, and **-l** illustrates an interesting effect of aryl moiety placement in the connecting chain on class III and class I activities. In the N-substituted compounds **3a** and **-h**, class III activity dominates with class I activity present only at the higher concentrations in the Purkinje fiber assay. Moving the aryl moiety to the carbon atom α to the amide nitrogen, as in **3i** and **-j**, significantly decreases the class III activity relative to **3a** and **-h** and increases the amount of class I activity observed. Further movement of the aryl groups to the carbon β to the amide nitrogen (**3k** and **-l**) leads to compounds with class III electrophysiological activity which are essentially devoid of class I activity. Thus, the amount of class I electrophysiological activity observed in this series is dependent on the point of attachment of the aryl moiety on the connecting chain.

(12) T. M. Argentieri, unpublished results.

Three compounds (**3g**, **-h**, and **-j**) were studied for efficacy in two canine arrhythmia models. On the basis of the electrophysiological and ouabain screens **3h** was more selective for class III activity, **3g** had a mixture of class III and class I activities, and **3j** was more selective for class I activity. All three compounds were at least 50% effective in the PES model, while only **3g** and **-j** were effective in the Harris model. All three compounds produced emesis in some animals after intravenous administration, which is suggestive of undesirable CNS effects.

Molecular Modeling

In view of the differing activities of the positional isomers **3h**, **-j**, and **-l**, we decided to determine whether the conformation could be correlated to electrophysiological activity by examining the effects of the position of the aryl group on conformation of the side chain using molecular modeling. A series of model compounds in which the (methylsulfonyl)amino substituent was replaced by an acetylamino group[13] was studied by using the CHEMLAB II[14] series of programs. The geometries of the model compounds were optimized by molecular mechanics calculations at various fixed N–C–C–N dihedral angles (60° increments). The results are presented in Table V and Figure 2. The relative energies of the three staggered conformations of the model of **3h** lie within 2.5 kcal. The staggered conformation of the model of **3j** in which the nitrogens are trans is 3.5 kcal lower than either of the other two staggered conformations. One of the staggered conformations of the model of **3l** in which the nitrogens are gauche is 4.2 kcal lower than the conformation in which the nitrogens are trans. These studies suggest that in this series compounds in which class III activity predominates prefer a gauche relationship of the nitrogens in the ethylenediamine chain (Figure 3A) while for compounds in which the class I activity predominates, a trans relationship of the nitrogens is preferred (Figure 3B). We have

(13) An acetamide was used instead of a methanesulfonamide due to a lack of parameters for sulfonamides.

(14) Local minima were calculated by using a variation of Allinger's MM2 (MMFF) program employed in CHEMLAB II. CHEMLAB II is a product of Molecular Design, Ltd., San Leandro, CA 94577.

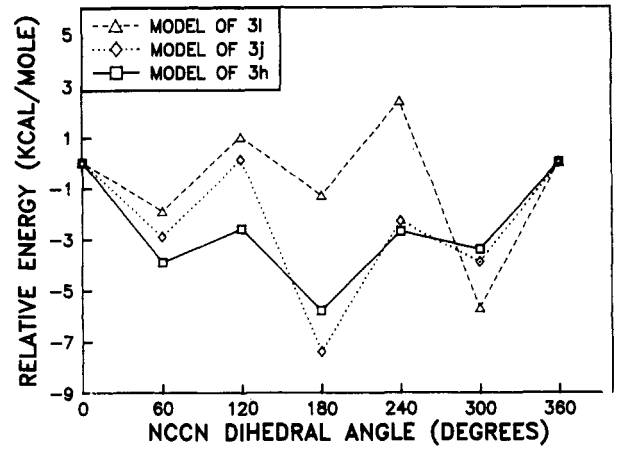
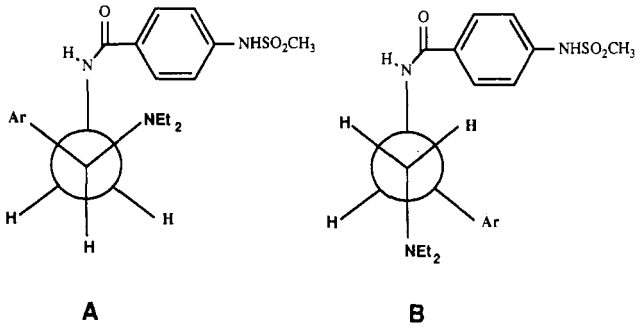


