stituted aryl group augments sweetness potency in the guanidine sweetener class. The sweet-tasting guanidines which lack this aryl moiety which we have described clearly indicate that the aryl group is not a requisite for sweetness. However, these analogues are in general 3 orders of magnitude less potent than corresponding aryl-substituted derivatives. Thus, we conclude that the essential pharmacophore in the guanidinoacetic acid sweeteners is an *N*-substituted-*N'*-(carboxymethyl)guanidine. Important functionality for receptor binding is present in guanidinoacetic acid. However, it appears to be insufficient for receptor activation and this critical role may be provided by either, or both, the aryl- or alkylguanidine substituents.

Experimental Section

Sensory data was obtained by evaluation of compounds at 0.01, 0.1, and 1.0 mg/mL in distilled water by two trained tasters, and the resulting sensory data was averaged.

Melting points were obtained on a Thomas-Hoover Unimelt capillary apparatus and are not corrected. IR spectra were taken as KBr pellets using a Perkin-Elmer Model 283 or 681. NMR spectra were obtained either on a Varian FT-80 or on a General Electric QE-300 spectrometer. Microanalyses were performed by Midwest Microlab, 7212 N. Shadeland Ave, Indianapolis, IN. Chromatography was performed according to the method of Still[19] on silica gel. The isothiocyanates were purchased from Fairfield Chemical Company and Trans World Chemicals. Care should be taken in running the hydrogen peroxide oxidation reaction due to its exothermicity.

***N*-(Cyclohexylmethyl)thiourea (2a).** To a stirred solution of cyclohexylmethyl isothiocyanate (9.14 g, 58.9 mmol) in 90 mL of acetonitrile was added 11.3 mL of 15 N ammonium hydroxide (170 mmol). After 19 h, the reaction mixture was filtered, and the white solid was washed with copious amounts of ether. The solid was air-dried to afford 4.60 g (45%) of the desired thiourea. The filtrate was concentrated and the residue was slurried in ether. The slurry was filtered to afford an additional 2.96 g (29%) of thiourea: mp 151-153 °C; ^{1}H NMR (DMSO-d_6) δ 7.7-7.5 (m, 1 H, NH), 7.5-6.65 (2 m, 2 H, NH_2), 3.3-3.1, 3.0-2.75 (2 m, 2 H), 1.8-1.4 (m, 6 H), 1.3-1.0 (m, 3 H), 1.0-0.7 (m, 2 H); IR (KBr, cm^{-1}) 3400, 3280, 3180, 2990, 2850, 1629, 1595, 1564, 1480. Anal. ($C_8H_{16}N_2$) C, H, N.

[*N*-(Cyclohexylmethyl)imino]aminomethanesulfonic Acid (3a). To a stirred, ice bath cooled suspension of **2a** (7.11 g, 41.3 mmol) and sodium molybdate dihydrate (0.15 g, 0.62 mmol) in 40 mL of methanol was added 13.5 mL of 30% hydrogen peroxide at a rate such that the reaction temperature did not rise above 20 °C. After the addition was complete, the ice bath was removed. The reaction temperature rose. When the reaction exotherm was complete, the reaction mixture was cooled to 10 °C and filtered, and the solid was washed with water. The solid was dried in vacuo (40 °C, <1 mm) to yield 6.80 g (75%) of the sulfonic acid: mp 190-191.5 °C; ^{1}H NMR (DMSO-d_6) δ 9.65-9.50 (m, 1 H, NH), 9.25-9.0 (m, 2 H, NH_2), 3.06 (t, 2 H, J = 6.1 Hz, NCH_2), 1.65-1.45 (m, 6 H), 1.25-1.0 (m, 3 H), 1.0-0.75 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 165.6, 47.6, 36.0, 29.7, 25.9, 25.1.

***N*-(Cyclohexylmethyl)-*N'*-(carboxymethyl)guanidine (1a).** To a stirred solution of glycine (0.563 g, 7.50 mmol) and potassium carbonate (1.04 g, 7.50 mmol) in 17 mL of water was added **3a** (1.65 g, 7.50 mmol) in small portions over 5 min. The reaction mixture was stirred for 48 h at room temperature and for 1 h at reflux. The reaction mixture was filtered, and the solid was washed with water, followed by ether, and dried to afford 0.714 g (45%) of crude product. The crude product (604 mg) was purified by recrystallization to yield to 0.410 g (30% overall) of the desired guanidine: mp 226-227 °C; ^{1}H NMR (CD_3CO_2D) δ 4.04 (s, 2 H, CH_2CO), 3.04 (d, 2 H, J = 7.0 Hz, NCH_2), 1.8-1.45 (m, 6 H), 1.35-1.05 (m, 3 H), 1.01-0.80 (m, 2 H); IR (KBr, cm^{-1}) 3420, 3290, 2920, 2850, 1704, 1650, 1620, 1405, 1380, 1370, 1350. Anal. ($C_{10}H_{19}N_3O_2$) C, H, N.

Registry No. **1a**, 138460-19-2; (*S*)-**1b**, 138460-20-5; **1c**, 128169-40-4; **1d**, 138460-21-6; **2a**, 66892-28-2; (*S*)-**2b**, 25144-91-6; **2c**, 128169-48-2; **2d**, 92192-94-4; **3a**, 138460-22-7; (*S*)-**3b**, 138460-23-8; **3c**, 128194-24-1; **3d**, 138460-24-9; **7a**, 116869-63-7; (*S*)-**7b**, 116869-20-6; **7c**, 116869-52-4; **7d**, 138460-25-0; $(NH_2)_2$-C=NH, 113-00-8; (*S*)-PhCH(CH_3)NCS, 24277-43-8; $(Ph)_2$CHNCS, 3550-21-8; cyclohexylmethyl isothiocyanate, 52395-66-1; cyclooctyl isothiocyanate, 33522-04-2.

Supplementary Material Available: Experimental data for compounds **1b-d**, **2b-d**, and **3b-d** (5 pages). Ordering information is given on any current masthead page.

(19) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* 1978, *43*, 2923.

Synthesis, Cardiac Electrophysiology, and β-Blocking Activity of Novel Arylpiperazines with Potential as Class II/III Antiarrhythmic Agents

Gary B. Phillips,* Thomas K. Morgan, Jr., William C. Lumma, Jr., Robert P. Gomez, Joan M. Lind, Randall Lis, Thomas Argentieri, and Mark E. Sullivan

Departments of Medicinal Chemistry and Pharmacology, Berlex Laboratories, Inc., 110 East Hanover Avenue, Cedar Knolls, New Jersey 07927. *Received June 25, 1991*

A series of novel arylpiperazines have been prepared in an attempt to incorporate both class II (β-receptor blocking) and class III antiarrhythmic properties in a single molecule. The key step in the preparation of the new compounds involves a regioselective heterocyclic ring formation. All but four compounds significantly prolonged action potential duration in canine cardiac Purkinje fibers (class III activity). All but one of the compounds demonstrated β-receptor affinity in a competitive binding assay and three had β_1-receptor selectivity. Compared to sotalol, a reference class II/III agent, arylpiperazine **7a** (4-[(methylsulfonyl)amino]-*N*-[(4-phenylpiperazin-2-yl)methyl]benzamide) demonstrated β_1-selectivity and was 1 order of magnitude more potent in the in vitro class III and the β_1-receptor screens. Compound **7a** was evaluated further and found to be effective in preventing programmed electrical stimulation-induced arrhythmias in conscious dogs (class III activity) and against epinephrine-induced arrhythmias in halothane anesthetized dogs (class II activity).

Due to the variety of pathophysiological causes that may contribute to the development of a life-threatening arrhythmia, no single agent is effective in all cases. Our approach has been to prospectively develop an agent with multiple focused activities within a single compound based on the assumption that the combined therapies will be

0022-2623/92/1835-0743$03.00/0

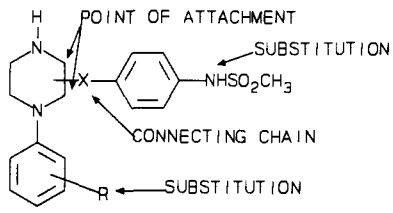
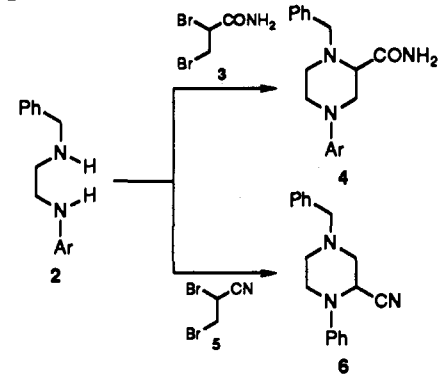


Figure 1. General structure.

