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Communications to the Editor

Rational Design of 4-[(Methylsulfonyl)amino]benzamides as Class III Antiarrhythmic Agents

Sir:

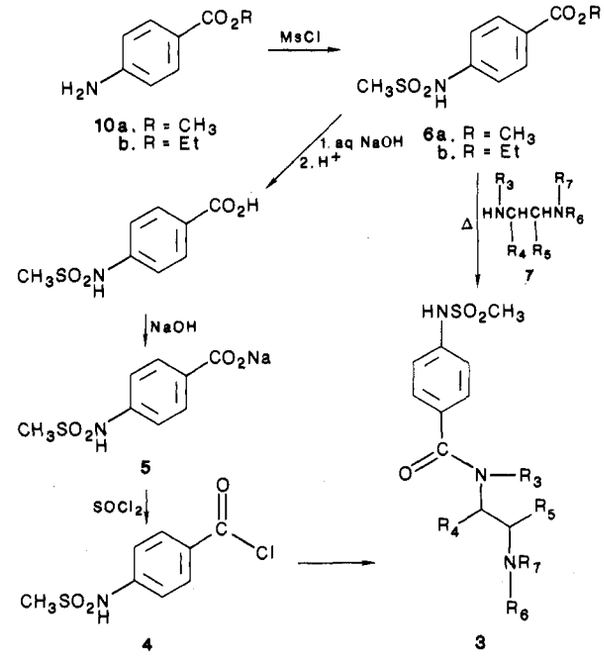
Sudden cardiac death occurs for more than 400 000 Americans each year.[1] It is generally accepted that ventricular arrhythmias play a major role in these deaths. For example, in a study of 123 patients by Graboys et al., advanced grades of ventricular tachycardia could be controlled in 98 patients (80%, group A), but in 25 patients (20%, group B) only partial control could be achieved with a variety of antiarrhythmic drugs.[2] Mortality in group A from sudden cardiac death was 2.3% annually vs. 43.6% in group B during 19–32 months follow-up periods.

There are three main approaches to controlling reentrant ventricular arrhythmias. One is blockade of conduction (class I antiarrhythmics) of abnormal impulses by slowing electrical conduction in conducting tissue and ventricular muscle, a second is suppression of ectopic foci which may trigger such reentrant arrhythmias (class I and II antiarrhythmics), and a third is increasing refractoriness (class III and certain class I antiarrhythmics) in cardiac tissue.[3]

Class I antiarrhythmic agents are widely used for their conduction slowing (local anesthetic) effects. Class II agents (β-adrenergic blockers) are effective in arrhythmias related to catecholamine release and in the postmyocardial infarct setting[4] where sudden death is a prevalent cause of mortality. A given class I agent is effective in only 10–30% of patients analyzed by programmed electrical stimulation (PES) and frequently must be discontinued due to gastrointestinal, hemodynamic, or central nervous system side effects.[5] In addition, all such agents can be proarrhythmic by the same mechanisms by which they suppress arrhythmias.[6]

Class III antiarrhythmic agents[7] such as bretylium, amiodarone, and clofilium are thought to exert their primary antiarrhythmic effects by prolonging action potential duration (APD) and thereby increasing refractoriness with little or no effect on conduction. Of these only clofilium can be regarded as a selective class III agent. Clearly, there is a need for additional safe and efficacious agents acting by this mechanism since the drugs mentioned have other major pharmacological effects or unpredictable pharmacokinetic behavior that limit their utility.

Scheme I. Synthetic Methods



In the present work, we began with the knowledge of the striking difference in electrophysiological actions of procainamide (1) (PA) and its *N*-acetyl derivative **2** (NAPA). The former, a relatively pure class IA antiarrhythmic, is acetylated in humans to form *N*-acetylprocainamide **2**,[8] primarily a class III agent.[9] The problem is that this transformation is variable and reversible in vivo and allows for manifestation of the toxic effects of procainamide. Our hypothesis was that an amide function was essential for the class III activity of **2** and that a more stable amide, such as methanesulfonamide, would prove advantageous. Sotalol, a β-adrenergic blocker with class III activity (class II/III agent) also contains the (methylsulfonyl)amino group.