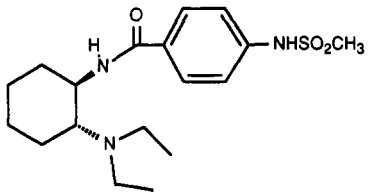
Figure 2. Graphic representation of Table V.



A B

Figure 3.

previously reported **10**, a compound conformationally restricted in the gauche conformation, to have selective class III activity.[3a]



10

Conclusion

We have prepared twelve aryl derivatives of the selective class III agent sematilide with the goal of obtaining compounds that possess both class I and class III electrophysiological activities. All of the compounds prepared exhibit class III activity, and some exhibit class I activity in our in vitro model. Three of the compounds, **3g**, **-i**, and **-j**, show activity against ouabain-induced arrhythmias in the guinea pig, and two of those, **3g** and **-j**, were effective in canine models of reentrant and automatic arrhythmias. Expression of the class I component appears to depend on the lipophilicity of the aryl moiety or on the point of attachment of the aryl moiety to the parent compound. On the basis of modeling studies, the point of attachment of the aryl moiety has an effect on the ethylenediamine chain conformation, which appears to be a controlling factor of the electrophysiological profile of these compounds. Further studies of these compounds are in progress.

Experimental Section

Melting points were taken on a Fisher-Johns or a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Berlex Analytical Section, Cedar Knolls, NJ, or Microlit Laboratories, Caldwell, NJ, and results were within ±0.4% of the calculated values except where indicated. NMR spectra were recorded with a Varian XL-300 (300 MHz) spectrometer. Tetramethylsilane was used as the internal standard in all solvents. All NMR spectra were consistent with the assigned structures.

***N*-[2-(Diethylamino)ethyl]-4-[(methylsulfonyl)amino]-*N*-phenylbenzamide Hydrochloride (3a).** *N,N*-Diethyl-*N'*-phenyl-1,2-ethanediamine[15] (5.2 g, 27 mmol) was dissolved in dry THF (50 mL) under N_2, and **5** (7.0 g, 30 mmol) in THF (25 mL) was added dropwise. After stirring for 17 h, the solvent was removed in vacuo and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with EtOAc. The organic layers were combined and dried (Na_2SO_4). The drying agent was removed by filtration, and the solvent was removed in vacuo. The residue was recrystallized from EtOAc to give 3.7 g (35%) of a white solid. The solid was dissolved in methanolic HCl, and the solvent was removed in vacuo to give an oil. Crystallization gave 1.4 g of **3a**: NMR (DMSO-d_6) δ 1.21 (t, 6 H), 2.98 (s, 3 H), 3.20 (m, 6 H), 4.19 (t, 2 H), 7.00 (d, 2 H), 7.25 (m, 5 H), 7.34 (m, 2 H).

***N,N*-Diethyl-*N'*-(4-ethylphenyl)-1,2-ethanediamine (4b).** 2-(Diethylamino)-*N*-(4-ethylphenyl)acetamide[16] (31 g, 0.13 mol) was dissolved in THF (100 mL), and lithium aluminum hydride (10 g, 0.26 mol) was added portionwise. After refluxing for 16 h, the reaction was cooled to room temperature, and H_2O (10 mL), 2 N aqueous NaOH (10 mL), and H_2O (30 mL) were added sequentially. The precipitate was removed by suction filtration through Celite, and the solvent was removed in vacuo to give 27.6 g (95%) of **4b**. The HCl salt was made from a portion of **4b** and recrystallized from EtOAc/CH_3CN to give a white solid: mp 92–93 °C; NMR (DMSO-d_6) δ 1.11 (t, 3 H), 1.22 (t, 6 H), 2.45 (q, 2 H), 3.1–3.2 (m, 6 H), 3.36 (s, 2 H), 3.43 (m, 2 H), 6.58 (d, 2 H), 6.96 (d, 2 H). Anal. ($C_{14}H_{25}ClN_2$) C, H, N.