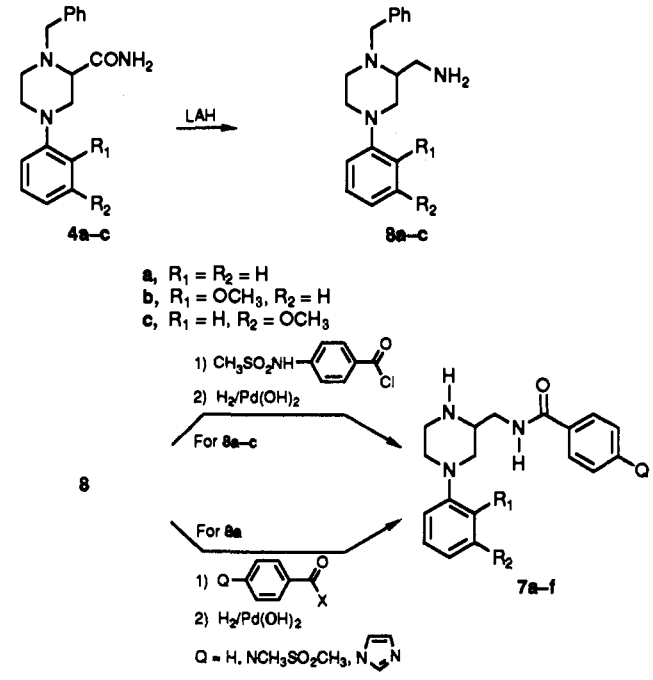
effective in a broader patient population.[1,2] We have concentrated on developing agents with both class II and class III electrophysiological activities (Vaughan Williams classification).[3] Class III antiarrhythmic agents prolong action potential duration (increase refractoriness) and have been shown to be effective against the initiation and propagation of reentrant arrhythmias.[4-8] Class II agents (β-blockers) inhibit sympathetic activity, which has been linked to the initiation and maintenance of reentrant arrhythmias.[9-10] Independently, β-blockers and class III agents have been reported to reduce mortality in patients after a myocardial infarction.[10,11] Therefore, a combination class II/III agent may produce a greater beneficial effect in these patients. Sotalol may be considered a prototypical class II/III agent although it lacks potency as a class III agent and is a nonselective β-blocker.

Our initial approach to the preparation of a class II/III agent was to link a class III pharmacophore to the typical aryloxypropanolamine class II pharmacophore.[12] Our best

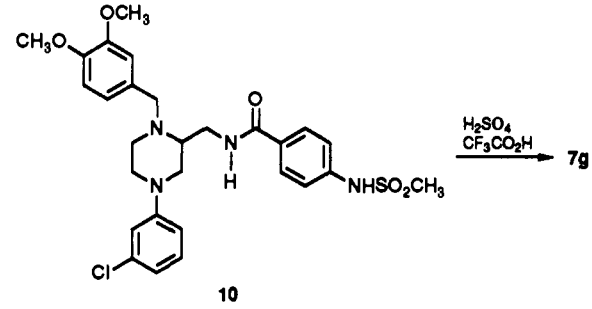
Scheme I



Scheme II



Scheme III



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

(2) Phillips, G. B.; Morgan, T. K., Jr.; Nickisch, K.; Lind, J. M.; Gomez, R. P.; Wohl, R. A.; Argentieri, T. M.; Sullivan, M. E. Synthesis and Cardiac Electrophysiological Activity of Aryl-Substituted Derivatives of the Class III Antiarrhythmic Agent Sematilide. Potential Class I/III Agents. *J. Med. Chem.* **1990**, *33*, 627–633.

(3) Vaughan Williams, E. M. Classification of Antiarrhythmic Drugs. In *Symposium on Cardiac Arrhythmias*; Sandoe, E., Flensted-Jansen, E., Olesen, K. H., Eds.; AB Astra: Sodertalje, Sweden, 1970; pp 449–72.

(4) Lumma, W. C., Jr.; Wohl, R. A.; Davey, D. D.; Argentieri, T. M.; De Vita, 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. Rational Design of 4-[(Methylsulfonyl)amino]-benzamides as Class III Antiarrhythmic Agents. *J. Med. Chem.* **1987**, *30*, 755–758.

(5) Morgan, T. K., Jr.; Wohl, R. A.; Lumma, W. C., Jr.; Wan, C.-N.; Davey, D. D.; Gomez, R. P.; Marisca, A. J.; Briggs, M.; Sullivan, M. E.; Wong, S. S. Synthesis and Class III Antiarrhythmic Activity of (Phenylbut-2-enyl)ammonium Salts. Effect of Conformation on Activity. *J. Med. Chem.* **1986**, *29*, 1398–1405.

(6) Morgan, T. K., Jr.; Lis, R.; Marisca, A. J.; Argentieri, T. M.; Sullivan, M. E.; Wong, S. S. Synthesis and Cardiac Electrophysiological Activity of 2- and 3-[(Substituted phenyl)alkyl]quinuclidines. Structure–Activity Relationships. *J. Med. Chem.* **1987**, *30*, 2259–2269.

(7) Lis, R.; Morgan, T. K., Jr.; De Vita, R. J.; Davey, D. D.; Lumma, W. C., Jr.; Wohl, R. A.; Diamond, J.; Wong, S. S.; Sullivan, M. E. Synthesis and Antiarrhythmic Activity of Novel 3-Alkyl-1-[ω-[4-[(alkylsulfonyl)amino]phenyl]-ω-hydroxyalkyl]-1*H*-imidazolium Salts and Related Compounds. *J. Med. Chem.* **1987**, *30*, 696–704.

(8) Reiser, H. J.; Sullivan, M. E. Antiarrhythmic Drug Therapy: New Drugs and Changing Concepts. *Fed. Proc.* **1986**, *45*, 2206–2212.

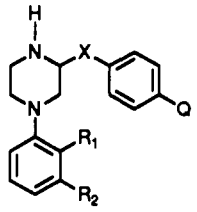
(9) Lynch, J. J.; Lucchesi, B. R. How Are Animal Models Best Used for the Study of Antiarrhythmic Drugs? In *Life Threatening Arrhythmias During Ischemia and Infarction*; Hearse, D. J., Manning, A. S., Janse, M. J., Eds.; Raven Press: New York, 1987; pp 169–196.

(10) Frishman, W. H.; Laifer, L. I. Beta-Adrenergic Blockade in the Treatment of Arrhythmias. In *Mechanisms and Treatment of Cardiac Arrhythmias; Relevance of Basic Studies to Clinical Management*; Reiser, H. J., Horowitz, L. N., Eds.; Urban and Schwarzenberg: Baltimore, MD, 1985; pp 207–248.

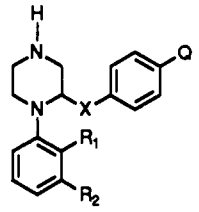
(11) Singh, B. N. Advantages of Beta-Blockers Versus Antiarrhythmic Agents and Calcium Antagonists in Secondary Prevention After Myocardial Infarction. *Am. J. Cardiol.* **1990**, *66*, 9c–19c.

(12) Lis, R.; Morgan, T. K., Jr.; Marisca, A. J.; Gomez, R. P.; Lind, J. M.; Davey, D. D.; Phillips, G. B.; Sullivan, M. E. Synthesis of Novel (Aryloxy)propanolamines and Related Compounds Possessing Both Class II and Class III Antiarrhythmic Activity. *J. Med. Chem.* **1990**, *33*, 2883–2891.

Table I. Substituted *N*-Arylpiperazines



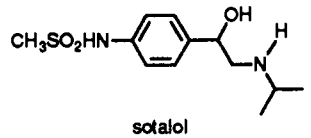
7



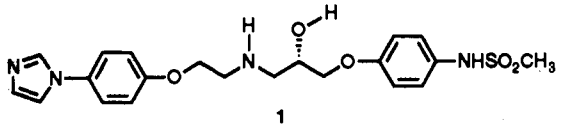
11

compd	X	R_1	R_2	Q	Z	mp (°C)	recryst solvent	anal.
7a	CH_2NHCO	H	H	$NHSO_2CH_3$	HCl	249 dec	CH_3OH	C,H,N,Cl,S
7b	CH_2NHCO	OCH_3	H	$NHSO_2CH_3$	$HCl{\cdot}0.5H_2O$	223–225	IPA/C_2H_5OH	C,H,N,Cl,S
7c	CH_2NHCO	H	OCH_3	$NHSO_2CH_3$	2HCl	212–215	CH_3CN/CH_3OH	C,H,N
7d	CH_2NHCO	H	H	1*H*-imidazol-1-yl	$3HCl{\cdot}0.8H_2O$	208–212	CH_3CN/CH_3OH	C,H,N,Cl
7e	CH_2NHCO	H	H	$N(CH_3)SO_2CH_3$	HCl	237–240	CH_3OH	C,H,N
7f	CH_2NHCO	H	H	H	HCl	182–183	CH_3CN/CH_3OH	C,H,N
7g	CH_2NHCO	H	Cl	$NHSO_2CH_3$	$1.5HCl{\cdot}0.5H_2O$	156–160	CH_3CN/CH_3OH	C,H,N,Cl,S
7h	CH_2NHCH_2	H	H	$NHSO_2CH_3$	$H_2SO_4{\cdot}H_2O$	230 dec	CH_3OH	C,H,N,S
7i	CH_2O	H	H	$NHSO_2CH_3$	HCl	237–240	CH_3OH/C_2H_5OH	C,H,N
7j	CH_2NH	H	H	$NHSO_2CH_3$	$0.1H_2O$	190–193	CH_2Cl_2	C,H,N,S
7k	CONH	H	H	$NHSO_2CH_3$		174–177	CH_3CN	C,H,N
11a	CH_2NHCO	H	H	$NHSO_2CH_3$		135–139	CH_3CN/CH_3OH	C,H,N
11b	CH_2NH	H	H	$NHSO_2CH_3$		73–80	CH_2Cl_2	C,H,N

