Communications to the Editor

4'-[(4-Piperidyl)carbonyl]methanesulfonanilides as Potent, Selective, Bioavailable Class III Antiarrhythmic Agents

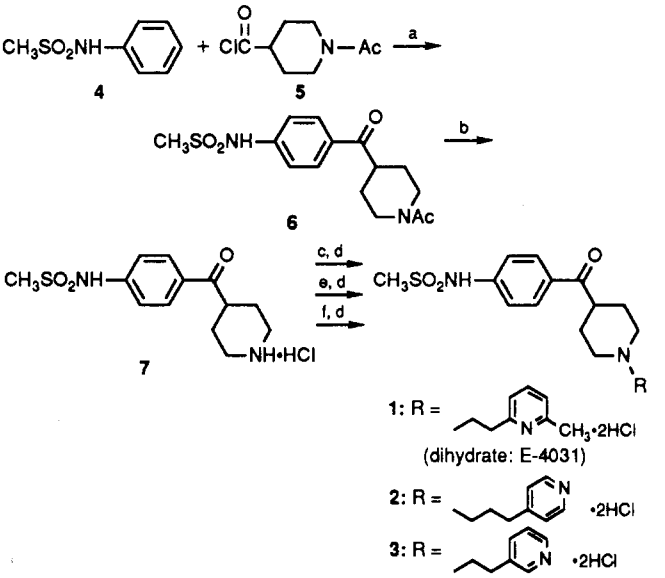
Sir:

Sudden cardiac death in patients with coronary disease remains a major medical problem. In many cases, these deaths are closely associated with the unexpected development of ventricular fibrillation (VF).[1,2] The major goal of antiarrhythmic therapy is to prevent the occurrence of such lethal arrhythmias. In this regard, therapy using class III antiarrhythmic agents has begun to attract attention as a promising approach.[3]

Clofilium[4] and *d*-sotalol[5] have been studied in clinical trials as selective class III agents and proven to be effective against ventricular arrhythmias.[6,7] However, the bioavailability of clofilium phosphate is very low owing to its quaternary ammonium structure,[8] and *d*-sotalol exhibits significant β-blocking properties at higher concentrations.[9]

In our study on new class III agents, we speculated that the methanesulfonanilide group of *d*-sotalol is a very important moiety for specific class III activity.[10] We thus attempted to develop bioavailable methanesulfonanilide analogues with potent class III activity and no β-blocking effects. Of these, 1 (E-4031; 4'-[[1-[2-(6-methyl-2-pyridyl)ethyl]-4-piperidyl]carbonyl]methanesulfonanilide), **2**, and **3** were found to be potent, highly selective class III antiarrhythmic agents[11] and were found to have a significant bioavailability in animals.

Scheme I. Preparation of 4'-[(4-Piperidyl)carbonyl]methanesulfonanilides[a]



[a] Reagents: a, $AlCl_3$, CH_2Cl_2 (82%); b, 3 N HCl (84%); c, 6-methyl-2-vinylpyridine (**8**), CH_3CO_2Na, MeOH-H_2O (81%); d, HCl-EtOH; e, 4-(3-chloropropyl)pyridine hydrochloride (**9**), KI, K_2CO_3, DMF (66%); f, 3-(2-chloroethyl)pyridine hydrochloride (**10**), KI, K_2CO_3, DMF (57%).

Table I. Effects of 4'-[(4-Piperidyl)carbonyl]methanesulfonanilides, Clofilium, and *d*-Sotalol on Action Potential Characteristics of Guinea Pig Right Ventricular Papillary Muscles[17]

compd	n[a]	concn range, μM	$C_{10}APD_{90}$ (Δ%),[b] μM	maxAPD_{90} (Δ%)[c] (concn, μM)	V_{max} (Δ%)[d]
1 (E-4031)[e]	6	0.1-10.0	0.13	25 (10)	ns[f]
2[g]	4	0.1-100.0	0.19	33 (100)	ns
3[h]	4	1.0-100.0	1.51	20 (100)	ns
d-sotalol	5	1.0-100.0	16.3	21 (100)	ns
clofilium	3	1.0-10.0	1.00	13 (10)	ns

[a] Number of experiments. [b] The concentration of compound that causes a 10% prolongation in the action potential duration (APD) at 90% repolarization. [c] The maximum percent increase in APD_{90} and the concentration at which this occurred. [d] The maximum percent change in the maximum rate of rise of the action potential. [e] Mp 219 °C dec, anal.: ($C_{21}H_{27}N_3O_3S$·2HCl) C, H, N. [f] The percent change in V_{max} (Δ%) was not significant. [g] Mp 230 °C dec, anal.: ($C_{21}H_{27}N_3O_3S$·2HCl) C, H, N. [h] Mp 200-203 °C, anal.: ($C_{20}H_{25}N_3O_3S$·2HCl) C, H, N.