***N*-[2-(Diethylamino)ethyl]-*N*-(4-ethylphenyl)-4-[(methylsulfonyl)amino]benzamide Hydrochloride (3b).** Reaction of **4b** (6.4 g, 29 mmol) with **5** (6.0 g, 32 mmol) as described for **3a** gave 3.2 g (24%) of **3b**: NMR (DMSO-d_6) δ 1.12 (t, 3 H), 1.21 (t, 6 H), 1.25 (q, 2 H), 2.98 (s, 3 H), 3.18 (m, 6 H), 4.15 (t, 2 H), 6.99 (d, 2 H), 7.14 (s, 4 H), 7.24 (d, 2 H), 10.02 (s, 1 H), 10.4 (br, 1 H).

***N*-(4-Chlorophenyl)-*N*-[2-(diethylamino)ethyl]-4-[(methylsulfonyl)amino]benzamide Hydrochloride (3c).** Reaction of *N*-(4-chlorophenyl)-*N',N'*-diethyl-1,2-ethanediamine[17] (13.5 g, 60 mmol) with **5** (22.0 g, 94 mmol) as described for **3a** gave 6.0 g (22%) of **3c**: NMR (DMSO-d_6) δ 1.22 (t, 6 H), 3.00 (m, 3 H), 3.18 (m, 6 H), 4.19 (t, 2 H), 7.03 (d, 2 H), 7.28 (m, 4 H), 7.38 (d, 2 H), 10.06 (s, 1 H), 10.86 (br s, 1 H).

***N*-[2-(Diethylamino)ethyl]-*N*-(4-methoxyphenyl)-4-[(methylsulfonyl)amino]benzamide Fumaric Acid Salt (1:1) (3d).** Reaction of *N,N*-diethyl-*N'*-(4-methoxyphenyl)-1,2-ethanediamine[18] (6.9 g, 31 mmol) with **5** (11.6 g, 50 mmol) as described for **3a** gave an oil that was chromatographed on silica (200 g) with CH_3CN/MeOH/NH_4OH (90/5/5) to give 7.0 g (59%) of an oil. The oil was dissolved in MeOH, and fumaric acid (2.0 g, 17 mmol) was added. The solvent was removed in vacuo, and recrystallization gave 2.0 g of **3d**: NMR (DMSO-d_6) δ 0.96 (t, 6 H), 2.59 (q, 4 H), 2.7 (t, 2 H), 2.98 (s, 3 H), 3.70 (s, 3 H), 3.85 (t, 2 H), 6.58 (s, 2 H), 6.82 (d, 2 H), 7.00 (d, 2 H), 7.11 (d, 2 H), 7.20 (d, 2 H).

***N*-[4-[[2-(Diethylamino)ethyl]amino]phenyl]methanesulfonamide Hydrobromide (4e).** *N*-(4-Aminophenyl)-methanesulfonamide[19] (100 g, 0.54 mol) and (diethylamino)ethyl chloride hydrochloride (30.8 g, 0.18 mol) were suspended in 2 L of toluene. After refluxing for 18 h, the solution was cooled and

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the solvent was decanted away. The resulting gum was dissolved in CH_3OH, CH_2Cl_2, and H_2O. The aqueous layer was made basic with saturated aqueous sodium bicarbonate. The aqueous layer was separated and extracted three times with CH_2Cl_2. The organic layers were combined, and the solvent was removed in vacuo. The residue was chromatographed on silica gel with CH_3CN/NH_4OH (95/5) as eluent to give 31.5 g (62%) of the diamine. A portion was converted to the hydrobromide (recrystallized from Et_2O/CH_3OH): mp 144–146 °C; NMR (DMSO-d_6) δ 1.22 (t, 6 H), 2.85 (s, 3 H), 3.22 (m, 6 H), 3.35 (m, 2 H), 6.66 (d, 2 H), 7.04 (d, 2 H), 9.08 (s, 1 H). Anal. ($C_{13}H_{23}N_3O_2S$·1.1HBr) C, H, N, Br, S.