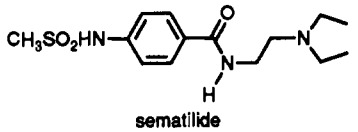
compound in this series (1) is presently undergoing further studies.[1] In this communication, the linkage of the selective class III agent, sematilide, with a 1-arylpiperazine, a seldom used class II pharmacophore, is described.[13] A general structure for this linkage is shown (Figure 1). Modifications were made to four portions of the general structure in an attempt to elucidate the structure–activity relationships. The variations were investigated in the point of attachment of the two pharmacophores, the connecting chain, substitution on the aryl moiety, and replacements for the methanesulfonamide. From earlier studies on class III agents, we did not expect the first three variations to have much of an effect on class III activity, but the effects on the β-blocking activity were unknown. Replacements for the methanesulfonamide were expected to have little effect on β-blocking activity but have profound effects on class III activity.



sotalol



1

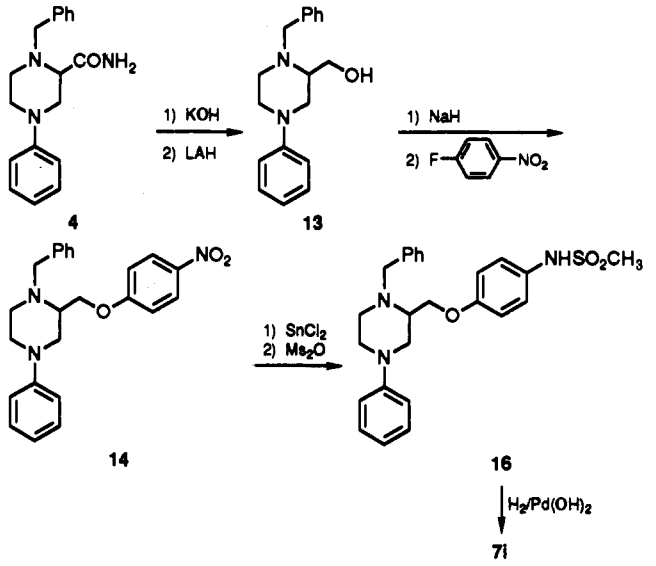


sematilide

Chemistry

The key step in the preparation of the desired compounds (Table I) is illustrated in Scheme I. Reaction of *N*-phenyl-*N'*-(phenylmethyl)-1,2-ethanediamine (2) with 2,3-dibromopropionamide (3) gave regioisomer 4 in 50% isolated yield.[14] The crude reaction mixture contained a 6:1 mixture of 4 and the other regioisomer. Alternatively, reaction of 2 with 2,3-dibromopropionitrile (5) gave the regioisomer 6 in a 90% isolated yield. None of the other regioisomer was detected on examination of the NMR spectrum of the crude reaction mixture. Substituents on either aryl moiety of 2 do not seem to effect the regioselectivity of the reaction.

Scheme IV

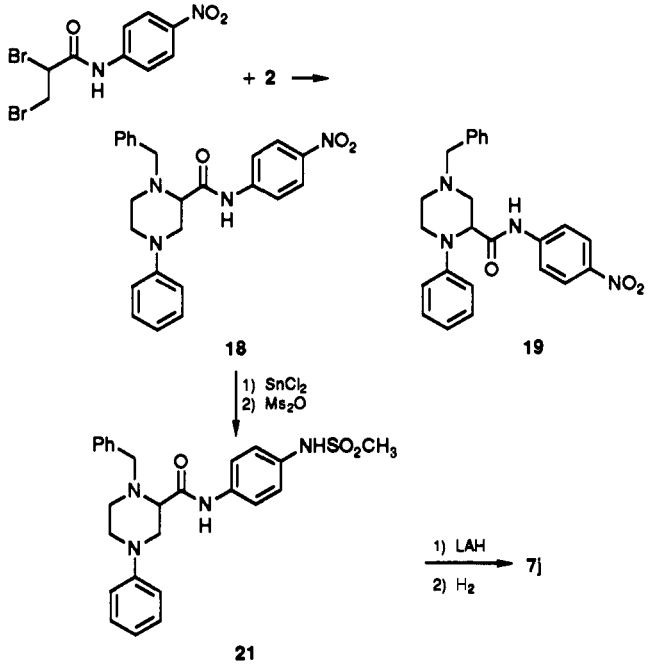


The preparation of compounds 7a–f is shown in Scheme II. Reduction of the amide 4 with lithium aluminum hydride gave the primary amine 8, which was reacted with an appropriately activated acid to give the benzamide 9. Hydrogenolysis of the benzyl protecting group gives 7a–f. The same procedure was not amendable to the preparation

(13) While arylpiperazines are not typically considered β-blockers, reports have appeared where they do have β-blocking activity: (a) Cohen, M. R.; Hinsch, E.; Palkoski, Z.; Vergona, R.; Urbano, S.; Sztokalo, J. The Cardiovascular and Autonomic Properties of N-Phenylpiperazines (NPP) in Several Animal Models. *J. Pharmacol. Exp. Ther.* **1982**, *223*, 110–119. (b) Baldwin, J. J.; Wagner, A. F.; Tolman, R. L.; Pietruszkiewicz, A. Preparation and Testing of Piperazinylpyrimidines as Beta-adrenergic Receptor Blocking Agents for Use in Treating Glaucoma. EP 276,057.

(14) The structure of 4 was verified by hydrogenation to a known compound: Toja, E.; Omodei-Sale, A.; Corsico, N. Hexahydroimidazo[1,5-a]pyrazines. II. Synthesis of 7-Phenyl-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyrazin-3(2H)-one and Derivatives. *Farmaco, Ed. Sci.* **1984**, *39*, 450–462.

Scheme V



of **7g** due to partial loss of the chlorine in the hydrogenolysis of the benzyl group. To prepare **7g**, a 3,4-dimethoxybenzyl protecting group was used in place of the benzyl group, and the same procedure outlined in Scheme II was employed. The protecting group was removed by treatment with acid in the final step (Scheme III). Compound **11a** was prepared from the nitrile **6** in the same manner as outlined in Scheme II. Borane reduction of **7a** in THF gave **7h**.

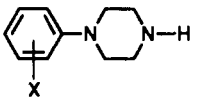
The preparation of **7i** is outlined in Scheme IV. Hydrolysis of the amide **4** provided the acid **12** and subsequent reduction afforded the alcohol **13**. Reaction of **13** with NaH followed by 4-fluoronitrobenzene yielded the ether **14**. Reduction of the nitro group gave the aniline **15**, and subsequent reaction with methanesulfonic anhydride afforded the methanesulfonamide **16**. Hydrogenolysis of the protecting group provided **7i**.

The preparation of **7j** is outlined in Scheme V. Reaction of **2** with the dibromide **17** afforded a mixture of the two regioisomers **18** and **19** in a 1:3 ratio. Reduction of the nitro group gave the aniline **20**, and subsequent reaction with methanesulfonic anhydride yielded **21**. Treatment with lithium aluminum hydride gave **22** followed by removal of the protecting group to provide **7j**. Compound **11b** was prepared in the same manner from **19**. Hydrogenolysis of **21** afforded **7k**.

Pharmacology

Standard competition binding studies using [^{3}H]dihydroalprenolol as the ligand were used to determine β-adrenergic receptor affinities.[15] β_1-receptor affinities were determined in partially purified membrane fractions from canine ventricular muscle in the presence of 1 μM zinterol to block the β_2-receptors. β_2-receptor affinities were determined in partially purified membrane fractions from canine lung tissue in the presence of 0.1 μM metoprolol to block β_1-receptors. In Table II, we report the compound concentration which inhibited the ligand binding by 50% (IC_{50}) for a series of substituted arylpiperazines. These compounds were used as models to indicate which type of aryl substitution might have the best β_1/β_2 selectivity. In Table III, the IC_{50} for each new compound is given. The new compounds were compared to sotalol.

