Synthesis and Pharmacological Studies of N-Substituted 6-[(2-Aminoethyl)amino]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinediones, Novel Class III Antiarrhythmic Agents[1]

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A series of 6-[(2-aminoethyl)amino]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione derivatives were synthesized and studied for their class III electrophysiological activity and class II (β-blocking) effects in in vitro and in vivo models. Structure–activity relationships are discussed for a series of compounds. Several members of this series prolonged the action potential duration at 75% repolarization of isolated canine Purkinje fibers and were 10–30-fold more potent than *d*-sotalol. 1,3-Dimethyl-6-[[2-[*N*-[3-(4-nitrophenyl)propyl]-*N*-(hydroxyethyl)amino]ethyl]amino]-2,4-(1*H*,3*H*)-pyrimidinedione (**40**), is one of the most potent compounds in this series.[2]

Sudden cardiac death due to ventricular arrhythmia has become a major public health problem in recent years. A number of antiarrhythmic agents (predominantly class I) are available for clinical use to prevent life-threatening arrhythmia. However no single agent is effective in all cases because of the variety of pathophysiological conditions associated with the development of lethal arrhythmia. The results of the cardiac arrhythmia suppression trial (CAST) have clearly shown that potential negative side effects of potent class I agents can outweigh their clinical benefits.[3] Under these circumstances, much attention is being directed toward the development of selective class III antiarrhythmic agents which homogeneously prolong the transmembrane action potential duration (APD) and, consequently, refractoriness, without slowing intercardiac conduction, and which can terminate reentry.[4]

A number of class III antiarrhythmic agents have been recently reported and are under clinical evaluation. These include *d*-sotalol (**2**),[5] which has weak β-blocking activity, sematilide (**3**),[6] and E-4031 (**4**).[7]

Pharmacological screening for new cardiovascular agents led us to discover the class III activity of 1,3-dimethyl-6-[[2-[[3-(2-fluorophenoxy)-2-hydroxypropyl]amino]-ethyl]amino]-2,4(1*H*,3*H*)-pyrimidinedione (**1**) (MS-3579), which we originally prepared as a β-blocking agent.[8] Since compound **1** lacks potency as a class III agent and its (aryloxy)propanolamine moiety was thought to be the typical β-blocking pharmacophore,[9] we decided to manipulate this moiety to diminish β-blocking activity and to potentiate class III activity. In this paper we present our efforts to prepare a series of 2,4(1*H*,3*H*)-pyrimidinedione derivatives for the development of novel class III selective agents with little or no β-blocking activities and also discuss the structure–activity relationships of these agents.

Chemistry

The synthetic routes toward target compounds **16–40** are depicted in Schemes I and II. Propanolamine **16** was readily obtained from ethylenediamine **5** and epoxide **6** (method A). Alkylation of amine **5** with alkyl bromide **7** in the presence of triethylamine yielded **19** (method B). Alternatively, alkylation of amine **5** with hydroxyalkyl bromide **8** and subsequent condensation with corresponding phenol **10** by the Mitsunobu reaction[10] afforded **21** (method C). Amine **12**, required for the preparation of **40**, was obtained from alcohol **11a** via *p*-toluenesulfonate **11b**. Alcohol **14a** was prepared from chloride **13** and