We thus synthesized (Scheme I) compound **3a** (CK-1752) and compared its effects to those of **1** and **2** on the APD of canine Purkinje fibers in vitro (Figure 1). The data (see also Table II) show that compound **3a** is >50 times as potent as **2** in prolonging APD and that, in agreement with the literature, compound **2** prolongs APD

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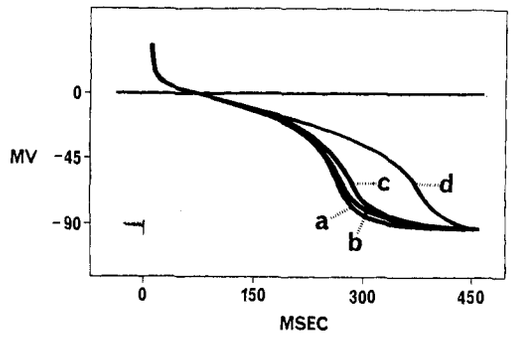


Figure 1. Electrophysiological effects in isolated canine Purkinje fibers. a, control; b, procainamide (1) at 10 μM, ΔAPD_{95} = +1%; c, *N*-acetylprocainamide (NAPA, 2) at 10 μM, ΔAPD_{95} = +3%; d, compound **3a** (CK-1752A) at 10 μM, ΔAPD_{95} = +32%.

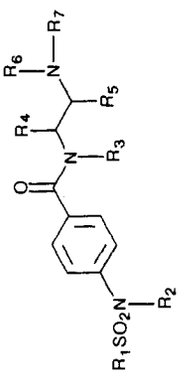
with minimal effect on maximal rate of depolarization ($\dot{V}_{max}$). Synthetic methodology and structure–activity relationships within this novel[10] series of antiarrhythmic benzamide drugs will be discussed in light of their unique physicochemical properties.

Methods and Results

Pharmacology. Screening for electrophysiological effects was carried out in two in vitro systems. Standard electrophysiological techniques were used to determine APD_{95} and $\dot{V}_{max}$ in isolated canine Purkinje fibers by the method previously described[11] (intracellular screen). Extracellular measurements of functional refractory periods (FRP) and conduction time (CT) were carried out in canine ventricular muscle strips by the extrastimulus technique. This screen represents an in vitro adaptation of the in vivo method of Carson and Dresel.[12] To meet our criteria of selective class III electrophysiological action, an active compound must prolong APD_{95} and FRP by 20% (C_{20}) with minimal effects on $\dot{V}_{max}$ (<10% decrease at 10 or 100 μM) and CT (<10% increase at 10 or 100 μM). With the exception of **3k** (see below), none of the new compounds significantly decreased $\dot{V}_{max}$; conduction time was minimally affected in all cases. In our experience, most compounds of the benzamide series **3** show parallel activity in both in vitro screens. Compounds that were inactive or very weakly active in both screens were not studied in vivo. Active compounds were retested. Only the compounds with the best in vitro profile were then selected for in vivo testing.

In vivo electrophysiological studies were conducted in dogs by modification of literature methods. Programmed electrical stimulation techniques were used to determine antiarrhythmic efficacy in anesthetized dogs[13] with a two-stage infarct according to the method of Harris[14a] and in chronically instrumented conscious dogs infarcted by an occlusion–reperfusion technique similar to the method of Karagueuzian et al.[14b] This latter model is considered

Table I. Structures and Physicochemical Data of 4-[(Alkylsulfonyl)amino]benzamides **3**



compd	R_1	R_2	R_3	R_4	R_5	R_6	R_7	salt (mp, °C)	formula	analyses
3a	CH_3	H	H	H	H	Et	Et	HCl (141–142)	$C_{14}H_{23}N_3O_3S\cdot HCl$	C, H, Cl, N, S
3b	CH_3	CH_3	H	H	H	Et	Et	HCl (142–145)	$C_{15}H_{25}N_3O_3S\cdot HCl$	C, H, Cl, N, S
3c	Et	H	H	H	H	Et	Et	HCl (146–148)	$C_{15}H_{25}N_3O_3S\cdot HCl$	C, H, Cl, N, S
3d	CF_3	H	H	H	H	Et	Et	(207.5–209)	$C_{14}H_{20}F_3N_3O_3S$	C, H, F, N, S
3e	CH_3	H	$CH_2CH{=}CH_2$	H	H	Et	Et	H_3PO_4 (90–98)	$C_{17}H_{27}N_3O_3S\cdot H_3PO_4\cdot 1.5H_2O$	C, H, N, P, S
3f[a]	CH_3	H	H	$-(CH_2)_4-$		Et	Et	HCl·0.3EtOH[d]	$C_{18}H_{29}N_3O_3S\cdot HCl\cdot 0.3EtOH$	C, H, Cl, N, S
3g[b]	CH_3	H	H	$-(CH_2)_4-$		Et	Et	HCl (228–231)	$C_{18}H_{29}N_3O_3S\cdot HCl\cdot 0.25\ H_2O$	C, H, Cl, N, S
3h[c]	CH_3	H	H	$-(CH_2)_4-$		Et	Et	HCl (228–231)	$C_{18}H_{29}N_3O_3S\cdot HCl\cdot 0.75\ H_2O$	C, H, Cl, N, S
3i	CH_3	H	H	H	H	Et	n-C_7H_{15}	H_3PO_4 (163)	$C_{19}H_{33}N_3O_3S\cdot H_3PO_4$	C, H, N, P, S
3j	CH_3	H	H	H	H	H	Et	HCl (238–242.5)	$C_{12}H_{19}N_3O_3S\cdot HCl$	C, H, Cl, N, S
3k	CH_3	H	H	H	H	H	n-C_7H_{15}	HCl (252–257)	$C_{17}H_{29}N_3O_3S\cdot HCl$	C, H, N
3l	CH_3	H	H	R_4CHCHR_5 = $-(CH_2)_3-$		Et	Et	H_3PO_4 (247–250)	$C_{15}H_{25}N_3O_3S\cdot H_3PO_4$	C, H, N, P, S