The synthetic sequence leading to the methanesulfonanilides **1-3** is outlined in Scheme I. The Friedel-Crafts reaction of methanesulfonanilide **4**[12] with isonipecotic acid chloride **5**[13] in the presence of aluminum chloride afforded the benzoyl compound **6** in 82% yield. The protecting acyl group of **6** was hydrolyzed to give the key intermediate amine **7** (84%). The target compound **1** was prepared by

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(2) Reiser, H. J.; Sullivan, M. E. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1986**, *45*, 2206.

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(10) Recently, Lis and Lumma et al. prepared CK-1649 and CK-1752A, which also contain a methanesulfonanilide moiety: (a) Lis, R.; Davey, D. D.; Morgan, T. K., Jr.; Lumma, W. C., Jr.; Wohl, R. A.; Jain, V. K.; Wan, C.; Argentieri, T. M.; Sullivan, M. E.; Cantor, E. H. *J. Med. Chem.* **1987**, *30*, 2303. (b) 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. K.; Wiggins, J.; Wong, S. S. *J. Med. Chem.* **1987**, *30*, 758.

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Table II. Effects of 4'-[(4-Piperidyl)carbonyl]methanesulfonanilides and *d*-Sotalol on Cardiovascular System and Electrocardiogram after Intravenous Administration in Anesthetized Dogs[a,19]

compd	dose, mg/kg	QTc (Δ%)[b]	ERP (Δ%)[c]	HR (Δ%)[d]	mBP (Δ%)[e]	LV dP/dT_{max} (Δ%)[f]
1	0.003	13 ± 10	6 ± 0	−8 ± 3	−1 ± 1	4 ± 9
	0.01	37 ± 25	15 ± 2	−20 ± 6	−4 ± 1	15 ± 5
	0.03	52 ± 21	24 ± 4	−30 ± 7	−6 ± 1	25 ± 0
2	0.01	7 ± 6	11 ± 1	−6 ± 6	2 ± 6	7 ± 3
	0.03	15 ± 8	15 ± 3	−20 ± 5	−5 ± 6	13 ± 2
	0.1	21 ± 3	19 ± 6	−28 ± 6	−9 ± 6	13 ± 4
3	0.01	5 ± 2	6 ± 1	−3 ± 2	−2 ± 2	8 ± 4
	0.03	13 ± 7	10 ± 2	−8 ± 4	−2 ± 4	22 ± 10
	0.1	25 ± 12	19 ± 1	−17 ± 6	−8 ± 7	26 ± 17
d-sotalol	0.3	4 ± 1	5 ± 1	−6 ± 4	0 ± 2	−1 ± 6
	1.0	11 ± 3	14 ± 1	−19 ± 4	−7 ± 3	−4 ± 7
	3.0	23 ± 3	26 ± 2	−30 ± 6	−13 ± 2	5 ± 12

[a] All measurements were made at the time of maximum drug effect, i.e., >30 min. Values are mean ± SEM of four experiments. [b] The percent change in QTc interval. [c] The percent change in effective refractory period (ERP) of left ventricle. [d] The percent change in heart rate. [e] The percent change in mean blood pressure. [f] The percent change in the rate of left ventricular pressure (dP/dT).

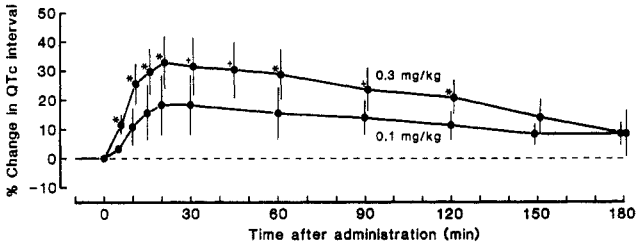

Figure 1. Intraduodenal efficacy of compound 1 on QTc interval of ECG in anesthetized dogs. The QTc interval was measured with standard lead II electrocardiogram according to the method described in ref 18a. A small insicion was made into the duodenum and a chatheter was inserted for administration. Compound 1 was injected as an aqueous solution. +, $p < 0.10$; *, $p < 0.05$ vs control. The values are mean ± SEM of four experiments.