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(1) Presented in part at the 22nd National Medicinal Chemistry Symposium, Austin, TX, July 1990. MS-551, A Novel Class III Antiarrhythmic Agent: Synthesis and Activities. Poster abstracts, p 78.
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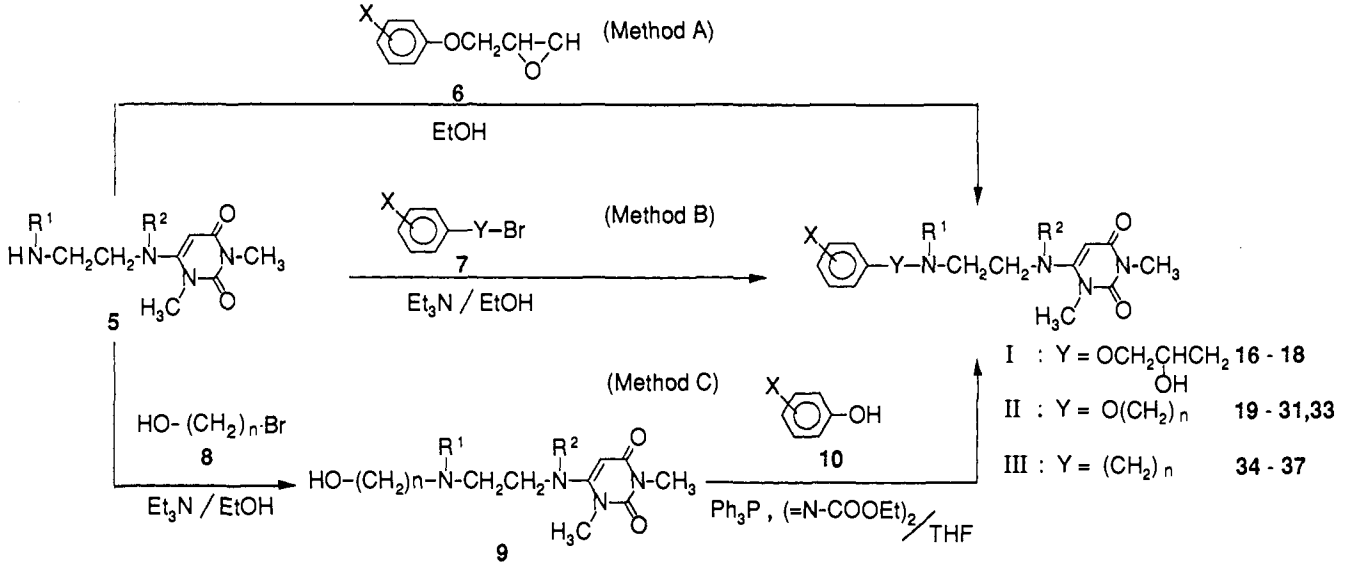
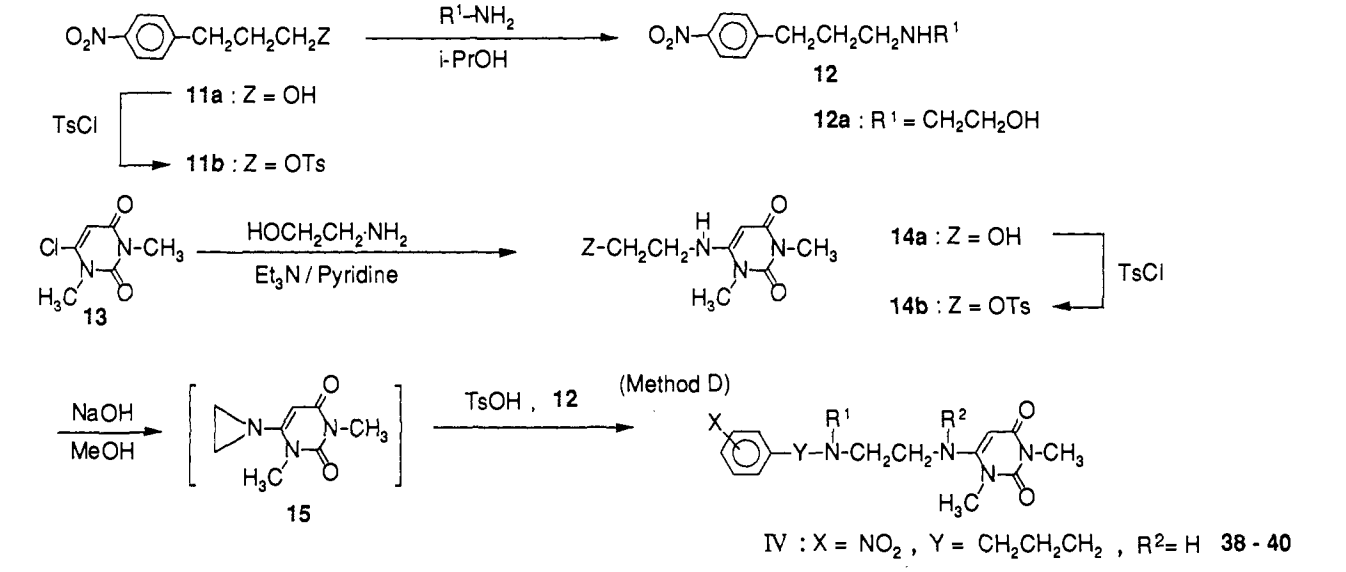
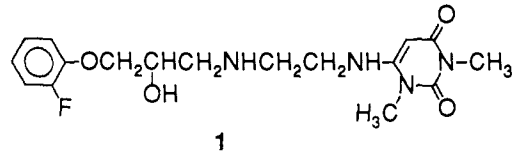
Scheme I



Scheme II





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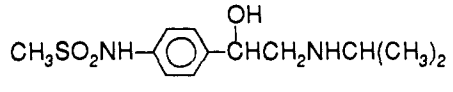
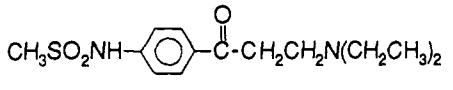


Sotalol 2



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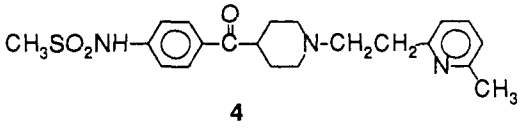

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Figure 1.

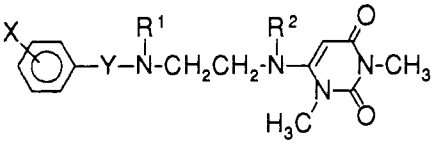
ethanolamine, and then converted to *p*-toluenesulfonate **14b** with *p*-toluenesulfonyl chloride. Aziridine **15**, prepared from *p*-toluenesulfonate **14b** by treatment with NaOH in MeOH, was made to react with amine **12** in the presence of a catalytic amount of *p*-toluenesulfonic acid to obtain **40** (method D).