Table II. β-Receptor Affinity for Selected Arylpiperazines



X	β_1-receptor n^a	β_1-receptor IC_{50} (μM)^b	β_2-receptor n^a	β_2-receptor IC_{50} (μM)^c
2-Cl	4	12 ± 4	3	16 ± 4
3-Cl	3	2 ± 1	3	18 ± 3
4-Cl	4	15 ± 4	3	70 ± 1
2-OCH_3	3	2 ± 1	3	34 ± 8
3-OCH_3	3	8 ± 2	3	29 ± 14
4-OCH_3	3	38 ± 9	3	>100
2-CH_3	4	14 ± 3	3	29 ± 1
3-CH_3	3	12 ± 3	3	40 ± 3
4-CH_3	4	38 ± 12	3	>100
4-NO_2	3	13 ± 3	3	56 ± 5
H	4	19 ± 6	3	>100
4-$COCH_3$	3	>100	3	>100

[a] Number of experiments. [b] Concentration of compound which inhibited the binding of [^{3}H]dihydroalprenolol (4.5 nM) by 50% in partially purified membrane fractions from canine ventricular muscle in the presence of 1 μM zinterol. [c] Concentrations of compound which inhibited the binding of [^{3}H]dihydroalprenolol (4.5 nM) by 50% in partially purified membrane fractions from canine lung tissue in the presence of 0.1 μM metoprolol.

The electrophysiological assay was carried out in canine cardiac Purkinje fibers.[16] Standard microelectrode techniques with a cycle length of 1 s were used to determine the effects on action potential duration (APD) and the rate of depolarization of phase zero (V_{max}). In Table III, we report the concentration necessary to prolong the APD at 95% repolarization by 20% from control (C_{20} APD_{95}). Compounds that exhibited a C_{20} APD_{95} of less than 10 μM were considered to show good activity as class III agents. We have found that such compounds generally show efficacy in in vivo models at reasonable doses (<10 mg/kg). None of the compounds produced a significant change in V_{max} (an indication of class I electrophysiological activity). The new compounds were compared to sotalol.

The effect of the compounds on contractile function was determined in isolated guinea pig papillary muscle.[17] In Table III, the percent change in force of contraction from control at a 10 μM concentration of compound is reported (% ΔF). Class III agents are typically positive inotropes while β-blockers are typically negative inotropes. Other studies have indicated that these two effects may counterbalance one another.[1] In support of these counterbalancing effects on contractility, none of the new compounds showed a significant change in contractile function.

Compound **7a** was evaluated further in two canine arrhythmia models, and the hemodynamic effects were evaluated in anesthetized dogs (Table IV). In the first model, conscious dogs were studied by utilizing programmed electrical stimulation (PES) techniques 3–8 days after

(15) Modified from the procedure of Beer et al.: Beer, M.; Richardson, A.; Poat, J.; Iversen, L. L.; Stahl, S. M. *In Vitro* Selectivity of Agonists and Antagonists for $Beta_1$ and $Beta_2$ Adrenoceptor Subtypes in Rat Brain. *Biochem. Pharmacol.* 1988, *37*, 1145–1151.

(16) Davis, L. D.; Temte, J. V. Electrophysiological Actions of Lidocaine on Canine Ventricular Muscle and Purkinje Fibers. *Circ. Res.* 1969, *24*, 639–655.

(17) Adapted from Hagedorn, A. A., III; Erhardt, P. W.; Lumma, W. C., Jr.; Wohl, R. A.; Cantor, E.; Chou, Y.-L.; Ingebretsen, W. R.; Lampe, J. W.; Pang, D.; Pease, C. A.; Wiggins, J. Cardiotonic Agents. 2. (Imidazolyl)aroylimidazolones, Highly Potent and Selective Positive Inotropic Agents. *J. Med. Chem.* 1987, *30*, 1342–1347.

Table III. In Vitro Pharmacology

compound	β-receptor affinity n^b	β-receptor affinity IC_{50} $\beta_1/\beta_2{}^c$ (μM)	electrophysiology[a] n^b	electrophysiology[a] $C_{20}APD_{95}{}^d$ (μM)	contractile function n^b	contractile function ΔF at 10 μM[e] (%)
7a	5/4	0.16 ± 0.02/3.4 ± 0.8	4	0.8 (0.2–3.9)	2	8 ± 0
7b	3/3	0.23 ± 0.1/0.63 ± 0.07	4	18 (9–32)	3	0 ± 3
7c	3/3	1.7 ± 0.8/3.5 ± 0.4	4	2.5 (0.4–7.9)	2	1 ± 8
7d	3/3	0.54 ± 0.08/4.3 ± 0.2	3	0.9 (0.3–1.6)	2	22 ± 4
7e	3/3	1.1 ± 0.84/4.3 ± 0.2	4	NR[f]	2	−12 ± 4
7f	3/3	0.68 ± 0.6/6.2 ± 2	4	NR[f]	2	−8 ± 2
7g	3/3	1.1 ± 0.4/3.8 ± 0.4	2	0.8 (0.7–0.8)	4	11 ± 7
7h	3/3	3.0 ± 1/4.6 ± 0.6	4	0.4 (0.2–1.5)	2	7 ± 7
7i	3/3	3.3 ± 0.8/4.5 ± 0.5	4	1.0 (0.2–7.1)	2	5 ± 2
7j	3/3	2.3 ± 1.4/1.0 ± 0.2	4	2.0 (0.9–6.7)	2	8 ± 0
7k	3/3	>100/>100	2	21 (15–29)	3	6 ± 2
11a	3/3	31 ± 7/31 ± 4	4	3.2 (1.5–6.4)	2	16 ± 15
11b	3/3	26 ± 5/42 ± 3	4	9.2 (2.4–23)	2	2 ± 2
sotalol	3/3	9 ± 5/5 ± 1	7	18 (9–63)	4	−2 ± 2

[a] No significant changes in V_{max} were observed. [b] Number of experiments. [c] Concentration of compound which inhibited the binding of [^{3}H]dihydroalprenelol (4.5 nM) by 50% in partially purified membrane fractions. β_1-Receptor affinities were determined in canine ventricular muscle in the presence of 1 μM zinterol. β_2-Receptor affinities were determined in canine lung tissue in the presence of 0.1 μM metoprolol. [d] The concentrations necessary to prolong APD at 95% repolarization by 20% from control. The log mean average of n experiments with the range given in parentheses. [e] The percent change in force of contraction from control at a 10 μM concentration of compound. [f] Not reached at 30 μM.

Table IV. In Vivo Pharmacology

study	7a	sotalol
PES model[a]		
no. active/no. tested	6/6	7/9
mean effective dose (mg/kg, iv)	2.8	3.1
halothane/epinephrine model		
no. effective/no. tested at 3 mg/kg	6/7	6/6
hemodynamic dog (n = 4)		
MAP[b]	5 ± 13	−26 ± 4
cardiac output	−14 ± 8	−44 ± 9
TPR[c]	22 ± 12	41 ± 17
LV dP/dt[d]	−3 ± 10	−33 ± 3
heart rate	−38 ± 5	−39 ± 3

[a] Programmed electrical stimulation. [b] Mean arterial pressure. [c] Total peripheral resistance. [d] Peak rate of change in left ventricular pressure.

undergoing an occlusion/reperfusion infarction according to the method of Karagueuzian.[18] Two control arrhythmias were induced prior to compound administration to verify inducibility. Ventricular fibrillation (VF) was terminated by DC countershock, and sustained ventricular tachycardia (SVT) was terminated by burst pacing. After compound administration, reinduction of the arrhythmia was attempted. A compound was considered effective in this model if SVT or VF could not be induced in 50% of the animals. We have found that class III agents are typically effective in this model while class II agents are much less effective. In the second model, the effect of the compounds on the time to an epinephrine-induced SVT/VF in halothane-anesthetized dogs was studied.[19] Following induction of anesthesia and stabilization of the animal, the test compound was administered as a 10-min intravenous infusion. Thirty minutes after compound administration, an epinephrine infusion (1.5 μg/kg per min for 15 min) was administered until an SVT or VF occurred. In a saline-treated animal SVT/VF was induced within 2–4 min. A compound was considered effective in this model if SVT/VF could not be induced during the entire 15-min epinephrine infusion. The values are reported as the number of successful experiments per number of experiments and the dose tested. Class II agents are typically effective in this model while selective class III agents are not effective. Hemodynamic effects of **7a** were measured in pentobarbital-anesthetized mongrel dogs, and the effects are reported for the test dose 10 mg/kg. The compounds were administered intravenously over 5 min, and the reported values were recorded 15 min after dosing. The reported values are mean arterial pressure (MAP), cardiac output (CO), total peripheral resistance (TPR), peak rate of change in left ventricular pressure (LV dP/dt), and heart rate (HR). Statistical comparisons were made using the Student t-test. A p value less than or equal to 0.05 was considered significant.