***N*-[2-(Diethylamino)ethyl]-4-[(methylsulfonyl)amino]-*N*-[4-[(methylsulfonyl)amino]phenyl]benzamide (3e).** Reaction of **4e** (5.20 g, 18.2 mmol) with **5** (4.68 g, 20 mmol) as described for **3a** gave 3.3 g (35%) of **3e**: NMR (DMSO-d_6) δ 0.89 (t, 6 H), 2.44 (q, 4 H) 2.57 (t, 2 H), 2.92 (s, 3 H), 2.96 (s, 3 H), 3.80 (t, 2 H), 6.98 (d, 2 H), 7.10 (dd, 4 H), 7.18 (d, 2 H), 9.8 (br s, 2 H).

***N*-[2-(Diethylamino)ethyl]-*N*-(2,6-dimethylphenyl)-4-[(methylsulfonyl)amino]benzamide Hydrochloride (3f).** Reaction of *N*,*N*-diethyl-*N'*-(2,6-dimethylphenyl)-1,2-ethanediamine[20] (30.0 g, 136 mmol) with **5** (34.9 g, 150 mmol) as described for **3a** gave 27.9 g (45%) of **3f** as a white solid: NMR (DMSO-d_6) δ 1.23 (t, 6 H), 2.19 (s, 6 H), 3.00 (s, 3 H), 3.21 (m, 4 H), 3.34 (m, 2 H), 3.97 (m, 2 H), 6.96 (d, 2 H), 7.13 (m, 5 H), 10.05 (br s, 2 H).

2-(Diethylamino)-*N*-[2,6-bis(1-methylethyl)phenyl]acetamide (6g). 2-Chloro-*N*-[2,6-bis(1-methylethyl)phenyl]acetamide[21] (40.4 g, 159 mmol) was dissolved in EtOH (200 mL), and diethylamine (35.0 g, 478 mmol) was added. After refluxing for 14 h, the solvent was removed in vacuo and the residue partitioned between Et_2O and 1.5 M aqueous hydrochloric acid. The aqueous layer was separated, made basic with 50% aqueous sodium hydroxide, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to give a solid. Recrystallization from hexane gave 34.3 g (74%) of **6g**: mp 165–167 °C; NMR (DMSO-d_6) δ 1.07 (t, 6 H), 1.11 (d, 12 H), 2.61 (q, 4 H), 3.01 (m, 2 H), 4.14 (s, 2 H), 7.17 (d, 2 H), 7.29 (m, 1 H), 9.13 (br s, 1 H). Anal. ($C_{18}H_{30}N_2O$) C, H, N.

***N*,*N*-Diethyl-*N'*-[2,6-bis(1-methylethyl)phenyl]-1,2-ethanediamine (4g).** Reaction of **6g** (33.8 g, 0.12 mol) as described for **4b** gave 22.9 g (71%) of **4g** after recrystallization from hexane: mp 39–40 °C; NMR (DMSO-d_6) δ 1.00 (t, 6 H), 1.16 (d, 12 H), 2.49 (m, 4 H), 2.58 (t, 2 H), 2.81 (m, 2 H), 3.31 (m, 2 H), 3.80 (br s, 1 H), 6.95 (t, 1 H), 7.02 (d, 2 H). Anal. ($C_{18}H_{32}N_2$) C, H, N.

***N*-[2-(Diethylamino)ethyl]-*N*-[2,6-bis(1-methylethyl)-phenyl]-4-[(methylsulfonyl)amino]benzamide Hydrochloride (3g).** Reaction of **4g** (7.0 g, 25 mmol) with **5** (6.5 g, 28 mmol) as described for **3a** gave 5.5 g (43%) of **3g**: NMR (DMSO-d_6) δ 0.90 (d, 6 H), 1.26 (d, 6 H), 1.31 (t, 6 H), 2.96 (m, 2 H), 2.99 (s, 3 H), 3.24 (m, 4 H), 3.38 (m, 2 H), 4.05 (m, 2 H), 7.02 (d, 2 H), 7.17 (d, 2 H), 7.28 (d, 2 H), 7.39 (m, 1 H), 10.17 (s, 1 H), 10.88 (br, 1 H).

