(TBAR) as also described previously.[4a] Most compounds were prepared in H_2O. Although **30** is soluble in 1 equiv of HCl, at concentrations below 100 μM the compound binds avidly to glass and plastic. Therefore, all stock solutions and dilutions of **30** were prepared in ethanol, in which glass binding was not a problem.

Mouse Head-Injury Assay. Male CF-1 mice (Charles River plant, Portage, MI) weighing 16–22 g were utilized in this study. A concussive head injury was inflicted in each mouse. A 900 g cm injury force was used in mice weighing 16–20 g, while a 950 g cm force was used in mice weighing 20–22 g. Each trial consisted of four groups of 20 mice (a vehicle group and three doses of test compound). Each mouse was injured and within 3–5 min post-injury was administered either vehicle or test compounds iv, 0.1 mL bolus, blindly. The four groups were injured and treated 5–7 min apart. Various aqueous vehicles were used to obtain satisfactory solubility of each compound tested. The most commonly employed vehicle was 0.5% Tween 80. Anesthesia was not required since this injury consistently caused immediate unconsciousness as judged from the loss of righting reflex and the loss of any pain response.

At 1 h after injury, the sensorimotor status of the head-injured mice was tested by using a grip test. The mice were individually picked up by the tail and placed on a taut string 60 cm in length suspended 40 cm above a padded table between two upright metal bars. Care was taken so that both front paws came in contact with the string, allowing each mouse an equal chance to grasp the string. The tail was gently released, at which time the mouse either fell, due to inability to hold on, or remained on the string. The length of time the mice could remain on the string in some manner (i.e., one to four paws, tail, or paws plus tail) was measured with a 30-s maximum. The 1-h neurological recovery data was evaluated by a mean grip test score for each treatment group. This test consisted of an average time that all mice in the group could remain on the string.

Cytotoxic Hypoxia: KCN Lethality. Upjohn Male CF-1 mice weighing 18–22 g were pretreated with vehicle (0.9% saline or 0.5% Tween-80) or test drug via single dose tail-vein injections given in a volume of 0.2 mL/mouse. After 15 min, the mice were weighed and challenged with a rapid tail-vein injection of KCN 0.01 mL/g, dissolved in 0.9% saline. After another 15 min, the number of deaths was assessed. Ascending doses (0.5 mg/kg interval) of KCN were administered to groups of six mice, and the LD50's and 95% confidence intervals were determined with the Spearman-Karber program in EZSTATS.

The antihypoxic effect of the various test drugs was evaluated by comparing the resulting LD_{50}'s of the same day and using the 95% confidence intervals to determine significance.

Acknowledgment. We thank Physical and Analytical Chemistry for their support.

Registry No. **2**, 111669-15-9; **3**, 111641-17-9; **4**, 111641-07-7; **5A**, 125173-52-6; **5B**, 125173-53-7; **6**, 125173-54-8; **7**, 125173-55-9; **7** *tert*-butyl carbamate derivative, 125173-56-0; **8**, 125173-57-1; **9**, 125173-58-2; **10**, 111669-24-0; **11**, 125173-59-3; **11** free base, 111669-45-5; **12**, 125173-60-6; **13**, 125173-61-7; **13** free base, 111640-37-0; **14**, 111640-53-0; **15**, 111640-54-1; **16**, 125173-62-8; **16** free base, 111640-56-3; **17**, 125173-63-9; **17** free base, 116894-86-1; **18**, 111668-42-9; **18** free base, 111640-69-8; **19**, 125173-64-0; **19** free base, 111640-72-3; **20**, 125276-12-2; **20** free base, 125276-13-3; **21**, 111668-47-4; **21** free base, 111640-73-4; **22**, 125173-65-1; **22** free base, 125173-66-2; **23**, 125173-67-3; **23** free base, 111667-63-1; **24**, 125197-00-4; **24** free base, 111667-71-1; **25**, 111640-44-9; **26**, 111668-30-5; **26** free base, 111640-55-2; **27**, 125173-68-4; **27** free base, 111667-58-4; **28**, 125173-69-5; **28** free base, 111667-59-5; **29**, 125173-70-8; **29** free base, 111667-61-9; **30**, 110101-67-2; **30** free base, 110101-66-1; **31**, 125173-72-0; **31** free base, 125173-71-9; **32**, 125197-01-5; **32** free base, 125173-73-1; Et_2NH, 109-89-7; 2,4,6-trichloropyrimidine, 3764-01-0; pyrrolidine, 123-75-1; piperazine, 110-85-0; 2,6-dichloro-3-nitropyridine, 16013-85-7; acetaldehyde, 75-07-0; 21-bromo-17-hydroxypregna-4,9(11)-diene-3,20-dione, 63973-98-8; 1-(2-methoxyphenyl)piperazine, 35386-24-4; 21-hydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione, 56016-90-1.