Results and Discussion

The point at which the two pharmacophores are attached has a profound effect on the in vitro β-blocking activity and a small effect on class III activity. The class III activity of **7a** was not significantly different from the regioisomer **11a** while the β-blocking activity of the two compounds differ by more than 1 order of magnitude. In addition, the β_1/β_2 selectivity was much higher for **7a**. Similar differences can be seen in a comparison of **7j** with **11b**.

Substitutions for the (methylsulfonyl)amino group had the expected effects on class III activity and little effect on β-affinity. A 1*H*-imidazol-1-yl moiety (as in **7d**) has been found to be a good replacement for a (methylsulfonyl)amino group[20] while replacement of the hydrogen on the methylsulfonylamino nitrogen by a methyl (as in **7e**) has been shown to eliminate class III activity.[4] Removal of the substituent entirely (as in **7f**) gave a compound void of class III effects. All of the compounds had comparable β_1/β_2 selectivities.

In previous studies, variations in the connecting chain did not have a large effect on class III activity.[21] This was found to be the case in comparing **7a,h–j**. In contrast, the β-blocking activity of the compounds was quite sensitive to modifications in the connecting chain. Compound **7a**

(18) Karagueuzian, H. S.; Fenoglio, J. J., Jr.; Weiss, M. B.; Wit, A. L. Protracted Ventricular Tachycardia Induced by Premature Stimulation of the Canine Heart after Coronary Artery Occlusion and Reperfusion. *Circ. Res.* **1979**, *44*, 833–846.
(19) Shibuya, T.; Hashimoto, K.; Imai, S. Effective Plasma Concentrations of Antiarrhythmic Drugs Against Sustained Halothane-Adrenaline Arrhythmia in Dogs. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 538–545.
(20) Morgan, T. K., Jr.; Lis, R.; Lumma, W. C., Jr.; Nickisch, K.; Wohl, R. A.; Phillips, G. B.; Gomez, R. P.; Lampe, J. W.; Di Meo, S. V.; Marisca, A. J.; Forst, J. Synthesis and Cardiac Electrophysiological Activity of N-Substituted-4-(1*H*-imidazol-1-yl)benzamides - New Selective Class III Agents. *J. Med. Chem.* **1990**, *33*, 1091–1097.
(21) Morgan, T. K., Jr.; Phillips, G. B., unpublished results.

was 1 order of magnitude more potent than **7h–j**. Furthermore, little or no selectivity was observed for **7h–j**. Unexpectedly, class III activity was decreased and no β-blocking activity was observed for **7k**.

The β-affinity data of the model 1-arylpiperazines are presented in Table II. In all three series the 4-substituted analogues are the least active. The compounds that were the most potent and selective were those substituted with a 3-Cl, 2-OCH_3, and 3-OCH_3. The corresponding substituted analogues of **7a** were prepared (**7b,c,g**). In these compounds the β-selectivity observed for the 1-arylpiperazine was completely lost. Other than **7b**, the class III activity of the other compounds was similar. The inactivity of **7b** may indicate that the orientation of the phenyl moiety with the piperazine is important.

All of the 2,4-substituted piperazines (**7**) were more potent than sotalol in the β-receptor affinity screen except for **7k** and compounds **7a,b,d–g** were significantly more potent. In addition, sotalol is a nonselective β-blocker while **7a,d,f** are β_1-selective. All of the compounds designed to have class III activity are at least as potent as sotalol and compounds **7a,d,g–i** were significantly more potent. Compounds **7a** and **7d** showed the best profile from this series of compounds. Due to the nearly 2-fold greater β_1-selectivity, **7a** was chosen for further testing.[22]

Compound **7a** was tested in vivo and compared to sotalol, a prototypical class II/III agent. Both compounds were found to be effective at similar doses in the PES model. Compound **7a** was as effective as sotalol in the epinephrine-induced arrhythmia model. This was somewhat surprising when considering the observed difference in β-affinity and class III activity in the in vitro model. In the hemodynamic dog, both compounds produced similar effects on HR and TPR. Consistent with the in vitro papillary muscle data, compound **7a**, compared to sotalol, had no significant effect on contractility as determined by the effect on LV dP/dt. In addition, **7a** decreased CO significantly less than sotalol. Although the effects on MAP were not statistically significant, the same trend as noted above persisted. Overall, the hemodynamic data suggests that **7a** would be less depressant and better tolerated than sotalol at equivalent doses.

Summary

We have prepared 13 compounds in which an attempt has been made to combine the antiarrhythmic effects of the selective class III agent, sematilide, with the β-blocking effects of 1-arylpiperazines. All of the compounds exhibited class III activity, except **7e,f**, which were designed to have no class III activity. All of the 2,4-substituted arylpiperazines exhibited class II effects in our in vitro models except for **7k**. In addition, three compounds were β_1-selective. Although compound **7a** was an order of magnitude more potent than sotalol in both in vitro screens, this higher potency was not observed in vivo. Compound **1a** was found to be as effective as sotalol in the canine PES model and in the halothane–epinephrine canine model. The hemodynamic profile of **7a** was significantly less depressant than that of sotalol. Work on this novel structural type which exhibits both Class III and β-blocking activity is continuing.

Experimental Section

Melting points were taken on a Fisher-Johns 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 spectrometer. Tetramethylsilane was used as internal standard in all solvents. All NMR spectra were consistent with the assigned structures.

4-Phenyl-1-(phenylmethyl)-2-piperazinecarboxamide (4a). Compound **2**[23] (179 g, 0.791 mol) and **3**[24] (349 g, 1.51 mol) were dissolved in DMF (700 mL). Triethylamine (303 g, 2.99 mol) was added to give a slurry which was heated in an oil bath at 110 °C for 17 h. The reaction was cooled to room temperature and 1 N NaOH (950 mL) was added. The resulting solid was collected by filtration and washed with ether. Recrystallization from 2-propanol gave 111 g (50%) of **4a** as a white solid: mp 161–163 °C; NMR ($CDCl_3$) δ 2.45 (m, 1 H), 2.92 (m, 2 H), 3.10 (dd, 1 H), 3.28 (dd, 1 H), 3.40 (m, 2 H), 3.75 (m, 1 H), 3.99 (d, 1 H), 5.70 (br s, 1 H), 6.90 (m, 4 H), 7.32 (m, 7 H). Anal. ($C_{18}H_{21}N_3O$) C, H, N.

4-Phenyl-1-(phenylmethyl)-2-piperazinemethanamine (8a). Lithium aluminum hydride (31.3 g, 0.824 mol) and **4a** (97.4 g, 0.330 mol) were slurried in THF (900 mL). After refluxing for 16 h, the reaction was cooled to room temperature and water (31 mL), 2 N aqueous NaOH (31 mL), and water (93 mL) were added sequentially. The precipitate was removed by suction filtration through Celite, and the solvent was removed in vacuo to give 88 g (95%) of **8a** as an oil: NMR ($CDCl_3$) δ 2.4 (m, 1 H), 2.6 (m, 1 H), 2.9 (m, 3 H), 3.05 (dd, 1 H), 3.15 (dd, 1 H), 3.3 (m, 1 H), 3.35 (d, 1 H), 3.45 (d, 1 H), 4.1 (d, 1 H), 6.85 (t, 1 H), 6.95 (d, 2 H), 7.2–7.4 (m, 7 H). Anal. ($C_{18}H_{23}N_3 \cdot 2.7HCl$) C, H, N, Cl.

4-[(Methylsulfonyl)amino]-*N*-[[4-phenyl-1-(phenylmethyl)piperazin-2-yl]methyl]benzamide Hydrochloride (9a). 4-[(Methylsulfonyl)amino]benzoyl chloride[25] (67.1 g, 0.287 mol) and **8a** were dissolved in THF (900 mL). After stirring for 2 days the solid was collected by filtration to give 134 g (100%) of **9a** as a white solid: mp 176–178 °C; NMR (DMSO-d_6) δ 3.08 (s, 3 H), 3.10–3.66 (m, 5 H), 3.71 (d, 1 H), 3.85–4.10 (m, 3 H), 4.32 (m, 1 H), 5.15 (d, 1 H), 6.88 (t, 1 H), 7.00 (d, 2 H), 7.28 (m, 4 H), 7.39 (m, 3 H), 7.70 (m, 2 H), 7.95 (m, 2 H), 9.02 (m, 1 H), 10.22 (s, 1 H), 10.98 (br s, 1 H). Anal. ($C_{26}H_{30}N_4O_3S \cdot HCl \cdot H_2O$) C, H, Cl, N, S.