Pharmacological Results and Discussion

Our initial screening for electrophysiological activity was carried out with canine cardiac Purkinje fibers as described in the Experimental Section. The activities of each compound at concentrations of 1, 3, or 10 μg/mL were expressed by the percent change of action potential duration (APD).[11] β-Blocking activity was determined by the dose of the compound required for 50% inhibition (ID_{50}) of tachycardia induced by isoproterenol (0.5 μg/kg, iv) in anesthetized dog. The prolongation effect of the atrial and ventricular effective refractory period (ERP)[12] was mea-

(11) Satoh, H.; Ishii, M.; Hashimoto, K. Effect of Cibenzoline, a Class III Antiarrhythmic Drug, on Action Potential in Canine Ventricular Muscle. *Jpn. J. Pharmacol.* 1987, *44*, 113–119.

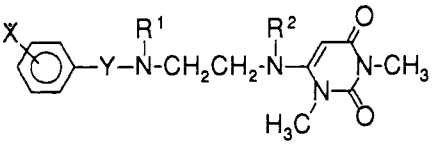
Table I. Physical Properties and Pharmacological Data of Compounds (I and II)



compd	X	Y	R^1	R^2	mp, °C (recrystn solvent)[a]	formula[b]	% yield (prepn method)	β_1-blocking act.:[c] ID_{50} (mg/kg, iv)	% APD_{75}[d] at concn in μg/mL 1.0	3.0	10.0
1	(MS-3579)							0.003	4.1	8.3	15.6
16	H	$-OCH_2CH(OH)CH_2-$	H	H	182–184 (A)	$C_{17}H_{24}N_4O_4 \cdot 2HCl \cdot EtOH$	22 (A)	0.01		6.9	10.1
17	H	$-OCH_2CH(OH)CH_2-$	CH_3	CH_3	amorphous (A)		64	1	2.9	8.0	
18	H	$-OCH_2CH(OH)CH_2-$	$-CH_2CH_2-$		199–201 (B)	$C_{19}H_{26}N_4O_4 \cdot 2HCl$	81 (A)	>5	3.5	13.7	
19	H	$-OCH_2CH_2CH_2-$	H	H	218–220 (B)	$C_{17}H_{24}N_4O_3 \cdot HBr \cdot 0.5H_2O$	7 (B)	0.1–1	4.0	11.9	
20	H	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		185–187 (C)	$C_{19}H_{26}N_4O_3 \cdot CH_3SO_3H$	56 (B)	>5	7.0	22.0	
d-sotalol									0.7	8.0	11.2
sematilide									19.0	29.0	

[a] A = hexane/EtOH; B = EtOAc/MeOH; C = $CHCl_3$. [b] Analyses were within 0.4% of the calculated value. [c] Dose required for 50% inhibition of tachycardia induced by isoproterenol (0.5 μg, iv) in anesthetized dog. Three experiments each were done unless otherwise stated. [d] See Experimental Section. Three experiments each were done unless otherwise stated.

Table II. Physical Properties and Pharmacological Data of Compounds (II)



compd	X	Y	R^1	R^2	mp, °C (recrystn solvent)[a]	formula[b]	% yield (prepn method)	% APD_{75}[d] at concn in μg/mL 1.0	3.0	10.0	% ERP[c] at concn in mg/kg 0.3	1.0	3.0
21	4-F	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		234–236 (A)	$C_{19}H_{25}N_4FO_3 \cdot HCl \cdot 0.25H_2O$	70 (C)	9.0	13.0		5.9	5.9	11.8
22	4-Cl	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		253–254 (B)	$C_{19}H_{25}N_4ClO_3 \cdot HCl$	82 (B)	14.0	25.0		6.3	13.0	24.3
23	3-Cl	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		249–252 dec (C)	$C_{19}H_{25}N_4ClO_3 \cdot HCl$	54 (B)		6.0	7.0			
24	2-Cl	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		246–247.5 dec (C)	$C_{19}H_{25}N_4ClO_3 \cdot HCl \cdot H_2O$	49 (B)		0	7.0			
25	4-SCH_3	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		186–188 dec (C)	$C_{20}H_{28}N_4O_3S \cdot HCl \cdot H_2O$	20 (B)	4.0	13.0	25.0	0	7.7	15.4
26	2-SCH_3	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		215 (C)	$C_{20}H_{28}N_4O_3S \cdot HCl \cdot H_2O$	78 (C)	0	0	0			
27	4-NO_2	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		244–246 dec (C)	$C_{19}H_{25}N_5O_5 \cdot 2HCl$	80 (B)	17.0	22.0	30.0	12.0	15.8	25.3
28	3-NO_2	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		143–144 (C)	$C_{19}H_{25}N_5O_5 \cdot HCl \cdot CH_3OH$	67 (B)	15.0	34.0		0	7.0	14.0
29	2-NO_2	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		251–252 dec (C)	$C_{19}H_{25}N_5O_5 \cdot HCl$	71 (B)		18.0	39.0	0	6.8	13.6
30	4-NH_2	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		260 (D)	$C_{19}H_{27}N_5O_3 \cdot 2HCl \cdot 0.5H_2O$	68[e]		4.0				
31	4-SO_2NH-CH_3	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		249–251 (A)	$C_{20}H_{29}N_5O_5S \cdot HCl \cdot 0.5H_2O$	62 (B)		0				
32	4-$NHSO_2$-CH_3	$-OCH_2CH_2CH_2-$	$-CH_2CH_2-$		263–267 dec (C)	$C_{20}H_{29}N_5O_5S \cdot HCl$	52[e]	1.0	3.0	10.0	7.1	9.3	16.4
d-sotalol								0.7	8.0	11.2	7.0	9.0	16.0