***N*-[2-(Diethylamino)ethyl]-4-[(methylsulfonyl)amino]-*N*-(1-naphthalenyl)benzamide Hydrochloride (3h).** Reaction of *N*,*N*-diethyl-*N'*-(1-naphthalenyl)-1,2-ethanediamine[22] (12.4 g, 51 mmol) with **5** (13.1 g, 56 mmol) as described for **3a** gave 16.4 g (68%) of **3h**: NMR (DMSO-d_6) δ 1.20 (m, 6 H), 2.91 (s, 3 H), 3.10–3.60 (m, 6 H), 3.73 (m, 1 H), 4.64 (m, 1 H), 6.81 (d, 2 H), 7.17 (d, 2 H), 7.51 (m, 2 H), 7.65 (t, 1 H), 7.70 (t, 1 H), 7.92 (d, 1 H), 8.00 (t, 2 H), 9.93 (br s, 1 H), 10.34 (br s, 1 H).

***N*-[2-(Diethylamino)-1-phenylethyl]-4-[(methylsulfonyl)amino]benzamide Hydrochloride (3i).** Reaction of N^2,N^2-diethyl-1-phenyl-1,2-ethanediamine[23] (6.5 g, 34 mmol) with **5** (8.6 g, 37 mmol) as described for **3a** gave 3.5 g (24%) of **3i**: NMR (DMSO-d_6) δ 1.27 (t, 6 H), 3.07 (s, 3 H), 3.24 (m, 4 H), 3.34 (m, 1 H), 3.81 (br t, 1 H), 5.55 (br t, 1 H) 7.25 (m, 5 H), 7.55 (d, 2 H), 8.04 (d, 2 H), 9.38 (d, 1 H), 9.80 (br s, 1 H), 10.22 (s, 1 H).

2-(Diethylamino)-1-(1-naphthalenyl)ethanone Oxalic Acid Salt (1:1) (7j). To a solution of diethylamine (1.8 g, 24 mmol) in toluene (5 mL) in an ice bath was added dropwise a solution of 2-bromo-1-(1-naphthalenyl)ethanone[24] (3.0 g, 12 mmol) in toluene (20 mL). After stirring for 17 h, the reaction mixture was extracted with 3 N aqueous hydrochloric acid. The aqueous layer was made basic with 50% aqueous sodium hydroxide, and CH_2Cl_2 was added. The organic layer was separated and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was dissolved in MeOH, and oxalic acid (1.1 g, 1.2 mmol) was added. The solvent was removed in vacuo, and the solid was recrystallized from CH_3CN and CH_3OH to give 1.5 g (38%) of **7j** as a white solid: mp 128–130 °C; NMR (DMSO-d_6) δ 1.22 (t, 6 H), 3.13 (q, 4 H), 4.81 (s, 2 H), 5.0–6.38 (br, 2 H), 7.67 (m, 3 H), 8.08 (d, 1 H), 8.26 (d, 2 H), 8.62 (d, 1 H). Anal. ($C_{18}H_{21}NO_5$·0.25H_2O) C, H, N.

2-(Diethylamino)-1-(1-naphthalenyl)ethanone Oxime (8j). To a solution of potassium hydroxide (97.6 g, 1.48 mol) in CH_3OH (320 mL) were added hydroxylamine hydrochloride in H_2O (48 mL) and **7j** (free base) (16 g, 64 mmol) in CH_3OH (21 mL). After stirring for 17 h, the solvent was removed in vacuo. The residue was partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. The residue was chromatographed on silica gel with EtOAc/hexane (3/2) as eluent to give 10.2 g (62%) of **8j**. A portion was recrystallized from hexane to give a tan solid: mp 128–130 °C; NMR ($CDCl_3$) δ 0.99 (t, 6 H), 2.68 (q, 4 H), 3.61 (br s, 2 H), 7.46 (m, 1 H), 7.60 (m, 3 H), 7.81 (m, 1 H), 7.95 (m, 2 H), 8.17 (br, 1 H). Anal. ($C_{16}H_{20}N_2O$) C, H, N.