4-[(Methylsulfonyl)amino]-*N*-[(4-phenylpiperazin-2-yl)methyl]benzamide Hydrochloride (7a). Compound **9a** (68 g, 0.13 mol) was hydrogenated in methanol (700 mL) on palladium hydroxide (7 g) at 50 psi for 2 days. The catalyst was removed by suction filtration through Celite. A portion of the solvent was removed in vacuo (ca. 300 mL) and a solid precipitated. The solid was collected by filtration to give 44.4 g (79%) of **7a** as a white solid: mp 241–243 °C; NMR (DMSO-d_6) δ 2.98 (dd, 1 H), 3.07 (s, 3 H), 3.1 (m, 1 H), 3.3–3.9 (m, 7 H), 6.87 (t, 1 H), 7.00 (d, 2 H), 7.3 (m, 4 H), 7.97 (d, 2 H), 8.88 (t, 1 H), 9.54 (br, 2 H), 10.2 (br, 1 H).

1-Phenyl-4-(phenylmethyl)-2-piperazinecarbonitrile (6). Compound **2** (0.41 g, 1.8 mmol) and 2,3-dibromopropionitrile (0.77 g, 3.6 mmol) were dissolved in toluene and reacted as described for the preparation of **4**. The reaction was partitioned between EtOAc and 2 N aqueous NaOH. The organic layer was separated, dried (Na_2SO_4), and the solvent was removed to give 0.59 g of a dark solid. Chromatography on silica (50 g) with hexane/EtOAc (1:1) gave 0.45 (90%) of **6** as an off-white solid. A portion was recrystallized from hexane/EtOAc to give an analytical sample: mp 123–124 °C; NMR ($CDCl_3$) δ 2.40 (dt, 1 H), 2.55 (dd, 1 H), 3.0 (d, 1 H), 3.15 (dt, 1 H), 3.3 (dt, 1 H), 3.40 (d, 1 H), 3.60 (d, 1 H), 3.75 (d, 1 H), 4.53 (br s, 1 H), 7.0 (m, 3 H), 7.3 (m, 7 H). Anal. ($C_{18}H_{19}N_3$) C, H, N.

***N*-[[4-(3-Chlorophenyl)piperazin-2-yl]methyl]-4-[(me-**

(22) Compound **7a** had a slight effect at 10 μM against norepinephrine-induced contractions in canine mesenteric artery indicating some α-blocking activity.

(23) Lis, R.; Marisca, A. J. A Convenient Synthesis of N-Aryl-N'-Benzyl-1,2-Ethanediamines. *Synth. Commun.* **1988**, *18*, 45–50.
(24) Feuer, H.; Bello, J. The Synthesis and Reactions of Brominated N-Methylolamides. *J. Am. Chem. Soc.* **1956**, *78*, 4367–4369.
(25) 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. Benzofurans. LX. Potential Antianginal Sulfonylaminobenzoylbenzofurans. *Eur. J. Med. Chem.* **1977**, *12*, 81–86.

thylsulfonyl)amino]benzamide 1.5-Hydrochloride Hemihydrate (7g). To a 5% solution of H_2SO_4 in CF_3CO_2H (12 mL) was added **10** (2.6 g, 5.0 mmol) and methoxybenzene (1.1 g, 10 mmol). After the reaction was heated at 60 °C for 40 h, water (5 mL), 1 N NaOH (10 mL), saturated $NaHCO_3$ (10 mL), and CH_2Cl_2 were added. The organic layer was separated and dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography of the residue on silica (100 g) with CH_3CN/CH_3OH (85:15) gave 850 mg of a solid. The material was dissolved in methanolic HCl, and the solvent was removed in vacuo. Recrystallization from CH_3CN/CH_3OH gave 0.60 g (29%) of **7g** as a solid: mp 156–160 °C; NMR (DMSO-d_6) δ 2.95–3.22 (m, 2 H), 3.07 (s, 3 H), 3.32–3.55 (m, 2 H), 3.58–3.92 (m, 5 H), 6.90 (d, 1 H), 7.07 (d, 1 H), 7.24 (s, 1 H), 7.28 (m, 3 H), 7.96 (d, 2 H), 8.87 (t, 1 H), 9.38–9.68 (m, 2 H), 10.22 (s, 1 H). Anal. ($C_{19}H_{23}ClN_4O_3S\cdot1.5HCl\cdot0.5H_2O$) C, H, Cl, N, S.

***N*-[4-[[[(4-Phenylpiperazin-2-yl)methyl]amino]methyl]phenyl]methanesulfonamide Sulfuric Acid Salt Monohydrate (7h).** Borane–dimethyl sulfide (2.5 mL of a 10 M solution, 25 mmol) was added to **7a** (free base, 3.2 g, 8.2 mmol) dissolved in THF (100 mL). After refluxing for 17 h, methanolic HCl was added. After refluxing for 2 h, the solvent was removed in vacuo. The residue was dissolved in methanol/water and treated with an ion-exchange resin (AG 1-X8, 12.5 g) to pH ca. 8. The resin was removed by filtration, and the solvent was removed in vacuo. Chromatography of the residue on silica (200 g) with methylene chloride/methanol/ammonium hydroxide (90:10:1) gave 1.7 g (55%) of the free base which was dissolved in methanol and sulfuric acid (0.23 mL, 4.3 mmol) was added to give a white solid. The solid was filtered to give **7h** as a white solid: mp 230 °C; NMR (DMSO-d_6) δ 2.65 (t, 1 H), 2.7–2.9 (m, 3 H), 2.98 (s, 3 H), 3.00 (m, 1 H), 3.26 (m, 2 H), 3.6 (d, 1 H), 3.7 (d, 1 H), 3.81 (d, 1 H), 3.84 (d, 1 H), 4.0 (br, 2 H + H_2O), 6.84 (t, 1 H), 6.97 (t, 2 H), 7.19 (d, 2 H), 7.26 (d, 2 H), 7.39 (d, 2 H), 9.8 (br, 1 H). Anal. ($C_{19}H_{26}N_4O_2S\cdot H_2SO_4\cdot H_2O$) C, H, N, S.

4-Phenyl-1-(phenylmethyl)-2-piperazinecarboxylic Acid (12). Potassium hydroxide (27.5 g, 490 mmol) was added to a suspension of **4** (14.5 g, 49 mmol) in ethylene glycol (400 mL). After heating the reaction at 150 °C for 18 h, the solvent was removed in vacuo. The residue was slurried in water (300 mL), treated with 6 M aqueous HCl (81.5 mL, 0.49 mol), and filtered to give 12.6 g (87%) of **12** as an off-white solid: mp 204–206 °C; NMR (DMSO-d_6) δ 2.78 (m, 1 H), 3.28 (m, 3 H), 3.56 (m, 2 H), 3.70 (m, 1 H), 3.98 (d, 1 H), 4.24 (d, 1 H), 4.3–6.6 (br, 1 H), 6.83 (t, 1 H), 6.92 (d, 2 H), 7.15–7.55 (m, 7 H).

4-Phenyl-1-(phenylmethyl)-2-piperazinemethanol (13). Reaction of **12** (12.2 g, 41 mmol) in a manner similar to the reaction of **4** gave a residue which was purified by chromatography on silica with EtOAc gave 9.03 g (78%) of **13** as a solid: mp 73–75 °C; NMR ($CDCl_3$) δ 2.27 (m, 1 H), 2.55 (m, 1 H), 2.68–2.86 (m, 3 H), 3.23–3.58 (m, 4 H), 3.79 (m, 1 H), 4.10 (dd, 1 H), 4.71 (m, 1 H), 6.76 (m, 1 H), 6.90 (d, 2 H), 7.14–7.39 (m, 7 H). Anal. ($C_{18}H_{22}N_2O$) C, H, N.

2-[(4-Nitrophenoxy)methyl]-4-phenyl-1-(phenylmethyl)piperazine (14). NaH (1.27 g of a 60% mixture with mineral oil, 30.4) was added to **13** (7.8 g, 28 mmol) suspended in DMF (100 mL) and stirred for 20 min. 1-Fluoro-4-nitrobenzene (4.29 g, 30.4 mmol) was added, and the solution was stirred for 4 h. The solution was diluted with water (100 mL) and extracted with CH_2Cl_2. The organic extract was washed with water, and the solvent was removed in vacuo. Crystallization of the residue from EtOAc/hexanes (1:1) gave 8.53 g (77%) of **14** as a solid: mp 96–98 °C; NMR (DMSO-d_6) δ 2.47 (m, 1 H), 2.84 (m, 1 H), 3.05 (m, 1 H), 3.20 (m, 1 H), 3.45 (m, 1 H), 3.56 (d, 1 H), 3.56 (d, 1 H), 4.05 (d, 1 H), 4.36 (m, 1 H), 4.51 (m, 1 H), 6.75 (t, 1 H), 6.93 (d, 2 H), 7.12–7.43 (m, 9 H), 8.19 (d, 2 H). Anal. ($C_{24}H_{25}N_3O_3$) C, H, N.