[a] *RS*. [b] (+) enantiomer (1*S*-trans). [c] (−) enantiomer (1*R*-trans). [d] (188–189).

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Table II. Biological Data of 4-[(Alkylsulfonyl)amino]benzamides

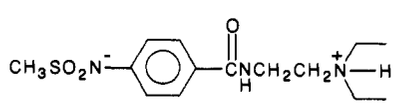
	Purkinje fiber[a]		ventricular muscle[b]		efficacy in dog[c]	
compd	n[d]	$C_{20}APD_{95}$,[e] μM (range)	n[d]	$C_{20}FRP$,[f] μM (range)	anesth[g] (iv)	conscious[h] (iv)
3a	6	3.5 (2.0–11.4)	46	17 ($9 < M < 35$)[i]	4/4 (1)	5/6 (1)[j]
3b	2	NR[k]	1	NR	NT	NT[l]
3c	2	NR	1	NR	NT	NT
3d	2	NR	1	NR	NT	NT
3e	4	0.5 (0.2–5)	2	0.5 (0.3–1.1)	5/9 (0.8)	NT
3f	2	1.9 (1.8–2.0)	3	3 (1.2–150)	3/4 (1.0)	4/4 (0.5)
3g	5	3.0 (1.6–44)	3	0.3 (0.03–2.1)	3/6 (1.4)	5/6 (1.9)
3h	5	0.4 (0.2–0.5)	5	40 (5.6–1200)	4/4 (0.5)	5/5 (0.8)
3i	3	0.02 (0.01–0.03)	6	0.5 (0.05–3.7)	NT	NT
3j	2	NR	3	NR	NT	NT
3k	3	0.2 (0.08–5)[m]	4	4.0 (0.8–11)	NT	NT
3l	2	2.0 (1.0–34)	3	4.0 (1.6–25)	3/5 (1.4)	NT
2	4	NR[n]	4	60 (5.6–800)	4/4 (9)	NT
(∓)-sotalol	6	22 (9–63)	4	52 (9–4000)[o]	2/7 (1)[p]	4/4 (3)
clofilium	10	0.2 (0.03–2)[q]	4	NR[r]	7/10 (0.3)	5/6 (1)[s]