Selective Class III Antiarrhythmic Agents. 1. Bis(arylalkyl)amines

Peter E. Cross,*[†] John E. Arrowsmith,[†] Geoffrey N. Thomas,[†] Michael Gwilt,[‡] Roger A. Burges,[‡] and Alan J. Higgins[§]

Pfizer Central Research, Sandwich, Kent CT13 9NJ, United Kingdom. *Received May 18, 1989*

A series of bis(arylalkyl)amines is described and their effects on prolonging effective refractory period in isolated cardiac tissue listed. Most compounds prolonged the cardiac action potential without significantly altering the maximum rate of depolarization and may be defined as selective class III antiarrhythmic agents. It was found that a particularly advantageous structural feature was to have a methanesulfonamido moiety on both of the aryl rings. Thus, compound **16** [1-(4-methanesulfonamidophenoxy)-2-[*N*-(4-methanesulfonamidophenethyl)-*N*-methylamine]ethane] was selected for further investigations. The compound is highly potent and selective class III agent which acts by blockade of cardiac potassium channels.

Sudden cardiac death (SCD) is a leading cause of mortality among the adult population of the world's industrialized nations. SCD results from electrical instability of the heart muscle leading to a loss of regular cardiac rhythm, and it is accepted that ventricular arrhythmias such as sustained tachycardia (VT) and fibrillation (VF) play the major role in these deaths. Supraventricular arrhythmias cause life-threatening hemodynamic disturbances and thrombotic events such as strokes. Serious arrhythmias occur in two major settings, the first is acute myocardial infarction (AMI), where 45% of those who die generally do so within the first hour of the ischemic event. The second is a chronic situation where a patient may show a disposition to arrhythmias as a result of ischemic damage post-MI or from congestive heart failure (CHF). Prophylactic treatment of these high-risk patients with a safe antiarrhythmic agent represents a major therapeutic challenge.[1]

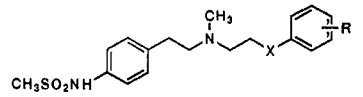
The Vaughan Williams classification[2] of antiarrhythmic drugs recognizes four distinct categories. The largest group are the class I drugs, whose mechanism of action is that of interference with the fast sodium channels in cell membranes. These drugs are effective against simple ventricular and, in some cases, supraventricular arrhythmias, but they are ineffective as long-term prophylactics for prevention of sudden cardiac death caused by VF.[1] Moreover, they generally have a low therapeutic ratio, their

[†] Department of Chemistry.
[‡] Department of Biology.
[§] Now with Roche.

(1) Patterson, E.; Lucchesi, B. R. *Am. Heart J.* **1983**, *106*, 426.
(2) Vaughan Williams, E. M. *J. Clin. Pharmacol.* **1984**, *24*, 129.

0022-2623/90/1833-1151$02.50/0

Table I. Data for Compounds Used in This Study



no.	X	R	mp, °C	recrystn solvent[a]	formula[b]	% yield	ERP ED_{25}[c]	% Cardiac depression at 10^{-4} M[d]
6	O	4-$COOCH_3$	108	EtOAc/petrol	$C_{20}H_{26}N_2O_5S$	66	4.1×10^{-6}	47
7	O	4-$CONH_2$	147	EtOAc/toluene	$C_{19}H_{25}N_3O_4S$	25	1.5×10^{-6}	7
8	O	4-$CONHCH_3$	160	EtOAc/MeOH	$C_{20}H_{27}N_3O_4S \cdot HCl$	19	1.5×10^{-6}	5
9	O	4-$CONEt_2$	97–98	EtOAc/DIPE	$C_{23}H_{33}N_3O_4S$	29	3.2×10^{-5}	9
10	O	4-CO-c-$N(CH_2CH_2)_2O$	198–201	EtOAc/MeOH	$C_{23}H_{31}N_3O_5S \cdot HCl$[e]	12	2×10^{-5}	15
11	O	3-$CONH_2$	104–106	EtOAc	$C_{19}H_{25}N_3O_4S$	14	8.2×10^{-7}	3
12	O	4-CF_3	142–144	EtOAc/MeOH	$C_{19}H_{23}F_3N_2O_3S \cdot HCl$	43	9×10^{-6}	30
13	O	2-$CONH_2$-4-CH_3	124–126	EtOAc/MeOH	$C_{20}H_{27}N_3O_4S \cdot HCl$	40	1×10^{-6}	22
14	O	4-CH_2CONH_2	*f*	EtOAc/MeOH	$C_{20}H_{27}N_3O_4S \cdot CH_4O_3S$	25	1×10^{-5}	7
15	O	4-SO_2NH_2	133–135	EtOAc/MeOH	$C_{18}H_{25}N_3O_5S_2$	26	2.2×10^{-6}	7
16	O	4-$NHSO_2CH_3$	147–149	EtOAc/petrol	$C_{19}H_{27}N_3O_5S_2$	51	1.3×10^{-7}[g]	0
17	O	3-$NHSO_2CH_3$	113–114	EtOAc/petrol	$C_{19}H_{27}N_3O_5S_2$	10	3×10^{-6}	9
18	O	2-$NHSO_2CH_3$	178–180	EtOAc/MeOH	$C_{19}H_{27}N_3O_5S_2 \cdot HCl$	26	2.5×10^{-6}	19
19	O	4-$NHCONHCH_3$	115[h]	EtOAc	$C_{20}H_{28}N_4O_4S \cdot HCl$[e]	18	7×10^{-5}	0
20	S	4-$NHSO_2CH_3$	160–163	EtOAc	$C_{19}H_{27}N_3O_4S_3$	25	3×10^{-7}	21
21	O	2-$NHSO_2CH_3$-5-CH_3	185	EtOAc/MeOH	$C_{20}H_{29}N_3O_5S_2 \cdot HCl$[i]	6	1.7×10^{-5}	24
22	O	2-Cl-4-$NHSO_2CH_3$	141–143	Et_2O	$C_{19}H_{26}ClN_3O_5S_2$	32	1.8×10^{-6}	16
23		4-$NHSO_2CH_3$	170–171	*j*	$C_{19}H_{27}N_3O_4S_2$	18	2×10^{-6}	20
24	$-CH_2-$	4-$NHSO_2CH_3$	*j*	*j*	$C_{20}H_{29}N_3O_4S_2$[k]	35	2.7×10^{-6}	23
25	$-CH_2O-$	4-$NHSO_2CH_3$	125[g]	EtOAc/MeOH	$C_{20}H_{29}N_3O_5S_2 \cdot HCl$	34	2×10^{-5}	44
26	$-(CH_2)_2O-$	4-$NHSO_2CH_3$	90[g]	EtOAc/MeOH	$C_{21}H_{31}N_3O_5S_2 \cdot HCl$[e]	32	4×10^{-5}	23
27	$(CH_2)_2$	4-$NHSO_2CH_3$	*j*	*j*	$C_{21}H_{31}N_3O_4S_2$[e]	65	6.7×10^{-5}	32
28	$-OCH(Ph)-$	4-$NHSO_2CH_3$	*j*	*j*	$C_{26}H_{33}N_3O_5S_2$	9	1.2×10^{-5}	35
d-sotalol							2×10^{-4}[l]	5