2-[(4-Aminophenyl)methyl]-4-phenyl-1-(phenylmethyl)piperazine (15). To **14** (7.15 g, 17.7 mmol) dissolved in methanol (175 mL) and ethyl acetate (175 mL) was added $SnCl_2$ (20.0 g, 88.6 mmol). After refluxing for 18 h, the reaction was poured into water (200 mL) and 4 N NaOH was added to pH = 12. After extracting with EtOAc/MeOH (2:1), the organic layer was washed with water (200 mL), and the solvent was removed. Chromatography on silica with EtOAc/hexane as solvent gave 6.39 g (85%) of **15** as a oil: NMR ($CDCl_3$) δ 2.47 (m, 1 H), 2.87 (m, 1 H), 2.97–3.28 (m, 3 H), 3.43 (br s, 2 H), 3.55 (m, 1 H), 4.02–4.27 (m, 3 H), 6.64 (d, 2 H), 8.84 (t, 1 H), 6.93 (d, 2 H), 7.20–7.42 (m, 7 H).

***N*-[4-[[4-Phenyl-1-(phenylmethyl)piperazin-2-yl]methoxy]phenyl]methanesulfonamide (16).** To **15** (6.28 g, 16.8 mmol) dissolved in CH_3CN (100 mL) was added methanesulfonic anhydride (3.22 g, 18.5 mmol). After stirring for 1 h, aqueous $NaHCO_3$ and EtOAc were added. The organic layer was separated and the solvent was removed in vacuo to give 7.10 g (88%) of **16** as a foam: NMR (DMSO-d_6) δ 2.42 (m, 1 H), 2.82 (m, 1 H), 2.89 (s, 3 H), 2.99 (m, 1 H), 3.11 (m, 1 H), 3.21 (m, 1 H), 3.52 (d, 1 H), 4.07 (d, 1 H), 4.17 (m, 1 H), 4.31 (m, 1 H), 6.77 (t, 1 H), 6.93 (d, 2 H), 6.98 (d, 2 H), 7.10–7.45 (m, 9 H), 9.37 (br s, 1 H).

***N*-[4-[(4-Phenylpiperazin-2-yl)methoxy]phenyl]methanesulfonamide Hydrochloride (7i).** Reaction of **16** (6.90 g, 15.3 mmol) in a manner similar to **8a** gave 3.25 g (55%) of **7i** as a solid after recrystallization from ethanol/methanol: mp 237–240 °C; NMR (DMSO-d_6) δ 2.90 (s, 3 H), 3.1 (m, 3 H), 3.4 (m, 1 H), 3.75 (m, 2 H), 3.91 (m, 1 H), 4.28 (m, 2 H), 6.86 (t, 1 H), 7.03 (m, 4 H), 7.22 (m, 4 H), 9.51 (s, 1 H), 9.65 (br s, 2 H). Anal. ($C_{18}H_{23}N_3O_3S\cdot HCl$) C, H, N.

2,3-Dibromo-*N*-(4-nitrophenyl)propanamide (17). *N*-(4-Nitrophenyl)-2-propenamide (58 g, 0.30 mol) was suspended in carbon tetrachloride (200 mL) and cooled to 0 °C in an ice bath. Bromine (16.25 mL, 0.317 mol) was added slowly over 1 h. This suspension was mechanically stirred for 4 days at ambient temperature, and the reaction was filtered to afford 100 g (95%) of **17** as a solid: mp 145–149 °C; NMR (DMSO-d_6) δ 3.96–4.14 (m, 2 H), 4.85 (dd, 1 H), 7.88 (d, 2 H), 8.28 (d, 2 H), 11.20 (s, 3 H). Anal. ($C_9H_8Br_2N_2O_3$) C, H, N.

***N*-(4-Nitrophenyl)-4-phenyl-1-(phenylmethyl)-2-piperazinecarboxamide (18) and *N*-(4-Nitrophenyl)-1-phenyl-4-(phenylmethyl)-2-piperazinecarboxamide (19).** Compounds **2** (29 g, 0.13 mol) and **17** (45 g, 0.13 mol) were dissolved in DMF (100 mL). Triethylamine (36 mL, 0.26 mol) was added to give a slurry which was heated at 105 °C for 48 h. The reaction was cooled to room temperature and 1 N aqueous NaOH was added until the solution was basic. The resulting precipitate was collected, and the filtrate was diluted with saturated aqueous NaCl (200 mL) and extracted with 2-propanol (300 mL). The solvent was removed from the organic layer, and the residue was combined with the previous precipitate. Chromatography of the residue on silica (525 g) with EtOAc/hexanes (1:3) gave two compounds. Recrystallization of the first compound from ether/hexanes (1:3) gave 5.95 g (11%) of **18** as a yellow solid: mp 104–107 °C; NMR (DMSO-d_6) δ 2.38 (m, 1 H), 2.94 (m, 2 H), 3.19 (dd, 1 H), 3.36 (m, 2 H), 3.43 (d, 1 H), 3.71 (d, 1 H), 3.88 (d, 1 H), 6.79 (t, 1 H), 6.96 (d, 2 H), 7.31 (m, 7 H), 7.97 (d, 2 H), 8.25 (d, 2 H), 10.66 (s, 1 H). Anal. ($C_{24}H_{24}N_4O_3$) C, H, N. Recrystallization of the second compound from ethyl acetate/hexanes (1:1) gave 17.9 g (34%) of **19** as a yellow solid: mp 150–152 °C; NMR (DMSO-d_6) δ 2.36 (td, 1 H), 2.44 (dd, 1 H), 2.96 (d, 1 H), 3.25 (d, 1 H), 3.42 (d, 1 H), 3.53 (d, 1 H), 3.65 (m, 1 H), 3.68 (m, 1 H), 4.54 (s, 1 H), 6.72 (t, 1 H), 6.86 (d, 2 H), 7.19 (m, 7 H), 7.50 (d, 2 H), 8.22 (d, 2 H), 10.49 (s, 1 H). Anal. ($C_{24}H_{24}N_4O_3$) C, H, N.

***N*-(4-Aminophenyl)-4-phenyl-1-(phenylmethyl)-2-piperazinecarboxamide (20).** Tin chloride dihydrate (18.5 g, 82 mmol) and **18** (6.85 g, 16.4 mmol) were dissolved in EtOAc (650 mL) and heated for 1 h. The reaction was poured over crushed ice, neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, and the solvent was removed in vacuo to give 6.33 g (100%) of **20** as an oil: NMR (DMSO-d_6) δ 2.28 (m, 1 H), 2.82 (m, 2 H), 3.08 (m, 1 H), 3.18 (m, 1 H), 3.28 (d, 1 H), 3.48 (m, 1 H), 3.64 (m, 1 H), 3.86 (d, 2 H), 4.90 (s, 2 H), 6.62 (d, 2 H), 6.78 (t, 1 H), 6.94 (d, 2 H), 7.18–7.44 (m, 9 H), 9.6 (s, 1 H).

***N*-[4-[(Methylsulfonyl)amino]phenyl]-4-phenyl-1-(phenylmethyl)-2-piperazinecarboxamide (21).** Methanesulfonic anhydride (2.91 g, 16.7 mmol) was added to **20** (5.88 g, 15.2 mmol) dissolved in acetonitrile (140 mL). After warming to 60 °C for 20 min, the reaction was cooled to room temperature and aqueous $NaHCO_3$ was added. The organic layer was separated, washed with brine, dried (Na_2SO_4), and the solvent was removed in vacuo. Chromatography of the residue on silica with EtOAc/hexanes (1:1) gave 6.46 g (91%) of **21** as a white solid: mp 83–86 °C; NMR (DMSO-d_6) δ 2.30 (m, 1 H), 2.86 (m, 2 H), 2.92 (s, 3 H), 3.11 (t,

1 H), 3.25 (dd, 1 H), 3.32 (d, 1 H), 3.46 (d, 1 H), 3.66 (d, 1 H), 3.86 (d, 1 H), 6.79 (t, 1 H), 6.95 (d, 2 H), 7.14-7.44 (m, 9 H), 7.63 (d, 2 H), 9.57 (s, 1 H), 10.03 (s, 1 H). Anal. ($C_{25}H_{28}N_4O_3S$) C, H, N, S.