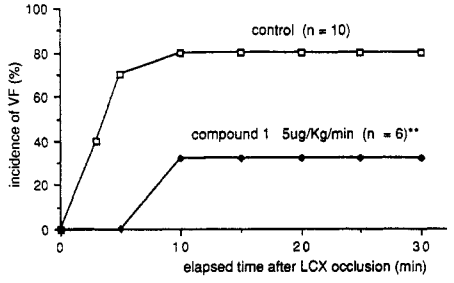

Figure 2. Antiarrhythmic effects of compound 1 on incidence of VF during early phase of ischemia in coronary ligated anesthetized dogs. The dogs were made hypokalemic by id administration of a potassium ion exchange resin and the left circumflex coronary artery (LCX) was occluded for 30 min. Compound 1 was infused intravenously prior to the ligation as an aqueous solution. **, $p < 0.01$ vs control.

the modified Michael reaction of **7** with 6-methyl-2-vinylpyridine (**8**)[14] in 81% yield. The compounds **2** and **3** were obtained by the alkylation of **7** with the corresponding pyridylalkyl halides **9**[15] and **10**,[16] respectively (66 and 57%).

The effects on action potentials were evaluated by using standard microelectrode recording techniques in isolated quinea pig right ventricular papillary muscles.[17] Table I shows the effects of compounds **1–3**, *d*-sotalol, and clofilium phosphate on action potential duration measured at 90% repolarization (APD_{90}) and the maximum rate of rise (V_{max}) of the action potential.[18]

Table III. Pharmacokinetic Parameters of 4'-[(4-Piperidyl)carbonyl]methanesulfonanilides in Plasma after Administration in Conscious Dogs[a]

compd	$t_{1/2}\beta$ h	$(AUC_{po}/AUC_{iv}) \times 100$ (%)[c]
1	1.3–1.4	56–58
2	2.2–2.9	61–76
3	1.4–2.1	72–79

[a] The compounds (10 and 50 mg/kg) were administered orally to beagles as a capsule mixed with glucose. All values were determined by two experiments for each dose. [b] Half-life of the β-elimination phase. [c] Values were extent of bioavailability and were estimated from the ratio of AUC (area under the concentration vs time curve) in plasma after po administration to that after iv administration.

The concentration of **1** that caused 10% prolongation in APD_{90} ($C_{10}APD_{90}$) was 0.13 μM. This class III activity was approximately 8 and over 100 times more potent than that of clofilium phosphate and *d*-sotalol, respectively. The 3-pyridylpropyl derivative **2** increased APD_{90} to a similar extent as **1** (i.e. $C_{10}APD_{90}$ = 0.19 μM). It should be noticed that all of the compounds **1–3** selectively prolonged APD_{90} with minimal decrease of V_{max} (<10%) and that they did not block β receptors (data not shown). These in vitro results clearly demonstrate that the compounds **1–3** were highly selective class III agents.

In vivo electrophysiological effects were studied after intravenous administration (iv) to anesthetized dogs (Table II).[19] Compound **1** selectively increased the QTc interval

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(17) Right ventricular papillary muscles of male Hartley guinea pig (300–500 g) were anchored in a tissue bath and perfused with Tyrode's solution. The solution was saturated with a 95:5 O_2/CO_2 mixture and kept at 37 °C. The muscles were stimulated at 1 Hz with rectangular pulses of 1-ms duration and at the strength of supramaximal voltage. Action potentials were recorded with a glass microelectrode (3 M KCl). Parameters measured were action potential duration (APD) at 50% and 90% repolarizations, maximum upstroke velocity (V_{max}), and action potential amplitude.

(18) The decrease in V_{max} of action potential is generally caused by the blockade of sodium cannels and is defined as class I activity.

and ERP (0.003–0.03 mg/kg). Compound 2 showed similar high class III activity (0.01–0.10 mg/kg). *d*-Sotalol prolonged QTc interval at doses higher than 0.10 mg/kg. The relative potency of 1 to *d*-sotalol in in vivo experiments was similar to that in the in vitro study.

The pharmacokinetic properties of compounds 1–3 were assessed in conscious dogs (Table III). All of the compounds 1–3 were orally bioavailable (56–79%) and had moderate half-lives (i.e., $t_{1/2}\beta$ = 1.3–2.9 h).

Figure 1 shows the effects of intraduodenal (id) administration of 1, the most active compound in vivo, on QTc intervals at doses of 0.10 and 0.30 mg/kg. The changes in the QTc interval were dose-dependent. The maximum response after id administration of 0.30 mg/kg was comparable to that after iv administration of 0.10 mg/kg. The prolongation of the QTc interval was significant even after 2 h.

Compounds that selectively prolong ERP in an in vivo system are expected to prevent VF by suppressing reentrant impulses in cardiac tissue.[1] Therefore, the antiarrhythmic effects of 1 on VF were further investigated in anesthetized coronary ligated dogs (Figure 2).[20] Iv infusion (5 μg/kg per min) of 1 during the ligation reduced the incidence of VF. This result suggests the potential utility of 1 in the prevention of VF associated with acute myocardial ischemia.