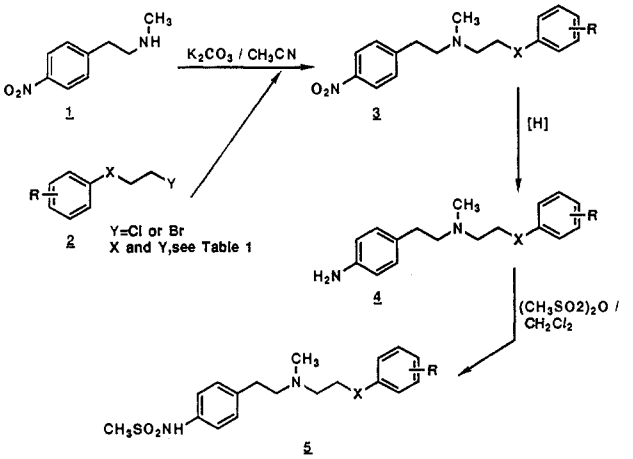
[a] DIPE, diisopropyl ether; petrol, 60–80 °C petroleum ether. [b] All compounds were analyzed for C, H, and N to within ±0.4% of the theoretical value. [c] Molar concentration of compound required to prolong effective refractory period (ERP) in isolated guinea pig left atria. Mean of two similar determinations, ±4%. [d] Mean of two similar determinations, ±4%. [e] Hemihydrate. [f] Accurate melting point could not be determined as the compound was hygroscopic. [g] Mean of 12 determinations; standard error ± 0.5×10^{-7} M. [h] Compound foamed. [i] Monohydrate. [j] Compound isolated as a foam that could not be crystallized. [k] Characterized by ^1H NMR. [l] Mean of four determinations; standard error ± 0.4×10^{-4} M.

common side effects being neurotoxicity, gastrointestinal disturbances, cardiac depression, and arrhythmogenic actions.

Class III agents[2] by definition owe their antiarrhythmic activity to their ability to increase the refractory period, via an increase in transmembrane action potential duration (APD), without altering the maximum rate of depolarization (MRD). Such an action is well-suited to the prevention of reentrant excitation of myocardial cells, which is considered to play the dominant role in the generation of VT and VF.[3] Furthermore, because refractoriness is uniformly increased throughout the myocardium, class III agents have the added advantage of being effective against many types of rhythm abnormality which are reentrant in origin, whether atrial, junctional, or ventricular.

We now wish to report a series of novel bis(arylalkyl)-amines which selectively prolong APD without altering MRD in cardiac muscle and so increase refractoriness to premature stimuli. Thus, they are class III agents according to the definition of Vaughan Williams.[2] Moreover, some of these agents are 100–1000 times more potent than *d*-sotalol,[4,5] which is known to suppress programmed electrically stimulated VT in patients. Our preliminary work in this area had demonstrated to us the importance of a methanesulfonamido moiety for good class III activity, and when this moiety was attached to the para position of a phenylethylamine structure, suitable variation of the substituents at the basic center enabled us to change parameters such as potency and pharmacokinetics.

Scheme I



Chemistry

All of the compounds listed in Table I were synthesized by the route shown in Scheme I. *N*-Methyl-4-nitrophenylethylamine[6] (**1**) was allowed to react with an appropriately substituted alkyl halide (**2**) to give **3**, followed by reduction of the nitro group to give aniline intermediate **4**. The reducing agent used to give **4** was normally either Raney nickel/hydrogen or palladium charcoal/hydrogen at room temperature and 3 or 50 psi of pressure, respectively. However, in the case of compound **17** the reductive step involved stannous chloride in HCl. Mesylation to give

(3) Singh, B. N.; Nademance, K. *Am. Heart J.* **1985**, *109*, 421.
(4) McComb, J. M.; McGowan, J. B.; McGovern, B. A.; Garvan, H.; Ruskin, J. *J. Am. Coll. Cardiol.* **1985**, *5*, 438.
(5) Rowland, E.; Perrins, E. J.; Donaldson, R. M.; Richards, A. F. *J. Am. Coll. Cardiol.* **1985**, *5*, 498.
(6) Dale, W. J.; Buell, C. *J. Org. Chem.* **1956**, *21*, 45.