***N*²,*N*²-Diethyl-1-(1-naphthalenyl)-1,2-ethanediamine Oxalic Acid Salt (1:1) (4j).** Reaction of **8j** (4.0 g, 16 mmol) with lithium aluminum hydride (1.2 g, 32 mmol) as described for **4b** gave an oil, which was converted to the oxalic acid salt (1:1). Recrystallization from CH_3CN/CH_3OH gave 2.4 g (45%) of **4j** as a white solid: mp 226–228 °C; NMR (DMSO-d_6) δ 1.25 (t, 6 H), 3.10–3.35 (m, 6 H), 6.00–6.11 (m, 1 H), 7.51–7.70 (m, 3 H), 7.74 (d, 1 H), 7.91 (d, 1 H), 8.00 (d, 1 H), 8.30 (d, 1 H), 9.26 (d, 1 H).

***N*-[2-(Diethylamino)-1-(1-naphthalenyl)ethyl]-4-[(methylsulfonyl)amino]benzamide (3j).** Reaction of **4j** (12.7 g, 52.4 mmol) with **5** (24.5 g, 105 mmol) as described for **3a** gave 6.1 g (26%) of **6b**: NMR (DMSO-d_6) δ 0.94 (t, 6 H), 2.50–2.70 (m, 4 H), 2.85 (dd, 1 H), 2.95 (dd, 1 H), 3.05 (s, 3 H), 5.95–6.08 (m, 1 H), 7.25 (d, 2 H), 7.44–7.64 (m, 3 H), 7.71 (d, 1 H), 7.85 (d, 1 H), 7.87 (d, 2 H), 7.95 (d, 1 H), 8.25 (d, 1 H), 8.68 (d, 1 H), 9.95–10.22 (br, 1 H).

***N*-[2-(Diethylamino)-2-phenylethyl]-4-[(methylsulfonyl)amino]benzamide (3k).** Reaction of N^1,N^1-diethyl-1-phenyl-1,2-ethanediamine[23] (7.5 g, 39.0 mmol) with **5** (10.0 g, 42.8 mmol) as described for **3a** gave 10.5 g (69%) of a solid. Recrystallization gave 5.7 g (38%) of **3k**: NMR (DMSO-d_6) δ 0.97 (t, 6 H), 2.28 (m, 2 H), 2.61 (m, 2 H), 3.04 (s, 3 H), 3.60 (m, 1 H), 3.74 (m, 1 H), 4.06 (t, 1 H), 7.20 (m, 3 H), 7.17–7.33 (m, 4 H), 7.70 (d, 2 H), 8.13 (t, 1 H), 10.10 (br s, 1 H).

α-(Diethylamino)-1-naphthaleneacetonitrile (9l). 1-Naphthalenecarboxaldehyde (3.1 g, 20 mmol) was added to $NaHSO_3$ (2.08 g, 20 mmol) in water (5 mL). After stirring for 20 min, a solution of diethylamine (1.5 g, 20 mmol) in water (8 mL) was added. After everything had dissolved, NaCN (0.98 g, 20 mmol) was added portionwise. After stirring for 4 h, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined and dried (Na_2SO_4), and the solvent was removed in vacuo to give 3.8 g (80%) of **9l** as a solid. A portion was recrystallized from hexane to give a white solid: mp 59–61 °C; NMR ($CDCl_3$) δ 1.09 (t, 6 H), 2.54 (m, 2 H), 2.80 (m, 2 H), 5.67 (s, 1 H), 7.52 (m, 3 H), 7.78 (m, 3 H), 8.27 (m, 1 H). Anal. ($C_{16}H_{18}N_2$) C, H, N.