In conclusion, the present study shows that 4′-[(4-piperidyl)carbonyl]methanesulfonanilides have selective class III activities. Of these, compound 1 (E-4031) is one of the most potent and bioavailable class III antiarrhythmic agents. Compound 1 is now in clinical trials. Further details of the medicinal chemistry of a series of 1–3 will be described in forthcoming publications.

Acknowledgment. We thank members of the Analytical Chemistry Section of our laboratories for interpretation of the mass spectra and elemental analysis data.

Registry No. 1 (free base), 113558-89-7; 1·2HCl, 113559-13-0; 2 (free base), 124536-77-2; 2·2HCl, 113559-12-9; 3 (free base), 113558-75-1; 3·2HCl, 113559-11-8; 4, 1197-22-4; 5, 59084-16-1; 6, 113558-94-4; 7, 113559-02-7; 8, 1122-70-9; 9, 17944-59-1; 10, 4226-36-2.

(19) (a) Mongrel dogs (8–16 kg) of either sex were anesthetized with enflurane and nitrous oxide. The right femoral artery and vein were cannulated to monitor aortic blood pressure and for the administration of test compound, respectively. Left ventricular pressure was monitored with use of a microtip catheter transducer into the left ventricle from left femoral artery. LV dP/dT was obtained by mechanical differential of left ventricular pressure. Heart rate (HR) was mechanically counted from the figure of the left ventricular pressure. QT interval of lead II ECG was calculated as the mean of measurments from three consecutive beats. Corrected QT (QTc) was calculated according to Bazett's formula: $QTc = QT/RR^{1/2}$. (b) In other mongrel dogs, the heart was exposed through a lateral thracotomy, and unipolar electrodes were sutured onto the surface of the left ventricle to monitor ventricular surface ECG. Effective refractory periods (ERPs) were measured by cathodal stimulation through each of three unipolar electrodes on a left ventricle with rectangular pulses of 3-ms duration at twice the diastolic threshold. A programmed single premature ventricular stimulus (S_2) was delivered after fixed-rate ventricular pacing (S_1) at a cycle length of 600 ms. The interval between S_1 and S_2 was decreased in 5-ms steps until S_2 was no longer captured. ERP was defined as the longest S_1–S_2 interval that did not elicit a ventricular capture, and ERP of an left ventricle was calculated as the mean of three sites of the left ventricular surface.

(20) Nomoto, K.; Katoh, H.; Sawada, K.; Shoji, T. *J. Mol. Cell Cardiol.* **1989**, *21*, Suppl II, s-20, 60.

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Neural Networks Applied to Structure–Activity Relationships

Sir:

The neural network is a computer-based system derived from the simplified concept of the brain in which a number of node, called processing elements or neurons, are interconnected in a netlike structure.[1] The characteristics of the neural network have been found to be suitable for data processing in which the relationship between the cause and its results cannot be exactly defined. Thus its use in biology-related responses is strongly suggested. Another prominent characteristic of the neural network is its ability to classify or grade. Therefore, we tried to apply neural networks to the study of structure–activity relationships (SAR) and obtained promising results.

Shown in Figure 1 is the neural network: the circles are neurons which are actually variables taking values ranging from 0 to 1. The number of the layers is arbitrary and the network generally consists of n layers. The data are input to A and are output from B. The value of a neuron (O_j) at the nth layer can be expressed by eq 1, where x_i is one

$$O_j = 1/[1 + \exp(-\alpha y_j)] \equiv f(y_j),\ y_j = \sum W_{ij}x_i - \theta_j \quad (1)$$

of the values of the neurons at the $n - 1$ layer; W_{ij}, an element of the weight matrix, expresses the weight value between neurons i and j; θ_j is a threshold value for neuron j; and α is a parameter which expresses the nonlinearity of the neuron's operation. On feeding the input data into A, the value of every neuron expressed by eq 1 is synchronously changed. The training is carried out according to the back-propagation algorithm[1] until

$$E = \sum(O_j - t_j)^2 \quad (2)$$

becomes small enough (where t is a training pattern (a vector)) to give a fixed-weight matrix. Even in the case that M sets of the input and training patterns are given, all of output patterns can be made close enough to the training patterns by the iteration through eq 1 and the back-propagation procedure. Then, the neural network has an ability to classify the input patterns into M groups.[2]

Table I. Parameters of Neural Networks

A				B			
layer	neurons	α	θ	layer	neurons	α	θ
1	6			1	7		
2	12	2.5	0.0	2	14	2.5	0.0
3	5	5.0	0.0	3	4	5.0	0.0

(1) For example: *Parallel Distributed Processing Exploration in Microstructure of Cognition*; Rumelhart, D. E., McClelland, J. L., Eds.; the MIT Press: Cambridge, MA, 1986; Vols. 1 and 2.

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