Table II. Effects of **16** on Action Potentials from Guinea Pig Right Papillary Muscle

	MRD,[a] V/s	APD_{50},[b] ms	APD_{90},[b] ms
control	270 ± 61	153 ± 22	192 ± 22
16 5×10^{-9} M	261 ± 55	170 ± 16*	209 ± 16**
16 5×10^{-8} M	273 ± 56	197 ± 22**	246 ± 22**
16 10^{-6} M	269 ± 49	223 ± 16**	288 ± 22**
16 2×10^{-5} M	273 ± 60	209 ± 16**	273 ± 33**

[a] MRD = rate of phase 0 depolarizations. Results are means ± SD of 30 or 31 observations from three preparations. [b] * = $P < 0.01$, ** = $P < 0.001$ by t test vs control.

5 used either methanesulfonic anhydride or methanesulfonyl chloride. When the substituent group R on **2** was nitro, the appropriate bis-anilino intermediate (**4**) was obtained after reduction; treatment with methanesulfonic anhydride than gave the final compounds **16–18** and **20–28**.

Results and Discussion

The molar concentration of compound required to prolong the effective refractory period (ERP) by 25% was measured in isolated guinea pig left atria by using an extra stimulus technique. The degree of cardiac depression produced by each compound at 10^{-4} M was also measured and used as an index of class I activity. As may be seen from Table I, all the compounds were significantly more potent in prolonging the ERP than was *d*-sotalol. Compound **6** for example was nearly 100 times more potent, but exhibited a marked depressant effect. However, converting the 4-ester substituent to a primary or secondary carboxamide (**7** and **8** respectively) not only improved the ERP activity, but also gave compounds with negligible cardiac depressant properties. Tertiary carboxamides **9** and **10** showed a 10-fold drop in ERP potency compared to **7** and **8**, and replacement of the amide of **7** by a carbamoylmethyl substituent, as in **14**, was also unfavorable. The primary amide substituent of **7** could be located in the meta (**11**) or ortho (**13**) positions on the aryl ring or may be replaced, with no drop in potency, by a sulfonamide (**15**). However, by far the most advantageous structural change was to have a 4-methanesulfonamido substituent on the aryl ring, as in compound **16**; this produced a 10-fold potency increase over that of compound **7**, with no depressant effects. The para position was the most favored for the methanesulfonamido substituent, the meta (**17**) and ortho (**18**) isomers being less active. The oxygen atom in the side chain linking the aryl ring to the basic center may be replaced by sulfur or methylene to give **20** and **24**, respectively; the slight drop in ERP potency was, however, accompanied by a rise in cardiac depressant activity. The linking ether oxygen atom of **16** may be replaced altogether to give dimer **23** with similar results. Further modifications to the side chain as in compounds **25–28** were unfavorable with respect both to potency and depressant effects. Consideration of the compounds in Table I led to **16** (UK-68,798) being selected for further evaluation.

In isolated guinea-pig papillary muscle **16** produced a dose-related prolongation of ERP from a concentration of 5×10^{-9} M upward. Table II shows the effect of the compound on the action potential duration at 50% (APD_{50}) and 90% (APD_{90}) repolarization. The results show that **16** significantly prolonged APD at all concentrations tested and had no effect on the maximum rate of depolarization during phase 0 (upstroke velocity). Thus, the compound is a potent and selective class III agent in vitro.

Prolongation of atrial and ventricular ERP's in pentobarbitone anesthetized dogs was used as a measure of in vivo activity.[7] Thus, compound **16**, over a range of 1–100

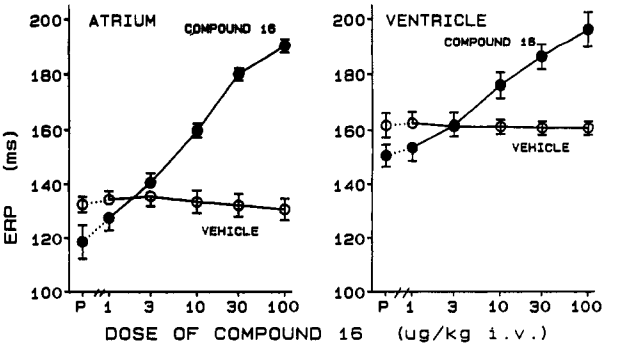


Figure 1. Evaluation of atrial (left panel) and ventricular (right panel) effective refractory periods (ERP) of pentobarbitone-anesthetized dogs by compound **16** (in acidified saline). Results expressed as mean ± SEM of observations from five dogs.