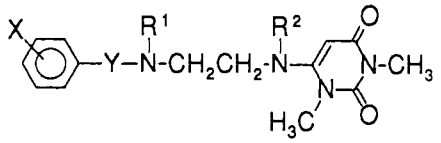
[a] A = EtOH; B = hexane/EtOH; C = MeOH; D = EtOAc/MeOH. [b,d] See corresponding footnotes in Table I. [c] See Experimental Section. Three experiments each were done unless otherwise stated. [e] See Experimental Section.

sured by the extrastimulus technique with open-chest anesthetized dogs. The results of these in vitro and in vivo studies are summarized in Tables I–III. We started with the structural modification of compound 1, which is equipotent with *d*-sotalol and has potent β-blocking activity. First, we examined the effects of introduction of substituents onto the ethylenediamine. *N,N'*-Dimethyl derivative **17** showed relatively weak β-blocking activity and moderate class III activity. When the ethylenediamine moiety was exchanged for piperazine, the β-blocking activity substantially diminished (**18**). Although (aryloxy)-propanolamine is a typical structural feature of β-blockers, the oxidation state of C-2 in the propyl ether does not seem to be essential for class III activity in this series of compounds. The deshydroxy derivatives (**19,20**) showed more potent class III activity than their corresponding hydroxy compounds (**16,18**).

We next explored the effects of substituents on the aromatic ring with (phenoxypropyl)piperazine type compound **20** (Table II). Introduction of the substituents at the 2- or 3-position on the phenyl ring resulted in reduction of the potency except for the nitro substituent. In contrast, most of the compounds substituted with lipophilic substituents at the 4-position consistently showed high potency. However, introducing hydrophilic substituents, such as amino and (methylamino)sulfonyl, led to substantial reduction in potency (**30,31**). Furthermore, the (methyl-

(12) Satoh, H.; Hashimoto, K. Effect of 3,4-Dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperiazinyl]-2(1*H*)-quinolinone (OPC-8212) on the Membrane Currents of Rabbit Sino-atrial Node Cells. *Arzneim.-Forsh.* **1984**, *34* (1), 3a, 376–380.

Table III. Physical Properties and Pharmacological Data of Compounds (II–IV)



compd	X	Y	R^1	R^2	mp, °C (recrystn solvent)[a]	formula[b]	% yield (prepn method)	% APD_{75}[d] at concn in μg/mL			% ERP[c] at concn in mg/kg		
								1.0	3.0	10.0	0.3	1.0	3.0
33	4-NO_2	$-OCH_2CH_2-$	$-CH_2CH_2-$		257.5–259.5 dec (A)	$C_{18}H_{23}N_5O_3 \cdot HCl \cdot 0.5H_2O$	80 (C)	8.0	22.0	43.0	23.0	30.1	
34	4-NO_2	$-CH_2CH_2CH_2CH_2-$	$-CH_2CH_2-$		202–205.5 (B)	$C_{20}H_{27}N_5O_4 \cdot HCl$	70 (B)		17.0	25.0			
35	4-NO_2	$-CH_2CH_2CH_2-$	$-CH_2CH_2-$		153–156 dec (A)	$C_{19}H_{25}N_5O_4 \cdot (COOH)_2 \cdot 1.5H_2O$	19 (B)	17.0	22.0	31.0	14.3	17.9	21.4
36	4-NO_2	$-CH_2CH_2-$	$-CH_2CH_2-$		263–266 dec (C)	$C_{18}H_{23}N_5O_4 \cdot HCl \cdot 0.5H_2O$	61 (B)	43.0			33.5		
37	4-NO_2	$-CH_2-$	$-CH_2CH_2-$		211–212 dec (C)	$C_{17}H_{21}N_5O_4 \cdot (COOH)_2$	73 (B)	3.0	7.0	11.0	0	0	7.0
38	4-NO_2	$-CH_2CH_2CH_2-$	H	H	206–207 (C)	$C_{17}H_{23}N_5O_4 \cdot (COOH)_2$	27 (D)	9.0	12.0	16.0			
39	4-NO_2	$-CH_2CH_2CH_2-$	Et	H	amorphous (C)	$C_{19}H_{27}N_5O_4 \cdot HCl$	77 (D)	11.0	16.0		11.1	16.7	16.7
40	4-NO_2	$-CH_2CH_2CH_2-$	C_2H_4OH	H	172–174 (C)	$C_{19}H_{27}N_5O_5 \cdot HCl$	89 (D)	22.0	38.0		10.7	21.4	
d-sotalol								0.7	8.0	11.2	7.0	9.0	16.0

[a] A = ether/MeOH; B = MeOH/$CHCl_3$; C = MeOH. [b,d] See corresponding footnotes in Table I. [c] See corresponding footnotes in Table II.