***N*¹,*N*¹-Diethyl-1-(1-naphthalenyl)-1,2-ethanediamine Oxalic Acid Salt (1:2) (4l).** Reaction of **9l** (2.3 g, 10 mmol) with lithium aluminum hydride as described for **4b** gave an oil. The oxalic acid salt was formed and recrystallized from CH_3CN/MeOH to give a white solid: mp 88–92 °C; NMR (DMSO-d_6) δ 0.95 (t, 6 H), 2.38 (m, 2 H), 2.69 (m, 2 H), 3.0 (br, 6 H), 3.19 (dd, 1 H), 3.54 (dd, 1 H), 4.90 (m, 1 H), 7.57 (m, 4 H), 7.92 (d, 1 H), 7.96

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(d, 1 H), 7.96 (d, 1 H), 8.23 (d, 1 H), 8.23 (d, 1 H). Anal. ($C_{20}H_{24}N_2O_8 \cdot H_2O$) C, H, N.

***N*-[2-(Diethylamino)-2-(1-naphthalenyl)ethyl]-4-[(methylsulfonyl)amino]benzamide Hydrochloride (3l).** Reaction of **4l** (10.6 g, 43.7 mmol) with **5** (11.2 g, 48 mmol) as described for **3a** gave 5.9 g (28%) of **3l**: NMR (DMSO-d_6) δ 1.03 (t, 3 H), 1.46 (t, 3 H), 2.86 (m, 2 H), 3.02 (s, 3 H), 3.62 (br, 2 H), 3.96 (m, 1 H), 4.32 (m, 1 H), 5.60 (br, 1 H), 7.13 (d, 2 H), 7.59 (m, 5 H), 8.00 (t, 2 H), 8.24 (d, 1 H), 8.50 (d, 1 H), 8.74 (m, 1 H), 10.15 (s, 1 H), 11.38 (br s, 1 H).

Pharmacology. The experimental protocols describing the intracellular electrophysiological studies in canine Purkinje fibers,[3] intraduodenal activity studies in anesthetized dogs,[3] and the PES efficacy model[3] have been reported previously.

Ouabain-Induced Ventricular Arrhythmias in the Guinea Pig.[9] The guinea pig was anesthetized with 50 mg/kg pentobarbital, iv, and a lead II ECG monitored. The trachea was cannulated and the animal respirated with room air. The right jugular was cannulated for administration of test agent and ouabain. After equilibrating for 5 min, the test agent was administered. Ten minutes later a bolus dose of ouabain (40 μg/kg) was administered followed by a constant fusion of 10 μg/kg/min ouabain. Time to first arrhythmia was measured, beginning at the start of the ouabain infusion.

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Registry No. **3a**, 116855-61-9; **3a** (free base), 116855-32-4; **3b**, 116855-68-6; **3b** (free base), 123507-50-6; **3c**, 116855-69-7; **3c** (free base), 123507-51-7; **3d**, 123507-53-9; **3d** (free base), 123507-52-8; **3e**, 123507-54-0; **3f**, 116855-60-8; **3f** (free base), 116855-31-3; **3g**, 116855-63-1; **3g** (free base), 116855-34-6; **3h**, 116855-62-0; **3h** (free base), 116855-33-5; **3i**, 116855-64-2; **3i** (free base), 116855-40-4; **3j**, 116855-41-5; **3k**, 123507-55-1; **3l**, 116855-66-4; **3l** (free base), 116855-42-6; **4b**, 123507-56-2; **4b**·HCl, 123507-57-3; **4e**, 123507-58-4; **4e** (free base), 123507-59-5; **4g**, 116855-49-3; **4j**, 123507-60-8; **4j** (free base), 116855-55-1; **4l**, 123507-61-9; **4l** (free base), 116855-52-8; **5**, 63421-72-7; **6g**, 116855-48-2; **7j**, 123507-62-0; **8j**, 116855-54-0; **9l**, 123507-63-1; *N*,*N*-diethyl-*N*′-phenyl-1,2-ethanediamine, 1665-59-4; 2-(diethylamino)-*N*-(4-ethylphenyl)acetamide, 56974-52-8; *N*-(4-chlorophenyl)-*N*′,*N*′-diethyl-1,2-ethanediamine, 5427-35-0; *N*,*N*-diethyl-*N*′-(4-methoxyphenyl)-1,2-ethanediamine, 123507-64-2; *N*-(4-aminophenyl)methanesulfonamide, 53250-82-1; (diethylamino)ethyl chloride hydrochloride, 869-24-9; *N*,*N*-diethyl-*N*′-(2,6-dimethylphenyl)-1,2-ethanediamine, 21236-57-7; 2-chloro-*N*-[2,6-bis(1-methylethyl)phenyl]acetamide, 20781-86-6; diethylamine, 109-89-7; *N*,*N*-diethyl-*N*′-(1-naphthalenyl)-1,2-ethanediamine, 5235-86-9; N^2,N^2-diethyl-1-phenyl-1,2-ethanediamine, 31788-87-1; 2-bromo-1-(1-naphthalenyl)ethanone, 13686-51-6; N^1,N^1-diethyl-1-phenyl-1,2-ethanediamine, 31788-97-3; 1-naphthalenecarboxaldehyde, 66-77-3.