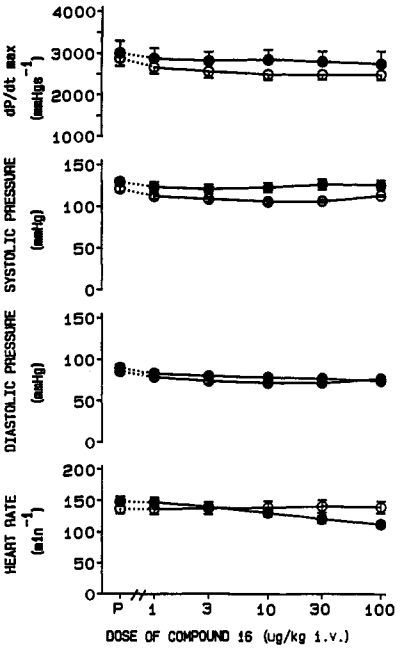


Figure 2. Hemodynamic effects of intravenous compound **16** and vehicle (acidified saline) in pentobarbitone-anesthetized dogs. Results expressed a mean ± SEM of observations from five dogs.

μg/kg iv dose dependently increased both AERP and VERP (Figure 1). ERP prolongations in atria were larger in extent than in ventricles (63% vs 30% of control), although the minimum effective doses were the same in each tissue. At 10 μg/kg the effects were well maintained for more than 90 min. No falls in blood pressure of left ventricular pressure were seen at any doses, and hemodynamic effects were slight and comprised mild bradycardia and slight increases in contractility[7] (dP/dt) (Figure 2).

Blockade of cardiac potassium channels has been proposed as being inherently antifibrillatory,[8] and such a mechanism could account for the properties of **16**. The antiarrhythmic action of *d*-sotalol has been reported to arise from blockade of the potassium current associated with the delayed rectifier I_k.[9] In voltage-clamp experiments using single guinea pig ventricular myocytes (whole cell patch technique), **16** reduced the amplitude of the time-dependent K^+ current (I_k) without reducing time-

(7) Gwilt, M.; Solca, A. M.; Burges, R. A.; Blackburn, K. J.; Higgins, A. J. *J. Mol. Cell Cardiol.* **1989**, *21* (suppl. II), S11.
(8) Bacaner, M. B.; Clay, J. R.; Shrier, A.; Brochu, R. M. *Proc. Natl. Acad. Sci.* **1986**, *83*, 2223.
(9) Carmeliet, E. *J. Pharmacol. Exp. Ther.* **1985**, *232*, 817.

independent background currents (I_{k1}).[10] Thus, by selective blockade of the delayed rectifier (I_k), **16** prolongs cardiac refractoriness without slowing conduction.

The importance of the methanesulfonamido moiety for good class III activity has been noted by ourselves as well as other workers.[11] In compound **16** the addition of the second methanesulfonamido group produces an almost symmetrical structure. It is interesting that the potassium channel has been shown[12] to be a large protein containing four homologous domains and is therefore highly symmetrical. The interaction of **16** on the channel may perhaps reflect a specific recognition of both ends of the molecule by the gating mechanism. However, the fully symmetrical compound **23** is nearly 10-fold less active than **16**, but this may reflect a slightly suboptimal size for full interaction with the channel protein. The size of the molecule appears to be of some importance, since increasing the side-chain length of **16** by one or two methylene units (**25**, **26**) led to a marked diminution of activity.

Pharmacokinetic studies on **16** were carried out in dog and man and it was found[13] that the oral bioavailability was 72 and 100%, respectively. In the dog the compound has an elimination of half-life ($t_{1/2}$) of 4–6 h, which reflects the clearance rate of 10.2 mL/min per kg and the moderate volume of distribution (Vd) of 4.0 L/kg. The physicochemical properties of **16** show that it is a weak acid (pK_a 9.0 and 9.6), due to the methanesulfonamido protons, and a moderate base (pK_a 7.0). Thus at physiological pH the sulfonamido groups are 2.45 and 0.63% ionized, respectively, and the amine is 28.5% protonated. It would appear, therefore, that the zwitterion is not a dominant species. The distribution coefficient (log D)[14] of the compound at pH 7.4 is 0.96.

Experimental Section

Pharmacology. For assessment of the effects of the compounds on atrial refractoriness, guinea pig left atria were mounted in a bath containing physiological salt sodium and one end was connected to a force transducer. The tissues were stimulated at 1 Hz with field electrodes, and the effective refractory period (ERP) was measured by introducing premature stimuli (S_2) after every eighth basic stimulus (S_1). The S_1S_2 coupling interval was gradually increased until S_2 reproducibly failed to elicit a propagated response. This is defined as the ERP. The concentration of compound required to increase ERP by 25% (ED_{25}) was then determined. ERP was also measured in guinea pig right papillary muscles stimulated at one end with bipolar electrodes and the propagated electrogram was recorded at the opposite end via a unipolar surface electrode. ERP was determined as above by using the extrastimulus techniques. Conduction time (class I effect) was obtained by measuring the interval between the stimulus artifact and the peak of the electrogram (i.e. the time required for the impulse to travel along the length of the muscle).

Beagle dogs were anesthetized with pentobarbitone (60 mg/kg + 6 mg/kg per h) and artifically ventilated with room air. Hearts were exposed via a right thoracotomy for placement of electrodes. AERP and VERP were determined by using an extrastimulus technique during continuous pacing (200 min^{-1}) of atria or ventricles via bipolar platinum electrodes.