[a] Intracellular electrophysiology. Unless otherwise noted decreases in $\dot{V}_{max}$ (class I activity) were ≤10% for all compounds at 10 and 100 μM. Full $\dot{V}_{max}$ data are available in the supplementary material. [b] Extracellular electrophysiology. Increases in conduction time (CT) (class I activity) were ≤10% for all compounds at 10 and 100 μM. Full CT data are available in the supplementary material. [c] Efficacy in blocking sustained ventricular tachycardia (rate >250 bpm) elicited by programmed electrical stimulation. For each compound the number of successful experiments vs. the total number of experiments is given (mean effective dose in milligrams/kilogram in parentheses). [d] Number of experiments. [e] Concentration producing 20% increase in action potential duration of Purkinje fiber in vitro measured at 95% repolarization, stimulated at a basic driving frequency of 1.0 Hz. The mean value for n experiments is listed with the actual range given in parentheses. [f] Concentration producing a 20% increase in the functional refractory period of canine ventricular muscle in vitro stimulated at a basic driving frequency of 1.0 Hz. The mean value for n experiments is listed with the range given in parentheses where appropriate. [g] Transmural infarct, PES protocol run 24 h after infarction. [h] Mottled infarct, PES protocol run 3–8 days after infarction. [i] The median C_{20} value is listed. The 95% confidence limits for the median are given in parentheses. [j] When administered orally, the conscious dog **3a** was effective in 6/6 experiments at a mean dose of 2.5 mg/kg. [k] Not reached. [l] Not tested. [m] $\dot{V}_{max}$ decreased by 20% [−17%–(−23%)] at 100 μM. [n] A 10% increase in APD_{95} ($C_{10}APD_{95}$) was observed at 30 μM (22–40 μM). [o] The four values are 9, 20, 84, and 4000 (extrapolated) μM. [p] In our experience, animals used in this model are highly dependent on sympathetic tone to maintain viable cardiovascular function. Use of β-blockers (propranolol, timolol, nadolol, and sotalol) in this anesthetized, infarcted animal preparation frequently results in cardiovascular collapse and death. [q] $\dot{V}_{max}$ = −18% [50–(+1)] at 10 μM; −59% [−80–(−22)] at 100 μM. [r] At 10 μM the FRP was increased 13% [−3–(+38)]. [s] Data from: Kopia, G. A.; Eller, B. T.; Patterson, E.; Shea, M. J.; Lucchesi, B. R. *Eur. J. Pharmacol.* **1985**, *116*, 49.

predictive of the human clinical PES protocol. A compound was considered an effective antiarrhythmic agent if it prevented the induction of ventricular tachycardia in at least half of the animals studied.

Synthesis. The most obvious route to compound **3a**, namely methanesulfonylation of procainamide (1), gave **3a** contaminated by traces of 1. Forcing the reaction with excess CH_3SO_2Cl led to a number of byproducts. Synthesis of the acid chloride **4** required the sodium salt **5** and proved to be tedious (see Scheme I). Furthermore, since compounds **3** with few exceptions are highly water soluble and difficult to isolate by aqueous workup, the preferred method for their synthesis is heating the ester **6** neat in diamine **7**, followed by conversion of the crude amide **3** to its crystalline salt with an appropriate acid. By this method, compound **3a** was synthesized on a 100-kg scale (overall yield of >46%) with a purity of >99.7%.

Structure–Activity Relationships. The physicochemical properties of compounds **3** are markedly different from those of the corresponding carboxamide analogues such as *N*-acetylprocainamide (**2**). This difference stems in large part from the ionization of the acidic CH_3SO_2NH function in the pH range 7–9. Compound **3a** shows two ionization steps with apparent pK_{a1} = 7.60 and pK_{a2} = 9.51 (similar to sotalol pK_{a1} = 8.11, pK_{a2} = 9.65). Thus, at physiological pH, compound **3a** can be transported to various tissue compartments as the neutral species, cation, anion, and zwitterion (Z) which may contribute to its potency and efficacy in cardiac tissues. The octanol/buffer (pH 7.4) distribution coefficient of **3a** depends on concentration (0.104 ± 0.005 at 10 mM) and is not significantly different from that of *N*-acetylprocainamide (**2**) (0.24). The marked bathochromic shift in the ultraviolet spectrum of **3** in 0.1 N NaOH vs. 0.1 N HCl (HCl, λ_{max} 254 nm, ϵ = 1.78×10^4 LM^{-1} cm^{-1}) (NaOH, λ_{max} 289 nm, ϵ = 1.91×10^4 LM^{-1} cm^{-1}) is further evidence for the formation of the conjugate base.



3a (as zwitterion Z)

On the basis of in vitro data, substitution on the CH_3SO_2 carbon (**3c,d**) reduces activity and at R_2 (**3b**) abolishes activity. Substitution on the benzamide nitrogen retains activity (**3e**). Secondary amines (**3j**) are less active unless one of the N substituents is more lipophilic than Et (**3k**). While **3k** is a potent compound, it also shows significant class I activity at higher concentrations. Cyclic modifications of the side-chain diamine moiety (**3f–h**) generally lead to active compounds. Extension of the connecting chain to three C atoms (**3l**) does not diminish activity. Large (lipophilic) groups on the amine nitrogen lead to very potent compounds (e.g., **3i**) (see Tables I and II).