Table IV. Effects of Compound **40** on the Action Potential Parameters of Canine Purkinje Fibers[a]

concentration (μg/mL)	RMP[b] (mV)	APA[c] (mV)	APD_{50}[d] (ms)	APD_{75}[d] (ms)	APD_{90}[d] (ms)	max dV/dt (V/s)
0	−88 ± 2	104 ± 6	266 ± 27	313 ± 30	344 ± 34	356 ± 26
0.1	−85 ± 4	101 ± 6	293 ± 21	340 ± 29	371 ± 32	351 ± 29
0.3	−87 ± 2	102 ± 7	315 ± 34*	372 ± 47*	409 ± 54*	348 ± 29
1	−87 ± 3	103 ± 6	349 ± 32**	428 ± 48**	471 ± 55**	344 ± 35
3	−87 ± 4	104 ± 7	369 ± 41**	485 ± 59**	533 ± 68**	341 ± 41
10	−90 ± 5	107 ± 8	386 ± 48**	529 ± 62**	584 ± 76**	339 ± 48

[a] Values are shown as means ± SD of seven experiments. (*) $p < 0.05$, (**) $p < 0.01$, as compared to the control values. [b] RMP; resting membrane potential. [c] APA; action potential amplitude. [d] $APD_{50,75,90}$; action potential duration at 50, 75, and 90% repolarization.

sulfonyl)amino moiety, which had been noted as an optimal substituent for class III agents by other workers,[13] reduced the activity in this series of compounds.

Compounds that showed higher activities than *d*-sotalol in in vitro screening (APD), were extensively evaluated in in vivo electrophysiological studies (ERP). 4-Chloro (**22**) and 4-nitro (**27**) derivatives were effective in both in vitro and in vivo models. Compounds **25**, **28**, and **29** were very effective in vitro, but were less active in vivo.

Finally the propoxy chain, linking the phenyl ring to the basic region, was modified to optimize the class III activity. Replacement of oxygen atom with methylene did not affect the activity. Comparison of a series of homologous compounds (**27** and **33–37**) showed us that propylene (**35**) and ethylene (**36**) were most favorable for class III activity. However, **36** was ineffective in anesthetized canine ventricular tachyarrhythmia models.[14]

Because of limited solubility of **35** for intravenous administration, further manipulation was attempted to overcome this problem. Opening the piperazine ring of **35** gave **39** which was soluble enough for intravenous administration. Furthermore, introduction of a hydroxy group onto ethyl in **39** provided us with the more hydrophilic compound **40**, which had potent class III activity and no β-blocking effect.[15]

Compound **40**, which has good physical properties and low toxicity,[16] was extensively evaluated. The electrophysiological profiles of **40** are displayed in Table IV. Compound **40** prolonged cardiac action potential duration (APD) in canine Purkinje fibers without affecting parameters of action potential depolarization such as maximum upstroke velocity (max dV/dt).

We concluded that 1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione derivatives represent a potent new class of antiarrhythmic agents. Compound **40** (MS-551), one of the most potent agents and a class III selective one in this series is now undergoing clinical trials.

Experimental Section

Chemistry. Melting points were obtained on a Buchi capillary melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on a JEOL JNM-MH-100 (100 MHz) instrument. Infrared spectra were recorded with a JASCO IRA-2 spectrometer using KBr pellets. Elemental analyses were within 0.4% of the theoretical values unless otherwise stated. All structural assignments were consistent with IR and NMR spectra.

Method A. 1,3-Dimethyl-6-[4-(2-hydroxy-3-phenoxypropyl)piperazin-1-yl]-2,4(1*H*,3*H*)-pyrimidinedione (18). General Procedure. To a solution of 1,3-dimethyl-6-(1-piperazinyl)-2,4(1*H*,3*H*)-pyrimidinedione (**5**)[17] (3.14 g, 14 mmol)

(13) Morgan, T. K., Jr.; Lis, R.; Lumma, W. C., Jr.; Nickish, 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)benzamide—New Selective Class III Agents. *J. Med. Chem.* **1990**, *33*, 1091–1097.

(14) (a) Patterson, E.; Gibson, J. K.; Lucchesi, B. R. Postmyocardial Infarction Reentrant Ventricular Arrhythmias in Conscious Dogs: Suppression by Bretylium Tosylate. *J. Pharmacol. Exp. Ther.* **1981**, *216* (3), 453–458. (b) Gibson, J. K.; Lucchesi, B. R. Electrophysiological Action of UM-272 (Pranolium) on Reentrant Ventricular Arrhythmias in Postinfarction Canine Myocardium. *J. Pharmacol. Exp. Ther.* **1980**, *214* (2), 347–353.

(15) The ID_{50} Value (β1-blocking activity) of compound **40** is larger than 5 mg/kg, iv.

(16) Yoshinari, M.; Toizumi, S.; Kamiya, J. Unpublished results.

in ethanol (30 mL) was added a solution of 1-phenoxy-2,3-epoxypropane (6) (2.4 g, 18 mmol) in ethanol (20 mL) dropwise with stirring at 80 °C. After refluxing for 2 h, the reaction mixture was concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$/MeOH, 100:1 to 50:3) and recrystallized from MeOH/ether to give 18 (5.0 g, 95%): mp 146–147 °C.