1,9-Alkano-Bridged 2,3,4,5-Tetrahydro-1*H*-3-benzazepines with Affinity for the α_2-Adrenoceptor and the 5-HT_{1A} Receptor

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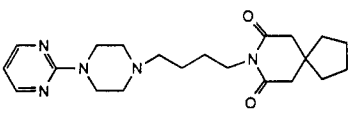
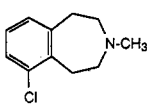
A number of 1,9-alkano-bridged 2,3,4,5-tetrahydro-1*H*-3-benzazepines were prepared and evaluated for 5-HT_{1A} receptor and α_2-adrenoceptor affinity by using radioligand receptor binding techniques. Several compounds displayed 5-HT_{1A} receptor affinity comparable to, or greater than, the known 5-HT_{1A} ligand buspirone. The highest affinity 5-HT_{1A} receptor ligands were *N*-alkyl-, *N*-allyl-5-chloro-, and 5-methoxy-1,2,3,4,8,9,10,10a-octahydronaphth[1,8-*cd*]azapines (**4c**, **4m**, **4n**), which had pK_i values of 7.9–8.1. The *S* enantiomer of **4c** had a higher affinity for the 5-HT_{1A} receptor than the corresponding *R* isomer (pK_i of 8.2 for (***S***)-**4c** vs 7.7 for (***R***)-**4c**). These compounds had a relatively low affinity for the α_2-adrenoceptor (pK_i of 7 or less). On the other hand, the closely related 5-chloro-2-methyl-2,3,4,8,9,9a-hexahydro-1*H*-indeno[1,7-*cd*]azepine (**3b**) had high affinity for both the α_2-adrenoceptor (pK_i = 8.1) and 5-HT_{1A} receptor (pK_i = 7.6). These results indicate that the two receptors may share common recognition sites.

Classification of receptors into subtypes based on binding of selective ligands continues to be an active area of research. For example, reviews on α-adrenoceptor[1-3] and 5-hydroxytryptamine receptor[4,5] classification emphasize the extensive progress which has been made in these areas.

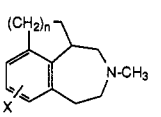
Interest in ligands with high affinity for the 5-HT_{1A} receptor subtype has been stimulated by the finding that one such agent, buspirone (1), is a clinically efficacious anxiolytic.[6a-d] The α_2-adrenoceptor antagonism of the buspirone metabolite 1-(2-pyrimidyl)piperazine[7] prompted us to investigate interrelationships between other α_2-adrenoceptor and 5-HT_{1A} receptor ligands. We determined that the α_2-adrenoceptor antagonist **2** (SKF 86466)[8] had affinity for the 5-HT_{1A} receptor and investigated the effect of structural modification of **2** on this spectrum of receptor affinity. We now wish to report the preparation and α_2-adrenoceptor/5-HT_{1A} receptor affinity of bridged ana-



1 Buspirone



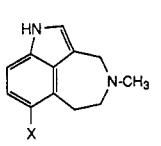
2 SKF 86466



3 n=1

4 n=2

5 n=3



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