Chemistry. All melting points are uncorrected. The structures of all compounds were confirmed by ^1H NMR spectra, which were obtained on a General Electric QE300 spectrometer.

1-(4-Nitrophenoxy)-2-[*N*-methyl-*N*-(4-nitrophenethyl)-amino]ethane (*3*, **X = O; R = 4-NO_2**). To a solution of *N*-methyl-4-nitrophenethylamine[6] (1.5 g, 8 mmol) and 2-[4-nitrophenoxy]ethyl chloride (1.55 g, 7.7 mmol) in acetonitrile (50 mL) was added potassium carbonate (1.25 g) and sodium iodide (1.2 g) and the suspension was stirred at reflux for 72 h. After evaporation to dryness, the residual oily solid was partitioned between a 2 N aqueous sodium bicarbonate solution (100 mL) and ethyl acetate (100 mL). After two further extractions with ethyl acetate (50 mL), the organic portions were combined, washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered, and evaporated. The resultant solid was then crystallized from EtOH to give the title compound **3**: yield 1.7 g (64%); mp 74 °C. Anal. $C_{17}H_{19}N_3O_5$ (C, H, N).

1-(4-Aminophenoxy)-2-[*N*-(4-aminophenethyl)-*N*-methylamino]ethane (**4**, **X = O; R = 4-NH_2**). A solution of 1-(4-nitrophenoxy)-2-[*N*-methyl-*N*-(4-nitrophenethyl)amino]-ethane (1.5 g, 4.5 mmol) in EtOH (100 mL) was stirred for 16 h at room temperature under 3 atm of hydrogen in the presence of Raney nickel. The reaction mixture was filtered and evaporated to dryness. The residual oil was redissolved in ether, filtered, and evaporated to give yellow solid which was recrystallized from 1:1 EtOAc/petroleum ether (60–80 °C) to give the title compound **4**: yield 0.90 g (72%); mp 73–74 °C. Anal. $C_{17}H_{23}N_3O$ (C, H, N).

1-(4-Methanesulfonamidophenoxy)-2-[*N*-(4-methanesulfonamidophenethyl)-*N*-methylamino]ethane (16). A solution of 1-(4-aminophenoxy)-2-[*N*-(4-aminophenethyl)-*N*-methylamino]ethane (0.75 g, 2.6 mmol) and methanesulfonic anhydride (1.0 g, 4 mmol) in dry methylene chloride (50 mL) was stirred at room temperature overnight. After evaporation, the resultant oil was partitioned between a 2 N aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (50 mL). After two further extractions with ethyl acetate (2 × 25 mL), the organic portions were combined, dried over $MgSO_4$, filtered, and evaporated. The resultant solid was crystallized from EtOAc/MeOH (10:1) to give the title compound: yield 0.6 g (51%); mp 147–149 °C; ^1H NMR (DMSO-d_6) δ 9.43 (2 H, br s), 7.00–7.30 (6 H, complex) 6.80–7.00 (2 H, d), 3.90–4.10 (2 H, t) 2.80, 3.00 (2 × 3 H, s), 2.55–2.80 (6 H, complex) 2.27 (3 H, s). Anal. $C_{19}H_{27}N_3O_5S_2$ (C, H, N).

Acknowledgment. We thank A. Solca, L. Smith, and J. Brooks for their able technical assistance and P. J. Wadsworth and his staff for analytical and spectral data. We also thank D. A. Smith and D. Walker for pharmacokinetic data. We are grateful to Bristol-Myers for a gift of *d*-sotalol.

Registry No. 1, 85176-37-0; **2** (X = O, R = 4-CO_2Me, Y = Br), 56850-91-0; **2** (X = O, R = 4-$CONH_2$, Y = Br), 58757-02-1; **2** (X = O, R = 4-CONHMe, Y = Br), 125174-21-2; **2** (X = O, R = 4-$CONEt_2$, Y = Br), 125174-22-3; **2** (X = O, R = 4-CO-c-N-$(CH_2CH_2)_2O$, Y = Br), 125174-23-4; **2** (X = O, R = 3-$CONH_2$, Y = Br), 125174-24-5; **2** (X = O, R = 4-CF_3, Y = Br), 125174-25-6; **2** (X = O, R = 2-$CONH_2$-4-CH_3, Y = Br), 125174-26-7; **2** (X = O, R = 4-CH_2CONH_2, Y = Br), 125174-27-8; **2** (X = O, R = 4-SO_2NH_2, Y = Br), 125174-28-9; **2** (X = O, R = 4-NO_2, Y = Cl), 3383-72-0; **2** (X = O, R = 3-NO_2, Y = Br), 13831-59-9; **2** (X = O, R = 2-NO_2, Y = Br), 18800-37-8; **2** (X = O, R = 4-NHCONHMe, Y = Br), 125174-29-0; **2** (X = S, R = 4-NO_2, Y = Br), 13290-29-4; **2** (X = O, R = 2-NO_2-5-Me, Y = Br), 96315-07-0; **2** (X = O, R = 2-Cl-4-NO_2, Y = Br), 125174-30-3; **2** (R = 4-NO_2, Y = Br), 5339-26-4; **2** (X = $-CH_2-$, R = 4-NO_2, Y = Br), 53712-77-9; **2** (X = $-CH_2O-$, R = 4-NO_2, Y = Br), 125174-31-4; **2** (X = $(CH_2)_2O$, R = 4-NO_2, Y = Br), 125174-32-5; **2** (X = $(CH_2)_2$, R = 4-NO_2, Y = Br), 99359-34-9; **2** (X = OCH(Ph), R = 4-NO_2, Y = Br), 125174-33-6; **3** (X = O, R = 4-CO_2Me), 125174-34-7; **3** (X = O, R = 4-$CONH_2$), 115256-18-3; **3** (X = O, R = 4-CONHMe), 115256-26-3; **3** (X = O, R = 4-$CONEt_2$), 125174-35-8; **3** (X = O, R = 4-CO-c-N$(CH_2CH_2)_2O$), 125174-36-9; **3** (X = O, R = 3-$CONH_2$), 125174-37-0; **3** (X = O, R = 4-CF_3), 125174-38-1; **3** (X = O, R = 2-$CONH_2$-4-Me), 125197-03-7; **3** (X = O, R = 4-CH_2CONH_2), 125174-39-2; **3** (X = O, R = 4-SO_2NH_2), 125174-40-5; **3** (X = O, R = 4-NO_2), 115287-37-1; **3** (X = O, R = 3-NO_2),