***N*-[[[[4-Phenyl-1-(phenylmethyl)piperazin-2-yl]methyl]amino]phenyl]methanesulfonamide (22).** Borane-dimethyl sulfide complex (2.65 mL of a 10 M solution, 26.5 mmol) was added to **21** (4.1 g, 8.8 mmol) dissolved in THF (100 mL) under N_2. The solution was refluxed for 18 h and cooled to room temperature. Methanol (25 mL) was added dropwise followed by 2.0 N methanolic HCl (50 mL). The solution was refluxed for 5 h, and the solvent was removed in vacuo. The residue was dissolved in methanol (150 mL) and 50% aqueous NaOH was added to pH 8.5. Chromatography on silica (250 g) with EtOAc and recrystallization with EtOAc gave 2.4 g (60%) of **22** as a white solid: mp 155-156 °C; NMR (DMSO-d_6) δ 2.39 (br t, 1 H), 2.83 (s, 3 H), 2.83-3.03 (m, 4 H), 3.2-3.5 (m, 5 H), 4.13 (d, 1 H), 5.63 (br s, 1 H), 6.60 (d, 2 H), 6.80 (t, 1 H), 6.95 (m, 4 H), 7.20-7.43 (m, 7 H), 9.00 (s, 1 H). Anal. ($C_{25}H_{30}N_4O_2S$) C, H, N.

***N*-[4-[[(4-Phenylpiperazin-2-yl)methyl]amino]phenyl]methanesulfonamide 0.1-Hydrate (7j).** Reaction of **22** (1.90 g, 4.22 mmol) in a manner similar to **9a** gave 1.09 g (72%) of **7j** as an off-white solid: mp 190-193 °C; NMR ($CDCl_3$) δ 2.61 (dd, 1 H), 2.82 (td, 1 H), 2.93 (s, 3 H), 3.04 (td, 1 H), 3.11-3.35 (m, 4 H), 3.56 (m, 2 H), 4.18 (br s, 1 H), 6.08 (br, 1 H), 6.65 (d, 2 H), 6.91 (t, 1 H), 6.97 (d, 2 H), 7.12 (d, 2 H), 7.30 (m, 2 H). Anal. ($C_{18}H_{24}N_4O_2S \cdot 0.1H_2O$) C, H, N.

Acknowledgment. We thank the Berlex Analytical section for support of this project. We are grateful to Hannah Troy, Anne Smart, Mary Corbett, C. Michael Doroshuk, and Jane Creasy, who carried out the pharmacology experiments. For the preparation of the manuscript we thank Dot Gula.

Registry No. **2**, 58077-34-2; **3**, 15102-42-8; **4a**, 135036-19-0; **4b**, 138286-66-5; **4c**, 135036-27-0; **5**, 4554-16-9; **6**, 135036-22-5; **7a**, 135036-03-2; **7a**·HCl, 135036-12-3; **7b**, 135036-06-5; **7b**·HCl, 138286-70-1; **7c**, 135036-05-4; **7c**·2HCl, 135036-15-6; **7d**, 135036-04-3; **7d**·3HCl, 135036-14-5; **7e**, 135036-11-2; **7e**·HCl, 135036-18-9; **7f**, 138286-68-7; **7f**·HCl, 138286-71-2; **7g**, 135036-08-7; **7g**·$^3/_2$HCl, 138286-72-3; **7h**, 135036-01-0; **7h**·H_2SO_4, 135036-13-4; **7i**, 135036-07-6; **7i**·HCl, 135036-16-7; **7j**, 135036-02-1; **7k**, 138286-69-8; **8a**, 135036-20-3; **9a**, 138286-67-6; **9a**·HCl, 135036-56-5; **10**, 135036-53-2; **11a**, 135036-09-8; **11b**, 135036-10-1; **12**, 138286-73-4; **13**, 135036-34-9; **14**, 135036-35-0; **15**, 138286-74-5; **16**, 135036-37-2; **17**, 135036-38-3; **18**, 135036-39-4; **19**, 135063-15-9; **20**, 138286-75-6; **21**, 135036-40-7; **22**, 135036-41-8; methoxybenzene, 100-66-3; 1-fluoro-4-nitrobenzene, 350-46-9; *N*-(4-nitrophenyl)-2-propenamide, 7766-38-3; 1-(2-chlorophenyl)piperazine, 39512-50-0; 1-(3-chlorophenyl)piperazine, 6640-24-0; 1-(4-chlorophenyl)piperazine, 38212-33-8; 1-(*o*-anisyl)piperazine, 35386-24-4; 1-(*m*-anisyl)piperazine, 16015-71-7; 1-(*p*-anisyl)piperazine, 38212-30-5; 1-(*o*-tolyl)piperazine, 39512-51-1; 1-(*m*-tolyl)piperazine, 41186-03-2; 1-(*p*-tolyl)piperazine, 39593-08-3; 1-(4-nitrophenyl)piperazine, 6269-89-2; 1-phenylpiperazine, 92-54-6; 1-(4-acetylphenyl)piperazine, 51639-48-6.

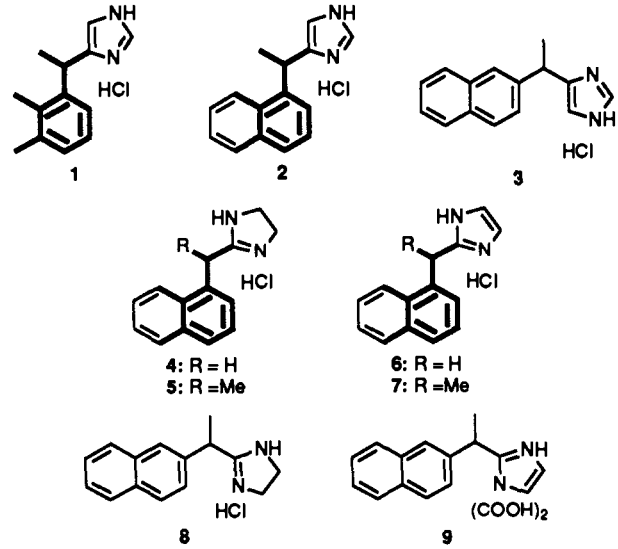
Synthesis and α-Adrenergic Activities of 2- and 4-Substituted Imidazoline and Imidazole Analogues

Yoshiya Amemiya,[†] Seoung S. Hong,[†] Burrah V. Venkataraman,[‡] Popat N. Patil,[‡] Gamal Shams,[‡] Karl Romstedt,[‡] Dennis R. Feller,[‡] Fu-Lian Hsu,[§] and Duane D. Miller*[,†]

Divisions of Medicinal Chemistry and Pharmacognosy, and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210, and U.S. Army Chemical Research, Aberdeen Proving Ground, Maryland 21021.
Received January 29, 1991

Seven analogues of medetomidine and naphazoline were synthesized and evaluated for their α_1 (aorta) and α_2 (platelet) activities. The analogues were composed of 2- and 4-substituted imidazoles and imidazolines attached through a methylene bridge to either the 1- or 2-naphthalene ring system. In general the 1-naphthalene analogues were the most potent inhibitors of epinephrine-induced platelet aggregation. Of considerable interest was the fact that the 1-naphthalene analogues (**2**, **5-7**) were partial agonists while the 2-naphthalene analogues (**3**, **8**, **9**) were antagonists in an α_1-adrenergic system (aorta). Thus, appropriately substituted naphthalene analogues of medetomidine and naphthazoline provide a spectrum of α_1-agonist, α_1-antagonist, and α_2-antagonist activity.

There are two major classes of drug that interact with adrenergic receptors.[1] It is known that phenethylamines adhere strictly to the Easson-Stedman hypothesis and show significant activity differences between optical isomers.[1-3] On the other hand, the imidazoline class of drugs does not follow the Easson-Stedman hypothesis and shows small differences between optical isomers. Recently, it has been reported that medetomidine (**1**)[4] is a new imidazole drug that possesses selective and potent α_2-adrenergic properties. Medetomidine has been reported to have an α_2/α_1 binding ratio of 5060 as compared to clonidine with a ratio of 969.[5] α_2-Adrenergic stimulation is known to mediate a variety of biological actions including hypertension, sedation, antianxiety, analgesia, hypothermia, decreased salivary secretions, and mydriasis.[6] Platelet aggregation induced by epinephrine is also an α_2-adrenergic mediated response[7] and it has recently been subclassified as an α_{2A}-adrenergic receptor system by Byland.[8]



To date, no reports of the action of medetomidine analogues on platelets have appeared. Accordingly, we

[†] Division of Medicinal Chemistry and Pharmacognosy, The Ohio State University.
[‡] Division of Pharmacology, The Ohio State University.
[§] U.S. Army Chemical Research, Aberdeen Proving Ground.

0022-2623/92/1835-0750$03.00/0