Noteworthy is the enantioselectivity shown for the 1-*S*-trans isomer (**3g**) in the ventricular muscle (n = 3); in our Purkinje fiber screen the 1-*R*-trans isomer (**3h**) seems slightly more potent (n = 5). Both compounds were efficacious in vivo. These important compounds show promise as probes of the relative importance of refractoriness in conductive vs. contractile tissue in the genesis of reentry arrhythmias (i.e., from different substrates) and in study of the phenomenon of "dispersion of refractoriness".[15]

In view of its overall profile, compound **3a** was chosen for further development for the therapy of life-threatening ventricular arrhythmias. It is a potent and selective class III anthiarrhythmic agent. It has low acute toxicity (LD_{50} ~ 250–300 mg/kg, ip, mouse), lacks mutagenic activity in

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the Ames bacterial assay, and is not metabolized to procainamide (dog). The compound is orally bioavailable (41–98%, dog, 3 mg/kg, po; elimination $t_{1/2} \approx 2.7$ h) and shows efficacy with a duration >2 h in canine models of reentrant ventricular tachycardia. Further details of medicinal chemistry and preclinical pharmacology are given in the supplementary material or will be reported in forthcoming publications.

Supplementary Material Available: Synthetic procedure for **3a**, pharmacology procedures (intracellular electrophysiology, extracellular electrophysiology, intraduodenal bioavailability, and PES protocol) and additional V_{max} and CT data (Table III) (14 pages). Ordering information is given on any current masthead page.

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Articles

Synthesis and Biological Activity of Partially Modified Retro-Inverso Pseudopeptide Derivatives of the C-Terminal Tetrapeptide of Gastrin

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The effects of partial retro-inverso modifications of selected peptide bonds of the N-terminal tetrapeptide of gastrin have been studied. In some of the synthesized compounds, the phenylalanyl residue has been replaced by the (*R,S*)-2-benzylmalonyl, 3-phenylpropionyl, benzylcarbamoyl, or benzyloxycarbonyl moieties. All pseudopeptides showed affinity for the gastrin receptor, in vitro, with potencies varying from $IC_{50} = 10^{-7}$ to $IC_{50} = 10^{-4}$ M. These compounds exhibited little or no activity on acid secretion in the anesthetized rat but were able to antagonize the action of gastrin. Among the most potent were Boc-Trp-Leu-gAsp-CO-$CH_2CH_2C_6H_5$ (**20**) ($ED_{50} = 0.15$ μM/kg), Boc-Trp-Leu-gAsp-m(*R,S*)Phe-NH_2 (**3**) ($ED_{50} = 0.15$ μM/kg), and Boc-Trp-gLeu-D-Asp-m(*R,S*)Phe-NH_2 (**7**) ($ED_{50} = 0.3$ μM/kg).

Gastrin, a polypeptide hormone, has been isolated from hog antral mucosa by Gregory and Tracy[1] and exists as gastrin I (sulfated form) and gastrin II (unsulfated form). Gastrin exhibits a wide range of biological actions, the most potent of which is stimulation of gastric acid secretion and antral smooth muscle activity.[2] Extensive structure–function relation studies in several laboratories have provided convincing evidence on the role of the C-terminal tetrapeptide of gastrin and of each of its amino acid residues. The biological potency of the gastrins is related to the C-terminal tetrapeptide amide Trp-Met-Asp-Phe-NH_2.[3] Replacement of the tryptophan lowers but does not destroy the activity. Many changes can be made at the methionine position without a resulting loss of activity (particularly the replacement by leucine or norleucine), whereas all changes affecting the aspartic acid lead to very weak or inactive compounds.[4] Although some modifications are permitted at the phenylalanyl residue, its suppression led to compounds that are able to antagonize the action of gastrin on acid secretion.[5] Removal of the terminal amide function resulted in completely inactive derivative on acid secretion,[4] whereas these compounds were able to recognize the gastrin receptor and to antagonize the action of gastrin on acid secretion.[6,7] We recently showed the significance of the peptide bonds of the C-terminal tetrapeptide of gastrin for the biological activity, particularly of the bond between methionine and aspartic acid.[8] For exhibiting biological activity on acid secretion, the bond between methionine and aspartic acid should be a peptide bond. Pseudopeptide derivatives in which this peptide bond has been replaced by a noncleavable bond, e.g., a CH_2NH bond, were shown to bind to the gastrin receptor and to inhibit gastrin-induced acid secretion[8,9] ($IC_{50} = 0.3$ μM, $ED_{50} = 0.45$ μM/kg). These results prompted us to hypothesize about the role of the C-terminal dipeptide of gastrin that might be the result of the

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