(10) Gwilt, M.; Dalrymple, H. W.; Burges, R. A.; Blackburn, K. J.; Arrowsmith, J. E.; Cross, P. E.; Higgins, A. J. *J. Mol. Cell Cardiol.* **1989**, *21* (suppl II), 511.
(11) Lis, R.; Morgan, T. K.; DeVita, R. J.; Davey, D. D.; Lumma, W. C.; Wohl, R. A.; Diamond, J.; Wong, S. S.; Sullivan, M. E. *J. Med. Chem.* **1987**, *30*, 696.
(12) Agnew, W. S. *Nature* **1988**, *331*, 114.
(13) Smith, D. A.; Walker, D., unpublished results.
(14) Manners, C. N.; Payling, D. W.; Smith, D. A. *Xenobiotica* **1988**, *18*, 331.

125174-41-6; 3 (X = O, R = 2-NO_2), 125174-42-7; 3 (X = O, R = 4-NHCONHMe), 125174-43-8; 3 (X = S, R = 4-NO_2), 115256-40-1; 3 (X = O, R = 2-NO_2-5-Me), 125174-44-9; 3 (X = O, R = 2-Cl-4-NO_2), 125174-45-0; 3 (R = 4-NO_2), 115256-47-8; 3 (R = 4-NO_2, X = $-CH_2-$), 125174-46-1; 3 (X = $-CH_2O-$, R = 4-NO_2), 125174-47-2; 3 (X = $(CH_2)_2O$, R = 4-NO_2), 125174-48-3; 3 (X = $(CH_2)_2$, R = 4-NO_2), 125174-49-4; 3 (X = OCH(Ph), R = 4-NO_2), 125174-50-7; 4 (X = O, R = 4-CO_2Me), 125174-51-8; 4 (X = O, R = 4-$CONH_2$), 115256-19-4; 4 (X = O, R = 4-CONHMe), 115256-27-4; 4 (X = O, R = $CONEt_2$), 125174-52-9; 4 (X = O, R = 4-CO-c-$N(CH_2CH_2)_2O$), 125174-53-0; 4 (X = O, R = 3-$CONH_2$), 125174-54-1; 4 (X = O, R = 4-CF_3), 125174-55-2; 4 (X = O, R = 2-$CONH_2$-4-Me), 125174-56-3; 4 (X = O, R = 4-CH_2CONH_2), 125174-57-4; 4 (X = O, R = 4-SO_2NH_2), 125174-58-5; 4 (X = O, R = 4-NH_2), 115256-13-8; 4 (X = O, R = 3-NH_2), 125174-59-6; 4 (X = O, R = 2-NH_2), 125174-60-9; 4 (X = O, R = 4-NHCONHMe), 125174-61-0; 4 (X = S, R = 4-NH_2), 115256-41-2; 4 (X = O, R = 2-NH_2-5-Me), 125174-62-1; 4 (X = O, R = 2-Cl-4-NH_2), 125174-63-2; 4 (R = 4-NH_2), 115256-48-9; 4 (X = $-CH_2-$, R = 4-NH_2), 125174-64-3; 4 (X = $-CH_2O-$, R = 4-NH_2), 125174-65-4; 4 (X = $(CH_2)_2O$, R = 4-NH_2), 125174-66-5; 4 (X = $(CH_2)_2$, R = 4-NH_2), 125174-67-6; 4 (X = OCH(Ph), R = 4-NH_2), 125174-68-7; **6**, 125174-69-8; **7**, 115256-20-7; **8**, 115256-29-6; **8**·HCl, 115256-28-5; **9**, 115256-21-8; **10**, 125174-70-1; **10**·HCl, 115256-22-9; **11**, 115256-23-0; **12**, 125174-71-2; **12**·HCl, 125174-72-3; **13**, 125174-73-4; **13**·HCl, 115256-24-1; **14**, 125174-74-5; **14**·$MeSO_3H$, 125174-75-6; **15**, 125197-04-8; **16**, 115256-11-6; **17**, 115256-30-9; **18**, 125174-76-7; **18**·HCl, 115256-31-0; **19**, 125174-77-8; **19**·HCl, 125174-78-9; **20**, 115256-42-3; **21**, 125174-79-0; **21**·HCl, 115256-32-1; **22**, 115256-43-4; **23**, 115256-50-3; **24**, 125174-80-3; **25**, 125174-81-4; **25**·HCl, 115256-33-2; **26**, 125174-82-5; **26**·HCl, 115256-34-3; **27**, 125174-83-6; **28**, 125174-84-7.