Method B. 1,3-Dimethyl-6-[4-[3-(4-Chlorophenoxy)propyl]piperazin-1-yl]-2,4(1*H*,3*H*)-pyrimidinedione (22). General Procedure. To a solution of 3-(4-chlorophenoxy)propyl bromide (2.5 g, 10 mmol) and 5 (1.3 g, 5.8 mmol) in ethanol (10 mL) was added triethylamine (3 mL), and the resulting solution was refluxed for 3 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in $CHCl_3$ and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. Recrystallization of the residue from ethanol/hexane gave 22 (1.96 g, 86%) as colorless crystals: mp 130–131 °C.

1,3-Dimethyl-6-[4-(3-hydroxypropyl)piperazin-1-yl]-2,4-(1*H*,3*H*)-pyrimidinedione (9). A mixture of 1,3-dimethyl-6-(1-piperazinyl)-2,4(1*H*,3*H*)-pyrimidinedione (14.1 g, 63 mmol), 3-bromo-1-propanol (11.7 g, 84 mmol), and triethylamine (13 g, 128 mmol) in ethanol (250 mL) was refluxed for 20 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in $CHCl_3$ (300 mL) and washed with water (100 mL × 2). The organic layer was dried over Na_2SO_4 and evaporated. Recrystallization of the residue from ether gave compound 9 (12.4 g, 70%) as colorless crystals: 119–121 °C, IR (KBr) 3380, 3180, 2830, 1695, 1650, 1605, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8 (m, 2 H), 2.5–2.8 (m, 6 H), 2.9–3.1 (m, 4 H), 3.36 (s, 3 H), 3.43 (s, 3 H), 3.82 (t, J = 5.5 Hz, 2 H), 4.34 (br s, 1 H), 5.26 (s, 1 H).

Method C. 1,3-Dimethyl-6-[4-[3-(4-fluorophenoxy)propyl]piperazin-1-yl]-2,4(1*H*,3*H*)-pyrimidinedione (21). General Procedure. To a suspension of 9 (1.0 g, 3.5 mmol), triphenylphosphine (1.1 g, 4 mmol), and 4-fluorophenol (0.47 g, 4 mmol) in tetrahydrofuran (10 mL) at room temperature was added a solution of diethyl azodicarboxylate (0.71 g, 4 mmol) in tetrahydrofuran (5 mL). After stirring for 10 min, the reaction mixture was concentrated in vacuo. The residue was chromatographed on silica gel (ethyl acetate/MeOH, 20:1 to 5:1) to obtain 21 as colorless crystals (1.1 g, 82.5%): mp 121–122 °C.

6-[4-[3-(4-Aminophenoxy)propyl]piperazin-1-yl]-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (30). A suspension of 27 (2 g, 5 mmol) in MeOH (300 mL) containing 10% Pd/C (500 mg) was hydrogenated under atmospheric pressure for 30 min. After filtration of the catalyst, the solution was concentrated in vacuo. The residue was dissolved in ethyl acetate and treated with 10% HCl/MeOH. The precipitated crystals were collected and recrystallized from MeOH/ethyl acetate to obtain the dihydrochloride salt of 30 (1.6 g, 86%).

1,3-Dimethyl-6-[4-[3-[4-[(methylsulfonyl)amino]phenoxy]propyl]piperazin-1-yl]-2,4(1*H*,3*H*)-pyrimidinedione (32). To a solution of 30 (1.1 g, 3 mmol) and pyridine (1.8 mL) in dioxane (20 mL) was added trimethylsilyl chloride (0.8 g, 7.5 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 5 min and then at room temperature for 30 min. Methanesulfonyl chloride (0.7 g, 6 mmol) was added dropwise to the reaction mixture at 0 °C. After the reaction mixture had been stirred at the same temperature for 5 min and then at room temperature for 1 h, cold water (60 mL) and 1 N NaOH (70 mL) were added sequentially. The resulting solution was washed with $CHCl_3$, then made weakly acidic with concentrated HCl, and washed with $CHCl_3$. The aqueous solution was neutralized with aqueous K_2CO_3 and extracted with $CHCl_3$. The extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in ether and treated with 10% HCl/MeOH, and precipitated crystals were collected to yield the monohydrochloride salt of 32 (0.8 g, 54.6%).

***N*-(2-Hydroxyethyl)-*N*-[3-(4-nitrophenyl)propyl]amine (12a).** To a solution of 3-(4-nitrophenyl)propanol (11a) (22 g, 0.12 mol) and pyridine (28.4 g, 0.36 mol) in $CHCl_3$ (250 mL) was added *p*-toluenesulfonyl chloride (33.9 g, 0.18 mol) at 0 °C. After stirring at the same temperature for 10 min and then at room temperature for 16 h, the reaction mixture was poured into water (200 mL). Organic layer was separated and washed with 1 N HCl (100 mL) and 1 N NaOH (100 mL). After drying over Na_2SO_4, the organic solution was concentrated to obtain crude 3-(4-nitrophenyl)propyl *p*-toluenesulfonate (11b) (39 g, 97%). A mixture of 11b (37.5 g, 0.11 mol), 2-aminoethanol (125 g, 0.2 mol), and dioxane (65 mL) was heated at 90–100 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and dissolved in $CHCl_3$ (800 mL). The resulting solution was washed with water (1 L), 0.5 N NaOH (300 mL), and water (1 L) and dried over Na_2SO_4. After evaporation, the residue was recrystallized from toluene to give 12a (21 g, 85%): mp 82.5–84.5 °C; IR (KBr) 2800, 1590, 1505, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (m, 2 H), 2.7 (t, 2 H, J = 7 Hz), 2.75–2.85 (m, 4 H), 3.6 (m, 2 H), 7.35 (d, 2 H, J = 9 Hz), 8.1 (d, 2 H, J = 9 Hz).

1,3-Dimethyl-6-[[2-[(*p*-toluenesulfonyl)oxy]ethyl]amino]-2,4(1*H*,3*H*)-pyrimidinedione (14b). To a suspension of 6-chloro-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (13) (3.7 g, 21 mmol) in 2-propanol (15 mL) was added triethylamine (4.3 g, 42 mmol) and 2-aminomethanol (1.5 g, 25 mmol). The resulting mixture was refluxed for 3 h and concentrated under reduced pressure. The residue was dried by codistillation with toluene and suspended in pyridine (15 mL). After cooling, *p*-toluenesulfonyl chloride (6.8 g, 36 mmol) was added to the reaction mixture portionwise at 0 °C. The reaction mixture was stirred at the same temperature for 3 h, poured into cold saturated aqueous K_2CO_3 (90 mL), and allowed to stand at room temperature overnight. The precipitated crystals were collected and recrystallized from MeOH to give 14b (3.6 g, 76%): mp 146–149 °C; IR (KBr) 3270, 1682, 1615, 1550, 1480, 1435 cm^{-1}.

Method D. 1,3-Dimethyl-6-[[2-[*N*-[3-(4-nitrophenyl)propyl]-*N*-(hydroxyethyl)amino]ethyl]amino]-2,4-(1*H*,3*H*)-pyrimidinedione (40). General Procedure. To a solution of 14b (2.3 g, 6.5 mmol) in MeOH (35 mL) was added NaOH (270 mg) at 50 °C. After stirring at the same temperature, the reaction mixture was concentrated under reduced pressure. The residue was suspended in $CHCl_3$ (12 mL) and filtered. The filtrate was concentrated under reduced pressure, and 12 (1.7 g, 7.6 mmol) and *p*-toluenesulfonic acid monohydrates (66 mg) were added to the residue. The resulting mixture was heated with stirring at 80 °C for 1 h. After cooling to room temperature, the reaction mixture was dissolved in $CHCl_3$ (48 mL) and extracted with 0.5 N HCl (30 mL × 2). The extracts were made basic with K_2CO_3, and stirred at room temperature for 1 h. The precipitated solid was collected, dried, and recrystallized from ethanol to afford 40 (2.2 g, 79%) as colorless crystals: mp 125–126 °C; IR (KBr) 3250, 1690, 1650, 1610, 1550, 1345 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.7 (m, 2 H), 2.4–2.6 (m, 6 H), 2.6–2.8 (m, 4 H), 3.09 (s, 3 H), 3.26 (s, 3 H), 3.47 (m, 2 H), 4.5 (br s, 1 H), 4.7 (s, 1 H), 6.55 (br s, 1 H), 7.47 (d, 2 H, J = 9 Hz), 8.12 (d, 2 H, J = 9 Hz).

Pharmacology.[18] In Vitro Pharmacology: Action Potential Duration (APD). Mongrel dogs, weighing 7–11 kg, were anesthetized with thiopental sodium (30 mg/kg, iv). The heart was quickly excised. Purkinje fibers obtained from the right ventricle were placed in an organ bath and superfused with Tyrode's solution at 36 °C. Field stimulation at 60 beats/min pulses of 5 ms-duration was applied, and the action potential was recorded using a standard glass microelectrode technique (the resistance of the electrodes was 5–10 MΩ) on an oscilloscope (VC-11, Nihon Kohden, Japan) and photographed (M-085D, Asanuma Camera, Japan).

The composition of the Tyrode's solution was (mM): NaCl 137, NaH_2PO_4 0.32, $NaHCO_3$ 11.9, $MgCl_2$ 0.5, KCl 2.7, $CaCl_2$ 1.8, glucose 1.4, and dextrose 5.5. It was bubbled with 95% O_2 and 5% CO_2, and the pH was adjusted to 7.5. Each compound was prepared as a 1 mM stock solution in distilled water and diluted in Tyrode's solution to the final concentrations. The perfusing Tyrode's solution in the bath was exchanged within 3 min. Drugs were administered cumulatively and the data obtained 20 min after changing to a new solution were used for analysis. The

(17) Bender, H.; Rabbe, T.; Bohn, H.; Martorana, P. DE 3011809, 1981.