Potential Antipsychotic Agents. 5.† Synthesis and Antidopaminergic Properties of Substituted 5,6-Dimethoxysalicylamides and Related Compounds‡

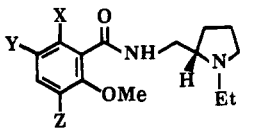
Thomas Högberg,*,§ Stefan Bengtsson,§ Tomas de Paulis,‖ Lars Johansson,§ Peter Ström,§ Håkan Hall,⊥ and Sven Ove Ögren⊥

Astra Research Centre AB, CNS Research & Development, S-151 85 Södertälje, Sweden. *Received June 23, 1989*

A series of 3-substituted 5,6-dimethoxysalicylamides III (**9**–**13** and **15**) has been synthesized from the corresponding 2,5,6-trimethoxybenzoic acids. Relaxation times T_1 and carbon chemical shifts of the methoxy groups in III showed that the 6-methoxy group adopts a nearly perpendicular orientation and the 5-methoxy group takes on a more coplanar orientation with respect to the ring plane in solution. The salicylamides III display a very high and stereoselective affinity for the [^{3}H]spiperone and [^{3}H]raclopride binding sites in vitro. Regioisomeric salicylamides IV also exhibit pronounced, but lower than III, affinity for the [^{3}H]spiperone binding site. The structural requirements were further assessed by studies of the related amino analogues **23** and **24** and hydroxy analogue **27**. The 3-bromo compound **11** (FLB 463) was studied in various in vivo models and compared with the dopamine-D_2 antagonists sulpiride, raclopride, eticlopride, and haloperidol. The high potency of **11** to selectively block dopamine-D_2 receptors in vitro and in vivo combined with indications on a low potential for motor side effects makes it a very interesting new member of the class of substituted salicylamides.

The clinical efficacy of most currently used antipsychotic agents, e.g. the phenothiazines and butyrophenones, is attributed to their ability to block dopamine-D_2 receptors.[1,2] The introduction of more selective compounds, e.g. the substituted benzamides sulpiride,[3,4] and remoxipride,[5,6] indicated that the antidopaminergic effect associated with the clinical efficacy could be separated from the induction of extrapyramidal side effects (EPS).[1,7] A recently developed series of salicylamides, e.g. **28** (FLA 797),[8] eticlopride,[9] and raclopride (Chart I),[9,10] are highly potent and selective dopamine-D_2 antagonists.[7] Importantly, these compounds combine a very high and stereoselective affinity for dopamine-D_2 receptors with a low liability to produce EPS in behavioral studies in the rat.[1,7–10] Accordingly, raclopride has been selected for clinical investigations and found to be well tolerated.[11] The suitable binding characteristics also led to the development of tritiated and carbon-11 labeled raclopride as radioligands.[12–14] As further support for the above-mentioned mode of action of antipsychotics, positron

Chart I



	X	Y	Z
(S)-sulpiride	H	NH_2SO_2	H
remoxipride	OCH_3	Br	H
FLA 797 (28)	OH	Br	H
raclopride (29)	OH	Cl	Cl
eticlopride (30)	OH	C_2H_5	Cl

† Part 6: de Paulis, T.; Hall, H.; Kumar, Y.; Rämsby, S.; Ögren, S. O.; Högberg, T. *Eur. J. Med. Chem.* In press.

‡ Presented in part at the 194th National Meeting at the American Chemical Society, New Orleans, 1987, MEDI 43 and the Xth International Symposium on Medicinal Chemistry, Budapest, 1988, p 66.

§ Department of Medicinal Chemistry.

‖ Present address: Chemistry Department, Vanderbilt University, Nashville, TN 37235.

⊥ Department of Neuropharmacology.

(1) Ögren, S. O.; Högberg, T. *ISI Atlas Sci.: Pharmacol.* **1988**, *2*, 141–147.
(2) (a) Seeman, P. *Pharmacol. Rev.* **1980**, *32*, 229–313. (b) Seeman, P. *Synapse* **1987**, *1*, 133–152.
(3) Borenstein, P.; Champion, C.; Cujo, P.; Olivenstein, C. *Ann. Méd.-Psychol.* **1968**, *126*, 90–99.
(4) Jenner, P.; Marsden, C. D. *Neuropharmacology* **1981**, *20*, 1285–1293.
(5) Florvall, L.; Ögren, S.-O. *J. Med. Chem.* **1982**, *25*, 1280–1286.
(6) Ögren, S.-O.; Hall, H.; Köhler, C.; Magnusson, O.; Lindbom, L. O.; Ängeby, K.; Florvall, L. *Eur. J. Pharmacol.* **1984**, *102*, 459–474.

0022-2623/90/1833-1155$02.50/0