(18) Kamiya, J.; Ishii, M.; Katakami, T. Antiarrhythmic Effects of MS-551, A New Class III Antiarrhythmic Agent, on Canine Models of Ventricular Arrhythmia. *Jpn. J. Pharmacol.* **1992**, *58*, 107–115.

percent change of the duration of action potential at 75% repolarization (APD_{75}) was measured before and after the drug application.

This test was carried out in accordance with the method of Satoh et al.[11]

In Vivo Pharmacology: Effective Refractory Period (ERP). All animal studies were performed on mongrel dogs of either sex, weighing 7–13 kg, anesthetized with pentobarbital sodium (30 mg/kg, iv). The left femoral artery and vein were cannulated for recording of the arterial pressure and for drug administration, respectively.

The heart was exposed by left thoracotomy under artificial respiration (with room air in a tidal volume of 20 mL/kg at 18 breaths/min). Bipolar stimulating electrodes (1-mm diameter silver–silver chloride electrode) were sutured on the right atrium and ventricle of the exposed heart. Atrial pacing was performed at a rate of 150 beats/min (cycle length 400 ms) after extinguishing sinus pacemaker activity by ethanol injection into the sinus node artery or by crushing the sinus node area. The QT interval was measured at this atrial pacing rate. ERPs of the atrium and ventricle were measured by the extrastimulus technique (DHM-230, DIA Medical, Japan). Extrastimuli (2) were introduced after 10 paced beats (S1) at a basic cycle length of 400 ms, and the S1S2 intervals were decreased in 10-ms steps from 400 ms. ERPs were defined as the longest coupling intervals of extrastimuli which did not result in depolarization. The percent change in ERP was measured before and after the drug application.

Acknowledgment. We thank the members of the Analytical Department, Central Research Institute, Mitsui Toatsu Chemicals Inc., for the NMR and elemental analyses.

Registry No. **5**, 80210-72-6; **5** (R^1, R^2 = Me), 130634-20-7; **5** (R^1, R^2 = H), 96739-89-8; **9**, 130634-46-7; **11a**, 20716-25-0; **11b**, 130636-37-2; **12**, 80258-61-3; **12a**, 130634-09-2; **13**, 6972-27-6; **14b**, 130634-04-7; **16**, 69479-11-4; **16**·2HCl, 124994-99-6; **17**, 142422-36-4; **18**, 142422-37-5; **18**·2HCl, 142422-38-6; **19**, 142422-39-7; **19**·HBr, 138540-13-3; **20**, 142422-40-0; **21**, 138538-55-3; **21**·HCl, 138539-74-9; **22**, 138539-75-0; **22**·HCl, 138539-76-1; **23**, 142422-41-1; **23**·HCl, 142422-42-2; **24**, 138556-98-6; **24**·HCl, 142422-43-3; **25**, 138557-02-5; **25**·HCl, 138557-03-6; **26**, 138538-81-5; **26**·HCl, 138539-41-0; **27**, 130637-00-2; **27**·2HCl, 142422-44-4; **28**, 130636-45-2; **28**·HCl, 130634-47-8; **29**, 130636-48-5; **29**·HCl, 130634-61-6; **30**, 138539-81-8; **30**·2HCl, 142422-45-5; **31**, 138539-79-4; **31**·HCl, 138539-80-7; **32**, 138539-83-0; **32**·HCl, 138539-84-1; **33**, 130636-46-3; **33**·HCl, 130634-60-5; **34**, 138557-91-2; **34**·HCl, 130634-44-5; **35**, 130634-42-3; **36**, 138557-88-7; **36**·HCl, 130634-13-8; **37**, 130634-02-5; **38**, 142422-46-6; **39**, 130636-42-9; **39**·HCl, 130656-45-0; **40**, 130636-43-0; **40**·HCl, 130656-51-8; $HOCH_2CH_2NH_2$, 141-43-5; $PhO(CH_2)_3Br$, 588-63-6; *m*-$ClC_6H_4O(CH_2)_3Br$, 37142-46-4; *o*-$ClC_6H_4O(CH_2)_3Br$, 50912-59-9; *p*-$MeSC_6H_4O(CH_2)_3Br$, 97384-43-5; *o*-$MeSC_6H_4O(CH_2)_3Br$, 142422-47-7; *p*-$NO_2C_6H_4O(CH_2)_3Br$, 13094-50-3; *m*-$NO_2C_6H_4O(CH_2)_3BR$, 31191-43-2; *o*-$NO_2C_6H_4O(CH_2)_3Br$, 104147-69-5; *p*-$NO_2C_6H_4O(CH_2)_2Br$, 13288-06-7; *p*-$CH_3NHSO_2C_6H_4O(CH_2)_3Br$, 138557-93-4; *p*-$NO_2C_6H_4(CH_2)_4Br$, 99359-34-9; *p*-$NO_2C_6H_4(CH_2)_2GBr$, 5339-26-4; *p*-$NO_2C_6H_4CH_2Br$, 100-11-8; *p*-$FC_6H_4O(CH_2)_3BR$, 1129-78-8; 3-bromo-1-propanol, 627-18-9; 1-phenoxy-2,3-epoxypropane, 122-60-1; 3-(4-chlorophenoxy)propyl bromide, 27983-04-6; 4-fluorophenol, 371-41-5.